NLRP3 MODULATORS

CROSS-REFERENCE

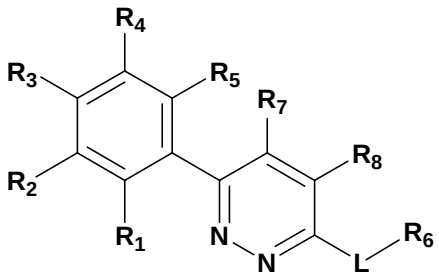
[0001] This application claims benefit of U.S. Provisional Application No. 63/320,157, filed on March 15, 2022, and U.S. Provisional Application No. 63/356,415, filed on June 28, 2022, each of which is herein incorporated by reference in its entirety.

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 example, 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 $-C(=N-OR_{16})-$;

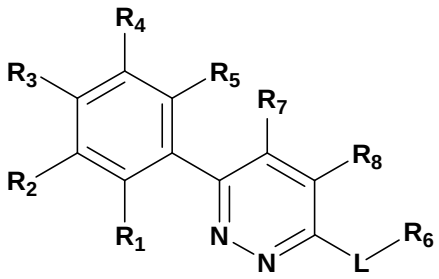
R_1, R_2, R_3, R_4, and R_5 are each independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR_{10}$, $-SR_{10}$, $-N(R_{10})(R_{11})$, $-C(O)OR_{10}$, $-OC(O)N(R_{10})(R_{11})$,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

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.

[0003a] In one aspect, the present disclosure provides a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof:



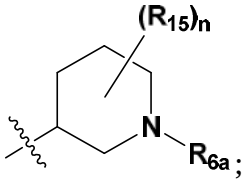
Formula (I');

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 the 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_6 is 

;

R_{6a} is hydrogen or C_{1-6}alkyl;

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 the 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_{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 the 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 from 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 the 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;

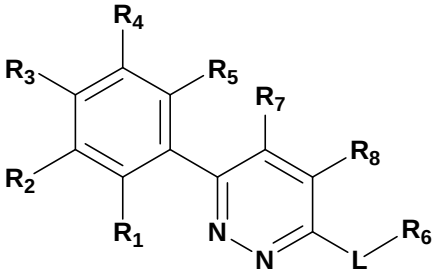
each R_{14} is independently selected from halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR_{10}$, $-SR_{10}$, $-N(R_{10})(R_{11})$, $-C(O)OR_{10}$, $-OC(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)OR_{13}$, $-N(R_{12})S(O)_2R_{13}$, $-C(O)R_{13}$, $-S(O)R_{13}$, $-OC(O)R_{13}$, $-C(O)N(R_{10})(R_{11})$, $-C(O)C(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)R_{13}$, $-S(O)_2R_{13}$, $-S(O)_2N(R_{10})(R_{11})$, $S(=O)(=NH)N(R_{10})(R_{11})$, $-CH_2C(O)N(R_{10})(R_{11})$, $-CH_2N(R_{12})C(O)R_{13}$, $-CH_2S(O)_2R_{13}$, and $-CH_2S(O)_2N(R_{10})(R_{11})$, wherein the 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 the 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.

[0004] In another example, 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 $-C(=N-OR_{16})$-;

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

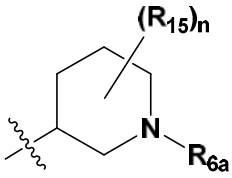
$_{6}$alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

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, $-OR_{10}$, $-SR_{10}$, $-N(R_{10})(R_{11})$, $-C(O)OR_{10}$, $-OC(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)OR_{13}$, $-N(R_{12})S(O)_2R_{13}$, $-C(O)R_{13}$, $-S(O)R_{13}$, $-OC(O)R_{13}$, $-C(O)N(R_{10})(R_{11})$, $-C(O)C(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)R_{13}$, $-S(O)_2R_{13}$, $-S(O)_2N(R_{10})(R_{11})$-, $S(=O)(=NH)N(R_{10})(R_{11})$, $-CH_2C(O)N(R_{10})(R_{11})$, $-CH_2N(R_{12})C(O)R_{13}$, $-CH_2S(O)_2R_{13}$, 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 $-N(R_{10})(R_{11})$;

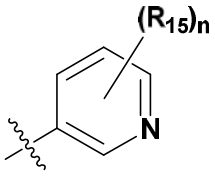
each R_{15} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR_{10}$, $-SR_{10}$, $-N(R_{10})(R_{11})$, $-C(O)OR_{10}$, $-OC(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)OR_{13}$, $-N(R_{12})S(O)_2R_{13}$, $-C(O)R_{13}$, $-S(O)R_{13}$, $-OC(O)R_{13}$, $-C(O)N(R_{10})(R_{11})$, $-C(O)C(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)R_{13}$, $-S(O)_2R_{13}$, $-S(O)_2N(R_{10})(R_{11})$-, $S(=O)(=NH)N(R_{10})(R_{11})$, $-CH_2C(O)N(R_{10})(R_{11})$, $-CH_2N(R_{12})C(O)R_{13}$, $-CH_2S(O)_2R_{13}$, 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 $-N(R_{10})(R_{11})$;

