

ASK1 INHIBITOR COMPOUNDS AND USES THEREOF

CROSS-REFERENCE

[0001] This application claims benefit of U.S. Provisional Application No. 62/482,085, filed on April 5, 2017, which is herein incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

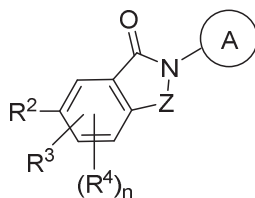
[0002] Non-alcoholic steatohepatitis (NASH) is an extreme form of non-alcoholic fatty liver disease (NAFLD), a condition resembling alcohol-induced liver injury associated with obesity and metabolic syndrome rather than alcohol abuse. In NAFLD, triglycerides accumulate within hepatocytes due to alterations in lipid synthesis, storage, movement, or clearance processes causing steatosis. While steatosis typically has no large risk implications on its own, in a subset of NAFLD patients the steatosis progresses to include inflammation (hepatitis), necrosis and fibrosis, a condition known as NASH. These NASH patients have highly elevated risks of both hepatocellular carcinoma (HCC, as high as 7.6% total risk in one study) and cirrhosis (as high as 25% total risk), ultimately leading to liver failure or death.

[0003] Current population-based studies indicate that at least 25% of the US population has NAFLD and about 25% of NAFLD patients will go on to develop NASH, making these conditions a significant epidemiologic contributor to organ failure and cancer. As these conditions are associated with obesity and metabolic disease, their prevalence is likely to increase in the future.

SUMMARY OF THE DISCLOSURE

[0004] In one example, described herein are compounds, or pharmaceutically acceptable salts or solvates thereof that inhibit ASK1.

[0005] In one example, presented herein are compounds of the structure of Formula I, or a pharmaceutically acceptable salt or solvate thereof:



Formula I;

wherein

R^8 is selected from the group consisting of hydrogen and C_1 - C_6 alkyl;
each R^9 is independently selected from the group consisting of hydrogen, halogen, and C_1 - C_6 alkyl;
each R^{13} is independently selected from the group consisting of hydrogen, C_1 - C_6 alkyl, and C_3 - C_8 cycloalkyl; or two R^{13} on the same heteroatom are taken together with that heteroatom to which they are attached to form a C_{2-9} heterocycle;
each R^{14} is independently selected from the group consisting of C_1 - C_6 alkyl and C_3 - C_8 cycloalkyl;
n is 0, 1, or 2;
p is 0, 1, 2, or 3; and
q is 0, 1, or 2.

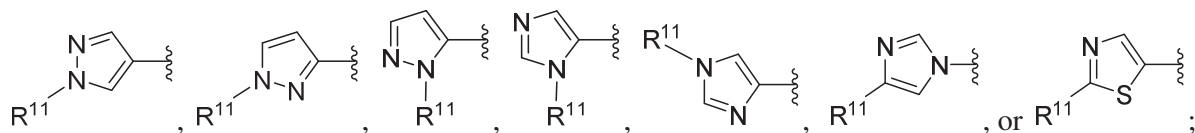
[0006] In some examples, R^2 is selected from a group consisting of C_{3-8} cycloalkyl, C_{2-9} heterocycle, C_{6-10} aryl, C_{1-9} heteroaryl, and a fused C_{5-9} heteroaryl-cycloalkyl; wherein C_{3-8} cycloalkyl, C_{2-9} heterocycle, C_{6-10} aryl, C_{1-9} heteroaryl, and fused C_{5-9} heteroaryl-cycloalkyl are optionally substituted with one, two, or three substituents selected from the group consisting of halo, -CN, C_{1-6} alkyl, - C_{1-6} alkyl-OH, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{2-9} heterocycle, C_{6-10} aryl, C_{1-9} heteroaryl, -C(=O) R^{14} , -C(=O)OR¹³, -C(=O)N(R^{13})₂, -S(=O) R^{14} , -S(=O)₂ R^{13} , -S(=O)₂-N(R^{13})₂, -N(R^{13})₂, -N(R^{13})C(=O) R^{14} , and -N(R^{13})S(=O)₂ R^{13} .

[0007] In some examples, R^2 is selected from a group consisting of C_{2-9} heterocycle and C_{1-9} heteroaryl; wherein C_{2-9} heterocycle and C_{1-9} heteroaryl are optionally substituted with one, two, or three substituents selected from the group consisting of halo, -CN, C_{1-6} alkyl, - C_{1-6} alkyl-OH, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{2-9} heterocycle, C_{6-10} aryl, C_{1-9} heteroaryl, -C(=O) R^{14} , -C(=O)OR¹³, -C(=O)N(R^{13})₂, -S(=O) R^{14} , -S(=O)₂ R^{13} , -S(=O)₂-N(R^{13})₂, -N(R^{13})₂, -N(R^{13})C(=O) R^{14} , and -N(R^{13})S(=O)₂ R^{13} .

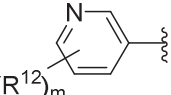
[0008] In some examples, R^2 is selected from a group consisting of C_{2-9} heterocycle and C_{1-9} heteroaryl; wherein C_{2-9} heterocycle and C_{1-9} heteroaryl are optionally substituted with one or two substituents selected from the group consisting of halo, -CN, C_{1-6} alkyl, - C_{1-6} alkyl-OH, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{2-9} heterocycle, C_{6-10} aryl, C_{1-9} heteroaryl, -C(=O) R^{14} , -C(=O)OR¹³, -C(=O)N(R^{13})₂, -S(=O) R^{14} , -S(=O)₂ R^{13} , -S(=O)₂-N(R^{13})₂, -N(R^{13})₂, -N(R^{13})C(=O) R^{14} , and -N(R^{13})S(=O)₂ R^{13} .

[0009] In some examples, R^2 is selected from a group consisting of pyrazole, imidazole, thiazole, and pyridine; wherein pyrazole, imidazole, thiazole, and pyridine are optionally substituted with one or two substituents selected from the group consisting of halo, -CN, C_{1-6} alkyl, - C_{1-6} alkyl-OH, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{2-9} heterocycle, C_{6-10} aryl, C_{1-9} heteroaryl, -C(=O) R^{14} , -C(=O)OR¹³, -C(=O)N(R^{13})₂, -S(=O) R^{14} , -S(=O)₂ R^{13} , -S(=O)₂-N(R^{13})₂, -N(R^{13})₂, -N(R^{13})C(=O) R^{14} , and -N(R^{13})S(=O)₂ R^{13} .

[0010] In some examples, R^2 is selected from a group consisting of pyrazole, imidazole, thiazole, and pyridine; wherein pyrazole, imidazole, thiazole, and pyridine are optionally substituted with one or two substituents selected from the group consisting of halo, C_{1-6} alkyl, and C_{3-8} cycloalkyl. In some examples, R^2 is



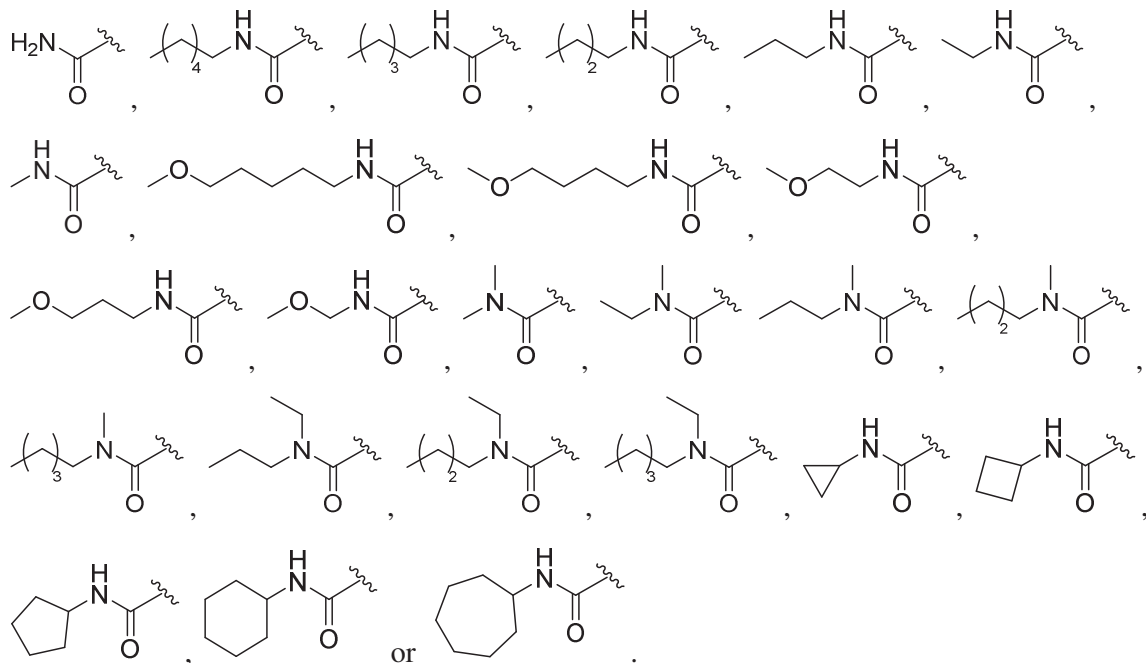
wherein R^{11} is C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl.

[0011] In some examples, R^2 is $(R^{12})_m$ , wherein R^{12} is halo, C_1 - C_6 alkyl, or C_3 - C_6 cycloalkyl; and m is 1 or 2.

