and secretion of IL-37. A number of other caspase-1 substrates such as components of the cytoskeleton and glycolysis pathway may contribute to caspase-1-dependent inflammation.

[0006] NLRP3-dependent ASC specks are released into the extracellular environment where they can activate caspase-1, induce processing of caspase-1 substrates and propagate inflammation.

[0007] Active cytokines derived from NLRP3 inflammasome activation are important drivers of inflammation and interact with other cytokine pathways to shape the immune response to infection and injury. For example, IL-1β signalling induces the secretion of the pro-inflammatory cytokines IL-6 and TNF. IL-1β and IL-18 synergize with IL-23 to induce IL-17 production by memory CD4 Th17 cells and by γδ T cells in the absence of T cell receptor engagement. IL-18 and IL-12 also synergize to induce IFN-γ production from memory T cells and NK cell driving a Th1 response.

[0008] Other intracellular pattern recognition receptors (PRRs) are also capable of forming inflammasomes. These include other NLR family members such as NLRP1 and NLRC4, as well as non-NLR PRRs such as the double-stranded DNA (dsDNA) sensors absent in melanoma 2 (AIM2) and interferon, gamma inducible protein 16 (IFI16). NLRP3-dependent IL-1β processing can also be activated by an indirect, non-canonical pathway downstream of caspase-11.

[0009] The inherited CAPS disease Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome, and neonatal-onset multisystem inflammatory disease are caused by gain-of-function mutations in NLRP3, thus defining NLRP3 as a critical component of the inflammatory process. NLRP3 has also been implicated in the pathogenesis of a number of complex diseases, notably including metabolic disorders such as type 2 diabetes, atherosclerosis, obesity, and gout.

[0010] A role for NLRP3 in diseases of the central nervous system is emerging, and lung diseases have also been shown to be influenced by NLRP3. Furthermore, NLRP3 has a role in the development of liver disease, kidney disease and aging. Many of these associations were defined using mice with constitutive NLRP3 activation, but there have also been insights into the specific activation of NLRP3 in these diseases. In type 2 diabetes, the deposition of islet amyloid polypeptide in the pancreas activates NLRP3 and IL-1β signaling, resulting in cell death and inflammation.

[0011] There is a need to provide compounds and pharmaceutical compositions with improved pharmacological and/or physiological and/or physicochemical properties and/or those that provide a useful alternative to known compounds and pharmaceutical compositions.

BRIEF SUMMARY

[0012] In some examples, provided herein is a compound of Formula (I-A):

q and r are independently integers from 0 to 8;

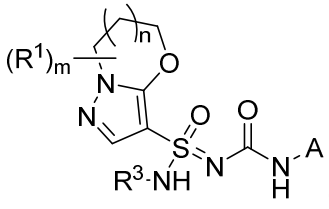
R^{A1} and R^{A2} are independently selected from the group consisting of halo, -CN, -OR^{A4}, -$NR^{A5}R^{A6}$, -$NR^{A5}SO_2R^{A6}$, -$C(O)NR^{A5}R^{A6}$, -$C(O)OR^{A5}$, -$C(O)NR^{A5}SO_2R^{A6}$, -$NR^{A5}C(O)R^{A6}$, C_1-C_6alkyl, C_3-C_6cycloalkyl, 3-6-membered heterocycloalkyl, aryl, and heteroaryl; wherein each C_1-C_6alkyl, C_3-C_6cycloalkyl, 3-6-membered heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, -CN, -OR^{A7}, -$NR^{A8}R^{A9}$, -$NR^{A8}SO_2R^{A9}$, -$NR^{A8}C(O)R^{A9}$, -$OC(O)R^{A9}$, -$C(O)NR^{A8}R^{A9}$, and -$C(O)NR^{A8}SO_2R^{A9}$;

wherein each R^{A4} and R^{A7} is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_3-C_6cycloalkyl, or C_3-C_6halocycloalkyl; and each R^{A5}, R^{A6}, R^{A8}, and R^{A9} is independently H, C_1-C_6alkyl, or C_1-C_6haloalkyl, or when attached to the same nitrogen may cyclize to form heterocycloalkyl or haloheterocycloalkyl;

and two R^{A1}, or two R^{A2}, together with the atoms to which they are attached independently may form C_3-C_6cycloalkyl, C_3-C_6halocycloalkyl, 3-6-membered heterocycloalkyl, or 3-6-membered haloheterocycloalkyl; and

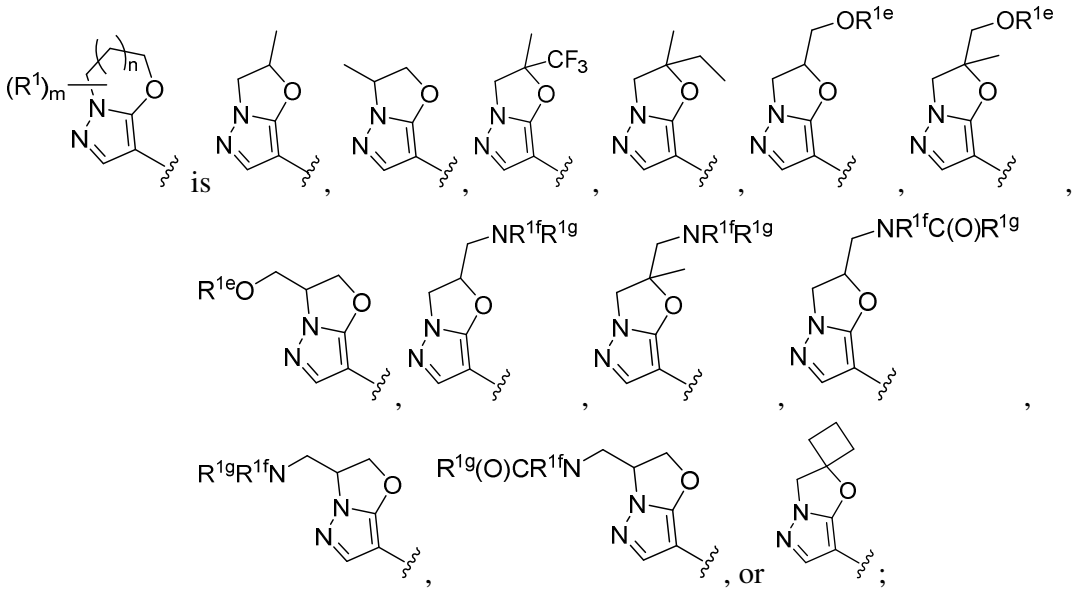
R^{A3} is H, halo, C_1-C_6alkyl, C_1-C_6haloalkyl, -CN, or -OR^{A10}, wherein R^{A10} is H, C_1-C_6alkyl, or C_1-C_6haloalkyl.

[0012a] In one aspect, provided herein is a compound of formula (I-A):


(I-A),

or a solvate, tautomer, or pharmaceutically acceptable salt thereof, wherein:

R^3 is H;


is , , ,

and heteroaryl; wherein each C_1-C_6alkyl, C_3-C_6cycloalkyl, 3-6-membered heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, -CN, -OR^{A7}, -$NR^{A8}R^{A9}$, -$NR^{A8}SO_2R^{A9}$, -$NR^{A8}C(O)R^{A9}$, -$OC(O)R^{A9}$, -$C(O)NR^{A8}R^{A9}$, and -$C(O)NR^{A8}SO_2R^{A9}$;

wherein each R^{A4} and R^{A7} is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_3-C_6cycloalkyl, or C_3-C_6halocycloalkyl; and each R^{A5}, R^{A6}, R^{A8}, and R^{A9} is independently H, C_1-C_6alkyl, or C_1-C_6haloalkyl, or when attached to the same nitrogen may cyclize to form heterocycloalkyl or haloheterocycloalkyl;

and two R^{A1}, or two R^{A2}, together with the atoms to which they are attached independently may form C_3-C_6cycloalkyl, C_3-C_6halocycloalkyl, 3-6-membered heterocycloalkyl, or 3-6-membered haloheterocycloalkyl; and

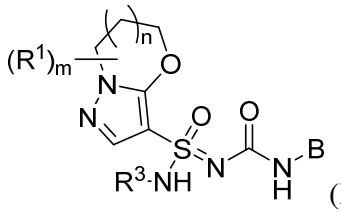
R^{A3} is H, halo, C_1-C_6alkyl, C_1-C_6haloalkyl, -CN, or -OR^{A10}, wherein R^{A10} is H, C_1-C_6alkyl, or C_1-C_6haloalkyl.

[0013] In some examples of Formula (I-A), or a solvate, tautomer, or pharmaceutically acceptable salt thereof, R^{A1} and R^{A2} are independently selected from the group consisting of Cl, Br, I, -CN, -OR^{A4}, -$NR^{A5}R^{A6}$, -$C(O)NR^{A5}R^{A6}$, -$C(O)OR^{A5}$, -$NR^{A5}C(O)R^{A6}$, C_1-C_6alkyl, C_3-C_6cycloalkyl, 3-6-membered heterocycloalkyl, aryl, and heteroaryl; wherein each C_1alkyl is substituted, and each C_2-C_6alkyl, C_3-C_6cycloalkyl, 3-6-membered heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted, wherein each substitutuent is independently halo, -CN, -OR^{A7}, -$NR^{A8}R^{A9}$, -$NR^{A8}C(O)R^{A9}$, or -$C(O)NR^{A8}R^{A9}$; and two R^{A1}, or two R^{A2}, together with the atoms to which they are attached independently may form C_3-C_6cycloalkyl, C_3-C_6halocycloalkyl, 3-6-membered heterocycloalkyl, or 3-6-membered haloheterocycloalkyl. In some examples, p and s are both 1. In certain examples, q and r are independently integers from 0 to 4. In some examples, R^{A3} is H, halo, -CN, or -OR^{A10}, wherein R^{A10} is C_1-C_6alkyl. In certain examples, R^{A3} is H or fluoro.

[0014] In other examples, provided herein is a compound of Formula (I-B):

R^{B18}, R^{B20}, and R^{B21} is independently H, C_1-C_6alkyl, or C_1-C_6haloalkyl, or when attached to the same nitrogen atom may cyclize to form heterocycloalkyl or haloheterocycloalkyl.

[0014a] In one aspect, provided herein is a compound of Formula (I-B):



(I-B),

or a solvate, tautomer, or pharmaceutically acceptable salt thereof, wherein:

m is an integer from 0 to 4;

n is 0;

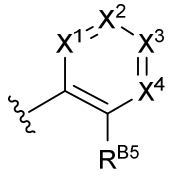
R^3 is H;

each R^1 is independently halo, -CN, -OR^{1a}, -$NR^{1b}R^{1c}$, -$NR^{1b}SO_2R^{1c}$, -O-R^{1d}-$NR^{1b}R^{1c}$, -O-R^{1d}-OR^{1a}, -N(R^{1b})-R^{1d}-OR^{1a}, -$NR^{1b}C(O)R^{1c}$, -$C(O)NR^{1b}R^{1c}$, C_1-C_6alkyl, or 3-6-membered heterocycloalkyl; wherein each C_1-C_6alkyl and 3-6-membered heterocycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, oxo, -CN, -OR^{1e}, -$NR^{1f}R^{1g}$, -$NR^{1f}SO_2R^{1g}$, -$NR^{1f}C(O)R^{1g}$, -$C(O)NR^{1f}R^{1g}$, and -$R^{1h}OR^{1e}$;

wherein each R^{1a} and R^{1e} is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_3-C_6cycloalkyl, or C_3-C_6halocycloalkyl; each R^{1b}, R^{1c}, R^{1f}, and R^{1g} is independently H, C_1-C_6alkyl, or C_1-C_6haloalkyl, or when attached to the same nitrogen atom may cyclize to form heterocycloalkyl or haloheterocycloalkyl; and each R^{1d} and R^{1h} is independently C_1-C_6alkyl or C_1-C_6haloalkyl;

and two R^1 attached to the same carbon may form C_3-C_6cycloalkyl, C_3-C_6halocycloalkyl, 3-6-membered heterocycloalkyl, or 3-6-membered haloheterocycloalkyl;

B is:



B

,

wherein:

X^1 is CR^{B1} or N;

X^2 is CR^{B2} or N;

X^3 is CR^{B3} or N, wherein R^{B3} is H, halo, C_1-C_6alkyl, C_1-C_6haloalkyl, -CN, or $-OR^{B22}$;

X^4 is CR^{B4} or N;

R^{B1}, R^{B2}, and R^{B4} are independently selected from the group consisting of H, halo, -CN, $-OR^{B6}$, $-NR^{B7}R^{B8}$, $-NR^{B7}SO_2R^{B8}$, $-NR^{B7}C(O)R^{B8}$, $-C(O)NR^{B7}R^{B8}$, $-C(O)NR^{B7}SO_2R^{B8}$, C_1-C_6alkyl, C_3-C_6cycloalkyl, 3-6-membered heterocycloalkyl, aryl, and heteroaryl; wherein each C_1-C_6alkyl, C_3-C_6cycloalkyl, 3-6-membered heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, -CN, C_1-C_6alkyl, C_1-C_6haloalkyl, $-OR^{B9}$, $-NR^{B10}R^{B11}$, $-NR^{B10}SO_2R^{B11}$, $-NR^{B10}C(O)R^{B11}$, $-C(O)NR^{B10}R^{B11}$, and $-C(O)NR^{B10}SO_2R^{B11}$;

R^{B5} is pyridine, unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, C_1-C_6alkyl, C_1-C_6haloalkyl, -CN, $-NR^{B13}R^{B14}$, $-NR^{B13}C(O)R^{B14}$, $-C(O)NR^{B13}R^{B14}$, and $-OR^{B15}$;

or R^{B1} and R^{B2} together with the atoms to which they are attached may form C_4-C_6cycloalkyl or 4-6-membered heterocycloalkyl;

and independently R^{B4} and R^{B5} together with the atoms to which they are attached may form 4-6-membered heterocycloalkyl;

wherein the heterocycloalkyl or cycloalkyl formed by R^{B1} and R^{B2}, and heterocycloalkyl formed by R^{B4} and R^{B5}, are independently unsubstituted or substituted with one or more substituents selected from the group consisting of halo, -CN, $-OR^{B16}$, $-NR^{B17}R^{B18}$, $-NR^{B17}SO_2R^{B18}$, $-NR^{B17}C(O)R^{B18}$, $-C(O)NR^{B17}R^{B18}$, $-C(O)OR^{B17}$, $-C(O)NR^{B17}SO_2R^{B18}$, C_1-C_6alkyl, C_3-C_6cycloalkyl, 3-6-membered heterocycloalkyl, aryl, and heteroaryl; wherein each C_1-C_6alkyl, C_3-C_6cycloalkyl, 3-6-membered heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, -CN, $-OR^{B19}$, $-NR^{B20}R^{B21}$, $-NR^{B20}SO_2R^{B21}$, $-NR^{B20}C(O)R^{B21}$, $-OC(O)R^{B21}$, $-C(O)NR^{B20}R^{B21}$, and $-C(O)NR^{B20}SO_2R^{B21}$; and

each R^{B6}, R^{B9}, R^{B12}, R^{B15}, R^{B16}, R^{B19}, and R^{B22} is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_3-C_6cycloalkyl, or C_3-C_6halocycloalkyl; and each R^{B7}, R^{B8}, R^{B10}, R^{B11}, R^{B13}, R^{B14}, R^{B17}, R^{B18}, R^{B20}, and R^{B21} is independently H, C_1-C_6alkyl, or C_1-C_6haloalkyl, or when attached to the same nitrogen atom may cyclize to form heterocycloalkyl or haloheterocycloalkyl.

[0015] In some examples Formula (I-B), or a solvate, tautomer, or pharmaceutically acceptable salt thereof:

(i) when n is 1; m is 0, 1, or 2; R^1 if present is $-OCH_3$, methyl, -NH(CH3), or methoxy-substituted azetidinyl; R^{B1} and R^{B5} are isopropyl; and one or both of X^2 and X^4 are N; then X^3 is N or $-CR^{B3}$, wherein R^{B3} is selected from the group consisting of H, halo, C_1-C_6alkyl, C_1-C_6haloalkyl, -CN, or $-OR^{B22}$, wherein R^{B22} is H, C_2-C_6alkyl, C_1-C_6haloalkyl, C_3-C_6cycloalkyl, or C_3-C_6halocycloalkyl; or

(ii) when n is 1; m is 0 or 1; R^1 if present is $-OCH_3$ or $-N(H)CH_3$; R^{B1} and R^{B5} are isopropyl; R^{B2} and R^{B4} are H; and X^3 is $-CR^{B3}$; then R^{B3} is H, Cl, Br, I, C_1-C_6alkyl, C_1-C_6haloalkyl, -CN, or $-OR^{B22}$; or

(iii) when n is 1; m is 0; R^{B5} is methoxy-substituted pyridine; R^{B4} is H; R^{B1} is isopropyl or forms a 5-membered heterocycloalkyl comprising one ring oxygen with R^{B2}; and R^{B2} is H if not forming a ring with R^{B1}; then R^{B3} is Cl, Br, I, C_1-C_6alkyl, C_1-C_6haloalkyl, -CN, or $-OR^{B22}$;

or any combination of (i), (ii), and (iii).

[0016] In some examples of Formula (I-B), or a solvate, tautomer, or pharmaceutically acceptable salt thereof, R^{B5} is H, halo, C_1-C_6alkyl, C_3-C_6cycloalkyl, or heteroaryl; wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, or heteroaryl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, C_1-C_6alkyl, C_1-C_6haloalkyl, -CN, $-NR^{B13}R^{B14}$, $-NR^{B13}C(O)R^{B14}$, $-C(O)NR^{B13}R^{B14}$, and $-OR^{B15}$.

[0017] In some examples of Formula (I-A) or (I-B), or a solvate, tautomer, or pharmaceutically acceptable salt thereof, m is an integer from 0 to 4. In some examples, m is 1 or 2. In some examples, n is 0. In other examples, n is 1. In some examples, each R^1 is independently halo, -CN, -OH, $-OC_1$-C_3alkyl, C_1-C_3alkyl, C_1-C_3haloalkyl, unsubstituted 3-4-membered heterocycloalkyl, or 3-4-membered heterocycloalkyl substituted with $-OC_1$-C_3alkyl, or $-NR^{1b}R^{1c}$. In certain examples, R^3 is H.

[0018] In further examples, provided herein is a compound selected from Table 1, or a solvate, tautomer, or pharmaceutically acceptable salt thereof.

[0019] In other examples, provided herein is a compound selected from List 1, or a solvate, tautomer, or pharmaceutically acceptable salt thereof.

[0020] In yet further examples, provided herein is a compound selected from List 2, or a solvate, tautomer, or pharmaceutically acceptable salt thereof.

[0021] In some examples, provided herein is a compound selected from List 3, or a solvate, tautomer, or pharmaceutically acceptable salt thereof.

[0022] In still further examples, provided herein is a compound selected from List 4, or a solvate, tautomer, or pharmaceutically acceptable salt thereof.

[0023] In other aspects, provided herein is a pharmaceutical composition, comprising a compound as described herein, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In some examples, the compound is a compound of Formula (I-A) or Formula (I-B), or from Table 1, List 1, List 2, List 3, or List 4; or a solvate, tautomer, or pharmaceutically acceptable salt thereof.

[0024] In some examples, provided herein is a method of treating a disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound as described herein, a solvate, tautomer, or pharmaceutically acceptable salt thereof; or a pharmaceutical composition as described herein. In some examples, the compound is a compound of Formula (I-A) or Formula (I-B), or from Table 1, List 1, List 2, List 3, or List 4; or a solvate, tautomer, or pharmaceutically acceptable salt thereof.

[0025] In other examples, provided herein is a compound as described herein, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, for use in the treatment of a disorder in a subject in need thereof. In some examples, provided herein is a pharmaceutical composition comprising a compound as described herein, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, for use in the treatment of a disorder in a subject in need thereof. In some examples, the compound is a compound of Formula (I-A) or Formula (I-B), or from Table 1, List 1, List 2, List 3, or List 4; or a solvate, tautomer, or pharmaceutically acceptable salt thereof.

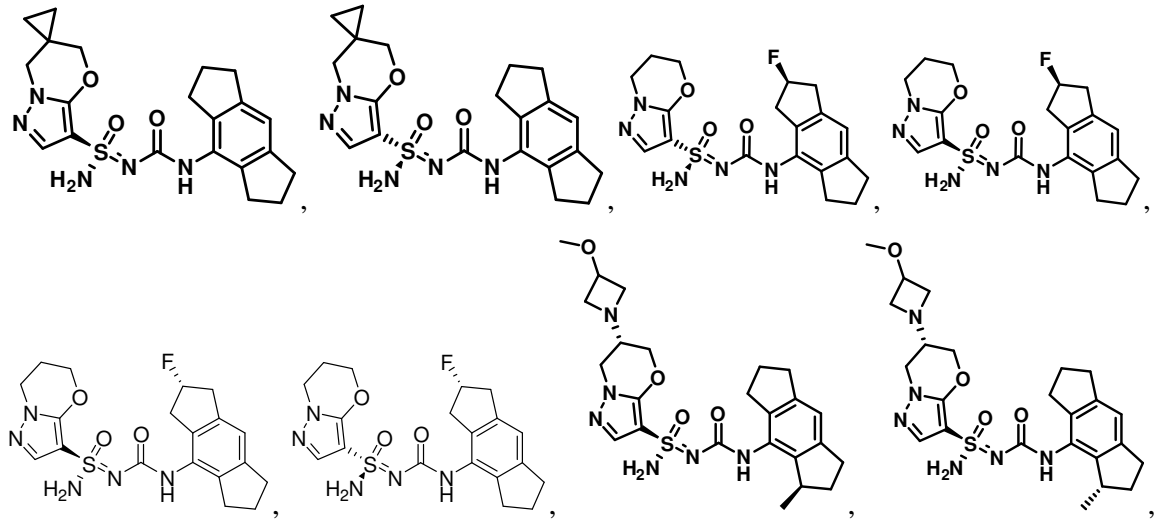
[0026] In still further examples, provided herein is the use of a compound as described herein, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, in the treatment of a disorder in a subject in need thereof. In some examples, provided herein is the use of a pharmaceutical composition comprising a compound as described herein, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, in the treatment of a disorder in a subject in need thereof. In some examples, the compound is a compound of Formula (I-A) or Formula (I-B), or from Table 1, List 1, List 2, List 3, or List 4; or a solvate, tautomer, or pharmaceutically acceptable salt thereof.

