

NLRP3 MODULATORS

CROSS-REFERENCE

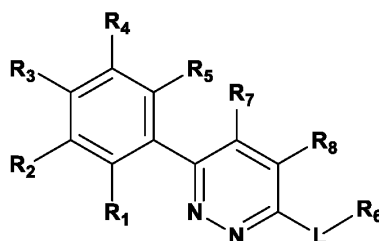
[0001] This application claims benefit of U.S. Provisional Application No. 63/320,157, filed on March 15, 2022, and U.S. Provisional Application No. 63/356,415, filed on June 28, 2022, each of which is herein incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] The NOD-like receptor (NLR) family, pyrin domain-containing protein 3 (NLRP3) inflammasome is a critical component of the innate immune response and inflammatory process, and its aberrant activity is pathogenic in inherited disorders such as cryopyrin-associated periodic syndromes (CAPS) and complex diseases such as multiple sclerosis, type 2 diabetes, Alzheimer's disease and atherosclerosis. Current treatments for NLRP3-related diseases include biologic agents that target IL-1. Small molecule inhibitors of NLRP3 provide an attractive alternative to these biologics, given their potential for improved safety and patient comfort and compliance.

SUMMARY OF THE INVENTION

[0003] In one aspect, provided herein are compounds of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof:



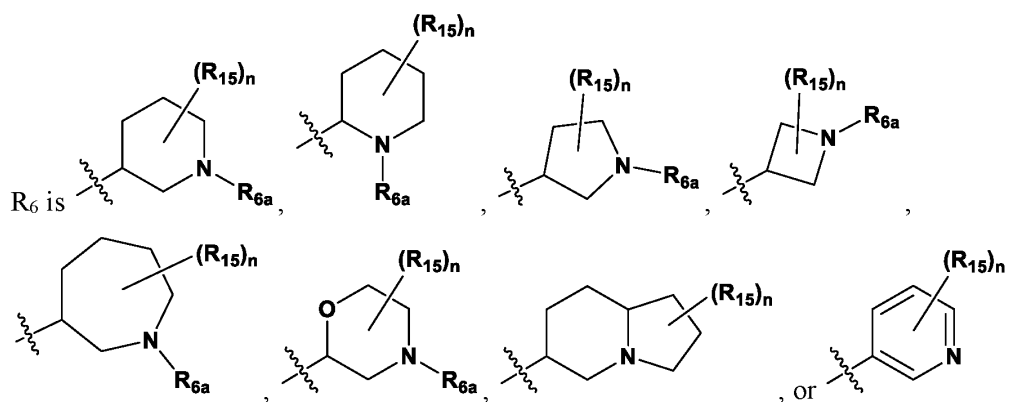
Formula (I');

wherein:

L is -C(R_{9a})(R_{9b})-, -C(O)-, or -C(=N-OR₁₆)-;

R₁, R₂, R₃, R₄, and R₅ are each independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁), -S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three

groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁); or R₁ and R₂ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups; or R₂ and R₃ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups; or R₃ and R₄ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups; or R₄ and R₅ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups;



R_{6a} is selected from hydrogen, C₁₋₆alkyl, and C₃₋₆cycloalkyl, wherein C₁₋₆alkyl and C₃₋₆cycloalkyl optionally substituted with one, two, or three R₁₄ groups; or R_{6a} and an R₁₅ are taken together to form a bridge that is -CH₂- or -CH₂CH₂-;

R₇ and R₈ are each independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁); or R₇ and R₈ are combined to

form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups;

R_{9a} and R_{9b} are each independently selected from hydrogen, halogen, -OH, C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy;

each R₁₀ is independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

each R₁₁ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R₁₂ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R₁₃ is independently selected C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

each R₁₄ is independently selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁), S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR¹⁰, and -N(R₁₀)(R₁₁);

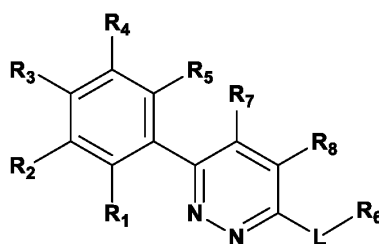
each R₁₅ is independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁), S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -

OR¹⁰, and -N(R₁₀)(R₁₁); or two R₁₅ are taken together to form a bridge that is -CH₂- or -CH₂CH₂-;

R₁₆ is selected from hydrogen and C₁₋₆alkyl; and

n is 0, 1, 2, 3, or 4.

[0004] In another aspect, provided herein are compounds of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



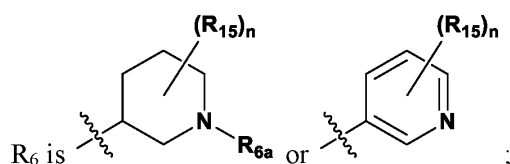
Formula (I);

wherein:

L is -C(R_{9a})(R_{9b})-, -C(O)-, or -C(=N-OR₁₆)-;

R₁, R₂, R₃, R₄, and R₅ are each independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁)-, S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁); or R₁ and R₂ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups; or R₂ and R₃ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups; or R₃ and R₄ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered

cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups; or R_4 and R_5 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups;



R_{6a} is selected from hydrogen and C_{1-6} alkyl optionally substituted with one, two, or three R_{14} groups;

R_7 and R_8 are each independently selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁); or R_7 and R_8 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups;

R_{9a} and R_{9b} are each independently selected from hydrogen, halogen, -OH, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

each R_{10} is independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl;

each R_{11} is independently selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R_{12} is independently selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R_{13} is independently selected C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6}

alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

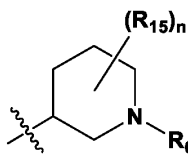
each R₁₄ is independently selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁)-, S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR¹⁰, and -N(R₁₀)(R₁₁);

each R₁₅ is independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁)-, S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR¹⁰, and -N(R₁₀)(R₁₁);

R₁₆ is selected from hydrogen and C₁₋₆alkyl; and

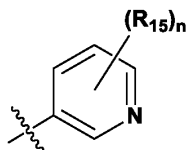
n is 0, 1, 2, 3, or 4.

[0005] In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically



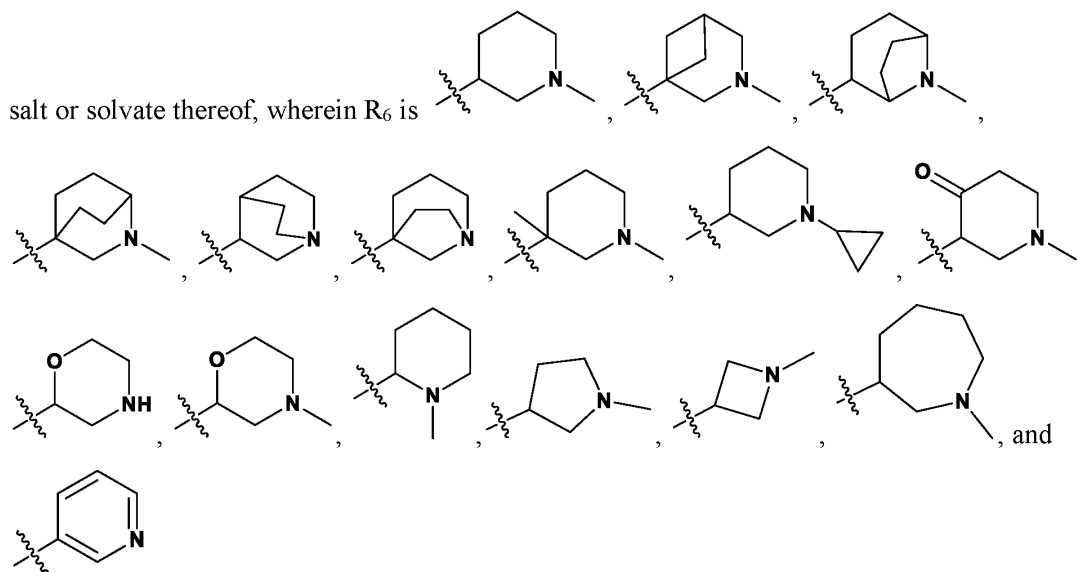
acceptable salt or solvate thereof, wherein R₆ is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is C₁₋₆alkyl optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is unsubstituted C₁₋₆alkyl. In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is -CH₃.

[0006] In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically



acceptable salt or solvate thereof, wherein R_6 is . In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0.

[0007] In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable



[0008] In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are each independently selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁). In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are each independently selected from hydrogen, halogen, C_{1-6} alkyl, and C_{1-6} haloalkyl. In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are each independently selected from hydrogen and C_{1-6} alkyl. In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are hydrogen. In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 is hydrogen and R_8 is -CH₃. In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt

or solvate thereof, wherein R₇ is -CH₃ and R₈ is hydrogen. In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are -CH₃.

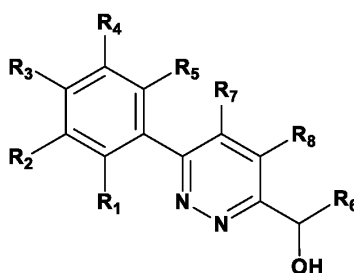
[0009] In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted phenyl ring.

[0010] In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, or -C(O)N(R₁₀)(R₁₁). In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, or -OH. In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is -OH. In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₂ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, or -OR₁₀. In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₂ is hydrogen. In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₃ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, or -N(R₁₀)(R₁₁). In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₃ is C₁₋₆alkyl or C₁₋₆haloalkyl. In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₄ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, or -OR₁₀. In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₄ is hydrogen.

[0011] In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₅ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, or -N(R₁₀)(R₁₁). In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₅ is hydrogen or C₁₋₆alkyl. In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein L is -C(R_{9a})(R_{9b})-. In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{9a} is selected from

hydrogen, halogen, and C₁₋₆alkyl. In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{9a} is hydrogen. In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{9b} is selected from hydrogen, halogen, and -OH. In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{9b} is -OH. In some embodiments is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein L is -C(O)-.

[0012] In one aspect, provided herein are compounds of Formula (II), or a pharmaceutically acceptable salt or solvate thereof:

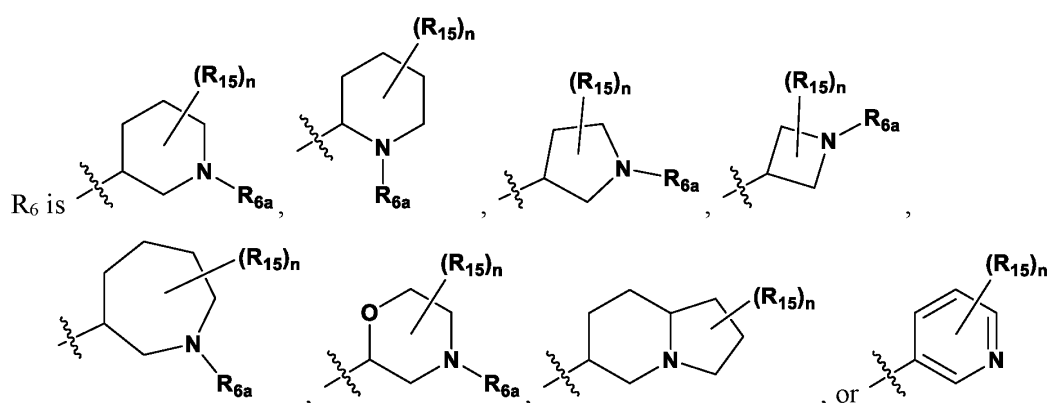


Formula (II);

wherein:

R₁, R₂, R₃, R₄, and R₅ are each independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁), -S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁); or R₁ and R₂ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups; or R₂ and R₃ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally

substituted with one, two, or three R_{14} groups; or R_3 and R_4 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups; or R_4 and R_5 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups;



R_{6a} is selected from hydrogen, C_{1-6} alkyl, and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl optionally substituted with one, two, or three R_{14} groups; or R_{6a} and an R_{15} are taken together to form a bridge that is $-CH_2-$ or $-CH_2CH_2-$;

R_7 and R_8 are each independently selected from hydrogen, halogen, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR_{10}$, and $-N(R_{10})(R_{11})$; or R_7 and R_8 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups;

each R_{10} is independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9}

₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

each R₁₁ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R₁₂ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

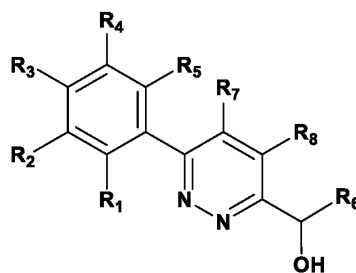
each R₁₃ is independently selected C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

each R₁₄ is independently selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁)-, S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR¹⁰, and -N(R₁₀)(R₁₁);

each R₁₅ is independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁)-, S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR¹⁰, and -N(R₁₀)(R₁₁); or two R₁₅ are taken together to form a bridge that is -CH₂- or -CH₂CH₂-; and

n is 0, 1, 2, 3, or 4.

[0013] In another aspect, provided herein are compounds of Formula (III), or a pharmaceutically acceptable salt or solvate thereof:

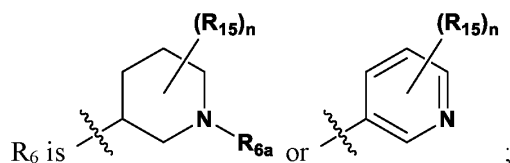


Formula (III);

wherein:

R_1 , R_2 , R_3 , R_4 , and R_5 are each independently selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, C_{1-9} heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁), -S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁); or R_1 and R_2 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups; or R_2 and R_3 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups; or R_3 and R_4 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups; or R_4 and R_5 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered

heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups;



R_{6a} is selected from hydrogen and C_{1-6} alkyl optionally substituted with one, two, or three R_{14} groups;

R_7 and R_8 are each independently selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁); or R_7 and R_8 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups;

each R_{10} is independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl;

each R_{11} is independently selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R_{12} is independently selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R_{13} is independently selected C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl;

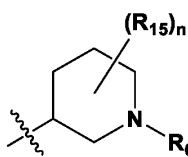
each R_{14} is independently selected from halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, C_{1-9} heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -

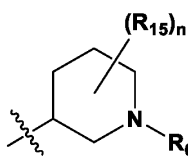
$C(O)C(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)R_{13}$, $-S(O)_2R_{13}$, $-S(O)_2N(R_{10})(R_{11})$,
 $S(=O)(=NH)N(R_{10})(R_{11})$, $-CH_2C(O)N(R_{10})(R_{11})$, $-CH_2N(R_{12})C(O)R_{13}$, $-CH_2S(O)_2R_{13}$,
 and $-CH_2S(O)_2N(R_{10})(R_{11})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl,
 C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one,
 two, or three groups selected from halogen, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^{10}$, and $-N(R_{10})(R_{11})$;

each R_{15} is independently selected from halogen, oxo, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, C_{1-9} heteroaryl, $-OR_{10}$, $-SR_{10}$, $-N(R_{10})(R_{11})$, $-C(O)OR_{10}$, $-OC(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)OR_{13}$, $-N(R_{12})S(O)_2R_{13}$, $-C(O)R_{13}$, $-S(O)R_{13}$, $-OC(O)R_{13}$, $-C(O)N(R_{10})(R_{11})$, $-C(O)C(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)R_{13}$, $-S(O)_2R_{13}$, $-S(O)_2N(R_{10})(R_{11})$,
 $S(=O)(=NH)N(R_{10})(R_{11})$, $-CH_2C(O)N(R_{10})(R_{11})$, $-CH_2N(R_{12})C(O)R_{13}$, $-CH_2S(O)_2R_{13}$,
 and $-CH_2S(O)_2N(R_{10})(R_{11})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl,
 C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one,
 two, or three groups selected from halogen, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^{10}$, and $-N(R_{10})(R_{11})$; and

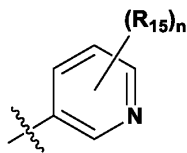
n is 0, 1, 2, 3, or 4.

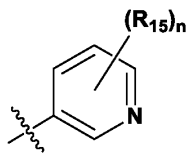
[0014] In some embodiments is a compound of Formula (II) or (III), or a pharmaceutically



acceptable salt or solvate thereof, wherein R_6 is . In some embodiments is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is C_{1-6} alkyl optionally substituted with one, two, or three R_{14} groups. In some embodiments is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is unsubstituted C_{1-6} alkyl. In some embodiments is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is $-CH_3$.

[0015] In some embodiments is a compound of Formula (II) or (III), or a pharmaceutically



acceptable salt or solvate thereof, wherein R_6 is . In some embodiments is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0.

membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted phenyl ring.

[0019] In some embodiments is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, or -C(O)N(R₁₀)(R₁₁). In some embodiments is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, or -OH. In some embodiments is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is -OH. In some embodiments is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₂ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, or -OR₁₀. In some embodiments is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₂ is hydrogen. In some embodiments is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₃ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, or -N(R₁₀)(R₁₁). In some embodiments is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₃ is C₁₋₆alkyl or C₁₋₆haloalkyl. In some embodiments is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₄ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, or -OR₁₀. In some embodiments is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₄ is hydrogen.

[0020] In some embodiments is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₅ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, or -N(R₁₀)(R₁₁). In some embodiments is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₅ is hydrogen or C₁₋₆alkyl.

[0021] In another aspect described herein is a pharmaceutical composition comprising a compound of Formula (I'), (I), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

[0022] In some embodiments described herein is a method of treating a metabolic disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I'), (I), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments described herein is a method of treating a metabolic disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I'), (I), (II), or (III), or a pharmaceutically

acceptable salt or solvate thereof, wherein the metabolic disease is selected from type 2 diabetes, atherosclerosis, obesity, and gout.

[0023] In some embodiments described herein is a method of treating a liver disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I'), (I), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments described herein is a method of treating a liver disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I'), (I), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein the liver disease is selected from non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), viral hepatitis, and cirrhosis.

[0024] In some embodiments described herein is a method of treating a lung disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I'), (I), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments described herein is a method of treating a lung disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I'), (I), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein the lung disease is selected from asthma, chronic obstructive pulmonary disease (COPD), and pulmonary idiopathic fibrosis.

[0025] In some embodiments described herein is a method of treating a central nervous system disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I'), (I), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments described herein is a method of treating a central nervous system disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I'), (I), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein the central nervous system disease is selected from Alzheimer's disease, multiple sclerosis, Amyotrophic Lateral Sclerosis, Parkinson's disease, Huntington's disease, traumatic brain injury, ischemic stroke and reperfusion, haemorrhagic stroke, epilepsy, and depression.

[0026] In some embodiments described herein is a method of treating an inflammatory or autoimmune disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I'), (I), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments described herein is a method of treating an inflammatory or autoimmune disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of

Formula (I'), (I), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein the inflammatory or autoimmune disease is selected from rheumatoid arthritis, multiple sclerosis, psoriasis, lupus, inflammatory bowel disease, Crohn's disease, and ulcerative colitis.

[0027] In some embodiments described herein is a method of treating a cardiovascular disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I'), (I), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments described herein is a method of treating a cardiovascular disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I'), (I), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein the cardiovascular disease is atherosclerosis or stroke.

INCORPORATION BY REFERENCE

[0028] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0029] In the context of this disclosure, a number of terms shall be utilized.

[0030] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood to which the claimed subject matter belongs. In the event that there are a plurality of definitions for terms herein, those in this section prevail. All patents, patent applications, publications and published nucleotide and amino acid sequences (*e.g.*, sequences available in GenBank or other databases) referred to herein are incorporated by reference. Where reference is made to a URL or other such identifier or address, it is understood that such identifiers can change and particular information on the internet can come and go, but equivalent information can be found by searching the internet. Reference thereto evidences the availability and public dissemination of such information.

[0031] It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. In this application, the use of "or" means "and/or" unless stated otherwise.

Furthermore, use of the term “including” as well as other forms, such as “include”, “includes,” and “included,” is not limiting.

[0032] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0033] Definition of standard chemistry terms may be found in reference works, including but not limited to, Carey and Sundberg “Advanced Organic Chemistry 4th Ed.” Vols. A (2000) and B (2001), Plenum Press, New York. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology.

[0034] Unless specific definitions are provided, the nomenclature employed in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those recognized in the field. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients. Standard techniques can be used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (e.g., electroporation, lipofection). Reactions and purification techniques can be performed e.g., using kits of manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures can be generally performed of conventional methods and as described in various general and more specific references that are cited and discussed throughout the present specification.

[0035] It is to be understood that the methods and compositions described herein are not limited to the particular methodology, protocols, cell lines, constructs, and reagents described herein and as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the methods, compounds, compositions described herein.

[0036] As used herein, C₁-C_x includes C₁-C₂, C₁-C₃ . . . C₁-C_x. C₁-C_x refers to the number of carbon atoms that make up the moiety to which it designates (excluding optional substituents).

[0037] An “alkyl” group refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation. In some embodiments, the “alkyl” group may have 1 to 6 carbon atoms (whenever it appears herein, a numerical range such as “1 to 6” refers to each integer in the given range; e.g., “1 to 6 carbon atoms” means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 6 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated). The alkyl group of the compounds described herein may be designated as “C₁-C₆alkyl” or similar designations. By way of example only, “C₁-

C₆alkyl” indicates that there are one to six carbon atoms in the alkyl chain, *i.e.*, the alkyl chain is selected from the group consisting of methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, iso-pentyl, neo-pentyl, and hexyl. Alkyl groups can be substituted or unsubstituted. Depending on the structure, an alkyl group can be a monoradical or a diradical (*i.e.*, an alkylene group).

[0038] An “alkoxy” refers to a “-O-alkyl” group, where alkyl is as defined herein.

[0039] The term “alkenyl” refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon double bond. Non-limiting examples of an alkenyl group include -CH=CH₂, -C(CH₃)=CH₂, -CH=CHCH₃, -CH=C(CH₃)₂ and -C(CH₃)=CHCH₃. In some embodiments, an alkenyl groups may have 2 to 6 carbons. Alkenyl groups can be substituted or unsubstituted. Depending on the structure, an alkenyl group can be a monoradical or a diradical (*i.e.*, an alkenylene group).

[0040] The term “alkynyl” refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon triple bond. Non-limiting examples of an alkynyl group include -C≡CH, -C≡CCH₃, -C≡CCH₂CH₃ and -C≡CCH₂CH₂CH₃. In some embodiments, an alkynyl group can have 2 to 6 carbons. Alkynyl groups can be substituted or unsubstituted. Depending on the structure, an alkynyl group can be a monoradical or a diradical (*i.e.*, an alkynylene group).

[0041] “Amino” refers to a -NH₂ group.

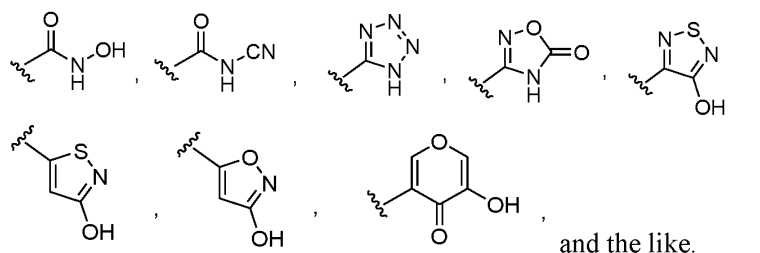
[0042] The term “alkylamine” or “alkylamino” refers to the -N(alkyl)_xH_y group, where alkyl is as defined herein and x and y are selected from the group x=1, y=1 and x=2, y=0. When x=2, the alkyl groups, taken together with the nitrogen to which they are attached, can optionally form a cyclic ring system. “Dialkylamino” refers to a -N(alkyl)₂ group, where alkyl is as defined herein.

[0043] The term “aromatic” refers to a planar ring having a delocalized π -electron system containing $4n+2$ π electrons, where n is an integer. Aromatic rings can be formed from five, six, seven, eight, nine, or more than nine atoms. Aromatics can be optionally substituted. The term “aromatic” includes both aryl groups (*e.g.*, phenyl, naphthalenyl) and heteroaryl groups (*e.g.*, pyridinyl, quinolinyl).

[0044] As used herein, the term “aryl” refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. Aryl rings can be formed by five, six, seven, eight, nine, or more than nine carbon atoms. Aryl groups can be optionally substituted. Examples of aryl groups include, but are not limited to phenyl, and naphthalenyl. Depending on the structure, an aryl group can be a monoradical or a diradical (*i.e.*, an arylene group).

[0045] “Carboxy” refers to -CO₂H. In some embodiments, carboxy moieties may be replaced with a “carboxylic acid bioisostere”, which refers to a functional group or moiety that exhibits

similar physical and/or chemical properties as a carboxylic acid moiety. A carboxylic acid bioisostere has similar biological properties to that of a carboxylic acid group. A compound with a carboxylic acid moiety can have the carboxylic acid moiety exchanged with a carboxylic acid bioisostere and have similar physical and/or biological properties when compared to the carboxylic acid-containing compound. For example, in one embodiment, a carboxylic acid bioisostere would ionize at physiological pH to roughly the same extent as a carboxylic acid group. Examples of bioisosteres of a carboxylic acid include, but are not limited to,



[0046] The term “cycloalkyl” refers to a monocyclic or polycyclic non-aromatic radical, wherein each of the atoms forming the ring (i.e. skeletal atoms) is a carbon atom. Cycloalkyls may be saturated, or partially unsaturated. Cycloalkyls may be fused with an aromatic ring (in which case the cycloalkyl is bonded through a non-aromatic ring carbon atom). In some embodiments, cycloalkyl groups include groups having from 3 to 10 ring atoms.

[0047] The terms “heteroaryl” or, alternatively, “heteroaromatic” refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. An *N*-containing “heteroaromatic” or “heteroaryl” moiety refers to an aromatic group in which at least one of the skeletal atoms of the ring is a nitrogen atom.

[0048] A “heterocycloalkyl” group or “heteroalicyclic” group refers to a cycloalkyl group, wherein at least one skeletal ring atom is a heteroatom selected from nitrogen, oxygen and sulfur. The radicals may be fused with an aryl or heteroaryl. The term heteroalicyclic also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. Unless otherwise noted, heterocycloalkyls have from 2 to 10 carbons in the ring. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (i.e. skeletal atoms of the heterocycloalkyl ring).

[0049] The term “halo” or, alternatively, “halogen” means fluoro, chloro, bromo and iodo.

[0050] The term “haloalkyl” refers to an alkyl group that is substituted with one or more halogens. The halogens may be the same or they may be different. Non-limiting examples of haloalkyls include $-\text{CH}_2\text{Cl}$, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{CF}_3$, $-\text{CF}_2\text{CF}_3$, and the like.

[0051] The terms “fluoroalkyl” and “fluoroalkoxy” include alkyl and alkoxy groups, respectively, that are substituted with one or more fluorine atoms. Non-limiting examples of fluoroalkyls include -CF₃, -CHF₂, -CH₂F, -CH₂CF₃, -CF₂CF₃, -CF₂CF₂CF₃, -CF(CH₃)₃, and the like. Non-limiting examples of fluoroalkoxy groups, include -OCF₃, -OCHF₂, -OCH₂F, -OCH₂CF₃, -OCF₂CF₃, -OCF₂CF₂CF₃, -OCF(CH₃)₂, and the like.

[0052] The term “heteroalkyl” refers to an alkyl radical where one or more skeletal chain atoms is selected from an atom other than carbon, *e.g.*, oxygen, nitrogen, sulfur, phosphorus, silicon, or combinations thereof. The heteroatom(s) may be placed at any interior position of the heteroalkyl group. Examples include, but are not limited to, -CH₂-O-CH₃, -CH₂-CH₂-O-CH₃, -CH₂-NH-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-N(CH₃)-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-CH₂-S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH₂-NH-OCH₃, -CH₂-O-Si(CH₃)₃, -CH₂-CH=N-OCH₃, and -CH=CH-N(CH₃)-CH₃. In addition, up to two heteroatoms may be consecutive, such as, by way of example, -CH₂-NH-OCH₃ and -CH₂-O-Si(CH₃)₃. Excluding the number of heteroatoms, a “heteroalkyl” may have from 1 to 6 carbon atoms.

[0053] The term “bond” or “single bond” refers to a chemical bond between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure.

[0054] The term “moiety” refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[0055] As used herein, the substituent “R” appearing by itself and without a number designation refers to a substituent selected from among alkyl, haloalkyl, heteroalkyl, alkenyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon), and heterocycloalkyl.

[0056] “Optional” or “optionally” means that a subsequently described event or circumstance may or may not occur and that the description includes instances when the event or circumstance occurs and instances in which it does not.

[0057] The term “optionally substituted” or “substituted” means that the referenced group may be substituted with one or more additional group(s) individually and independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, -OH, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, arylsulfone, -CN, alkyne, C₁-C₆alkylalkyne, halo, acyl, acyloxy, -CO₂H, -CO₂-alkyl, nitro, haloalkyl, fluoroalkyl, and amino, including mono- and di-substituted amino groups (*e.g.* -NH₂, -NHR, -N(R)₂), and the protected derivatives thereof. By way of example, an optional substituents may be L^sR^s, wherein each L^s is independently selected from a bond, -O-, -C(=O)-, -S-, -S(=O)-, -S(=O)₂-, -NH-, -NHC(O)-, -C(O)NH-, S(=O)₂NH-, -NHS(=O)₂-, -OC(O)NH-, -NHC(O)O-, -(C₁-C₆alkyl)-, or -(C₂-

C₆alkenyl)-; and each R⁸ is independently selected from among H, (C₁-C₆alkyl), (C₃-C₈cycloalkyl), aryl, heteroaryl, heterocycloalkyl, and C₁-C₆heteroalkyl. The protecting groups that may form the protective derivatives of the above substituents are found in sources such as Greene and Wuts, above.

[0058] As used herein, the term “about” or “approximately” means within 20%, preferably within 10%, and more preferably within 5% of a given value or range.

[0059] The term a “therapeutically effective amount” as used herein refers to the amount of a NLRP3 inhibitor that, when administered to a mammal in need, is effective to at least partially ameliorate or to at least partially prevent conditions or diseases described herein.

[0060] As used herein, the term “expression” includes the process by which polynucleotides are transcribed into mRNA and translated into peptides, polypeptides, or proteins.

[0061] The term “modulate” encompasses either a decrease or an increase in activity or expression depending on the target molecule.

[0062] The term "activator" is used in this specification to denote any molecular species that results in activation of the indicated receptor, regardless of whether the species itself binds to the receptor or a metabolite of the species binds to the receptor when the species is administered topically. Thus, the activator can be a ligand of the receptor or it can be an activator that is metabolized to the ligand of the receptor, i.e., a metabolite that is formed in tissue and is the actual ligand.

[0063] The term “patient” or “mammal” refers to a human, a non-human primate, canine, feline, bovine, ovine, porcine, murine, or other veterinary or laboratory mammal. Those skilled in the art recognize that a therapy which reduces the severity of a pathology in one species of mammal is predictive of the effect of the therapy on another species of mammal.

[0064] "Pharmaceutically acceptable salt" includes both acid and base addition salts. A pharmaceutically acceptable salt of any one of the compounds described herein is intended to encompass any and all pharmaceutically suitable salt forms. Preferred pharmaceutically acceptable salts of the compounds described herein are pharmaceutically acceptable acid addition salts, and pharmaceutically acceptable base addition salts.

[0065] "Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, hydroiodic acid, hydrofluoric acid, phosphorous acid, and the like. Also included are salts that are formed with organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. and include, for example, acetic acid,

trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, salicylic acid, and the like. Exemplary salts thus include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, nitrates, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, trifluoroacetates, propionates, caprylates, isobutyrate, oxalates, malonates, succinate suberates, sebacates, fumarates, maleates, mandelates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, phthalates, benzenesulfonates, toluenesulfonates, phenylacetates, citrates, lactates, malates, tartrates, methanesulfonates, and the like. Also contemplated are salts of amino acids, such as arginates, gluconates, and galacturonates (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Science*, 66:1-19 (1997)). Acid addition salts of basic compounds are prepared by contacting the free base forms with a sufficient amount of the desired acid to produce the salt.

[0066] "Pharmaceutically acceptable base addition salt" refers to those salts that retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. In some embodiments, pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Salts derived from inorganic bases include, but are not limited to, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts, and the like. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, for example, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, *N,N*-dibenzylethylenediamine, chlorprocaine, hydrabamine, choline, betaine, ethylenediamine, ethylenedianiline, *N*-methylglucamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins, and the like. See Berge et al., *supra*.

[0067] As used herein, "treatment" or "treating" or "palliating" or "ameliorating" are used interchangeably herein. These terms refer to an approach for obtaining beneficial or desired results including but not limited to therapeutic benefit and/or a prophylactic benefit. By "therapeutic benefit" is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient is still afflicted with the

underlying disorder. For prophylactic benefit, the compositions are administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease has not been made.

NLRP3 modulators

[0068] NLRP3 is an intracellular signaling molecule that senses many pathogen-derived, environmental and host-derived factors. Upon activation, NLRP3 binds to apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC). ASC then polymerizes to form a large aggregate known as an ASC speck.

[0069] Polymerized ASC associates with the cysteine protease caspase-1 to form a complex termed the inflammasome. This results in the activation of active caspase-1, which cleaves the precursor forms of the proinflammatory cytokines IL-1 β and IL-18 (termed pro-IL-1 β and pro-IL-18 respectively) to thereby activate these cytokines. Caspase-1 also mediates a type of inflammatory cell death known as pyroptosis. The ASC speck aggregate can also recruit and activate caspase-8, which is able to process pro-IL-1 β and pro-IL-18 and trigger apoptotic cell death.

[0070] Caspase-1 cleaves pro-IL-1 β and pro-IL-18 to their active forms, which are secreted from the cell. Active caspase-1 also cleaves gasdermin-D to trigger pyroptosis. Through its control of the pyroptotic cell death pathway, caspase-1 also mediates the release of alarmin molecules such as IL-33 and high mobility group box 1 protein (HMGB1). Caspase-1 also cleaves intracellular IL-1R2 resulting in its degradation and allowing the release of IL-1 α . In human cells caspase-1 may also control the processing and secretion of IL-37. A number of other caspase-1 substrates such as components of the cytoskeleton and glycolysis pathway may contribute to caspase-1 dependent inflammation.

[0071] NLRP3-dependent ASC specks are released into the extracellular environment where they can activate caspase-1, induce processing of caspase-1 substrates and propagate inflammation. Active cytokines derived from NLRP3 inflammasome activation are important drivers of inflammation and interact with other cytokine pathways to shape the immune response to infection and injury. For example, IL-1 β signaling induces the secretion of the pro-inflammatory cytokines IL-6 and TNF. IL-1 β and IL-18 synergize with IL-23 to induce IL-17 production by memory CD4 Th17 cells and by $\gamma\delta$ T cells in the absence of T cell receptor engagement. IL-18 and IL-12 also synergize to induce IFN- γ production from memory T cells and NK cells driving a Th1 response.

[0072] The inherited CAPS diseases Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS) and neonatal-onset multisystem inflammatory disease

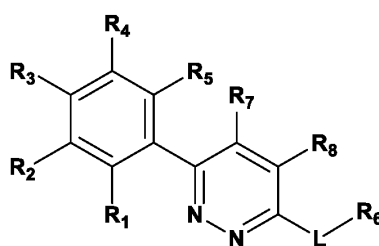
(NOMID) are caused by gain-of-function mutations in NLRP3, thus defining NLRP3 as a critical component of the inflammatory process. NLRP3 has also been implicated in the pathogenesis of a number of complex diseases, notably including metabolic disorders such as type 2 diabetes, atherosclerosis, obesity and gout.

[0073] A role for NLRP3 in diseases of the central nervous system is emerging, and lung diseases have also been shown to be influenced by NLRP3. Furthermore, NLRP3 has a role in the development of liver disease, kidney disease and aging. Many of these associations were defined using NLRP3 KO mice, but there have also been insights into the specific activation of NLRP3 in these diseases. In Type 2 diabetes mellitus (T2D), the deposition of islet amyloid polypeptide in the pancreas activates NLRP3 and IL-1 β signaling, resulting in cell death and inflammation.

[0074] Current treatments for NLRP3-related diseases include biologic agents that target IL-1. These are the recombinant IL-1 receptor antagonist anakinra, the neutralizing IL-1 β antibody canakinumab and the soluble decoy IL1 receptor rilonacept. These approaches have proven successful in the treatment of CAPS, and these biologic agents have been used in clinical trials for other IL-1 β associated diseases. Small molecule inhibitors of NLRP3 provide an attractive alternative to these biologics, given their potential for improved safety (minimal risk of infection and ease of withdrawal compared to biologics) and patient comfort and compliance.

[0075] The compounds of Formula (I'), (I), (Ia), (Ib), (II), or (III), described herein are NLRP3 modulators. The compounds of Formula (I'), (I), (Ia), (Ib), (II), or (III), described herein, and compositions comprising these compounds, are useful for the treatment of NLRP3 associated diseases including, but not limited to, type 2 diabetes, atherosclerosis, obesity and gout.

[0076] In some embodiments, provided herein is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof:



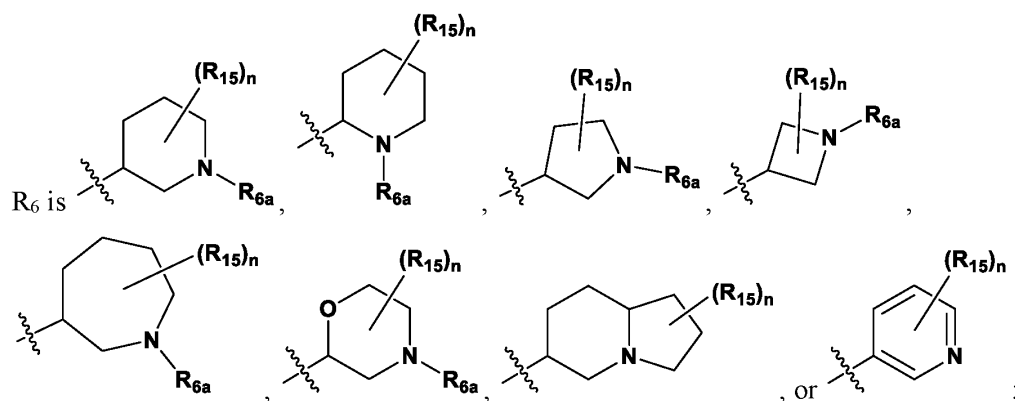
Formula (I');

wherein:

L is -C(R_{9a})(R_{9b})-, -C(O)-, or -C(=N-OR₁₆)-;

R₁, R₂, R₃, R₄, and R₅ are each independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -

$N(R_{12})C(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)OR_{13}$, $-N(R_{12})S(O)_2R_{13}$, $-C(O)R_{13}$, $-S(O)R_{13}$, $-OC(O)R_{13}$, $-C(O)N(R_{10})(R_{11})$, $-C(O)C(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)R_{13}$, $-S(O)_2R_{13}$, $-S(O)_2N(R_{10})(R_{11})$, $S(=O)(=NH)N(R_{10})(R_{11})$, $-CH_2C(O)N(R_{10})(R_{11})$, $-CH_2N(R_{12})C(O)R_{13}$, $-CH_2S(O)_2R_{13}$, and $-CH_2S(O)_2N(R_{10})(R_{11})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_2 -heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR_{10}$, and $-N(R_{10})(R_{11})$; or R_1 and R_2 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups; or R_2 and R_3 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups; or R_3 and R_4 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups; or R_4 and R_5 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups;



R_{6a} is selected from hydrogen, C_{1-6} alkyl, and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl optionally substituted with one, two, or three R_{14} groups; or R_{6a} and an R_{15} are taken together to form a bridge that is $-CH_2-$ or $-CH_2CH_2-$;

R₇ and R₈ are each independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁); or R₇ and R₈ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups;

R_{9a} and R_{9b} are each independently selected from hydrogen, halogen, -OH, C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy;

each R₁₀ is independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

each R₁₁ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R₁₂ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R₁₃ is independently selected C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

each R₁₄ is independently selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁), S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁);

each R₁₅ is independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -

$N(R_{12})S(O)_2R_{13}$, $-C(O)R_{13}$, $-S(O)R_{13}$, $-OC(O)R_{13}$, $-C(O)N(R_{10})(R_{11})$, $-C(O)C(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)R_{13}$, $-S(O)_2R_{13}$, $-S(O)_2N(R_{10})(R_{11})$, $S(=O)(=NH)N(R_{10})(R_{11})$, $-CH_2C(O)N(R_{10})(R_{11})$, $-CH_2N(R_{12})C(O)R_{13}$, $-CH_2S(O)_2R_{13}$, and $-CH_2S(O)_2N(R_{10})(R_{11})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^{10}$, and $-N(R_{10})(R_{11})$; or two R_{15} are taken together to form a bridge that is $-CH_2-$ or $-CH_2CH_2-$;

R_{16} is selected from hydrogen and C_{1-6} alkyl; and

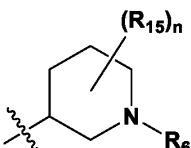
n is 0, 1, 2, 3, or 4.