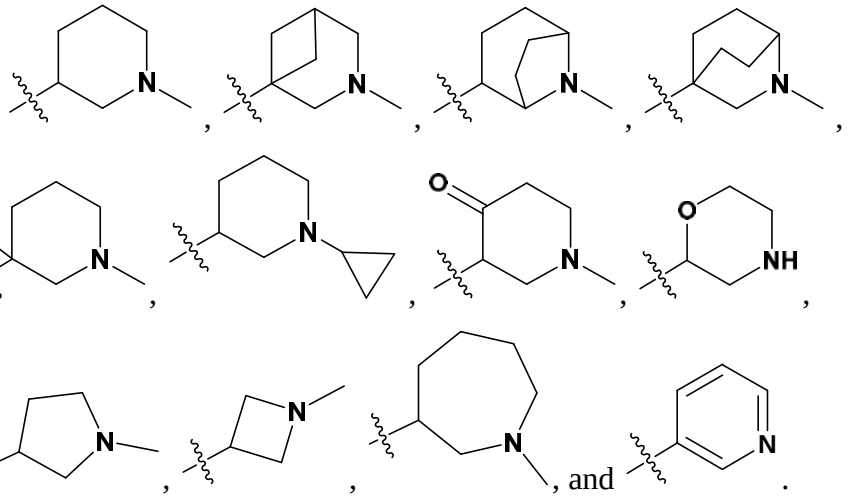
R_{16} is selected from hydrogen and C_{1-6}alkyl; and

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

[0005] In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_6 is 

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

[0006] In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_6 is . In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0.

[0007] In some examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_6 is .

[0008] In some examples 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, -OR_{10}, and -$N(R_{10})(R_{11})$. In some examples 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 examples 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 examples 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 -CH_3. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt

or solvate thereof, wherein R_7 is $-CH_3$ and R_8 is hydrogen. 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 $-CH_3$.

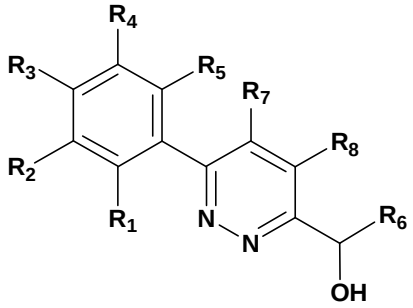
[0009] In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, 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 R_{14} groups. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are combined to form an unsubstituted phenyl ring.

[0010] In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, $-OR_{10}$, $-N(R_{10})(R_{11})$, $-C(O)OR_{10}$, or $-C(O)N(R_{10})(R_{11})$. In some exampless is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, or -OH. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is -OH. In some examples is a compound of Formula (I') or (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 examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is hydrogen. In some examples is a compound of Formula (I') or (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 examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is C_{1-6}alkyl or C_{1-6}haloalkyl. In some examples is a compound of Formula (I') or (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 examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is hydrogen.

[0011] In some examples is a compound of Formula (I') or (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 examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is hydrogen or C_{1-6}alkyl. In some examples 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 examples 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 C_{1-6}alkyl. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{9a} is hydrogen. In some examples 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 examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{9b} is -OH. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein L is -C(O)-.

[0012] In one example, provided herein are compounds 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, -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

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, $-OR_{10}$, $-SR_{10}$, $-N(R_{10})(R_{11})$, $-C(O)OR_{10}$, $-OC(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)OR_{13}$, $-N(R_{12})S(O)_2R_{13}$, $-C(O)R_{13}$, $-S(O)R_{13}$, $-OC(O)R_{13}$, $-C(O)N(R_{10})(R_{11})$, $-C(O)C(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)R_{13}$, $-S(O)_2R_{13}$, $-S(O)_2N(R_{10})(R_{11})$-, $S(=O)(=NH)N(R_{10})(R_{11})$, $-CH_2C(O)N(R_{10})(R_{11})$, $-CH_2N(R_{12})C(O)R_{13}$, $-CH_2S(O)_2R_{13}$, 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 $-N(R_{10})(R_{11})$;

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 $-N(R_{10})(R_{11})$; or two R_{15} are taken together to form a bridge that is $-CH_2-$ or $-CH_2CH_2-$; and

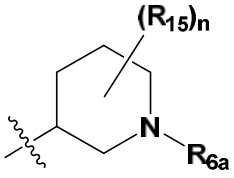
n is 0, 1, 2, 3, or 4.