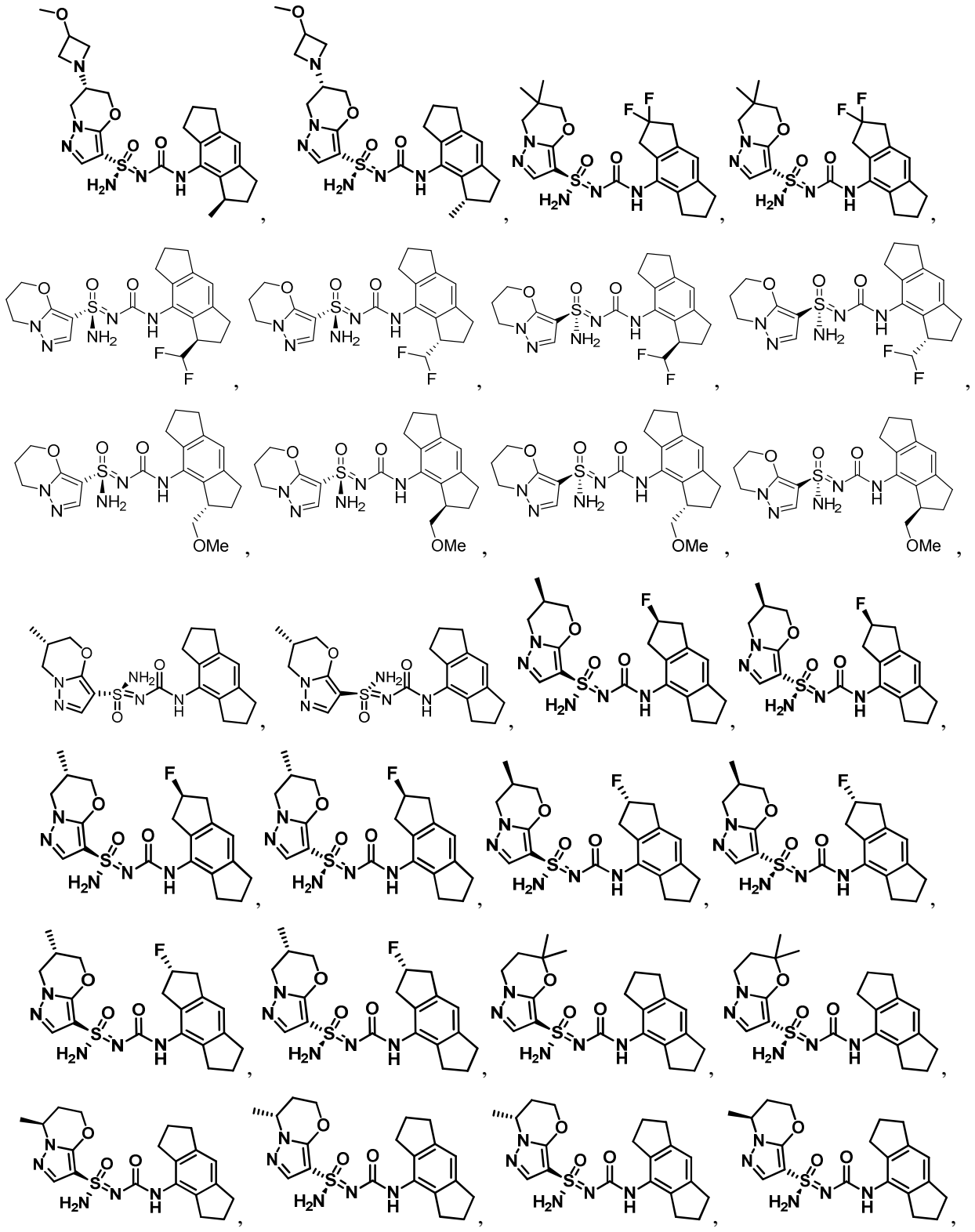
[0027] In another aspect, provided herein is use of a compound as described herein, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disorder in a subject in need thereof. In some examples, provided herein is a compound as descried herein, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for treatment of a disorder in a subject in need thereof. In certain examples, provided herein is a a pharmaceutical composition comprising a compound as described herein, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, for use in the manufacture of a medicament for treatment of a disorder in a subject in need thereof. In some examples, the compound is a compound of Formula (I-A) or Formula (I-B), or from Table 1, List 1, List 2, List 3, or List 4; or a solvate, tautomer, or pharmaceutically acceptable salt thereof.

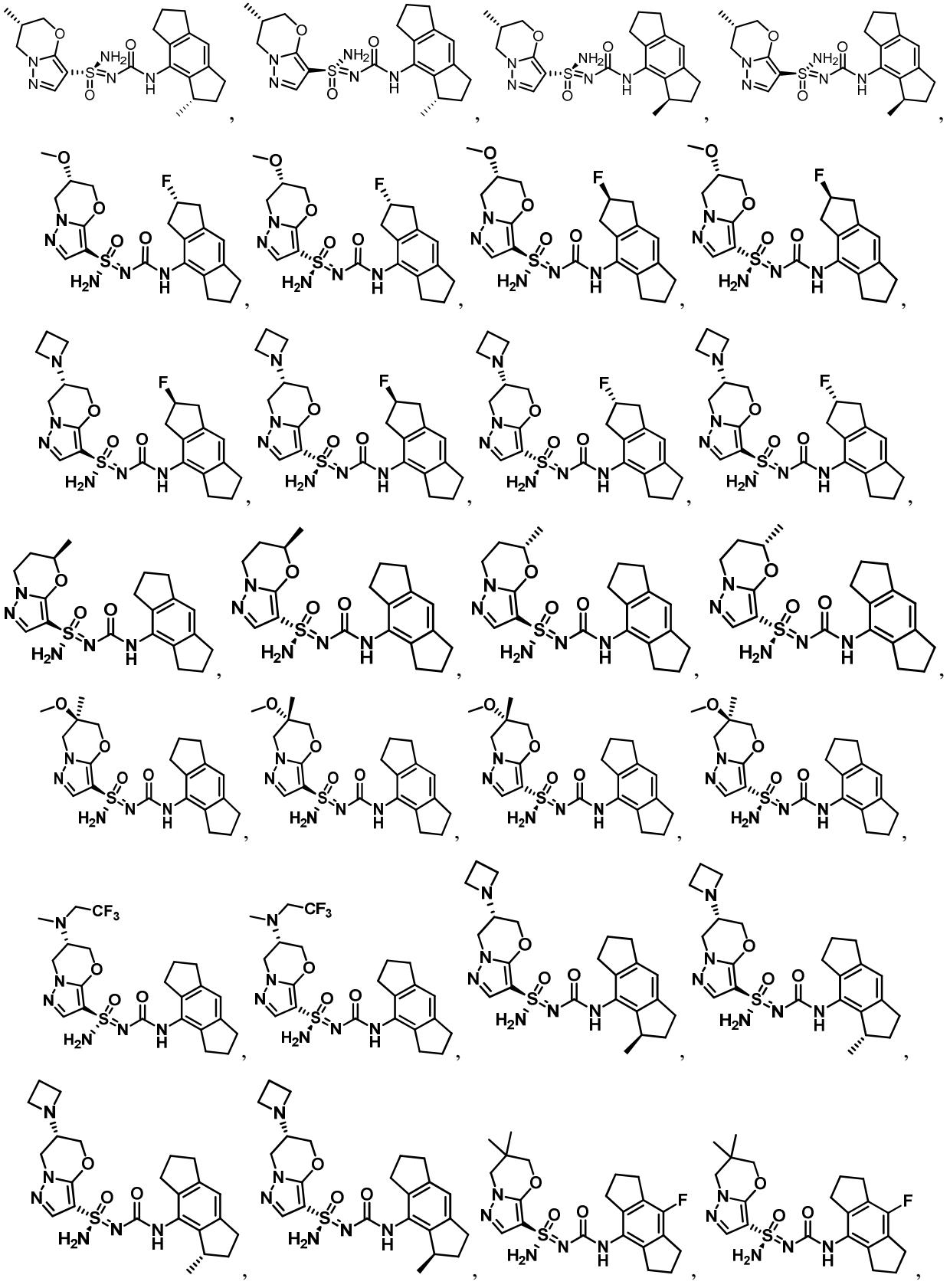
[0028] In some examples, the disorder is responsive to inhibition of the inflammasome. In certain examples, the disorder is responsive to inhibition of activation of the NLRP3 inflammasome.

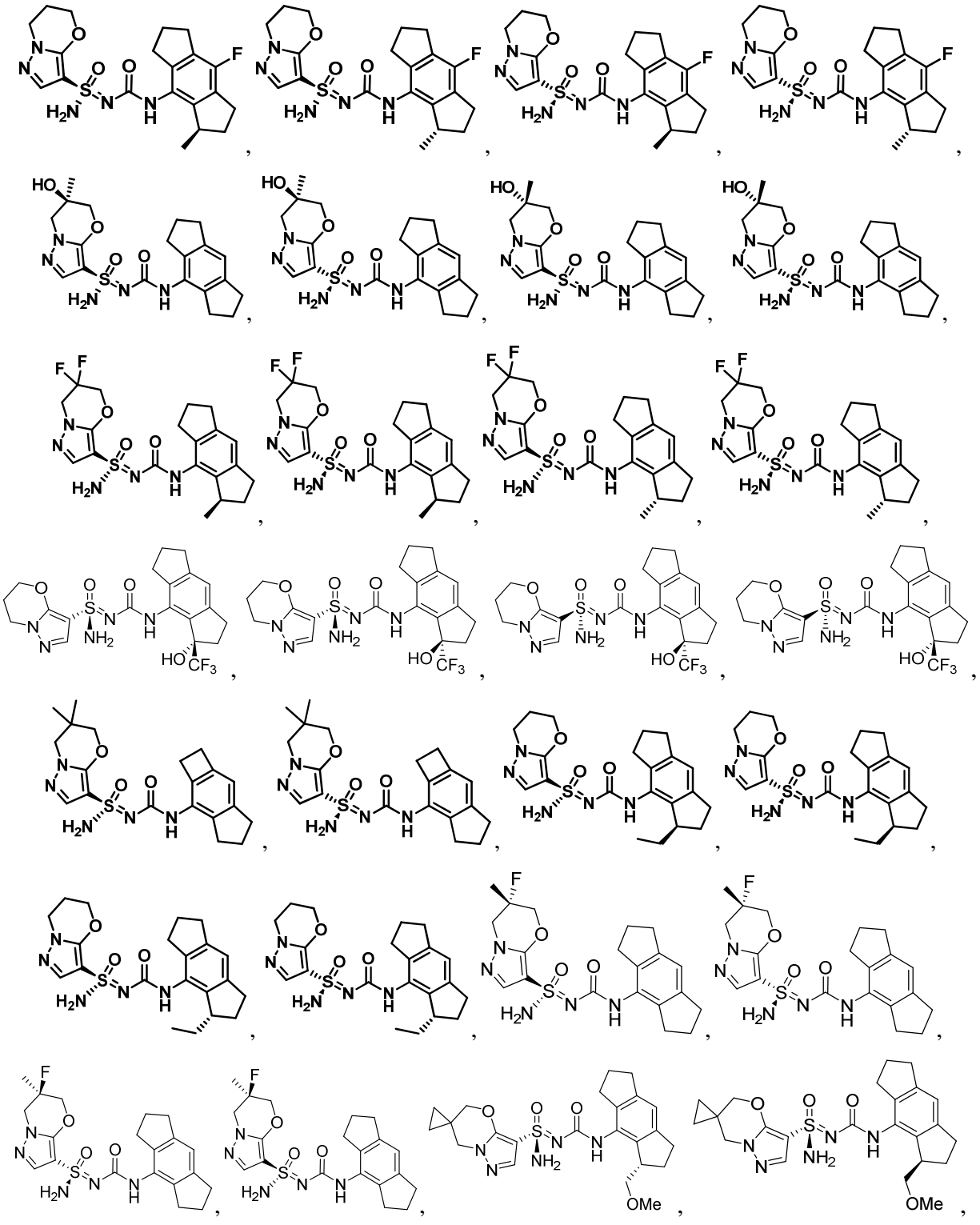
[0029] In yet further examples, provided is a kit comprising a compound as described herein, or a solvate, tautomer, or pharmaceutically acceptable salt thereof; or a pharmaceutical composition as described herein; and instructions for use. In some examples, the compound is a compound of Formula (I-A) or Formula (I-B), or from Table 1, List 1, List 2, List 3, or List 4; or a solvate, tautomer, or pharmaceutically acceptable salt thereof.

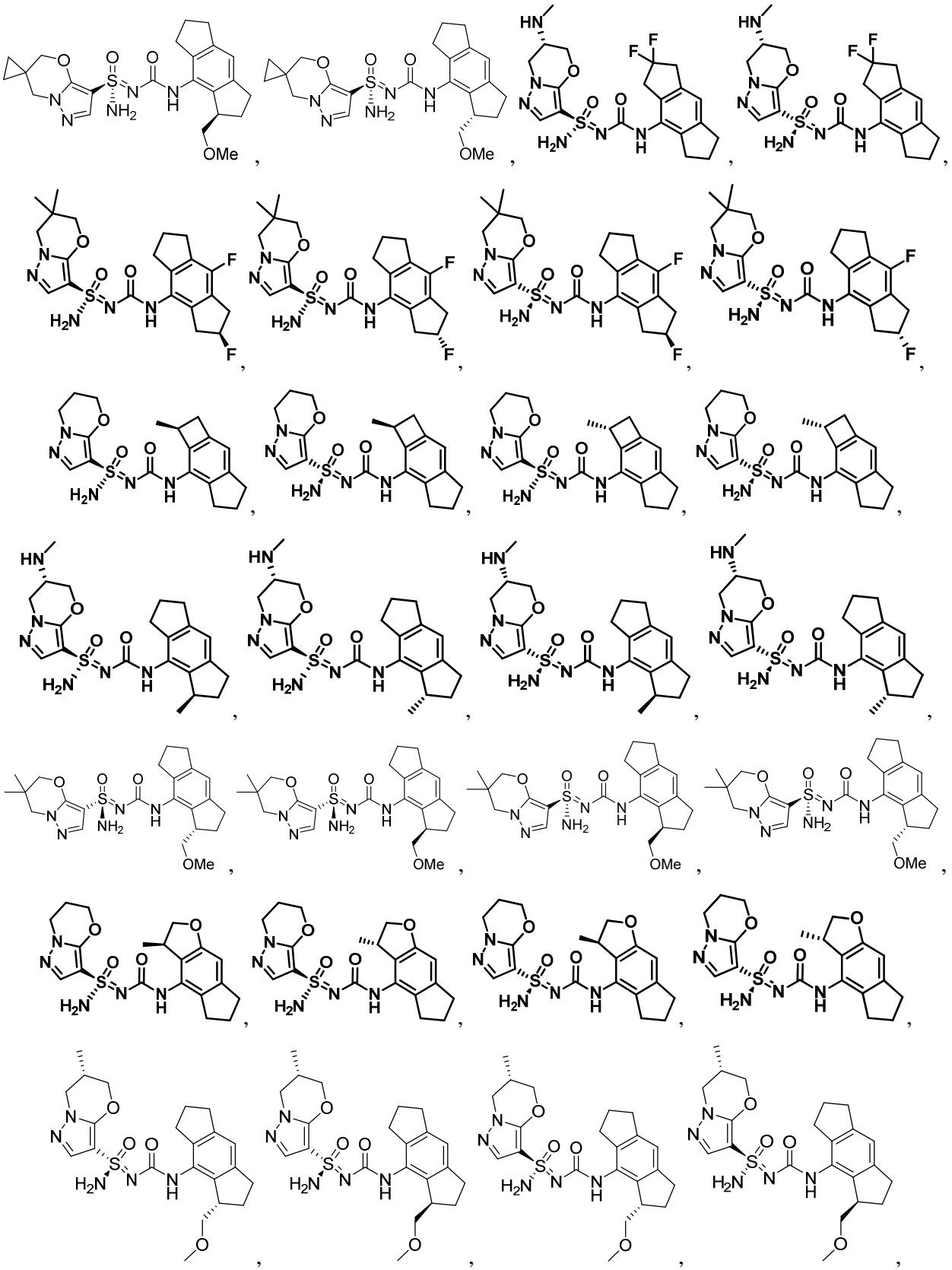
[0029a] In one aspect, provided herein is a compound, wherein the compound is:

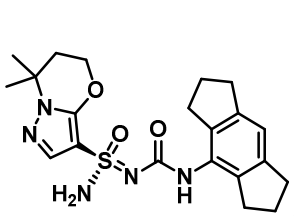
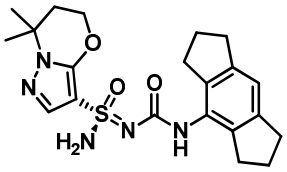
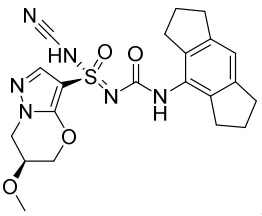
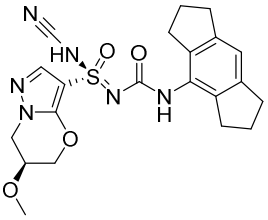
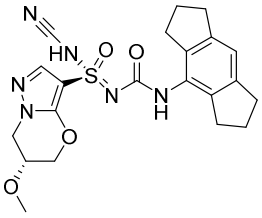
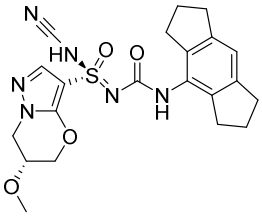
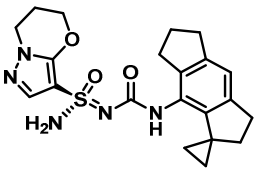
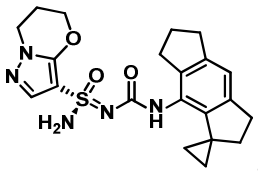
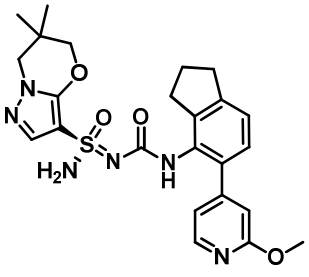
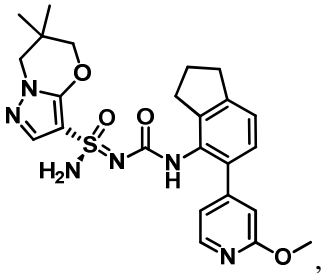
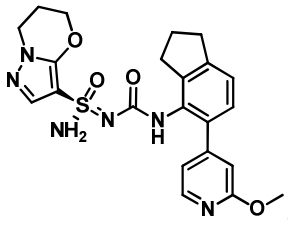
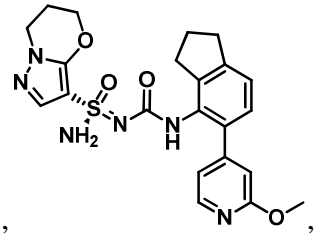
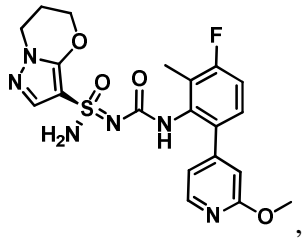
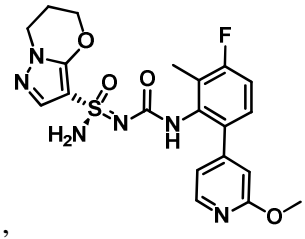
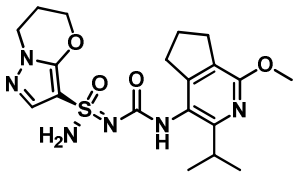
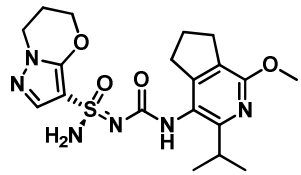
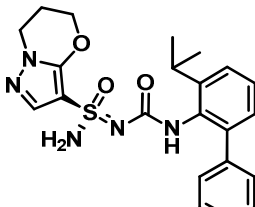
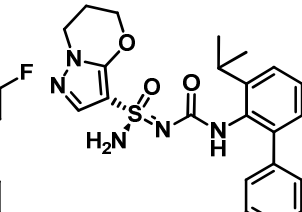
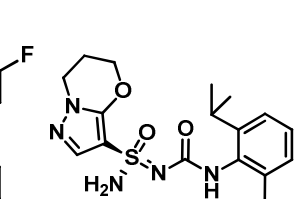
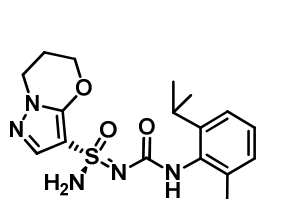
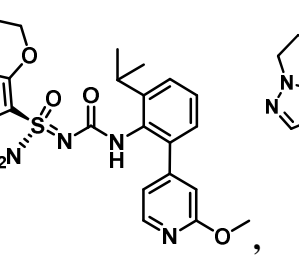
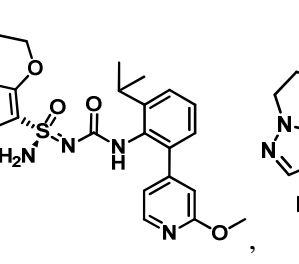
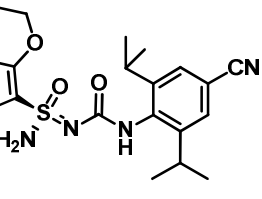
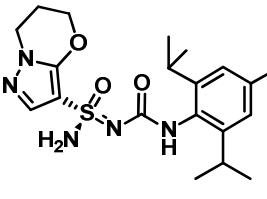