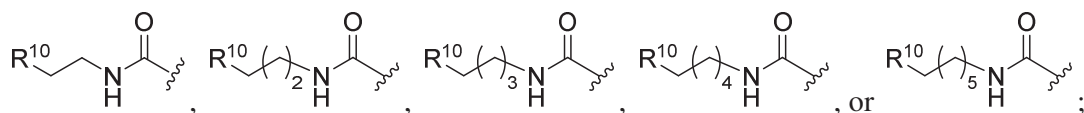
[0012] In some examples, R^2 is selected from a group consisting of unsubstituted pyrazole, unsubstituted imidazole, unsubstituted thiazole, and unsubstituted pyridine.

[0013] In some examples, R^2 is $-C(=O)N(R^6)_2$ and each R^6 is independently selected from the group consisting of hydrogen, C_1 - C_6 alkyl, $-C_1$ - C_6 alkyl- O - C_1 - C_6 alkyl, $-C_1$ - C_6 alkyl- C_{2-9} heterocycle, $-C_1$ - C_6 alkyl- C_{2-9} heteroaryl, C_3 - C_8 cycloalkyl, and C_{2-9} heterocycle.

[0014] In some examples, R^2 is



[0015] In some examples, R^2 is



wherein R^{10} is a heteroaryl.

[0016] In some examples, R^3 is hydrogen. In some examples, R^3 is C_1 - C_6 alkyl.

[0017] In some examples, R^3 is selected from a group consisting of C_{3-8} cycloalkyl, C_{2-9} heterocycle, C_{6-10} aryl, C_{1-9} heteroaryl, and a fused C_{5-9} heteroaryl-cycloalkyl; wherein C_{3-8} cycloalkyl, C_{2-9} heterocycle, C_{6-10} aryl, C_{1-9} heteroaryl, and fused C_{5-9} heteroaryl-cycloalkyl, wherein C_{3-8} cycloalkyl, C_{2-9} heterocycle, C_{6-10} aryl, C_{1-9} heteroaryl, and fused C_{5-9} heteroaryl-cycloalkyl are optionally substituted with one, two, or three substituents selected from the group consisting of halo, -CN, C_{1-6} alkyl, $-C_{1-6}$ alkyl-OH, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{2-9} heterocycle, C_{6-10} aryl, C_{1-9} heteroaryl, $-C(=O)R^{14}$, $-C(=O)OR^{13}$, $-C(=O)N(R^{13})_2$, $-S(=O)R^{14}$, $-S(=O)_2R^{13}$, $-S(=O)_2-N(R^{13})_2$, $-N(R^{13})_2$, $-N(R^{13})C(=O)R^{14}$, and $-N(R^{13})S(=O)_2R^{13}$.

[0018] In some examples, R^3 is selected from a group consisting of C_{2-9} heterocycle and C_{1-9} heteroaryl; wherein C_{2-9} heterocycle and C_{1-9} heteroaryl are optionally substituted with one, two, or three substituents selected from the group consisting of halo, -CN, C_{1-6} alkyl, $-C_{1-6}$ alkyl-OH, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{2-9} heterocycle, C_{6-10} aryl, C_{1-9} heteroaryl, $-C(=O)R^{14}$, $-C(=O)OR^{13}$, $-C(=O)N(R^{13})_2$, $-S(=O)R^{14}$, $-S(=O)_2R^{13}$, $-S(=O)_2-N(R^{13})_2$, $-N(R^{13})_2$, $-N(R^{13})C(=O)R^{14}$, and $-N(R^{13})S(=O)_2R^{13}$.

[0019] In some examples, R^3 is selected from a group consisting of C_{2-9} heterocycle and C_{1-9} heteroaryl; wherein C_{2-9} heterocycle and C_{1-9} heteroaryl are optionally substituted with one or two substituents selected from the group consisting of halo, -CN, C_{1-6} alkyl, $-C_{1-6}$ alkyl-OH, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{2-9} heterocycle, C_{6-10} aryl, C_{1-9} heteroaryl, $-C(=O)R^{14}$, $-C(=O)OR^{13}$, $-C(=O)N(R^{13})_2$, $-S(=O)R^{14}$, $-S(=O)_2R^{13}$, $-S(=O)_2-N(R^{13})_2$, $-N(R^{13})_2$, $-N(R^{13})C(=O)R^{14}$, and $-N(R^{13})S(=O)_2R^{13}$.

[0020] In some examples, R^3 is selected from a group consisting of pyrazole, imidazole, thiazole, and pyridine; wherein pyrazole, imidazole, thiazole, and pyridine are optionally substituted with one or two substituents selected from the group consisting of halo, -CN, C_{1-6} alkyl, $-C_{1-6}$ alkyl-OH, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{2-9} heterocycle, C_{6-10} aryl, C_{1-9} heteroaryl, $-C(=O)R^{14}$, $-C(=O)OR^{13}$, $-C(=O)N(R^{13})_2$, $-S(=O)R^{14}$, $-S(=O)_2R^{13}$, $-S(=O)_2-N(R^{13})_2$, $-N(R^{13})_2$, $-N(R^{13})C(=O)R^{14}$, and $-N(R^{13})S(=O)_2R^{13}$.

[0021] In some examples, R^3 is selected from a group consisting of pyrazole, imidazole, thiazole, and pyridine; wherein pyrazole, imidazole, thiazole, and pyridine are optionally substituted with one or two substituents selected from the group consisting of halo, C_{1-6} alkyl, and C_{3-8} cycloalkyl.

[0022] In some examples, R^3 is



 (R¹²)_m, wherein each R¹² is independently halo, C₁-C₆alkyl, or C₃-C₆cycloalkyl; and m is 1 or 2.

[0025] In some examples, R³ is -C(=O)N(R⁶)₂ and each R⁶ is independently selected from the group consisting of hydrogen, C₁-C₆alkyl, -C₁-C₆alkyl-O-C₁-C₆alkyl, -C₁-C₆alkyl-C₂₋₉heterocycle, -C₁-C₆alkyl-C₂₋₉heteroaryl, C₃-C₈cycloalkyl, and C₂₋₉heterocycle.

[illegible]
$$\text{R}^{10}\text{CH}_2\text{CH}_2\text{NHCO}\text{---}, \text{R}^{10}(\text{CH}_2)_2\text{NHCO}\text{---}, \text{R}^{10}(\text{CH}_2)_3\text{NHCO}\text{---}, \text{R}^{10}(\text{CH}_2)_4\text{NHCO}\text{---}, \text{or } \text{R}^{10}(\text{CH}_2)_5\text{NHCO}\text{---}$$

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[0028] In some examples, R^3 is $-OR^6$ and R^6 is selected from the group consisting of C_1 - C_6 alkyl, $-C_1$ - C_6 alkyl-O- C_1 - C_6 alkyl, and $-C_1$ - C_6 alkyl- C_{2-9} heterocycle. In some examples, R^2 is hydrogen. In some examples, R^2 is C_1 - C_6 alkyl.

[0029] In some examples, R^1 is selected from a group consisting of C_{3-8} cycloalkyl, C_{2-9} heterocycle, C_{6-10} aryl, C_{1-9} heteroaryl, and a fused C_{5-9} heteroaryl-cycloalkyl; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{2-9} heterocycle, C_{6-10} aryl, C_{1-9} heteroaryl, and fused C_{5-9} heteroaryl-cycloalkyl are optionally substituted with one, two, or three substituents selected from the group consisting of halo, $-CN$, C_{1-6} alkyl, $-C_{1-6}$ alkyl-OH, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{2-9} heterocycle, C_{6-10} aryl, C_{1-9} heteroaryl, $-C(=O)R^{14}$, $-C(=O)OR^{13}$, $-C(=O)N(R^{13})_2$, $-S(=O)R^{14}$, $-S(=O)_2R^{13}$, $-S(=O)_2N(R^{13})_2$, $-N(R^{13})_2$, $-N(R^{13})C(=O)R^{14}$, and $-N(R^{13})S(=O)_2R^{13}$.

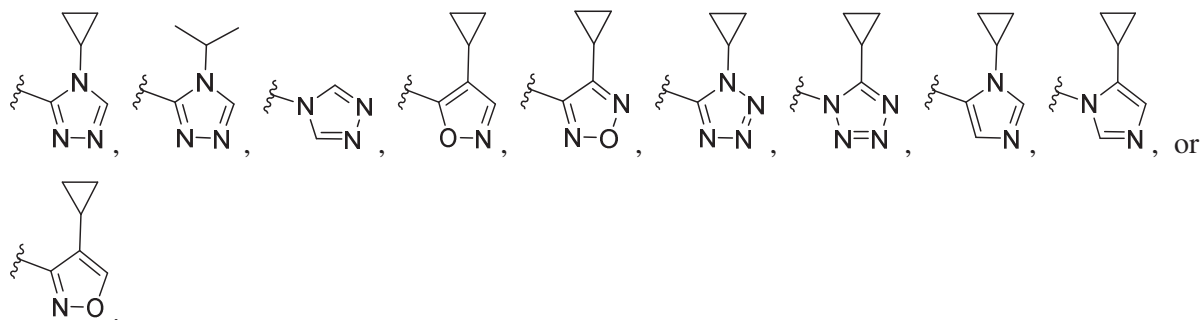
[0030] In some examples, R^1 is selected from a group consisting of a C_{1-9} heteroaryl and a fused C_{5-9} heteroaryl-cycloalkyl; wherein the C_{1-9} heteroaryl and fused C_{5-9} heteroaryl-cycloalkyl are optionally substituted with one, two, or three substituents selected from the group consisting of halo, $-CN$, C_{1-6} alkyl, $-C_{1-6}$ alkyl-OH, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{2-9} heterocycle, C_{6-10} aryl, C_{1-9} heteroaryl, $-C(=O)R^{14}$, $-C(=O)OR^{13}$, $-C(=O)N(R^{13})_2$, $-S(=O)R^{14}$, $-S(=O)_2R^{13}$, $-S(=O)_2N(R^{13})_2$, $-N(R^{13})_2$, $-N(R^{13})C(=O)R^{14}$, and $-N(R^{13})S(=O)_2R^{13}$.