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

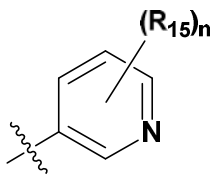
$C(O)C(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)R_{13}$, $-S(O)_2R_{13}$, $-S(O)_2N(R_{10})(R_{11})$-, $S(=O)(=NH)N(R_{10})(R_{11})$, $-CH_2C(O)N(R_{10})(R_{11})$, $-CH_2N(R_{12})C(O)R_{13}$, $-CH_2S(O)_2R_{13}$, and $-CH_2S(O)_2N(R_{10})(R_{11})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, 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

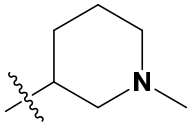
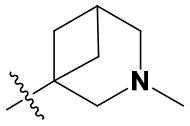
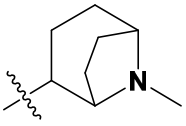
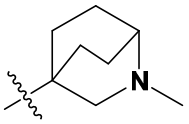
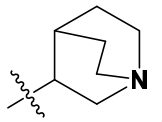
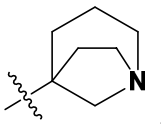
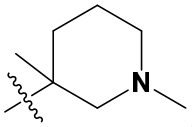
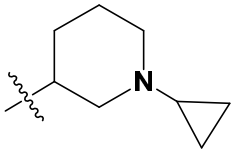
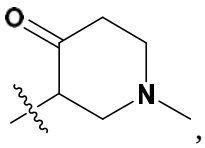
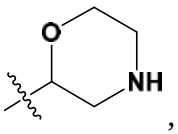
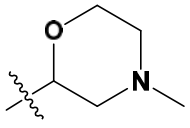
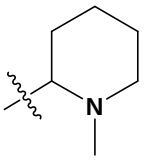
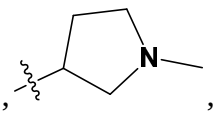
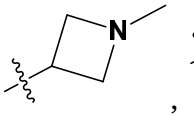
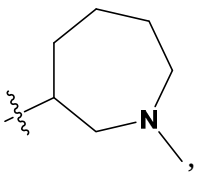
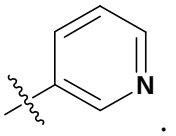
n is 0, 1, 2, 3, or 4.

[0014] In some examples is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_6 is 

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

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

[0016] In some examples is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_6 is , , , , , , , , , , , , , , , and .

[0017] In some examples is a compound of Formula (II) or (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 examples is a compound of Formula (II) or (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 examples is a compound of Formula (II) or (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 examples is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are hydrogen. In some examples is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 is hydrogen and R_8 is -CH_3. In some examples is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 is -CH_3 and R_8 is hydrogen. In some examples is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are -CH_3.

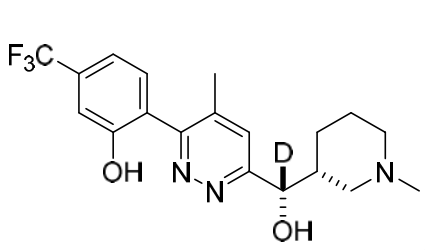
[0018] In some examples is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are combined to form a 4-, 5-, or 6-membered cycloalkyl ring, a 4-, 5-, or 6-membered heterocycloalkyl ring, a 5- or 6-membered heteroaryl ring, or a phenyl ring, wherein the 4-, 5-, or 6-membered cycloalkyl ring, 4-, 5-, or 6-

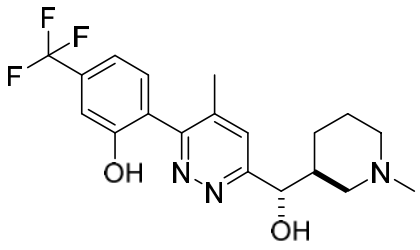
membered heterocycloalkyl ring, 5- or 6-membered heteroaryl ring, or phenyl ring are optionally substituted with one, two, or three R_{14} groups. In some examples is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are combined to form an unsubstituted phenyl ring.

[0019] In some examples is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, -OR_{10}, -$N(R_{10})(R_{11})$, -$C(O)OR_{10}$, or -$C(O)N(R_{10})(R_{11})$. In some examples is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, or -OH. In some examples is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is -OH. In some examples is a compound of Formula (II) or (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 examples is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is hydrogen. In some examples is a compound of Formula (II) or (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 examples is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is C_{1-6}alkyl or C_{1-6}haloalkyl. In some examples is a compound of Formula (II) or (III), 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 examples is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is hydrogen.

