

SOMATOSTATIN SUBTYPE RECEPTOR 3 (SSTR3) AGONISTS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of US Provisional Application No. 63/513,599 filed July 14, 2023, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] Described herein are compounds that are somatostatin receptor subtype 3 agonists (SSTR3), methods of making such compounds, pharmaceutical compositions and medicaments comprising such compounds, and methods of using such compounds in the treatment of conditions, diseases, or disorders that would benefit from modulating SSTR3 activity.

BACKGROUND OF THE INVENTION

[0003] Somatostatin is a peptide hormone that regulates the endocrine system and affects neurotransmission and cell proliferation via interaction with G-protein-coupled somatostatin receptors (GPCRs) and inhibition of the release of numerous secondary hormones. Six subtype somatostatin receptor proteins have been identified (SSTR1, SSTR2a, SSTR2b, SSTR3, SSTR4, SSTR5) and are encoded by five different somatostatin receptor genes. Modulation of a particular subtype somatostatin receptor or combination thereof, is attractive for the treatment of conditions, diseases, or disorders that would benefit from modulating somatostatin activity.

[0004] Somatostatin acts on five GPCRs (SSTR1 to 5). Binding to these receptors inhibits adenylyl cyclases (ACs) and mitogen-activated protein kinase, cell proliferation, and secretion of several hormones (growth hormone, insulin, glucagon, gastrin, cholecystokinin, vasoactive intestinal peptide and secretin, thyroid stimulating hormone, and adrenocorticotrophic hormone) and growth factors (IGF I and vascular endothelial growth factor). All five SSTRs are expressed in renal tubular epithelial cells and cholangiocytes. SSTR1 and SSTR2 are expressed in the thick ascending limb of Henle, distal tubule, and collecting duct. SSTR3, SSTR4, and SSTR5 are expressed in proximal tubules. In preclinical studies, somatostatin has been shown to inhibit cAMP generation in MDCK cells and rat collecting ducts and antagonizes vasopressin effects in the toad urinary bladder and dog collecting ducts, and also inhibits cAMP generation, fluid secretion, and cell proliferation in cholangiocytes and suppresses the growth of bile ducts and periportal connective tissue in rats with extrahepatic biliary obstruction. Because somatostatin

has a half-life of approximately 3 minutes, more stable synthetic peptides (octreotide, lanreotide, and pasireotide) have been developed for clinical use.

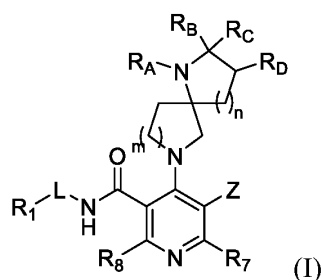
[0005] In preclinical studies, octreotide (which binds to SSTR2 and SSTR3, but preferentially to SSTR2) and pasireotide (which binds with high affinity to SSTR1, SSTR2, SSTR3, and SSTR5) reduce cAMP levels and proliferation of cholangiocytes *in vitro*, expansion of liver cysts in three-dimensional collagen culture, and development of kidney and liver cysts and fibrosis in PCK rats, *Pkd2*^{WS25/-} mice, and the *Pkd1*^{RC/RC} model.

[0006] In clinical trials using octreotide or lanreotide (which both bind to SSTR2 and SSTR3, but preferentially to SSTR2), kidney growth is halted during the first year of treatment and then resumes, possibly at a lower rate than without treatment. Liver volume decreases by 4%–6% during the first year of treatment, and this reduction is sustained during the second year. However, observation periods have been too short to assess an effect on renal function. While octreotide and lanreotide are overall well tolerated, the depot preparations of these peptide drugs are extremely expensive and require frequent doctor's office visits for painful injections that can lead to injection site reactions.