[0077] In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-C(R_{9a})(R_{9b})-$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-C(R_{9a})(R_{9b})-$ and R_{9a} is selected from hydrogen, halogen, and C_{1-6} alkyl. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-C(R_{9a})(R_{9b})-$ and R_{9b} is selected from hydrogen, halogen, and $-OH$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-C(R_{9a})(R_{9b})-$ and R_{9b} is selected from hydrogen, halogen, and $-OH$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-CH_2-$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-CH(OH)-$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-CH(CH_3)-$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-C(OH)(CH_3)-$.

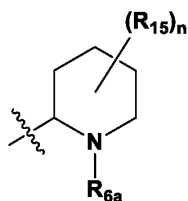
[0078] In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-C(O)-$.

[0079] In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-C(=N-OR_{16})-$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-C(=N-OH)-$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-C(=N-OR_{16})-$ and R_{16} is C_{1-6} alkyl.

[0080] In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable

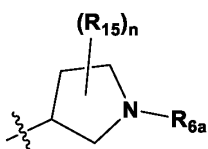
salt or solvate thereof, wherein R_6 is . In some embodiments is a compound of

Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_6 is



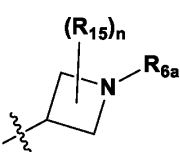
. In some embodiments is a compound of Formula (I'), or a pharmaceutically

acceptable salt or solvate thereof, wherein R_6 is



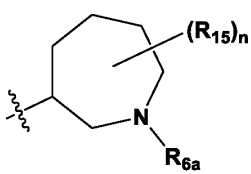
. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_6

is



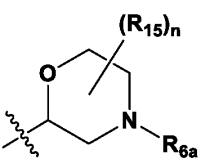
. In some embodiments is a compound of Formula (I'), or a pharmaceutically

acceptable salt or solvate thereof, wherein R_6 is



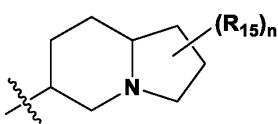
. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_6

is



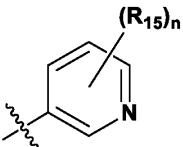
. In some embodiments is a compound of Formula (I'), or a

pharmaceutically acceptable salt or solvate thereof, wherein R_6 is

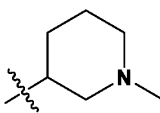
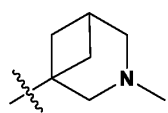
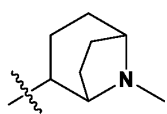
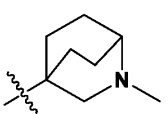
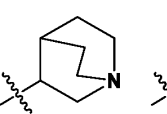
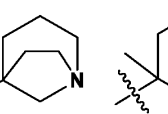
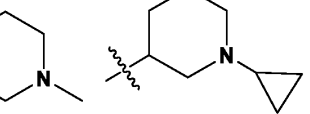
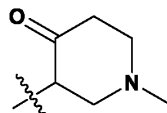
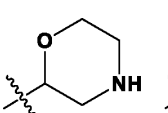
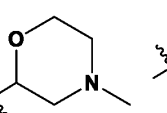
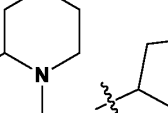
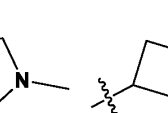
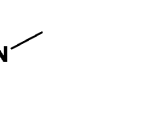
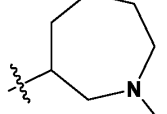
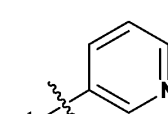


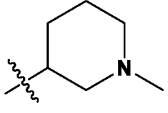
[0081] In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is C_{1-6} alkyl optionally substituted with one, two, or three R_{14} groups. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is unsubstituted C_{1-6} alkyl. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is $-CH_3$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is $-CH_2CH_3$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is hydrogen. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0.

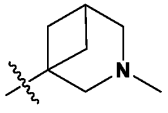
[0082] In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable

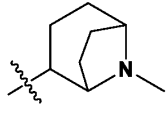
salt or solvate thereof, wherein R_6 is . In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0.

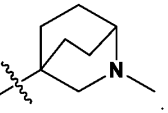
[0083] In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable

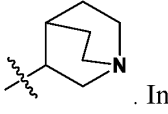
salt or solvate thereof, wherein R_6 is selected from , , , , , , , , , , , , , , and . In some embodiments is a compound of Formula (I'), or a

pharmaceutically acceptable salt or solvate thereof, wherein R_6 is . In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate

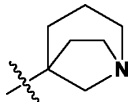
thereof, wherein R_6 is, . In some embodiments is a compound of Formula (I'), or

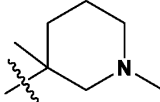
a pharmaceutically acceptable salt or solvate thereof, wherein R_6 is . In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate

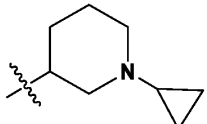
thereof, wherein R_6 is . In some embodiments is a compound of Formula (I'), or a

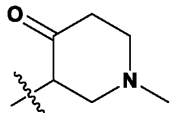
pharmaceutically acceptable salt or solvate thereof, wherein R_6 is . In some

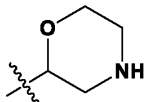
embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate

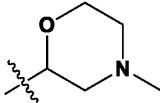
thereof, wherein R₆ is . In some embodiments is a compound of Formula (I'), or a

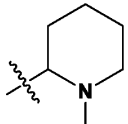
pharmaceutically acceptable salt or solvate thereof, wherein R₆ is . In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate

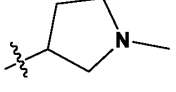
thereof, wherein R₆ is . In some embodiments is a compound of Formula (I'),

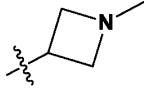
or a pharmaceutically acceptable salt or solvate thereof, wherein R₆ is . In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate

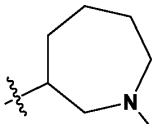
thereof, wherein R₆ is . In some embodiments is a compound of Formula (I'), or a

pharmaceutically acceptable salt or solvate thereof, wherein R₆ is . In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate

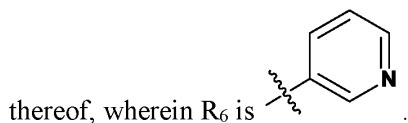
thereof, wherein R₆ is . In some embodiments is a compound of Formula (I'), or a

pharmaceutically acceptable salt or solvate thereof, wherein R₆ is . In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate

thereof, wherein R₆ is . In some embodiments is a compound of Formula (I'), or a

pharmaceutically acceptable salt or solvate thereof, wherein R₆ is . In some

embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate



[0084] In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are each independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁). In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are each independently selected from hydrogen, halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are each independently selected from hydrogen and C₁₋₆alkyl. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are hydrogen. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are C₁₋₆alkyl. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are -CH₃. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ is hydrogen and R₈ is -CH₃. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ is -CH₃ and R₈ is hydrogen.

[0085] In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a phenyl ring optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted phenyl ring. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a 5- or 6-membered heteroaryl ring optionally

substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted 5- or 6-membered heteroaryl ring. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a 4-, 5-, or 6-membered heterocycloalkyl ring optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted 4-, 5-, or 6-membered heterocycloalkyl ring. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted 4-, 5-, or 6-membered cycloalkyl ring.

[0086] In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, or -C(O)N(R₁₀)(R₁₁). In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, or -OH. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is -OR₁₀. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is -OH. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is halogen. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is C₁₋₆alkyl. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is -CH₃. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is C₁₋₆haloalkyl. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is -CF₃.

[0087] In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₂ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, or -OR₁₀. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₂ is hydrogen. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R₂ is halogen. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate

thereof, wherein R_2 is C_{1-6} alkyl. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is $-CH_3$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is C_{1-6} haloalkyl. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is $-CF_3$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is $-OR_{10}$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is $-OH$.

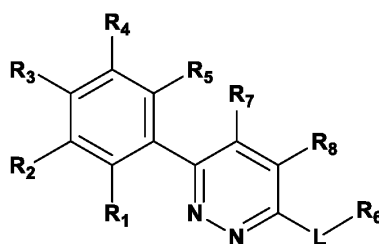
[0088] In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR_{10}$, or $-N(R_{10})(R_{11})$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is C_{1-6} alkyl or C_{1-6} haloalkyl. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is C_{1-6} alkyl. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-CH_3$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is C_{1-6} haloalkyl. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-CF_3$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is hydrogen. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is halogen. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-OR_{10}$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-OH$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-N(R_{10})(R_{11})$.

[0089] In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or $-OR_{10}$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is hydrogen. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is halogen. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is C_{1-6} alkyl. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is $-CH_3$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is C_{1-6} haloalkyl. In some embodiments is a compound of Formula (I'), or a pharmaceutically

acceptable salt or solvate thereof, wherein R_4 is $-CF_3$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is $-OR_{10}$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is $-OH$.

[0090] In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR_{10}$, or $-N(R_{10})(R_{11})$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is hydrogen or C_{1-6} alkyl. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is hydrogen. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is C_{1-6} alkyl. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is $-CH_3$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is halogen. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is C_{1-6} haloalkyl. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is $-CF_3$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is $-OR_{10}$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is $-OH$. In some embodiments is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is $-N(R_{10})(R_{11})$.

[0091] In some embodiments, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



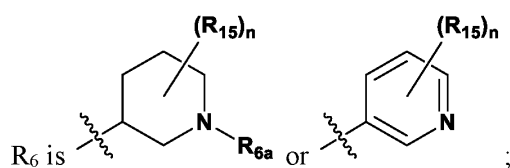
Formula (I);

wherein:

L is $-C(R_{9a})(R_{9b})-$, $-C(O)-$, or $-C(=N-OR_{16})-$;

R_1 , R_2 , R_3 , R_4 , and R_5 are each independently selected from hydrogen, halogen, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, C_{1-9} heteroaryl, $-OR_{10}$, $-SR_{10}$, $-N(R_{10})(R_{11})$, $-C(O)OR_{10}$, $-OC(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)OR_{13}$, $-N(R_{12})S(O)_2R_{13}$, $-C(O)R_{13}$, $-S(O)R_{13}$, $-$

OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁)-, S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁); or R₁ and R₂ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups; or R₂ and R₃ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups; or R₃ and R₄ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups; or R₄ and R₅ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups;



R_{6a} is selected from hydrogen and C₁₋₆alkyl optionally substituted with one, two, or three R₁₄ groups;

R₇ and R₈ are each independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, and -

N(R₁₀)(R₁₁); or R₇ and R₈ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups;

R_{9a} and R_{9b} are each independently selected from hydrogen, halogen, -OH, C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy;

each R₁₀ is independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

each R₁₁ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R₁₂ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R₁₃ is independently selected C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

each R₁₄ is independently selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁)-, S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁);

each R₁₅ is independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁)-,

$S(=O)(=NH)N(R_{10})(R_{11})$, $-CH_2C(O)N(R_{10})(R_{11})$, $-CH_2N(R_{12})C(O)R_{13}$, $-CH_2S(O)_2R_{13}$, and $-CH_2S(O)_2N(R_{10})(R_{11})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^{10}$, and $-N(R_{10})(R_{11})$;

R_{16} is selected from hydrogen and C_{1-6} alkyl; and

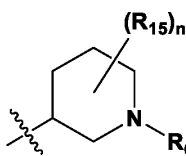
n is 0, 1, 2, 3, or 4.

[0092] In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-C(R_{9a})(R_{9b})-$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-C(R_{9a})(R_{9b})-$ and R_{9a} is selected from hydrogen, halogen, and C_{1-6} alkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-C(R_{9a})(R_{9b})-$ and R_{9b} is selected from hydrogen, halogen, and $-OH$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-C(R_{9a})(R_{9b})-$ and R_{9b} is selected from hydrogen, halogen, and $-OH$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-CH_2-$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-CH(OH)-$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-CH(CH_3)-$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-C(OH)(CH_3)-$.

[0093] In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-C(O)-$.

[0094] In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-C(=N-OR_{16})-$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-C(=N-OH)-$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-C(=N-OR_{16})-$ and R_{16} is C_{1-6} alkyl.

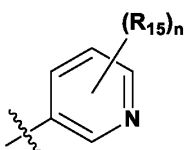
[0095] In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable



salt or solvate thereof, wherein R_6 is $-C(=O)R_{14}$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is C_{1-6} alkyl optionally substituted with one, two, or three R_{14} groups. In some embodiments is a compound

of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is unsubstituted C_{1-6} alkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is $-CH_3$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is $-CH_2CH_3$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is hydrogen. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0.

[0096] In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable



salt or solvate thereof, wherein R_6 is . In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0.

[0097] In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are each independently selected from hydrogen, halogen, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR_{10}$, and $-N(R_{10})(R_{11})$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are each independently selected from hydrogen, halogen, C_{1-6} alkyl, and C_{1-6} haloalkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are each independently selected from hydrogen and C_{1-6} alkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are hydrogen. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are C_{1-6} alkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are $-CH_3$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 is hydrogen and R_8 is $-CH_3$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 is $-CH_3$ and R_8 is hydrogen.

[0098] In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl

ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a phenyl ring optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted phenyl ring. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a 5- or 6-membered heteroaryl ring optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted 5- or 6-membered heteroaryl ring. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a 4-, 5-, or 6-membered heterocycloalkyl ring optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted 4-, 5-, or 6-membered heterocycloalkyl ring. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted 4-, 5-, or 6-membered heterocycloalkyl ring. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted 4-, 5-, or 6-membered cycloalkyl ring.

[0099] In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, or -C(O)N(R₁₀)(R₁₁). In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, or -OH. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is -OR₁₀. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is -OH. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is halogen. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is C₁₋₆alkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is -CH₃. In some embodiments

is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is C_{1-6} haloalkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is $-CF_3$.

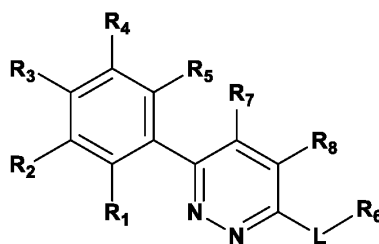
[00100] In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or $-OR_{10}$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is hydrogen. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is halogen. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is C_{1-6} alkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is $-CH_3$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is C_{1-6} haloalkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is $-CF_3$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is $-OR_{10}$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is $-OH$.

[00101] In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR_{10}$, or $-N(R_{10})(R_{11})$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is C_{1-6} alkyl or C_{1-6} haloalkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is C_{1-6} alkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-CH_3$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is C_{1-6} haloalkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-CF_3$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is hydrogen. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is halogen. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-OR_{10}$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-OH$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-N(R_{10})(R_{11})$.

[00102] In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or $-OR_{10}$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is hydrogen. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is halogen. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is C_{1-6} alkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is $-CH_3$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is C_{1-6} haloalkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is $-CF_3$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is $-OR_{10}$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is $-OH$.

[00103] In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR_{10}$, or $-N(R_{10})(R_{11})$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is hydrogen or C_{1-6} alkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is hydrogen. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is C_{1-6} alkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is $-CH_3$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is halogen. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is C_{1-6} haloalkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is $-CF_3$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is $-OR_{10}$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is $-OH$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is $-N(R_{10})(R_{11})$.

[00104] In some embodiments, provided herein is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof:



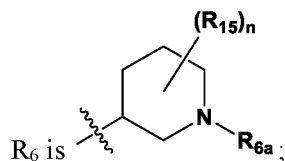
Formula (Ia);

wherein:

L is $-C(R_{9a})(R_{9b})-$, $-C(O)-$, or $-C(=N-OR_{16})-$;

R_1 , R_2 , R_3 , R_4 , and R_5 are each independently selected from hydrogen, halogen, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, C_{1-9} heteroaryl, $-OR_{10}$, $-SR_{10}$, $-N(R_{10})(R_{11})$, $-C(O)OR_{10}$, $-OC(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)OR_{13}$, $-N(R_{12})S(O)_2R_{13}$, $-C(O)R_{13}$, $-S(O)R_{13}$, $-OC(O)R_{13}$, $-C(O)N(R_{10})(R_{11})$, $-C(O)C(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)R_{13}$, $-S(O)_2R_{13}$, $-S(O)_2N(R_{10})(R_{11})$, $S(=O)(=NH)N(R_{10})(R_{11})$, $-CH_2C(O)N(R_{10})(R_{11})$, $-CH_2N(R_{12})C(O)R_{13}$, $-CH_2S(O)_2R_{13}$, and $-CH_2S(O)_2N(R_{10})(R_{11})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR_{10}$, and $-N(R_{10})(R_{11})$; or R_1 and R_2 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups; or R_2 and R_3 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups; or R_3 and R_4 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups; or R_4 and R_5 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered

heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups;



R_{6a} is selected from hydrogen and C_{1-6} alkyl optionally substituted with one, two, or three R_{14} groups;

R_7 and R_8 are each independently selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁); or R_7 and R_8 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups;

R_{9a} and R_{9b} are each independently selected from hydrogen, halogen, -OH, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

each R_{10} is independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl;

each R_{11} is independently selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R_{12} is independently selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R_{13} is independently selected C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl;

each R_{14} is independently selected from halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, C_{1-9} heteroaryl, -OR₁₀, -SR₁₀,

-N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁), -S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR¹⁰, and -N(R₁₀)(R₁₁);

each R₁₅ is independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁), -S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR¹⁰, and -N(R₁₀)(R₁₁);

R₁₆ is selected from hydrogen and C₁₋₆alkyl; and

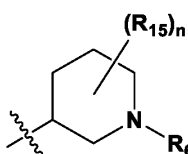
n is 0, 1, 2, 3, or 4.

[00105] In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein L is -C(R_{9a})(R_{9b})-. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein L is -C(R_{9a})(R_{9b})- and R_{9a} is selected from hydrogen, halogen, and C₁₋₆alkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein L is -C(R_{9a})(R_{9b})- and R_{9b} is selected from hydrogen, halogen, and -OH. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein L is -C(R_{9a})(R_{9b})- and R_{9b} is selected from hydrogen, halogen, and -OH. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein L is -CH₂-. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein L is -CH(OH)-. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein L is -CH(CH₃)-. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein L is -C(OH)(CH₃)-.

[00106] In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein L is -C(O)-.

[00107] In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein L is -C(=N-OR₁₆)-. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein L is -C(=N-OH)-. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein L is -C(=N-OR₁₆)- and R₁₆ is C₁₋₆alkyl.

[00108] In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable



salt or solvate thereof, wherein R₆ is . In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is C₁₋₆alkyl optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is unsubstituted C₁₋₆alkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is -CH₃. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is -CH₂CH₃. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is hydrogen. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0.

[00109] In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are each independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁). In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are each independently selected from hydrogen, halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are each independently selected from hydrogen and C₁₋₆alkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are hydrogen. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are C₁₋₆alkyl. In some embodiments is a

compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are -CH₃. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ is hydrogen and R₈ is -CH₃. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ is -CH₃ and R₈ is hydrogen.

[00110] In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a phenyl ring optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted phenyl ring. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a 5- or 6-membered heteroaryl ring optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted 5- or 6-membered heteroaryl ring. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a 4-, 5-, or 6-membered heterocycloalkyl ring optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted 4-, 5-, or 6-membered heterocycloalkyl ring. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted 4-, 5-, or 6-membered cycloalkyl ring.

[00111] In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, or -C(O)N(R₁₀)(R₁₁). In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, or -OH. In some embodiments is a compound of Formula (Ia), or a

pharmaceutically acceptable salt or solvate thereof, wherein R_1 is $-OR_{10}$. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is $-OH$. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is hydrogen. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is halogen. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is C_{1-6} alkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is $-CH_3$. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is C_{1-6} haloalkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is $-CF_3$.

[00112] In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or $-OR_{10}$. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is hydrogen. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is halogen. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is C_{1-6} alkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is $-CH_3$. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is C_{1-6} haloalkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is $-CF_3$. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is $-OR_{10}$. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is $-OH$.

[00113] In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR_{10}$, or $-N(R_{10})(R_{11})$. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is C_{1-6} alkyl or C_{1-6} haloalkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is C_{1-6} alkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-CH_3$. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is C_{1-6} haloalkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-CF_3$. In some embodiments is a compound of

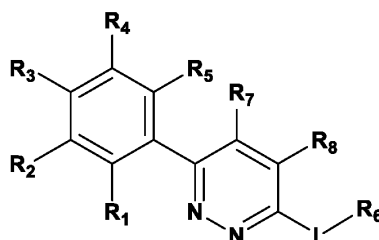
Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is hydrogen. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is halogen. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-OR_{10}$. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-OH$. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-N(R_{10})(R_{11})$.

[00114] In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or $-OR_{10}$. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is hydrogen. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is halogen. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is C_{1-6} alkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is $-CH_3$. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is C_{1-6} haloalkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is $-CF_3$. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is $-OR_{10}$. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is $-OH$.

[00115] In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR_{10}$, or $-N(R_{10})(R_{11})$. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is hydrogen or C_{1-6} alkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is hydrogen. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is C_{1-6} alkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is $-CH_3$. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is halogen. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is C_{1-6} haloalkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is $-CF_3$. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is $-OR_{10}$. In some embodiments

is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is -OH. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is -N(R_{10})(R_{11}).

[00116] In some embodiments, provided herein is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof:



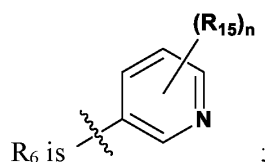
Formula (Ib);

wherein:

L is -C(R_{9a})(R_{9b})-, -C(O)-, or -C(=N-OR₁₆)-;

R_1 , R_2 , R_3 , R_4 , and R_5 are each independently selected from hydrogen, halogen, -CN, C₁-6alkyl, C₁-6haloalkyl, C₂-6alkenyl, C₂-6alkynyl, C₃-6cycloalkyl, C₂-9heterocycloalkyl, C₆-10aryl, C₁-9heteroaryl, -OR₁₀, -SR₁₀, -N(R_{10})(R_{11}), -C(O)OR₁₀, -OC(O)N(R_{10})(R_{11}), -N(R_{12})C(O)N(R_{10})(R_{11}), -N(R_{12})C(O)OR₁₃, -N(R_{12})S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R_{10})(R_{11}), -C(O)C(O)N(R_{10})(R_{11}), -N(R_{12})C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R_{10})(R_{11}), S(=O)(=NH)N(R_{10})(R_{11}), -CH₂C(O)N(R_{10})(R_{11}), -CH₂N(R_{12})C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R_{10})(R_{11}), wherein C₁-6alkyl, C₂-6alkenyl, C₂-6alkynyl, C₃-6cycloalkyl, C₂-9heterocycloalkyl, C₆-10aryl, and C₁-9heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁-6alkyl, C₁-6haloalkyl, -OR₁₀, and -N(R_{10})(R_{11}); or R_1 and R_2 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups; or R_2 and R_3 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups; or R_3 and R_4 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups; or R_4 and R_5 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups.

heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups; or R_4 and R_5 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups;



R_7 and R_8 are each independently selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁); or R_7 and R_8 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups;

R_{9a} and R_{9b} are each independently selected from hydrogen, halogen, -OH, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

each R_{10} is independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl;

each R_{11} is independently selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R_{12} is independently selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R_{13} is independently selected C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl;

each R₁₄ is independently selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁), -S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR¹⁰, and -N(R₁₀)(R₁₁);

each R₁₅ is independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁), -S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR¹⁰, and -N(R₁₀)(R₁₁);

R₁₆ is selected from hydrogen and C₁₋₆alkyl; and

n is 0, 1, 2, 3, or 4.

[00117] In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein L is -C(R_{9a})(R_{9b})-. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein L is -C(R_{9a})(R_{9b})- and R_{9a} is selected from hydrogen, halogen, and C₁₋₆alkyl. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein L is -C(R_{9a})(R_{9b})- and R_{9b} is selected from hydrogen, halogen, and -OH. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein L is -C(R_{9a})(R_{9b})- and R_{9b} is selected from hydrogen, halogen, and -OH. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein L is -CH₂-. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein L is -CH(OH)-. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein L is -CH(CH₃)-. In some

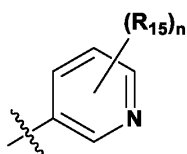
embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-\text{C}(\text{OH})(\text{CH}_3)-$.

[00118] In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-\text{C}(\text{O})-$.

[00119] In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-\text{C}(=\text{N}-\text{OR}_{16})-$. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-\text{C}(=\text{N}-\text{OH})-$.

In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein L is $-\text{C}(=\text{N}-\text{OR}_{16})-$ and R_{16} is C_{1-6} alkyl.

[00120] In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable



salt or solvate thereof, wherein R_6 is . In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0.

[00121] In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are each independently selected from hydrogen, halogen, $-\text{CN}$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, $-\text{CN}$, C_{1-6} alkyl, C_{1-6} haloalkyl, $-\text{OR}_{10}$, and $-\text{N}(\text{R}_{10})(\text{R}_{11})$. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are each independently selected from hydrogen, halogen, C_{1-6} alkyl, and C_{1-6} haloalkyl. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are each independently selected from hydrogen and C_{1-6} alkyl. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are hydrogen. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are C_{1-6} alkyl. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are $-\text{CH}_3$. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 is hydrogen and R_8 is $-\text{CH}_3$. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 is $-\text{CH}_3$ and R_8 is hydrogen.

[00122] In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a phenyl ring optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted phenyl ring. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a 5- or 6-membered heteroaryl ring optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted 5- or 6-membered heteroaryl ring. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a 4-, 5-, or 6-membered heterocycloalkyl ring optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted 4-, 5-, or 6-membered heterocycloalkyl ring. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted 4-, 5-, or 6-membered cycloalkyl ring.

[00123] In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, or -C(O)N(R₁₀)(R₁₁). In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, or -OH. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is -OR₁₀. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is -OH. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is halogen.

In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is C_{1-6} alkyl. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is $-CH_3$. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is C_{1-6} haloalkyl. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is $-CF_3$.

[00124] In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or $-OR_{10}$. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is hydrogen. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is halogen. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is C_{1-6} alkyl. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is $-CH_3$. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is C_{1-6} haloalkyl. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is $-CF_3$. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is $-OR_{10}$. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is $-OH$.

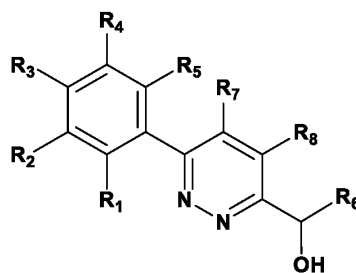
[00125] In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR_{10}$, or $-N(R_{10})(R_{11})$. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is C_{1-6} alkyl or C_{1-6} haloalkyl. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is C_{1-6} alkyl. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-CH_3$. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is C_{1-6} haloalkyl. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-CF_3$. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is hydrogen. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is halogen. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-OR_{10}$. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein

R₃ is -OH. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₃ is -N(R₁₀)(R₁₁).

[00126] In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₄ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, or -OR₁₀. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₄ is hydrogen. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₄ is halogen. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₄ is C₁₋₆alkyl. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₄ is -CH₃. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₄ is C₁₋₆haloalkyl. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₄ is -CF₃. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₄ is -OR₁₀. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₄ is -OH.

[00127] In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₅ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, or -N(R₁₀)(R₁₁). In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₅ is hydrogen or C₁₋₆alkyl. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₅ is hydrogen. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₅ is C₁₋₆alkyl. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₅ is -CH₃. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₅ is halogen. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₅ is C₁₋₆haloalkyl. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₅ is -CF₃. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₅ is -OR₁₀. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₅ is -OH. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof, wherein R₅ is -N(R₁₀)(R₁₁).

[00128] In some embodiments, provided herein is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof:

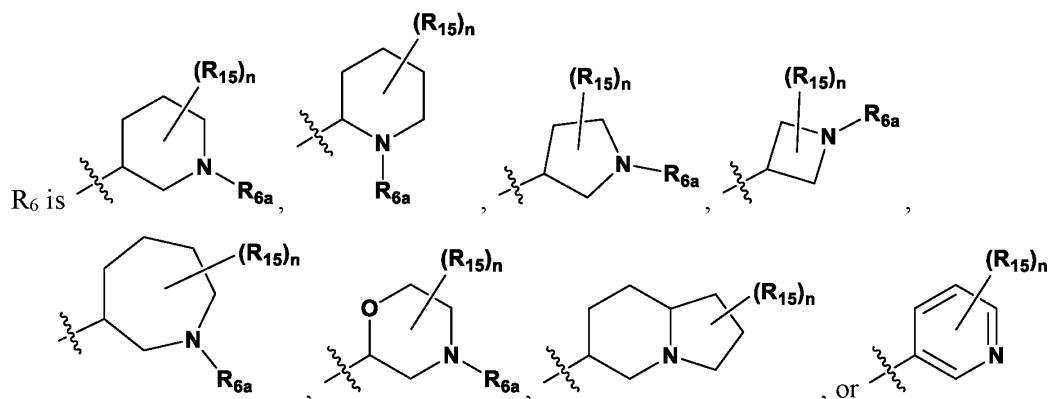


Formula (II);

wherein:

R_1 , R_2 , R_3 , R_4 , and R_5 are each independently selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, C_{1-9} heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁), S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁); or R_1 and R_2 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups; or R_2 and R_3 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups; or R_3 and R_4 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups; or R_4 and R_5 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered

heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups;



R_{6a} is selected from hydrogen, C_{1-6} alkyl, and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl optionally substituted with one, two, or three R_{14} groups; or R_{6a} and an R_{15} are taken together to form a bridge that is $-CH_2-$ or $-CH_2CH_2-$;

R_7 and R_8 are each independently selected from hydrogen, halogen, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR_{10}$, and $-N(R_{10})(R_{11})$; or R_7 and R_8 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups;

each R_{10} is independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl;

each R_{11} is independently selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R_{12} is independently selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

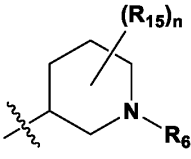
each R_{13} is independently selected C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally

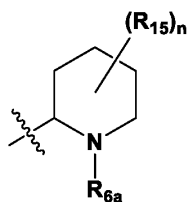
substituted with one, two, or three groups selected from halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;
 each R₁₄ is independently selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁)-, S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR¹⁰, and -N(R₁₀)(R₁₁);

each R₁₅ is independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁)-, S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR¹⁰, and -N(R₁₀)(R₁₁); or two R₁₅ are taken together to form a bridge that is -CH₂- or -CH₂CH₂-;
 and

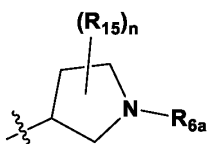
n is 0, 1, 2, 3, or 4.

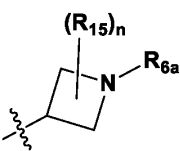
[00129] In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable

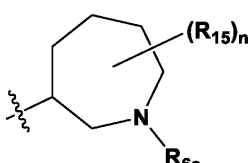
salt or solvate thereof, wherein R₆ is . In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₆ is

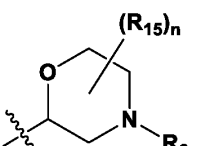


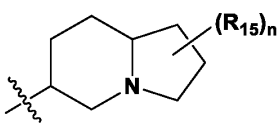
. In some embodiments is a compound of Formula (II), or a pharmaceutically

acceptable salt or solvate thereof, wherein R_6 is . In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_6

is . In some embodiments is a compound of Formula (II), or a pharmaceutically

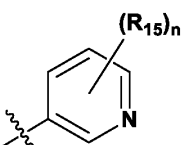
acceptable salt or solvate thereof, wherein R_6 is . In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_6

is . In some embodiments is a compound of Formula (II), or a

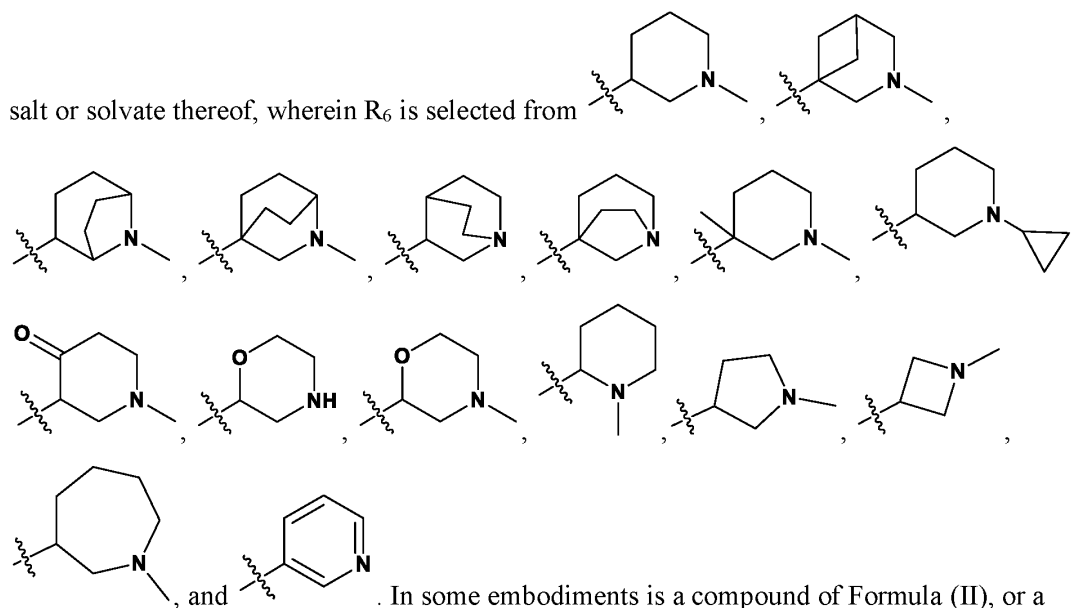
pharmaceutically acceptable salt or solvate thereof, wherein R_6 is .

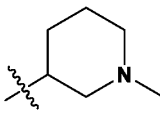
[00130] In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is C_{1-6} alkyl optionally substituted with one, two, or three R_{14} groups. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is unsubstituted C_{1-6} alkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is $-CH_3$. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is $-CH_2CH_3$. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is hydrogen. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0.

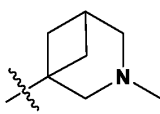
[00131] In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable

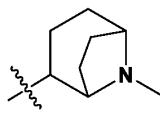
salt or solvate thereof, wherein R_6 is . In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0.

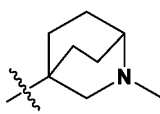
[00132] In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable

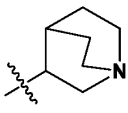


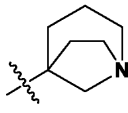
pharmaceutically acceptable salt or solvate thereof, wherein R_6 is . In some
embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate

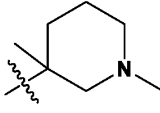
thereof, wherein R_6 is . In some embodiments is a compound of Formula (II), or a

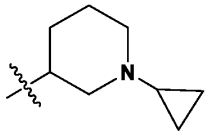
a pharmaceutically acceptable salt or solvate thereof, wherein R_6 is . In some
embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate

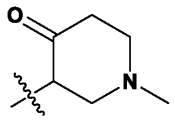
thereof, wherein R_6 is . In some embodiments is a compound of Formula (II), or a

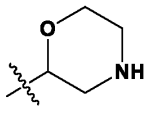
pharmaceutically acceptable salt or solvate thereof, wherein R_6 is . In some
embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate

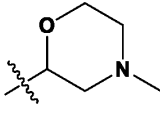
thereof, wherein R_6 is . In some embodiments is a compound of Formula (II), or a

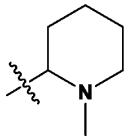
pharmaceutically acceptable salt or solvate thereof, wherein R_6 is . In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate

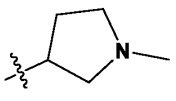
thereof, wherein R_6 is . In some embodiments is a compound of Formula (II),

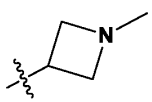
or a pharmaceutically acceptable salt or solvate thereof, wherein R_6 is . In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate

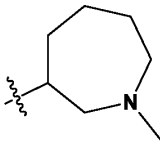
thereof, wherein R_6 is . In some embodiments is a compound of Formula (II), or a

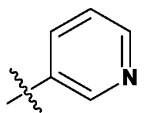
pharmaceutically acceptable salt or solvate thereof, wherein R_6 is . In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate

thereof, wherein R_6 is . In some embodiments is a compound of Formula (II), or a

pharmaceutically acceptable salt or solvate thereof, wherein R_6 is . In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate

thereof, wherein R_6 is . In some embodiments is a compound of Formula (II), or a

pharmaceutically acceptable salt or solvate thereof, wherein R_6 is . In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate

thereof, wherein R_6 is .

[00133] In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are each independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁). In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are each independently selected from hydrogen, halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are each independently selected from hydrogen and C₁₋₆alkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are hydrogen. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are C₁₋₆alkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are -CH₃. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ is hydrogen and R₈ is -CH₃. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ is -CH₃ and R₈ is hydrogen.

[00134] In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a phenyl ring optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted phenyl ring. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a 5- or 6-membered heteroaryl ring optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted 5- or 6-membered heteroaryl ring. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are

combined to form a 4-, 5-, or 6-membered heterocycloalkyl ring optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted 4-, 5-, or 6-membered heterocycloalkyl ring. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted 4-, 5-, or 6-membered cycloalkyl ring.

[00135] In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, or -C(O)N(R₁₀)(R₁₁). In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, or -OH. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is -OR₁₀. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is -OH. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is halogen. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is C₁₋₆alkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is -CH₃. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is C₁₋₆haloalkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is -CF₃.

[00136] In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₂ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, or -OR₁₀. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₂ is hydrogen. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₂ is halogen. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₂ is C₁₋₆alkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₂ is -CH₃. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R₂ is C₁₋₆haloalkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically

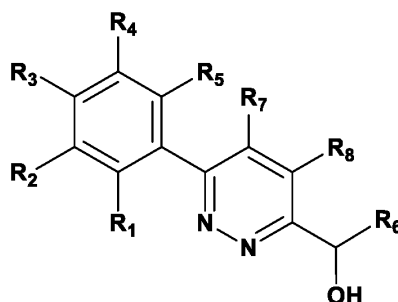
acceptable salt or solvate thereof, wherein R_2 is $-\text{CF}_3$. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is $-\text{OR}_{10}$. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is $-\text{OH}$.

[00137] In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-\text{OR}_{10}$, or $-\text{N}(\text{R}_{10})(\text{R}_{11})$. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is C_{1-6} alkyl or C_{1-6} haloalkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is C_{1-6} alkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-\text{CH}_3$. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is C_{1-6} haloalkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-\text{CF}_3$. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is hydrogen. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is halogen. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-\text{OR}_{10}$. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-\text{OH}$. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-\text{N}(\text{R}_{10})(\text{R}_{11})$.

[00138] In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or $-\text{OR}_{10}$. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is hydrogen. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is halogen. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is C_{1-6} alkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is $-\text{CH}_3$. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is C_{1-6} haloalkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is $-\text{CF}_3$. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is $-\text{OR}_{10}$. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is $-\text{OH}$.

[00139] In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR_{10}$, or $-N(R_{10})(R_{11})$. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is hydrogen or C_{1-6} alkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is hydrogen. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is C_{1-6} alkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is $-CH_3$. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is halogen. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is C_{1-6} haloalkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is $-CF_3$. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is $-OR_{10}$. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is $-OH$. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is $-N(R_{10})(R_{11})$.