[0031] In some examples, R^1 is selected from a group consisting of a C_{1-9} heteroaryl and a fused C_{5-9} heteroaryl-cycloalkyl; wherein the C_{1-9} heteroaryl and fused C_{5-9} heteroaryl-cycloalkyl are optionally substituted with one or two substituents selected from the group consisting of halo, $-CN$, C_{1-6} alkyl, $-C_{1-6}$ alkyl-OH, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{2-9} heterocycle, C_{6-10} aryl, C_{1-9} heteroaryl, $-C(=O)R^{14}$, $-C(=O)OR^{13}$, $-C(=O)N(R^{13})_2$, $-S(=O)R^{14}$, $-S(=O)_2R^{13}$, $-S(=O)_2N(R^{13})_2$, $-N(R^{13})_2$, $-N(R^{13})C(=O)R^{14}$, and $-N(R^{13})S(=O)_2R^{13}$.

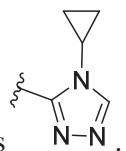
[0032] In some examples, R^1 is selected from a group consisting of triazole, imidazole, oxazole, isoxazole, oxadiazole, and tetrazole; wherein triazole, imidazole, oxazole, isoxazole, oxadiazole, and tetrazole are optionally substituted with one or two substituents selected from the group consisting of halo, $-CN$, C_{1-6} alkyl, $-C_{1-6}$ alkyl-OH, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{2-9} heterocycle, C_{6-10} aryl, C_{1-9} heteroaryl, $-C(=O)R^{14}$, $-C(=O)OR^{13}$, $-C(=O)N(R^{13})_2$, $-S(=O)R^{14}$, $-S(=O)_2R^{13}$, $-S(=O)_2N(R^{13})_2$, $-N(R^{13})_2$, $-N(R^{13})C(=O)R^{14}$, and $-N(R^{13})S(=O)_2R^{13}$.

[0033] In some examples, R^1 is selected from a group consisting of triazole, imidazole, oxazole, isoxazole, oxadiazole, and tetrazole; wherein triazole, imidazole, oxazole, isoxazole, oxadiazole, and tetrazole are optionally substituted with one or two substituents selected from the group consisting of halo, C_{1-6} alkyl, and C_{3-8} cycloalkyl.

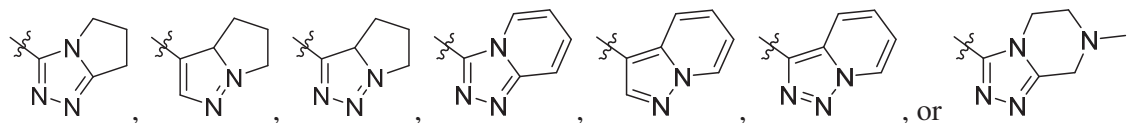
[0034] In some examples, R^1 is



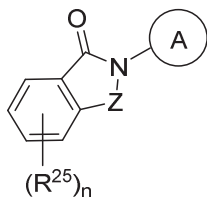
[0035] In some examples, R¹ is



[0036] In some examples, R¹ is

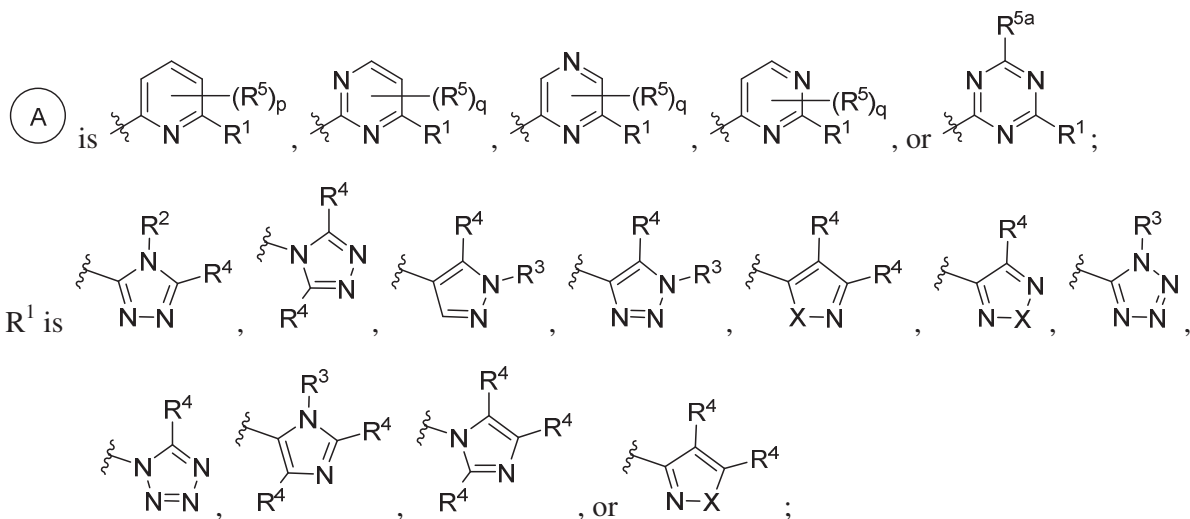


[0037] In another example described herein are compounds of Formula II, or a pharmaceutically acceptable salt or solvate thereof:



Formula II;

wherein

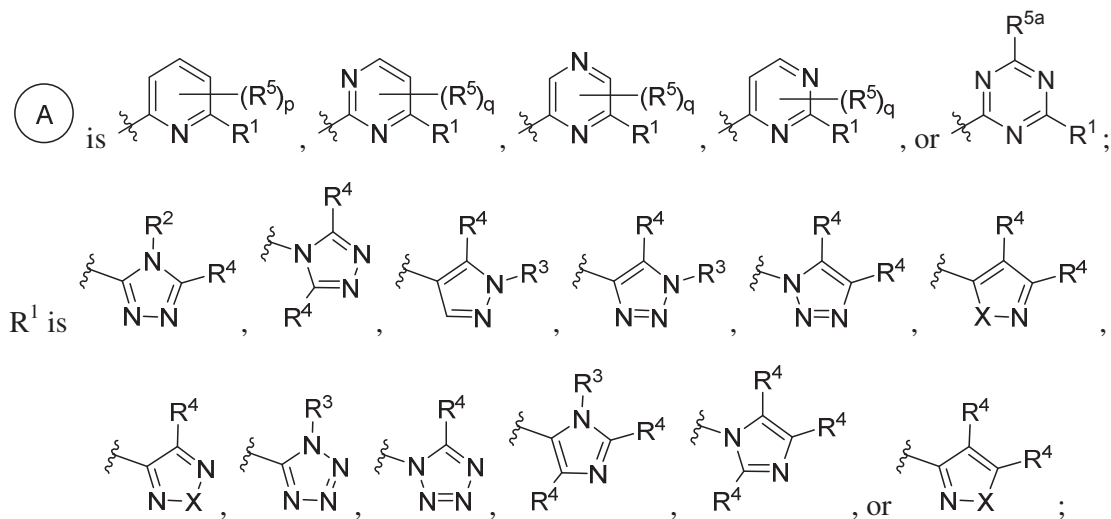


Z is O, S, C(=O), N(R⁸), or C(R⁹)₂;

X is O or S;

q is 0, 1, or 2.

wherein



halo, -CN, C₁₋₆alkyl, -C₁₋₆alkyl-OH, C₁₋₆haloalkyl, C₃₋₈cycloalkyl, C₂₋₉heterocycle,

each R^{13} is independently selected from the group consisting of hydrogen, C_1 - C_6 alkyl, and C_3 - C_8 cycloalkyl; or two R^{13} on the same heteroatom are taken together with that heteroatom to which they are attached to form a C_{2-9} heterocycle;

each R^{14} is independently selected from the group consisting of C_1 - C_6 alkyl and C_3 - C_8 cycloalkyl;

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

p is 0, 1, 2, or 3; and

q is 0, 1, or 2.

[0039] In some examples, R^{25} is selected from a group consisting of C_{3-8} cycloalkyl, C_{2-9} heterocycle, C_{6-10} aryl, C_{1-9} heteroaryl, and a fused C_{5-9} heteroaryl-cycloalkyl; wherein C_{3-8} cycloalkyl, C_{2-9} heterocycle, C_{6-10} aryl, C_{1-9} heteroaryl, and fused C_{5-9} heteroaryl-cycloalkyl are optionally substituted with one, two, or three substituents selected from the group consisting of halo, -CN, C_{1-6} alkyl, - C_{1-6} alkyl-OH, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{2-9} heterocycle, C_{6-10} aryl, C_{1-9} heteroaryl, -C(=O) R^{14} , -C(=O)OR¹³, -C(=O)N(R^{13})₂, -S(=O) R^{14} , -S(=O)₂ R^{13} , -S(=O)₂-N(R^{13})₂, -N(R^{13})₂, -N(R^{13})C(=O) R^{14} , and -N(R^{13})S(=O)₂ R^{13} .