[0007] To the best of the inventors' knowledge, to date, no SSTR3 selective small molecule modulator has been prepared or tested for the treatment of ciliopathies, such as polycystic kidney disease (PKD). The compounds described herein are non-peptide somatostatin agonists that selectively activate somatostatin receptor subtype 3 (SSTR3) that in turn reduce cAMP levels that can lead to the ciliopathies described herein, such as PKD.

SUMMARY OF THE INVENTION

[0008] In one embodiment, described herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof:

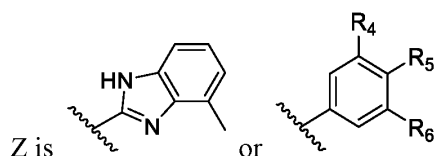


wherein:

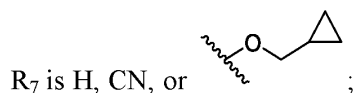
R₁ is unsubstituted or substituted C₁₋₆ alkyl, unsubstituted or substituted C₃₋₆ cycloalkyl, unsubstituted or substituted 6-membered heterocycloalkyl, unsubstituted or substituted C₅₋₇ bicycloalkyl, unsubstituted or substituted aryl, or unsubstituted or

substituted 6-membered heteroaryl; wherein if R_1 is substituted then R_1 is substituted with 1-3 X, wherein each X is independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} fluoroalkyl, C_{1-6} fluoroalkoxy, C_{3-6} cycloalkoxy, CN, and OH;

L is a bond or CR_2R_3 , wherein R_2 is H or C_{1-6} alkyl, and R_3 is H, C_{1-6} alkyl, C_{1-6} alkoxy, CH_2OCH_3 , or C_{1-6} fluoroalkyl; or R_2 and R_3 together with the carbon to which they are attached form a C_{3-6} cycloalkyl;



wherein R_4 is H or halogen; R_5 is H or halogen; and R_6 is H, halogen, CN, C_{1-6} alkyl, or C_{1-6} alkoxy;



R_8 is H, D, OH, C_{1-6} alkyl, C_{1-6} alkoxy, NH_2 , or $-NH(CH_2)_2OH$;

R_A is H, $C(O)OC_{1-6}$ alkyl, or $C(O)C_{1-6}$ alkyl;

R_B is H, D, or C_{1-6} alkyl;

R_C is H or D;

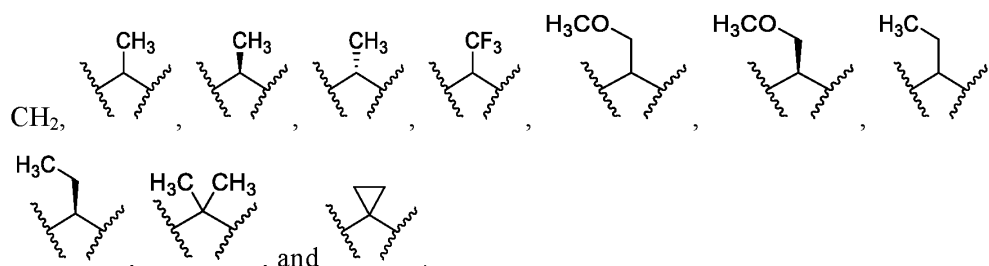
R_D is H or halogen;