[00140] In some embodiments, provided herein is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof:

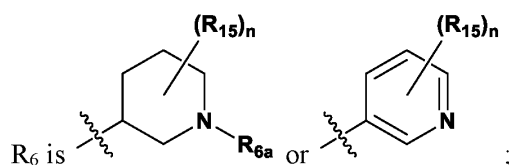


Formula (III);

wherein:

R_1 , R_2 , R_3 , R_4 , and R_5 are each independently selected from hydrogen, halogen, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, C_{1-9} heteroaryl, $-OR_{10}$, $-SR_{10}$, $-N(R_{10})(R_{11})$, $-C(O)OR_{10}$, $-OC(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)OR_{13}$, $-N(R_{12})S(O)_2R_{13}$, $-C(O)R_{13}$, $-S(O)R_{13}$, $-OC(O)R_{13}$, $-C(O)N(R_{10})(R_{11})$, $-C(O)C(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)R_{13}$, $-S(O)_2R_{13}$, $-S(O)_2N(R_{10})(R_{11})$, $S(=O)(=NH)N(R_{10})(R_{11})$, $-CH_2C(O)N(R_{10})(R_{11})$, $-CH_2N(R_{12})C(O)R_{13}$, $-CH_2S(O)_2R_{13}$, and $-CH_2S(O)_2N(R_{10})(R_{11})$, wherein C_{1-6} alkyl, C_{2-6}

₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁); or R₁ and R₂ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups; or R₂ and R₃ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups; or R₃ and R₄ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups; or R₄ and R₅ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups;



R_{6a} is selected from hydrogen and C₁₋₆alkyl optionally substituted with one, two, or three R₁₄ groups;

R₇ and R₈ are each independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁); or R₇ and R₈ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered

heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups;

each R₁₀ is independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

each R₁₁ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R₁₂ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

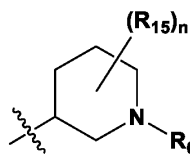
each R₁₃ is independently selected C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

each R₁₄ is independently selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁), -S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR¹⁰, and -N(R₁₀)(R₁₁);

each R₁₅ is independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁), -S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR¹⁰, and -N(R₁₀)(R₁₁); and

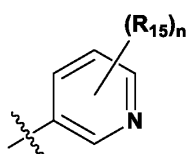
n is 0, 1, 2, 3, or 4.

[00141] In some embodiments is a compound of Formula (III), or a pharmaceutically



acceptable salt or solvate thereof, wherein R_6 is . In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is C_{1-6} alkyl optionally substituted with one, two, or three R_{14} groups. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is unsubstituted C_{1-6} alkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is $-CH_3$. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is $-CH_2CH_3$. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is hydrogen. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0.

[00142] In some embodiments is a compound of Formula (III), or a pharmaceutically



acceptable salt or solvate thereof, wherein R_6 is . In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0.

[00143] In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are each independently selected from hydrogen, halogen, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR_{10}$, and $-N(R_{10})(R_{11})$. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are each independently selected from hydrogen, halogen, C_{1-6} alkyl, and C_{1-6} haloalkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are each independently selected from hydrogen and C_{1-6} alkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are hydrogen. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are C_{1-6} alkyl. In some embodiments is a

compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are -CH₃. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ is hydrogen and R₈ is -CH₃. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ is -CH₃ and R₈ is hydrogen.

[00144] In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a phenyl ring optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted phenyl ring. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a 5- or 6-membered heteroaryl ring optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted 5- or 6-membered heteroaryl ring. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a 4-, 5-, or 6-membered heterocycloalkyl ring optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted 4-, 5-, or 6-membered heterocycloalkyl ring. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring optionally substituted with one, two, or three R₁₄ groups. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted 4-, 5-, or 6-membered cycloalkyl ring.

[00145] In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, or -C(O)N(R₁₀)(R₁₁). In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, or -OH. In some embodiments is a compound of Formula (III),

or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is $-OR_{10}$. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is $-OH$. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is hydrogen. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is halogen. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is C_{1-6} alkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is $-CH_3$. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is C_{1-6} haloalkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is $-CF_3$.

[00146] In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or $-OR_{10}$. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is hydrogen. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is halogen. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is C_{1-6} alkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is $-CH_3$. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is C_{1-6} haloalkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is $-CF_3$. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is $-OR_{10}$. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is $-OH$.

[00147] In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR_{10}$, or $-N(R_{10})(R_{11})$. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is C_{1-6} alkyl or C_{1-6} haloalkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is C_{1-6} alkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-CH_3$. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is C_{1-6} haloalkyl. In some embodiments is a compound of Formula (III), or a

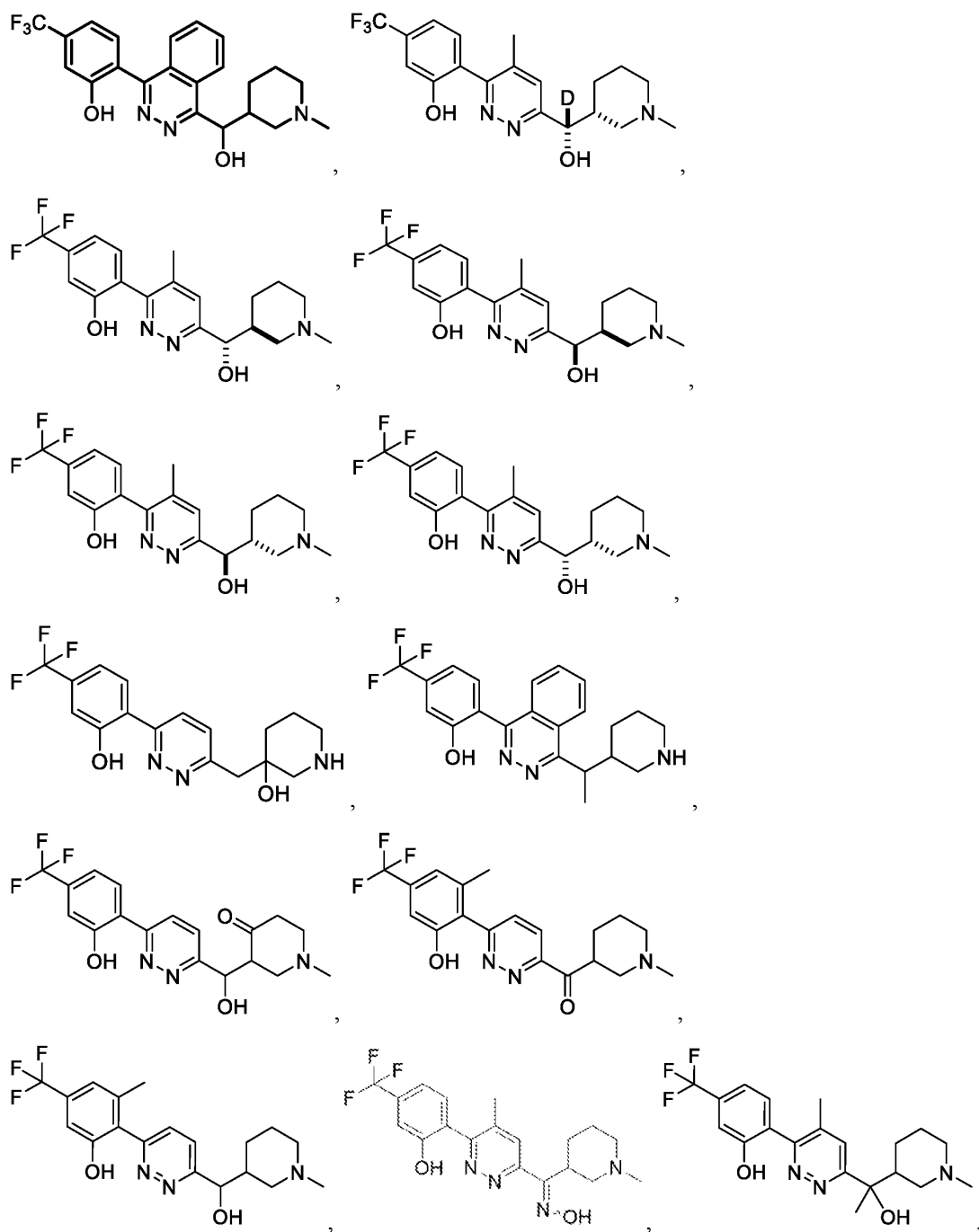
pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-\text{CF}_3$. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is hydrogen. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is halogen. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-\text{OR}_{10}$. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-\text{OH}$. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is $-\text{N}(\text{R}_{10})(\text{R}_{11})$.

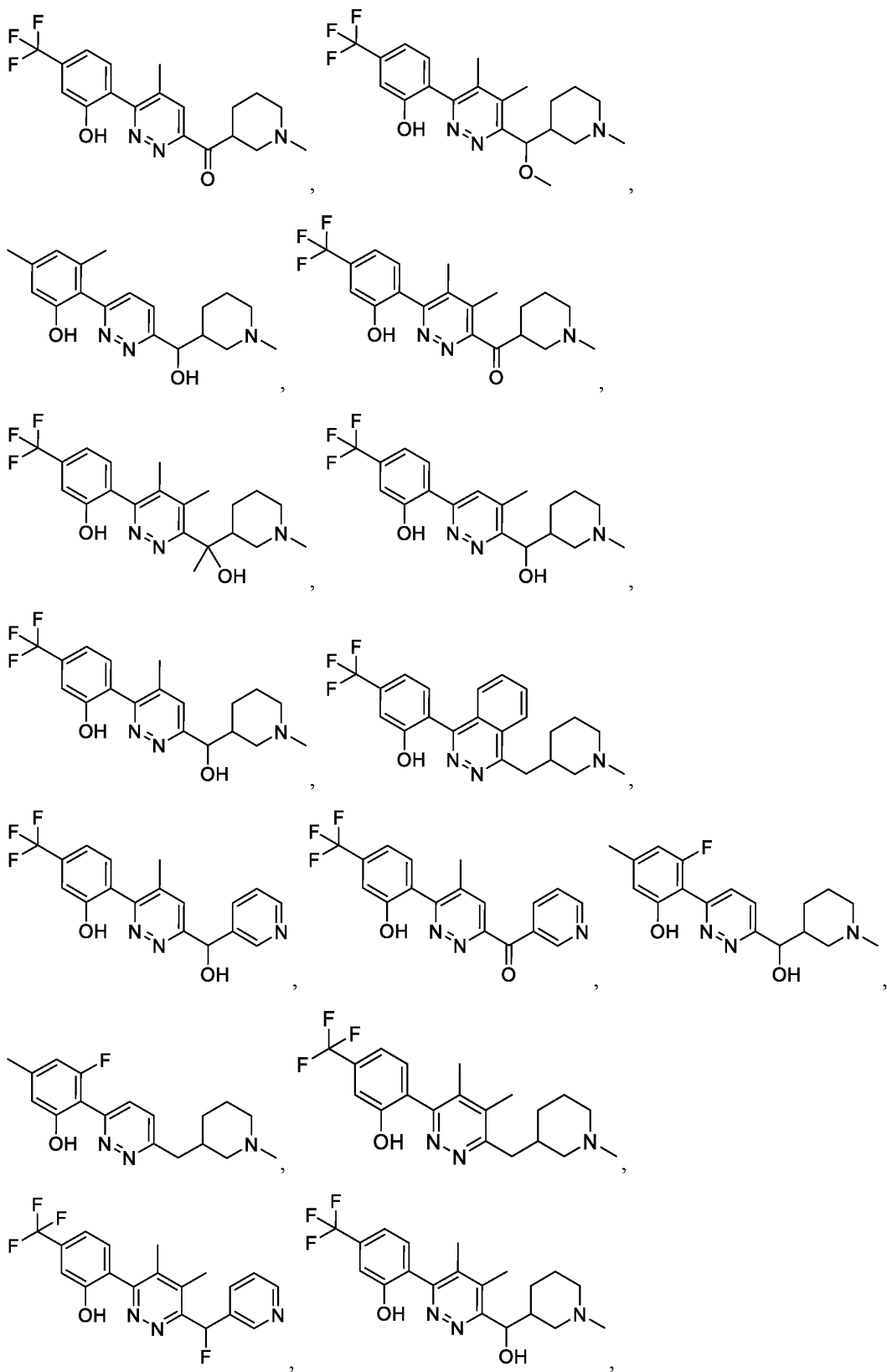
[00148] In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or $-\text{OR}_{10}$. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is hydrogen. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is halogen. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is C_{1-6} alkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is $-\text{CH}_3$. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is C_{1-6} haloalkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is $-\text{CF}_3$. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is $-\text{OR}_{10}$. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is $-\text{OH}$.

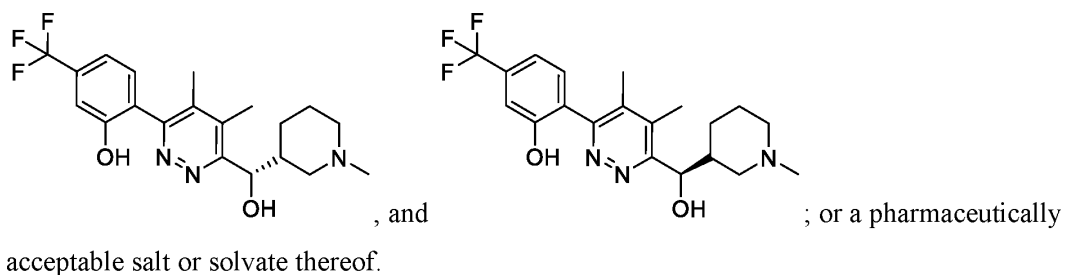
[00149] In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-\text{OR}_{10}$, or $-\text{N}(\text{R}_{10})(\text{R}_{11})$. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is hydrogen or C_{1-6} alkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is hydrogen. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is C_{1-6} alkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is $-\text{CH}_3$. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is halogen. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is C_{1-6} haloalkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is $-\text{CF}_3$. In some embodiments is

a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is $-OR_{10}$. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is $-OH$. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is $-N(R_{10})(R_{11})$.

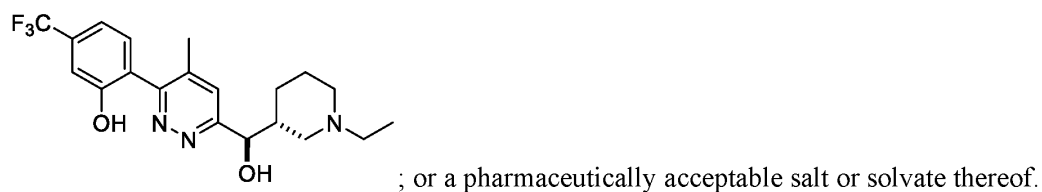
[00150] In some embodiments, provided herein is a compound selected from:



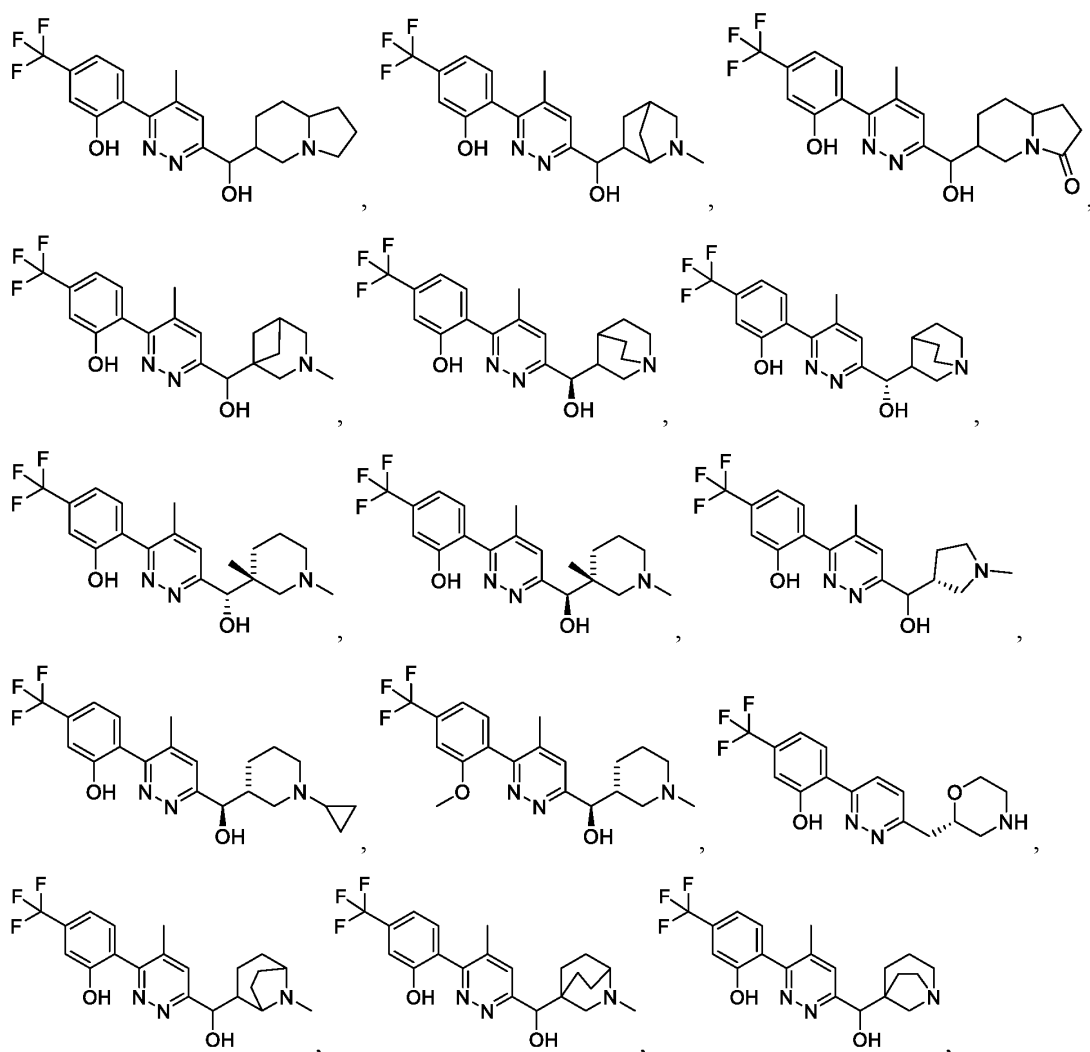


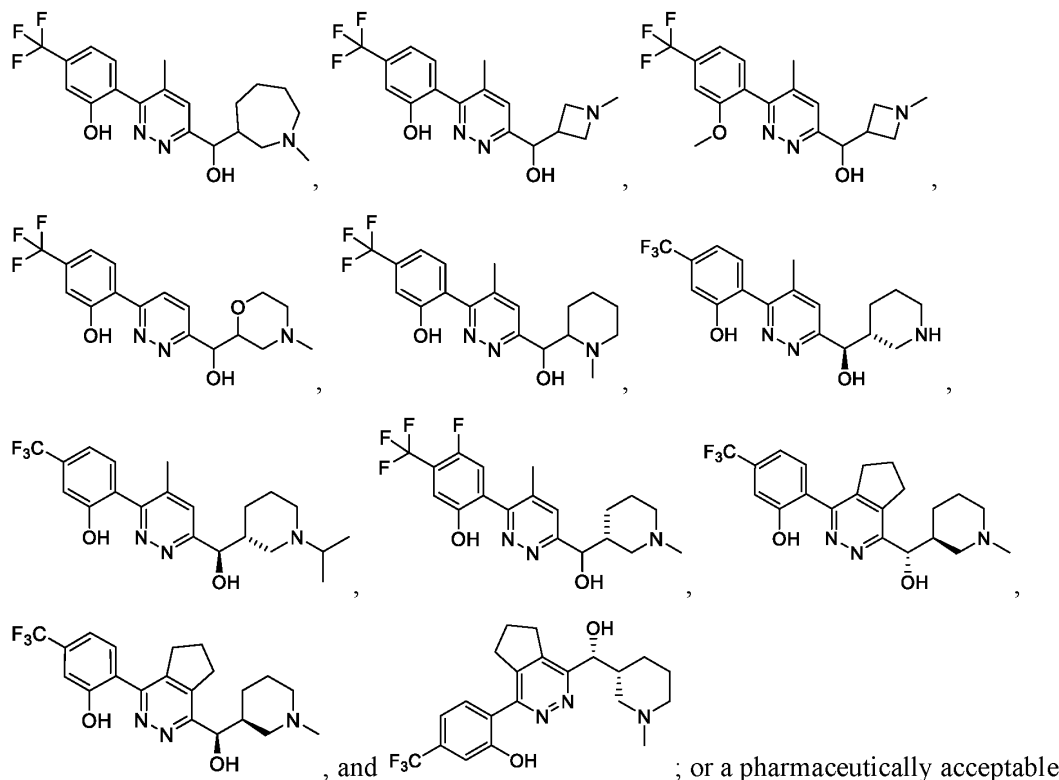


[00151] In some embodiments, provided herein is a compound that is:



[00152] In some embodiments, provided herein is a compound selected from:





salt or solvate thereof.

[00153] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof can be chosen by one skilled in the field to provide stable moieties and compounds.

[00154] In some embodiments, the therapeutic agent(s) (*e.g.* compound of Formula (I'), (I), (Ia), (Ib), (II), or (III)) is present in the pharmaceutical composition as a pharmaceutically acceptable salt. In some embodiments, any compound described above is suitable for any method or composition described herein.

Further Forms of Compounds Disclosed Herein

Isomers

[00155] Furthermore, in some embodiments, the compounds described herein exist as geometric isomers. In some embodiments, the compounds described herein possess one or more double bonds. The compounds presented herein include all *cis*, *trans*, *syn*, *anti*, entgegen (*E*), and zusammen (*Z*) isomers as well as the corresponding mixtures thereof. In some situations, compounds exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein. In some situations, the compounds described herein possess one or more chiral centers and each center exists in the *R* configuration or *S* configuration. The compounds described herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the

compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion, are useful for the applications described herein. In some embodiments, the compounds described herein are prepared as optically pure enantiomers by chiral chromatographic resolution of the racemic mixture. In some embodiments, the compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers, and recovering the optically pure enantiomers. In some embodiments, dissociable complexes are preferred (e.g., crystalline diastereomeric salts). In some embodiments, the diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these dissimilarities. In some embodiments, the diastereomers are separated by chiral chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In some embodiments, the optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that does not result in racemization.

Labeled compounds

[00156] In some embodiments, the compounds described herein exist in their isotopically-labeled forms. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds as pharmaceutical compositions. Thus, in some embodiments, the compounds disclosed herein include isotopically-labeled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that are incorporated into compounds described herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, and chloride, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Compounds described herein, and pharmaceutically acceptable salts, esters, solvate, hydrates, or derivatives thereof which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i. e., ^3H and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavy isotopes such as deuterium, i.e., ^2H , produces certain therapeutic advantages resulting from greater metabolic stability, for example increased

in vivo half-life or reduced dosage requirements. In some embodiments, the isotopically labeled compounds, pharmaceutically acceptable salt, ester, solvate, hydrate, or derivative thereof is prepared by any suitable method.

[00157] In some embodiments, the compounds described herein are labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

Pharmaceutically acceptable salts

[00158] In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

[00159] In some embodiments, the compounds described herein possess acidic or basic groups and therefore react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. In some embodiments, these salts are prepared *in situ* during the final isolation and purification of the compounds described herein, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

Solvates

[00160] In some embodiments, the compounds described herein exist as solvates. In some embodiments are methods of treating diseases by administering such solvates. Further described herein are methods of treating diseases by administering such solvates as pharmaceutical compositions.

[00161] Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and, in some embodiments, are formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of the compounds described herein are conveniently prepared or formed during the processes described herein. By way of example only, hydrates of the compounds described herein are conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents including, but not limited to, dioxane, tetrahydrofuran, or MeOH. In addition, the compounds provided herein exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

Synthesis of Compounds

[00162] In some embodiments, the synthesis of compounds described herein are accomplished using means described in the chemical literature, using the methods described herein, or by a combination thereof. In addition, solvents, temperatures and other reaction conditions presented herein may vary.

[00163] In other embodiments, the starting materials and reagents used for the synthesis of the compounds described herein are synthesized or are obtained from commercial sources, such as, but not limited to, Sigma-Aldrich, Fischer Scientific (Fischer Chemicals), and Acros Organics.

[00164] In further embodiments, the compounds described herein, and other related compounds having different substituents are synthesized using techniques and materials described herein as well as those that are recognized in the field, such as described, for example, in Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989), March, Advanced Organic Chemistry 4th Ed., (Wiley 1992); Carey and Sundberg, Advanced Organic Chemistry 4th Ed., Vols. A and B (Plenum 2000, 2001), and Green and Wuts, Protective Groups in Organic Synthesis 3rd Ed., (Wiley 1999) (all of which are incorporated by reference for such disclosure). General methods for the preparation of compound as disclosed herein may be derived from reactions and the reactions may be modified by the use of appropriate reagents and conditions, for the introduction of the various moieties found in the formulae as provided herein. As a guide the following synthetic methods may be utilized.

Use of Protecting Groups

[00165] In the reactions described, it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, in order to avoid their unwanted participation in reactions. Protecting groups are used to block some or all of the reactive moieties and prevent such groups from participating in chemical reactions until the protective group is removed. It is preferred that each protective group be removable by a different means. Protective groups that are cleaved under totally disparate reaction conditions fulfill the requirement of differential removal.

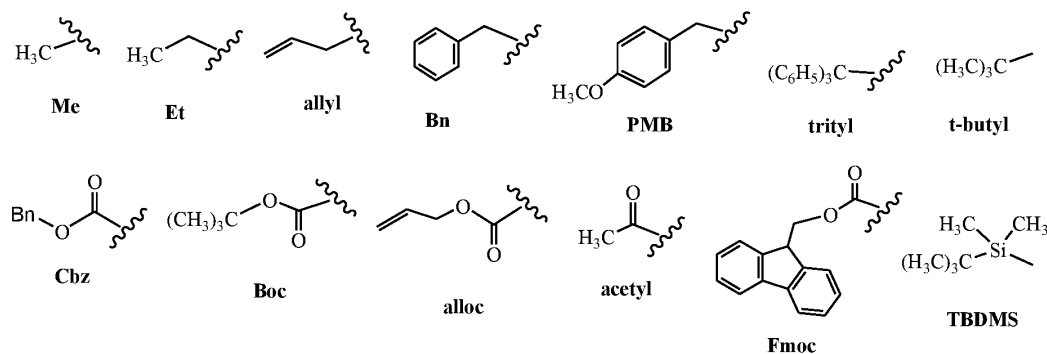
[00166] Protective groups can be removed by acid, base, reducing conditions (such as, for example, hydrogenolysis), and/or oxidative conditions. Groups such as trityl, dimethoxytrityl, acetal and t-butyldimethylsilyl are acid labile and may be used to protect carboxy and hydroxy reactive moieties in the presence of amino groups protected with Cbz groups, which are removable by hydrogenolysis, and Fmoc groups, which are base labile. Carboxylic acid and

hydroxy reactive moieties may be blocked with base labile groups such as, but not limited to, methyl, ethyl, and acetyl in the presence of amines blocked with acid labile groups such as t-butyl carbamate or with carbamates that are both acid and base stable but hydrolytically removable.

[00167] Carboxylic acid and hydroxy reactive moieties may also be blocked with hydrolytically removable protective groups such as the benzyl group, while amine groups capable of hydrogen bonding with acids may be blocked with base labile groups such as Fmoc. Carboxylic acid reactive moieties may be protected by conversion to simple ester compounds as exemplified herein, which include conversion to alkyl esters, or they may be blocked with oxidatively-removable protective groups such as 2,4-dimethoxybenzyl, while co-existing amino groups may be blocked with fluoride labile silyl carbamates.

[00168] Allyl blocking groups are useful in the presence of acid- and base- protecting groups since the former are stable and can be subsequently removed by metal or pi-acid catalysts. For example, an allyl-blocked carboxylic acid can be deprotected with a Pd⁰-catalyzed reaction in the presence of acid labile t-butyl carbamate or base-labile acetate amine protecting groups. Yet another form of protecting group is a resin to which a compound or intermediate may be attached. As long as the residue is attached to the resin, that functional group is blocked and cannot react. Once released from the resin, the functional group is available to react.

[00169] Typically blocking/protecting groups may be selected from:



[00170] Other protecting groups, plus a detailed description of techniques applicable to the creation of protecting groups and their removal are described in Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, and Kocienski, Protective Groups, Thieme Verlag, New York, NY, 1994, which are incorporated herein by reference for such disclosure).

Methods of Treatment and Prevention

[00171] In some embodiments is a method of treating a metabolic disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a

compound Formula I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a method of treating a metabolic disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein the metabolic disease is selected from type 2 diabetes, atherosclerosis, obesity and gout. In some embodiments is a method of treating type 2 diabetes in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a method of treating atherosclerosis in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a method of treating obesity in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a method of treating gout in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof.

[00172] In some embodiments is a method of treating a liver disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a method of treating a liver disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein the liver disease is selected from non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), viral hepatitis, or cirrhosis.

[00173] In some embodiments is a method of treating a lung disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein the lung disease is selected from asthma, COPD, and pulmonary idiopathic fibrosis.

[00174] In some embodiments is a method of treating a central nervous system disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein the central nervous system disease is selected Alzheimer's

disease, multiple sclerosis, Amyotrophic Lateral Sclerosis, Parkinson's disease, Huntington's disease, traumatic brain injury, ischemic stroke and reperfusion, haemorrhagic stroke, epilepsy, and depression. In some embodiments is a method of treating Alzheimer's disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a method of treating multiple sclerosis in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a method of treating Amyotrophic Lateral Sclerosis in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a method of treating multiple sclerosis in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a method of treating Parkinson's disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a method of treating Huntington's disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a method of treating traumatic brain injury in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a method of treating ischemic stroke and reperfusion in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a method of treating stroke in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a method of treating epilepsy in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a method of treating depression in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a

compound Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof.

[00175] In some embodiments is a method of treating a neurodegenerative disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof.

[00176] In some embodiments is a method of treating an inflammatory or autoimmune disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a method of treating an inflammatory or autoimmune disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease is rheumatoid arthritis. In some embodiments is a method of treating an inflammatory or autoimmune disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease is multiple sclerosis. In some embodiments is a method of treating an inflammatory or autoimmune disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease is psoriasis. In some embodiments is a method of treating an inflammatory or autoimmune disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease is lupus. In some embodiments is a method of treating an inflammatory or autoimmune disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease is intestinal bowel disease. In some embodiments is a method of treating an inflammatory or autoimmune disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease is Crohn's disease. In some embodiments is a method of treating an inflammatory or autoimmune disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula (I'), (I), (Ia), (Ib), (II), or

(III), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease is ulcerative colitis.

[00177] In some embodiments is a method of treating a cardiovascular disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a method of treating a cardiovascular disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein the cardiovascular disease is atherosclerosis or stroke. In some embodiments is a method of treating atherosclerosis in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a method of treating stroke in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof.

Pharmaceutical compositions and methods of administration

[00178] NLRP3 inhibitors described herein are administered to subjects in a biologically compatible form suitable for administration to treat or prevent diseases, disorders or conditions. Administration of NLRP3 inhibitors as described herein can be in any pharmacological form including a therapeutically effective amount of a NLRP3 inhibitor alone or in combination with a pharmaceutically acceptable carrier.

[00179] In certain embodiments, the compounds described herein are administered as a pure chemical. In other embodiments, the compounds described herein are combined with a pharmaceutically suitable or acceptable carrier (also referred to herein as a pharmaceutically suitable (or acceptable) excipient, physiologically suitable (or acceptable) excipient, or physiologically suitable (or acceptable) carrier) selected on the basis of a chosen route of administration and standard pharmaceutical practice as described, for example, in Remington: The Science and Practice of Pharmacy (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)).

[00180] Accordingly, provided herein is a pharmaceutical composition comprising at least one compound described herein, or a pharmaceutically acceptable salt, together with one or more pharmaceutically acceptable carriers. The carrier(s) (or excipient(s)) is acceptable or suitable if the carrier is compatible with the other ingredients of the composition and not deleterious to the recipient (i.e., the subject) of the composition.

[00181] In some embodiments is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof.

[00182] Another embodiment provides a pharmaceutical composition consisting essentially of a pharmaceutically acceptable carrier and a compound of Formula (I'), (I), (Ia), (Ib), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a pharmaceutical composition consisting essentially of a pharmaceutically acceptable carrier and a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a pharmaceutical composition consisting essentially of a pharmaceutically acceptable carrier and a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a pharmaceutical composition consisting essentially of a pharmaceutically acceptable carrier and a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a pharmaceutical composition consisting essentially of a pharmaceutically acceptable carrier and a compound of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a pharmaceutical composition consisting essentially of a pharmaceutically acceptable carrier and a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments is a pharmaceutical composition consisting essentially of a pharmaceutically acceptable carrier and a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof.

[00183] In certain embodiments, the compound as described herein is substantially pure, in that it contains less than about 5%, or less than about 1%, or less than about 0.1%, of other organic small molecules, such as contaminating intermediates or by-products that are created, for example, in one or more of the steps of a synthesis method.

[00184] These formulations include those suitable for oral, topical, buccal, parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous), or aerosol administration.

[00185] Exemplary pharmaceutical compositions are used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which includes one or more of a disclosed compound, as an active ingredient, in a mixture with an organic or inorganic carrier or

excipient suitable for external, enteral or parenteral applications. In some embodiments, the active ingredient is compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the disease.

[00186] In some embodiments, NLRP3 inhibitors described herein are administered to subjects in a biologically compatible form suitable for topical administration to treat or prevent dermal diseases, disorders, or conditions. By “biologically compatible form suitable for topical administration” is meant a form of the NLRP3 inhibitor to be administered in which any toxic effects are outweighed by the therapeutic effects of the inhibitor. Administration of NLRP3 inhibitors as described herein can be in any pharmacological form including a therapeutically effective amount of a NLRP3 inhibitor alone or in combination with a pharmaceutically acceptable carrier.

[00187] Topical administration of a NLRP3 inhibitor may be presented in the form of an aerosol, a semi-solid pharmaceutical composition, a powder, or a solution. By the term “a semi-solid composition” is meant an ointment, cream, salve, jelly, or other pharmaceutical composition of substantially similar consistency suitable for application to the skin. Examples of semi-solid compositions are given in Chapter 17 of *The Theory and Practice of Industrial Pharmacy*, Lachman, Lieberman and Kanig, published by Lea and Febiger (1970) and in Chapter 67 of *Remington's Pharmaceutical Sciences*, 15th Edition (1975) published by Mack Publishing Company.

[00188] Dermal or skin patches are another method for transdermal delivery of the therapeutic or pharmaceutical compositions described herein. Patches can provide an absorption enhancer such as DMSO to increase the absorption of the compounds. Patches can include those that control the rate of drug delivery to the skin. Patches may provide a variety of dosing systems including a reservoir system or a monolithic system, respectively. The reservoir design may, for example, have four layers: the adhesive layer that directly contacts the skin, the control membrane, which controls the diffusion of drug molecules, the reservoir of drug molecules, and a water-resistant backing. Such a design delivers uniform amounts of the drug over a specified time period, the rate of delivery has to be less than the saturation limit of different types of skin. The monolithic design, for example, typically has only three layers: the adhesive layer, a polymer matrix containing the compound, and a water-proof backing. This design brings a saturating amount of drug to the skin. Thereby, delivery is controlled by the skin. As the drug amount decreases in the patch to below the saturating level, the delivery rate falls.

[00189] In one embodiment, the topical composition may, for example, take the form of hydrogel based on polyacrylic acid or polyacrylamide; as an ointment, for example with polyethyleneglycol (PEG) as the carrier, like the standard ointment DAB 8 (50% PEG 300, 50% PEG 1500); or as an emulsion, especially a microemulsion based on water-in-oil or oil-in-water, optionally with added liposomes. Suitable permeation accelerators (entraining agents) include sulphoxide derivatives such as dimethylsulphoxide (DMSO) or decylmethylsulphoxide (decyl-MSO) and transcitol (diethyleneglycolmonoethylether) or cyclodextrin; as well as pyrrolidones, for example 2-pyrrolidone, N-methyl-2-pyrrolidone, 2-pyrrolidone-5-carboxylic acid, or the biodegradable N-(2-hydroxyethyl)-2-pyrrolidone and the fatty acid esters thereof; urea derivatives such as dodecylurea, 1,3-didodecylurea, and 1,3-diphenylurea; and terpenes, for example D-limonene, menthone, α -terpinol, carvol, limonene oxide, or 1,8-cineol.

[00190] Ointments, pastes, creams and gels also can contain excipients, such as starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, and talc, or mixtures thereof. Powders and sprays also can contain excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Solutions of nanocrystalline antimicrobial metals can be converted into aerosols or sprays by any of the known means routinely used for making aerosol pharmaceuticals. In general, such methods comprise pressurizing or providing a means for pressurizing a container of the solution, usually with an inert carrier gas, and passing the pressurized gas through a small orifice. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[00191] The carrier can also contain other pharmaceutically-acceptable excipients for modifying or maintaining the pH, osmolarity, viscosity, clarity, color, sterility, stability, rate of dissolution, or odor of the formulation. The anti-skin aging compositions can also further comprise antioxidants, sun screens, natural retinoids (e.g., retinol), and other additives commonly found in skin treatment compositions.

[00192] In some embodiments for preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g., conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g., water, to form a solid preformulation composition containing a homogeneous mixture of a disclosed compound or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition is readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

[00193] In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the subject composition is 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, cellulose, microcrystalline cellulose, silicified microcrystalline cellulose, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, hypromellose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as croscopovidone, croscarmellose sodium, sodium starch glycolate, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, 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, docusate sodium, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, in some embodiments, the compositions comprise buffering agents. In some embodiments, solid compositions of a similar type are also 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.

[00194] In some embodiments, a tablet is made by compression or molding, optionally with one or more accessory ingredients. In some embodiments, compressed tablets are 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. In some embodiments, molded tablets are made by molding in a suitable machine a mixture of the subject composition moistened with an inert liquid diluent. In some embodiments, tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, are scored or prepared with coatings and shells, such as enteric coatings and other coatings.

[00195] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the subject composition, in some embodiments, the liquid dosage forms contain inert diluents, 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, cyclodextrins and mixtures thereof.

[00196] In some embodiments, suspensions, in addition to the subject composition, 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.

[00197] In some embodiments, powders and sprays contain, in addition to a subject composition, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates, and polyamide powder, or mixtures of these substances. In some embodiments, sprays additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[00198] Compositions and compounds disclosed herein alternatively are administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation, or solid particles containing the compound. In some embodiments, a non-aqueous (e.g., fluorocarbon propellant) suspension is used. In some embodiments, sonic nebulizers are used because they minimize exposing the agent to shear, which results in degradation of the compounds contained in the subject compositions. Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of a subject composition together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular subject composition, but typically include non-ionic surfactants (Tweens, Pluronics, or 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.

[00199] Pharmaceutical compositions suitable for parenteral administration comprise a subject composition in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which are reconstituted into sterile injectable solutions or dispersions just prior to use, which, in some embodiments, contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient, or suspending or thickening agents.

[00200] Examples of suitable aqueous and non-aqueous carriers which are employed in the pharmaceutical compositions include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate and cyclodextrins. Proper fluidity is

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

[00201] The dose of the composition comprising at least one compound described herein differs, depending upon the patient's (*e.g.*, human) condition, that is, stage of the disease, general health status, age, and other factors.

[00202] Pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented). An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (*e.g.*, an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity). Optimal doses are generally determined using experimental models and/or clinical trials. In some embodiments, the optimal dose depends upon the body mass, weight, or blood volume of the patient.

[00203] Oral doses typically range from about 1.0 mg to about 1000 mg, one to four times, or more, per day.

[00204] Dose administration can be repeated depending upon the pharmacokinetic parameters of the dosage formulation and the route of administration used.

[00205] It is especially advantageous to formulate compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms are dictated by and directly dependent on (a) the unique characteristics of the NLRP3 inhibitor and the particular therapeutic effect to be achieved and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals. The specific dose can be readily calculated by one of ordinary skill in the art, *e.g.*, according to the approximate body weight or body surface area of the patient or the volume of body space to be occupied. The dose will also be calculated dependent upon the particular route of administration selected. Further refinement of the calculations necessary to determine the appropriate dosage for treatment is routinely made by those of ordinary skill in the art. Such calculations can be made without undue experimentation by one skilled in the art in light of the NLRP3 inhibitor activities disclosed herein in assay preparations of target cells. Exact dosages are determined in conjunction with standard dose-response studies. It will be understood that the

amount of the composition actually administered will be determined by a practitioner, in the light of the relevant circumstances including the condition or conditions to be treated, the choice of composition to be administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the chosen route of administration.

[00206] Toxicity and therapeutic efficacy of such NLRP3 inhibitors can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, for example, for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD₅₀/ED₅₀. NLRP3 inhibitors that exhibit large therapeutic indices are preferred. While NLRP3 inhibitors that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such inhibitors to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

[00207] The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such NLRP3 inhibitors lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any NLRP3 inhibitor used in a method described herein, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC₅₀ (i.e., the concentration of NLRP3 inhibitor that achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to determine useful doses in humans more accurately. Levels in plasma may be measured, for example, by high performance liquid chromatography.