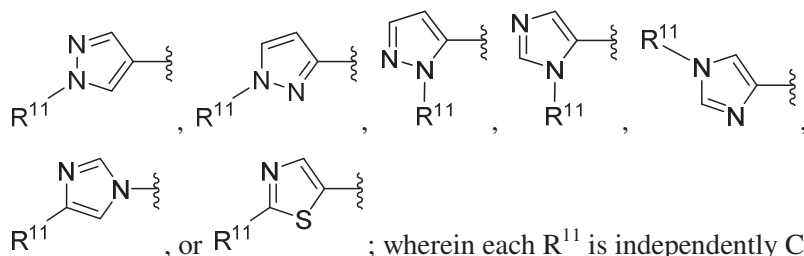
[0040] In some examples, R^{25} is selected from a group consisting of C_{2-9} heterocycle and C_{1-9} heteroaryl; wherein C_{2-9} heterocycle and C_{1-9} heteroaryl are optionally substituted with one, two, or three substituents selected from the group consisting of halo, -CN, C_{1-6} alkyl, - C_{1-6} alkyl-OH, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{2-9} heterocycle, C_{6-10} aryl, C_{1-9} heteroaryl, -C(=O) R^{14} , -C(=O)OR¹³, -C(=O)N(R^{13})₂, -S(=O) R^{14} , -S(=O)₂ R^{13} , -S(=O)₂-N(R^{13})₂, -N(R^{13})₂, -N(R^{13})C(=O) R^{14} , and -N(R^{13})S(=O)₂ R^{13} .

[0041] In some examples, R^{25} is selected from a group consisting of C_{2-9} heterocycle and C_{1-9} heteroaryl; wherein C_{2-9} heterocycle and C_{1-9} heteroaryl are optionally substituted with one or two substituents selected from the group consisting of halo, -CN, C_{1-6} alkyl, - C_{1-6} alkyl-OH, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{2-9} heterocycle, C_{6-10} aryl, C_{1-9} heteroaryl, -C(=O) R^{14} , -C(=O)OR¹³, -C(=O)N(R^{13})₂, -S(=O) R^{14} , -S(=O)₂ R^{13} , -S(=O)₂-N(R^{13})₂, -N(R^{13})₂, -N(R^{13})C(=O) R^{14} , and -N(R^{13})S(=O)₂ R^{13} .

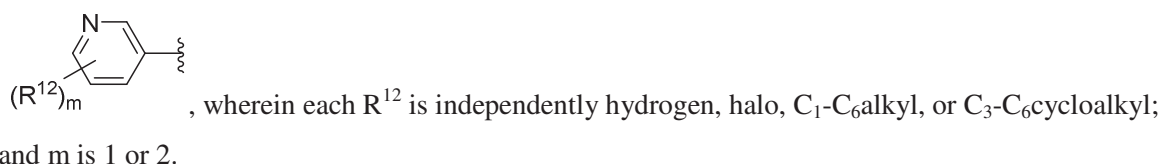
[0042] In some examples, R^{25} is selected from a group consisting of pyrazole, imidazole, thiazole, and pyridine; wherein pyrazole, imidazole, thiazole, and pyridine are optionally substituted with one or two substituents selected from the group consisting of halo, -CN, C_{1-6} alkyl, - C_{1-6} alkyl-OH, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{2-9} heterocycle, C_{6-10} aryl, C_{1-9} heteroaryl, -C(=O) R^{14} , -C(=O)OR¹³, -C(=O)N(R^{13})₂, -S(=O) R^{14} , -S(=O)₂ R^{13} , -S(=O)₂-N(R^{13})₂, -N(R^{13})₂, -N(R^{13})C(=O) R^{14} , and -N(R^{13})S(=O)₂ R^{13} .

[0043] In some examples, R^{25} is selected from a group consisting of pyrazole, imidazole, thiazole, and pyridine; wherein pyrazole, imidazole, thiazole, and pyridine are optionally substituted with one or two substituents selected from the group consisting of halo, C_{1-6} alkyl, and C_{3-8} cycloalkyl.

[0044] In some examples, R^{25} is



[0045] In some examples, R^{25} is



[0046] In some examples, R^{25} is selected from a group consisting of unsubstituted pyrazole, unsubstituted imidazole, unsubstituted thiazole, and unsubstituted pyridine.

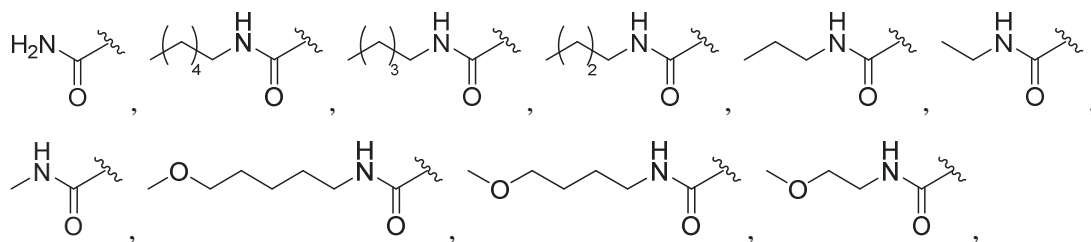
[0047] In some examples, R^{25} is selected from a group consisting of pyrimidine, pyrazine, and pyridazine; wherein pyrimidine, pyrazine, and pyridazine are optionally substituted with one or two substituents selected from the group consisting of halo, C_{1-6} alkyl, and C_{3-8} cycloalkyl.

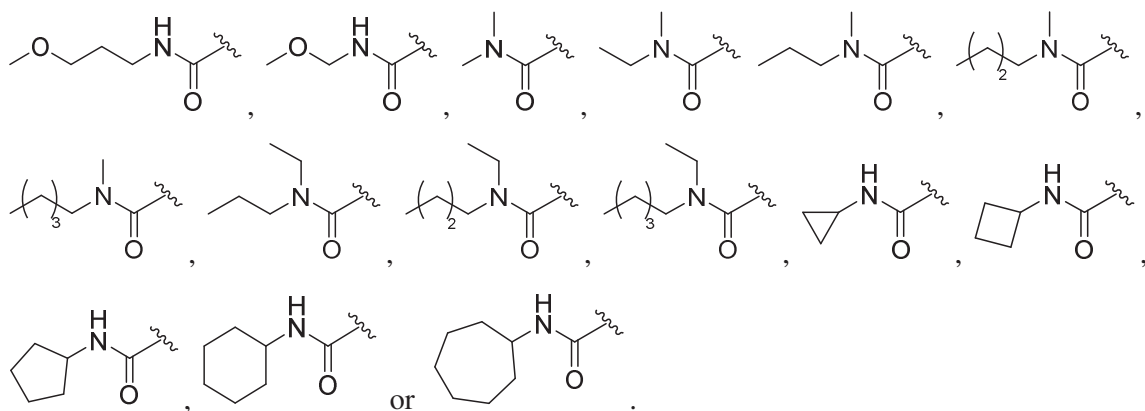
[0048] In some examples, R^{25} is selected from a group consisting of halogen, $-OR^6$, $-N(R^6)_2$, C_{1-6} alkyl, pyrazole, imidazole, thiazole, and pyridine; wherein pyrazole, imidazole, thiazole, and pyridine are optionally substituted with one or two substituents selected from the group consisting of halo, C_{1-6} alkyl, and C_{3-8} cycloalkyl.

[0049] In some examples, R^{25} is selected from a group consisting of halogen, $-OR^6$, $-N(R^6)_2$, C_{1-6} alkyl, and unsubstituted pyridine.

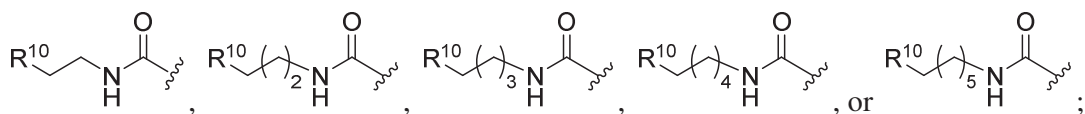
[0050] In some examples, R^{25} is $-C(=O)N(R^6)_2$ and each R^6 is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, $-C_{1-6}$ alkyl- O - C_{1-6} alkyl, $-C_{1-6}$ alkyl- C_{2-9} heterocycle, $-C_{1-6}$ alkyl- C_{2-9} heteroaryl, C_{3-8} cycloalkyl, and C_{2-9} heterocycle.

[0051] In some examples, R^{25} is



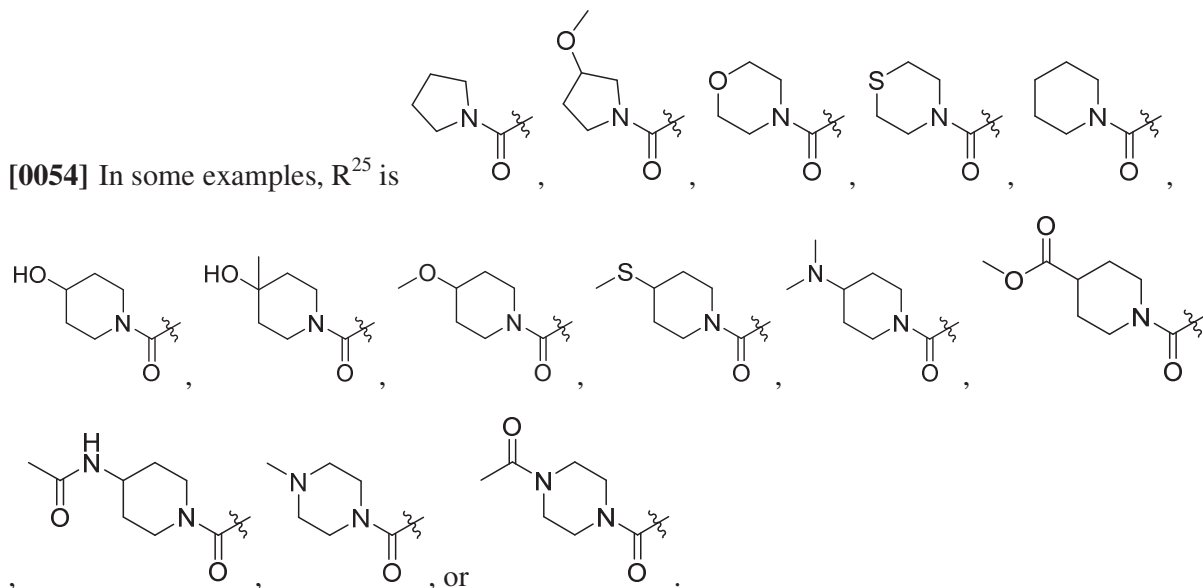


[0052] In some examples, R^{25} is



wherein R^{10} is a heteroaryl.