m is an integer selected from 0 and 1; and

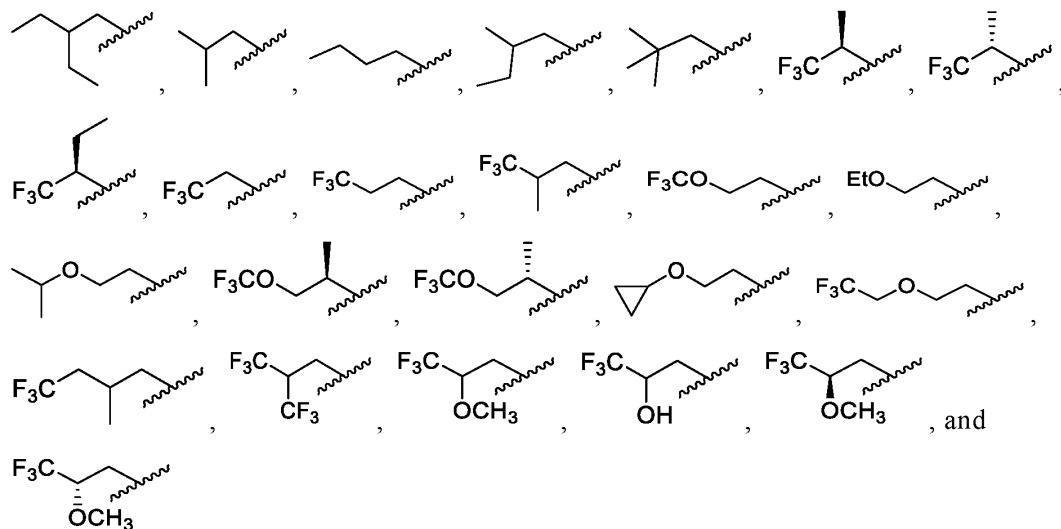
n is an integer selected from 0, 1, and 2.

[0009] In an embodiment, L is a bond.

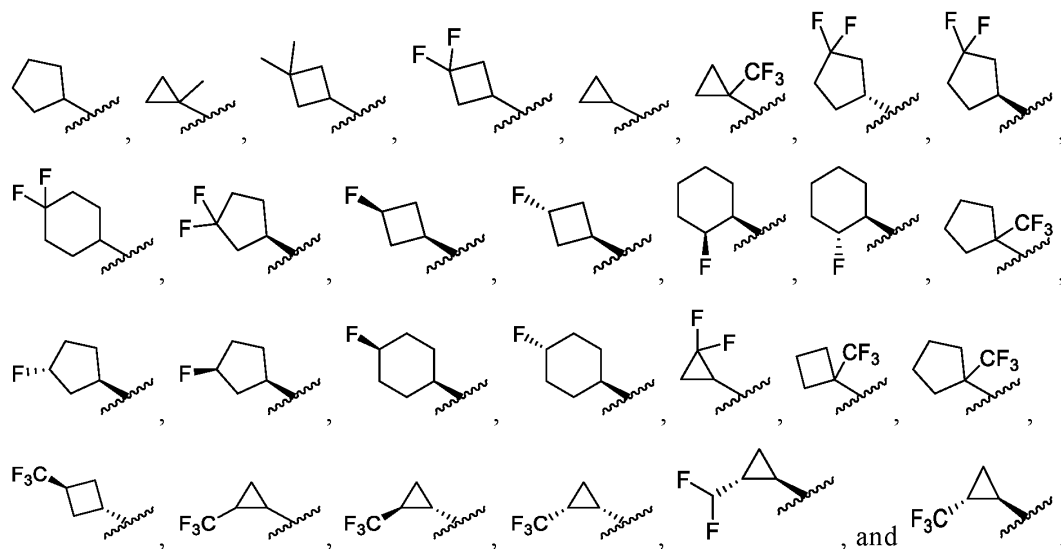
[0010] In an embodiment, L is CR_2R_3 . In some embodiments, R_2 is H or methyl. In some embodiments, R_3 is H, methyl, ethyl, trifluoromethyl, or CH_2OCH_3 . In some embodiments, R_2 and R_3 together with the carbon to which they are attached form a C_{3-6} cycloalkyl. In some embodiments, L is selected from:



[0011] In one aspect, R₁ is unsubstituted or substituted C₁₋₄ alkyl. In some embodiments, if R₁ is substituted then R₁ is substituted with 1-2 X, wherein each X is independently selected from the group consisting of methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH. In some embodiments, R₁ is selected from:

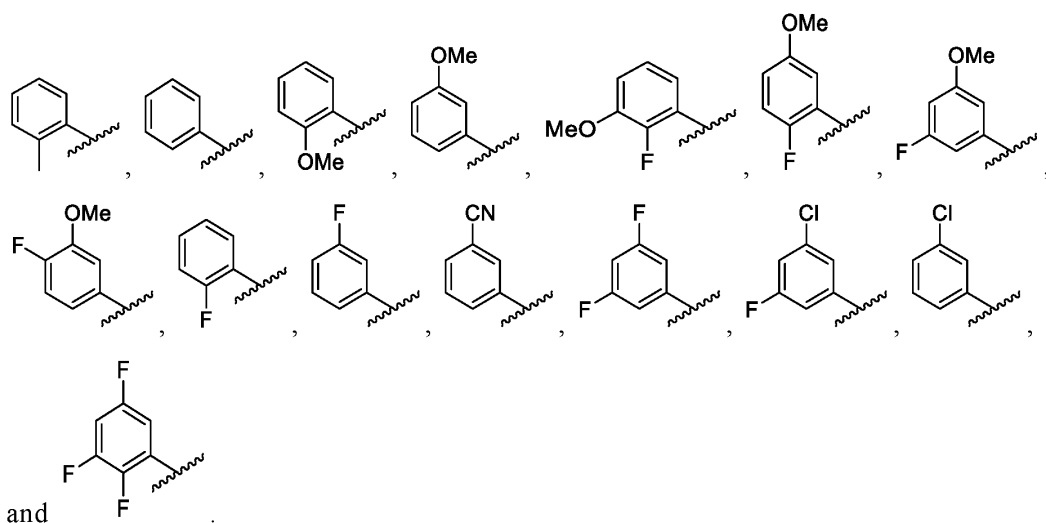


[0012] In one aspect, R₁ is unsubstituted or substituted C₃₋₆ cycloalkyl. In some embodiments, if R₁ is substituted then R₁ is substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro, methyl, and trifluoromethyl. In some embodiments, R₁ is selected from:

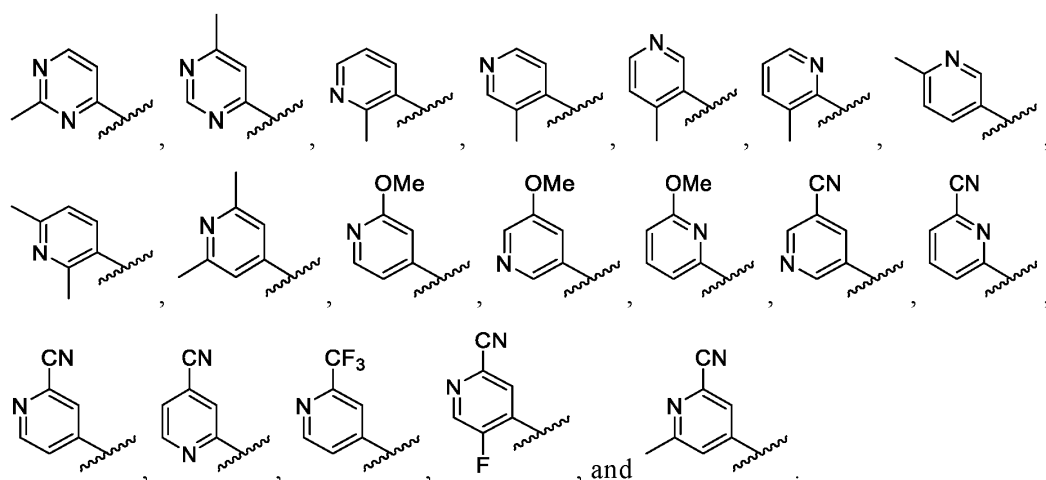


In one aspect, R₁ is unsubstituted or substituted phenyl. In some embodiments, if R₁ is substituted then R₁ is substituted with 1-3 X, wherein each X is independently selected from