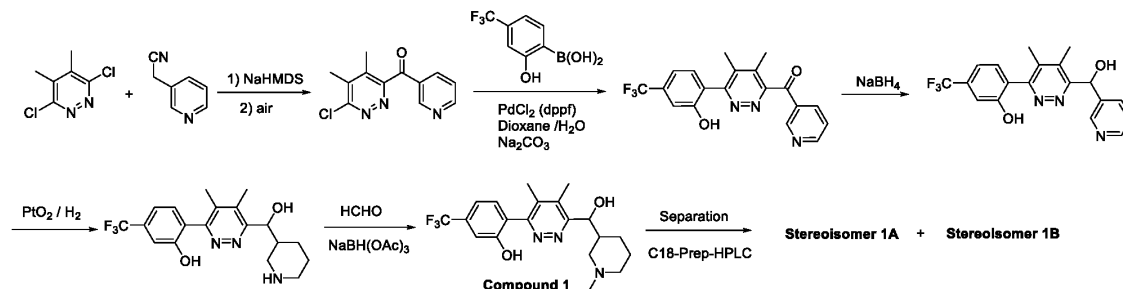
EXAMPLES

[00208] The following examples are offered for purposes of illustration and are not intended to limit the scope of the claims provided herein. All literature citations in these examples and throughout this specification are incorporated herein by references for all legal purposes to be served thereby. The starting materials and reagents used for the synthesis of the compounds described herein may be synthesized or can be obtained from commercial sources, such as, but not limited to, Sigma-Aldrich, Acros Organics, Fluka, and Fischer Scientific.

[00209] Standard abbreviations and acronyms as defined in *J. Org. Chem.* 2007 72(1): 23A-24A are used herein. Other abbreviations and acronyms used herein are as follows:

THF	tetrahydrofuran
ACN	acetonitrile
DMF	N, N-dimethylformamide
EtOH	ethanol
MeOH	methanol
DCM	dichloromethane
EtOAc	ethyl acetate
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
DIEA	N, N-diisopropylethylamine
P ₂ O ₅	phosphorus pentoxide
MsOH	methanesulfonic acid
NaH	sodium hydride
Mg	magnesium
LiAlH ₄	lithium aluminum hydride
PPH ₃	triphenylphosphine
DIAD	diisopropyl azodicarboxylate
SO ₃ .DMF	N,N-dimethylformamide sulfur trioxide Complex
SOCl ₂	thionyl chloride
NH ₄ OH	ammonium hydroxide
t-BuONa	sodium tert-butoxide
NaOH	sodium hydroxide
Mw	microwave
OVN	overnight
rt	room temperature
SM	starting material

Example 1: Synthesis of 2-(6-(hydroxy(1-methylpiperidin-3-yl)methyl)-4,5-dimethylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 1)



[00210] Step 1: To a solution of 3,6-dichloro-4,5-dimethylpyridazine (3.54 g, 20 mmol) in THF (150 mL) was added pyridine-3-yl-acetonitrile (2.5 g, 21 mmol). The solution was degassed, backfilled with N₂ and was cooled to 0°C. NaHMDS (2N, 21 mL in THF, 42 mmol) was added. The reaction mixture was warmed to rt for 2h. The reaction mixture was stirred vigorously under open to air for 5h. The reaction was quenched with saturated NaHCO₃ and diluted with EtOAc. The organic phase was separated and aqueous was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was triturated with hexane/EtOAc to give (6-chloro-4,5-dimethylpyridazin-3-yl)(pyridin-3-yl)methanone (3 g).

[00211] Step 2: (6-Chloro-4,5-dimethylpyridazin-3-yl)(pyridin-3-yl)methanone (300 mg, 1.0 eq), (2-hydroxy-4-(trifluoromethyl)phenyl)boronic acid (350 mg, 1.3 eq), PdCl₂(dppf) (80 mg, 10%) and Na₂CO₃ (290 mg, 2.0 eq) were combined in dioxane (20 mL) and water (5 mL) under N₂. The resulting mixture was heated at 100°C for 8h. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water, brine and concentrated in vacuo. The residue was purified on by silica gel chromatography to afford (6-(2-hydroxy-4-(trifluoromethyl)phenyl)-4,5-dimethylpyridazin-3-yl)(pyridin-3-yl)methanone (205 mg).

[00212] Step 3: (6-(2-Hydroxy-4-(trifluoromethyl)phenyl)-4,5-dimethylpyridazin-3-yl)(pyridin-3-yl)methanone (200 mg, 1.0 eq) was dissolved in MeOH (10 mL) and THF (10 mL) and the solution was cooled to 0°C. NaBH₄ (11 mg, 0.5 eq) was added at 0°C. The resulting mixture was stirred at 0°C for 15min. The reaction was quenched with saturated NaHCO₃. The mixture was extracted with EtOAc and the EtOAc solution was concentrated in vacuo to afford 2-(6-(hydroxy(pyridin-3-yl)methyl)-4,5-dimethylpyridazin-3-yl)-5-(trifluoromethyl)phenol (201 mg) which was used without further purification.

[00213] Step 4: To a solution of 2-(6-(hydroxy(pyridin-3-yl)methyl)-4,5-dimethylpyridazin-3-yl)-5-(trifluoromethyl)phenol (200 mg, 1.0 eq) in MeOH (100 mL) and water (1 mL) was added PtO₂ (98 mg, 0.8 eq). The mixture was degassed with bubbling N₂ gas for 20min, then

hydrogenated under H₂ (balloon) for 15h at rt. The catalyst was removed by filtration and solvent was concentrated in vacuo to afford 2-(6-(hydroxy(piperidin-3-yl)methyl)-4,5-dimethylpyridazin-3-yl)-5-(trifluoromethyl)phenol (185 mg) which was used without purification.

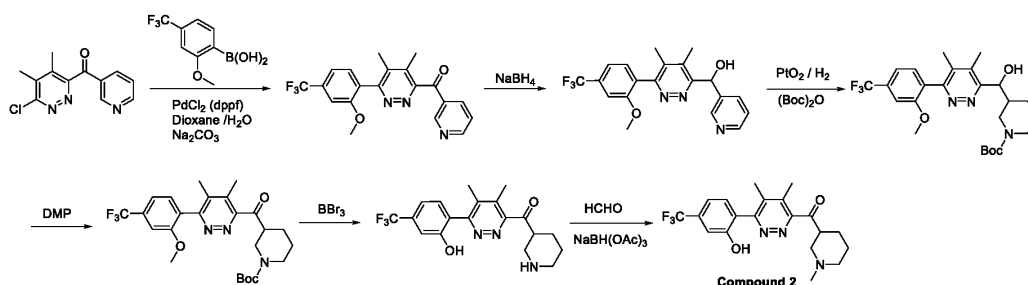
[00214] Step 5: 2-(6-(Hydroxy(piperidin-3-yl)methyl)-4,5-dimethylpyridazin-3-yl)-5-(trifluoromethyl)phenol (185 mg, 1.0 eq) was dissolved in 1,2-dichloroethane (20 mL) and added HCHO (48mg, 37% in water, 1.2 eq) and 2 drops of AcOH. The mixture was stirred at rt for 30min and NaBH(AcO)₃ (165 mg, 1.5 eq) was added. The resulting mixture was stirred at rt for 30min and quenched with saturated NaHCO₃ and stirred at rt for 10min. The mixture was extracted with DCM (4x25mL) and the combined DCM extracts were concentrated in vacuo. The residue was purified by silica gel chromatography to afford 2-(6-(hydroxy(1-methylpiperidin-3-yl)methyl)-4,5-dimethylpyridazin-3-yl)-5-(trifluoromethyl)phenol (**Compound 1**) (48 mg) as a white solid. ESI-MS (EI⁺, m/z): 396.1.

[00215] **Stereoisomer 1A** (a mixture of two compounds) and **Stereoisomer 1B** (a mixture of two compounds) were separated from **Compound 1** by C18 Prep-HPLC. Peak 1 was **Stereoisomer 1A**, peak 2 was **Stereoisomer 1B**.

Stereoisomer 1A ESI-MS (EI⁺, m/z): 396.2.

Stereoisomer 1B ESI-MS (EI⁺, m/z): 396.2.

Example 2: Synthesis of (6-(2-hydroxy-4-(trifluoromethyl)phenyl)-4,5-dimethylpyridazin-3-yl)(1-methylpiperidin-3-yl)methanone (**Compound 2**)



[00216] Step 1: (6-Chloro-4,5-dimethylpyridazin-3-yl)(pyridin-3-yl)methanone (300 mg, 1.0 eq), (2-methoxy-4-(trifluoromethyl)phenyl)boronic acid (360 mg, 1.3 eq), PdCl₂(dppf) (82 mg, 10%) and Na₂CO₃ (300 mg, 2.0 eq) were combined in dioxane (20 mL) and water (5 mL) under N₂. The resulting mixture was heated at 100°C for 8h. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water, brine and concentrated in vacuo. The residue was purified on silica gel column to afford (6-(2-methoxy-4-(trifluoromethyl)phenyl)-4,5-dimethylpyridazin-3-yl)(pyridin-3-yl)methanone (262 mg).

[00217] Step 2: (6-(2-Methoxy-4-(trifluoromethyl)phenyl)-4,5-dimethylpyridazin-3-yl)(pyridin-3-yl)methanone (260 mg, 1.0 eq) was dissolved in MeOH (20 mL) and THF (20

mL). To the solution was added NaBH₄ (13 mg, 0.5 eq) at 0°C. The resulting mixture was stirred at 0°C for 30min and quenched with saturated NaHCO₃. The mixture was extracted with EtOAc and the EtOAc solution was concentrated in vacuo to afford (6-(2-methoxy-4-(trifluoromethyl)phenyl)-4,5-dimethylpyridazin-3-yl)(pyridin-3-yl)methanol (259 mg) which was used without further purification.

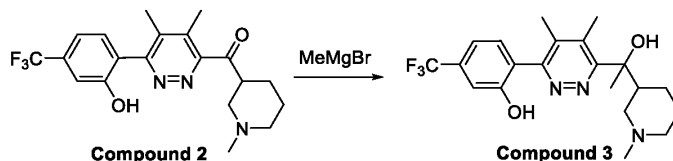
[00218] Step 3: To a solution of (6-(2-methoxy-4-(trifluoromethyl)phenyl)-4,5-dimethylpyridazin-3-yl)(pyridin-3-yl)methanol (250 mg, 1.0 eq) in MeOH (100 mL) and water (1 mL) was added PtO₂ (117 mg, 0.8 eq) and (Boc)₂O (168 mg, 1.2 eq). The mixture was degassed with bubbling N₂ gas for 20min, then hydrogenated under H₂ (balloon) for 1.5h at rt. Then the H₂ balloon was removed and the mixture was stirred at rt for overnight. The catalyst was removed by filtration and solvent was concentrated in vacuo. The residue was purified on a silica gel column to afford tert-butyl 3-(hydroxy(6-(2-methoxy-4-(trifluoromethyl)phenyl)-4,5-dimethylpyridazin-3-yl)methyl)piperidine-1-carboxylate (264 mg).

[00219] Step 4: To a solution of tert-butyl 3-(hydroxy(6-(2-methoxy-4-(trifluoromethyl)phenyl)-4,5-dimethylpyridazin-3-yl)methyl)piperidine-1-carboxylate (260 mg, 1.0 eq) in dry DCM (25 mL) was added DMP (268 mg, 1.2 eq) at 0°C and stirred at 0°C for 1h. Additional DMP (30 mg) was added and the reaction was stirred at rt for 30min and then quenched with saturated NaHCO₃. The mixture was concentrated and the residue was purified on a silica gel column to afford tert-butyl 3-(6-(2-methoxy-4-(trifluoromethyl)phenyl)-4,5-dimethylpyridazine-3-carbonyl)piperidine-1-carboxylate (198 mg).

[00220] Step 5: To a solution of tert-butyl 3-(6-(2-methoxy-4-(trifluoromethyl)phenyl)-4,5-dimethylpyridazine-3-carbonyl)piperidine-1-carboxylate (190 mg, 1.0 eq) in dry DCM (20 mL) was added BBr₃ (5 eq) at 0°C under N₂. The mixture was stirred at 0°C for 1h, and then at rt 6h. The reaction was quenched with water at 0°C and stirred at rt for 30min. Saturated NaHCO₃ was added to adjust the pH ~10. The mixture was extracted with DCM (3x50 mL). The combined extracts were concentrated in vacuo to afford (6-(2-hydroxy-4-(trifluoromethyl)phenyl)-4,5-dimethylpyridazin-3-yl)(piperidin-3-yl)methanone (97 mg).

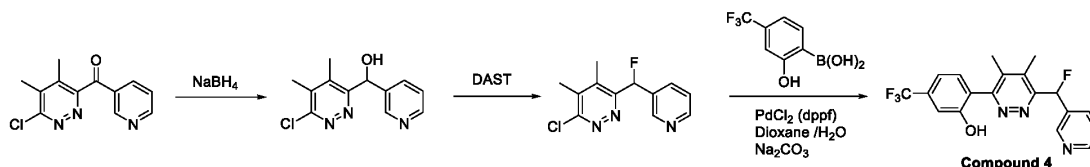
[00221] Step 6: Under reaction conditions described in Example 1, Step 5, from (6-(2-hydroxy-4-(trifluoromethyl)phenyl)-4,5-dimethylpyridazin-3-yl)(piperidin-3-yl)methanone (56 mg) yielded (6-(2-hydroxy-4-(trifluoromethyl)phenyl)-4,5-dimethylpyridazin-3-yl)(1-methylpiperidin-3-yl)methanone (28 mg) (**Compound 2**). ESI-MS (EI⁺, m/z): 394.2.

Example 3: Synthesis of 2-(6-(1-hydroxy-1-(1-methylpiperidin-3-yl)ethyl)-4,5-dimethylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 3)



[00222] A solution of **Compound 2** (6-(2-hydroxy-4-(trifluoromethyl)phenyl)-4,5-dimethylpyridazin-3-yl)(1-methylpiperidin-3-yl)methanone (15 mg) in dry THF was treated with MeMgBr (2N, 76 μ l, 4.0 eq) at 0°C. The mixture was stirred at rt for 1h. The reaction was quenched with saturated NH₄Cl and extracted with DCM (3x20 mL). The combined extracts were concentrated in vacuo and the residue was purified on HPLC to afford 2-(6-(1-hydroxy-1-(1-methylpiperidin-3-yl)ethyl)-4,5-dimethylpyridazin-3-yl)-5-(trifluoromethyl)phenol (8 mg) (**Compound 3**). ESI-MS (EI⁺, m/z): 410.2.

Example 4: Synthesis of 2-(6-(fluoro(pyridin-3-yl)methyl)-4,5-dimethylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 4)



[00223] Step 1: (6-Chloro-4,5-dimethylpyridazin-3-yl)(pyridin-3-yl)methanone (1.0 g, 1.0 eq) was dissolved in MeOH (20 mL) and THF (20 mL) and cooled to 0°C. NaBH₄ (80 mg, 0.5 eq) was added at 0°C. The resulting mixture was stirred at 0°C for 15min. The reaction was quenched with saturated NaHCO₃. The mixture was extracted with EtOAc and the EtOAc solution was concentrated in vacuo to afford (6-chloro-4,5-dimethylpyridazin-3-yl)(pyridin-3-yl)methanol (0.95 g) which was used without further purification.

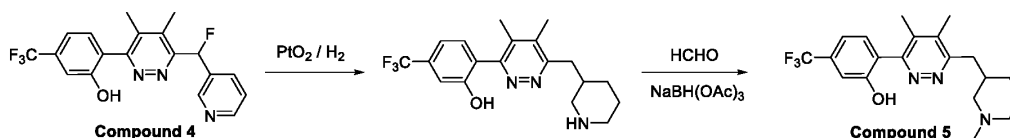
[00224] Step 2: To a solution of (6-chloro-4,5-dimethylpyridazin-3-yl)(pyridin-3-yl)methanol (300 mg, 1.0 eq) in dry DCM (10 mL) was added DAST (388 mg, 2.0 eq) at 0°C. The mixture was stirred at rt overnight. Additional DAST (100 mg) was added, and reaction was stirred at rt for additional 5h. The reaction was quenched with saturated NaHCO₃ at 0°C, and aqueous phase was extracted with DCM (2x20 mL). The combined extracts were concentrated in vacuo and the residue purified on a silica gel column to afford 3-chloro-6-(fluoro(pyridin-3-yl)methyl)-4,5-dimethylpyridazine (174 mg).

[00225] Step 3: 3-Chloro-6-(fluoro(pyridin-3-yl)methyl)-4,5-dimethylpyridazine (150 mg, 1.0 eq), (2-hydroxy-4-(trifluoromethyl)phenyl)boronic acid (160 mg, 1.3 eq), PdCl₂(dppf) (40 mg, 10%) and Na₂CO₃ (130 mg, 2.0 eq) were combined in dioxane (10 mL) and water (3 mL) under

N₂. The resulting mixture was heated at 100°C for 8h. The reaction mixture was diluted with ethyl acetate (50 mL), washed with water, brine and concentrated in vacuo. The residue was purified on a silica gel column to afford ZMG-3134 2-(6-(fluoro(pyridin-3-yl)methyl)-4,5-dimethylpyridazin-3-yl)-5-(trifluoromethyl)phenol (143 mg).

[00226] Step 4: To a solution of tert-butyl 3-(hydroxy(6-(2-methoxy-4-(trifluoromethyl)phenyl)-4,5-dimethylpyridazin-3-yl)methyl)piperidine-1-carboxylate (260 mg, 1.0 eq) in dry DCM (25 mL) was added DMP (268 mg, 1.2 eq) at 0°C and stirred at 0°C for 1h. Additional DMP (30 mg) was added and the reaction was stirred at rt for 30min and then quenched with saturated NaHCO₃. The mixture was concentrated and the residue was purified on a silica gel column to afford tert-butyl 3-(6-(2-methoxy-4-(trifluoromethyl)phenyl)-4,5-dimethylpyridazine-3-carbonyl)piperidine-1-carboxylate (**Compound 4**) (198 mg). ESI-MS (EI⁺, m/z): 378.3.

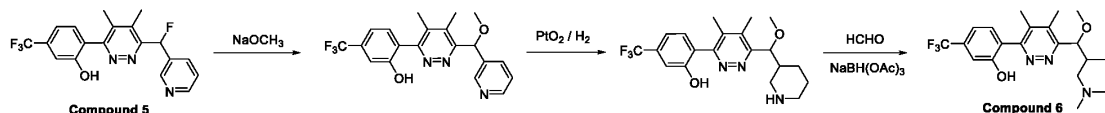
Example 5: Synthesis of 2-(4,5-dimethyl-6-((1-methylpiperidin-3-yl)methyl)pyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 5)



[00227] Step 1: To a solution of **Compound 4** (120 mg) in MeOH (40 mL) was added PtO₂ (40 mg) and degassed under vacuo then hydrogenated under balloon H₂ for 15h. The catalyst was removed through a celite pad, and the reaction mixture was concentrated in vacuo to afford 2-(4,5-dimethyl-6-(piperidin-3-ylmethyl)pyridazin-3-yl)-5-(trifluoromethyl)phenol (92 mg).

[00228] Step 2: Under reaction conditions described in Example 1, Step 5, from 2-(4,5-dimethyl-6-(piperidin-3-ylmethyl)pyridazin-3-yl)-5-(trifluoromethyl)phenol (92 mg) yielded 2-(4,5-dimethyl-6-((1-methylpiperidin-3-yl)methyl)pyridazin-3-yl)-5-(trifluoromethyl)phenol (21 mg) (**Compound 5**). ESI-MS (EI⁺, m/z): 380.3.

Example 6: Synthesis of 2-(6-(methoxy(1-methylpiperidin-3-yl)methyl)-4,5-dimethylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 6)



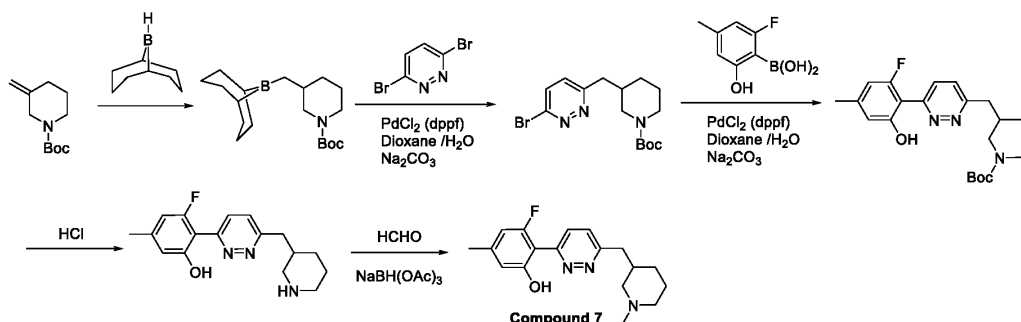
[00229] Step 1: To a solution of 2-(6-(fluoro(pyridin-3-yl)methyl)-4,5-dimethylpyridazin-3-yl)-5-(trifluoromethyl)phenol (100 mg) in dry THF (2 mL) was added 2M NaOMe in MeOH (2 mL). The resulting mixture was heated at 90°C in sealed-tube overnight. The mixture was cooled and diluted with water (40 mL) and extracted with ethyl acetate (3x40 mL). The

combined extracts were concentrated in vacuo. The residue was purified on a silica gel column to afford 2-(6-(methoxy(pyridin-3-yl)methyl)-4,5-dimethylpyridazin-3-yl)-5-(trifluoromethyl)phenol (81 mg).

[00230] Step 2: To a solution of 2-(6-(methoxy(pyridin-3-yl)methyl)-4,5-dimethylpyridazin-3-yl)-5-(trifluoromethyl)phenol (60 mg) was added PtO₂ (25 mg) and degassed under vacuo and hydrogenated under balloon H₂ for 15h to afford 2-(6-(methoxy(piperidin-3-yl)methyl)-4,5-dimethylpyridazin-3-yl)-5-(trifluoromethyl)phenol (42 mg).

[00231] Step 3: Under reaction conditions described in Example 1, Step 5, from 2-(6-(methoxy(piperidin-3-yl)methyl)-4,5-dimethylpyridazin-3-yl)-5-(trifluoromethyl)phenol (42 mg) yielded 2-(6-(methoxy(1-methylpiperidin-3-yl)methyl)-4,5-dimethylpyridazin-3-yl)-5-(trifluoromethyl)phenol (5 mg) (**Compound 6**). ESI-MS (EI⁺, m/z): 410.2.

Example 7: Synthesis of 3-fluoro-5-methyl-2-((1-methylpiperidin-3-yl)methyl)pyridazin-3-yl)phenol (Compound 7)



[00232] Step 1: tert-Butyl 3-methylenepiperidine-1-carboxylate (500 mg, 1.0 eq) was added 9-BBN (0.5M, 5.1 mL, 1.0 eq) at 0°C under N₂. The mixture was stirred at rt for 10min and then at 70°C for 1h in a sealed tube. The mixture was cooled and the solvent was removed in vacuo to afford tert-butyl 3-((9-borabicyclo[3.3.1]nonan-9-yl)methyl)piperidine-1-carboxylate which was used without further purification.

[00233] Step 2: tert-Butyl 3-((9-borabicyclo[3.3.1]nonan-9-yl)methyl)piperidine-1-carboxylate (200 mg, 1.0 eq), 3,6-dibromopyridazine (300 mg, 2.0 eq), PdCl₂ (dppf) (40 mg, 0.1eq) and Na₂CO₃ (135 mg, 2.0 eq) were combined in dioxane (15 mL) and water (5 mL). The mixture was heated at 100°C for 15h. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The solvent was removed in vacuo and the residue was purified on a silica gel column to afford tert-butyl 3-((6-bromopyridazin-3-yl)methyl)piperidine-1-carboxylate (162 mg).

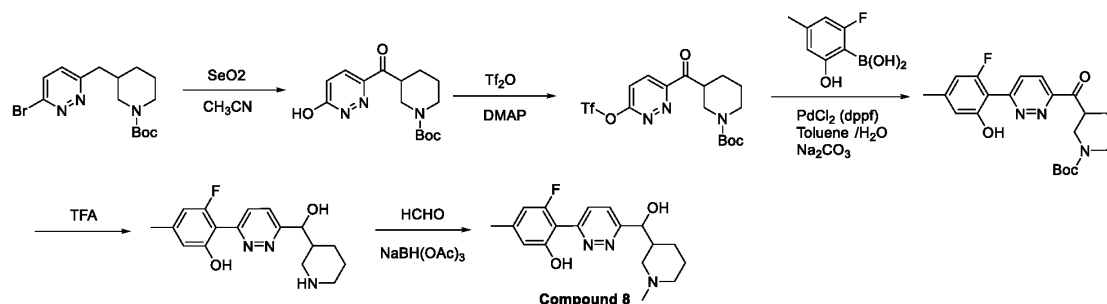
[00234] Step 3: tert-Butyl 3-((6-bromopyridazin-3-yl)methyl)piperidine-1-carboxylate (50 mg, 1.0 eq), (2-fluoro-6-hydroxy-4-methylphenyl)boronic acid (31 mg, 1.3eq), PdCl₂ (dppf) (9 mg, 0.1 eq) and Na₂CO₃ (30 mg, 2.0 eq) were combined in dioxane (5 mL) and water (2 mL). The

mixture was heated at 100°C for 8h. The crude mixture was purified on a silica gel column to afford tert-butyl 3-((6-(2-fluoro-6-hydroxy-4-methylphenyl)pyridazin-3-yl)methyl)piperidine-1-carboxylate (41 mg).

[00235] Step 4: tert-Butyl 3-((6-(2-fluoro-6-hydroxy-4-methylphenyl)pyridazin-3-yl)methyl)piperidine-1-carboxylate (41 mg) was treated with 4N HCl in dioxane (1 mL). The mixture was stirred at rt for 15 mins and concentrated in vacuo to afford 3-fluoro-5-methyl-2-(6-(piperidin-3-ylmethyl)pyridazin-3-yl)phenol HCl salt (35 mg).

[00236] Step 5: Under reaction conditions described in Example 1, Step 5, from 3-fluoro-5-methyl-2-(6-(piperidin-3-ylmethyl)pyridazin-3-yl)phenol (35 mg) yielded 3-fluoro-5-methyl-2-(6-((1-methylpiperidin-3-yl)methyl)pyridazin-3-yl)phenol (12 mg) (**Compound 7**). ESI-MS (EI⁺, m/z): 316.3.

Example 8: Synthesis of 3-fluoro-2-(6-(hydroxy(1-methylpiperidin-3-yl)methyl)pyridazin-3-yl)-5-methylphenol (Compound 8)



[00237] Step 1: tert-Butyl 3-((6-bromopyridazin-3-yl)methyl)piperidine-1-carboxylate (100 mg, 1.0 eq), SeO₂ (4.0 eq) in CH₃CN (2 mL) was heated at 135°C in a microwave reactor for 8h. The mixture was cooled to room temperature, quenched with conc. NH₄Cl, and extracted with DCM. The solvent was removed in vacuo and the residue was purified on a silica gel column to afford tert-butyl 3-(6-hydroxypyridazine-3-carbonyl)piperidine-1-carboxylate (48 mg).

[00238] Step 2: tert-Butyl 3-(6-hydroxypyridazine-3-carbonyl)piperidine-1-carboxylate (40 mg, 1.0 eq) and DMAP (40 mg) was dissolved in DCM (2 mL) and pyridine (1 mL) at 0°C. Tf₂O (2.0 eq) in DCM (1mL) was added dropwise at 0°C. The resulting mixture was stirred at rt for 15h. The reaction was quenched with water, and extracted with DCM. The solvent was removed in vacuo and the residue was purified on a silica gel column to afford tert-butyl 3-(6-(((trifluoromethyl)sulfonyl)oxy)pyridazine-3-carbonyl)piperidine-1-carboxylate (26 mg).

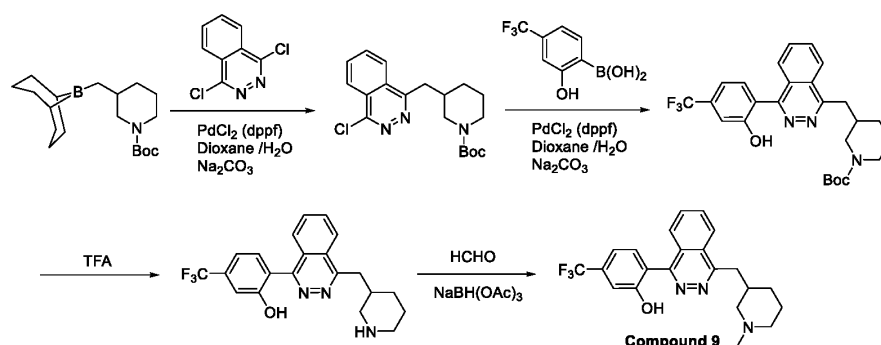
[00239] Step 3: tert-Butyl 3-(6-(((trifluoromethyl)sulfonyl)oxy)pyridazine-3-carbonyl)piperidine-1-carboxylate (26 mg, 1.0 eq), (2-fluoro-6-hydroxy-4-methylphenyl)boronic acid (1.5 eq), PdCl₂(dppf) (0.1 eq) and Na₂CO₃ (2.0 eq) was combined in toluene (3 mL) and water (1 mL). The mixture was heated at 85°C for 8h. The mixture was cooled to room

temperature and purified on a silica gel column to afford tert-butyl 3-(6-(2-fluoro-6-hydroxy-4-methylphenyl)pyridazine-3-carbonyl)piperidine-1-carboxylate (15 mg).

[00240] Step 4: tert-Butyl 3-(6-(2-fluoro-6-hydroxy-4-methylphenyl)pyridazine-3-carbonyl)piperidine-1-carboxylate (15 mg) in DCM (1 mL) was treated with TFA (1 mL) for 20min at RT. The solvent was removed in vacuo to give 3-fluoro-2-(6-(hydroxy(piperidin-3-yl)methyl)pyridazin-3-yl)-5-methylphenol TFA salt (18 mg).

[00241] Step 5: Under reaction conditions described in Example 1, Step 5, from 3-fluoro-2-(6-(hydroxy(piperidin-3-yl)methyl)pyridazin-3-yl)-5-methylphenol TFA salt (18 mg) yielded 3-fluoro-2-(6-(hydroxy(1-methylpiperidin-3-yl)methyl)pyridazin-3-yl)-5-methylphenol (**Compound 8**) (9 mg). ESI-MS (EI^+ , m/z): 332.3.

Example 9: Synthesis of 2-(4-(hydroxy(1-methylpiperidin-3-yl)methyl)phthalazin-1-yl)-5-(trifluoromethyl)phenol (Compound 9)



[00242] Step 1: tert-Butyl 3-((9-borabicyclo[3.3.1]nonan-9-yl)methyl)piperidine-1-carboxylate (200 mg, 1.0 eq), 1,4-dichlorophthalazine (250 mg, 2.0 eq), $\text{PdCl}_2(\text{dppf})$ (40 mg, 0.1 eq) and Na_2CO_3 (135 mg, 2.0 eq) were combined in dioxane (15 mL) and water (5 mL). The mixture was heated at 100°C for 15h. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The solvent was removed in vacuo and the residue was purified on a silica gel column to afford tert-butyl 3-((4-chlorophthalazin-1-yl)methyl)piperidine-1-carboxylate (85 mg).

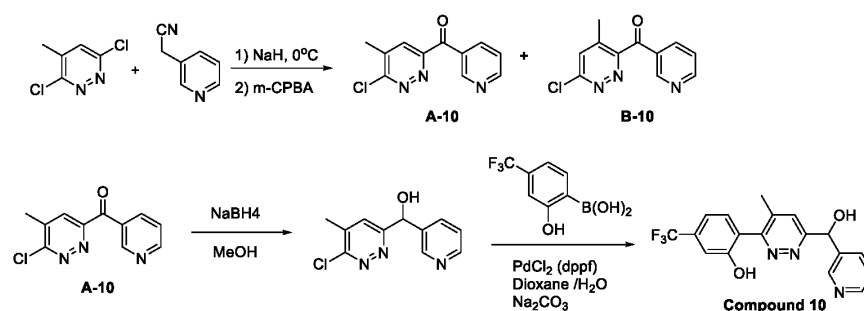
[00243] Step 2: tert-Butyl 3-((4-chlorophthalazin-1-yl)methyl)piperidine-1-carboxylate (80 mg, 1.0 eq), (2-hydroxy-4-(trifluoromethyl)phenyl)boronic acid (68 mg, 1.5 eq), $\text{PdCl}_2(\text{dppf})$ (15 mg, 0.1 eq) and Na_2CO_3 (48 mg, 2.0 eq) were combined in dioxane (5 mL) and water (2 mL). The mixture was heated at 100°C for 8h. The mixture was cooled to room temperature and purified on a silica gel column to afford tert-butyl 3-((4-(2-hydroxy-4-(trifluoromethyl)phenyl)phthalazin-1-yl)methyl)piperidine-1-carboxylate (38 mg).

[00244] Step 3: tert-Butyl 3-((4-(2-hydroxy-4-(trifluoromethyl)phenyl)phthalazin-1-yl)methyl)piperidine-1-carboxylate (38 mg) in DCM (1 mL) was treated with TFA (1 mL) for

15 min at rt. The mixture was concentrated in vacuo to afford 2-(4-(piperidin-3-ylmethyl)phthalazin-1-yl)-5-(trifluoromethyl)phenol TFA salt (42 mg).

[00245] Step 4: Under reaction conditions described in Example 1, Step 5, from 2-(4-(piperidin-3-ylmethyl)phthalazin-1-yl)-5-(trifluoromethyl)phenol TFA salt (42 mg) yielded 2-(4-(hydroxy(1-methylpiperidin-3-yl)methyl)phthalazin-1-yl)-5-(trifluoromethyl)phenol (18 mg) (**Compound 9**). ESI-MS (EI^+ , m/z): 402.2.

Example 10: Synthesis of 2-(6-(hydroxy(pyridin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 10)



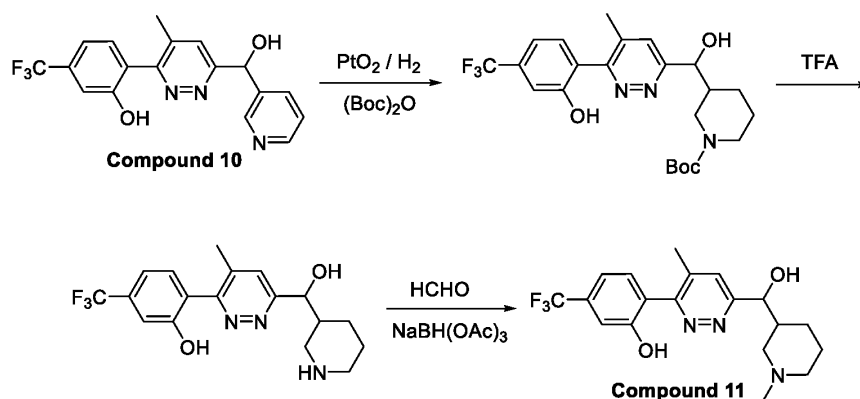
[00246] Step 1: To a degassed solution of 3,6-dichloro-4-methylpyridazine (8.2 g, 50 mmol) and 3-pyridylacetonitrile (6.1 g, 52 mmol) in dry DMA (60 mL) was added NaH (4.2 g, 105 mmol, 60%) in portions at 0°C under N₂. The reaction mixture was stirred for 1h at 0°C. m-CPBA (12 g, 72%) was added to the solution in portions over 10min at 0°C. The reaction mixture was diluted with EtOAc (200 mL) and stirred for an additional 10min at 0°C. Saturated NaHCO₃ (100 mL) was added at 0°C and the mixture was stirred for 10min. The mixture was diluted with water (200 mL). The organic layer was separated and aqueous phase was extracted with EtOAc (3x100 mL). The combined organic layer was washed with water (3 X 100 mL), saturated NaHCO₃ (100 mL), brine (100 mL) and dried over Na₂SO₄. The solvent was concentrated in vacuo. The solid was sonicated in EtOAc (50 mL), filtered, washed with EtOAc/hexane (1:1) (20 mL), and then slurried in EtOAc/hexane (1:1) (50 mL) at 50°C for 30min. The mixture was cooled to rt and the solid was removed by filtration to give (6-chloro-5-methylpyridazin-3-yl)(pyridin-3-yl)methanone (**A-10**) (4.2 g). The combined mother liquid was concentrated in vacuo and purified on a silica gel column to afford (6-chloro-4-methylpyridazin-3-yl)(pyridin-3-yl)methanone (**B-10**) (1.3 g).

[00247] Step 2: (6-Chloro-5-methylpyridazin-3-yl)(pyridin-3-yl)methanone (**A-10**) (1.0 g, 1.0 eq) was dissolved in MeOH (20 mL) and THF (20 mL) and cooled to 0°C. NaBH₄ (81mg, 0.5 eq) was added at 0°C. The resulting mixture was stirred at 0°C for 15min. The reaction was quenched with saturated NaHCO₃, and then extracted with ethyl acetate. The solvent was

removed in vacuo to afford (6-chloro-5-methylpyridazin-3-yl)(pyridin-3-yl)methanol (1.0 g) which was used without further purification.

[00248] Step 3: (6-Chloro-5-methylpyridazin-3-yl)(pyridin-3-yl)methanol (1.0 g, 1.0 eq), (2-hydroxy-4-(trifluoromethyl)phenyl)boronic acid (1.14 g, 1.3 eq), PdCl₂(dppf) (0.28 g, 0.1 eq) and Na₂CO₃ (0.9 g, 2.0 eq) were combined in dioxane (20 mL) and water (5 mL). The resulting mixture was heated at 100°C for 8h. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water, brine and concentrated in vacuo. The residue was purified on a silica gel column to afford 2-(6-(hydroxy(pyridin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (**Compound 10**) (0.75 g). ESI-MS (EI⁺, m/z): 362.2.

Example 11: Synthesis of 2-(6-(hydroxy(1-methylpiperidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 11)

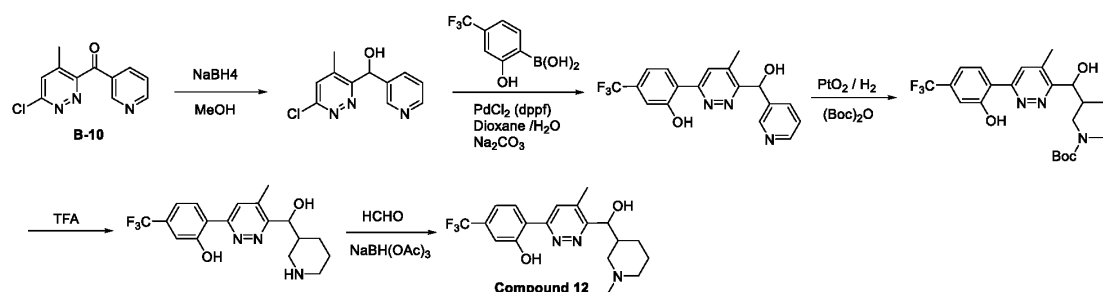


[00249] Step 1: To a solution of 2-(6-(hydroxy(pyridin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (**Compound 10**) (0.7 g, 1.0 eq) in MeOH (150 mL) and water (1 mL) was added PtO₂ (0.35g, 0.8 eq) and (Boc)₂O (0.47 g, 1.1 eq). The mixture was degassed with bubbling N₂ gas for 20 mins, then hydrogenated under H₂ (balloon) for 1.5h at rt. Then the H₂ balloon was removed and the mixture was stirred at rt for overnight. The catalyst was removed by filtration and the solvent was concentrated in vacuo. The residue was purified on a silica gel column to afford tert-butyl 3-(hydroxy(6-(2-hydroxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)methyl)piperidine-1-carboxylate (0.35 g).

[00250] Step 2: To a solution of tert-butyl 3-(hydroxy(6-(2-hydroxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)methyl)piperidine-1-carboxylate (300 mg) in DCM (5 mL) was added TFA (8 mL). The mixture was stirred at rt for 25min. The mixture was concentrated in vacuo. The residue was suspended in saturated NaHCO₃, and then extracted with DCM (5x20 mL). The combined extracts were concentrated in vacuo to afford 2-(6-(hydroxy(piperidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (180 mg) as a free base which was used without further purification.

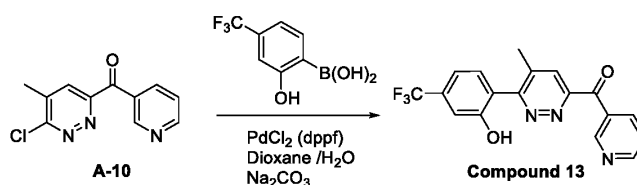
[00251] Step 3: To a solution of 2-(6-(hydroxy(piperidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (180 mg, 1.0 eq) in 1,2-dichloroethane (15 mL) was added HCHO (48 mg, 37% in water, 1.2 eq) and 2 drops of AcOH. The mixture was stirred at rt for 30min and NaBH(OAc)₃ (165 mg, 1.5eq) was added. The resulting mixture was stirred at rt for 30min, quenched with saturated NaHCO₃, and stirred at rt for 10mins. The mixture was extracted with DCM (4x25mL). The combined extracts were concentrated in vacuo. The residue was purified on a silica gel column to afford 2-(6-(hydroxy(1-methylpiperidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (**Compound 11**) (118 mg) as a white solid. ESI-MS (EI⁺, m/z): 382.2.