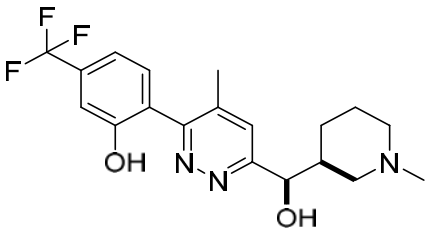
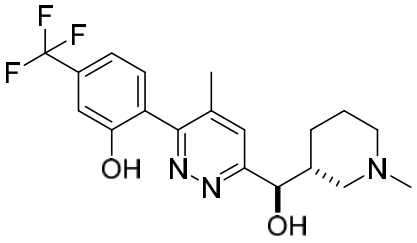
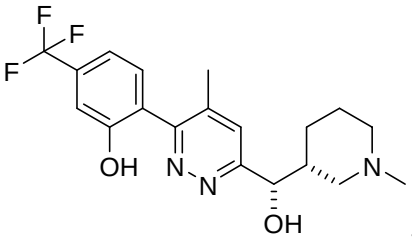
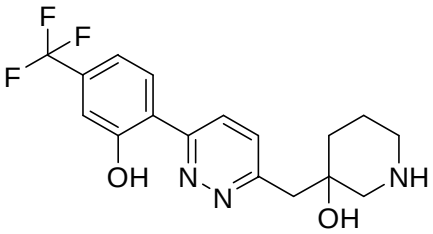
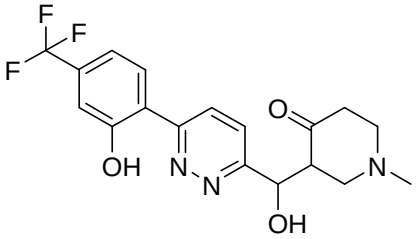
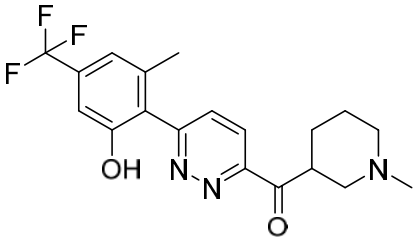
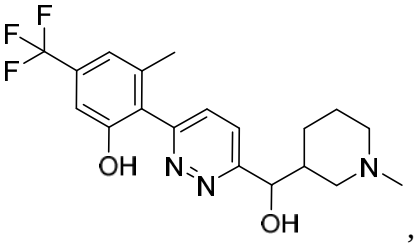
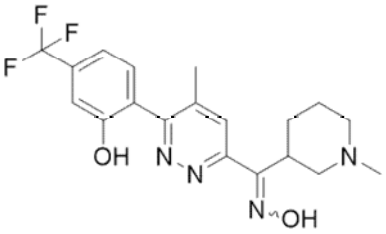
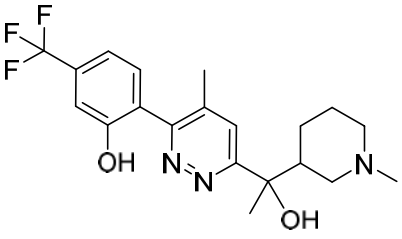
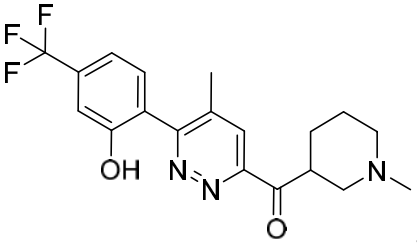
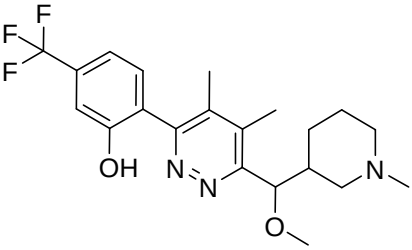
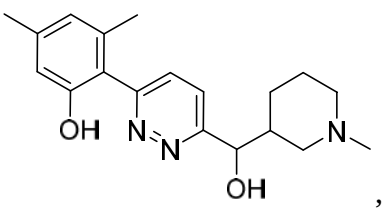
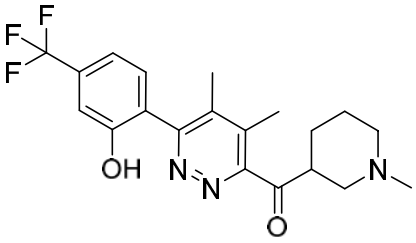
[0020] In some examples is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, -OR_{10}, or -$N(R_{10})(R_{11})$. In some examples is a compound of Formula (II) or (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is hydrogen or C_{1-6}alkyl.