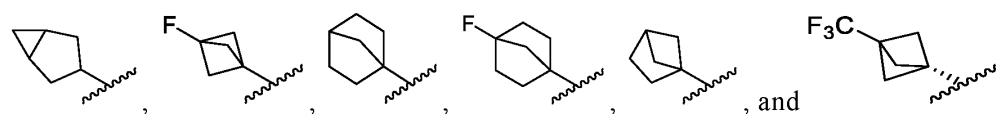
the group consisting of fluoro, chloro, methyl, methoxy, and CN. In some embodiments, R_1 is selected from:



[0013] In one aspect, R_1 is unsubstituted or substituted pyridinyl, or unsubstituted or substituted pyrimidinyl. In some embodiments if R_1 is substituted then R_1 is substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro, methyl, trifluoromethyl, methoxy, and CN. In some embodiments, R_1 is selected from:



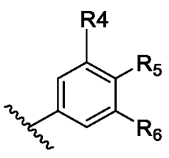
[0014] In one aspect, R_1 is unsubstituted or substituted C_{5-7} bicycloalkyl. In some embodiments, if R_1 is substituted then R_1 is substituted with fluoro or trifluoromethyl. In some embodiments, one or more of the carbon atoms of the C_{5-7} bicycloalkyl is a bridging carbon. In some embodiments, R_1 is selected from:

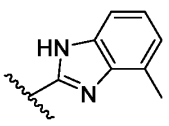


[0015] In one aspect, m is 1 and n is 1.

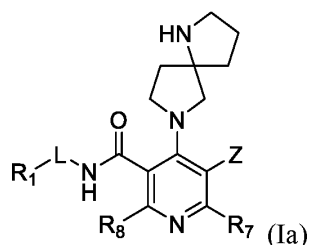
[0016] In one aspect, R_A is H.

[0017] In one aspect, R_B is H; R_C is H; and R_D is H.

[0018] In one aspect, Z is 

[0019] In one aspect, Z is 

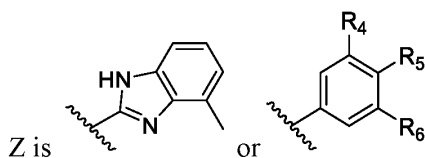
[0020] In another aspect, described herein is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof:



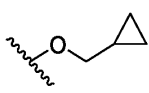
wherein:

R₁ is unsubstituted or substituted C₁₋₄ alkyl, unsubstituted or substituted C₃₋₆ cycloalkyl, tetrahydropyran, unsubstituted or substituted C₅₋₇ bicycloalkyl, unsubstituted or substituted aryl, or unsubstituted or substituted 6-membered heteroaryl, wherein if R₁ is substituted then R₁ is substituted with 1-2 X, wherein each X is independently selected from F, Cl, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, trifluoromethoxy, cyclopropoxy, OCH₂CF₃, CN, and OH;

L is a bond or CR₂R₃, wherein R₂ is H or methyl, and R₃ is H, methyl, ethyl, trifluoromethyl, or -CH₂OCH₃; or R₂ and R₃ together with the carbon to which they are attached form a cyclopropyl group;



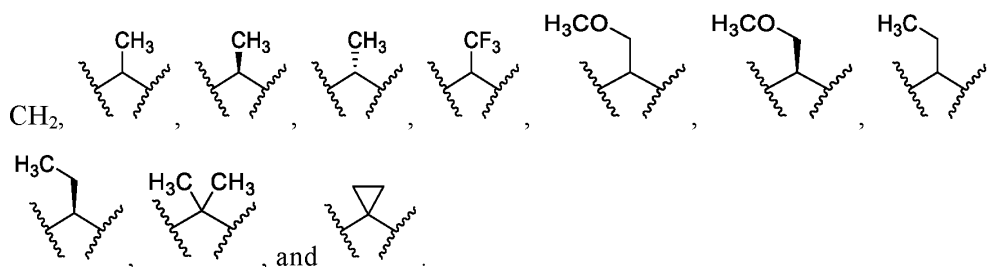
wherein R₄ is H, F, or Cl; R₅ is H or F; and R₆ is H, F, Cl, CN, methyl, or methoxy;