Example 12: Synthesis of 2-(6-(hydroxy(1-methylpiperidin-3-yl)methyl)-5-(trifluoromethyl)phenol (Compound 12)



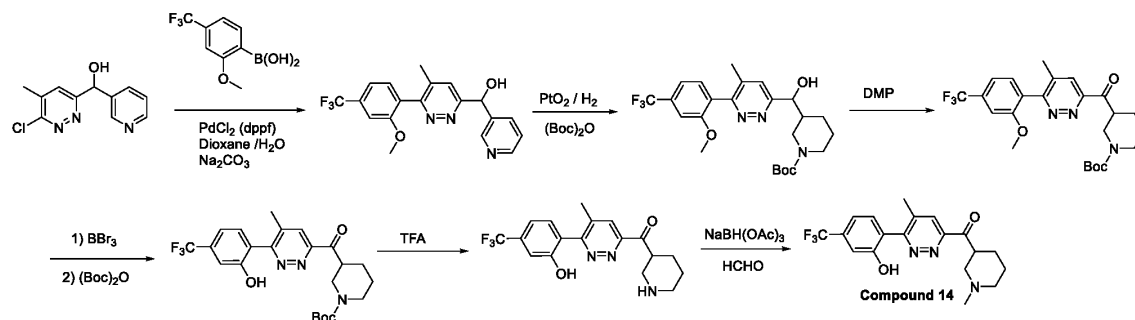
[00252] **Compound 12** was made by the procedure described in Example 11 starting with **B-10** from Example 10. ESI-MS (EI⁺, m/z): 382.3.

Example 13: Synthesis of (6-(2-hydroxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)(pyridin-3-yl)methanone (Compound 13)



[00253] (6-Chloro-5-methylpyridazin-3-yl)(pyridin-3-yl)methanone (30 mg, 1.0 eq), (2-hydroxy-4-(trifluoromethyl)phenyl)boronic acid (**A-10**) (35 mg, 1.3 eq), PdCl₂(dppf) (8 mg, 0.1eq), and Na₂CO₃ (28 mg, 2.0 eq) were combined in dioxane (5 mL) and water (2 mL). The resulting mixture was heated at 100°C for 8h. The reaction mixture was diluted with ethyl acetate (30 mL), washed with water, brine and concentrated in vacuo. The residue was purified on a silica gel column to afford (6-(2-hydroxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)(pyridin-3-yl)methanone (**Compound 13**) (26 mg). ESI-MS (EI⁺, m/z): 360.0.

Example 14: Synthesis of (6-(2-hydroxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)(1-methylpiperidin-3-yl)methanone (Compound 14)



[00254] Step 1: (6-Chloro-5-methylpyridazin-3-yl)(pyridin-3-yl)methanol (1.2 g, 1.0 eq), (2-methoxy-4-(trifluoromethyl)phenyl)boronic acid (1.45 g, 1.3 eq), PdCl₂(dppf) (325 mg, 0.1 eq), and Na₂CO₃ (1.2 g, 2.0 eq) were combined in dioxane (30 mL) and water (5 mL). The resulting mixture was heated at 100°C for 12 h. The reaction mixture was diluted with ethyl acetate (120 mL), washed with water, brine and concentrated in vacuo. The residue was purified on a silica gel column to afford (6-(2-methoxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)(pyridin-3-yl)methanol (1.18 g).

[00255] Step 2: To a solution of (6-(2-methoxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)(pyridin-3-yl)methanol (1.1 g, 1.0 eq) in MeOH (250 mL) and water (2 mL) was added PtO₂ (530 mg, 0.8 eq) and (Boc)₂O (720 mg, 1.1 eq). The mixture was degassed with bubbling N₂ gas for 20min, then hydrogenated under H₂ (balloon) for 1.5h at rt. Then the H₂ balloon was removed and the mixture was stirred at rt overnight. The catalyst was removed by filtration and solvent was concentrated in vacuo. The residue was purified on a silica gel column to afford tert-butyl 3-(hydroxy(6-(2-methoxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)methyl)piperidine-1-carboxylate (1.05 g).

[00256] Step 3: To a solution of tert-butyl 3-(hydroxy(6-(2-methoxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)methyl)piperidine-1-carboxylate (1 g, 1.0 eq) in dry DCM (30 mL) was added DMP (1.1 g, 1.2 eq) at 0°C. The reaction mixture was stirred at 0°C for 1h and then quenched with saturated NaHCO₃. The solvent was removed in vacuo and the residue was purified on a silica gel column to afford tert-butyl 3-(6-(2-methoxy-4-(trifluoromethyl)phenyl)-5-methylpyridazine-3-carbonyl)piperidine-1-carboxylate (890 mg).

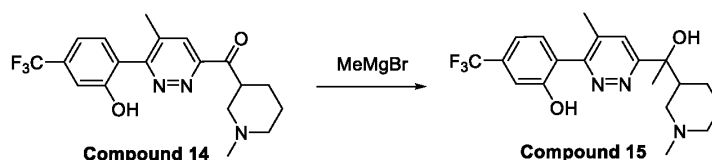
[00257] Step 4: To a solution of tert-butyl 3-(6-(2-methoxy-4-(trifluoromethyl)phenyl)-5-methylpyridazine-3-carbonyl)piperidine-1-carboxylate (890 mg, 1.0 eq) in dry DCM (30 mL) was added BBr₃ (5 eq) at 0°C under N₂. The mixture was stirred at 0°C for 1h, then rt 6 h. The reaction was quenched with water at 0°C, stirred at rt for 30min, then adjusted pH ~10 by adding

saturated NaHCO_3 and extracted with DCM (3x50 mL). To the DCM solution was added $(\text{Boc})_2\text{O}$ (425 mg, 1.0 eq) and the mixture was stirred at rt for 1h. The crude mixture was purified on a silica gel column to afford tert-butyl 3-(6-(2-hydroxy-4-(trifluoromethyl)phenyl)-5-methylpyridazine-3-carbonyl)piperidine-1-carboxylate (810 mg).

[00258] Step 5: tert-Butyl 3-(6-(2-hydroxy-4-(trifluoromethyl)phenyl)-5-methylpyridazine-3-carbonyl)piperidine-1-carboxylate (50 mg) in DCM (2 mL) was treated with TFA (1 mL). The mixture was stirred at rt for 30 mins and concentrated in vacuo to provide (6-(2-hydroxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)(piperidin-3-yl)methanone TFA salt (62 mg).

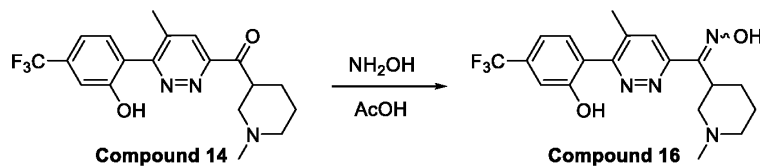
[00259] Step 6: Under reaction conditions described in Example 1, Step 5, from (6-(2-hydroxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)(piperidin-3-yl)methanone TFA salt (62 mg) yielded (6-(2-hydroxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)(1-methylpiperidin-3-yl)methanone (28 mg) (**Compound 14**). ESI-MS (EI^+ , m/z): 380.0.

Example 15: Synthesis of 2-(6-(1-hydroxy-1-(1-methylpiperidin-3-yl)ethyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 15)



[00260] A solution of (6-(2-hydroxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)(1-methylpiperidin-3-yl)methanone (**Compound 14**) (22 mg, 1.0 eq) in dry THF (2 mL) was treated with MeMgBr (2N, 0.12 mL, 4.0 eq) at 0°C . The mixture was stirred at rt for 1h, then quenched with saturated NH_4Cl and extracted with DCM (4x20 mL). The combined extracts were concentrated and the residue was purified on HPLC to afford 2-(6-(1-hydroxy-1-(1-methylpiperidin-3-yl)ethyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (9 mg) (**Compound 15**). ESI-MS (EI^+ , m/z): 396.2.

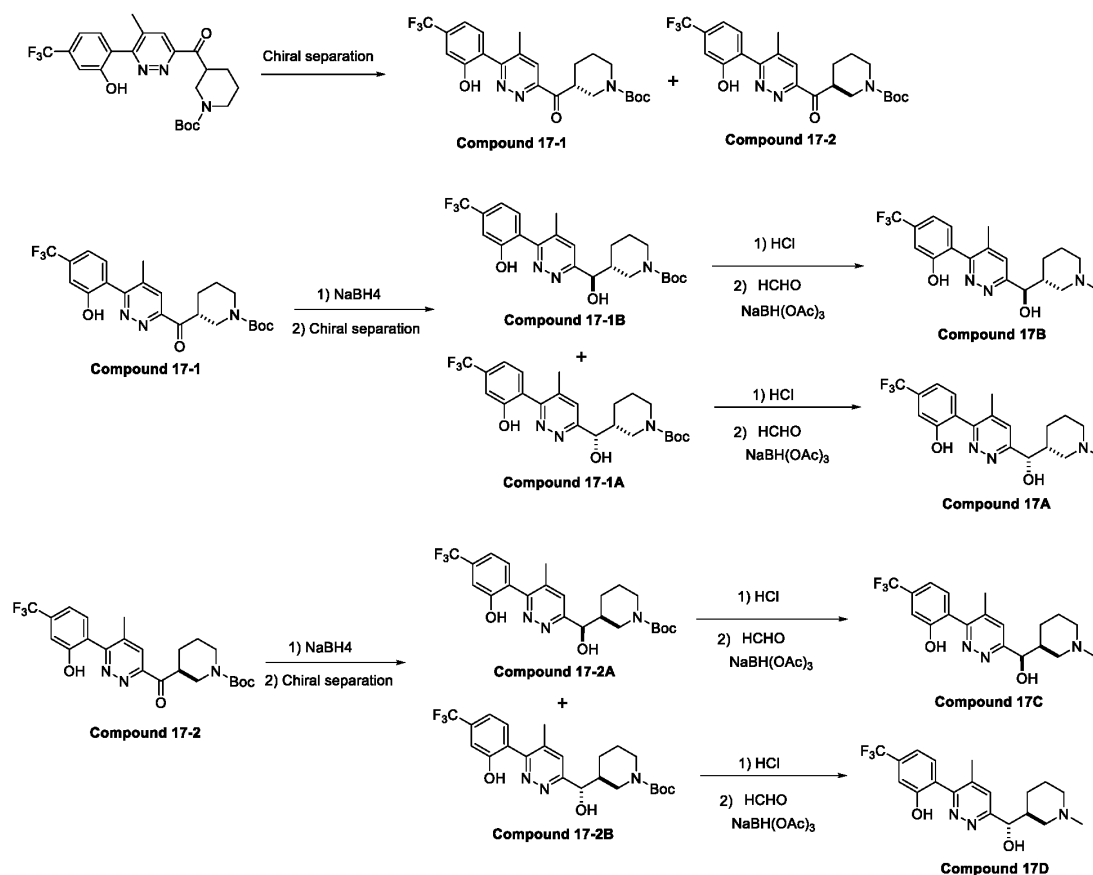
Example 16: Synthesis of (6-(2-hydroxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)(1-methylpiperidin-3-yl)methanone oxime (Compound 16)



[00261] To a solution of ZMG-3193 (6-(2-hydroxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)(1-methylpiperidin-3-yl)methanone (**Compound 14**) (20 mg, 1.0 eq) in anhydride EtOH (2mL) was added NH_2OH (1.2 eq) and 2 drops of AcOH. The resulting mixture was heated at 50°C for 5h and concentrated to dryness. The residue was purified on a silica gel

column to afford (6-(2-hydroxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)(1-methylpiperidin-3-yl)methanone oxime (7 mg) (**Compound 16**). ESI-MS (EI^+ , m/z): 395.1.

Example 17: Synthesis of 2-(6-((S)-hydroxy((R)-1-methylpiperidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 17A), 2-(6-((R)-hydroxy((R)-1-methylpiperidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 17B), 2-(6-((R)-hydroxy((S)-1-methylpiperidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 17C), 2-(6-((S)-hydroxy((S)-1-methylpiperidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 17D)



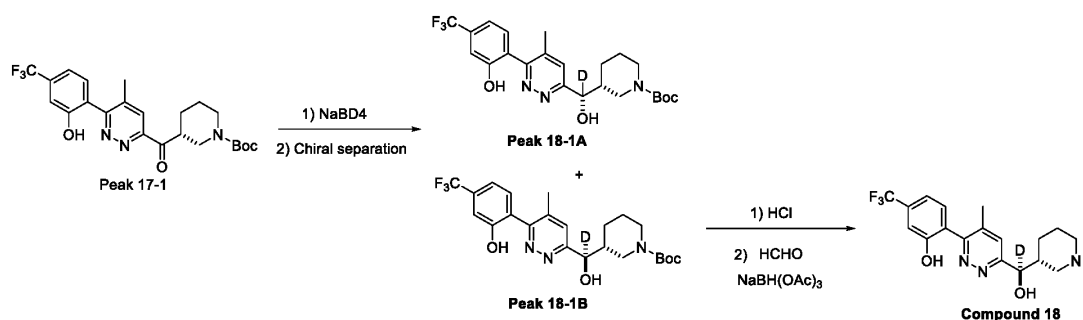
[00262] The product of Example 14, Step 4, 3-(6-(2-hydroxy-4-(trifluoromethyl)phenyl)-5-methylpyridazine-3-carbonyl)piperidine-1-carboxylate (250 mg) was subjected to SFC chiral separation to afford **Compound 17-1** (94 mg) and **Compound 17-2** (97 mg).

[00263] Under reaction conditions described in Example 1, Step 3, **Compound 17-1** (90 mg) yielded intermediate alcohol (90 mg) which was separated by chiral column to afford **Compound 17-1A** (36 mg) and **Compound 17-1B** (32 mg). **Compound 17-1A** (36 mg) was deprotected using the method described in Example 7, Step 4. To the resulting amine

intermediate HCl salt was carried out reductive amination using the method described in Example 1, Step 5, to afford **Compound 17A** (16.4 mg). ESI-MS (EI^+ , m/z): 382.1. The absolute stereochemistry of **Compound 17A** was confirmed by single crystal x-ray crystallography. Using the same chemistry, from **Compound 17-1B** yielded **Compound 17B** (13 mg). ESI-MS (EI^+ , m/z): 382.2.

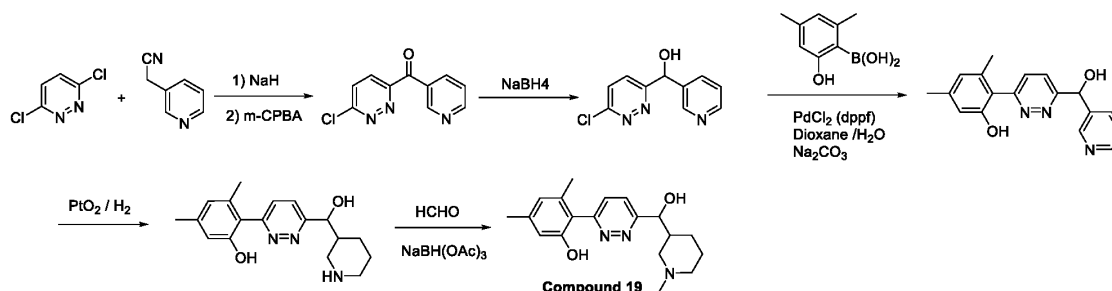
[00264] In a similar manner, **Compound 17-2** (95 mg) was reduced and subjected to SFC chiral separation to afford **Compound 17-2A** (38 mg) and **Compound 17-2B** (35 mg). Deprotection and reductive amination of **Compound 17-2A** (38 mg) and **Compound 17-2B** (35 mg) yielded **Compound 17C** (16 mg) and **Compound 17D** (13 mg) respectively. **Compound 17C**: ESI-MS (EI^+ , m/z): 382.2. **Compound 17D**: ESI-MS (EI^+ , m/z): 382.2.

Example 18: Synthesis of 2-(6-((S)-hydroxy((R)-1-methylpiperidin-3-yl)methyl-d)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 18)



[00265] Under reaction conditions described in Example 1, Step 3, and substituting d₄-MeOD and NaBD₄, from **Peak 17-1** (120 mg) in d₄-MeOD (2 mL) was added NaBD₄ (0.5 eq) at 0°C to provide intermediate alcohol (119 mg) which was separated by chiral column to afford peak 18-1A (65 mg) and peak 18-1B (40 mg). Intermediate peak 18-1B (40 mg) was treated with 4N HCl to yield amine intermediate which was carried out reductive amination with HCHO (1.2 eq) in present of NaBH(OAc)₃ (1.5 eq) to afford 2-(6-((S)-hydroxy((R)-1-methylpiperidin-3-yl)methyl-d)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (28 mg) (**Compound 18**). ESI-MS (EI^+ , m/z): 383.2.

Example 19: Synthesis of 2-(6-(hydroxy(1-methylpiperidin-3-yl)methyl)pyridazin-3-yl)-3,5-dimethylphenol (Compound 19)



[00266] Step 1: To a degassed solution of 3,6-dicholopyridazine (3 g, 20 mmol), pyridine-3-yl-acetonitrile (2.5 g, 21 mmol) in DMF (30 mL) was added NaH (1.68 g, 42 mmol, 60%) in portion under N₂ at 0 °C. The mixture was stirred at 0°C for 1h. mCPBA (4.8 g, 20 mmol, 72%) was added in portion and the mixture was diluted with EtOAc (200 mL). The mixture was washed with water, aqueous NaHCO₃ and brine, dried over Na₂SO₄, filtered and concentrated. The residue was triturated with hexane/EtOAc to give (6-chloropyridazin-3-yl)(pyridin-3-yl)methanone (2.3 g).

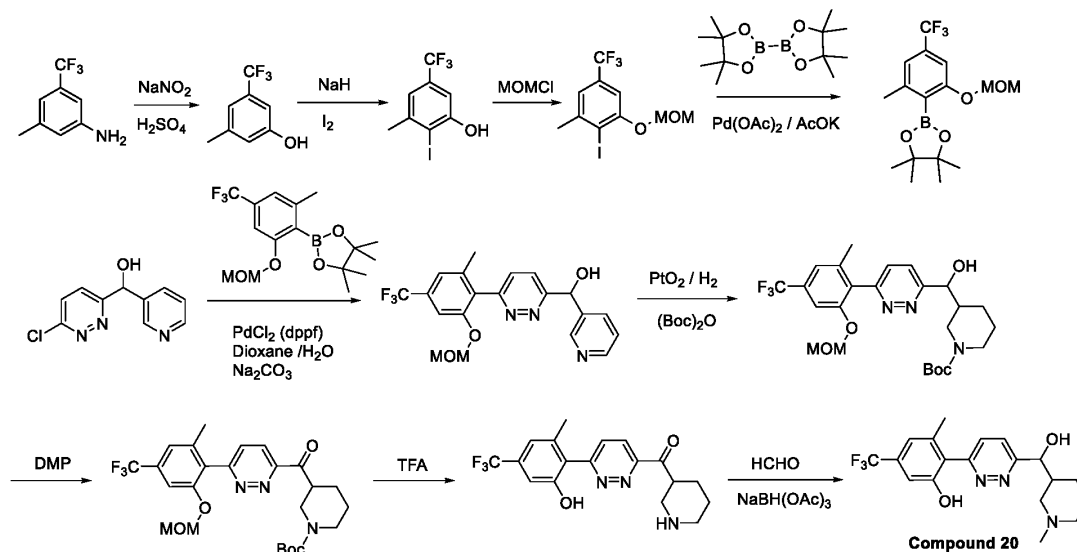
[00267] Step 2: Under reaction conditions described in Example 10, Step 2, from (6-chloropyridazin-3-yl)(pyridin-3-yl)methanone (1.0 g) yielded (6-chloropyridazin-3-yl)(pyridin-3-yl)methanol (1.0 g).

[00268] Step 3: (6-Chloropyridazin-3-yl)(pyridin-3-yl)methanol (600 mg, 1.0 eq), (2-hydroxy-4,6-dimethylphenyl)boronic acid (585 mg, 1.3 eq), PdCl₂(dppf) (160 mg, 10%) and Na₂CO₃ (600 mg, 2.0 eq) were combined in dioxane (30 mL) and water (5 mL). The resulting mixture was heated at 100°C for 8h. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water, brine and concentrated in vacuo. The residue was purified on a silica gel column to afford 2-(6-(hydroxy(pyridin-3-yl)methyl)pyridazin-3-yl)-3,5-dimethylphenol (625 mg).

[00269] Step 4: Under reaction conditions described in Example 1, Step 4, from 2-(6-(hydroxy(pyridin-3-yl)methyl)pyridazin-3-yl)-3,5-dimethylphenol (100 mg) yielded 2-(6-(hydroxy(piperidin-3-yl)methyl)pyridazin-3-yl)-3,5-dimethylphenol (120 mg) used without further purification.

[00270] Step 5: Under reaction conditions described in Example 1, Step 5, 2-(6-(hydroxy(piperidin-3-yl)methyl)pyridazin-3-yl)-3,5-dimethylphenol (120 mg, 1.0 eq) yielded 2-(6-(hydroxy(1-methylpiperidin-3-yl)methyl)pyridazin-3-yl)-3,5-dimethylphenol (35 mg) (**Compound 19**). ESI-MS (EI⁺, m/z): 328.1.

Example 20: Synthesis of 2-(6-(hydroxy(1-methylpiperidin-3-yl)methyl)pyridazin-3-yl)-3-methyl-5-(trifluoromethyl)phenol (Compound 20)



[00271] Step 1: 3-Methyl-5-(trifluoromethyl)aniline (2.63 g, 15 mmol) was added to a solution of conc. H₂SO₄ (30 mL) in water (150 mL) and the mixture was cooled to 0°C. NaNO₂ (1.1 g, 16 mmol) in water (10 mL) was added dropwise to the mixture and the reaction was stirred at 0°C for 1h. Conc. H₂SO₄ (30 mL) was added and the mixture was heated to 90°C for 5 h. The mixture was cooled to rt and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography to give 3-methyl-5-(trifluoromethyl)phenol (2.2 g).

[00272] Step 2: To a solution of 3-methyl-5-(trifluoromethyl)phenol (2.1 g, 12 mmol) in toluene (60 mL) was added NaH (0.96 g, 24 mmol, 60%) at 0°C. The suspension was stirred at 0°C for 30 min. Iodine (12 mmol) was slowly added in portions and the mixture was stirred for 3h at 0°C. The mixture was diluted with water (50 mL) and acidified to pH 5 with 2N HCl. The organic phase was separated and the aqueous was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography to give 2-iodo-3-methyl-5-(trifluoromethyl)phenol (2.7 g).

[00273] Step 3: (Chloromethoxy)methane (0.8 g, 10 mmol) was added dropwise to a suspension of 2-iodo-3-methyl-5-(trifluoromethyl)phenol (2.4 g, 8 mmol) and Cs₂CO₃ (3.26 g, 10 mmol) in DMF (10 mL) at 0°C. The reaction mixture was warmed to rt over 2h and diluted with EtOAc (50 mL). The mixture was washed with water and brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography to give 2-iodo-1-(methoxymethoxy)-3-methyl-5-(trifluoromethyl)benzene (2.3 g).

[00274] Step 4: A mixture of 2-iodo-1-(methoxymethoxy)-3-methyl-5-(trifluoromethyl)benzene (1.02 g, 3 mmol), bis(pinacolato)diborane (0.9 g, 3.6 mmol), Pd(OAc)₂ (67 mg, 0.3 mmol), and KOAc (0.6 g, 6 mmol) in anhydrous DMF (10 mL) was stirred at 100°C for 10h. The mixture was diluted with EtOAc, washed with water (3 times), brine, and dried over Na₂SO₄. The solvent was evaporated and the residue was purified by flash chromatography to afford 2-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (605 mg).

[00275] Step 5: (6-Chloropyridazin-3-yl)(pyridin-3-yl)methanol (120 mg, 1.0 eq), 2-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.3 eq), PdCl₂(dppf) (0.1 eq) and Na₂CO₃ (2.0 eq) were combined in dioxane (10 mL) and water (2 mL). The resulting mixture was heated at 100°C for 12h. The reaction mixture was diluted with ethyl acetate (50 mL), washed with water, brine and concentrated in vacuo. The residue was purified on a silica gel column to afford (6-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)pyridazin-3-yl)(pyridin-3-yl)methanol (115 mg).

[00276] Step 6: To a solution of (6-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)pyridazin-3-yl)(pyridin-3-yl)methanol (110 mg, 1.0 eq) in MeOH (100 mL) and water (1 mL) was added PtO₂ (0.8 eq) and (Boc)₂O (1.1 eq). The mixture was degassed with bubbling N₂ gas for 20min, then hydrogenated under H₂ (balloon) for 1.5h at rt. Then the H₂ balloon was removed and the mixture was stirred at rt overnight. The catalyst was removed by filtration and solvent was concentrated in vacuo. The residue was purified on a silica gel column to afford tert-butyl 3-(hydroxy(6-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)pyridazin-3-yl)methyl)piperidine-1-carboxylate (92 mg).

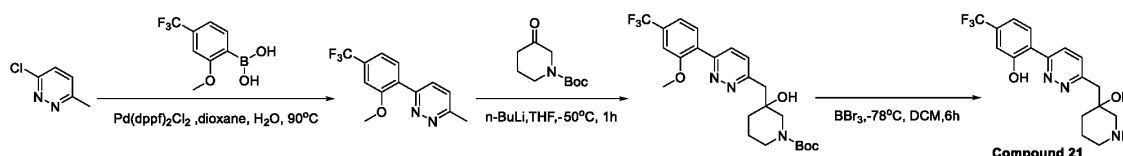
[00277] Step 7: To a solution of tert-butyl 3-(hydroxy(6-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)pyridazin-3-yl)methyl)piperidine-1-carboxylate (90 mg, 1.0 eq) in dry DCM was added DMP (1.2 eq) at 0°C. The reaction mixture was stirred at 0°C for 1h and then quenched with saturated NaHCO₃. The solvent was concentrated in vacuo and the residue was purified on a silica gel column to afford tert-butyl 3-(6-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)pyridazine-3-carbonyl)piperidine-1-carboxylate (62 mg).

[00278] Step 8: To a solution of tert-butyl 3-(6-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)pyridazine-3-carbonyl)piperidine-1-carboxylate (58 mg, 1.0 eq) in dry DCM (1 mL) was added TFA (1 mL) at 0°C under N₂. The mixture was stirred at 0°C for 1h and then at rt overnight. The reaction was concentrated in vacuo. The residue was suspended in water and adjusted pH ~10 by adding saturated NaHCO₃ and then extracted with DCM (3x50 mL). The combined organic layers were concentrated and the residue was purified on a silica gel

column to afford (6-(2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl)pyridazin-3-yl)(piperidin-3-yl)methanone (28 mg).

[00279] Step 9: Under reaction conditions described in Example 1, Step 5, from (6-(2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl)pyridazin-3-yl)(piperidin-3-yl)methanone (18 mg) yielded 2-(6-(hydroxy(1-methylpiperidin-3-yl)methyl)pyridazin-3-yl)-3-methyl-5-(trifluoromethyl)phenol (**Compound 20**) (11 mg). ESI-MS (EI^+ , m/z): 382.3.

Example 21: Synthesis of 3-((6-(2-hydroxy-4-(trifluoromethyl)phenyl)pyridazin-3-yl)methyl)piperidin-3-ol (Compound 21)



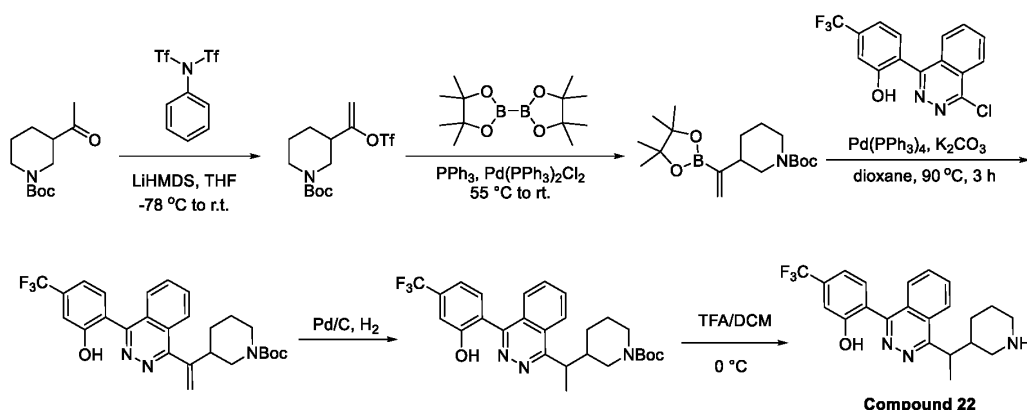
[00280] Step 1: A solution of 3-chloro-6-methylpyridazine (1.0 g, 7.81 mmol), (2-methoxy-4-(trifluoromethyl)phenyl)boronic acid (2.05 g, 9.37 mmol), Pd(dppf)Cl_2 (570 mg, 0.78 mmol) and Na_2CO_3 (1.65 g, 15.62 mmol) in dioxane (32 mL) and H_2O (8 mL) was stirred at 90°C under N_2 atmosphere. The mixture was quenched with brine (100 mL) and then extracted with ethyl acetate (3x100 mL). The combined organic layers were washed with water (3x100 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 3-(2-methoxy-4-(trifluoromethyl)phenyl)-6-methylpyridazine (1.91 g, 91%).

[00281] Step 2: To a solution 3-(2-methoxy-4-(trifluoromethyl)phenyl)-6-methylpyridazine (1.0 g, 3.73 mmol) in anhydrous THF (25 mL) was added $n\text{-BuLi}$ (2.2 mL, 5.59 mmol) dropwise at -50°C . The reaction mixture was stirred at -50°C for 30 min, and then tert-butyl 3-oxopiperidine-1-carboxylate (1.48 g, 7.46 mmol) in anhydrous THF (15 mL) was added dropwise at -50°C . The mixture was warmed to room temperature gradually. After 1h, the mixture was quenched with NH_4Cl (aq) (100 mL), and then extracted with ethyl acetate (3x100 mL). The combined organic layers were washed with brine (100 mL) and dried over Na_2SO_4 , concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford tert-butyl 3-hydroxy-3-((6-(2-methoxy-4-(trifluoromethyl)phenyl)pyridazin-3-yl)methyl)piperidine-1-carboxylate (1.32 g, 76%).

[00282] Step 3: A solution of tert-butyl 3-hydroxy-3-((6-(2-methoxy-4-(trifluoromethyl)phenyl)pyridazin-3-yl)methyl)piperidine-1-carboxylate (200 mg, 0.43 mmol) in anhydrous DCM (25 mL) was cooled to -78°C . BBr_3 (1.2 mL, 1.28 mmol) was added dropwise. The mixture was warmed to room temperature gradually and then stirred at room temperature for 6h. The mixture was quenched with NaHCO_3 (aq) (100 mL), and then extracted with DCM

(3x50 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford 3-(((6-(2-hydroxy-4-(trifluoromethyl)phenyl)pyridazin-3-yl)methyl)piperidin-3-yl)methylpiperidin-3-ol (**Compound 21**) (13 mg, 9%). ESI-MS(EI⁺, m/z): 354.2.

Example 22: Synthesis of 2-(4-(1-(piperidin-3-yl)ethyl)phthalazin-1-yl)-5-(trifluoromethyl)phenol (Compound 22)



[00283] Step 1: LiHMDS (1.0 M in THF) (21.8 mL, 21.8 mmol) was added to THF (50 mL) at -78°C under nitrogen. A solution of 1-(tetrahydro-2H-pyran-4-yl)ethanone (4.5 g, 19.8 mmol) in THF (10 mL) was added and the mixture was stirred at -78°C under nitrogen for 1.5h. A solution of N-(5-chloropyridin-2-yl)-1,1,1-trifluoro-N-(((trifluoromethyl)sulfonyl)methanesulfonyl)methanesulfonamide (7.78 g, 21.8 mmol) in THF (10 mL) was added over 20 minutes. The mixture was allowed to warm slowly to room temperature and stirred overnight. The reaction was quenched with NaHCO₃ and the crude product extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel column chromatography to afford tert-butyl 3-(1-(((trifluoromethyl)sulfonyl)oxy)vinyl)piperidine-1-carboxylate (6.17 g, 87%).

[00284] Step 2: To a solution of tert-butyl 3-(1-(((trifluoromethyl)sulfonyl)oxy)vinyl)piperidine-1-carboxylate (6.17 g, 17.2 mmol) in toluene (50 mL) was added bis(pinacolato)diboron (6.32 g, 25.8 mmol) followed by triphenyl phosphine (451.1 mg, 1.72 mmol), potassium phenoxide (3.4 g, 25.8 mmol) and dichlorobis(triphenylphosphine)palladium (II) (1.21 g, 1.72 mmol). The resulting mixture was allowed stirred at 55°C for 3h. The resulting mixture was cooled to room temperature and stirred overnight. The resulting mixture was diluted with saturated aqueous NaHCO₃ solution and EtOAc. The layers were separated and the organic layer was washed with brine, dried over Na₂SO₄, filtered and evaporated to dryness. The residue was purified by silica gel column

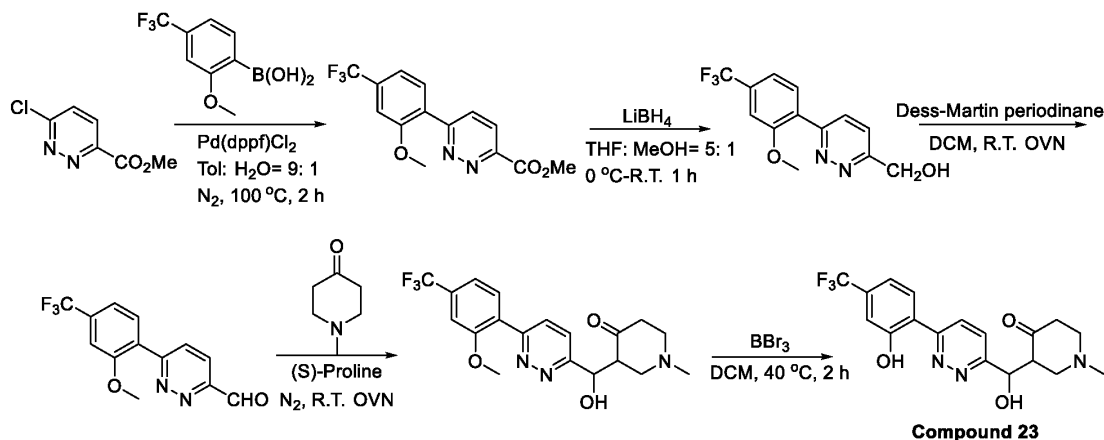
chromatography to afford tert-butyl 3-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)piperidine-1-carboxylate (1.81 g, 31%).

[00285] Step 3: To a solution of tert-butyl 3-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)piperidine-1-carboxylate (1.1 g, 3.3 mmol) in 1,4-dioxane (32 mL) and H₂O (8 mL) was added 2-(4-chlorophthalazin-1-yl)-5-(trifluoromethyl)phenol (1.0 g, 3.0 mmol), Pd(PPh₃)₄ (346.5 mg, 0.3 mmol) and K₂CO₃ (829.2 mg, 6.0 mmol). The reaction mixture was stirred at 90°C under nitrogen atmosphere for 3h. The reaction mixture was extracted with EtOAc. The organic solution was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford tert-butyl 3-(1-(4-(2-hydroxy-4-(trifluoromethyl)phenyl)phthalazin-1-yl)vinyl)piperidine-1-carboxylate (392 mg, 26%).

[00286] Step 4: To a solution of tert-butyl 3-(1-(4-(2-hydroxy-4-(trifluoromethyl)phenyl)phthalazin-1-yl)vinyl)piperidine-1-carboxylate (145 mg, 0.29 mmol) in EtOAc (5 mL) was added Pd/C (100 mg). The reaction mixture was stirred at room temperature under hydrogen atmosphere for 1h. The reaction mixture was filtered, and washed with MeOH. The residue was concentrated under vacuum. The residue was purified by silica gel column chromatography to afford tert-butyl 3-(1-(4-(2-hydroxy-4-(trifluoromethyl)phenyl)phthalazin-1-yl)ethyl)piperidine-1-carboxylate (72.4 mg, 48%).

[00287] Step 5: A solution of tert-butyl 3-(1-(4-(2-hydroxy-4-(trifluoromethyl)phenyl)phthalazin-1-yl)ethyl)piperidine-1-carboxylate (72.4 mg, 0.14 mmol) in DCM (8 mL) was cooled to 0 °C. TFA (1 mL) was slowly added dropwise and the reaction mixture was stirred at room temperature for 1h. The reaction mixture was concentrated in vacuo and the residue was purified by prep-HPLC to afford 2-(4-(1-(piperidin-3-yl)ethyl)phthalazin-1-yl)-5-(trifluoromethyl)phenol (**Compound 22**) (9.5 mg, 14%). ESI-MS(EI⁺, m/z): 402.3.

Example 23: Synthesis of 3-(hydroxy(6-(2-hydroxy-4-(trifluoromethyl)phenyl)pyridazin-3-yl)methyl)-1-methylpiperidin-4-one (Compound 23)



[00288] Step 1: To a solution of methyl 6-chloropyridazine-3-carboxylate (30.0 g, 174 mmol) in toluene (450 mL) and H₂O (50 mL) was added (2-methoxy-4-(trifluoromethyl)phenyl)boronic acid (42.0 g, 191 mmol), Pd(dppf)Cl₂ (10.0 g, 17.4 mmol), and K₃PO₄ (73.9 g, 348 mmol). The resulting mixture was stirred at 100°C for 2h. The reaction solution was diluted with water, extracted with EtOAc, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography to afford methyl 6-(2-methoxy-4-(trifluoromethyl)phenyl)pyridazine-3-carboxylate (31.0 g, 57%) as a yellow solid.

[00289] Step 2: To a solution of methyl 6-(2-methoxy-4-(trifluoromethyl)phenyl)pyridazine-3-carboxylate (25.0 g, 80.1 mmol) in THF (400 mL) and MeOH (80 mL) was added LiBH₄ (60 mL, 2M in THF, 1.5 eq.) slowly at 0°C. The resulting mixture was stirred at room temperature under N₂ for 1h. The reaction solution was quenched with water, extracted with EtOAc, dried over Na₂SO₄, filtered and concentrated in vacuo to afford (6-(2-methoxy-4-(trifluoromethyl)phenyl)pyridazin-3-yl)methanol (20.0 g, 88%) as a white solid.

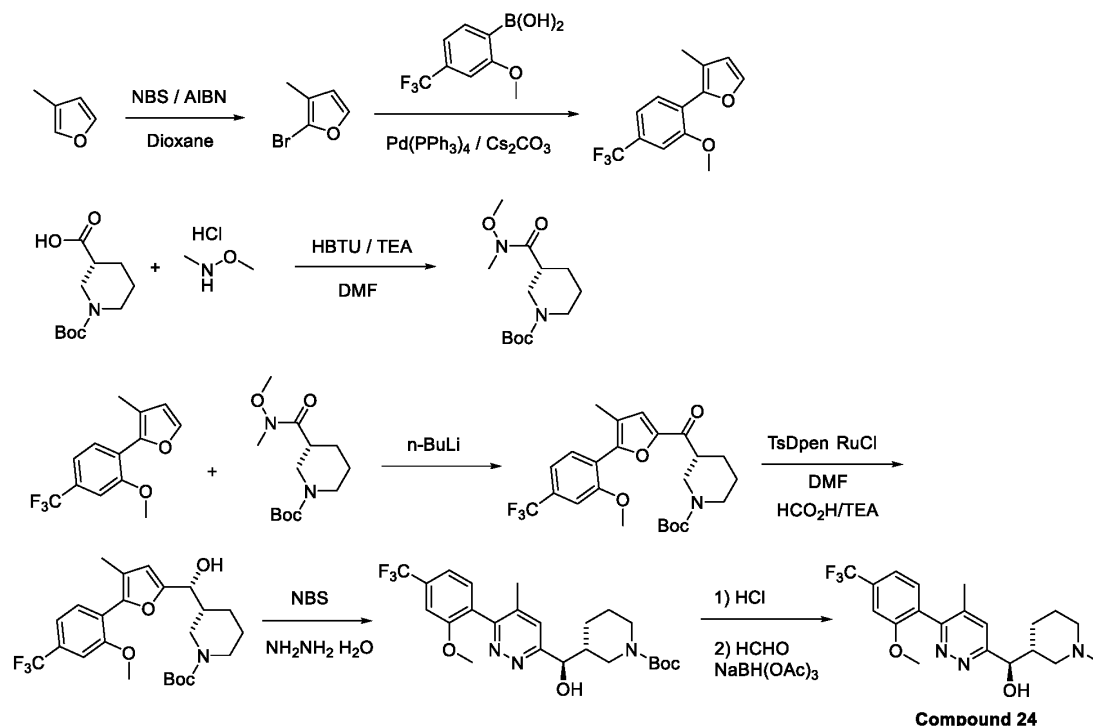
[00290] Step 3: To a solution of (6-(2-methoxy-4-(trifluoromethyl)phenyl)pyridazin-3-yl)methanol (19.0 mg, 66.9 mmol) in DCM (500 mL) was added Dess-Martin periodinane (42.4 g, 100 mmol) slowly at 0°C. The resulting mixture was stirred at room temperature for 16h. The reaction solution was quenched with water, extracted with DCM, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography to afford 6-(2-methoxy-4-(trifluoromethyl)phenyl)pyridazine-3-carbaldehyde (7.0 g, 37%) as a yellow solid.