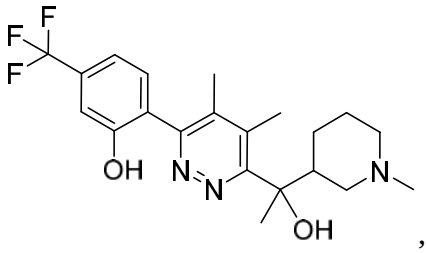
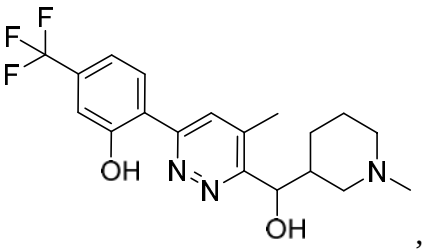
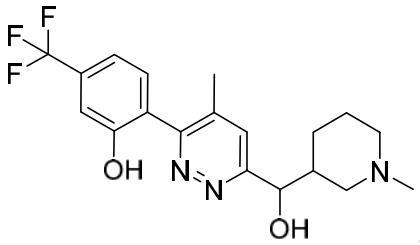
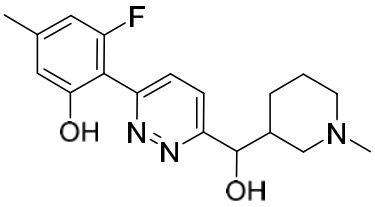
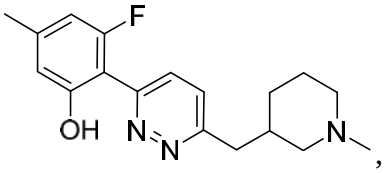
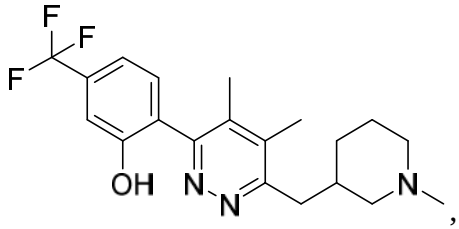
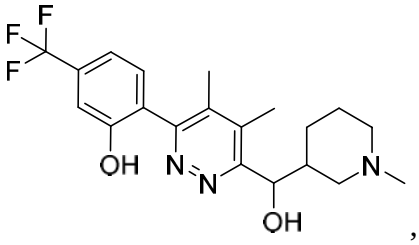
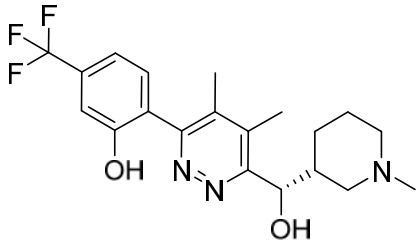
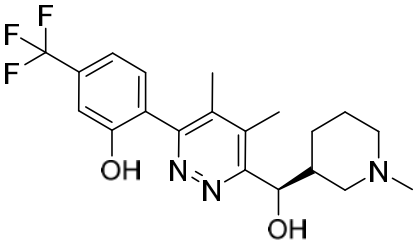
[0020a] In one aspect, there is provided a compound selected from



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; or a pharmaceutically acceptable salt or solvate thereof.

[0021] In another example 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 examples 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 examples 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

[0022a] In another aspect, the present disclosure provides a use of the compound as described herein, or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for treating a metabolic disease in a patient in need thereof, wherein the metabolic disease is selected from type 2 diabetes, atherosclerosis, and obesity; the liver disease is non-alcoholic steatohepatitis (NASH); the central nervous system disease is selected from Alzheimer's disease, multiple sclerosis, Amyotrophic Lateral Sclerosis, Parkinson's disease, and ischemic stroke; the cardiovascular disease is atherosclerosis or stroke; and the inflammatory or autoimmune disease is selected from rheumatoid arthritis, multiple sclerosis, and Crohn's disease.

[0023] In some examples 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 examples 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 examples 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 examples 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.

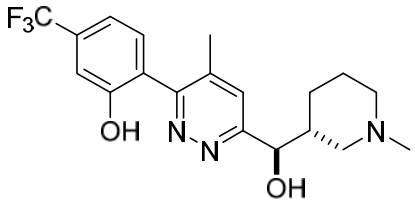
[0025] In some examples described herein is a method of treating a central nervous system disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I'), (I), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof. In some examples 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 examples 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 examples 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.

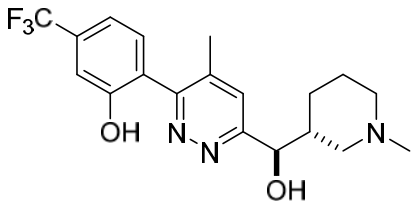
[0027] In some examples described herein is a method of treating a cardiovascular disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I'), (I), (II), or (III), or a pharmaceutically acceptable salt or solvate thereof.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

[0027a] In one aspect, the present disclosure provides a compound that is



; or a pharmaceutically acceptable salt thereof.