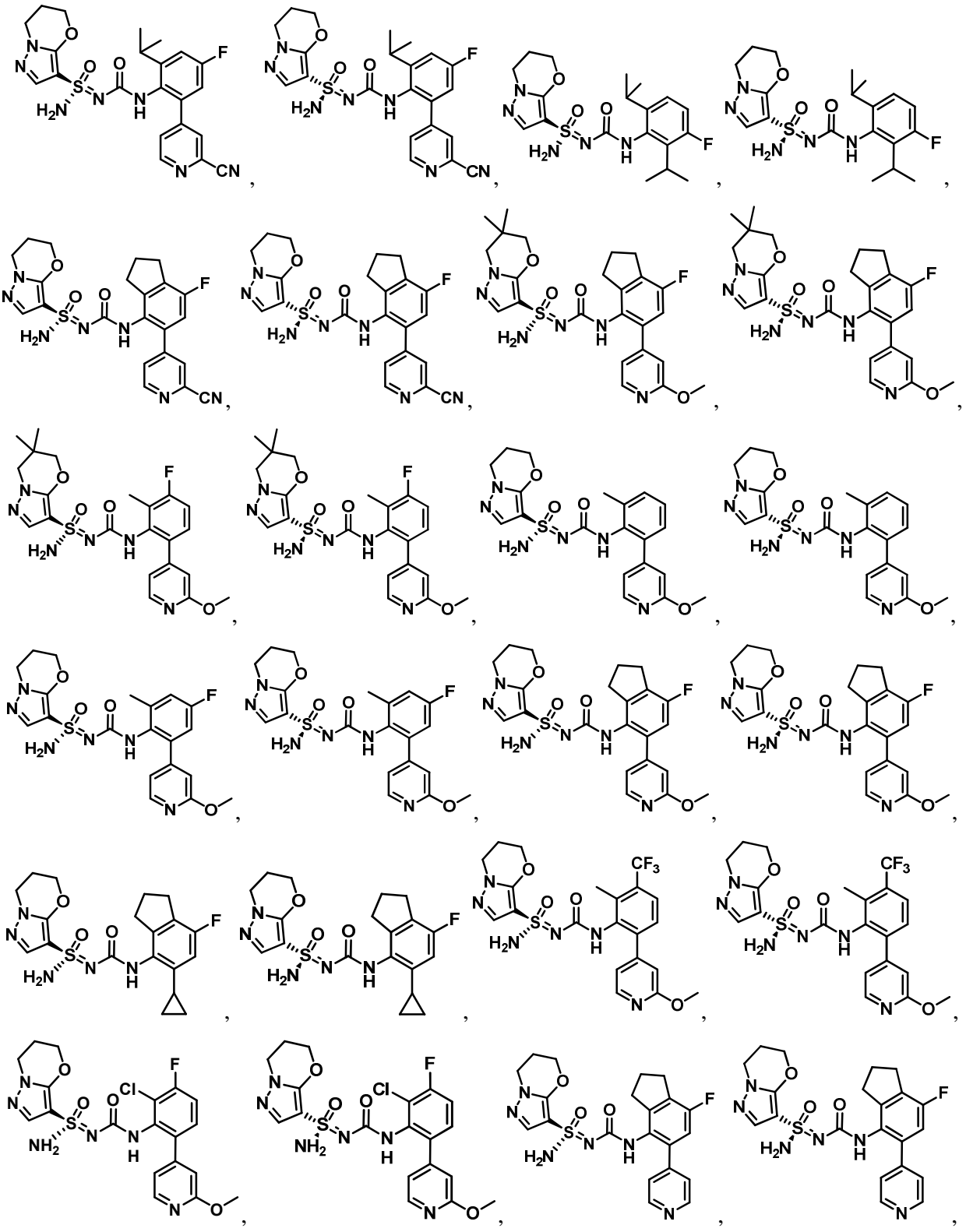

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

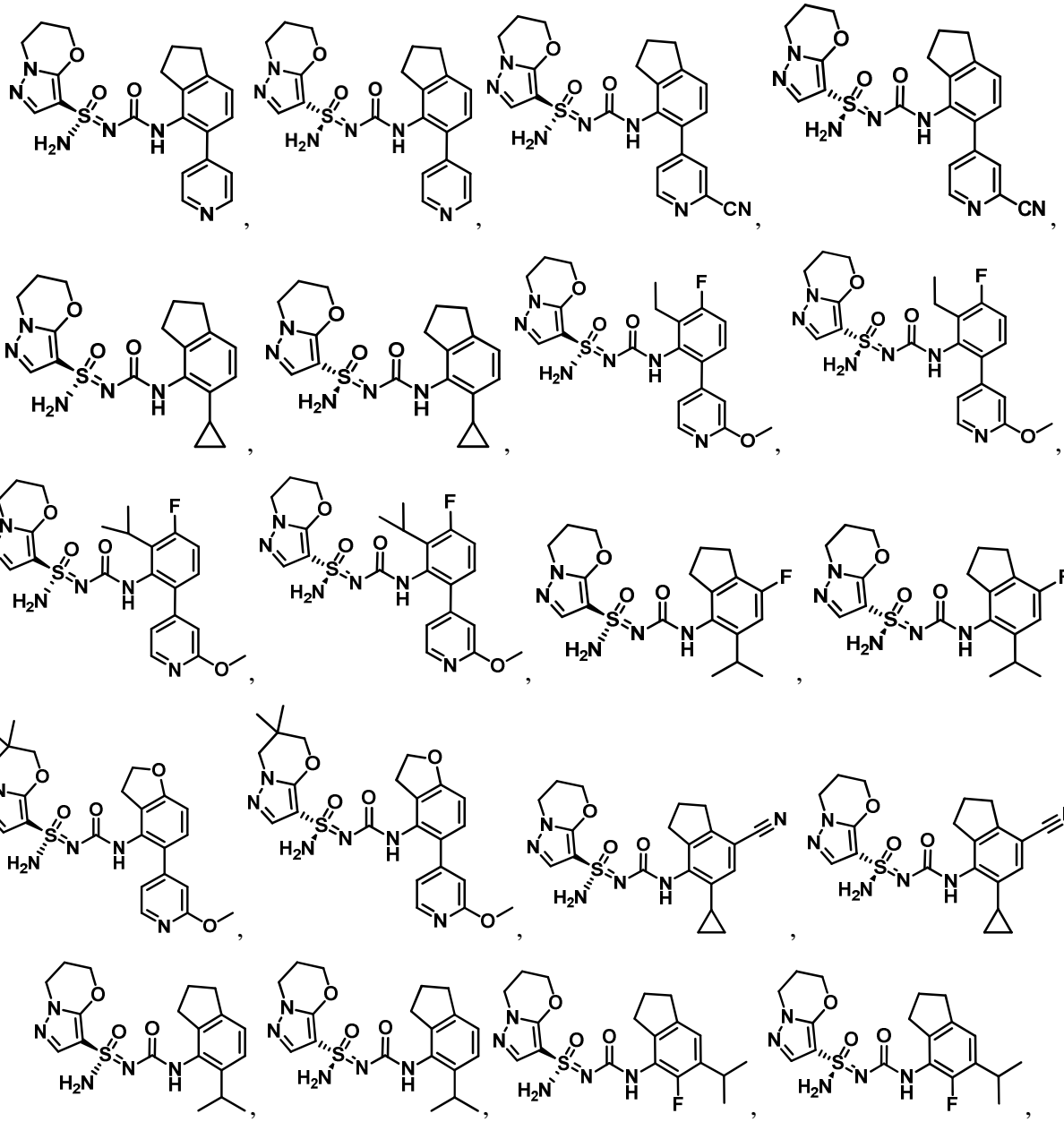
,

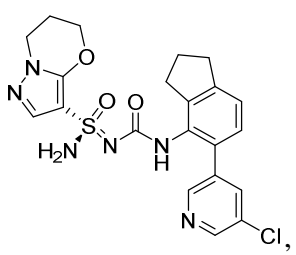
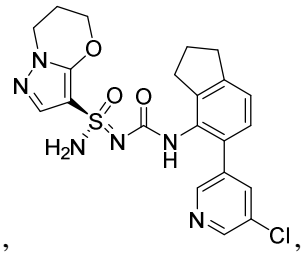
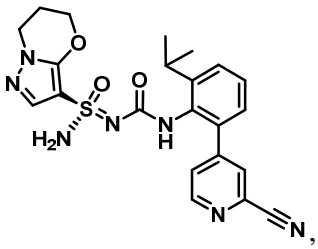
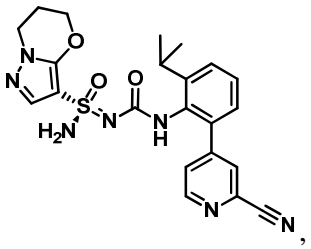
,

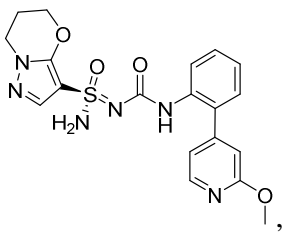
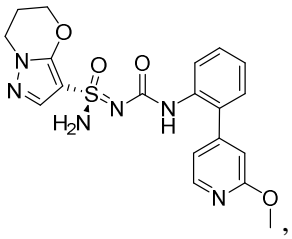
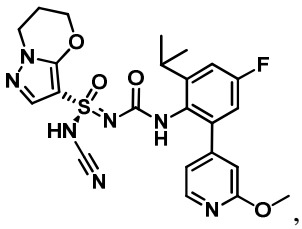
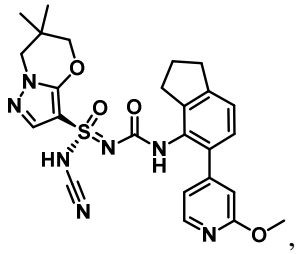
,

,



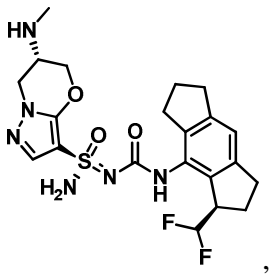
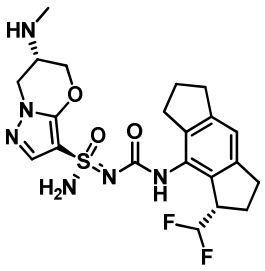
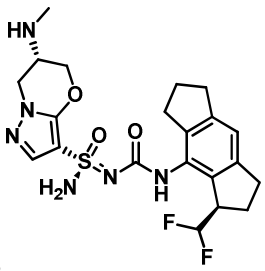
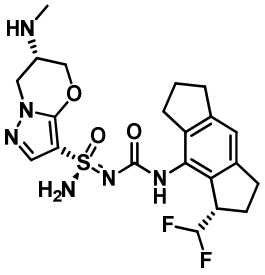


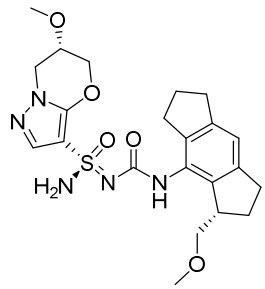
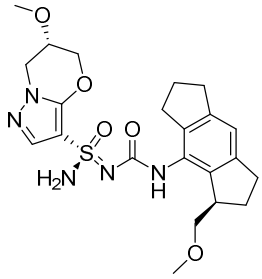
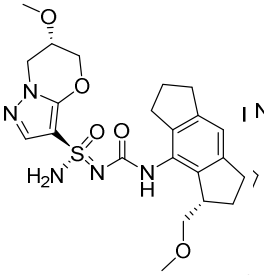
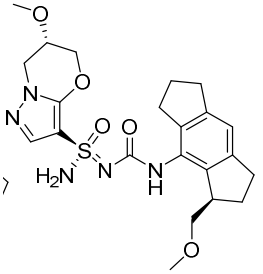
, , , ,

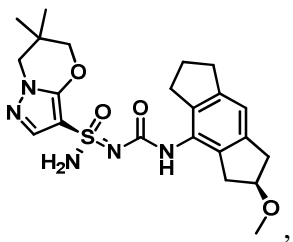
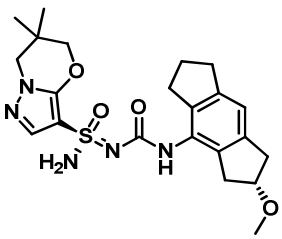
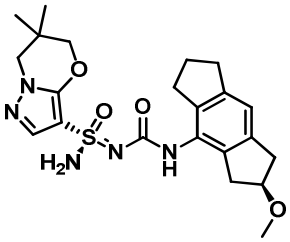
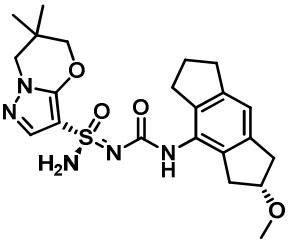
, , , or ,

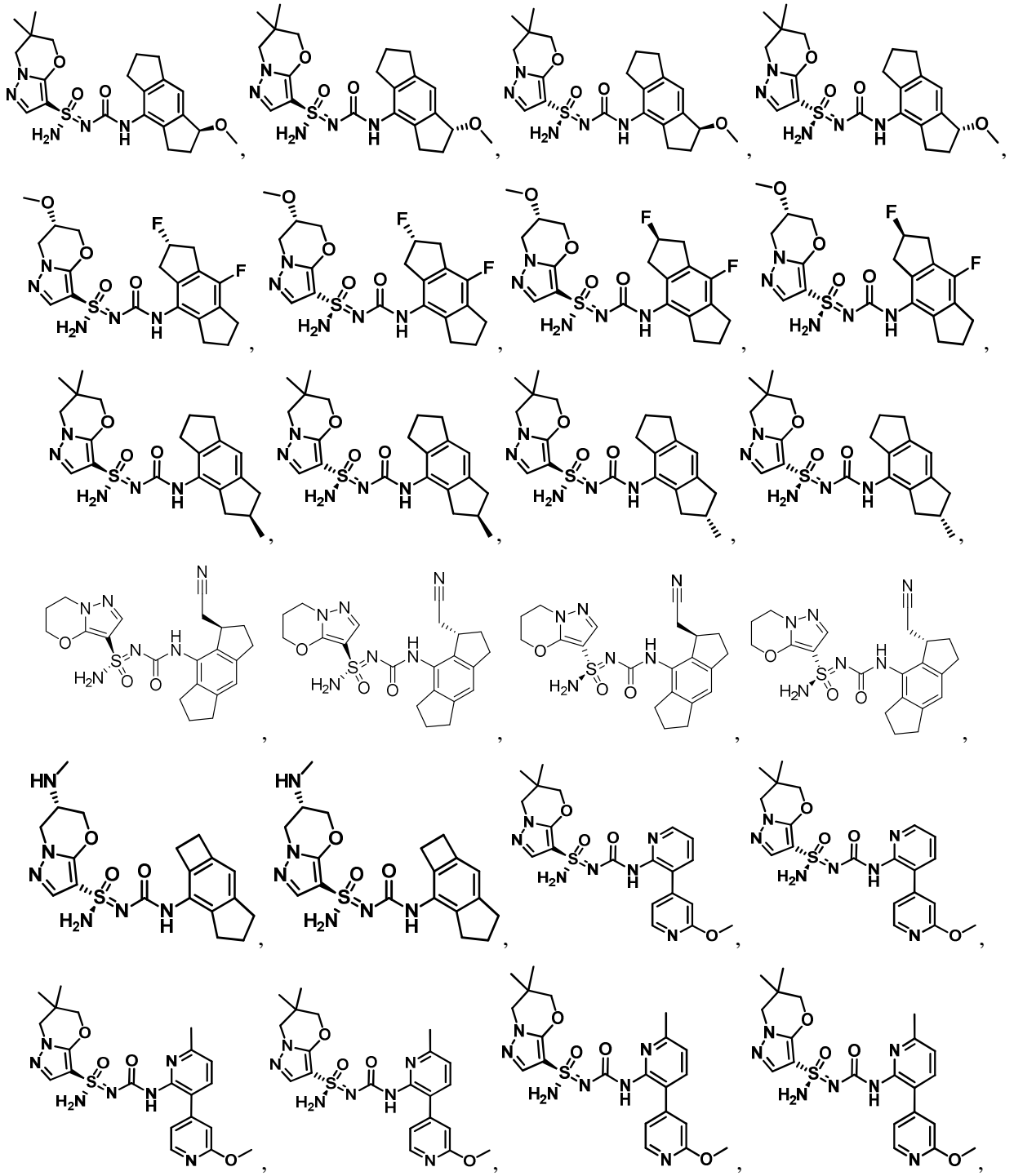
or a solvate, tautomer, or pharmaceutically acceptable salt thereof.

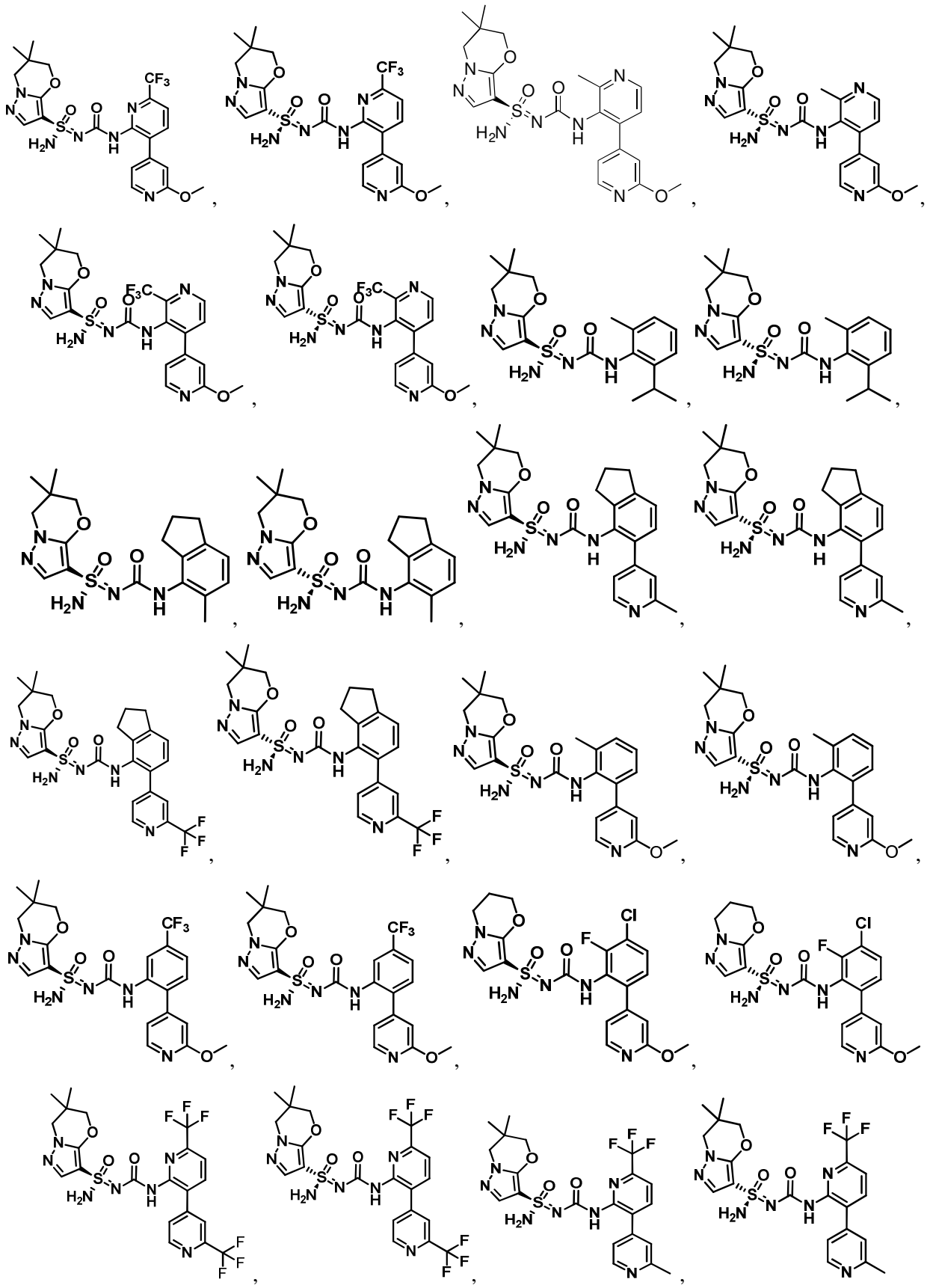
[0029b] In another aspect, provided herein is a compound, wherein the compound is:

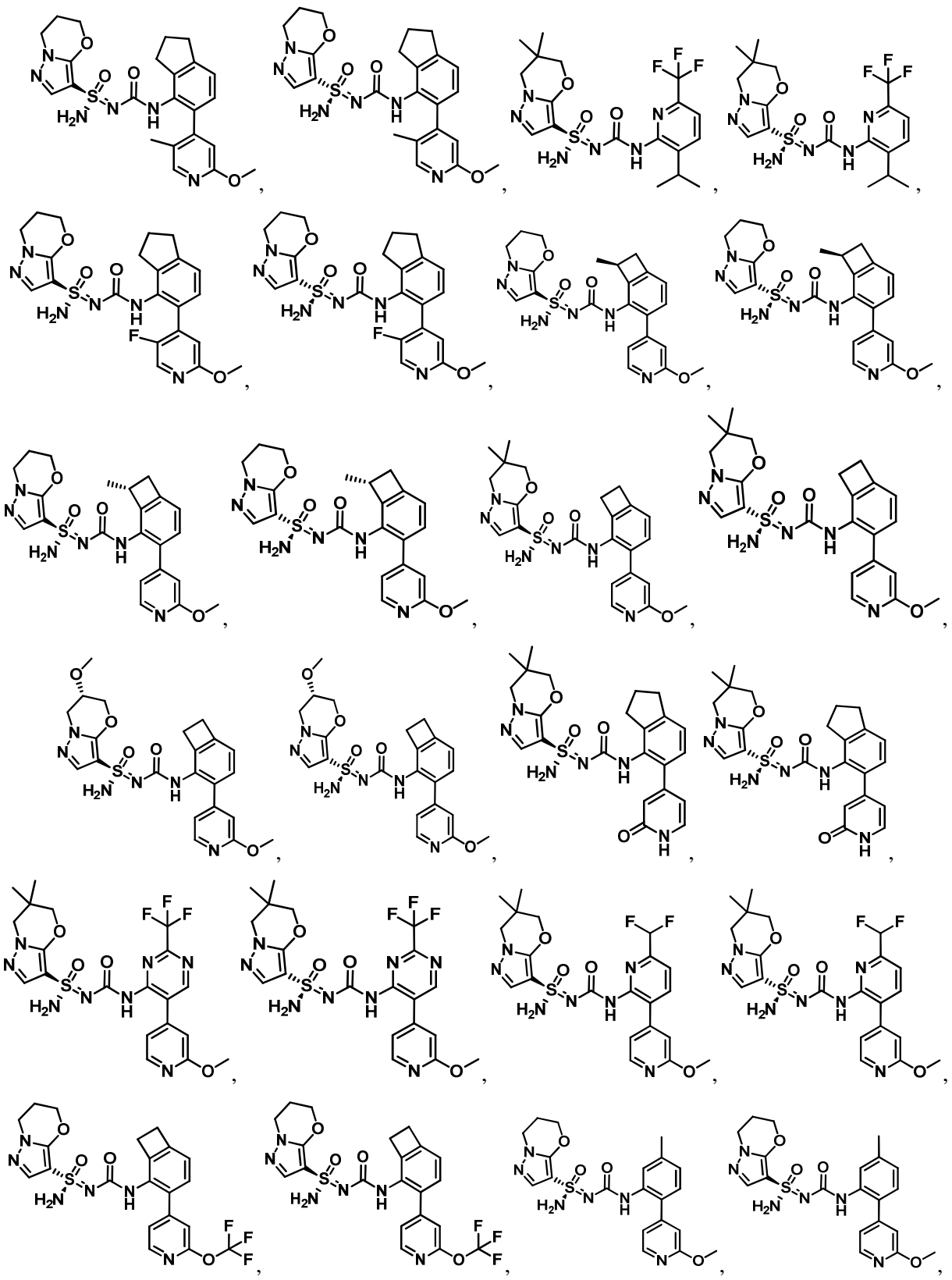
, , , ,

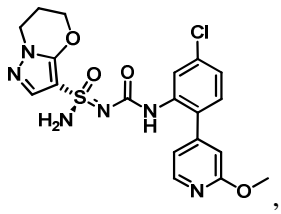
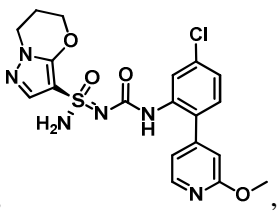
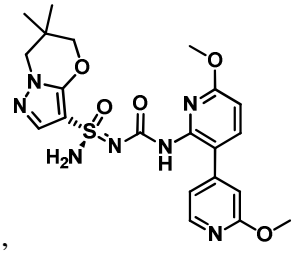
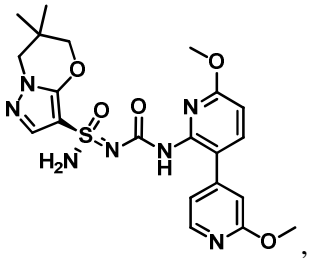
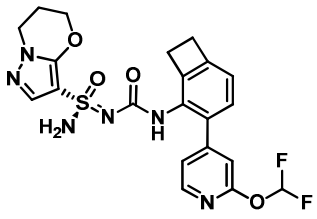
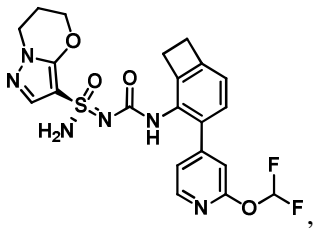
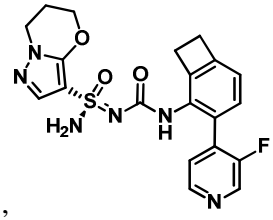
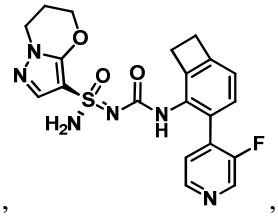
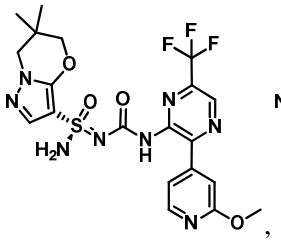
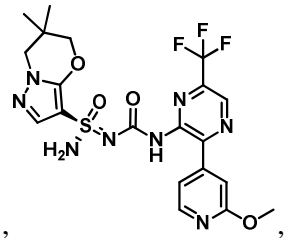
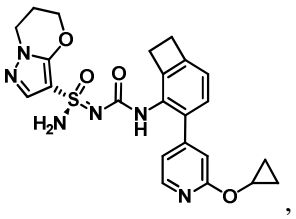
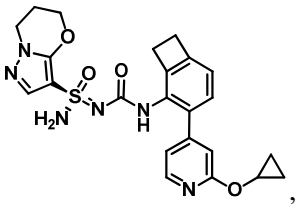
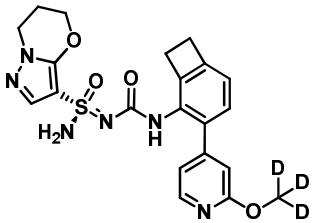
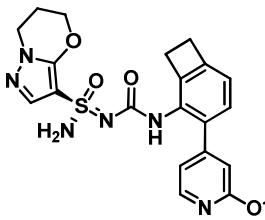
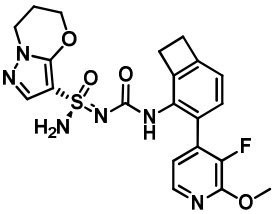
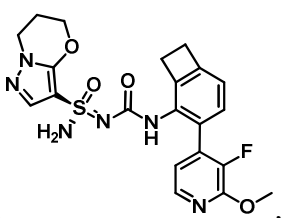
, , , ,

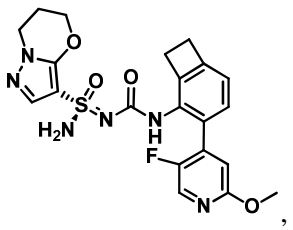
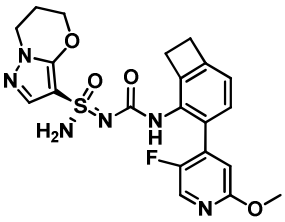
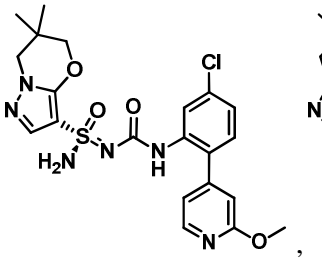
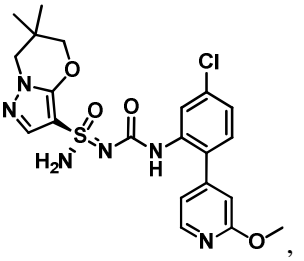
, , , ,

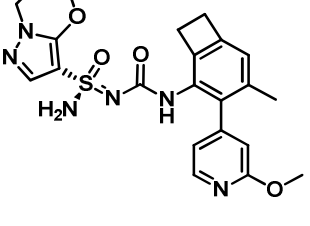
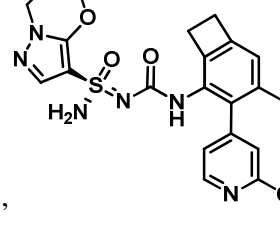
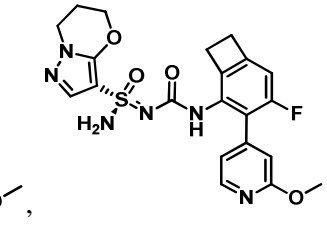
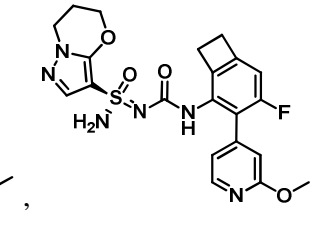




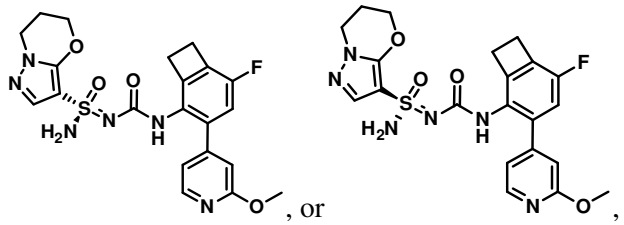


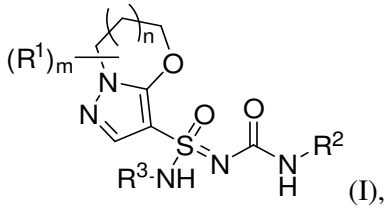




or is a solvate, tautomer, or pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

[0030] Provided herein are compounds of Formula (I):



(I),

or a tautomer, solvate, or pharmaceutically acceptable salt thereof, wherein:

m is an integer from 0 to 6;

n is 0 or 1;

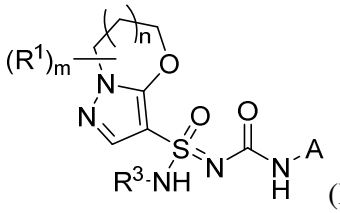
R^3 is H or -CN;

each R^1 is independently halo, -CN, -OR^{1a}, -$NR^{1b}R^{1c}$, -$NR^{1b}SO_2R^{1c}$, -O-R^{1d}-$NR^{1b}R^{1c}$, -O-R^{1d}-OR^{1a}, -N(R^{1b})-R^{1d}-OR^{1a}, -$NR^{1b}C(O)R^{1c}$, -$C(O)NR^{1b}R^{1c}$, C_1-C_6alkyl, or 3-6-membered heterocycloalkyl; wherein each C_1-C_6alkyl and 3-6-membered heterocycloalkyl is independently unsubstituted or substituted with one or more substituents independently

CLAIMS

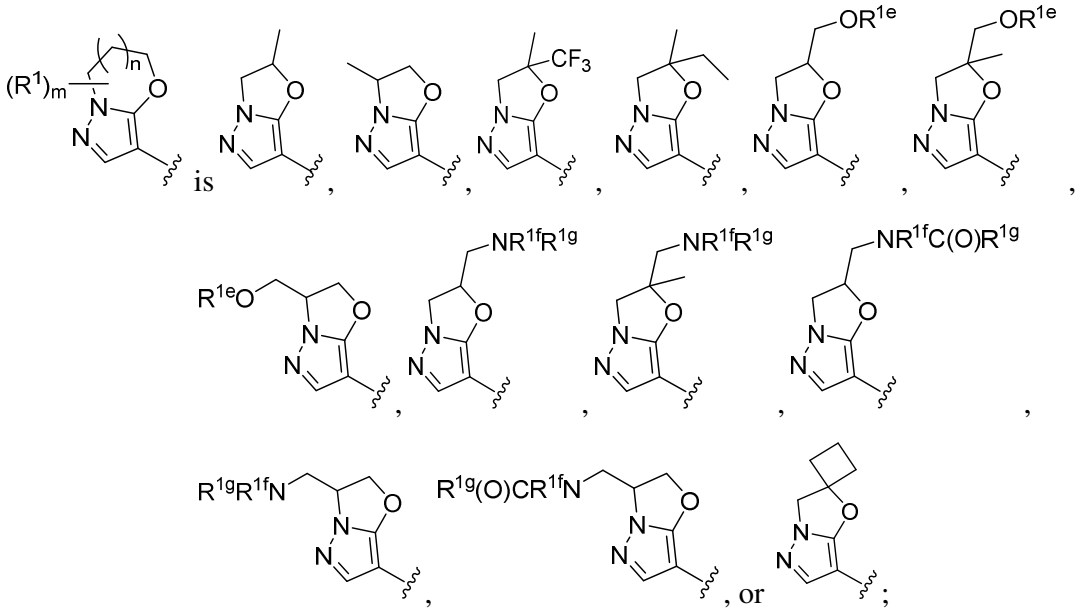
What is claimed is:

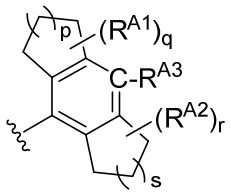
1. A compound of formula (I-A):


(I-A),

or a solvate, tautomer, or pharmaceutically acceptable salt thereof, wherein:

R^3 is H;


is , , ,



A ,

wherein:

p and s are independently 0, 1, or 2;

q and r are independently integers from 0 to 8;

R^{A1} and R^{A2} are independently selected from the group consisting of halo, -CN, -OR^{A4}, -$NR^{A5}R^{A6}$, -$NR^{A5}SO_2R^{A6}$, -$C(O)NR^{A5}R^{A6}$, -$C(O)OR^{A5}$, -$C(O)NR^{A5}SO_2R^{A6}$, -$NR^{A5}C(O)R^{A6}$, C_1-C_6alkyl, C_3-C_6cycloalkyl, 3-6-membered heterocycloalkyl, aryl, and heteroaryl; wherein each C_1-C_6alkyl, C_3-C_6cycloalkyl, 3-6-membered heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, -CN, -OR^{A7}, -$NR^{A8}R^{A9}$, -$NR^{A8}SO_2R^{A9}$, -$NR^{A8}C(O)R^{A9}$, -$OC(O)R^{A9}$, -$C(O)NR^{A8}R^{A9}$, and -$C(O)NR^{A8}SO_2R^{A9}$;

wherein each R^{A4} and R^{A7} is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_3-C_6cycloalkyl, or C_3-C_6halocycloalkyl; and each R^{A5}, R^{A6}, R^{A8}, and R^{A9} is independently H, C_1-C_6alkyl, or C_1-C_6haloalkyl, or when attached to the same nitrogen may cyclize to form heterocycloalkyl or haloheterocycloalkyl;

and two R^{A1}, or two R^{A2}, together with the atoms to which they are attached independently may form C_3-C_6cycloalkyl, C_3-C_6halocycloalkyl, 3-6-membered heterocycloalkyl, or 3-6-membered haloheterocycloalkyl; and

R^{A3} is H, halo, C_1-C_6alkyl, C_1-C_6haloalkyl, -CN, or -OR^{A10}, wherein R^{A10} is H, C_1-C_6alkyl, or C_1-C_6haloalkyl.

2. The compound of claim 1, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, wherein R^{A1} and R^{A2}, if present, are independently selected from the group consisting of halo, -OR^{A4}, -$NR^{A5}R^{A6}$, C_1-C_6alkyl, and C_3-C_6cycloalkyl; wherein each C_1-C_6alkyl and C_3-C_6cycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from

the group consisting of halo, -CN, and -OR^{A7}; or two R^{A1} or two R^{A2} if attached to the same carbon may form C_3-C_6cycloalkyl or C_3-C_6halocycloalkyl.

3. The compound of claim 2, or a solvate, tautomer, or pharmaceutically acceptable salt thereof wherein R^{A3} is H or fluoro.

4. The compound of claim 3, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, wherein p and s are both 1.

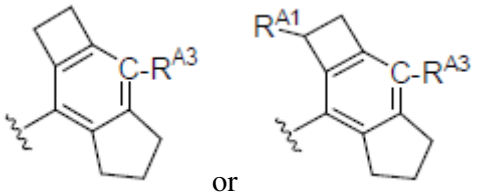
5. The compound of claim 3, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, wherein p is 0 and s is 1; or wherein p is 1 and s is 0.

6. The compound of any one of claims 1 to 5, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, wherein one of q and r is 0 and the other is 1 or 2.

7. The compound of claim 3, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, wherein both p and s are 0; one of q and r is 0; and the other is an integer from 0 to 4.

8. The compound of any one of claims 3 to 7, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, wherein q and r are 0.

9. The compound of claim 3, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, wherein ring A is



or .

10. The compound of any one of claims 1 to 9, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, wherein R^{1e} is H, C_1-C_6alkyl, or C_1-C_6haloalkyl; and each R^{1f} and R^{1g} is independently H, C_1-C_6alkyl, or C_1-C_6haloalkyl.

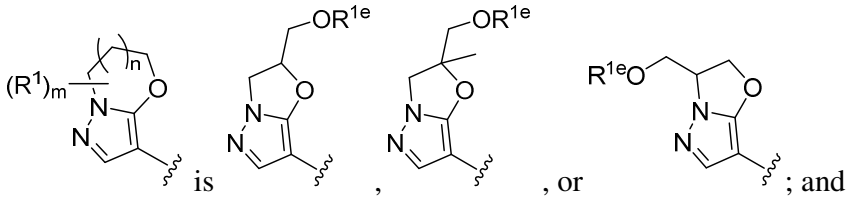
11. The compound of claim 3, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, wherein:

p and s are independently 0 or 1; and q and r are independently integers from 0 to 4; and

R^{1e} is H, C_1-C_6alkyl, or C_1-C_6haloalkyl; and each R^{1f} and R^{1g} is independently H, C_1-C_6alkyl, or C_1-C_6haloalkyl.

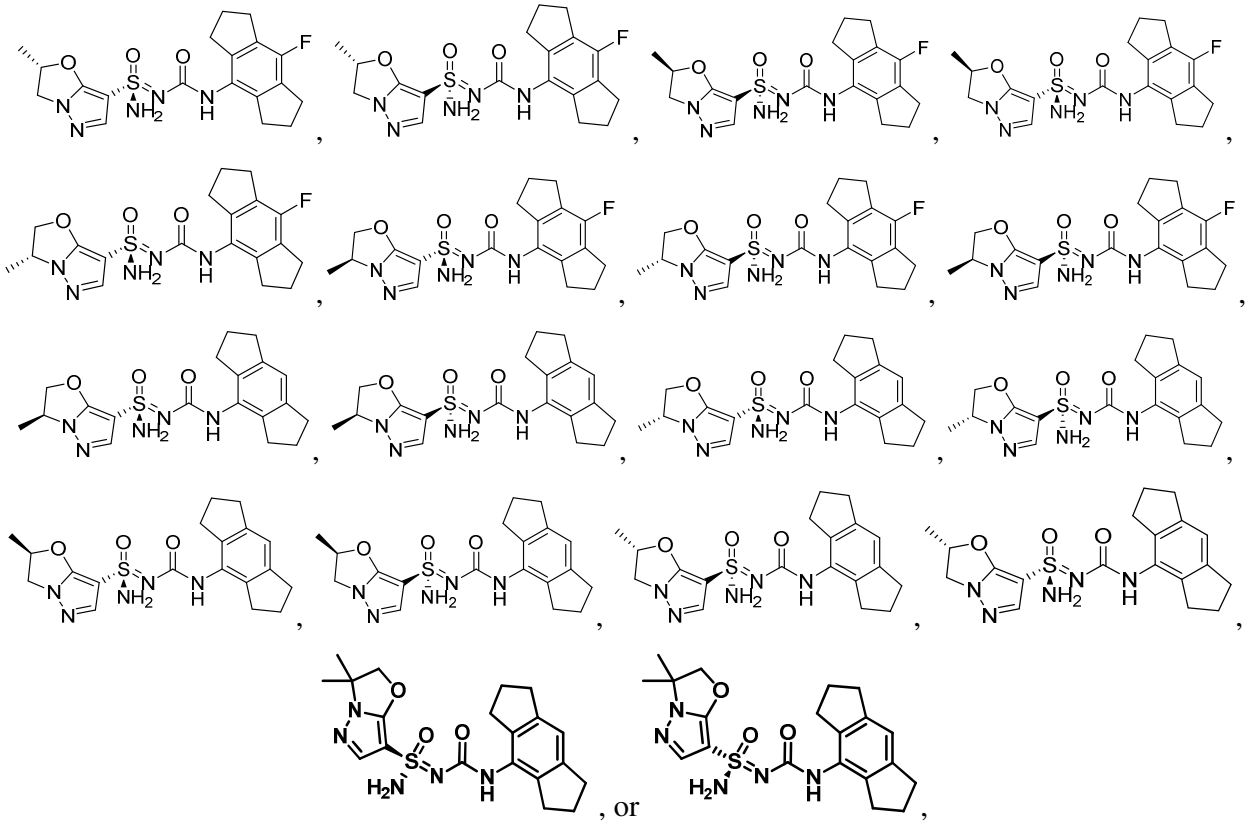
12. The compound of claim 11, or a solvate, tautomer, or pharmaceutically acceptable salt thereof wherein:

r is 0 and q is 1, or both r and q are 0;


is , , or ; and

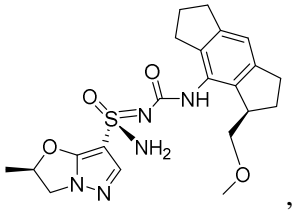
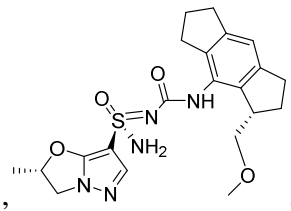
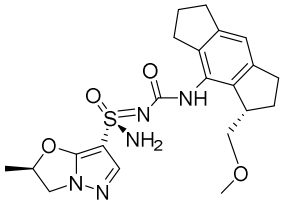
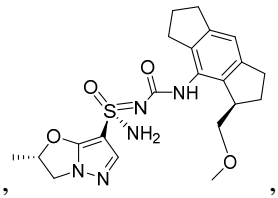
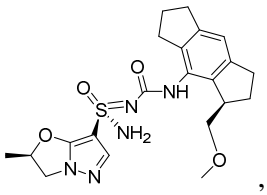
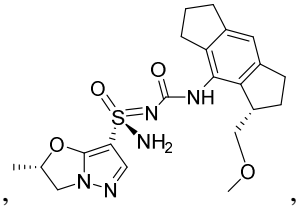
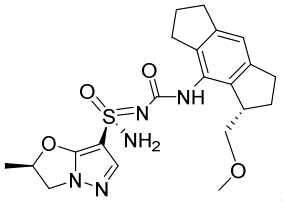
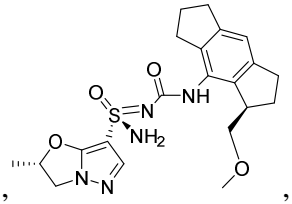
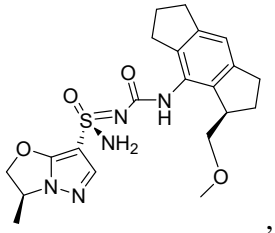
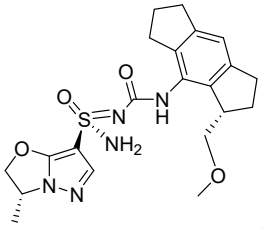
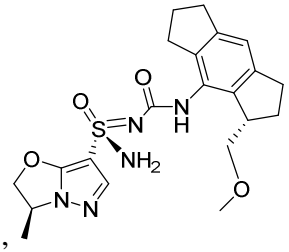
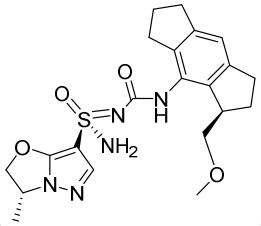
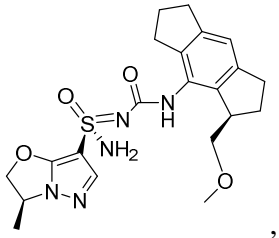
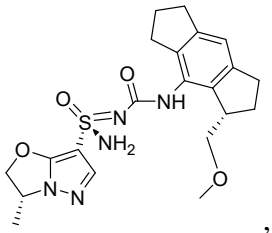
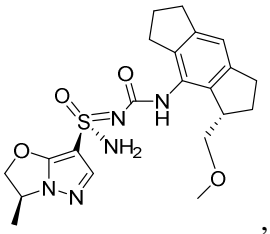
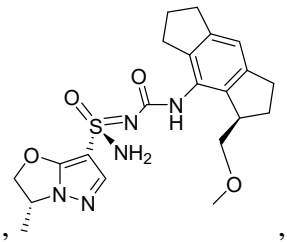
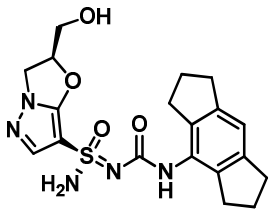
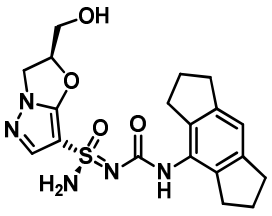
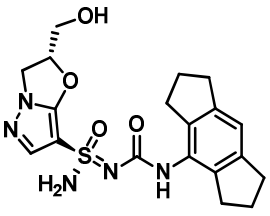
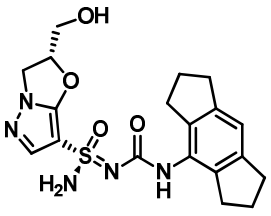
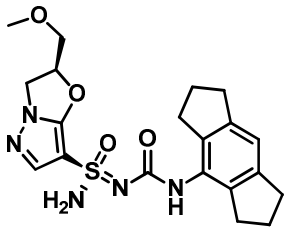
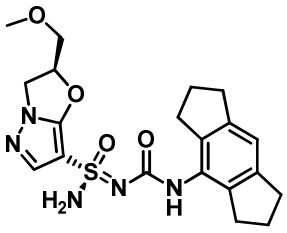
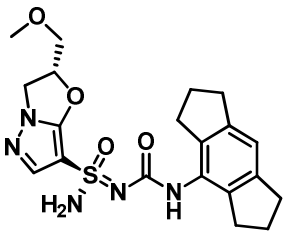
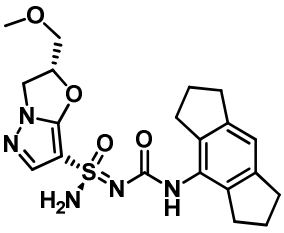
R^{A1} if present, is halo or C_1-C_6alkyl.