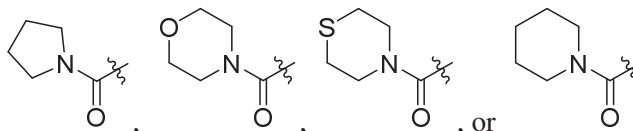
[0053] In some examples, R^{25} is $-C(=O)N(R^6)_2$ and two R^6 on the same heteroatom are taken together with that heteroatom to which they are attached to form a C_{2-9} heterocycle or a C_{2-9} heteroaryl, wherein C_{2-9} heterocycle or C_{2-9} heteroaryl are optionally substituted with one, two, or three substituents selected from the group consisting of halo, $-OR^8$, $-SR^8$, $-N(R^8)_2$, $-C_{1-6}$ alkyl, $-O-C_{1-6}$ alkyl, $-C(=O)R^{14}$, $-C(=O)OR^{13}$, and $-N(R^{13})C(=O)R^{14}$.



[0054] In some examples, R^{25} is

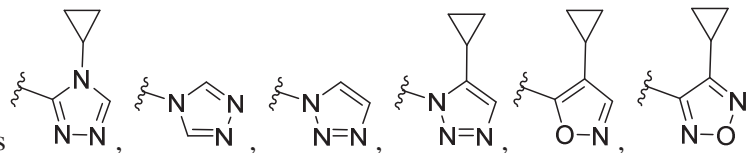
[0055] In some examples, R^{25} is $-C(=O)N(R^6)_2$ and two R^6 on the same heteroatom are taken together with that heteroatom to which they are attached to form a C_{2-9} heterocycle or a C_{2-9} heteroaryl.

[0056] In some examples, R^{25} is $-C(=O)N(R^6)_2$ and two R^6 are taken together with that heteroatom to which they are attached to form a C_{2-9} heterocycle or a C_{2-9} heteroaryl.

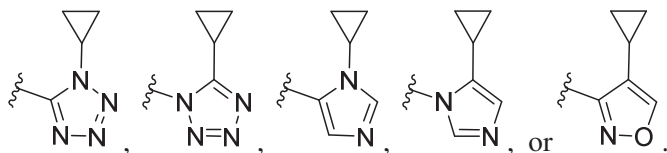
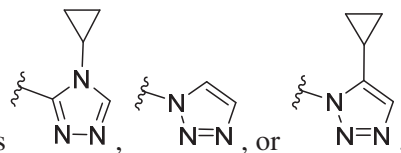


[0057] In some examples, R^{25} is , , or .

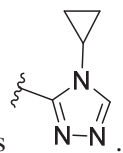
[0058] In some examples, R^{25} is $-OR^6$ and R^6 is selected from the group consisting of C_1 - C_6 alkyl, $-C_1$ - C_6 alkyl- O - C_1 - C_6 alkyl, and $-C_1$ - C_6 alkyl- C_{2-9} heterocycle.



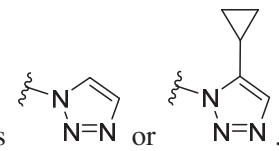
[0059] In some examples, R^1 is , , , , , or ,



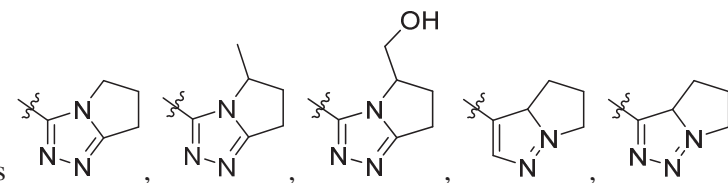
[0060] In some examples, R^1 is , or .



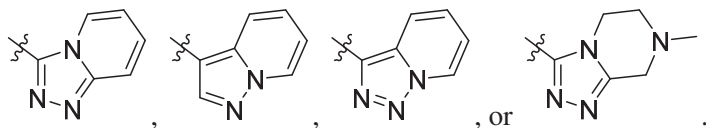
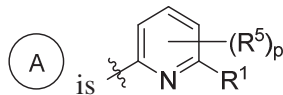
[0061] In some examples, R^1 is .



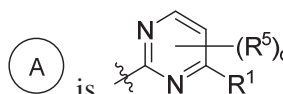
[0062] In some examples, R^1 is or .



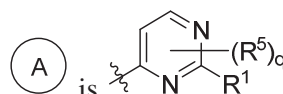
[0063] In some examples, R^1 is , , , , or ,



[0064] In some examples, (A) is . In some examples, p is 0.

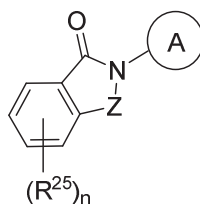


[0065] In some examples, (A) is . In some examples, (A) is . In some examples, q is 0.



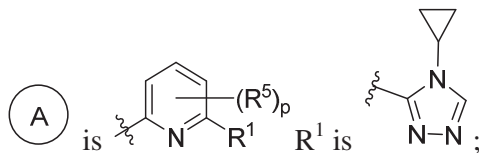
[0066] In some examples, n is 0. In some examples, n is 1. In some examples, n is 2. In some examples, Z is C(R⁹)₂. In some examples, R⁹ is H.

[0066a] In one aspect, the present disclosure refers to a compound of Formula II, or a pharmaceutically acceptable salt or solvate thereof:



Formula II;

wherein



Z is C(R⁹)₂;

each R⁵ is independently selected from a group consisting of halogen and C₁₋₆alkyl;

R²⁵ is selected from a group consisting of halogen, -OR⁶, -N(R⁶)₂, -C(=O)OR⁶, -C(=O)N(R⁶)₂, -NR⁶C(=O)N(R⁶)₂, and C₁₋₉heteroaryl selected from pyridinyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, and furazanyl; wherein the C₁₋₉heteroaryl is optionally substituted with one, two, or three substituents selected from the group consisting of halo, C₁₋₆alkyl, C₁₋₆haloalkyl, and C₃₋₈cycloalkyl; each R⁶ is independently selected from the group consisting of hydrogen, C₁₋₆alkyl, -C₁₋₆alkyl-O-C₁₋₆alkyl, -C₁₋₆alkyl-pyrazole, and C₃₋₈cycloalkyl; or two R⁶ on the same heteroatom are taken together with that heteroatom to which they are attached to form a C₂₋₉heterocycle or a C₂₋₉heteroaryl wherein the heteroaryl is selected from imidazolyl, pyrazolyl, and pyrrolyl, wherein the C₂₋₉heterocycle or C₂₋₉heteroaryl are optionally substituted with one, two, or three substituents selected from the group consisting of halo, -OR⁸, -SR⁸, -N(R⁸)₂, -C₁₋₆alkyl, -C(=O)R¹⁴, -C(=O)OR¹³, and -N(R¹³)C(=O)R¹⁴;

R⁸ is selected from the group consisting of hydrogen and C₁₋₆alkyl;

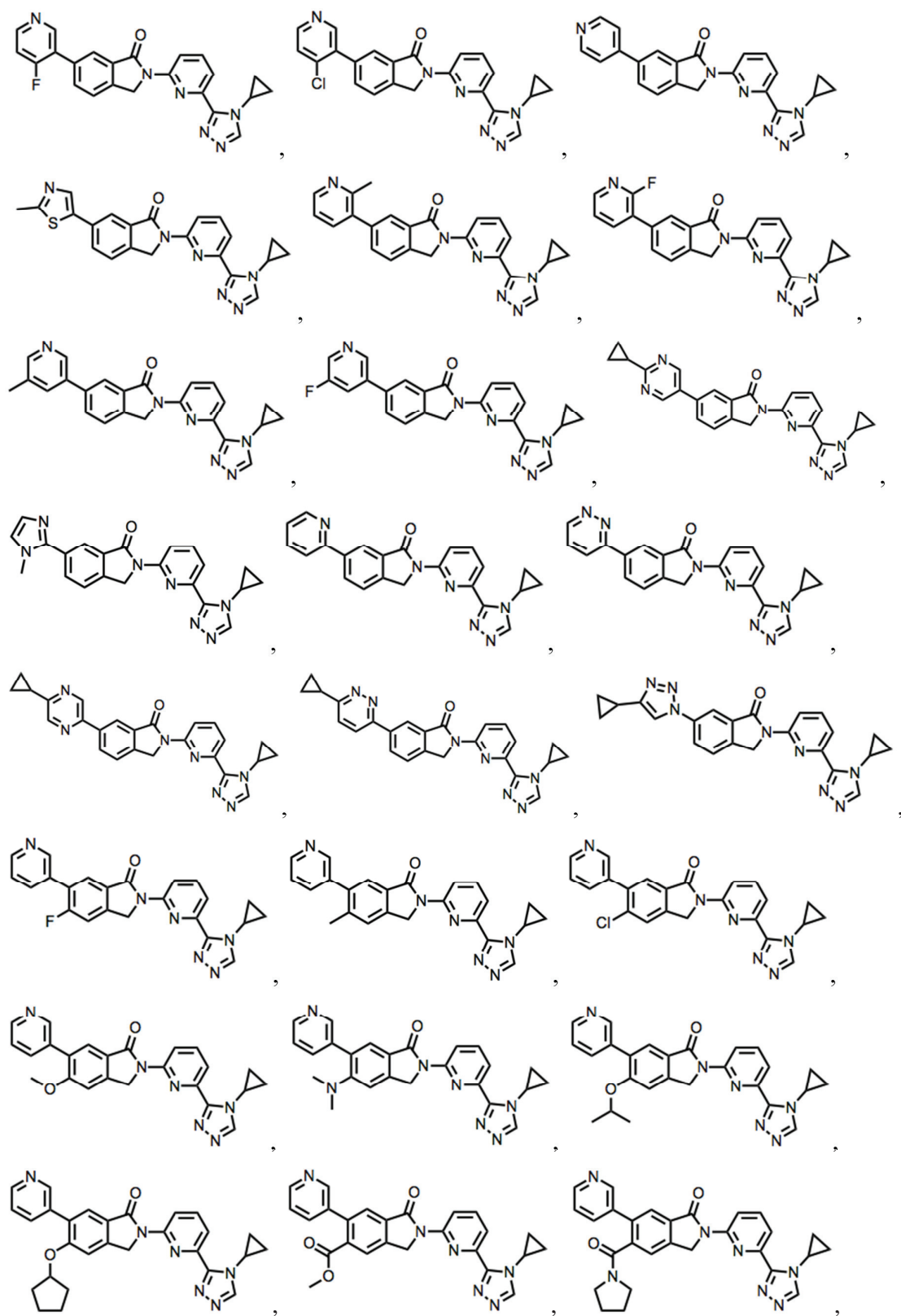
each R⁹ is hydrogen;