[00291] Step 4: To a solution of 6-(2-methoxy-4-(trifluoromethyl)phenyl)pyridazine-3-carbaldehyde (500 mg, 1.7 mmol) in 1-methylpiperidin-4-one (960 mg, 8.5 mmol) was added (S)-proline (20 mg, 0.17 mmol). The resulting mixture was stirred at room temperature under N₂

for 16 h. The reaction solution was diluted with DCM and concentrated in vacuo. The residue was purified by silica gel column chromatography to afford 3-(hydroxy(6-(2-methoxy-4-(trifluoromethyl)phenyl)pyridazin-3-yl)methyl)-1-methylpiperidin-4-one (450 mg, 67%) as a white solid.

[00292] Step 5: To a solution of 3-(hydroxy(6-(2-methoxy-4-(trifluoromethyl)phenyl)pyridazin-3-yl)methyl)-1-methylpiperidin-4-one (30 mg, 0.08 mmol) in DCM (0.5 mL) was added dropwise BBr_3 (0.5 mL) at 0°C under N_2 . The resulting mixture was stirred at 40°C for 2h. The reaction solution was diluted with MeOH and concentrated in vacuo. The residue was purified by prep-HPLC to afford 3-(hydroxy(6-(2-hydroxy-4-(trifluoromethyl)phenyl)pyridazin-3-yl)methyl)-1-methylpiperidin-4-one (**Compound 23**) (7.5 mg, 26%, anti: syn = 2: 1) as a brown solid. ESI-MS (EI^+ , m/z): 382.15.

Example 24: Synthesis of (R)-(6-(2-methoxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)((R)-1-methylpiperidin-3-yl)methanol (Compound 24)



[00293] Step 1: 3-Methylfuran (1.0 g, 1.0 eq), NBS (2.3 g, 1.05 eq) and AIBN (0.16 g, 0.08 eq) were combined in de-gassed anhydrous dioxane (25 mL) under N_2 in a sealed tube and heated at 50°C for 2h to afford 2-bromo-3-methylfuran solution in dioxane which was used directly in the next step.

[00294] Step 2: To a solution of 2-bromo-3-methylfuran was added (2-methoxy-4-(trifluoromethyl)phenyl)boronic acid (3.0 g, 1.12 eq), Cs_2CO_3 (10 g, 2.5 eq), $\text{Pd}(\text{PPh}_3)_4$ (0.7 g,

0.05 eq) and de-gassed DI water (25 mL). The resulting mixture was heated at 110 °C for 8h. The reaction mixture was cooled to rt and diluted with hexane (120 mL). The organic phase was separated and aqueous phase was re-extracted with hexane (30 mL). The combined organic phase was washed with water (50 mL), brine (50 mL) and concentrated in vacuo. The residue was purified on a silica gel column to provide 2-(2-methoxy-4-(trifluoromethyl)phenyl)-3-methylfuran (1.9 g, 61%) as an oil.

[00295] Step 3: To a solution of (R)-1-(tert-butoxycarbonyl)piperidine-3-carboxylic acid (5.0 g, 1.0 eq) in DMF (20 mL) at 0 °C was added HBTU (10.33 g, 1.25 eq), N,O-dimethylhydroxylamine hydrochloride (2.6 g, 1.2 eq) and triethylamine (9 mL, 3.0 eq). The resulting mixture was stirred at 0°C for 1h and then at rt for 5 h. The reaction mixture was diluted with acetate (80 mL) and hexane (80 mL), washed with sat. aqueous NaHCO₃ (50 mL), water (3x50 mL), HCl (0.5 N, 50 mL) and brine (50 mL). The organic phase was dried over Na₂SO₄ and concentrated in vacuo to afford tert-butyl (R)-3-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (5.4 g, 91%) as an oil.

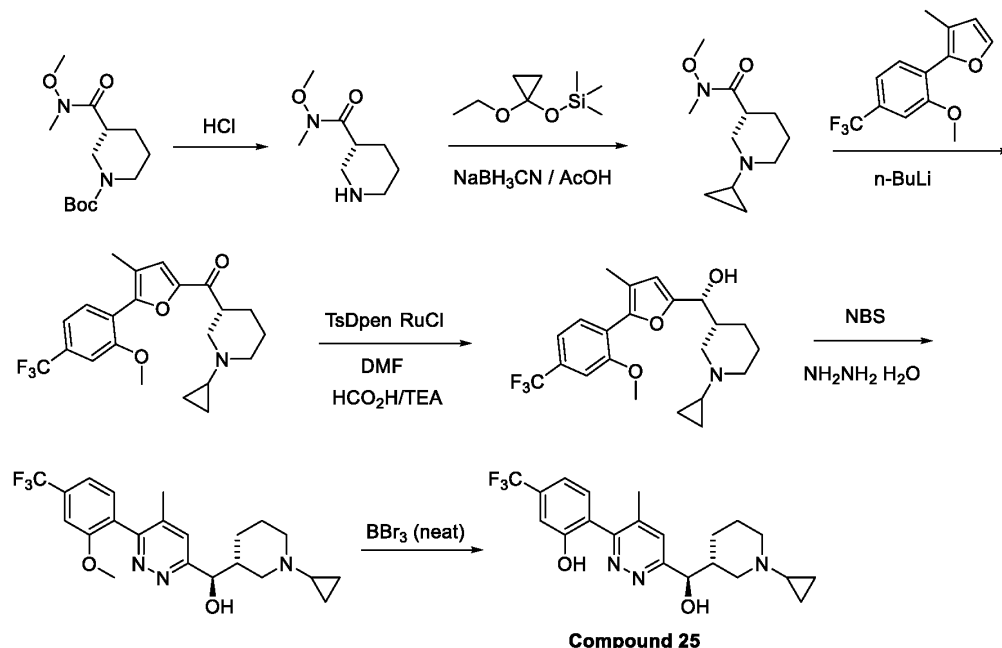
[00296] Step 4: To a solution of 2-(2-methoxy-4-(trifluoromethyl)phenyl)-3-methylfuran (500 mg, 1.0 eq) in anhydrous THF (25 mL) under N₂ at -30 °C was added n-BuLi (2.5M, 1.25 mL, 1.6 eq.) dropwise over 5min. After stirring at -30 °C for additional 45min, a solution of tert-butyl (R)-3-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (850 mg, 1.6 eq) in THF (4 mL) was added dropwise over 2min at -30 °C. The resulting mixture was stirred at -30 °C for 30min and then at rt for 2h. The reaction was quenched with saturated NH₄Cl (30 mL) at 0 °C, then extracted with DCM (2x50 mL). The combined organic phase was washed with brine and concentrated in vacuo. The crude mixture was purified on silica gel column to afford tert-butyl (R)-3-(5-(2-methoxy-4-(trifluoromethyl)phenyl)-4-methylfuran-2-carbonyl)piperidine-1-carboxylate (749 mg, 82%, 100% ee).

[00297] Step 5: To a solution of tert-butyl (R)-3-(5-(2-methoxy-4-(trifluoromethyl)phenyl)-4-methylfuran-2-carbonyl)piperidine-1-carboxylate (150 mg, 1.0 eq) in DMF (0.3 mL) at 0 °C was added formic acid (150 mg, 10 eq.) and TEA (330 mg, 10 eq.) dropwise. The mixture was de-gassed by bubbling N₂ gas for 2 min at room temperature and then added catalyst chlororuthenium(1+);[(1R,2R)-1,2-diphenyl-2-(3-phenylpropylamino)ethyl]-(4-methylphenyl)sulfonylzanide (6 mg, 0.03 eq). The resulting mixture was stirred at rt for 15h. The mixture was diluted with DCM (25 mL), washed with water, sat. NaHCO₃ and brine. The crude mixture was purified on silica gel column to afford tert-butyl (R)-3-((R)-hydroxy(5-(2-methoxy-4-(trifluoromethyl)phenyl)-4-methylfuran-2-yl)methyl)piperidine-1-carboxylate (138 mg, 92%, ~90% de).

[00298] Step 6: A solution of tert-butyl (R)-3-((R)-hydroxy(5-(2-methoxy-4-(trifluoromethyl)phenyl)-4-methylfuran-2-yl)methyl)piperidine-1-carboxylate (80 mg, 1.0 eq) in THF (5 mL) and water (0.5 mL) was stirred at -15 °C (acetone-ice bath) for 10min. Solid NBS (40 mg, 1.3 eq) was added in portions. After stirring for 30min at -15 °C, hydrazine hydrate (86 mg, 10 eq) was added dropwise. The resulting mixture was stirred at 0 °C for 1h, and then at rt for 3h. The reaction was quenched with sat. aq. NaHCO₃ (10 mL) and extracted with DCM (2x15 mL). The combined organic phase was washed with brine and concentrated in vacuo. The crude mixture was purified on silica gel to give tert-butyl (R)-3-((R)-hydroxy(6-(2-methoxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)methyl)piperidine-1-carboxylate (75 mg, 92%).

[00299] Step 7: To a solution of tert-butyl (R)-3-((R)-hydroxy(6-(2-methoxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)methyl)piperidine-1-carboxylate (46 mg) in DCM (1 mL) was added HCl (4N in dioxane, 1 mL). The mixture was stirred at rt for 20min under N₂. The solvent was removed in vacuo to afford intermediate HCl salt which was dissolved in MeOH (0.5 mL) and 1,2-dichloroethane (5 mL). To the mixture was added triethylamine (11 mg, 1.1 eq) to neutralize HCl salt. HCHO (37% in water, 12 mg, 1.5 eq) was added to the reaction mixture, followed by acetic acid (~5 mg). The mixture was stirred at rt for 15min, followed by addition of NaBH(OAc)₃ (50 mg, 2.5 eq). The reaction was quenched with saturated NaHCO₃ (10 mL). The reaction mixture was extracted with mix-solvent (5% IPA in DCM) (2 x 20 mL). The crude product was purified on a silica gel column to provide (R)-((6-(2-methoxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)((R)-1-methylpiperidin-3-yl)methanol (**Compound 24**) (35 mg, 93%). ESI-MS (EI⁺, m/z): 396.1.

Example 25: Synthesis of 2-(6-((R)-((R)-1-cyclopropylpiperidin-3-yl)(hydroxy)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 25)



[00300] Step 1: tert-Butyl (R)-3-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (1.0 g) in DCM (5 mL) was treated with HCl (4N in dioxane, 5 mL). The mixture was stirred at rt for 1h. The solvent was removed in vacuo to afford (R)-N-methoxy-N-methylpiperidine-3-carboxamide HCl salt (760 mg).

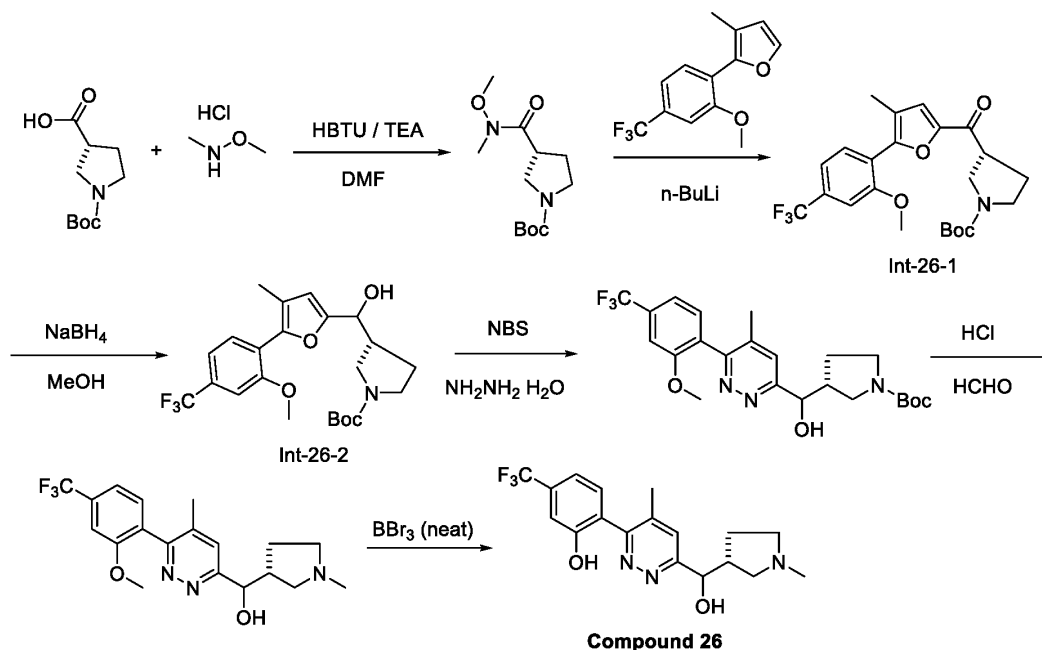
[00301] Step 2: (R)-N-Methoxy-N-methylpiperidine-3-carboxamide HCl salt was dissolved in anhydrous MeOH (4 mL) and anhydrous THF (20 mL). To the solution was added DIEA (520 mg, 1.0 eq), 4A molecular sieves (1.0 g), (1-ethoxycyclopropoxy)trimethylsilane (2.0 g, 3.0 eq), NaBH₃CN (700 mg, 3.0 eq) and AcOH (3.3 g, 15 eq) at room temperature. The resulting mixture was heated at 65 °C for 20h under N₂. The reaction was filtered through a celite pad and quenched with sat. aq. NaHCO₃ and extracted with DCM (2 X 60mL). The combined organic phase was washed with brine. The crude mixture was purified on a silica gel column to afford (R)-1-cyclopropyl-N-methoxy-N-methylpiperidine-3-carboxamide (410 mg, 52%).

[00302] Steps 3-5: (R)-((R)-1-cyclopropylpiperidin-3-yl)(6-(2-methoxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)methanol was prepared in three steps from (R)-1-cyclopropyl-N-methoxy-N-methylpiperidine-3-carboxamide as described in Example 24, steps 4-6.

[00303] Step 6: To a solution of (R)-((R)-1-cyclopropylpiperidin-3-yl)(6-(2-methoxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)methanol (50 mg, 1.0 eq) in dry DCM (2 mL) at 0°C was added BBr₃ (600 mg, 20 eq) dropwise. The mixture was stirred at 0°C for 1h, and

then at rt for an additional 1h. The reaction was quenched with sat. aq. NaHCO_3 at 0°C . The reaction mixture was extracted with mixture-solvent 5% IPA in DCM (3x15mL). The crude mixture was purified on a silica gel column to afford 2-(6-((R)-((R)-1-cyclopropylpiperidin-3-yl)(hydroxy)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (**Compound 25**) (40 mg, 84%). ESI-MS (EI^+ , m/z): 408.2.

Example 26: Synthesis of 2-(6-(hydroxy((R)-1-methylpyrrolidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 26)



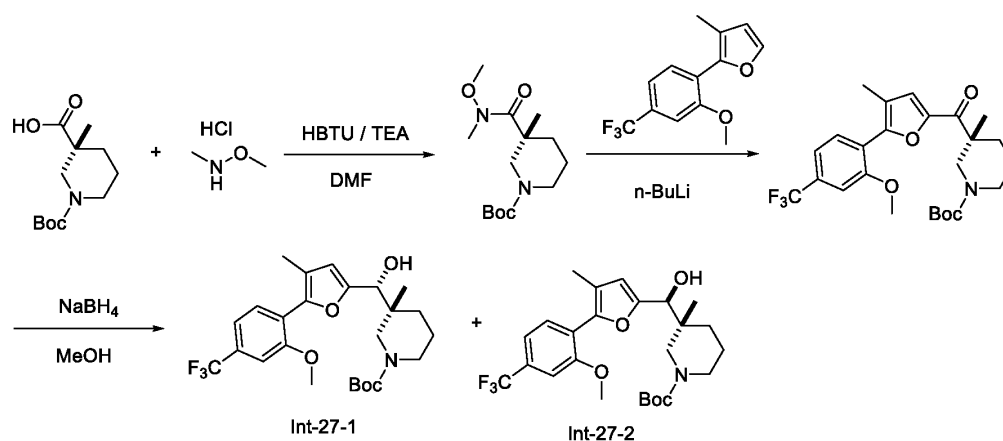
[00304] Steps 1 and 2: tert-Butyl (R)-3-(5-(2-methoxy-4-(trifluoromethyl)phenyl)-4-methylfuran-2-carbonyl)pyrrolidine-1-carboxylate (**Int-26-1**) (188 mg) was prepared as described in Example 24, steps 1-4, starting from (R)-1-(tert-butoxycarbonyl)pyrrolidine-3-carboxylic acid.

[00305] Step 3: To a solution of tert-butyl (R)-3-(5-(2-methoxy-4-(trifluoromethyl)phenyl)-4-methylfuran-2-carbonyl)pyrrolidine-1-carboxylate (**Int-26-1**) (180 mg, 1.0 eq) in MeOH (5 mL) at 0°C was added NaBH_4 (8 mg, 0.5 eq). The mixture was stirred at 0°C for 30min and quenched with sat. aq. NaHCO_3 . The mixture was extracted with DCM (2x25mL). The crude mixture was purified on a silica gel column to provide tert-butyl (3R)-3-(hydroxy(5-(2-methoxy-4-(trifluoromethyl)phenyl)-4-methylfuran-2-yl)methyl)pyrrolidine-1-carboxylate (**Int-26-2**) (162 mg, 89%).

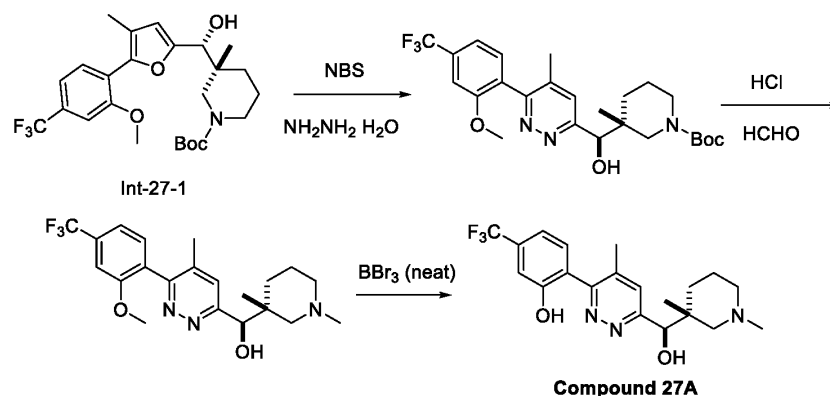
[00306] Steps 4-6: 2-(6-(Hydroxy((R)-1-methylpyrrolidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (**Compound 26**) (66 mg) was prepared as described in Example 24, steps 6 and 7, and Example 25, step 6, starting from tert-butyl (3R)-3-(hydroxy(5-(2-

methoxy-4-(trifluoromethyl)phenyl)-4-methylfuran-2-yl)methyl)pyrrolidine-1-carboxylate (**Int-26-2**). ESI-MS (EI^+ , m/z): 368.1.

Example 27: Synthesis of 2-(6-((R)-((R)-1,3-dimethylpiperidin-3-yl)(hydroxy)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 27A) and 2-(6-((S)-((R)-1,3-dimethylpiperidin-3-yl)(hydroxy)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 27B)

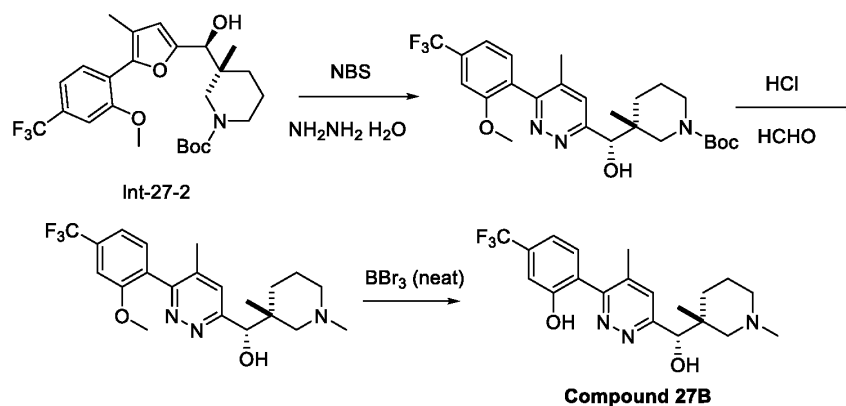


[00307] tert-Butyl (3R)-3-(hydroxy(5-(2-methoxy-4-(trifluoromethyl)phenyl)-4-methylfuran-2-yl)methyl)-3-methylpiperidine-1-carboxylate was prepared as described in Example 26, steps 1-3, starting from (R)-1-(tert-butoxycarbonyl)-3-methylpiperidine-3-carboxylic acid. tert-Butyl (3R)-3-(hydroxy(5-(2-methoxy-4-(trifluoromethyl)phenyl)-4-methylfuran-2-yl)methyl)-3-methylpiperidine-1-carboxylate was purified on a silica gel column to provide tert-butyl (R)-3-((R)-hydroxy(5-(2-methoxy-4-(trifluoromethyl)phenyl)-4-methylfuran-2-yl)methyl)-3-methylpiperidine-1-carboxylate (**Int-27-1**) (30 mg) and tert-butyl (R)-3-((S)-hydroxy(5-(2-methoxy-4-(trifluoromethyl)phenyl)-4-methylfuran-2-yl)methyl)-3-methylpiperidine-1-carboxylate (**Int-27-2**) (41 mg).



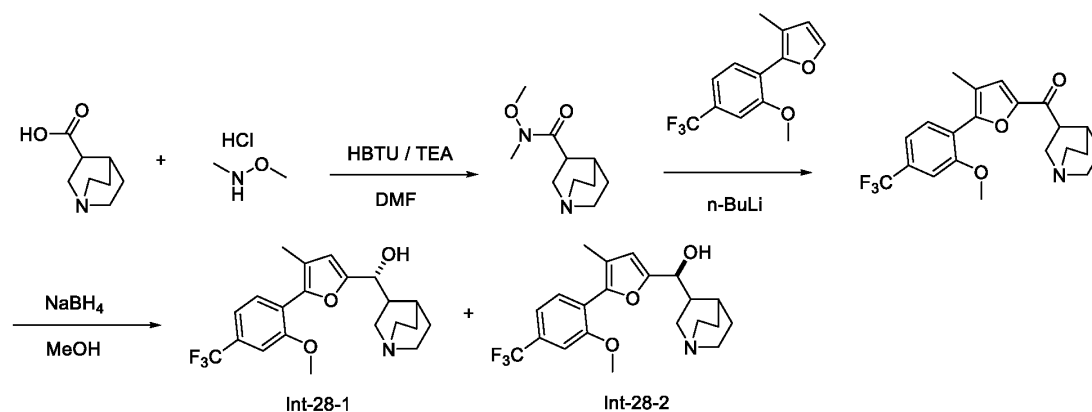
[00308] 2-(6-((R)-((R)-1,3-dimethylpiperidin-3-yl)(hydroxy)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (**Compound 27A**) (23 mg) was prepared as described in Example 24,

steps 6 and 7, and Example 25, step 6, starting from tert-butyl (R)-3-((R)-hydroxy(5-(2-methoxy-4-(trifluoromethyl)phenyl)-4-methylfuran-2-yl)methyl)-3-methylpiperidine-1-carboxylate. ESI-MS (EI^+ , m/z): 396.0.



[00309] 2-(6-((S)-((R)-1,3-dimethylpiperidin-3-yl)(hydroxy)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (**Compound 27B**) (19 mg) was prepared as described in Example 24, steps 6 and 7, and Example 25, step 6, starting from tert-butyl (R)-3-((S)-hydroxy(5-(2-methoxy-4-(trifluoromethyl)phenyl)-4-methylfuran-2-yl)methyl)-3-methylpiperidine-1-carboxylate. ESI-MS (EI^+ , m/z): 396.0.

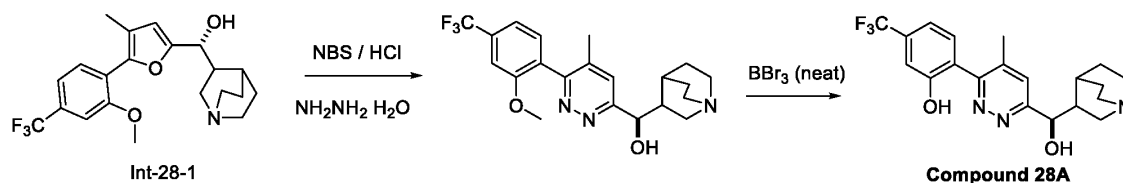
Example 28: Synthesis of 2-(6-((1R)-hydroxy(quinuclidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 28A) and 2-(6-((1S)-hydroxy(quinuclidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 28B)



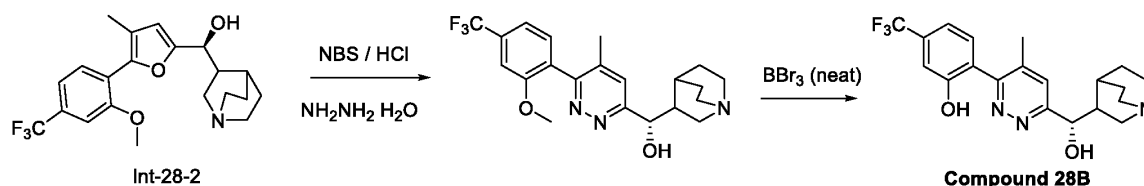
[00310] (5-(2-Methoxy-4-(trifluoromethyl)phenyl)-4-methylfuran-2-yl)(quinuclidin-3-yl)methanol was prepared as described in Example 26, steps 1-3, starting from quinuclidine-3-carboxylic acid. (5-(2-Methoxy-4-(trifluoromethyl)phenyl)-4-methylfuran-2-yl)(quinuclidin-3-yl)methanol was purified on a silica gel column to provide (1R)-5-(2-methoxy-4-(trifluoromethyl)phenyl)-4-methylfuran-2-yl)(quinuclidin-3-yl)methanol (**Int-28-1**) (40 mg) and

(1S)-(5-(2-methoxy-4-(trifluoromethyl)phenyl)-4-methylfuran-2-yl)(quinuclidin-3-yl)methanol

(**Int-28-2**) (29 mg).

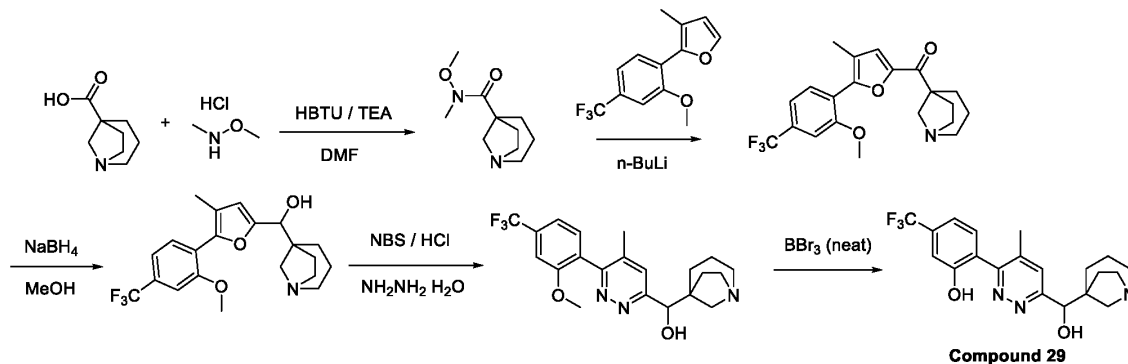


[00311] To a solution of **Int-28-1** (40 mg) in THF (2 mL) and water (0.2 mL) was added 4N HCl in dioxane (28 uL, 1.1 eq). The solution was cooled at -15 °C for 10min and then solid NBS (24 mg, 1.3 eq) was added in portions. The mixture was stirred at -15°C for 30min, then NH₂NH₂ hydrate (10 eq) was added dropwise. The resulting mixture was stirred at 0°C for 30min then at rt for 1h. The reaction was quenched with sat. NaHCO₃ and extracted by DCM (2x20mL). The crude mixture was purified on a silica gel column to afford (1R)-(6-(2-methoxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)(quinuclidin-3-yl)methanol (28 mg, 68%) which was treated with BBr₃ (345 mg, 20 eq) as in Example 25, step 6, to afford 2-(6-((1R)-hydroxy(quinuclidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (**Compound 28A**) (18 mg, 66%). ESI-MS (EI⁺, m/z): 394.1.



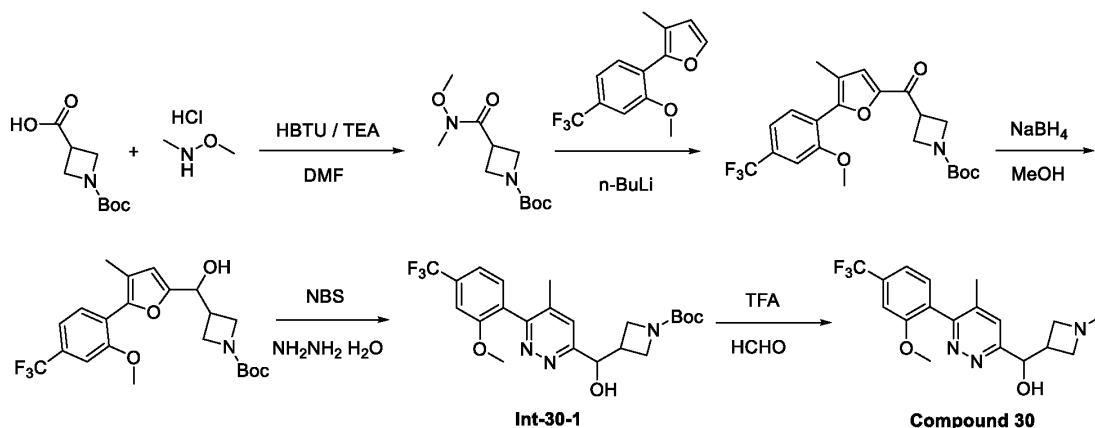
[00312] 2-(6-((1S)-hydroxy(quinuclidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (**Compound 28B**) (15 mg) was prepared in a similar manner starting from **Int-28-2**. ESI-MS (EI⁺, m/z): 394.0.

Example 29: Synthesis of 2-(6-((1-azabicyclo[3.2.1]octan-5-yl)(hydroxy)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 29)



[00313] 2-(6-((1-Azabicyclo[3.2.1]octan-5-yl)(hydroxy)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (**Compound 29**) was prepared as described in Example 28 starting from 1-azabicyclo[3.2.1]octane-5-carboxylic acid. ESI-MS (EI^+ , m/z): 394.2.

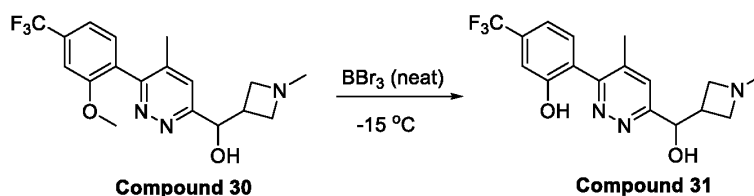
Example 30: Synthesis of (6-(2-methoxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)(1-methylazetidin-3-yl)methanol (Compound 30)



[00314] tert-Butyl 3-(hydroxy(6-(2-methoxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)methyl)azetidine-1-carboxylate (**Int-30-1**) was prepared as described in Example 26, steps 1-4 starting from 1-(tert-butoxycarbonyl)azetidine-3-carboxylic acid.

[00315] To a solution of **Int-30-1** (78 mg) in DCM (1 mL) was added TFA (0.5 mL). The mixture was stirred at rt for 1h. The solvent was removed in vacuo and dissolved in 1,2-dichloroethane. To the solution was added triethylamine (20 mg, 1.1 eq), HCHO (17 mg, 37% in water, 1.2 eq). The mixture was stirred at rt for 30min, then $\text{NaBH}(\text{OAc})_3$ (91 mg, 1.5 eq) was added. After completion, the reaction was quenched with sat. aq. NaHCO_3 . The crude mixture was purified on a silica gel column to afford (6-(2-methoxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)(1-methylazetidin-3-yl)methanol (**Compound 30**) (48 mg, 79%). ESI-MS (EI^+ , m/z): 368.2.

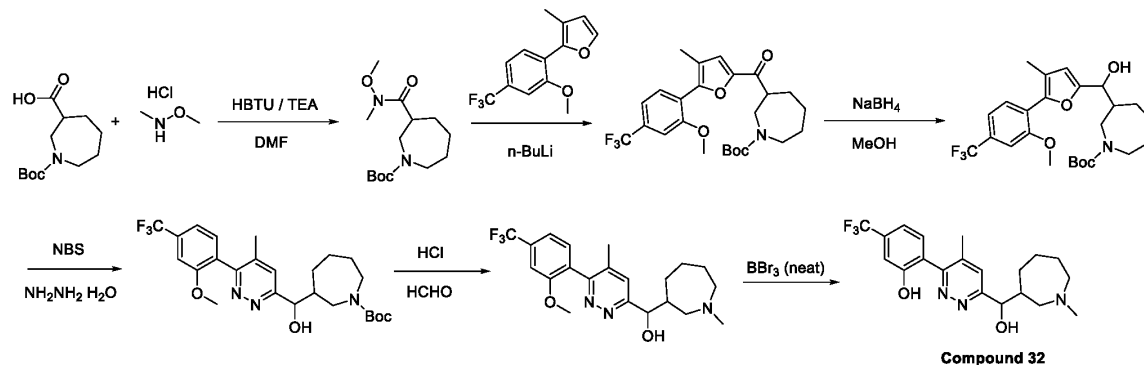
Example 31: Synthesis of 2-(6-(hydroxy(1-methylazetidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 31)



[00316] 2-(6-(Hydroxy(1-methylazetidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (**Compound 31**) was prepared as described in Example 25, step 6,

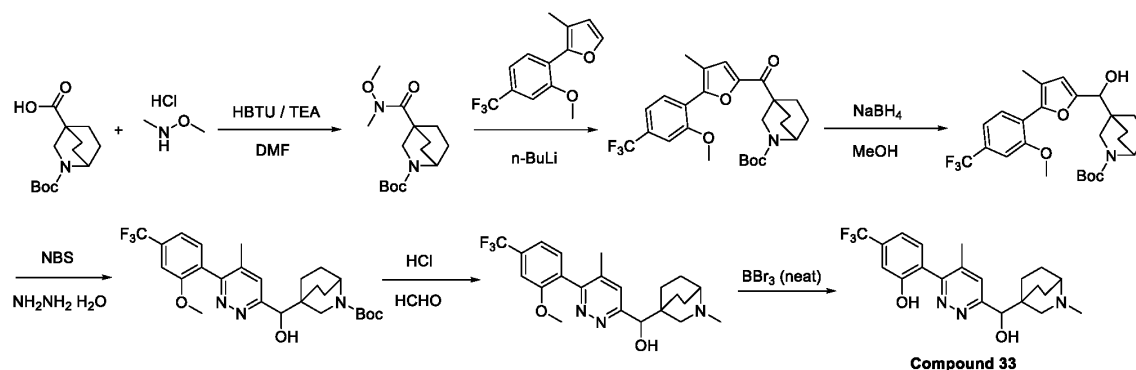
starting from (6-(2-methoxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)(1-methylazetidin-3-yl)methanol (**Compound 30**). ESI-MS (EI^+ , m/z): 354.0.

Example 32: Synthesis of 2-(6-(hydroxy(1-methylazepan-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 32)



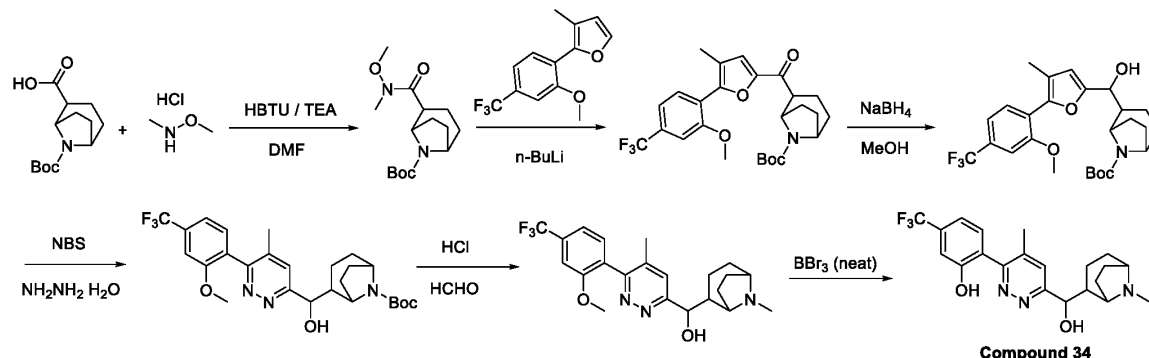
[00317] 2-(6-(Hydroxy(1-methylazepan-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (**Compound 32**) was prepared as described in Example 27 starting from 1-(tert-butoxycarbonyl)azepan-3-carboxylic acid. ESI-MS (EI^+ , m/z): 396.1.

Example 33: Synthesis of 2-(6-(hydroxy(2-methyl-2-azabicyclo[2.2.2]octan-4-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 33)



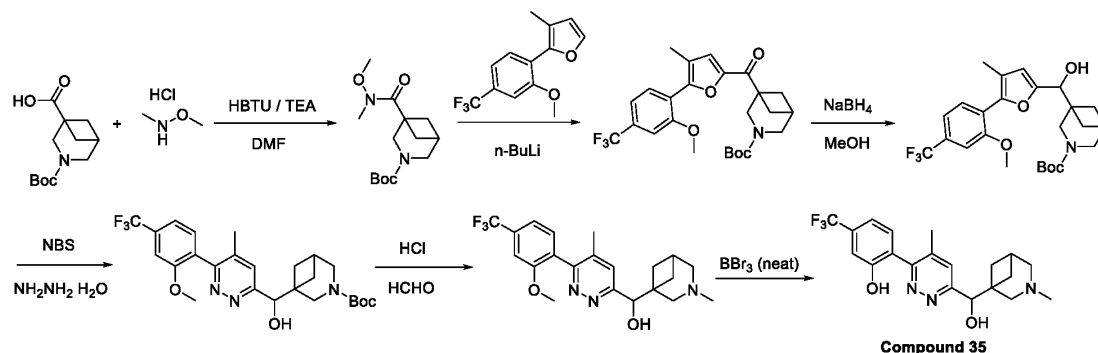
[00318] 2-(6-(Hydroxy(2-methyl-2-azabicyclo[2.2.2]octan-4-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (**Compound 33**) was prepared as described in Example 27 starting from 2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.2]octane-4-carboxylic acid. ESI-MS (EI^+ , m/z): 408.2.

Example 34: Synthesis of 2-(6-(hydroxy(8-methyl-8-azabicyclo[3.2.1]octan-2-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 34)



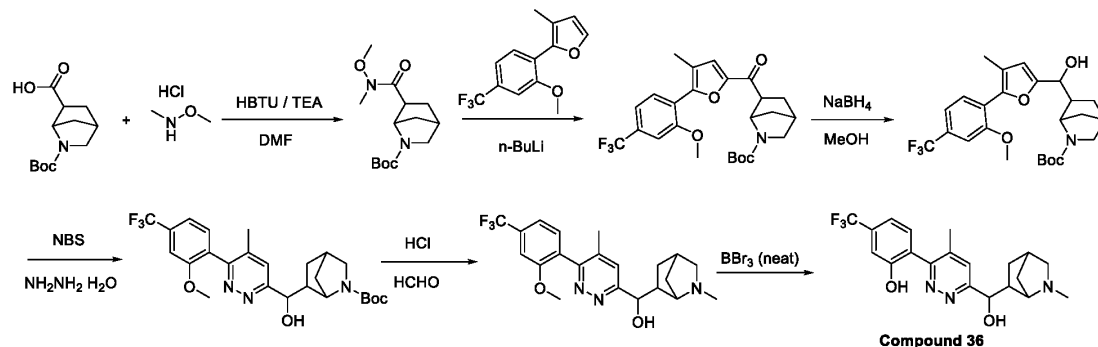
[00319] 2-(6-(Hydroxy(8-methyl-8-azabicyclo[3.2.1]octan-2-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (**Compound 34**) was prepared as described in Example 27 starting from 8-(tert-butoxycarbonyl)-8-azabicyclo[3.2.1]octane-2-carboxylic acid. ESI-MS (EI^+ , m/z): 408.1.