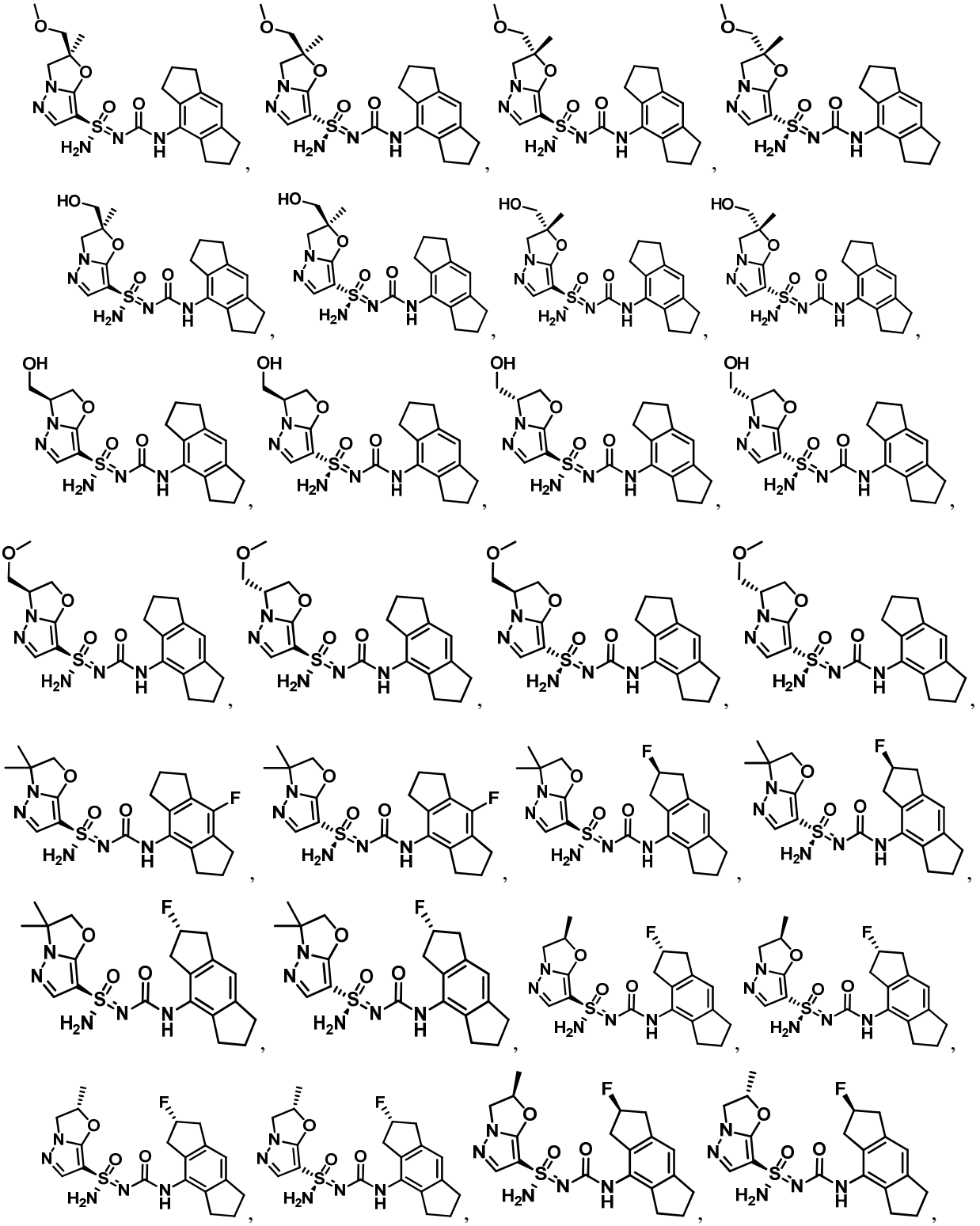
13. The compound of claim 1, wherein the compound is:

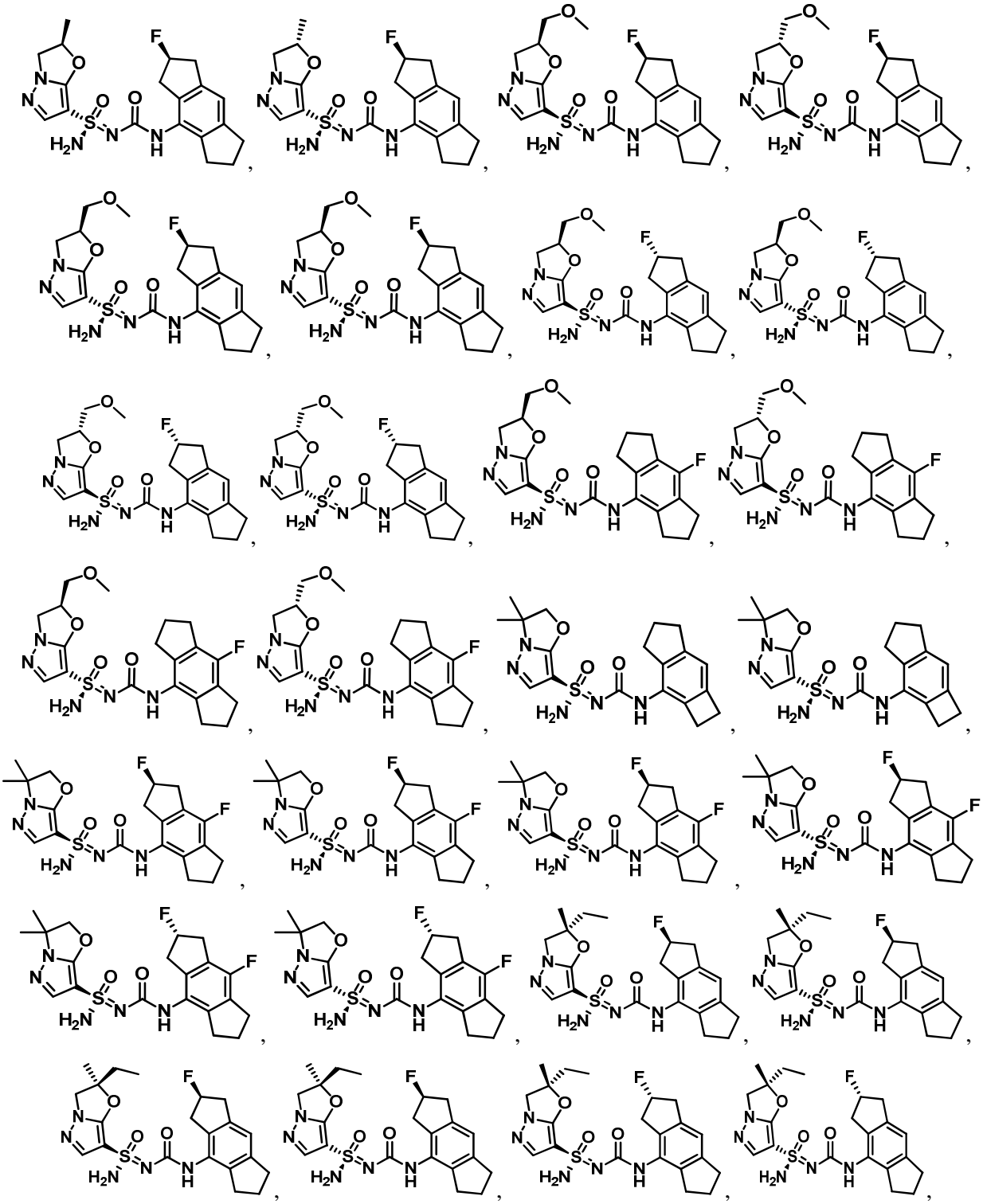

, or ,

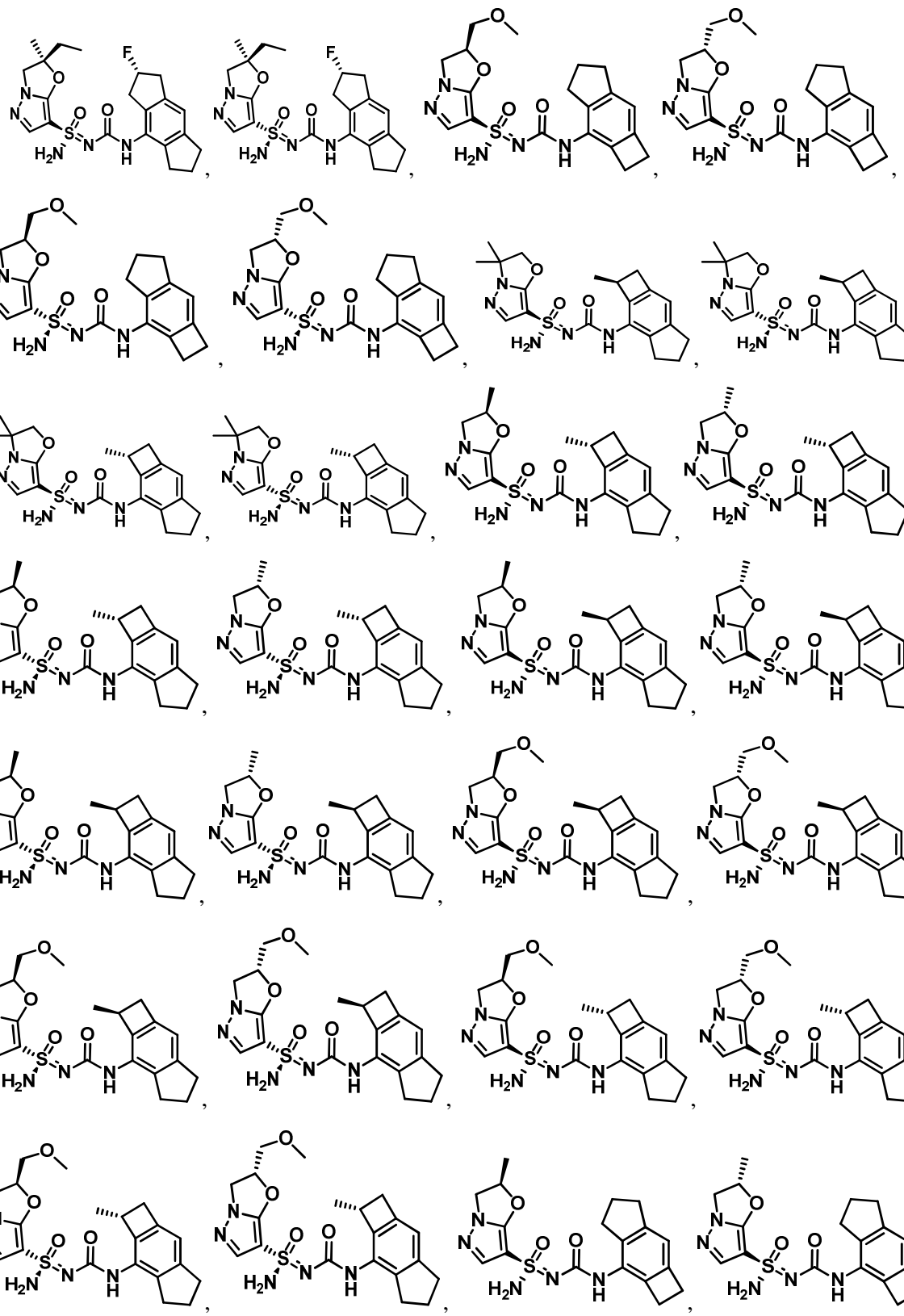
or is a solvate, tautomer, or pharmaceutically acceptable salt thereof.

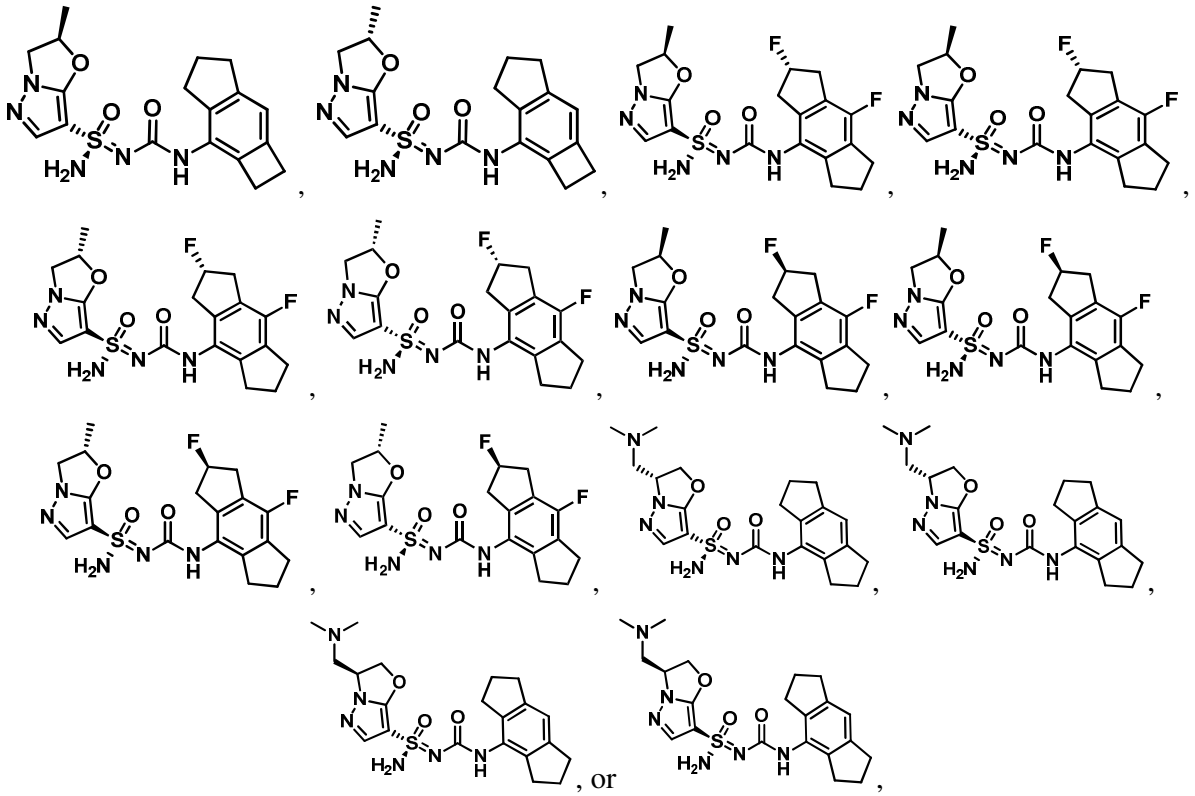
14. The compound of claim 1, wherein the compound is:


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,









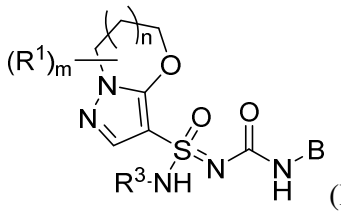
or is a solvate, tautomer, or pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition, comprising a compound of any one of claims 1 to 14, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, and a pharmaceutically accceptable carrier.

16. Use of a compound of any one of claims 1 to 14, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disorder in a subject in need thereof.

17. The use of claim 16, wherein the disorder is a disorder of the immune system, a disorder of the liver, a disorder of the lung, a disorder of the skin, a disorder of the cardiovascular system, a disorder of the renal system, a disorder of the gastro-intestinal tract, a disorder of the respiratory system, a disorder of the endocrine system, a disorder of the central nervous system (CNS), an inflammatory disorder, an autoimmune disorder, or a cancer, tumor, or other malignancy.

18. A compound of Formula (I-B):


(I-B),

or a solvate, tautomer, or pharmaceutically acceptable salt thereof, wherein:

m is an integer from 0 to 4;

n is 0;

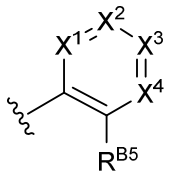
R^3 is H;

each R^1 is independently halo, -CN, -OR^{1a}, -$NR^{1b}R^{1c}$, -$NR^{1b}SO_2R^{1c}$, -O-R^{1d}-$NR^{1b}R^{1c}$, -O-R^{1d}-OR^{1a}, -N(R^{1b})-R^{1d}-OR^{1a}, -$NR^{1b}C(O)R^{1c}$, -$C(O)NR^{1b}R^{1c}$, C_1-C_6alkyl, or 3-6-membered heterocycloalkyl; wherein each C_1-C_6alkyl and 3-6-membered heterocycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, oxo, -CN, -OR^{1e}, -$NR^{1f}R^{1g}$, -$NR^{1f}SO_2R^{1g}$, -$NR^{1f}C(O)R^{1g}$, -$C(O)NR^{1f}R^{1g}$, and -$R^{1h}OR^{1e}$;

wherein each R^{1a} and R^{1e} is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_3-C_6cycloalkyl, or C_3-C_6halocycloalkyl; each R^{1b}, R^{1c}, R^{1f}, and R^{1g} is independently H, C_1-C_6alkyl, or C_1-C_6haloalkyl, or when attached to the same nitrogen atom may cyclize to form heterocycloalkyl or haloheterocycloalkyl; and each R^{1d} and R^{1h} is independently C_1-C_6alkyl or C_1-C_6haloalkyl;

and two R^1 attached to the same carbon may form C_3-C_6cycloalkyl, C_3-C_6halocycloalkyl, 3-6-membered heterocycloalkyl, or 3-6-membered haloheterocycloalkyl;

B is:


B ,

wherein:

X^1 is CR^{B1} or N;

X^2 is CR^{B2} or N;

X^3 is CR^{B3} or N, wherein R^{B3} is H, halo, C_1-C_6alkyl, C_1-C_6haloalkyl, -CN, or $-OR^{B22}$;

X^4 is CR^{B4} or N;

R^{B1}, R^{B2}, and R^{B4} are independently selected from the group consisting of H, halo, -CN, $-OR^{B6}$, $-NR^{B7}R^{B8}$, $-NR^{B7}SO_2R^{B8}$, $-NR^{B7}C(O)R^{B8}$, $-C(O)NR^{B7}R^{B8}$, $-C(O)NR^{B7}SO_2R^{B8}$, C_1-C_6alkyl, C_3-C_6cycloalkyl, 3-6-membered heterocycloalkyl, aryl, and heteroaryl; wherein each C_1-C_6alkyl, C_3-C_6cycloalkyl, 3-6-membered heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, -CN, C_1-C_6alkyl, C_1-C_6haloalkyl, $-OR^{B9}$, $-NR^{B10}R^{B11}$, $-NR^{B10}SO_2R^{B11}$, $-NR^{B10}C(O)R^{B11}$, $-C(O)NR^{B10}R^{B11}$, and $-C(O)NR^{B10}SO_2R^{B11}$;

R^{B5} is pyridine, unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, C_1-C_6alkyl, C_1-C_6haloalkyl, -CN, $-NR^{B13}R^{B14}$, $-NR^{B13}C(O)R^{B14}$, $-C(O)NR^{B13}R^{B14}$, and $-OR^{B15}$;

or R^{B1} and R^{B2} together with the atoms to which they are attached may form C_4-C_6cycloalkyl or 4-6-membered heterocycloalkyl;

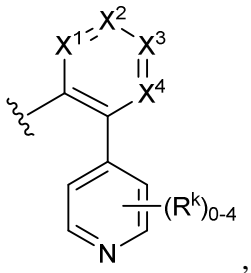
and independently R^{B4} and R^{B5} together with the atoms to which they are attached may form 4-6-membered heterocycloalkyl;

wherein the heterocycloalkyl or cycloalkyl formed by R^{B1} and R^{B2}, and heterocycloalkyl formed by R^{B4} and R^{B5}, are independently unsubstituted or substituted with one or more substituents selected from the group consisting of halo, -CN, $-OR^{B16}$, $-NR^{B17}R^{B18}$, $-NR^{B17}SO_2R^{B18}$, $-NR^{B17}C(O)R^{B18}$, $-C(O)NR^{B17}R^{B18}$, $-C(O)OR^{B17}$, $-C(O)NR^{B17}SO_2R^{B18}$, C_1-C_6alkyl, C_3-C_6cycloalkyl, 3-6-membered heterocycloalkyl, aryl, and heteroaryl; wherein each C_1-C_6alkyl, C_3-C_6cycloalkyl, 3-6-membered heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, -CN, $-OR^{B19}$, $-NR^{B20}R^{B21}$, $-NR^{B20}SO_2R^{B21}$, $-NR^{B20}C(O)R^{B21}$, $-OC(O)R^{B21}$, $-C(O)NR^{B20}R^{B21}$, and $-C(O)NR^{B20}SO_2R^{B21}$; and

each R^{B6}, R^{B9}, R^{B12}, R^{B15}, R^{B16}, R^{B19}, and R^{B22} is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_3-C_6cycloalkyl, or C_3-C_6halocycloalkyl; and each R^{B7}, R^{B8}, R^{B10}, R^{B11},

R^{B13}, R^{B14}, R^{B17}, R^{B18}, R^{B20}, and R^{B21} is independently H, C_1-C_6alkyl, or C_1-C_6haloalkyl, or when attached to the same nitrogen atom may cyclize to form heterocycloalkyl or haloheterocycloalkyl.