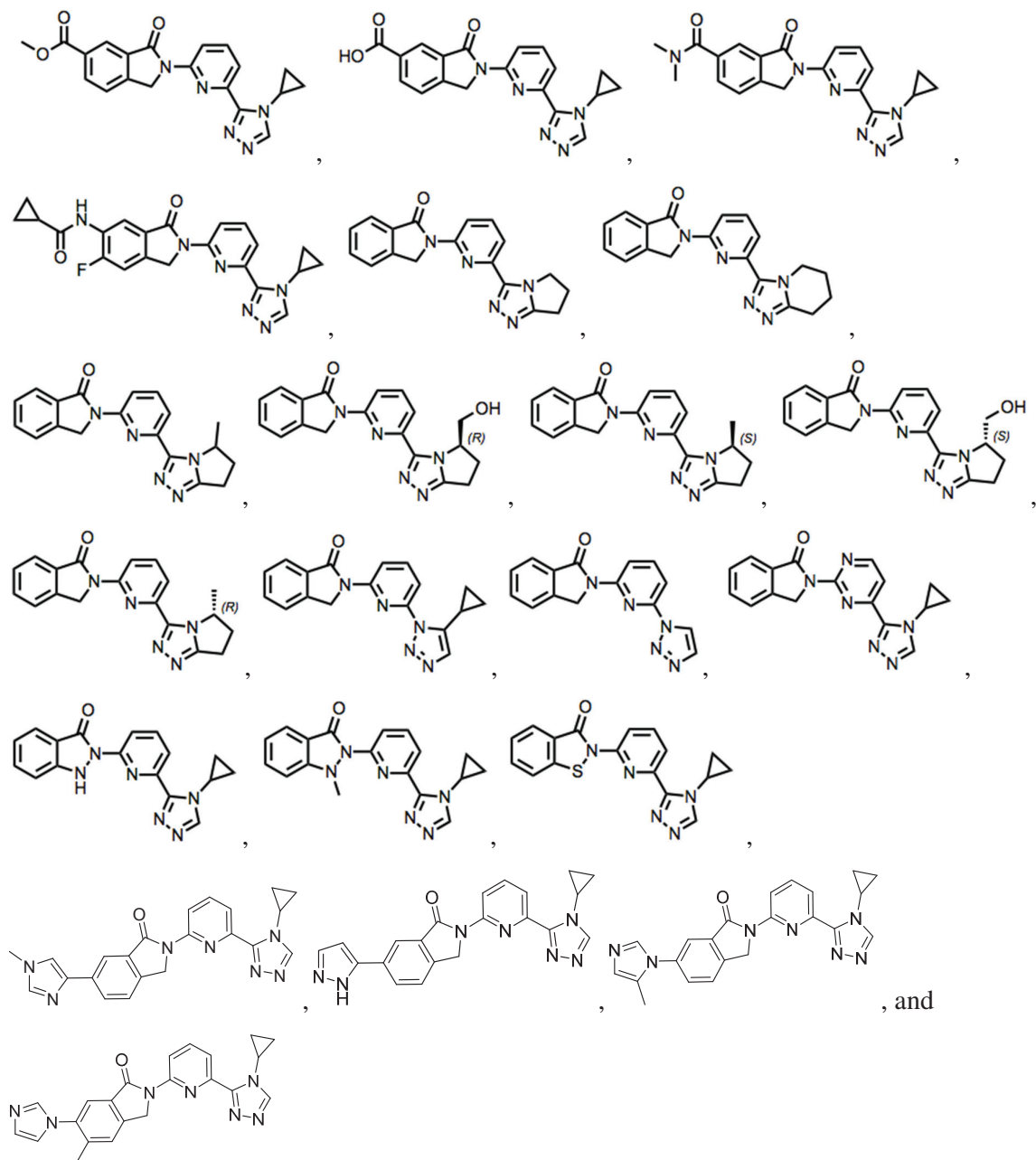
each R¹³ is independently selected from the group consisting of hydrogen and C₁₋₆alkyl;

p is 0 or 1.

Chemical structures of various compounds, including substituted indoles, pyridines, and triazoles, are shown. The structures are arranged in a grid, with some compounds having a common core structure (a benzimidazole derivative) and others being more complex derivatives. The structures are labeled with letters A through Z, and some are marked with a plus sign (+).







[0066c] In another aspect, the present disclosure refers to a use of a compound as described herein, or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for treating non-alcoholic steatohepatitis.

[0066d] In another aspect, the present disclosure refers to a compound as disclosed herein, or a pharmaceutically acceptable salt thereof for use as a medicament.

[0067] In a further aspect described herein are pharmaceutical compositions comprising a compound of Formula I, Formula II, or Formula III, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

[0068] In another example described herein are methods of treating non-alcoholic steatohepatitis in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula I, Formula II, or Formula III, or a pharmaceutically acceptable salt or solvate thereof. In another example described herein are methods of treating non-alcoholic steatohepatitis in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula I, Formula II, or Formula III, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

[0069] Other objects, features and advantages of the compounds, methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific examples, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWING

[0070] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawing of which:

[0071] **FIG. 1** shows a graph comparing the inhibition of the hERG potassium channel between compound **2** and compound **27** described herein (cmpd. 2 and cmpd. 27, respectively), ASK1 inhibitor GS-4997, and positive control Amitriptyline.

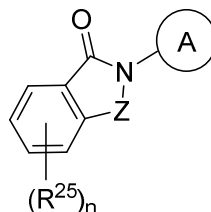
DETAILED DESCRIPTION OF THE INVENTION

[0072] ASK1 is a membrane-proximal MAP3K (MAP-kinase-kinase-kinase) upstream of pathways which play important roles in the cellular response to environmental stresses (e.g. the c-Jun and p38 pathways, which are known to be responsive to UV and oxidative damage), is a promising therapeutic target for NASH. A positive regulator of mitochondrial apoptosis, ASK1 is tightly regulated and activated by cellular damage signals as diverse as receptor-acting inflammatory

CLAIMS

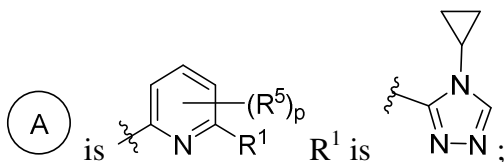
WHAT IS CLAIMED IS:

1. A compound of Formula II, or a pharmaceutically acceptable salt or solvate thereof:



Formula II;

wherein



Z is $C(R^9)_2$;

each R^5 is independently selected from a group consisting of halogen and C_{1-6} alkyl;

R^{25} is selected from a group consisting of halogen, $-OR^6$, $-N(R^6)_2$, $-C(=O)OR^6$, $-C(=O)N(R^6)_2$, $-NR^6C(=O)N(R^6)_2$, and C_{1-9} heteroaryl selected from pyridinyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, and furazanyl; wherein the C_{1-9} heteroaryl is optionally substituted with one, two, or three substituents selected from the group consisting of halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-8} cycloalkyl;

each R^6 is independently selected from the group consisting of hydrogen, C_1 - C_6 alkyl, $-C_1$ - C_6 alkyl- O - C_1 - C_6 alkyl, $-C_1$ - C_6 alkyl-pyrazole, and C_3 - C_8 cycloalkyl; or two R^6 on the same heteroatom are taken together with that heteroatom to which they are attached to form a C_{2-9} heterocycle or a C_{2-9} heteroaryl wherein the heteroaryl is selected from imidazolyl, pyrazolyl, and pyrrolyl, wherein the C_{2-9} heterocycle or C_{2-9} heteroaryl are optionally substituted with one, two, or three substituents selected from the group consisting of halo, $-OR^8$, $-SR^8$, $-N(R^8)_2$, $-C_{1-6}$ alkyl, $-C(=O)R^{14}$, $-C(=O)OR^{13}$, and $-N(R^{13})C(=O)R^{14}$;

R^8 is selected from the group consisting of hydrogen and C_1 - C_6 alkyl;

each R^9 is hydrogen;