Example 35: Synthesis of 2-(6-(hydroxy(3-methyl-3-azabicyclo[3.1.1]heptan-1-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 35)



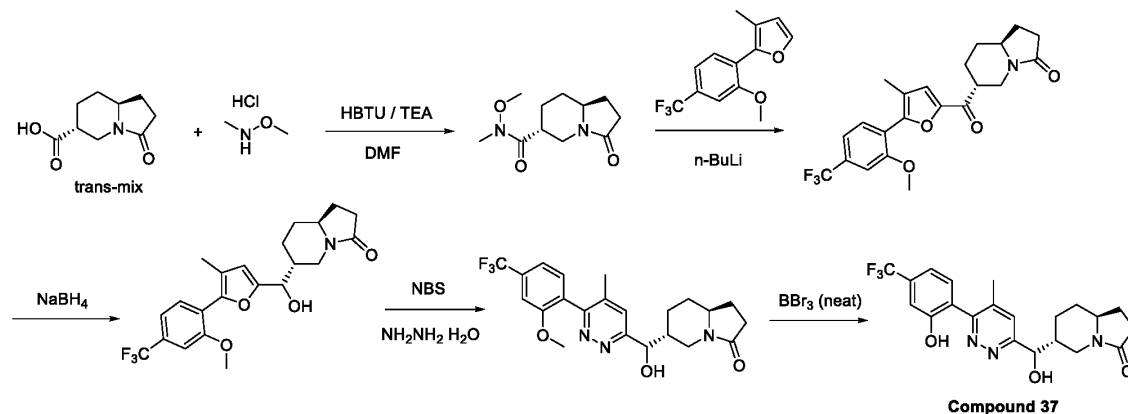
[00320] 2-(6-(Hydroxy(3-methyl-3-azabicyclo[3.1.1]heptan-1-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (**Compound 35**) was prepared as described in Example 27 starting from 3-(tert-butoxycarbonyl)-3-azabicyclo[3.1.1]heptane-1-carboxylic acid. ESI-MS (EI^+ , m/z): 394.2.

Example 36: Synthesis of 2-(6-(hydroxy(2-methyl-2-azabicyclo[2.2.1]heptan-6-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 36)



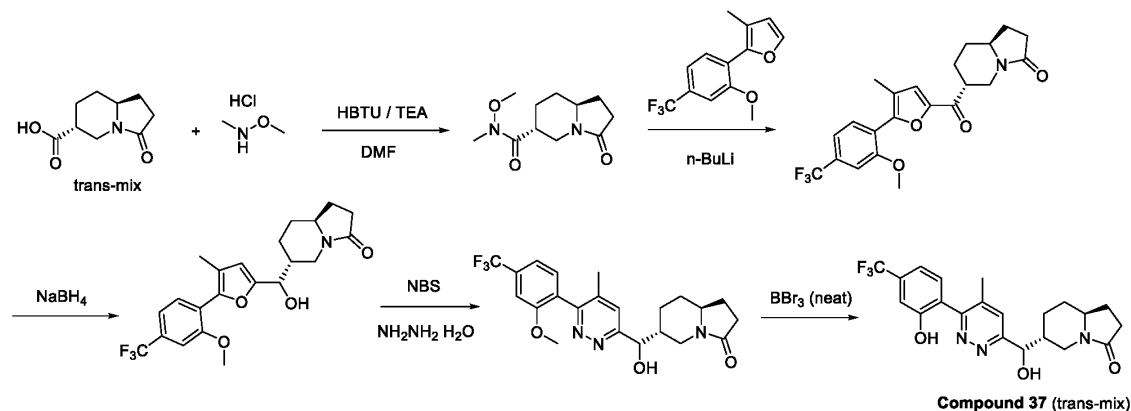
[00321] 2-(6-(Hydroxy(2-methyl-2-azabicyclo[2.2.1]heptan-6-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (**Compound 36**) was prepared as described in Example 27 starting from 2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptane-6-carboxylic acid. ESI-MS (EI^+ , m/z): 394.0.

Example 37: Synthesis of (6R,8aS)-6-((R)-hydroxy(6-(2-hydroxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)methyl)hexahydroindolizin-3(2H)-one (Compound 37)



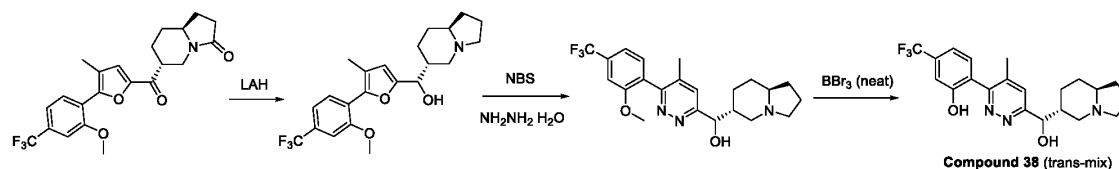
[00322] 6-(Hydroxy(6-(2-hydroxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)methyl)hexahydroindolizin-3(2H)-one (mixture of trans isomers) (**Compound 37**) was prepared as described in Example 27 starting from 3-oxooctahydroindolizine-6-carboxylic acid (mixture of trans isomers). ESI-MS (EI^+ , m/z): 422.2.

Example 37: Synthesis of (6R,8aS)-6-((R)-hydroxy(6-(2-hydroxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)methyl)hexahydroindolizin-3(2H)-one (mixture of trans isomers) (Compound 37)



[00323] 6-(Hydroxy(6-(2-hydroxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)methyl)hexahydroindolizin-3(2H)-one (mixture of trans isomers) (**Compound 37**) was prepared as described in Example 27 starting from 3-oxooctahydroindolizine-6-carboxylic acid (mixture of trans isomers). ESI-MS (EI^+ , m/z): 422.2.

Example 38: Synthesis of 2-(6-(hydroxy(octahydroindolizin-6-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (mixture of trans isomers) (Compound 38)

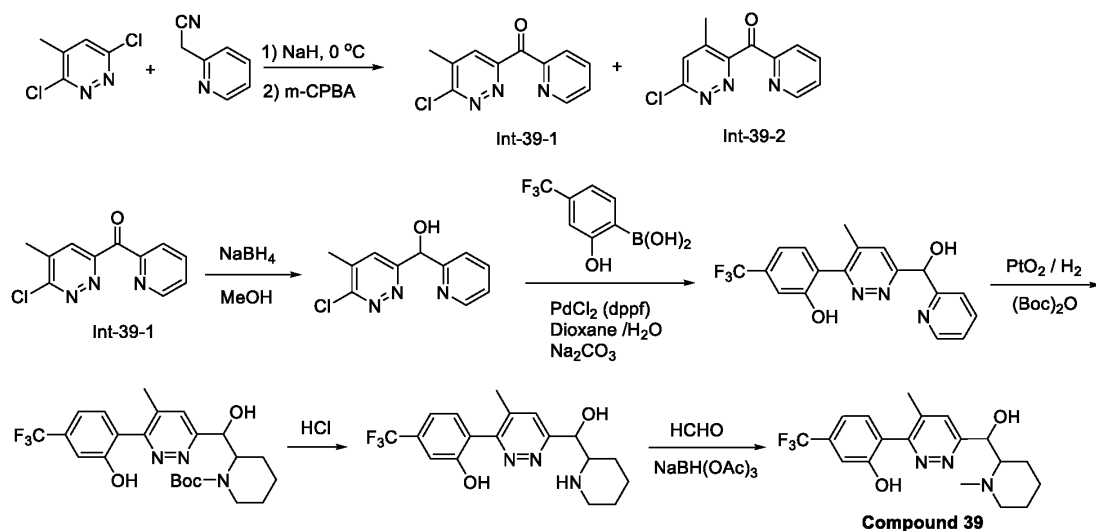


[00324] To a solution of 6-(5-(2-methoxy-4-(trifluoromethyl)phenyl)-4-methylfuran-2-carbonyl)hexahydroindolizin-3(2H)-one (mixture of trans isomers) from Example 37 (32 mg, 1.0 eq) in anhydrous THF (5 mL) was added LAH (1M in ether, 0.76mL, 10 eq) at 0 °C under N_2 . The resulting mixture was heated at 55 °C for 15h. The reaction was quenched with 1N NaOH and extracted with DCM (3x20 mL) and concentrated in vacuo to afford (5-(2-methoxy-4-(trifluoromethyl)phenyl)-4-methylfuran-2-yl)(octahydroindolizin-6-yl)methanol (24 mg, 77%).

[00325] 2-(6-(Hydroxy(octahydroindolizin-6-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (mixture of trans isomers) (**Compound 38**) was prepared as described in Example 24, step 6, and Example 25, step 6, starting from (5-(2-methoxy-4-

(trifluoromethyl)phenyl)-4-methylfuran-2-yl)(octahydroindolizin-6-yl)methanol (mixture of trans isomers). ESI-MS (EI^+ , m/z): 408.4.

Example 39: Synthesis of 2-(6-(hydroxy(1-methylpiperidin-2-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 39)



[00326] To a solution of 3,6-dichloro-4-methylpyridazine (820 mg, 5 mmol) and 2-pyridylacetonitrile (610 mg, 5.2 mmol) in dry DMA (8 mL) was added NaH (420 mg, 10.5 mmol, 60%) in portions at 0 °C. After 30min at 0 °C, m-CPBA (1.2 g, 5 mmol, 72% purity) was added to the solution in portions over 2min at 0 °C. The reaction mixture was diluted with EtOAc (20 mL) and stirred for additional 10min at 0 °C. Saturated aq. NaHCO₃ (20 mL) was added to the solution at 0 °C and the mixture was stirred for 10min. The mixture was diluted with water (20 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (3x20 mL). The combined organic layer was washed with water (3x30 mL), saturated NaHCO₃ (50 mL), brine (50 mL) and dried over Na₂SO₄. The solvent was concentrated and the solid was sonicated in EtOAc (10 mL) and collected by filtration. The solid was further purified on a silica gel column to give (6-chloro-5-methylpyridazin-3-yl)(pyridin-2-yl)methanone (**Int-39-1**) (298 mg).

[00327] To a solution of (6-chloro-5-methylpyridazin-3-yl)(pyridin-2-yl)methanone (**Int-39-1**) (100 mg, 1.0 eq) in MeOH (5 mL) THF (5 mL) at 0 °C was added NaBH₄ (8 mg, 0.5 eq). The resulting mixture was stirred at 0 °C for 15min. The reaction was quenched with saturated aq. NaHCO₃, and then extracted with ethyl acetate to afford (6-chloro-5-methylpyridazin-3-yl)(pyridin-2-yl)methanol (100 mg).

[00328] A mixture of (6-chloro-5-methylpyridazin-3-yl)(pyridin-2-yl)methanol (100 mg, 1.0 eq), (2-hydroxy-4-(trifluoromethyl)phenyl)boronic acid (115 mg, 1.3 eq), PdCl₂(dppf) (28 mg,

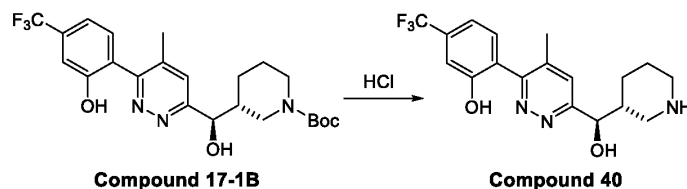
0.1 eq) and Na_2CO_3 (100 mg, 2.0 eq) in dioxane (5 mL) and water (2 mL) was heated at 100°C for 8h. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water, brine and concentrated in vacuo. The crude mixture was purified on a silica gel column to afford 2-(6-(hydroxy(pyridin-2-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (102 mg).

[00329] To a solution of 2-(6-(hydroxy(pyridin-2-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (100 mg, 1.0 eq) in MeOH (20 mL) and water (0.2 mL) was added PtO_2 (50 mg, 0.8 eq) and $(\text{Boc})_2\text{O}$ (78 mg, 1.3 eq). The mixture was degassed with bubbling N_2 gas for 20min, and then hydrogenated under H_2 (balloon) for 15h at rt. The catalyst was removed by filtration and solvent was concentrated in vacuo. The crude mixture was purified on a silica gel column to afford tert-butyl 3-(hydroxy(6-(2-hydroxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-2-yl)methyl)piperidine-1-carboxylate (42 mg).

[00330] To a solution of tert-butyl 2-(hydroxy(6-(2-hydroxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)methyl)piperidine-1-carboxylate (42 mg) in DCM (1 mL) was added HCl (4N, 1 mL). The mixture was stirred at rt for 25min. The mixture was concentrated in vacuo to afford 2-(6-(hydroxy(piperidin-2-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (35 mg, HCl salt).

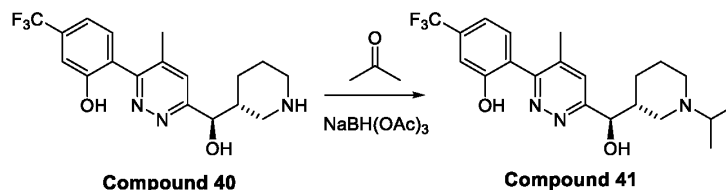
[00331] To a solution of 2-(6-(hydroxy(piperidin-2-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol HCl salt (35 mg, 1.0 eq) in 1,2-dichloroethane (5 mL) and MeOH (0.5 mL) was added triethylamine (1.0 eq), HCHO (8.5 mg, 37% in water, 1.2 eq) and 1 drop of AcOH. The mixture was stirred at rt for 15min and $\text{NaBH}(\text{OAc})_3$ (29 mg, 1.5 eq) was added. The resulting mixture was stirred at rt for 30min, quenched with saturated aq. NaHCO_3 and stirred at rt for 10min. The mixture was extracted with DCM (4x25 mL). The combined organic extracts were concentrated and the residue was purified on a silica gel column to afford 2-(6-(hydroxy(1-methylpiperidin-2-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (**Compound 39**) (22 mg) as a white solid. ESI-MS (EI^+ , m/z): 382.2.

Example 40: Synthesis of 2-(6-((R)-hydroxy((R)-piperidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 40**)**



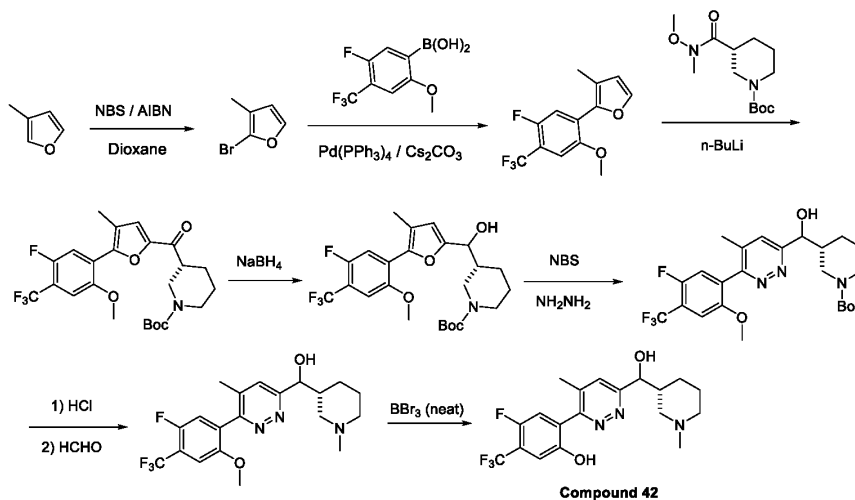
[00332] To a solution of compound 17-1B (55 mgs) in DCM (0.5 mL) was added 4N HCl in dioxane (1 mL). The mixture was stirred at rt for 30min and concentrated in vacuo to afford 2-(6-((R)-hydroxy((R)-piperidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (**Compound 40**) (46 mg, 98%). ESI-MS (EI^+ , m/z): 368.1.

Example 41: Synthesis of 2-(6-((R)-hydroxy((R)-1-isopropylpiperidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 41)



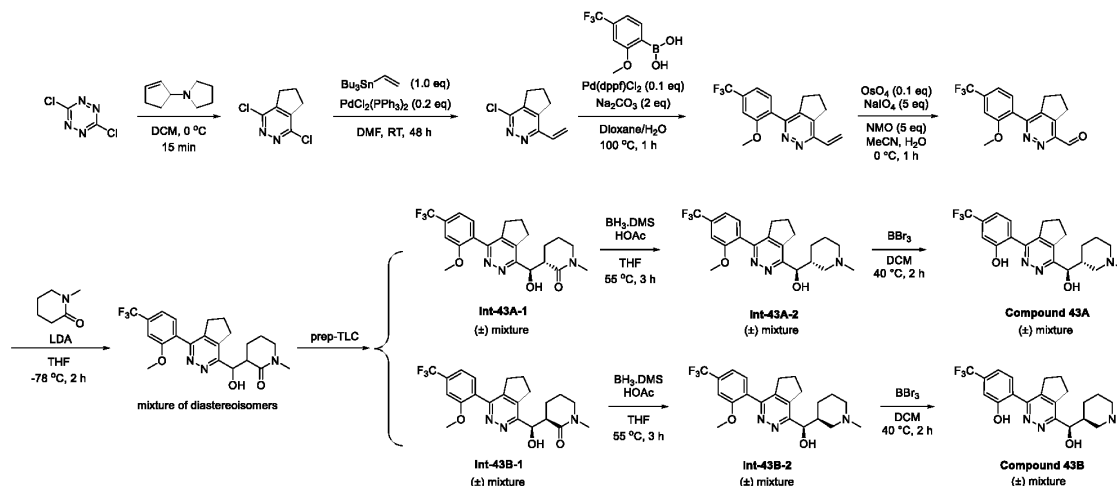
[00333] 2-(6-((R)-Hydroxy((R)-piperidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (**Compound 40**) (20 mg, 1.0 eq) HCl salt and anhydrous acetone (9 mg, 3 eq) were combined in anhydrous 1,2-dichloroethane (2 mL). To the mixture was added TEA (6 mg, 1.2 eq) and a drop of AcOH (~5 mg). The mixture was stirred rt for 5h and NaBH(OAc)₃ (52 mg, 5.0 eq) was added. The resulting mixture was stirred at rt for 1h and then heated at 50 °C overnight. The reaction mixture was cooled and quenched with saturated NaHCO₃. The residue was purified on a silica gel column to provide 2-(6-((R)-hydroxy((R)-1-isopropylpiperidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (**Compound 41**) (5 mg, 26%). ESI-MS (EI⁺, m/z): 410.2.

Example 42: Synthesis of 4-fluoro-2-(6-(hydroxy((R)-1-methylpiperidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 42)



[00334] 4-Fluoro-2-(6-(hydroxy((R)-1-methylpiperidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (**Compound 42**) was prepared as described in Example 24, steps 1-7, using (5-fluoro-2-methoxy-4-(trifluoromethyl)phenyl)boronic acid in step 2, and Example 25, step 6. ESI-MS (EI⁺, m/z): 400.1.

Example 43: Synthesis of 2-(4-((R)-hydroxy((R)-1-methylpiperidin-3-yl)methyl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)-5-(trifluoromethyl)phenol (±) mixture (Compound 43A) and 2-(4-((R/S)-hydroxy((R/S)-1-methylpiperidin-3-yl)methyl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)-5-(trifluoromethyl)phenol (±) mixture (Compound 43B)



[00335] To a solution of 3,6-dichloro-1,2,4,5-tetrazine (5.0 g, 33.1 mmol) in dichloromethane (50 mL) at 0 °C was added 1-(cyclopent-2-en-1-yl)pyrrolidine (4.83 mL, 33.1 mmol) dropwise over 15 minutes. After an additional 15 minutes, the reaction was quenched by the addition of 30 mL of 10% aq. citric acid (50 mL) and water (30 mL). The reaction was removed from the ice bath and vigorously stirred for 5 minutes. The reaction mixture was then extracted with 3 × 30 mL CH₂Cl₂. The combined organic layers were rinsed with brine (30 mL), dried with MgSO₄, filtered and concentrated to dryness. Purification by column chromatography afforded 1,4-dichloro-6,7-dihydro-5H-cyclopenta[d]pyridazine as a white solid (3.4 g, 54%). ¹H NMR (400 MHz, Chloroform-d): δ 3.10 (t, J = 7.8 Hz, 4H), 2.36 – 2.14 (m, 2H).

[00336] To a solution of 1,4-dichloro-6,7-dihydro-5H-cyclopenta[d]pyridazine (3.4 g, 17.99 mmol) in DMF (200 mL) was added tributyl(vinyl)stannane (5.7 g, 17.99 mmol, 1.0 eq.) and PdCl₂(PPh₃)₂ (1.26 g, 10.37 mmol, 0.2 eq.). The resulting mixture was stirred at RT for 48 h under an atmosphere of N₂. The reaction solution was diluted with water, extracted with EtOAc, dried over Na₂SO₄, filtered and purified by column chromatography to afford 1-chloro-4-vinyl-6,7-dihydro-5H-cyclopenta[d]pyridazine (1.78 g, 54%) as a white solid. ¹H NMR (400 MHz, Chloroform-d): δ 6.94 (dd, J = 11.2, 11.6 Hz, 1H), 6.38 (d, J = 17.6 Hz, 1H), 5.71 (d, J = 11.2 Hz, 1H), 3.08 (dt, J = 32.8, 7.6 Hz, 4H), 2.23 (q, J = 7.6 Hz, 2H).

[00337] To a solution of 1-chloro-4-vinyl-6,7-dihydro-5H-cyclopenta[d]pyridazine (1.78 g, 9.85 mmol) in 3:1 dioxane/H₂O (24 mL) was added (2-methoxy-4-

(trifluoromethyl)phenyl)boronic acid (3.25 g, 14.78 mmol, 1.5 eq.), Na₂CO₃ (2.09 g, 19.71 mmol, 2.0 eq.) and Pd(dppf)Cl₂ (721 mg, 0.99 mmol, 0.1 eq.). The resulting mixture was stirred at 100 °C for 1 h. The reaction solution was diluted with water, extracted with EtOAc, dried over Na₂SO₄, filtered and purified by column chromatography to afford 1-(2-methoxy-4-(trifluoromethyl)phenyl)-4-vinyl-6,7-dihydro-5H-cyclopenta[d]pyridazine (1.87 g, 59%) as a yellow solid. ESI-MS (EI⁺): m/z 321.10.

[00338] To a solution of 1-(2-methoxy-4-(trifluoromethyl)phenyl)-4-vinyl-6,7-dihydro-5H-cyclopenta[d]pyridazine (1.87 g, 5.84 mmol, 1 eq) in 1:1 ACN/H₂O (20 mL) was added NaIO₄ (6.24 g, 29.19 mmol, 5 eq), OsO₄ (0.1 mg, 0.58 mmol, 0.1 eq) and NMO (3.42 g, 29.19 mmol, 5 eq). The resulting mixture was stirred at 0 °C for 1 h. The reaction solution was diluted with EtOAc and H₂O, and the organic layer was dried (Na₂SO₄), filtered, and concentrated. The residue was purified by column chromatography to afford the 4-(2-methoxy-4-(trifluoromethyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyridazine-1-carbaldehyde (180 mg, 10%) as a yellow solid. ¹H NMR (400 MHz, Chloroform-d): δ 10.52 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.25 (s, 1H), 3.88 (s, 3H), 3.42 (t, J = 7.6 Hz, 2H), 2.88 (t, J = 7.6 Hz, 2H), 2.22 – 2.13 (m, 2H).

[00339] To a solution of 1-methylpiperidin-2-one (180 mg, 0.67 mmol, 1.2 eq) in THF (4 mL) was added LDA (698 mL, 2 M, 1.4 mmol, 2.5 eq) at -78 °C. After 1 h, 4-(2-methoxy-4-(trifluoromethyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyridazine-1-carbaldehyde (180 mg, 0.558 mmol, 1 eq) was added and the reaction was stirred at -78 °C for a further 1 h. The reaction solution was diluted with EtOAc and H₂O, and the organic layer was dried (Na₂SO₄), filtered and concentrated. Purification by column chromatography and then prep-TLC (1:20 MeOH/DCM) three times afforded (S/R)-3-((R/S)-hydroxy(4-(2-methoxy-4-(trifluoromethyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)methyl)-1-methylpiperidin-2-one (±) mixture (**Int-43A-1**) (80 mg, 33%) and (R/S)-3-((R/S)-hydroxy(4-(2-methoxy-4-(trifluoromethyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)methyl)-1-methylpiperidin-2-one (±) mixture (**Int-43B-1**) (80 mg, 33%).

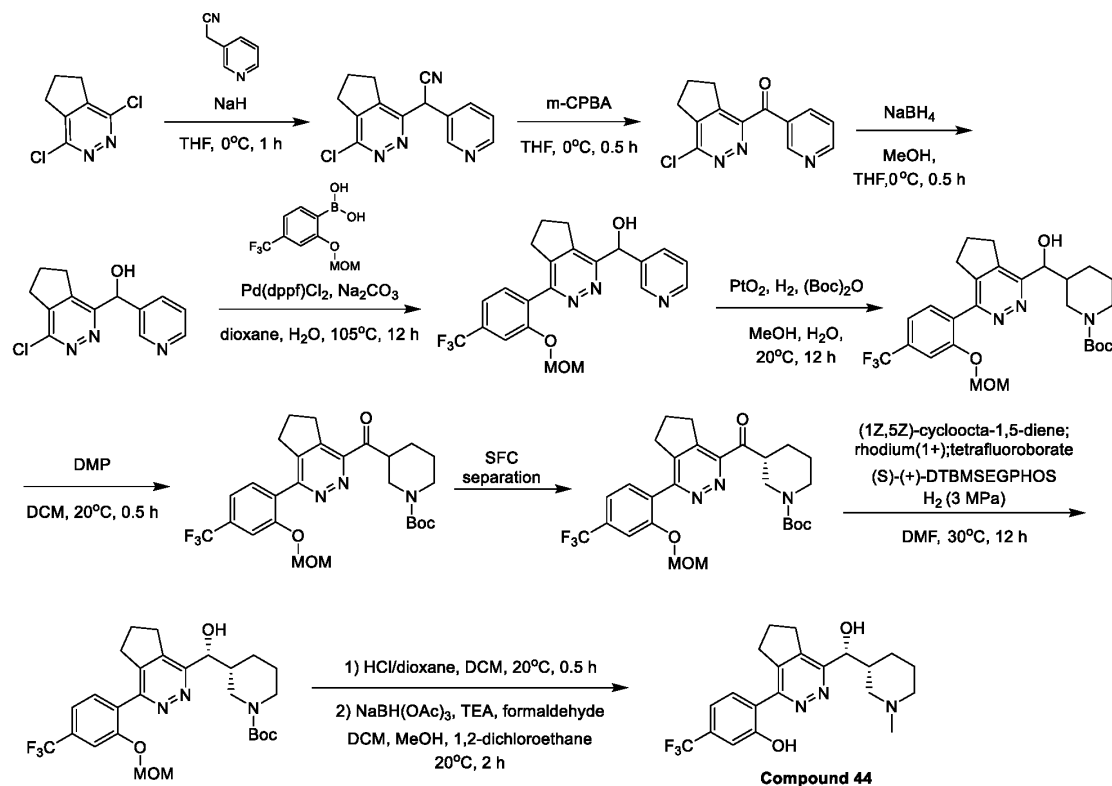
[00340] To a solution of **Int-43A-1** (80 mg, 0.18 mmol) in THF (1 mL) was added BH₃.DMS (140 mg, 1.84 mmol, 10.0 eq) at 0 °C under an atmosphere of N₂. The reaction mixture was heated to 55 °C for 2 h and then cooled to 0 °C and AcOH (0.5 mL) was added. The resulting mixture was stirred at 55 °C for 1 h. The reaction solution was diluted with MeOH and then concentrated in vacuo to afford (R)-(4-(2-methoxy-4-(trifluoromethyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)((R)-1-methylpiperidin-3-yl)methanol (±) mixture (**Int-43A-2**) (80 mg, crude) as a yellow oil. ESI-MS (EI⁺): m/z 422.15.

[00341] To a solution of **Int-43A-2** (80 mg) in DCM (1 mL) was added BBr₃ (3 mL) at 0 °C under N₂. The resulting mixture was stirred at 40 °C for 2 h. The reaction solution was diluted with MeOH, concentrated in vacuo and purified by prep-HPLC to afford 2-(4-((R)-hydroxy((R)-1-methylpiperidin-3-yl)methyl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)-5-(trifluoromethyl)phenol (±) mixture (**Compound 43A**) (9.5 mg, 12%) as a white solid. ESI-MS (EI⁺): m/z 408.10. ¹H NMR (400 MHz, Methanol-d₄): δ 8.52 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.25 (s, 1H), 4.89 (s, 1H), 3.78 (d, J = 12.2 Hz, 1H), 3.43 (d, J = 12.4 Hz, 1H), 3.30 – 3.17 (m, 2H), 3.11 (t, J = 7.6 Hz, 2H), 3.05 – 2.90 (m, 2H), 2.89 (s, 3H), 2.65 – 2.52 (m, 1H), 2.19 (p, J = 7.6 Hz, 2H), 1.97 (dq, J = 14.6, 3.6 Hz, 1H), 1.85 – 1.71 (m, 1H), 1.58 – 1.40 (m, 2H).

[00342] To a solution of **Int-43B-1** (80 mg, 0.18 mmol) in THF (1 mL) was added BH₃.DMS (140 mg, 1.84 mmol, 10.0 eq) at 0 °C under an atmosphere of N₂. The reaction mixture was heated to 55 °C for 2 h and then cooled to 0 °C and AcOH (0.5 mL) was added. The resulting mixture was stirred at 55 °C for 1 h. The reaction solution was diluted with MeOH and then concentrated in vacuo to afford (R)-(4-(2-methoxy-4-(trifluoromethyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)((R)-1-methylpiperidin-3-yl)methanol (±) mixture (**Int-43B-2**) (60 mg, crude) as a yellow oil. ESI-MS (EI⁺): m/z 422.15.

[00343] To a solution of **Int-43B-2** (60 mg) in DCM (1 mL) was added BBr₃ (3 mL) at 0 °C under N₂. The resulting mixture was stirred at 40 °C for 2 h. The reaction solution was diluted with MeOH, concentrated in vacuo and purified by prep-HPLC to afford 2-(4-((R/S)-hydroxy((R/S)-1-methylpiperidin-3-yl)methyl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)-5-(trifluoromethyl)phenol (±) mixture (**Compound 43B**) (9.2 mg, 16%) as a white solid. ESI-MS (EI⁺): m/z 408.10. ¹H NMR (400 MHz, Methanol-d₄): δ 8.52 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.32 – 7.29 (m, 2H), 4.96 (d, J = 6.4 Hz, 1H), 3.45 (d, J = 11.6 Hz, 1H), 3.34 – 3.20 (m, 5H), 3.15 – 3.11 (m, 2H), 3.00 – 2.84 (m, 2H), 2.60 – 2.56 (m, 1H), 2.25 – 2.17 (m, 2H), 2.07 – 2.04 (m, 2H), 1.87 – 1.77 (m, 1H), 1.57 – 1.48 (m, 1H).

Example 44: Synthesis of 2-(4-((R)-hydroxy((R)-1-methylpiperidin-3-yl)methyl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)-5-(trifluoromethyl)phenol (±) mixture (Compound 44)



[00344] To a mixture of 1,4-dichloro-6,7-dihydro-5H-cyclopenta[d]pyridazine (10.5 g, 55.54 mmol) and 2-(3-pyridyl)acetonitrile (6.56 g, 55.54 mmol, 5.97 mL) in THF (100 mL) was added NaH (4.67 g, 116.64 mmol, 60% purity) in portions at 0°C under N₂. The mixture was stirred at 0°C for 1 h. m-CPBA (17.57 g, 61.10 mmol, 60% purity) was added to the solution in portions over 10 min at 0°C. The mixture was stirred at 0°C for 0.5 h. LCMS showed the reaction was completed. The reaction was quenched by addition of saturated NaHCO₃ (100 mL) at 0°C and the mixture was stirred for 10 min. The mixture was diluted with water (200 mL) and extracted with EA (100 mL × 3). The combined organic layers were washed with brine (250 mL), dried over Na₂SO₄ and concentrated to give residue. The residue was triturated with MTBE (50 mL) at 20°C for 0.5 h and filtered to give (4-chloro-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)(pyridin-3-yl)methanone (7.28 g, 50%) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.08 (d, *J* = 1.6 Hz, 1H), 8.85 (dd, *J* = 2.0, 5.2 Hz, 1H), 8.32 (td, *J* = 2.0, 8.0 Hz, 1H), 7.66 - 7.57 (m, 1H), 3.32 (t, *J* = 7.6 Hz, 2H), 3.09 (t, *J* = 7.6 Hz, 2H), 2.17 (quin, *J* = 7.6 Hz, 2H).

[00345] To a mixture of (4-chloro-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)(pyridin-3-yl)methanone (7.2 g, 27.73 mmol) in THF (40 mL) and MeOH (40 mL) was added NaBH₄ (1.05

g, 27.73 mmol) in portions at 0°C. The mixture was stirred at 0°C for 0.5 h. The reaction was quenched with saturated NaHCO₃ (100 mL) at 0°C and extracted with EA (80 mL × 3). The organic layers were washed with brine (100 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by column chromatography to give (4-chloro-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)(pyridin-3-yl)methanol (5.1 g, 70%) as a colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.58 (d, *J* = 2.0 Hz, 1H), 8.47 (dd, *J* = 1.6, 5.2 Hz, 1H), 7.80 - 7.73 (m, 1H), 7.37 (dd, *J* = 4.8, 8.0 Hz, 1H), 6.55 (d, *J* = 5.2 Hz, 1H), 6.14 (d, *J* = 4.4 Hz, 1H), 3.23 - 3.10 (m, 1H), 2.93 (t, *J* = 7.6 Hz, 2H), 2.85 - 2.72 (m, 1H), 2.13 - 1.94 (m, 2H).

[00346] To a mixture of (4-chloro-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)(pyridin-3-yl)methanol (5.1 g, 19.49 mmol) and (2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)boronic acid (6.33 g, 25.33 mmol) in dioxane (40 mL) and H₂O (20 mL) was added Na₂CO₃ (5.16 g, 48.72 mmol) and Pd(dppf)Cl₂ (713 mg, 974.37 μmol) under N₂. The mixture was stirred at 105°C for 12 h. The mixture was poured into water (100 mL) and extracted with ethyl acetate (80 mL × 3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by column chromatography to give (4-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)(pyridin-3-yl)methanol (4.2 g, 50%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.65 (d, *J* = 2.0 Hz, 1H), 8.48 (dd, *J* = 1.6, 4.4 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.57 (s, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.39 (dd, *J* = 4.8, 7.6 Hz, 1H), 6.52 (d, *J* = 4.4 Hz, 1H), 6.22 (d, *J* = 4.4 Hz, 1H), 5.30 - 5.24 (m, 2H), 3.26 (s, 3H), 3.22 - 3.13 (m, 1H), 2.87 - 2.78 (m, 1H), 2.75 (dt, *J* = 3.6, 7.6 Hz, 2H), 2.04 - 1.89 (m, 2H).

[00347] To a mixture of (4-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)(pyridin-3-yl)methanol (4.2 g, 9.74 mmol) in MeOH (500 mL) and H₂O (5 mL) was added PtO₂ (1.77 g, 7.79 mmol) and Boc₂O (2.76 g, 12.66 mmol, 2.91 mL) at 20°C under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 20°C for 12 h. The mixture was filtered through celite and the filtrate was concentrated to give tert-butyl 3-(hydroxy(4-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)methyl)piperidine-1-carboxylate (5.4 g, 94%) as a yellow solid. ¹H NMR (400 MHz, Chloroform-*d*): δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.55 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 5.20 - 5.15 (m, 2H), 4.93 - 4.79 (m, 1H), 3.46 - 3.38 (m, 3H), 3.15 - 3.01 (m, 2H), 3.00 - 2.91 (m, 2H), 2.89 (dd, *J* = 5.2, 8.8 Hz, 2H), 2.21 (td, *J* = 6.8, 13.6 Hz, 1H), 2.12 (ddd, *J* = 4.8, 8.4, 16.4 Hz, 2H), 1.79 - 1.65 (m, 2H), 1.60 (s, 2H), 1.48 - 1.40 (m, 9H).

[00348] To a mixture of tert-butyl 3-(hydroxy(4-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)methyl)piperidine-1-

carboxylate (5.3 g, 9.86 mmol) in DCM (60 mL) was added DMP (4.60 g, 10.85 mmol, 3.36 mL) in portions at 0°C. The mixture was stirred at 20°C for 0.5 h. LCMS showed the reaction was completed. The reaction was quenched with saturated NaHCO₃ (100 mL) and extracted with DCM (80 mL × 3). The organic layers were washed with brine (100 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by column chromatography to give tert-butyl 3-(4-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyridazine-1-carbonyl)piperidine-1-carboxylate (3.18 g, 60%) as a yellow solid. ¹H NMR (400 MHz, Chloroform-d): δ 7.63 (d, *J* = 8.0 Hz, 1H), 7.57 (s, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 5.19 (s, 2H), 4.30 (s, 1H), 4.19 - 4.09 (m, 1H), 3.42 (s, 3H), 3.42 - 3.37 (m, 2H), 3.36 - 3.26 (m, 1H), 2.90 (t, *J* = 7.6 Hz, 2H), 2.29 - 2.21 (m, 1H), 2.14 (quin, *J* = 7.6 Hz, 2H), 1.83 (dd, *J* = 4.4, 8.8 Hz, 1H), 1.76 - 1.56 (m, 4H), 1.47 - 1.40 (m, 9H).

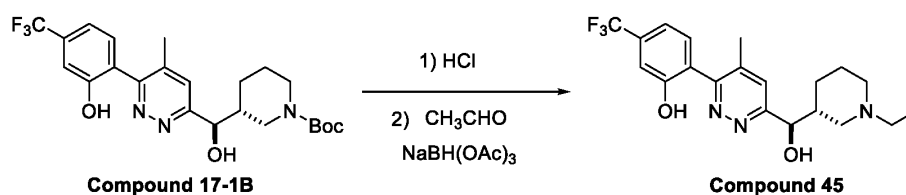
[00349] tert-Butyl 3-(4-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyridazine-1-carbonyl)piperidine-1-carboxylate (3.18 g, 5.94 mmol) was purified by SFC separation to give tert-butyl (R)-3-(4-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyridazine-1-carbonyl)piperidine-1-carboxylate (1.2 g, 38%) as a yellow solid. ¹H NMR (400 MHz, Chloroform-d): δ 7.63 (d, *J* = 7.6 Hz, 1H), 7.57 (s, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 5.19 (s, 2H), 4.30 (s, 1H), 4.14 (dd, *J* = 4.0, 13.2 Hz, 1H), 4.07 - 3.82 (m, 1H), 3.42 (s, 3H), 3.40 (s, 1H), 3.32 (d, *J* = 6.0 Hz, 1H), 3.09 - 2.94 (m, 1H), 2.90 (t, *J* = 8.0 Hz, 2H), 2.30 - 2.21 (m, 1H), 2.14 (quin, *J* = 7.6 Hz, 2H), 1.83 (dd, *J* = 4.8, 8.8 Hz, 1H), 1.69 (s, 3H), 1.51 - 1.37 (m, 9H).

[00350] To a solution of tert-butyl (R)-3-(4-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyridazine-1-carbonyl)piperidine-1-carboxylate (0.5 g, 933.61 μmol) in DMF (5 mL) was added (1Z, 5Z)-cycloocta-1,5-diene;rhodium(1+); tetrafluoroborate (38 mg, 93.36 μmol) and (S)-(+)-DTBMSEPHOS (132 mg, 112.03 μmol) under N₂ atmosphere. The suspension was degassed and purged with H₂ for 3 times. The mixture was stirred under H₂ (3 MPa) at 30°C for 12 h. The mixture was poured into water (10 mL) and extracted with ethyl acetate (5 mL × 3). The organic layers was washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give tert-butyl (R)-3-((R)-hydroxy(4-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)methyl)piperidine-1-carboxylate (0.5 g, 99.6%) as a yellow oil. ¹H NMR (400 MHz, Chloroform-d): δ 7.58 (d, *J* = 8.0 Hz, 1H), 7.55 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 5.18 (s, 2H), 4.84 (s, 1H), 3.97 - 3.77 (m, 2H), 3.43 (s, 3H), 3.14 - 3.05 (m, 2H), 2.95 - 2.90 (m, 1H), 2.27 - 2.19 (m, 1H), 2.17 - 2.08 (m, 1H), 1.80 - 1.69 (m, 2H), 1.46 (d, *J* = 1.6 Hz, 2H), 1.43 (s, 9H).