19. The compound of claim 18, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, wherein ring B is:



,

wherein each R^k is independently selected from the group consisting of halo, C_1-C_6alkyl, C_1-C_6haloalkyl, -CN, -$NR^{B13}R^{B14}$, -$NR^{B13}C(O)R^{B14}$, -$C(O)NR^{B13}R^{B14}$, and -OR^{B15}.

20. The compound of claim 19, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, wherein X^1 is C-R^{B1} and X^2 is C-R^{B2}, and the R^{B1} and R^{B2} together form unsubstituted C_4-C_6cycloalkyl or unsubstituted 4-6-membered heterocycloalkyl.

21. The compound of claim 19 or 20, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, wherein X^3 is CR^{B3}, R^{B3} is H and R^k is -O-C_1-C_6alkyl.

22. The compound of any one of claims 18 to 21, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, wherein X^1 is CR^{B1}; X^2 is CR^{B2}; X^3 is CR^{B3}; and X^4 is CR^{B4}.

23. The compound of any one of claims 18 to 22, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, wherein

R^{B1} is H, halo, -CN, -OC_1-C_6alkyl, C_1-C_6alkyl, or C_1-C_6haloalkyl;

R^{B2} is H, halo, -CN, -OC_1-C_6alkyl, C_1-C_6alkyl, or C_1-C_6haloalkyl;

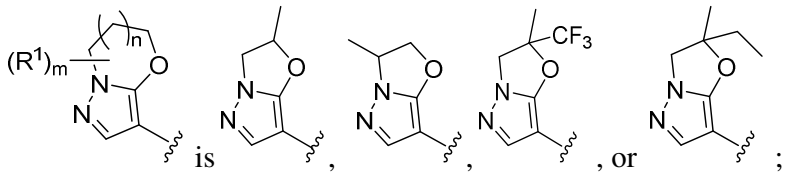
R^{B3} is H, F, or –CN; and

R^{B4} is H, halo, -CN, -OC_1-C_6alkyl, C_1-C_6alkyl, or C_1-C_6haloalkyl.

24. The compound of any one of claims 18 to 23, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, wherein each R^1 is independently halo, -CN, -OR^{1a}, -$NR^{1b}R^{1c}$, C_1-C_6alkyl, or 3-6-membered heterocycloalkyl; wherein each C_1-C_6alkyl and 3-6-membered heterocycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, -CN, -OR^{1e}, -$NR^{1f}R^{1g}$, and -$NR^{1f}C(O)R^{1g}$; and two R^1 attached to the same carbon may form C_3-C_6cycloalkyl or C_3-C_6halocycloalkyl.

25. The compound of claim 24, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, wherein each R^1 is independently methyl, methoxy, hydroxy, or azetidine; each of which is unsubstituted or substituted where possible with one or more fluoro, methoxy, or hydroxyl.

26. The compound of claim 19, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, wherein:



is , , , , or ;

X^1 is CR^{B1}; X^2 is CR^{B2}; X^3 is CR^{B3}; and X^4 is CR^{B4};

R^{B1} is H, halo, -CN, -OC_1-C_6alkyl, C_1-C_6alkyl, or C_1-C_6haloalkyl;

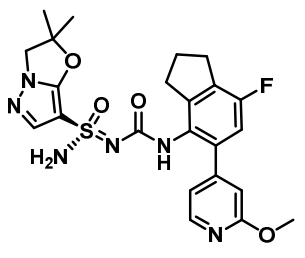
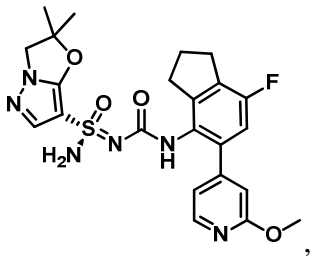
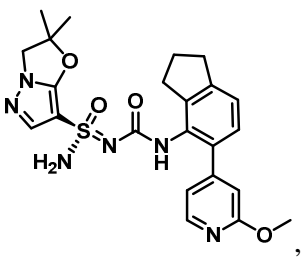
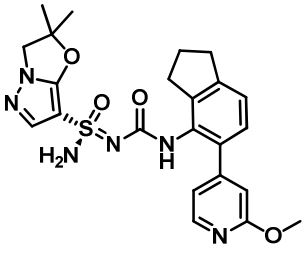
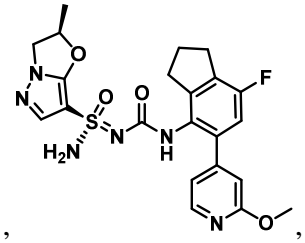
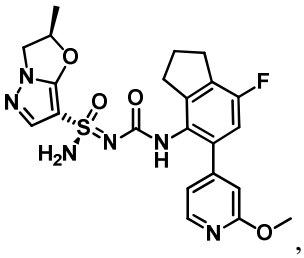
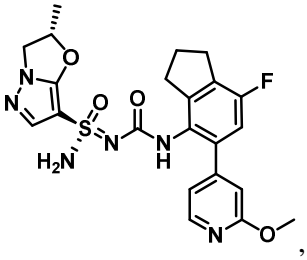
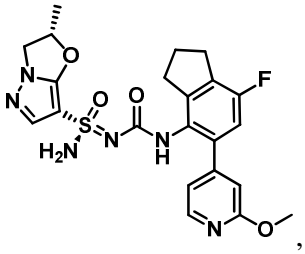
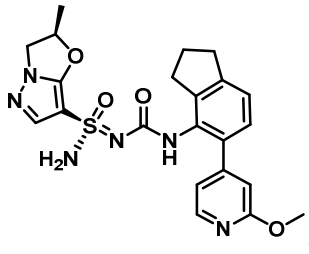
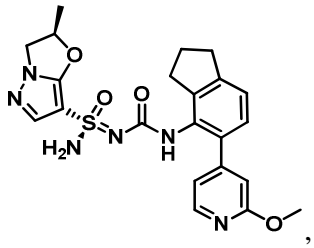
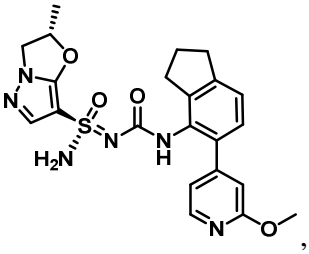
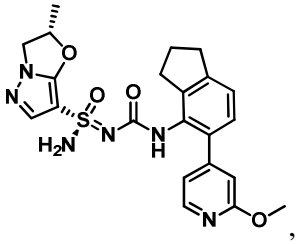
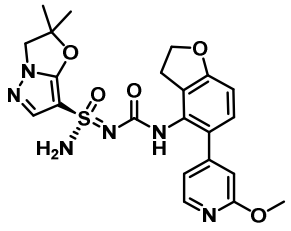
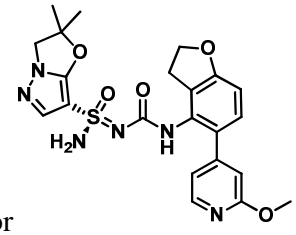
R^{B2} is H, halo, -CN, -OC_1-C_6alkyl, C_1-C_6alkyl, or C_1-C_6haloalkyl;

R^{B3} is H, F, or –CN; and

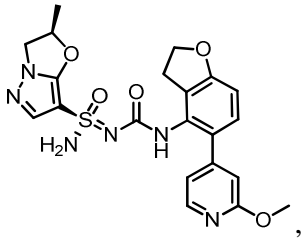
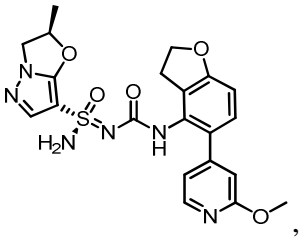
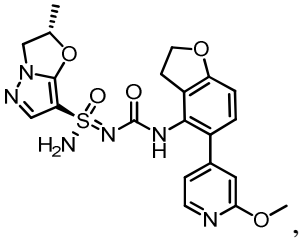
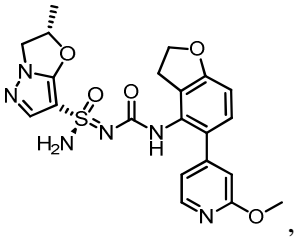
R^{B4} is H and;

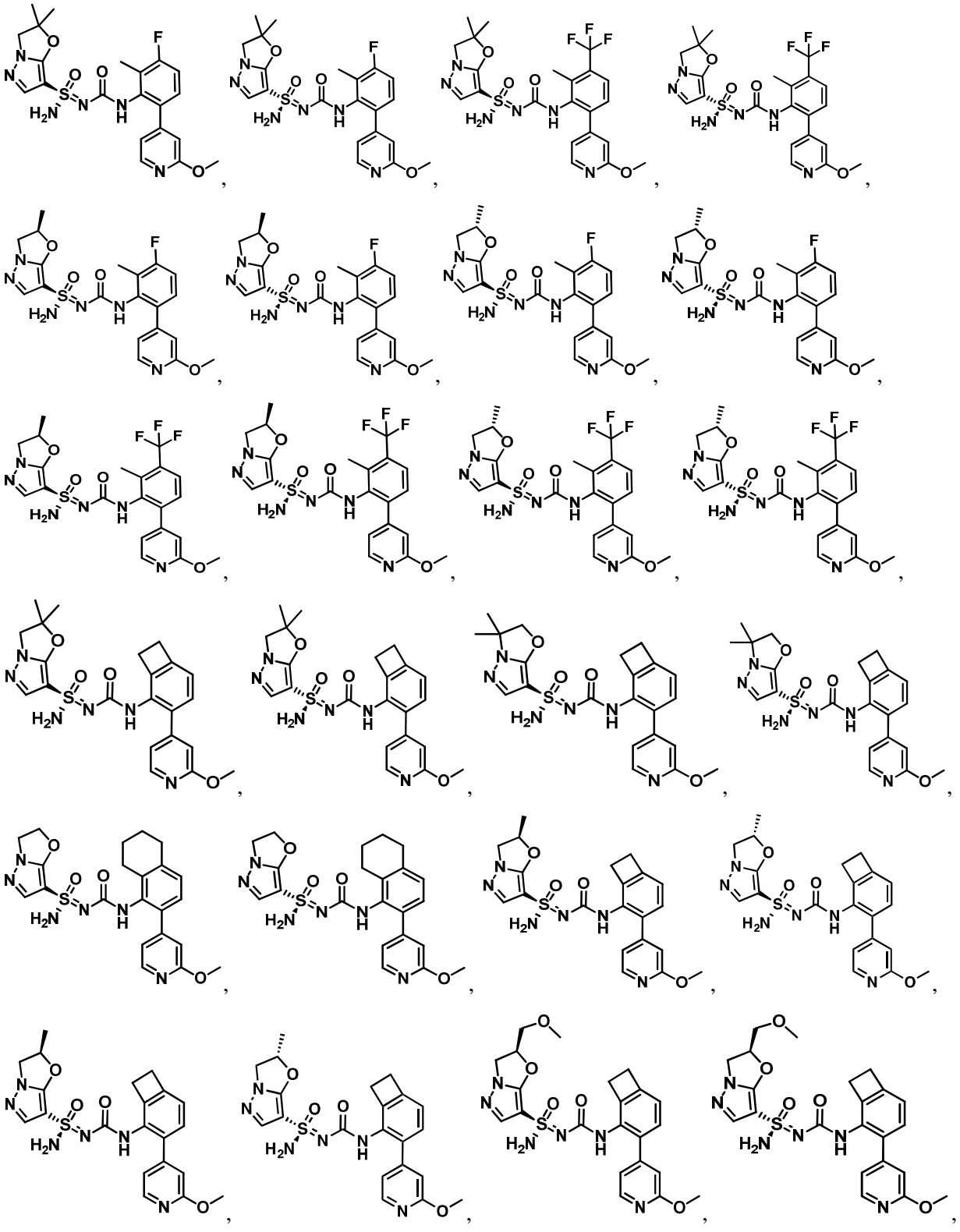
R^k is -O-C_1-C_6alkyl.

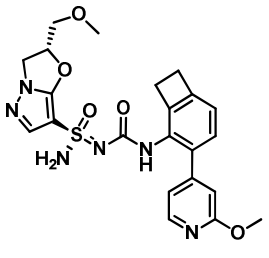
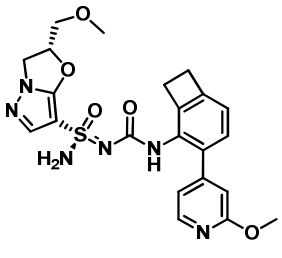
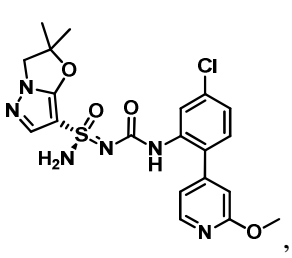
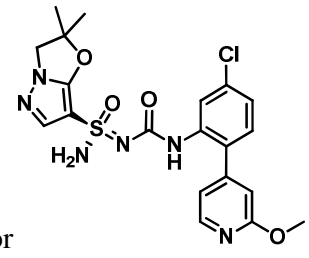
27. The compound of claim 18, wherein the compound is:

, , , ,
, , , ,
, , , ,
, or , or is a solvate, tautomer, or pharmaceutically acceptable salt therof.

28. The compound of claim 18, wherein the compound is:

, , , ,



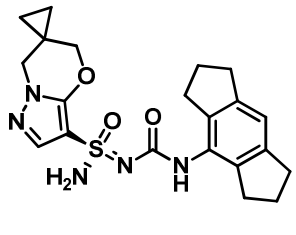
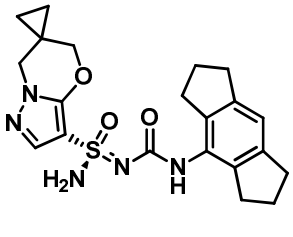
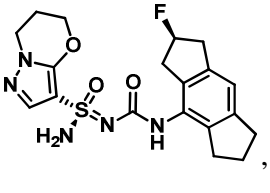
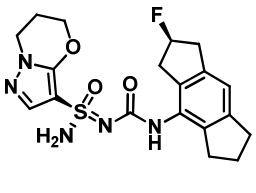
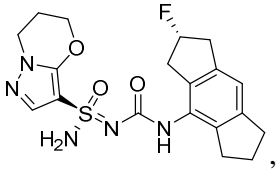
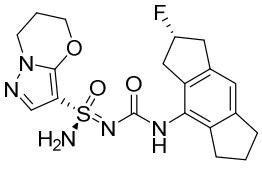
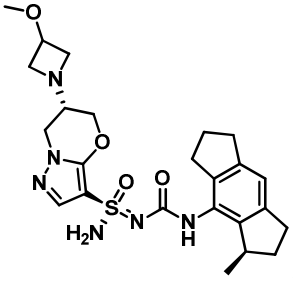
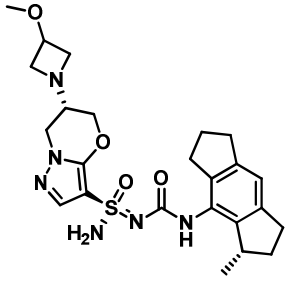
, , , or , or is a solvate, tautomer, or pharmaceutically acceptable salt thereof.

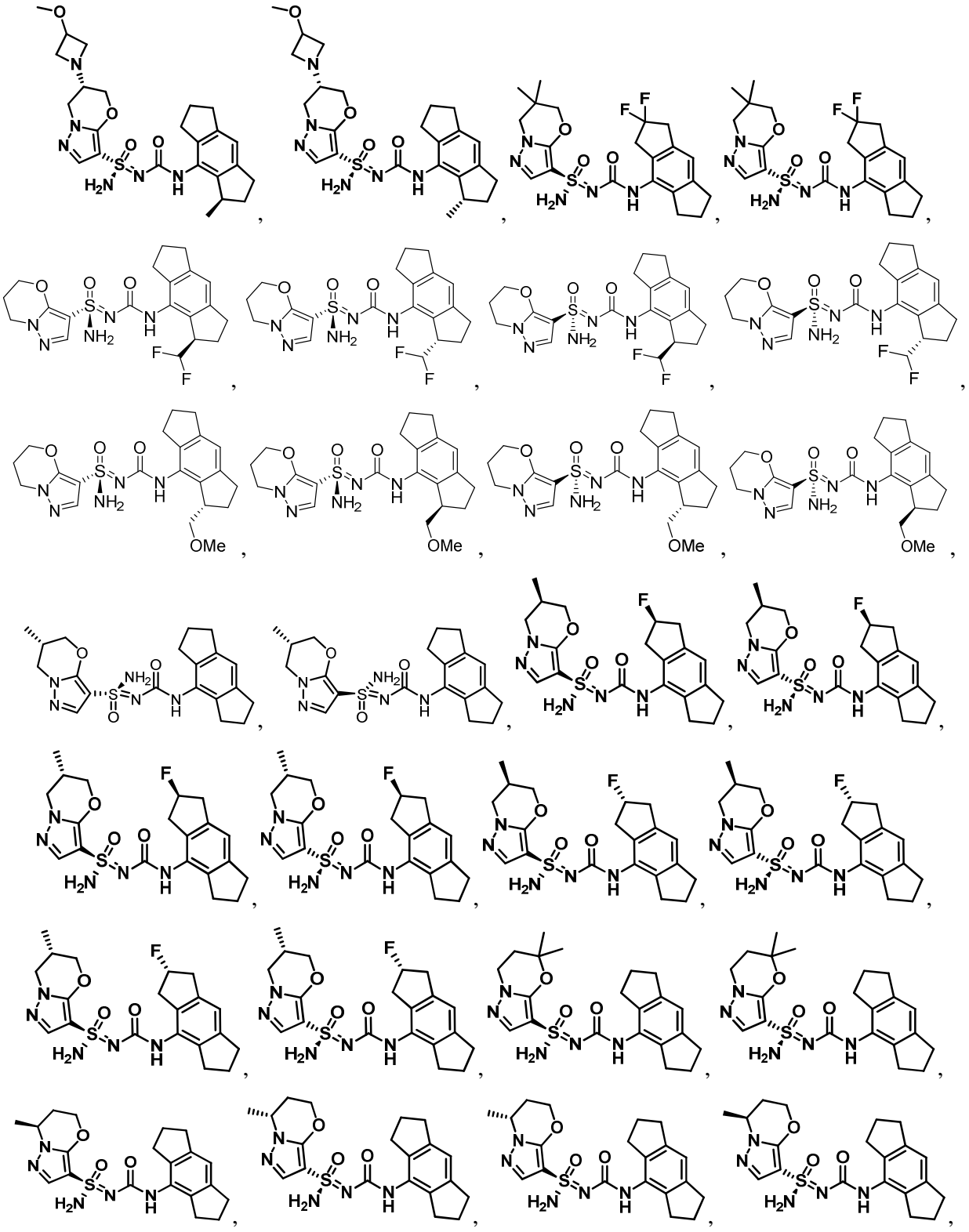
29. A pharmaceutical composition, comprising a compound of any one of claims 18 to 28, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, and a pharmaceutically accceptable carrier.

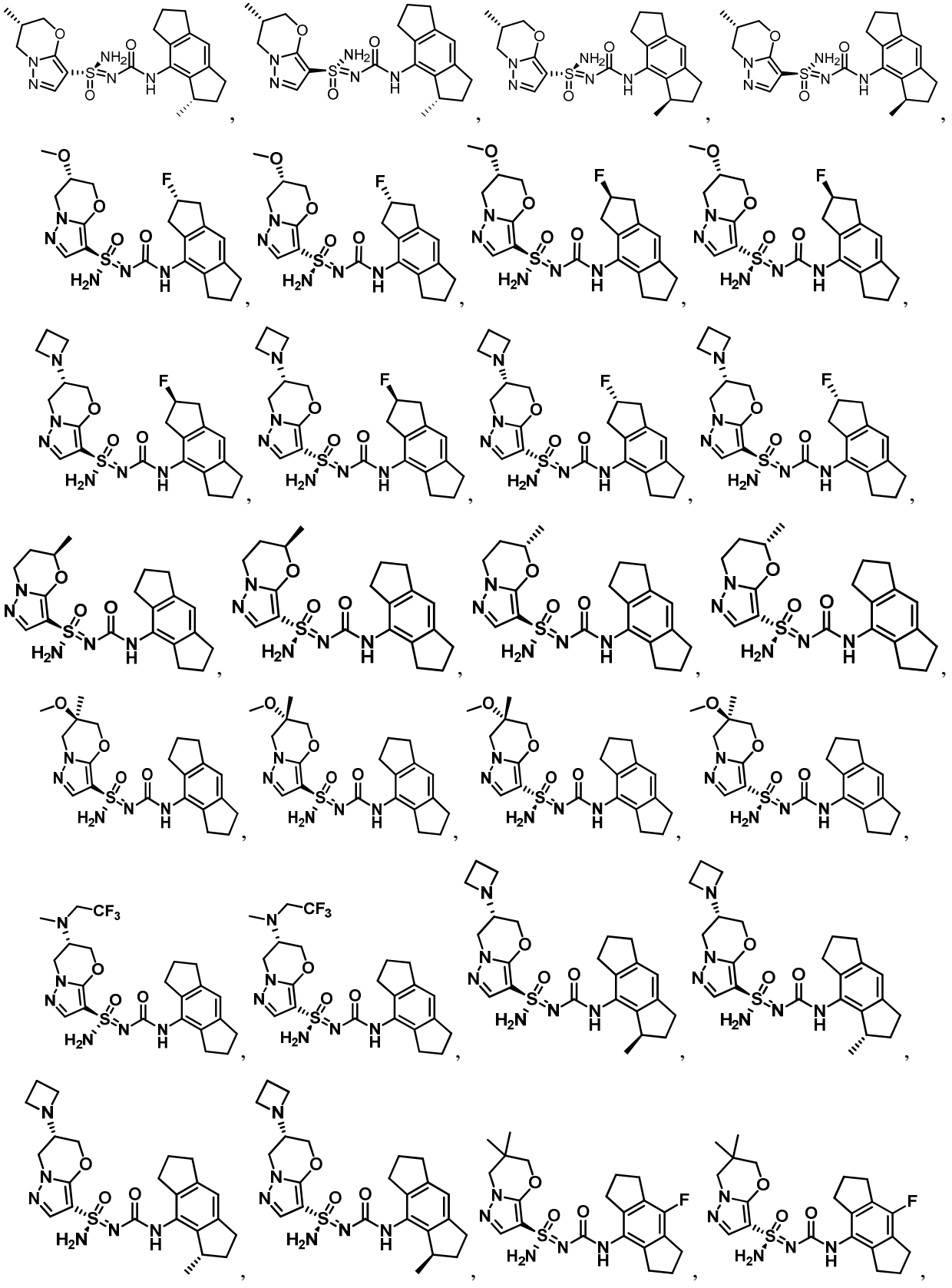
30. Use of a compound of any one of claims 18 to 28, or a solvate, tautomer, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disorder in a subject in need thereof.