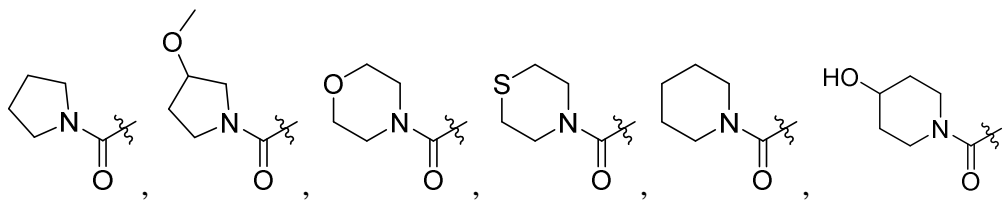
each R^{13} is independently selected from the group consisting of hydrogen and C_1 - C_6 alkyl;

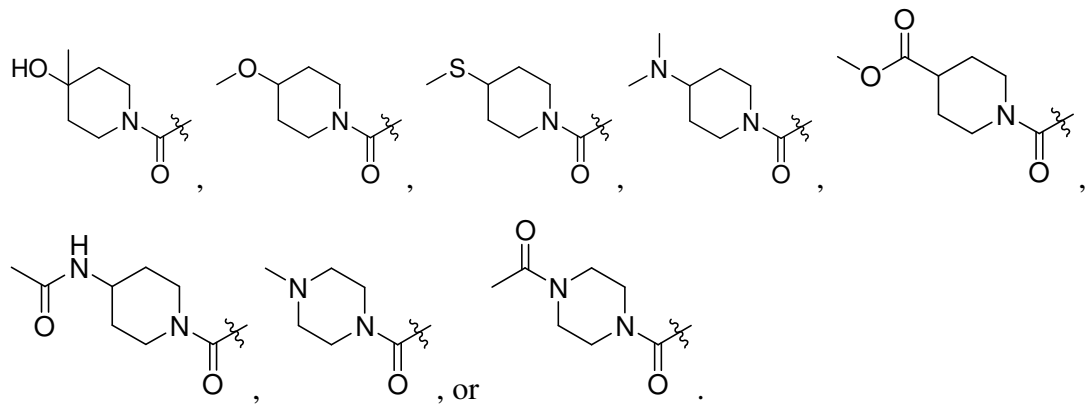
each R^{14} is independently selected from the group consisting of C_1 - C_6 alkyl;

n is 0, 1, or 2; and

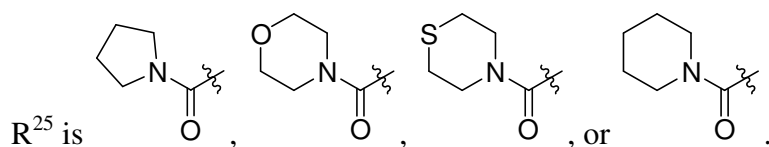
p is 0 or 1.

2. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein n is 1.
3. The compound of claim 2, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{25} is $-C(=O)N(R^6)_2$ and each R^6 is independently selected from the group consisting of hydrogen, C_1 - C_6 alkyl, $-C_1$ - C_6 alkyl-O- C_1 - C_6 alkyl, $-C_1$ - C_6 alkyl-pyrazole, and C_3 - C_8 cycloalkyl.
4. The compound of claim 2, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{25} is $-C(=O)N(R^6)_2$ and two R^6 on the same heteroatom are taken together with that heteroatom to which they are attached to form a C_{2-9} heterocycle or a C_{2-9} heteroaryl wherein the heteroaryl is selected from imidazolyl, pyrazolyl, and pyrrolyl, wherein the C_{2-9} heterocycle or C_{2-9} heteroaryl are optionally substituted with one substituent selected from the group consisting of $-OR^8$, $-SR^8$, $-N(R^8)_2$, $-C_1$ - C_6 alkyl, $-C(=O)R^{14}$, $-C(=O)OR^{13}$, and $-N(R^{13})C(=O)R^{14}$.
5. The compound of claim 4, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{25} is

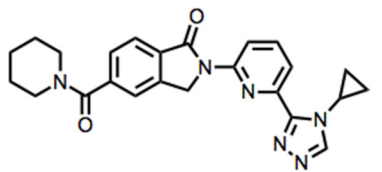




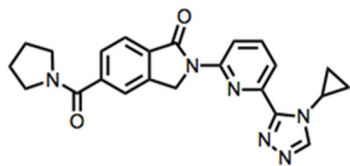
6. The compound of claim 5, or a pharmaceutically acceptable salt or solvate thereof, wherein



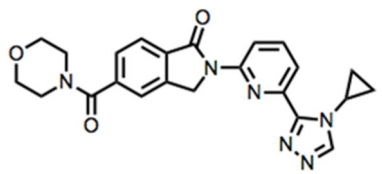
7. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound is



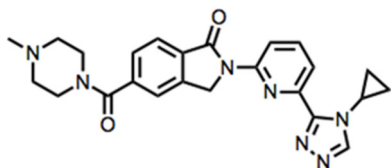
8. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound is



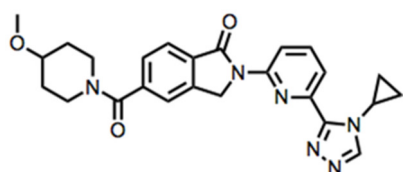
9. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound is



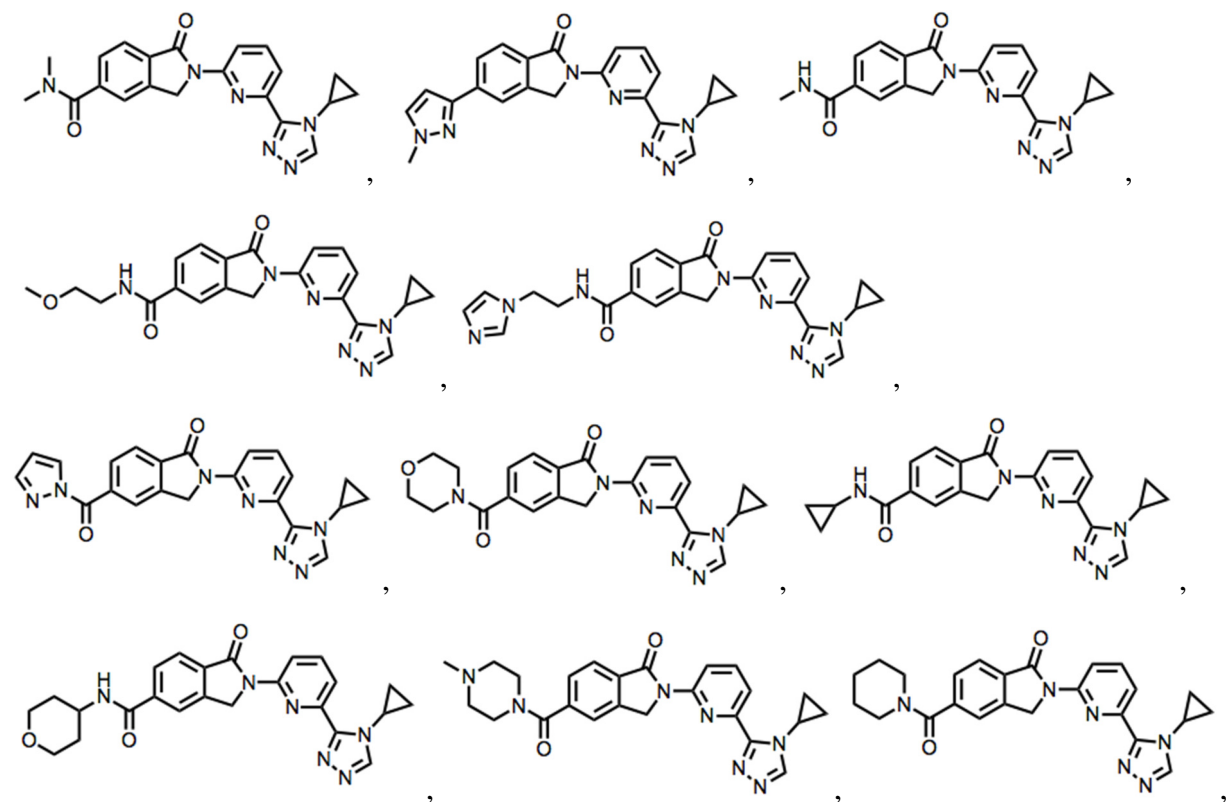
10. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound is