[0027b] In another aspect, the present disclosure provides a compound that is



.

[0027c] In yet another aspect, the present disclosure provides a compound selected from 2-(6-((S)-hydroxy((R)-1-methylpiperidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol, 2-(6-((R)-hydroxy((R)-1-methylpiperidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol, 2-(6-((R)-hydroxy((S)-1-methylpiperidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol, and 2-(6-((S)-hydroxy((S)-1-methylpiperidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol; or a pharmaceutically acceptable salt thereof.

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.

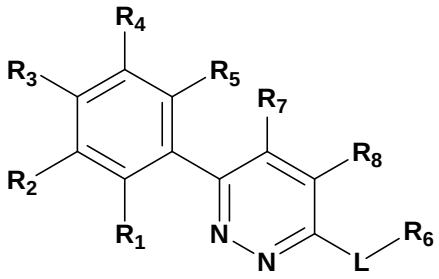
[0030] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood to which the claimed subject matter belongs. In the event that there are a plurality of definitions for terms herein, those in this section prevail. All patents, patent applications, 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.

CLAIMS

WHAT IS CLAIMED IS:

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



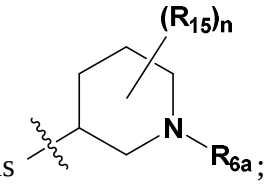
Formula (I');

wherein:

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

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 the 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_6 is 

;

R_{6a} is hydrogen or C_{1-6}alkyl;

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 the 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_{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 the 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 from 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 the 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, -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 the 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 $-N(R_{10})(R_{11})$;

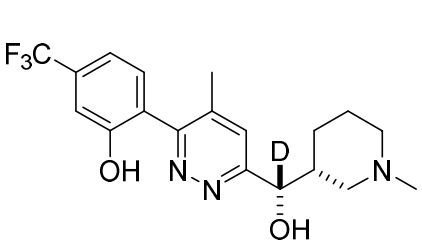
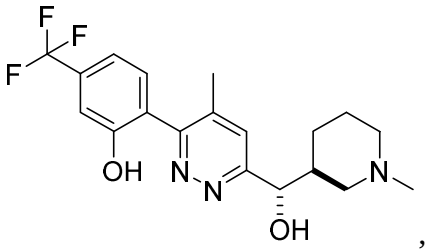
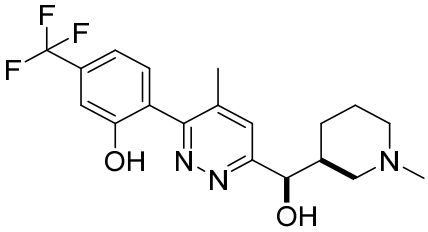
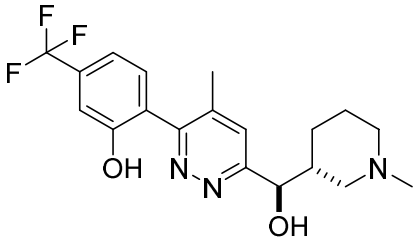
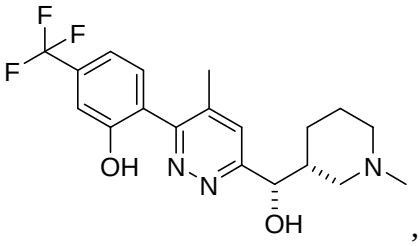
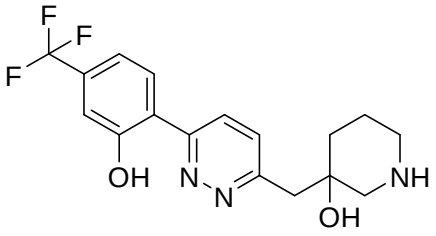
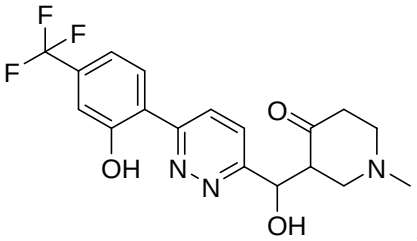
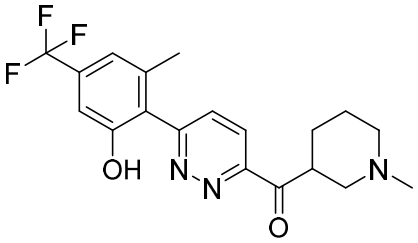
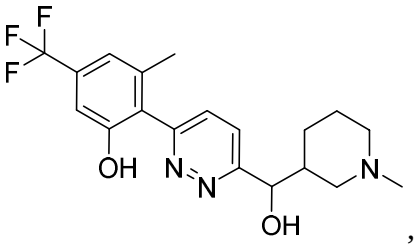
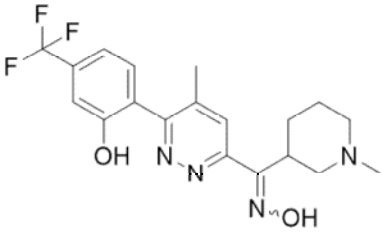
each R_{15} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR_{10}$, $-SR_{10}$, $-N(R_{10})(R_{11})$, $-C(O)OR_{10}$, $-OC(O)N(R_{10})(R_{11})$, $-N(R_{12})C(O)N(R_{10})(R_{11})$,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