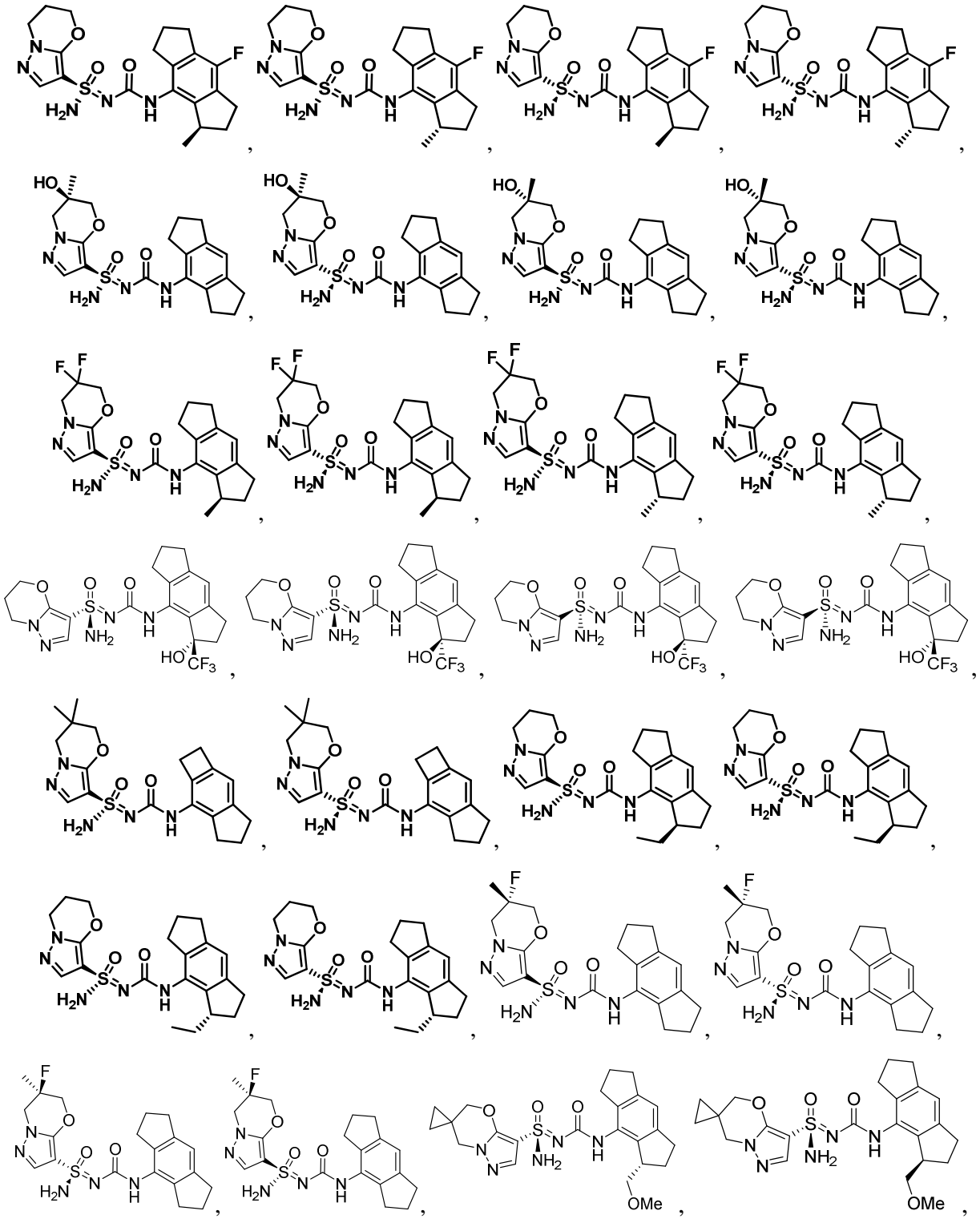
31. The use of claim 30, wherein the disorder is a disorder of the immune system, a disorder of the liver, a disorder of the lung, a disorder of the skin, a disorder of the cardiovascular system, a disorder of the renal system, a disorder of the gastro-intestinal tract, a disorder of the respiratory system, a disorder of the endocrine system, a disorder of the central nervous system (CNS), an inflammatory disorder, an autoimmune disorder, or a cancer, tumor, or other malignancy.

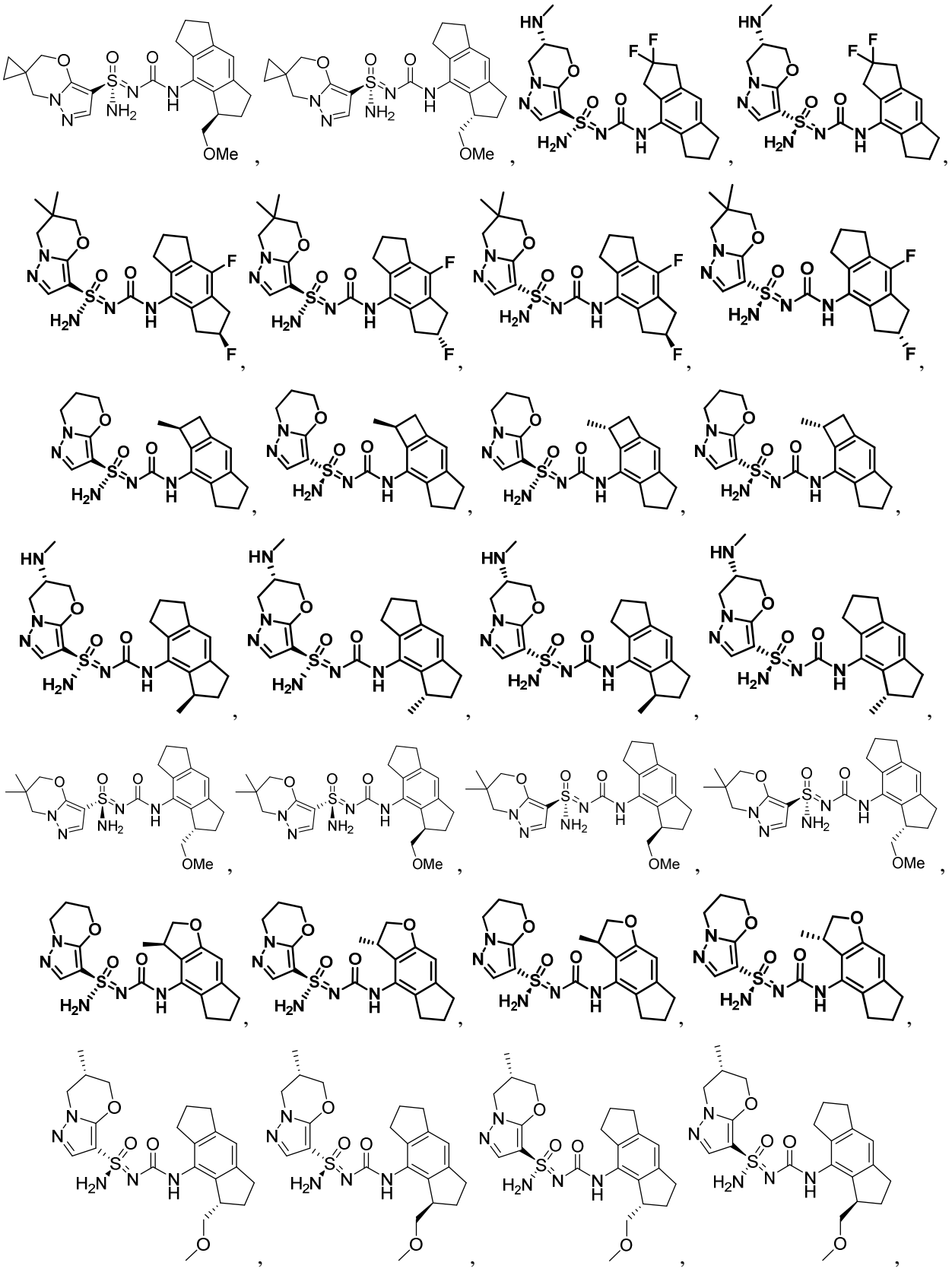
32. A compound, wherein the compound is:

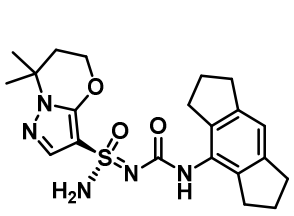
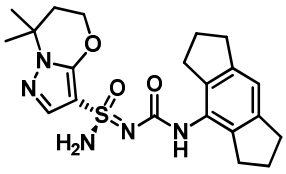
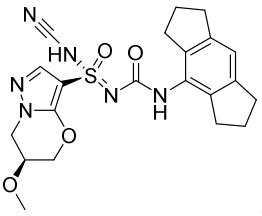
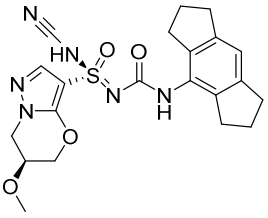
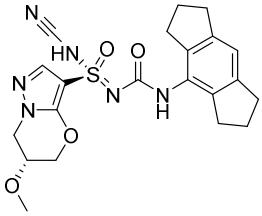
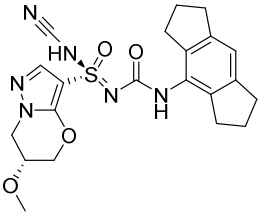
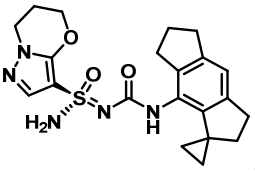
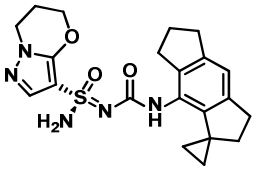
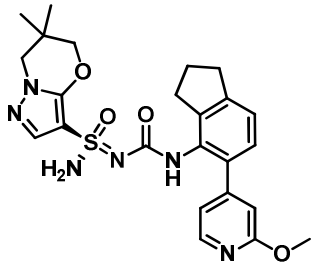
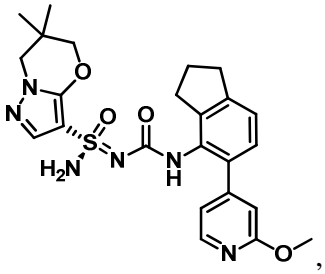
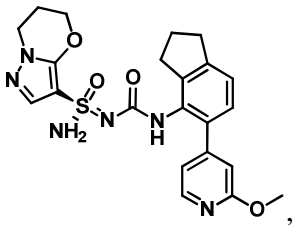
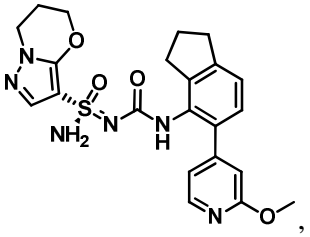
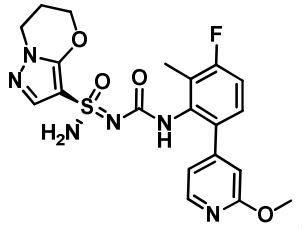
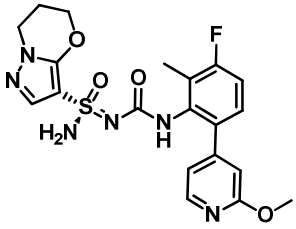
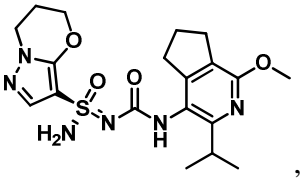
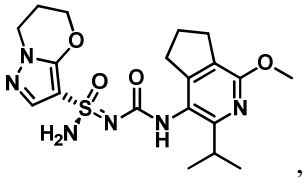
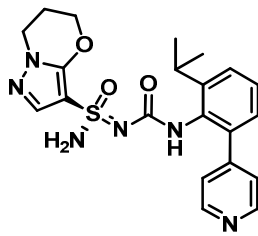
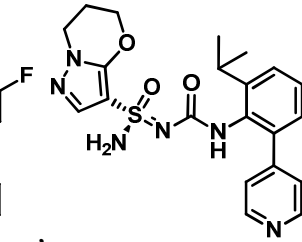
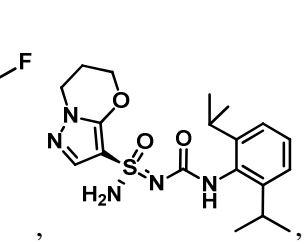
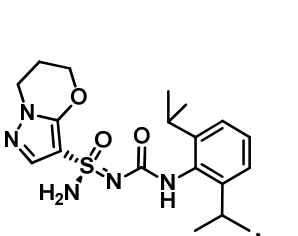
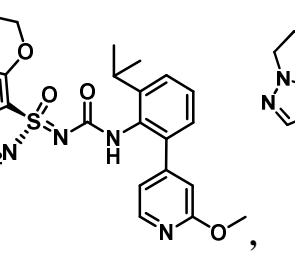
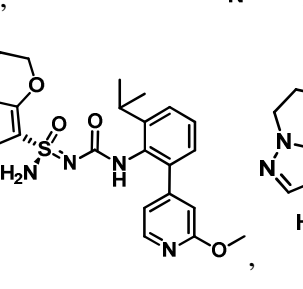
, , , , , , , ,










,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

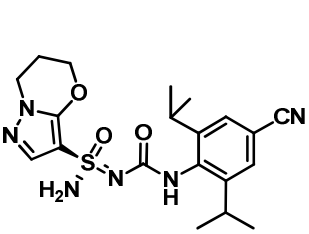
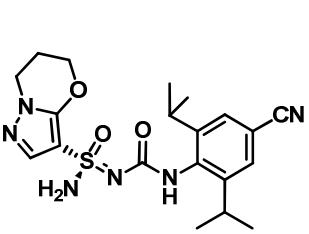
,

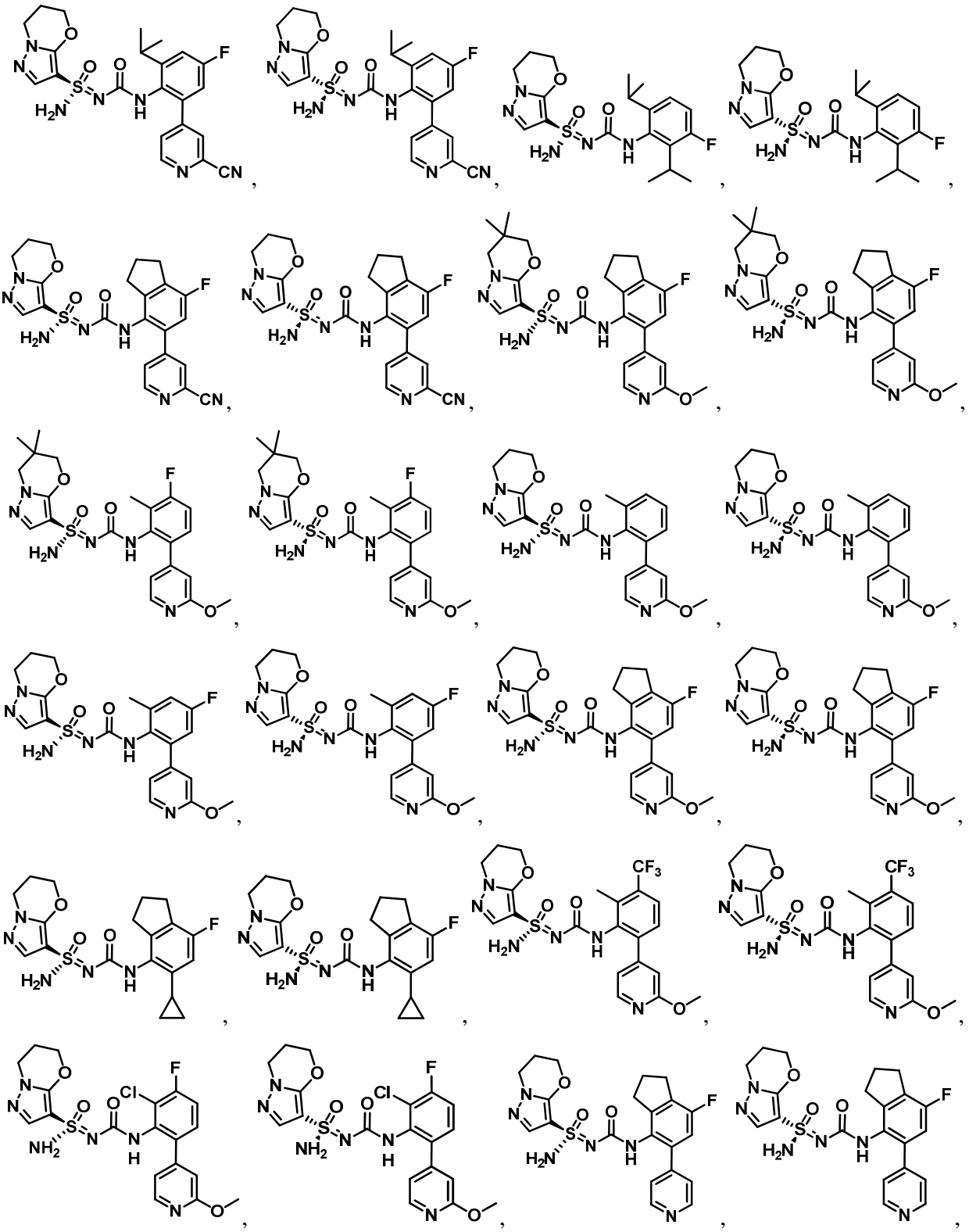
,

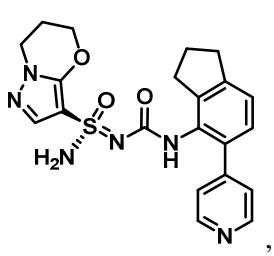
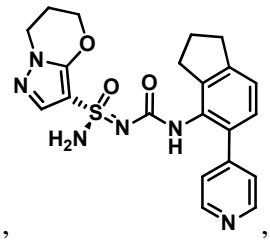
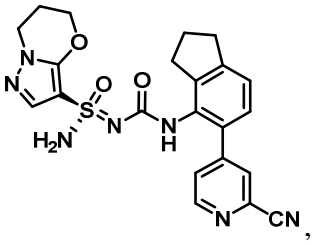
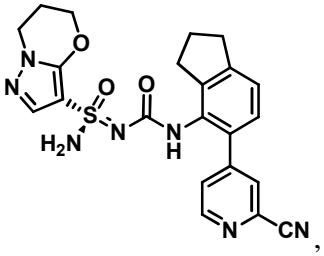
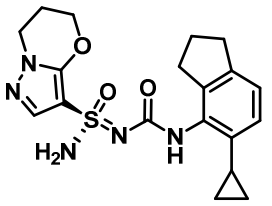
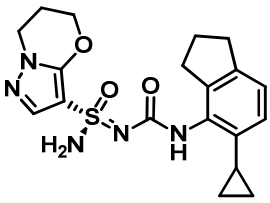
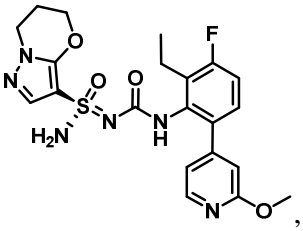
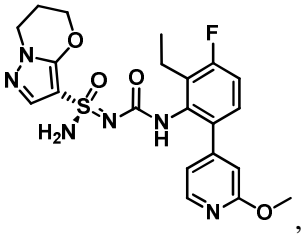
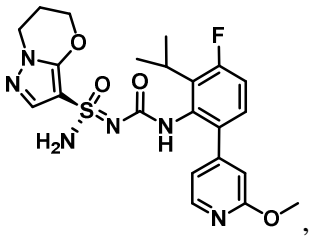
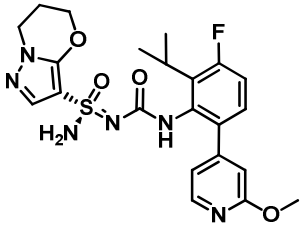
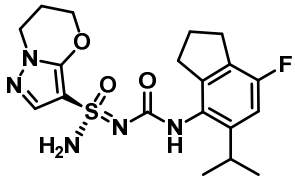
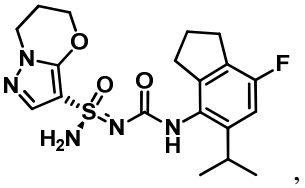
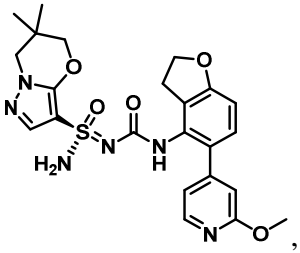
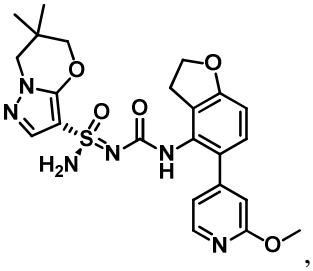
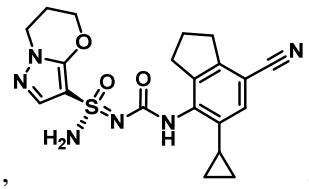
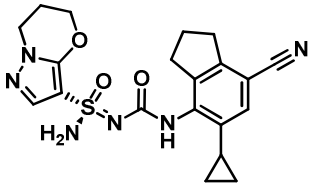
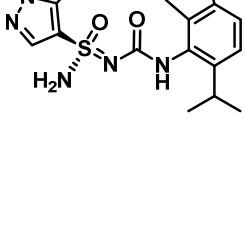
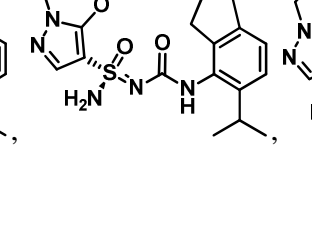
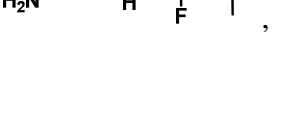
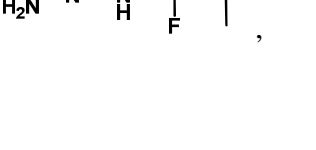
,