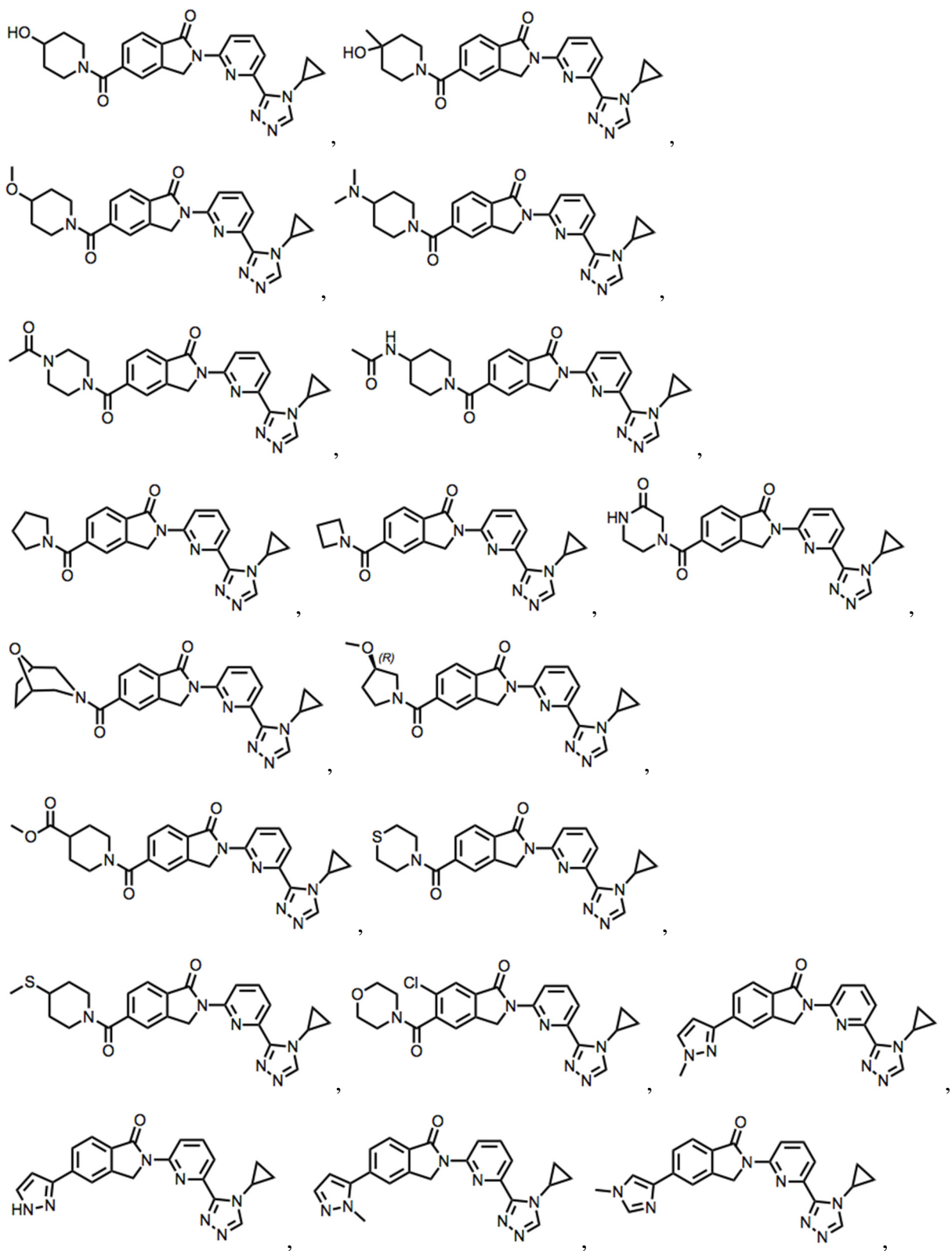


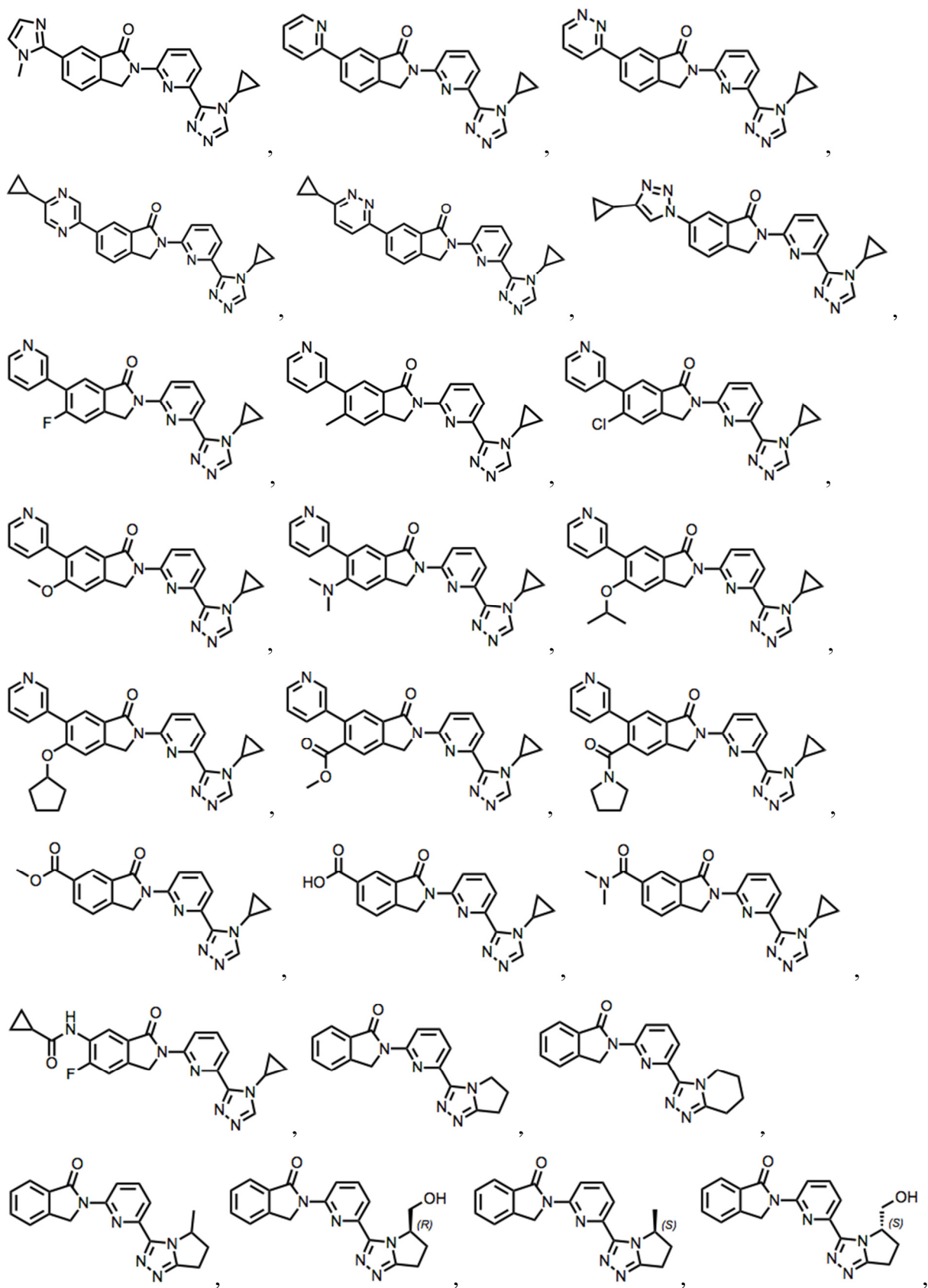
11. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound is

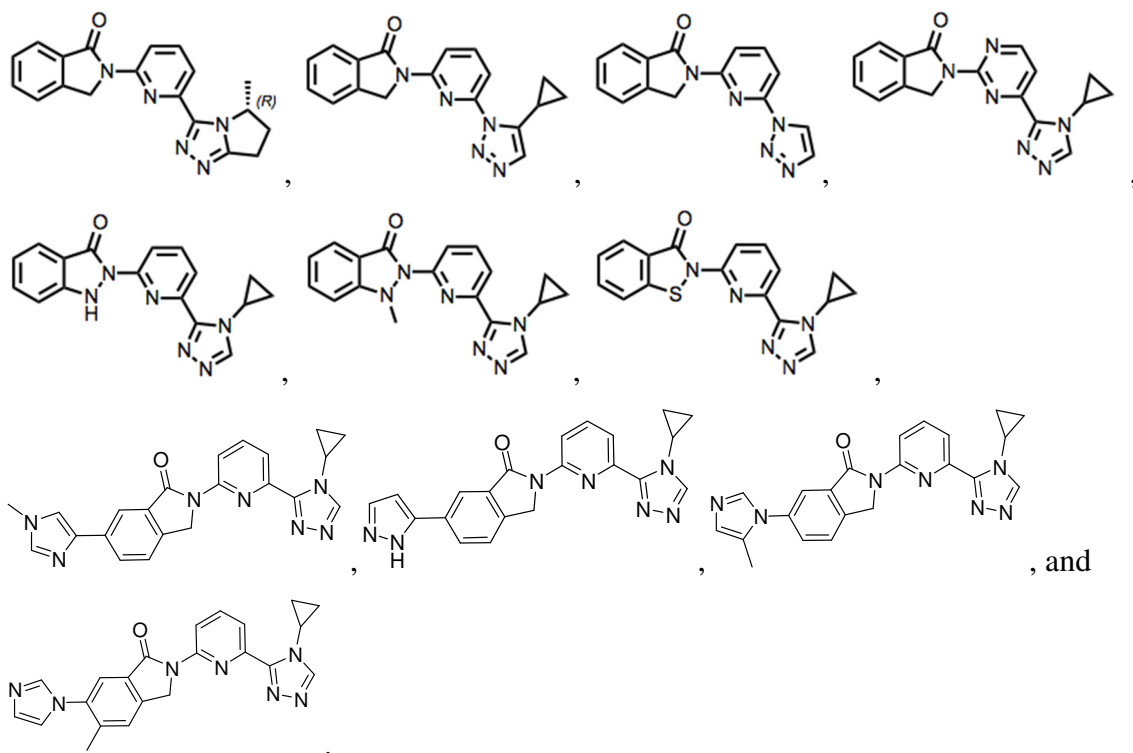


12. A compound, or a pharmaceutically acceptable salt or solvate thereof, selected from:









13. A pharmaceutical composition comprising a compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.
14. Use of a compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for treating non-alcoholic steatohepatitis.
15. A pharmaceutical composition comprising a compound of claim 12, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.
16. Use of a compound of claim 12, or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for treating non-alcoholic steatohepatitis.
17. A compound of claim 1 or claim 12, or a pharmaceutically acceptable salt or solvate thereof for use as a medicament.