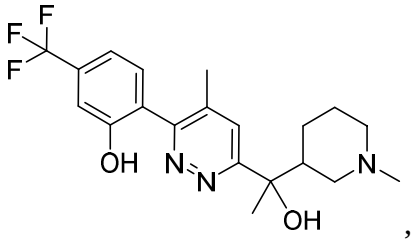
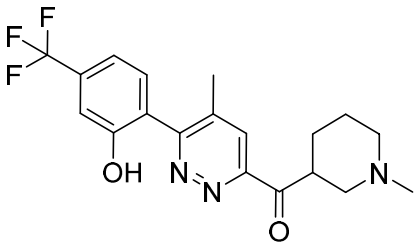
R_{16} is selected from hydrogen and C_{1-6}alkyl; and

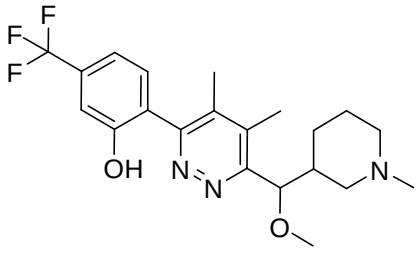
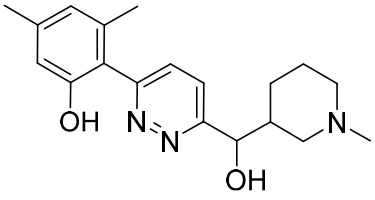
n is 0, 1, 2, 3, or 4.

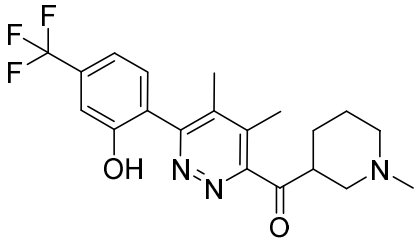
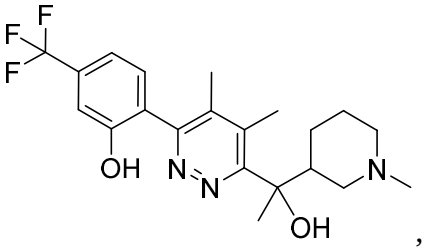
2. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is C_{1-6}alkyl.
3. The compound of claim 2, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{6a} is $-CH_3$.
4. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0.
5. The compound of claim 1, 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.
6. The compound of claim 5, 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.
7. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, or -OH.
8. The compound of claim 7, or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is -OH.
9. The compound of claim 7, or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is hydrogen, R_4 is hydrogen, and R_5 is hydrogen.

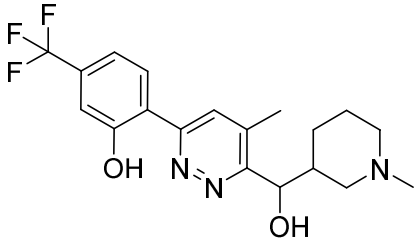
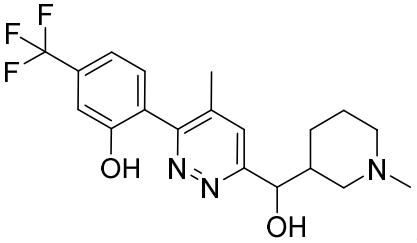
10. The compound of claim 9, or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is C_{1-6}alkyl or C_{1-6}haloalkyl.
11. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein L is -C(R_{9a})(R_{9b})-.
12. The compound of claim 11, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{9a} is selected from hydrogen, halogen, and C_{1-6}alkyl, and R_{9b} is selected from hydrogen, halogen, and -OH.
13. A compound selected from:

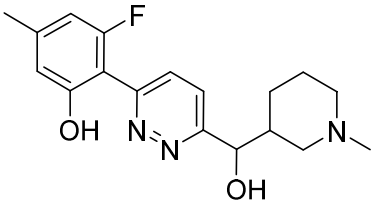
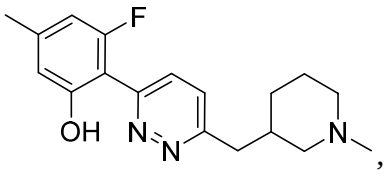

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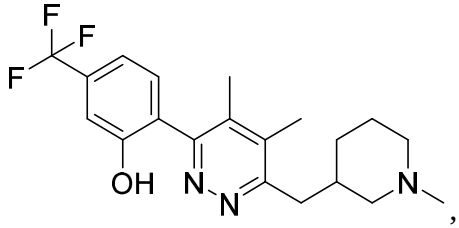
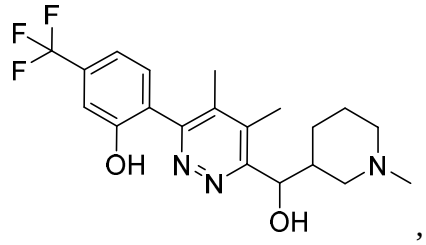
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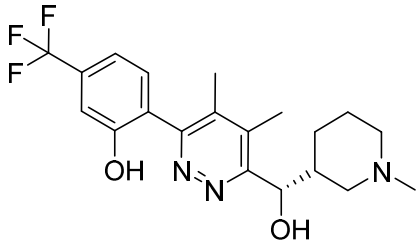
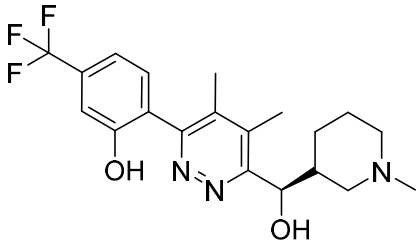
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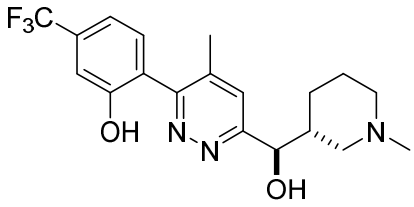
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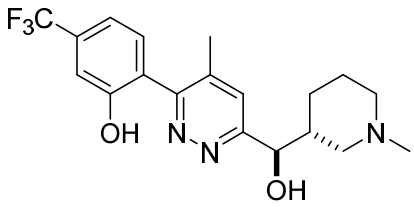
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, ; or a pharmaceutically acceptable salt or solvate thereof.

14. A pharmaceutical composition comprising the compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.
15. Use of the compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for treating a metabolic disease in a patient in need thereof, wherein the metabolic disease is selected from type 2 diabetes, atherosclerosis, and obesity; the liver disease is non-alcoholic steatohepatitis (NASH); the central nervous system disease is selected from Alzheimer's disease, multiple sclerosis, Amyotrophic Lateral Sclerosis, Parkinson's disease, and ischemic stroke; the cardiovascular disease is atherosclerosis or stroke; and the inflammatory or autoimmune disease is selected from rheumatoid arthritis, multiple sclerosis, and Crohn’s disease.
16. A compound that is:



; or a pharmaceutically acceptable salt thereof.
17. A compound that is:



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18. A compound selected from:
    2-(6-((S)-hydroxy((R)-1-methylpiperidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol,
    2-(6-((R)-hydroxy((R)-1-methylpiperidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol,
    2-(6-((R)-hydroxy((S)-1-methylpiperidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol, and
    2-(6-((S)-hydroxy((S)-1-methylpiperidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol; or a pharmaceutically acceptable salt thereof.
19. The compound of claim 18, wherein the compound is 2-(6-((R)-hydroxy((R)-1-methylpiperidin-3-yl)methyl)-4-methylpyridazin-3-yl)-5-(trifluoromethyl)phenol, or a pharmaceutically acceptable salt thereof.
20. A pharmaceutical composition comprising the compound of claim 16, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

21. Use of a compound of claim 16, or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for treating a metabolic disease, a liver disease, a central nervous system disease, a cardiovascular disease, an inflammatory or autoimmune disease in a patient in need thereof, wherein the metabolic disease is selected from type 2 diabetes, atherosclerosis, and obesity; the liver disease is non-alcoholic steatohepatitis (NASH); the central nervous system disease is selected from Alzheimer's disease, multiple sclerosis, Amyotrophic Lateral Sclerosis, Parkinson's disease, and ischemic stroke; the cardiovascular disease is atherosclerosis or stroke; and the inflammatory or autoimmune disease is selected from rheumatoid arthritis, multiple sclerosis, and Crohn’s disease.