,

,

,

,

,



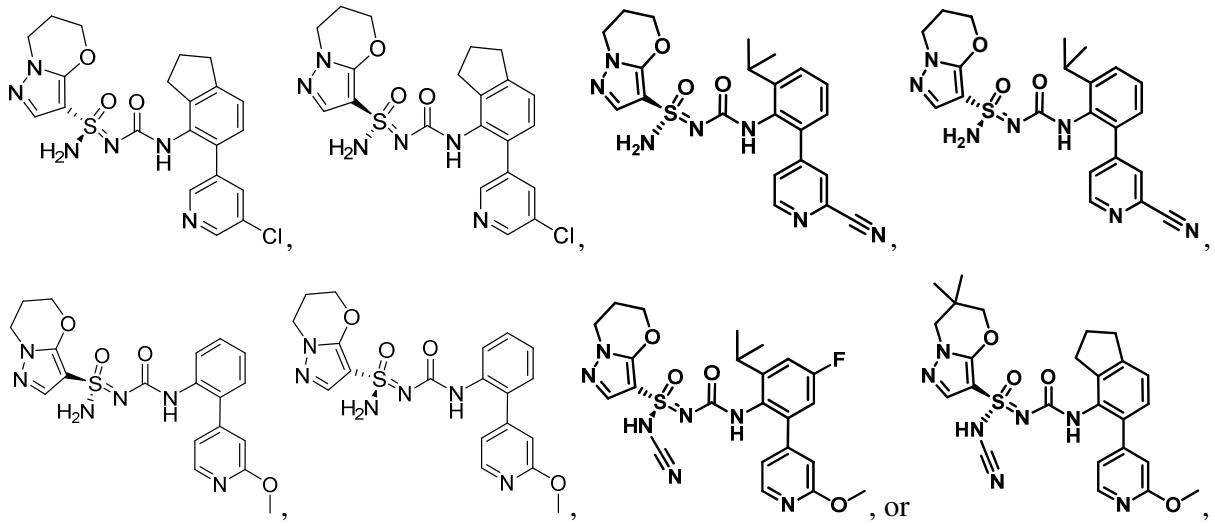

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

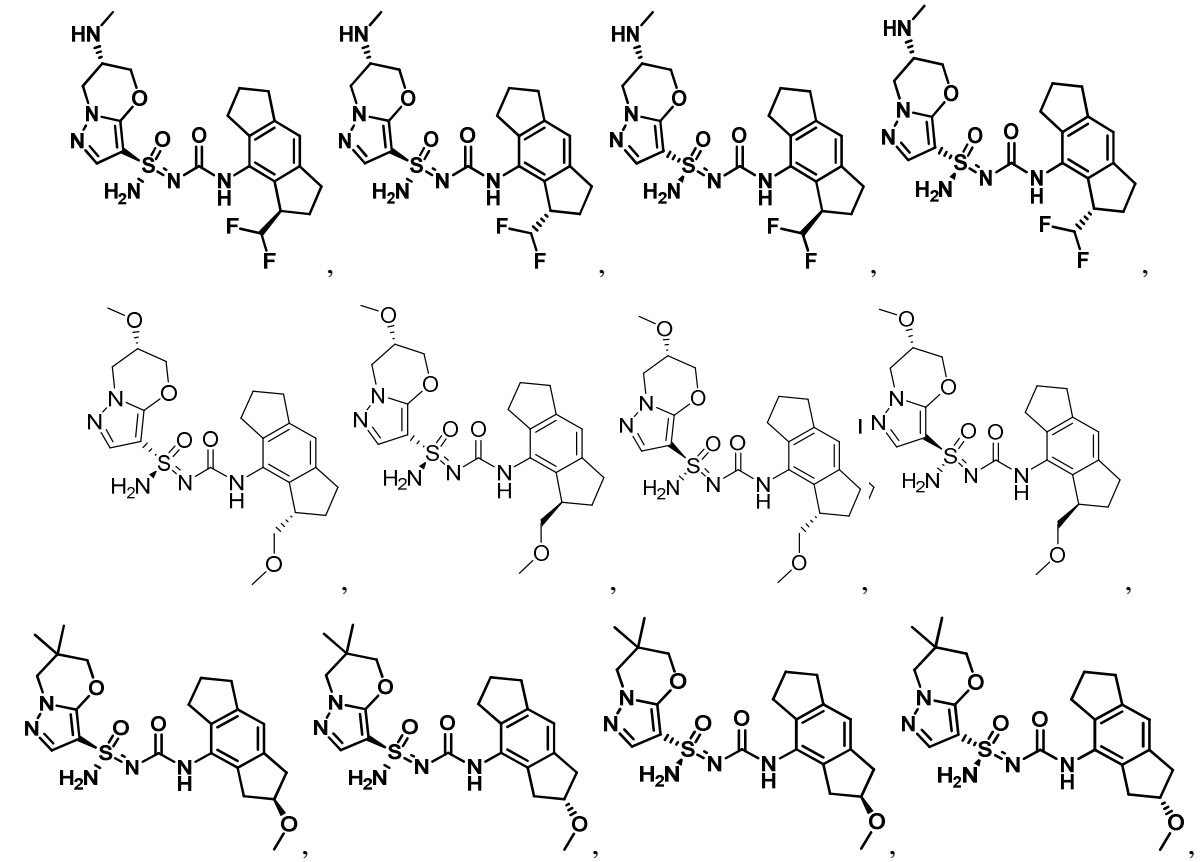
,

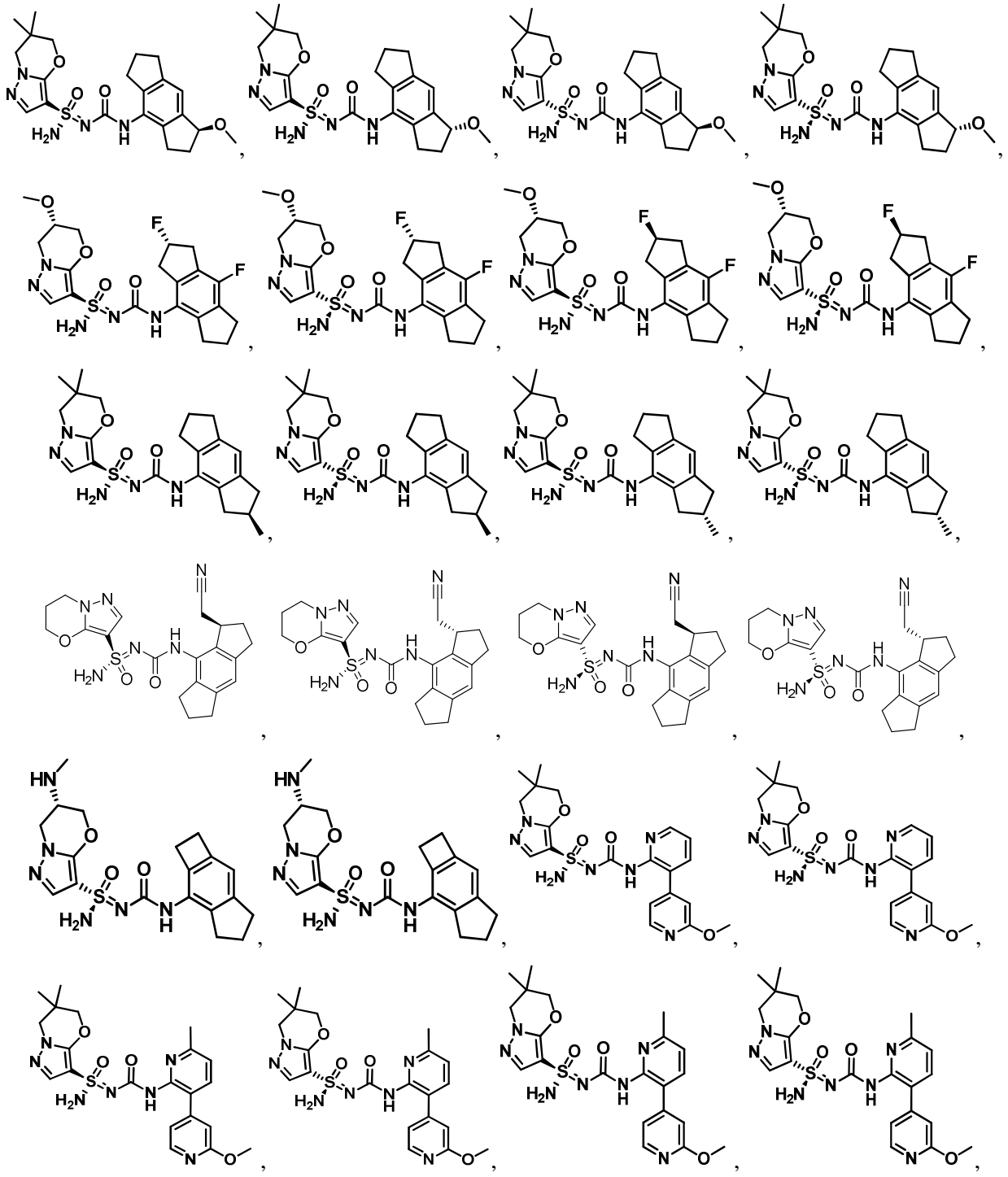
,

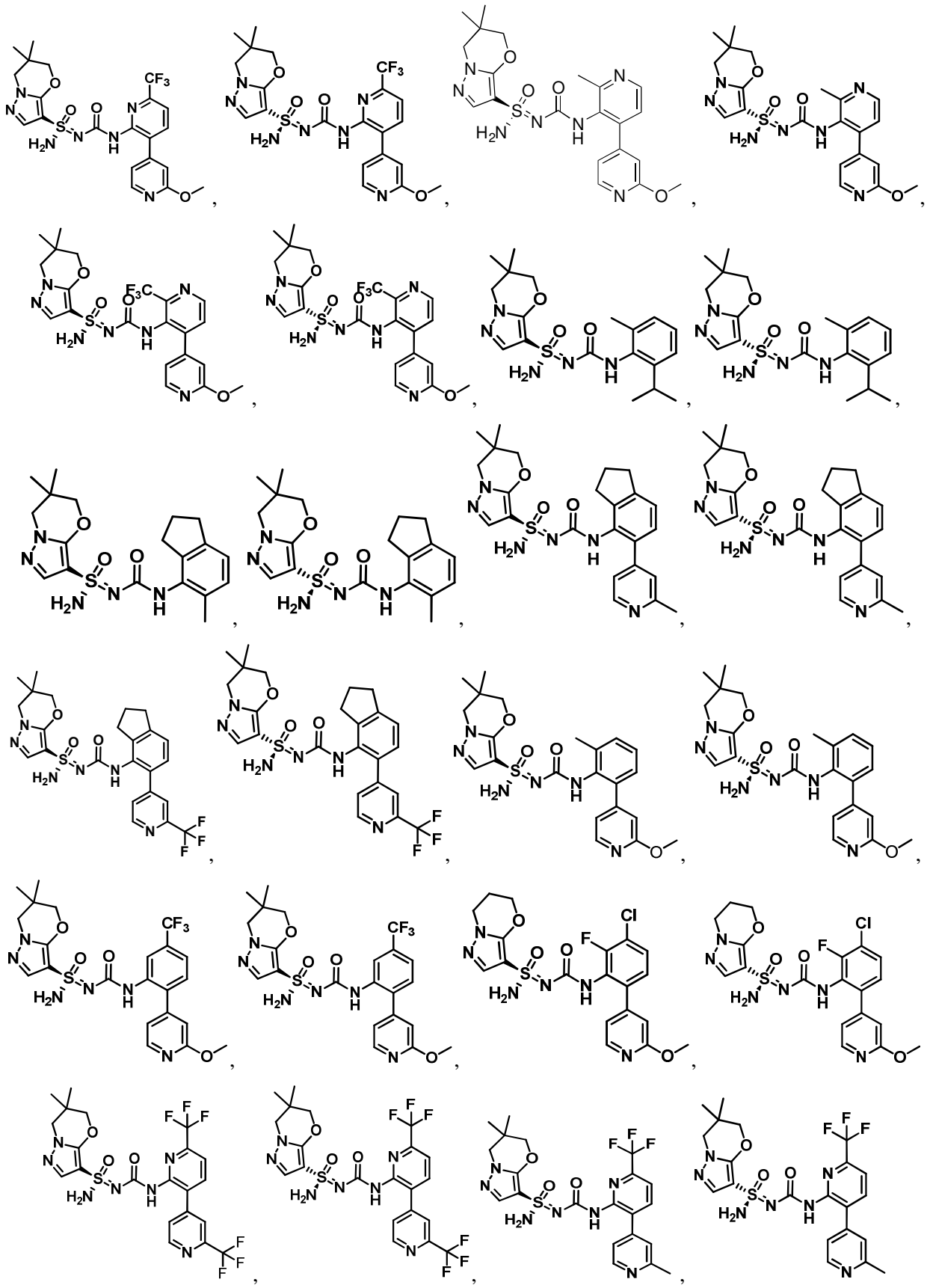


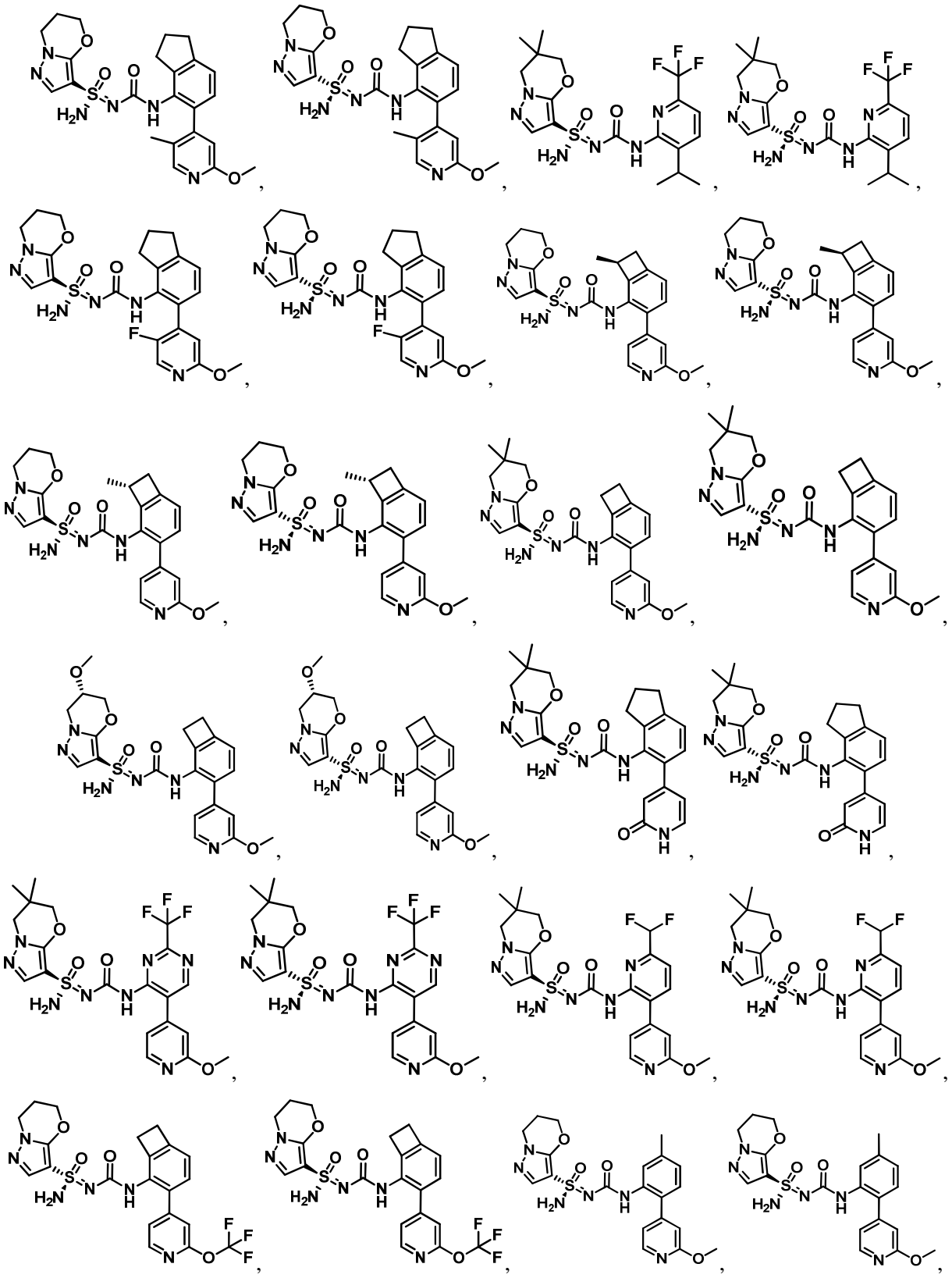
or a solvate, tautomer, or pharmaceutically acceptable salt thereof.

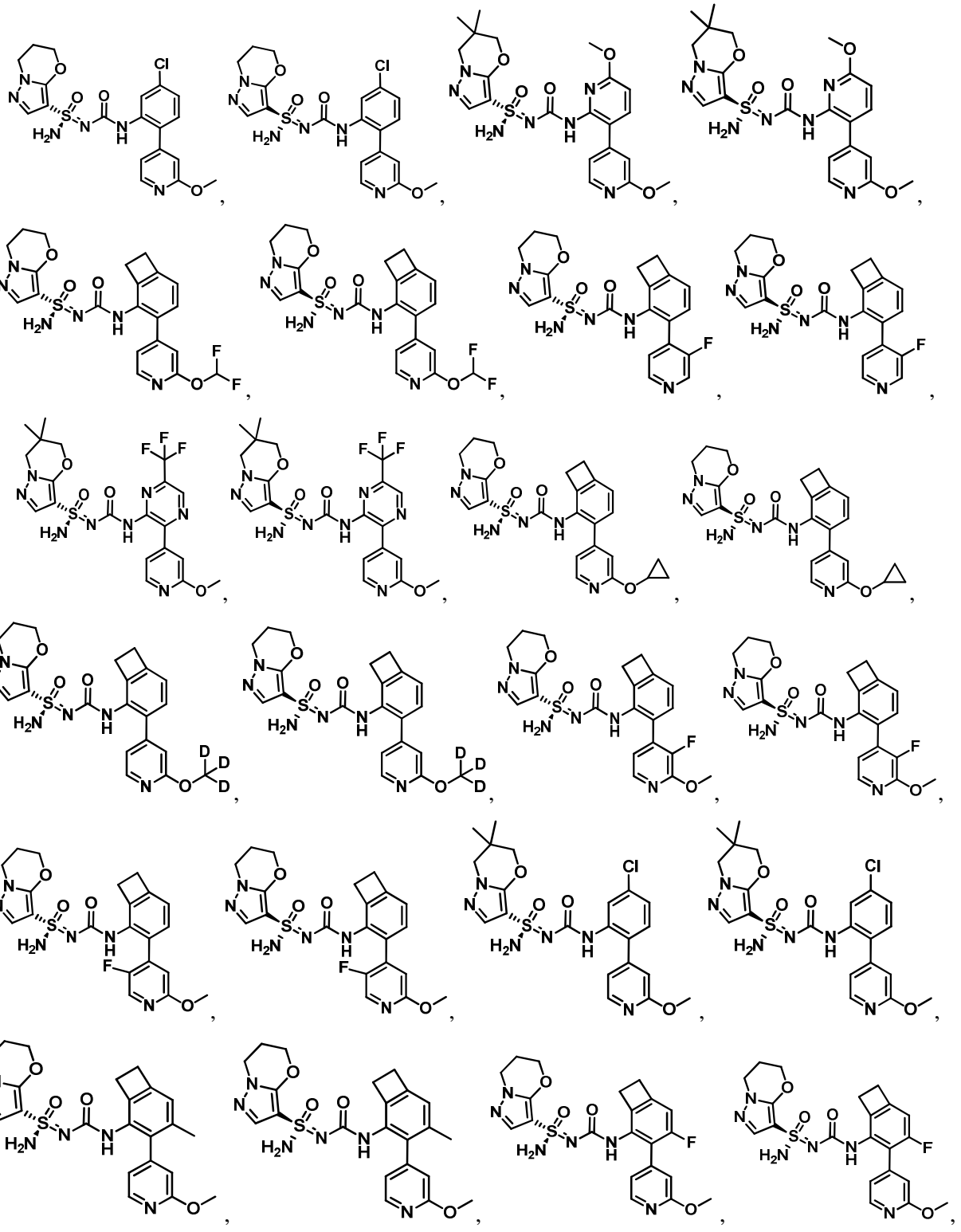
33. A compound, wherein the compound is:

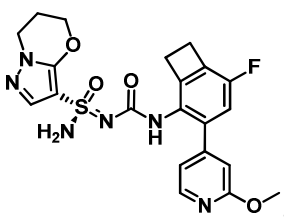
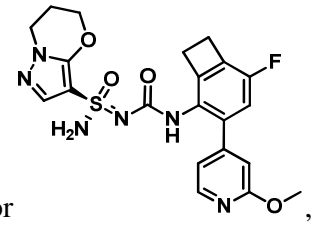










, or ,

or is a solvate, tautomer, or pharmaceutically acceptable salt thereof.