[00351] To a mixture of tert-butyl (R)-3-((R)-hydroxy(4-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)methyl)piperidine-1-

carboxylate (0.74 g, 1.38 mmol) in DCM (1 mL) was added 1,4-dioxane;hydrochloride (1 mL) at 20°C. The mixture was stirred at 20°C for 0.5 h. Removal solvent in vacuo afforded intermediate a sticky solid. The solid was dissolved in MeOH (2 mL) and 1,2-dichloroethane (10 mL). Then the mixture was added TEA (153 mg, 1.51 mmol), formaldehyde (112 mg, 1.38 mmol). The mixture was stirred at 20°C for 15 min, then NaBH(OAc)₃ (438 mg, 2.06 mmol) was added in portions and the mixture was stirred at 20°C for 2 h. LCMS showed the reaction was completed. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC (neutral condition) to give 2-(4-((R)-hydroxy((R)-1-methylpiperidin-3-yl)methyl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)-5-(trifluoromethyl)phenol (**Compound 44**) (33 mg, 6%) as a white solid. LCMS (ESI⁺): m/z 408.1 (M+H)⁺. ¹H NMR (400 MHz, Methanol-*d*₄): δ 7.68 (d, *J* = 8.0 Hz, 1H), 7.27 (s, 1H), 7.24 (s, 1H), 4.77 (d, *J* = 8.8 Hz, 1H), 3.38 - 3.33 (m, 1H), 3.27 (s, 1H), 3.20 (t, *J* = 7.6 Hz, 1H), 3.10 (t, *J* = 7.6 Hz, 2H), 2.90 (d, *J* = 11.6 Hz, 1H), 2.39 (s, 3H), 2.36 - 2.25 (m, 1H), 2.18 (quin, *J* = 7.6 Hz, 2H), 2.12 - 2.04 (m, 2H), 1.71 (d, *J* = 13.2 Hz, 1H), 1.63 - 1.49 (m, 1H), 1.36 - 1.22 (m, 1H), 1.17 - 1.03 (m, 1H).

Example 45: Synthesis of 2-(6-((R)-((R)-1-ethylpiperidin-3-yl)(hydroxy)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound 45)



[00352] 2-(6-((R)-((R)-1-Ethylpiperidin-3-yl)(hydroxy)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol (**Compound 45**) was prepared as described in Example 17 starting from tert-butyl (R)-3-((R)-hydroxy(6-(2-hydroxy-4-(trifluoromethyl)phenyl)-5-methylpyridazin-3-yl)methyl)piperidine-1-carboxylate (**Compound 17-1B**). ESI-MS (EI⁺, m/z): 396.2.

Example 46: Human Monocyte IL-1b Assay

[00353] Serially diluted testing compounds were incubated with 200 mL of fresh human whole blood for 0.5 hours. Cells were primed with 100 ng/mL lipopolysaccharide (LPS) for 3.5 hours at 37°C followed by stimulation with 5 mM ATP for an additional 45 minutes. The concentration of IL-1b concentration in the supernatant was determined with commercially available ELISA kits. Negative controls are wells without stimulation, while positive controls are wells with stimulation but only DMSO without compounds added. After background subtraction, compound treatment wells were then normalized to the positive controls for IC₅₀ calculations.

[00354] IC₅₀ values are shown in the table below.

Compound	IL-1b (IC ₅₀)	Compound	IL-1b (IC ₅₀)	Compound	IL-1b (IC ₅₀)	Compound	IL-1b (IC ₅₀)
1	B	1A	B	1B	A	2	B
3	A	4	C	5	A	6	B
7	A	8	A	9	A	10	C
11	A	12	B	13	B	14	A
15	A	16	A	17A	A	17B	A
17C	A	17D	B	18	A	19	A
20	A	21	C	22	A	23	C
24	A	25	A	26	A	27A	B
27B	C	28A	A	28B	B	29	B
30	C	31	A	32	A	33	B
34	A	35	B	36	A	37	B
38	B	39	A	40	A	41	A
42	A	43A	A	43B	B	44	A
45	A						

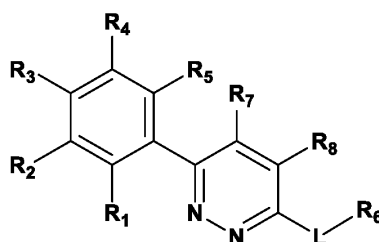
A: IC₅₀ < 500 nM; B: 500 nM ≤ IC₅₀ < 3 μM; C: 3 μM ≤ IC₅₀ < 10 μM

[00355] The examples and embodiments described herein are for illustrative purposes only and in some embodiments, various modifications or changes are to be included within the purview of disclosure and scope of the appended claims.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof:



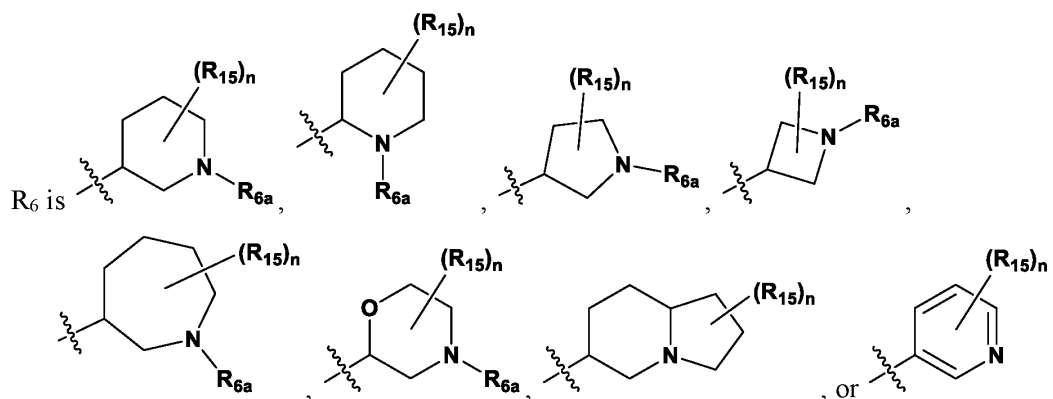
Formula (I');

wherein:

L is -C(R_{9a})(R_{9b})-, -C(O)-, or -C(=N-OR₁₆)-;

R₁, R₂, R₃, R₄, and R₅ are each independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁)-, S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁); or R₁ and R₂ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups; or R₂ and R₃ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups; or R₃ and R₄ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups; or R₄ and R₅ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-,

5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups;



R_{6a} is selected from hydrogen, C_{1-6} alkyl, and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl optionally substituted with one, two, or three R_{14} groups; or R_{6a} and an R_{15} are taken together to form a bridge that is $-CH_2-$ or $-CH_2CH_2-$;

R_7 and R_8 are each independently selected from hydrogen, halogen, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR_{10}$, and $-N(R_{10})(R_{11})$; or R_7 and R_8 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups;

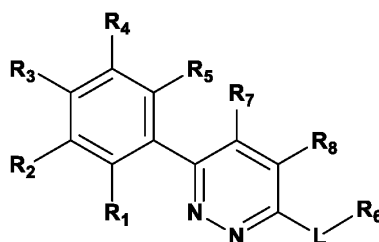
R_{9a} and R_{9b} are each independently selected from hydrogen, halogen, $-OH$, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

each R_{10} is independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl;

each R_{11} is independently selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

- each R_{12} is independently selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;
- each R_{13} is independently selected C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl;
- each R_{14} is independently selected from halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, C_{1-9} heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁), -S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, -OR¹⁰, and -N(R₁₀)(R₁₁);
- each R_{15} is independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, C_{1-9} heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁), -S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, -OR¹⁰, and -N(R₁₀)(R₁₁); or two R_{15} are taken together to form a bridge that is -CH₂- or -CH₂CH₂;
- R_{16} is selected from hydrogen and C_{1-6} alkyl; and
- n is 0, 1, 2, 3, or 4.

2. A compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:

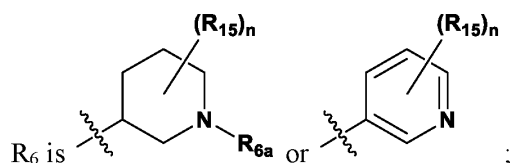


Formula (I);

wherein:

L is $-C(R_{9a})(R_{9b})-$, $-C(O)-$, or $-C(=N-OR_{16})-$;

R_1 , R_2 , R_3 , R_4 , and R_5 are each independently selected from hydrogen, halogen, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, C_{1-9} heteroaryl, $-OR_{10}$, $-SR_{10}$, $-N(R_{10})(R_{11})$, $-C(O)OR_{10}$, $-OC(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)OR_{13}$, $-N(R_{12})S(O)_2R_{13}$, $-C(O)R_{13}$, $-S(O)R_{13}$, $-OC(O)R_{13}$, $-C(O)N(R_{10})(R_{11})$, $-C(O)C(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)R_{13}$, $-S(O)_2R_{13}$, $-S(O)_2N(R_{10})(R_{11})$, $S(=O)(=NH)N(R_{10})(R_{11})$, $-CH_2C(O)N(R_{10})(R_{11})$, $-CH_2N(R_{12})C(O)R_{13}$, $-CH_2S(O)_2R_{13}$, and $-CH_2S(O)_2N(R_{10})(R_{11})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR_{10}$, and $-N(R_{10})(R_{11})$; or R_1 and R_2 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups; or R_2 and R_3 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups; or R_3 and R_4 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups; or R_4 and R_5 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups;



R_{6a} is selected from hydrogen and C₁₋₆alkyl optionally substituted with one, two, or three R₁₄ groups;

R₇ and R₈ are each independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁); or R₇ and R₈ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups;

R_{9a} and R_{9b} are each independently selected from hydrogen, halogen, -OH, C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy;

each R₁₀ is independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

each R₁₁ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R₁₂ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R₁₃ is independently selected C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

each R₁₄ is independently selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁), -S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one,

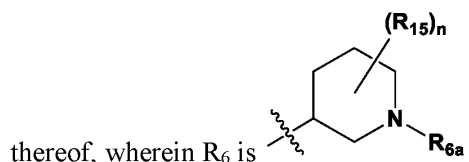
two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR¹⁰, and -N(R₁₀)(R₁₁);

each R₁₅ is independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁)-, S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR¹⁰, and -N(R₁₀)(R₁₁);

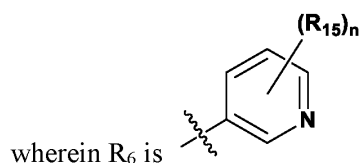
R₁₆ is selected from hydrogen and C₁₋₆alkyl; and

n is 0, 1, 2, 3, or 4.

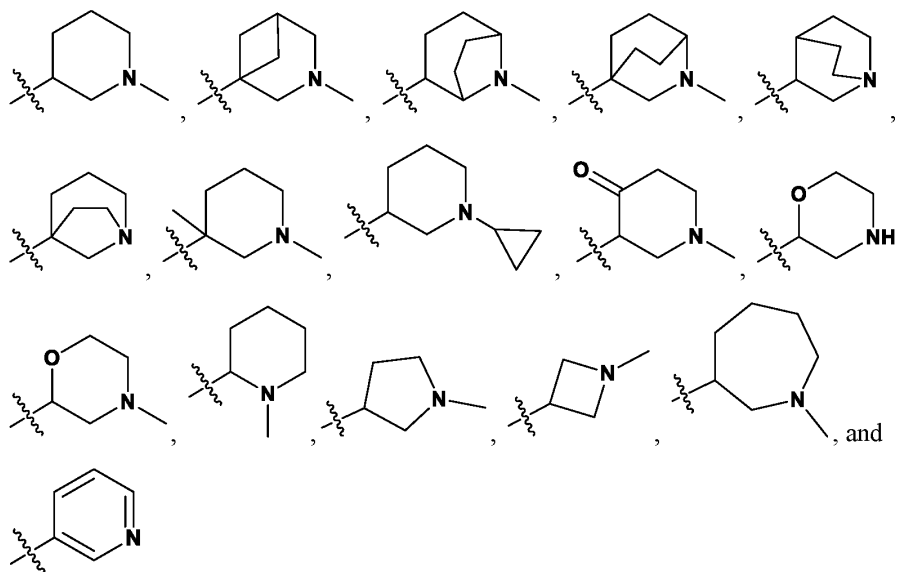
3. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt or solvate



4. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is C₁₋₆alkyl optionally substituted with one, two, or three R₁₄ groups.
5. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is unsubstituted C₁₋₆alkyl.
6. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is -CH₃.
7. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof,



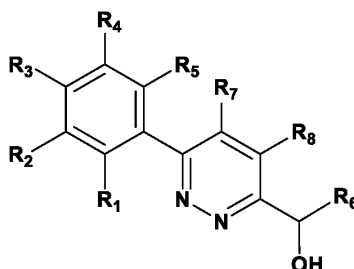
8. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0.
9. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein R₆ is selected from:



10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are each independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁).
11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are each independently selected from hydrogen, halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl.
12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are each independently selected from hydrogen and C₁₋₆alkyl.
13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are hydrogen.
14. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ is hydrogen and R₈ is -CH₃.
15. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ is -CH₃ and R₈ is hydrogen.
16. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are -CH₃.
17. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered

- heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups.
18. The compound of claim 17, or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ and R₈ are combined to form an unsubstituted phenyl ring.
 19. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, or -C(O)N(R₁₀)(R₁₁).
 20. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, or -OH.
 21. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is -OH.
 22. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt or solvate thereof, wherein R₂ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, or -OR₁₀.
 23. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt or solvate thereof, wherein R₂ is hydrogen.
 24. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt or solvate thereof, wherein R₃ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, or -N(R₁₀)(R₁₁).
 25. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt or solvate thereof, wherein R₃ is C₁₋₆alkyl or C₁₋₆haloalkyl.
 26. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt or solvate thereof, wherein R₄ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, or -OR₁₀.
 27. The compound of any one of claims 1-26, or a pharmaceutically acceptable salt or solvate thereof, wherein R₄ is hydrogen.
 28. The compound of any one of claims 1-27, or a pharmaceutically acceptable salt or solvate thereof, wherein R₅ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, or -N(R₁₀)(R₁₁).
 29. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt or solvate thereof, wherein R₅ is hydrogen or C₁₋₆alkyl.
 30. The compound of any one of claims 1-29, or a pharmaceutically acceptable salt or solvate thereof, wherein L is -C(R_{9a})(R_{9b})-.
 31. The compound of claim 30, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{9a} is selected from hydrogen, halogen, and C₁₋₆alkyl.
 32. The compound of claim 31, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{9a} is hydrogen.
 33. The compound of claim 30 or claim 31, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{9b} is selected from hydrogen, halogen, and -OH.

34. The compound of claim 33, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{9b} is -OH.
35. The compound of any one of claims 1-29, or a pharmaceutically acceptable salt or solvate thereof, wherein L is -C(O)-.
36. A compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof:

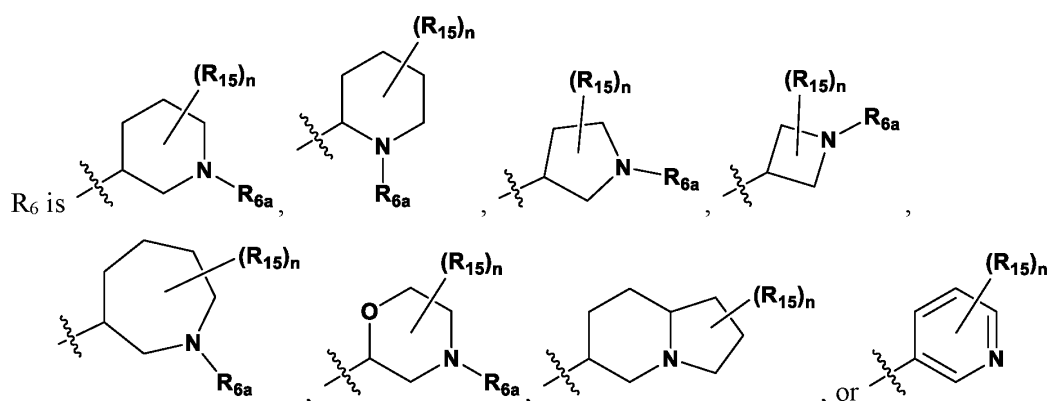


Formula (II);

wherein:

R_1 , R_2 , R_3 , R_4 , and R_5 are each independently selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, C_{1-9} heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁), -S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁); or R_1 and R_2 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups; or R_2 and R_3 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups; or R_3 and R_4 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered

heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups; or R_4 and R_5 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups;



R_{6a} is selected from hydrogen, C_{1-6} alkyl, and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl optionally substituted with one, two, or three R_{14} groups; or R_{6a} and an R_{15} are taken together to form a bridge that is $-CH_2-$ or $-CH_2CH_2-$;

R_7 and R_8 are each independently selected from hydrogen, halogen, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR_{10}$, and $-N(R_{10})(R_{11})$; or R_7 and R_8 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups;

each R_{10} is independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl;

each R_{11} is independently selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R_{12} is independently selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R_{13} is independently selected C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl;

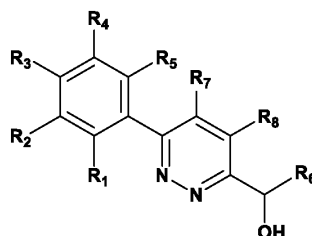
each R_{14} is independently selected from halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, C_{1-9} heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁), -S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, -OR¹⁰, and -N(R₁₀)(R₁₁);

each R_{15} is independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, C_{1-9} heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁), -S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, -OR¹⁰, and -N(R₁₀)(R₁₁); or two R_{15} are taken together to form a bridge that is -CH₂- or -CH₂CH₂-;

and

n is 0, 1, 2, 3, or 4.

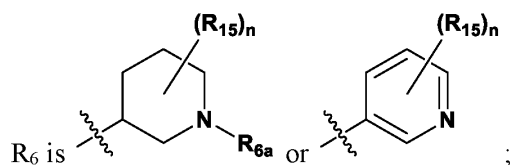
37. A compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof:



Formula (III);

wherein:

R₁, R₂, R₃, R₄, and R₅ are each independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁), S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁); or R₁ and R₂ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups; or R₂ and R₃ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups; or R₃ and R₄ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups; or R₄ and R₅ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups;



R_{6a} is selected from hydrogen and C₁₋₆alkyl optionally substituted with one, two, or three R₁₄ groups;

R₇ and R₈ are each independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁); or R₇ and R₈ are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups;

each R₁₀ is independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

each R₁₁ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R₁₂ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R₁₃ is independently selected C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

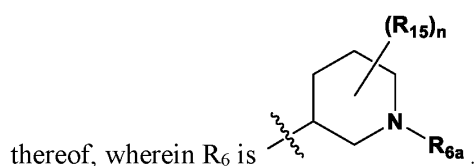
each R₁₄ is independently selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁), -S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR¹⁰, and -N(R₁₀)(R₁₁);

each R₁₅ is independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -

OR₁₀, -SR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, -OC(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)OR₁₃, -N(R₁₂)S(O)₂R₁₃, -C(O)R₁₃, -S(O)R₁₃, -OC(O)R₁₃, -C(O)N(R₁₀)(R₁₁), -C(O)C(O)N(R₁₀)(R₁₁), -N(R₁₂)C(O)R₁₃, -S(O)₂R₁₃, -S(O)₂N(R₁₀)(R₁₁), -S(=O)(=NH)N(R₁₀)(R₁₁), -CH₂C(O)N(R₁₀)(R₁₁), -CH₂N(R₁₂)C(O)R₁₃, -CH₂S(O)₂R₁₃, and -CH₂S(O)₂N(R₁₀)(R₁₁), wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR¹⁰, and -N(R₁₀)(R₁₁); and

n is 0, 1, 2, 3, or 4.

38. The compound of claim 36 or claim 37, or a pharmaceutically acceptable salt or solvate

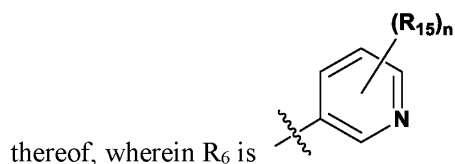


39. The compound of any one of claims 36-38, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is C₁₋₆alkyl optionally substituted with one, two, or three R₁₄ groups.

40. The compound of any one of claims 36-39, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is unsubstituted C₁₋₆alkyl.

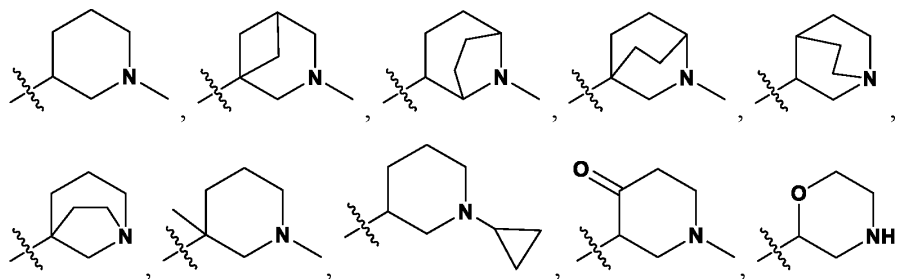
41. The compound of any one of claims 36-38, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is -CH₃.

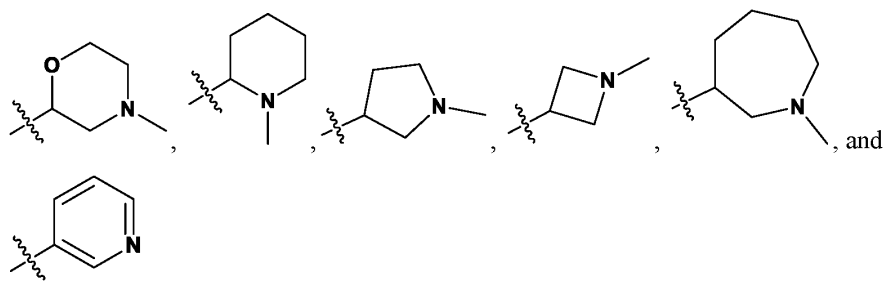
42. The compound of claim 36 or claim 37, or a pharmaceutically acceptable salt or solvate



43. The compound of any one of claims 36-42, or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0.

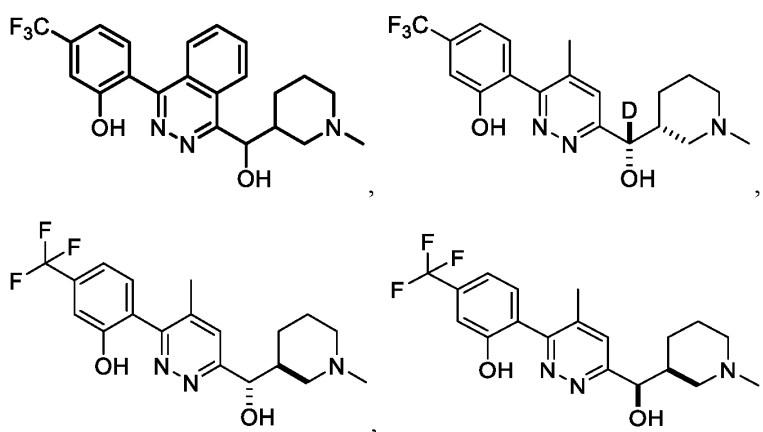
44. The compound of claim 36, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is selected from:

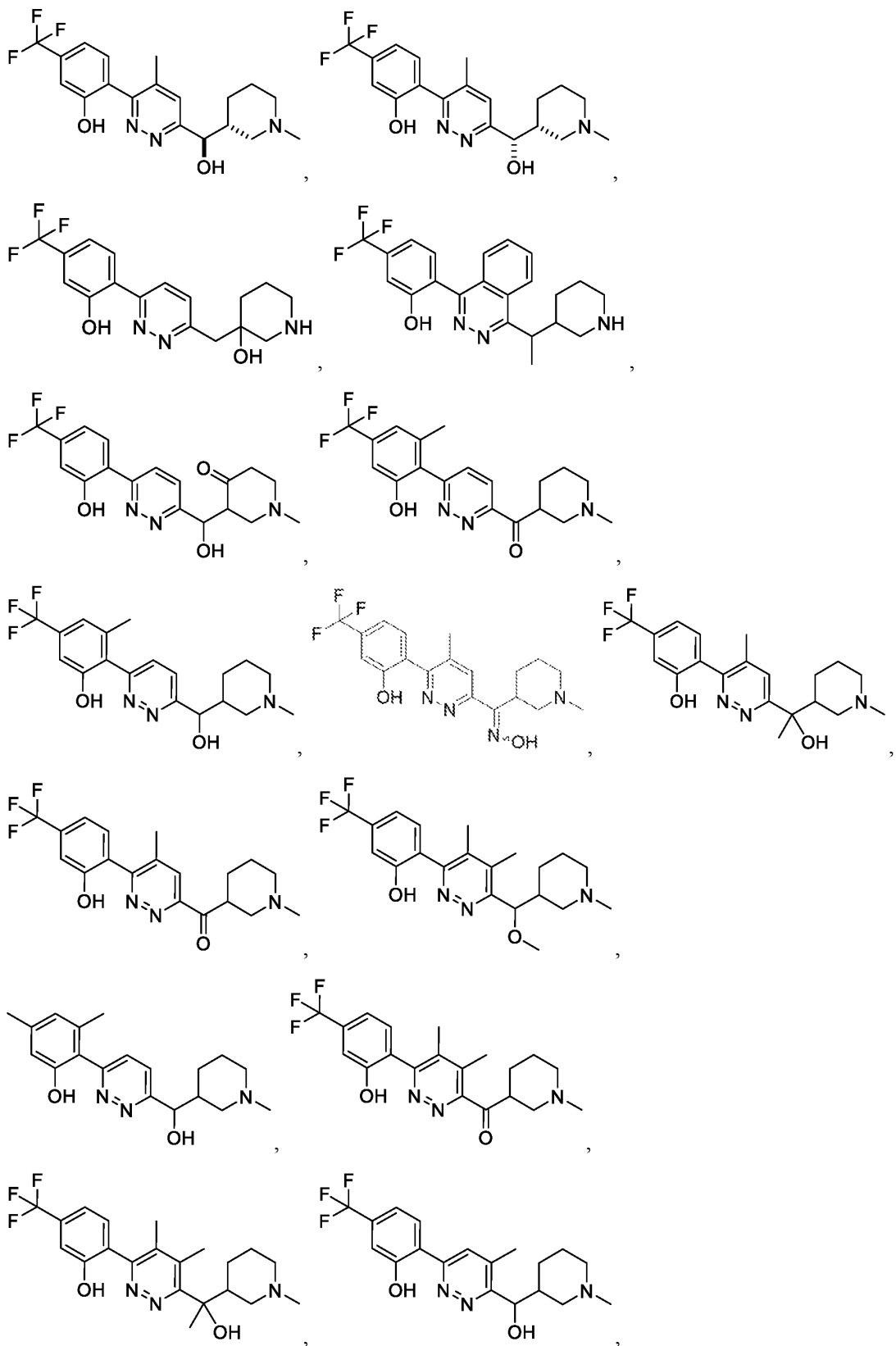


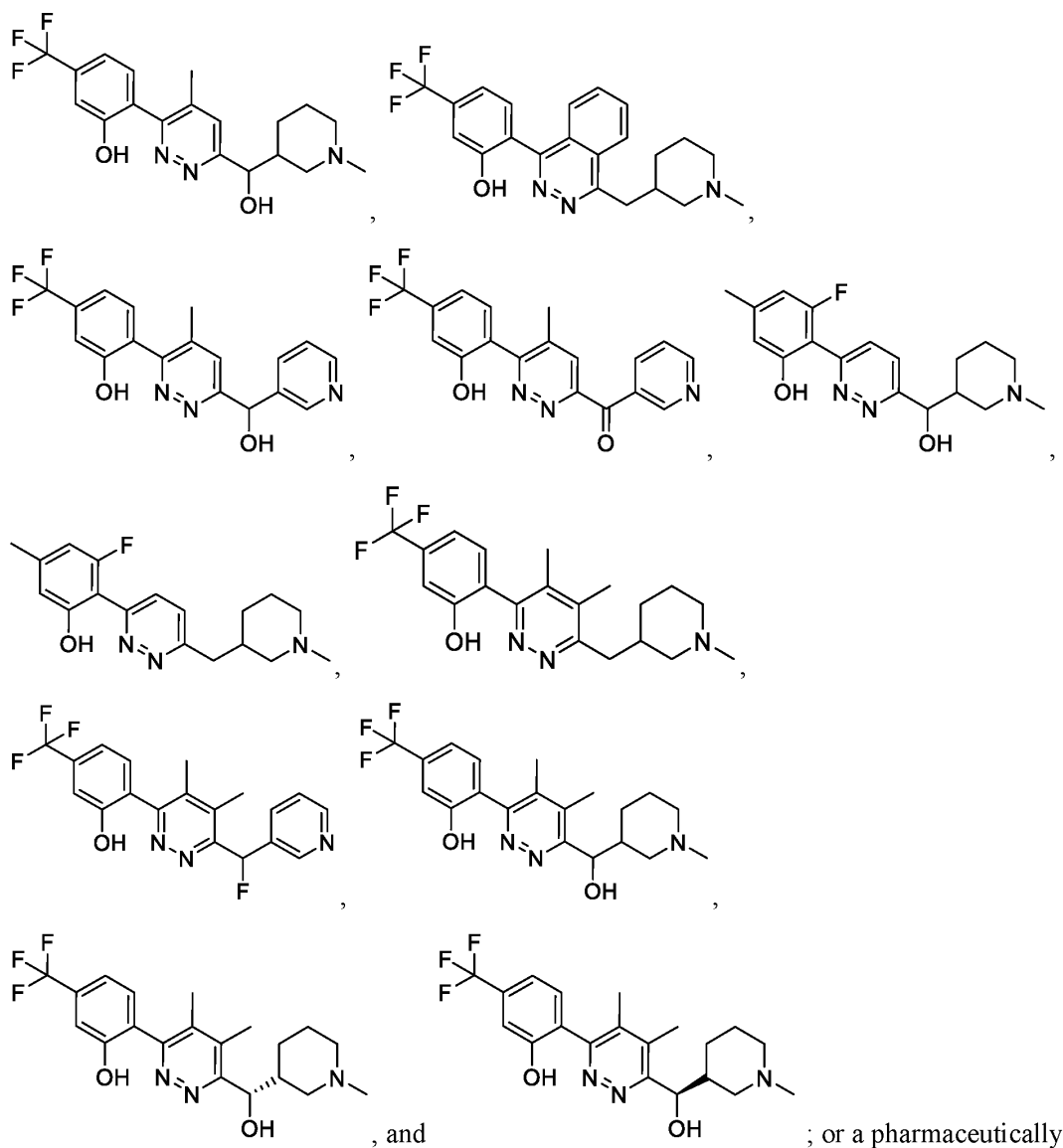


45. The compound of any one of claims 36-44, or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are each independently selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, -OR₁₀, and -N(R₁₀)(R₁₁).
46. The compound of any one of claims 36-45, or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are each independently selected from hydrogen, halogen, C_{1-6} alkyl, and C_{1-6} haloalkyl.
47. The compound of any one of claims 36-46, or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are each independently selected from hydrogen and C_{1-6} alkyl.
48. The compound of any one of claims 36-47, or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are hydrogen.
49. The compound of any one of claims 36-47, or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 is hydrogen and R_8 is -CH₃.
50. The compound of any one of claims 36-47, or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 is -CH₃ and R_8 is hydrogen.
51. The compound of any one of claims 36-47, or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are -CH₃.
52. The compound of any one of claims 36-44, or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R₁₄ groups.
53. The compound of claim 52, or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are combined to form an unsubstituted phenyl ring.

54. The compound of any one of claims 36-53, or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, -N(R₁₀)(R₁₁), -C(O)OR₁₀, or -C(O)N(R₁₀)(R₁₁).
55. The compound of any one of claims 36-54, or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, or -OH.
56. The compound of any one of claims 36-55, or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is -OH.
57. The compound of any one of claims 36-56, or a pharmaceutically acceptable salt or solvate thereof, wherein R₂ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, or -OR₁₀.
58. The compound of any one of claims 36-57, or a pharmaceutically acceptable salt or solvate thereof, wherein R₂ is hydrogen.
59. The compound of any one of claims 36-58, or a pharmaceutically acceptable salt or solvate thereof, wherein R₃ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, or -N(R₁₀)(R₁₁).
60. The compound of any one of claims 36-59, or a pharmaceutically acceptable salt or solvate thereof, wherein R₃ is C₁₋₆alkyl or C₁₋₆haloalkyl.
61. The compound of any one of claims 36-60, or a pharmaceutically acceptable salt or solvate thereof, wherein R₄ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, or -OR₁₀.
62. The compound of any one of claims 36-61, or a pharmaceutically acceptable salt or solvate thereof, wherein R₄ is hydrogen.
63. The compound of any one of claims 36-62, or a pharmaceutically acceptable salt or solvate thereof, wherein R₅ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR₁₀, or -N(R₁₀)(R₁₁).
64. The compound of any one of claims 36-63, or a pharmaceutically acceptable salt or solvate thereof, wherein R₅ is hydrogen or C₁₋₆alkyl.
65. A compound selected from:

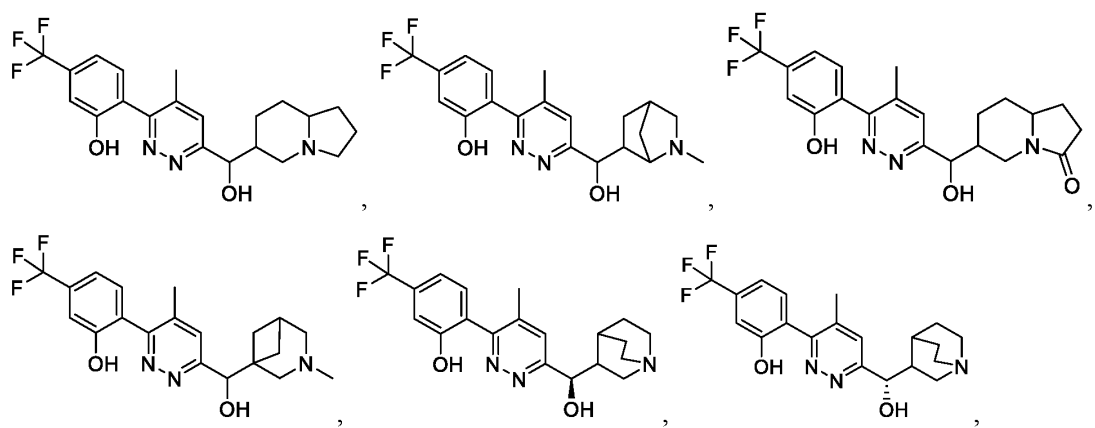


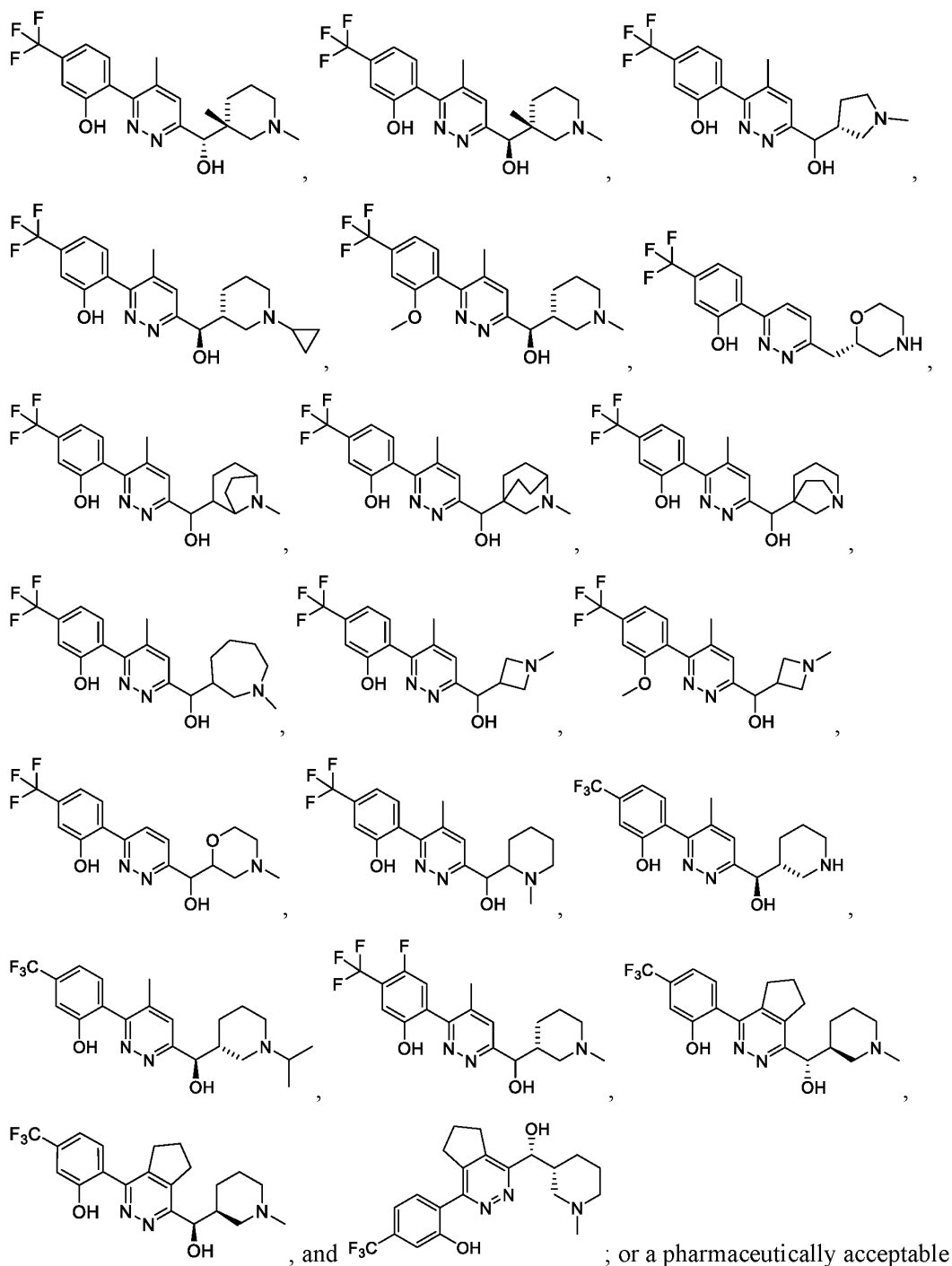




acceptable salt or solvate thereof.

66. A compound selected from:





salt or solvate thereof.

67. A pharmaceutical composition comprising a compound of any one of claims 1-66, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

68. A method of treating a metabolic disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-66, or a pharmaceutically acceptable salt or solvate thereof.
69. The method of claim 68, wherein the metabolic disease is selected from type 2 diabetes, atherosclerosis, obesity and gout.
70. A method of treating a liver disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-66, or a pharmaceutically acceptable salt or solvate thereof.
71. The method of claim 70, wherein the liver disease is selected from non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), viral hepatitis, and cirrhosis.
72. A method of treating a lung disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-66, or a pharmaceutically acceptable salt or solvate thereof.
73. The method of claim 72, wherein the lung disease is selected from asthma, chronic obstructive pulmonary disease (COPD), and pulmonary idiopathic fibrosis.
74. A method of treating a central nervous system disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-66, or a pharmaceutically acceptable salt or solvate thereof.
75. The method of claim 74, wherein the central nervous system disease is selected from Alzheimer's disease, multiple sclerosis, Amyotrophic Lateral Sclerosis, Parkinson's disease, Huntington's disease, traumatic brain injury, ischemic stroke and reperfusion, haemorrhagic stroke, epilepsy, and depression.
76. A method of treating an inflammatory or autoimmune disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-66, or a pharmaceutically acceptable salt or solvate thereof.
77. The method of claim 76, wherein the inflammatory or autoimmune disease is selected from rheumatoid arthritis, multiple sclerosis, psoriasis, lupus, inflammatory bowel disease, Crohn's disease, and ulcerative colitis.
78. A method of treating a cardiovascular disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-66, or a pharmaceutically acceptable salt or solvate thereof.
79. The method of claim 78, wherein the cardiovascular disease is atherosclerosis or stroke.