R₇ is H or ; and

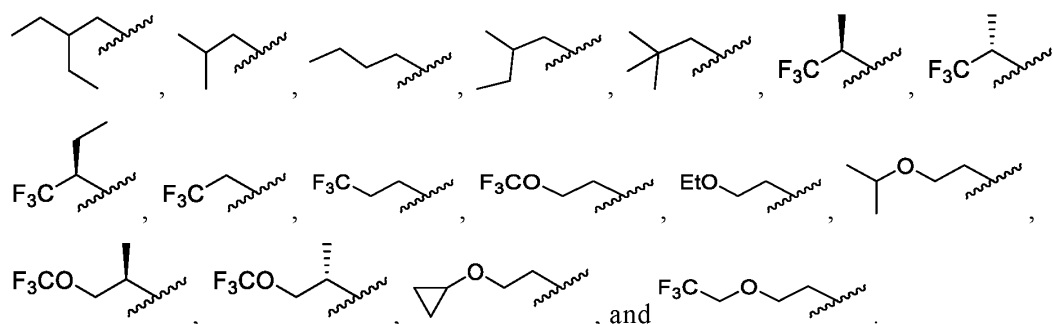
R₈ is H, NH₂, or methyl.

[0021] In one aspect, L is a bond.

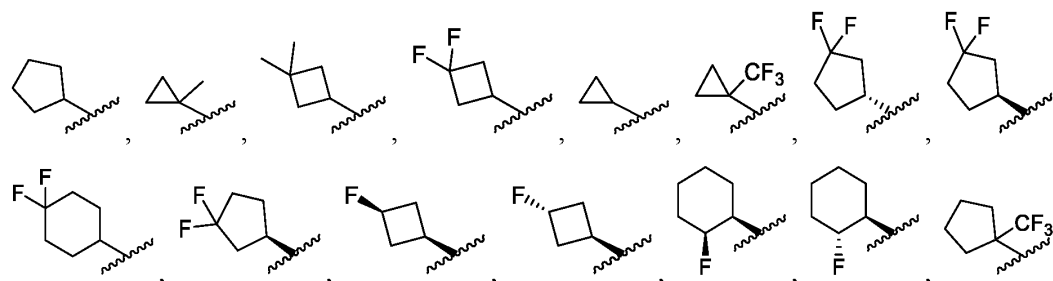
[0022] In one aspect, L is CR₂R₃. In some embodiments, L is selected from:

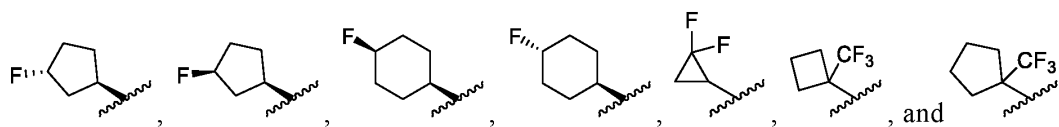


[0023] In one aspect, R₁ is unsubstituted or substituted C₁₋₄ alkyl. In some embodiments, if R₁ is substituted then R₁ is substituted with 1-2 X, wherein each X is independently selected from the group consisting of methyl, ethyl, trifluoromethyl, ethoxy, isopropoxy, trifluoromethoxy, trifluoroethoxy, and cyclopropoxy. In some embodiments, R₁ is selected from:

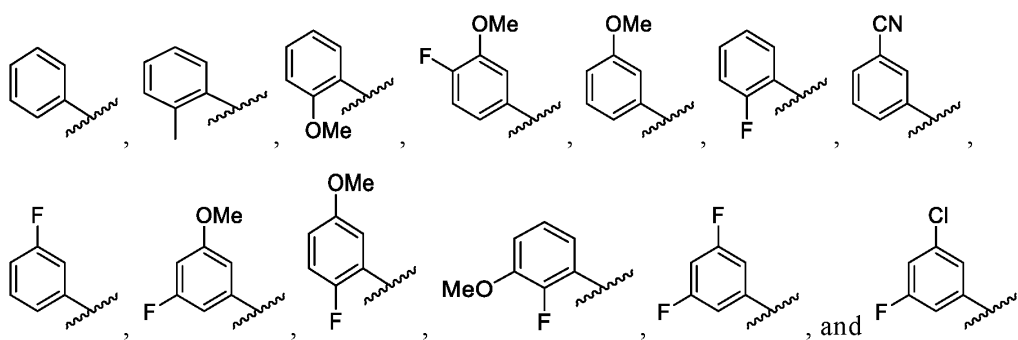


[0024] In one aspect, R₁ is unsubstituted or substituted C₃₋₆ cycloalkyl. In some embodiments, R₁ is substituted then R₁ is substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro, methyl, and trifluoromethyl. In some embodiments, R₁ is selected from:

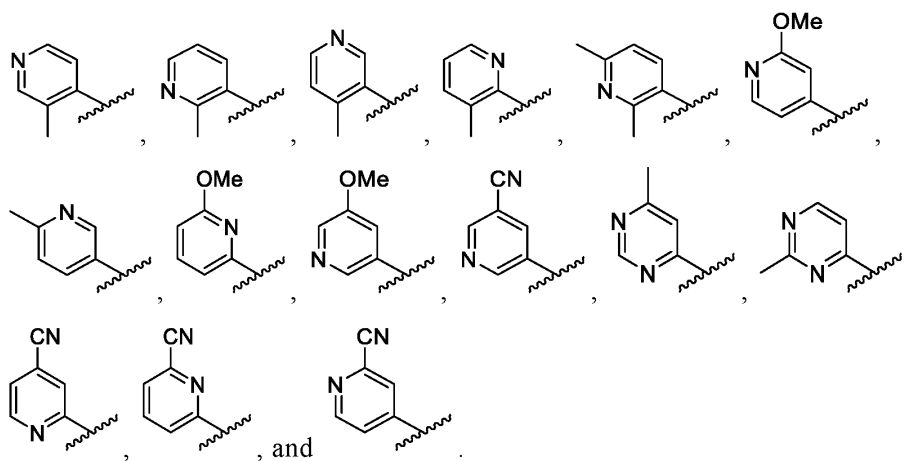




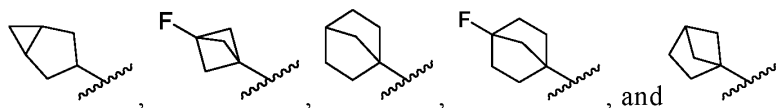
[0025] In one aspect, R_1 is unsubstituted or substituted phenyl. In some embodiments, R_1 is substituted then R_1 is substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro, chloro, methyl, methoxy, and CN. In some embodiments, R_1 is selected from:



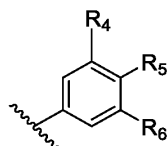
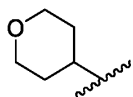
[0026] In one aspect, R_1 is unsubstituted or substituted pyridinyl, or unsubstituted or substituted pyrimidinyl. In some embodiments, if R_1 is substituted then R_1 is substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro, methyl, trifluoromethyl, methoxy, and CN. In some embodiments, R_1 is selected from:



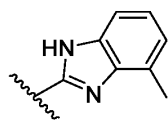
[0027] In one aspect, R_1 is unsubstituted or substituted C_{5-7} bicycloalkyl. In some embodiments, if R_1 is substituted then R_1 is substituted with fluoro. In some embodiments, one or more of the carbon atoms of the C_{5-7} bicycloalkyl is a bridging carbon. In some embodiments, R_1 is selected from:



[0028] In one aspect, R_1 is tetrahydropyran. In some embodiments, R_1 is:

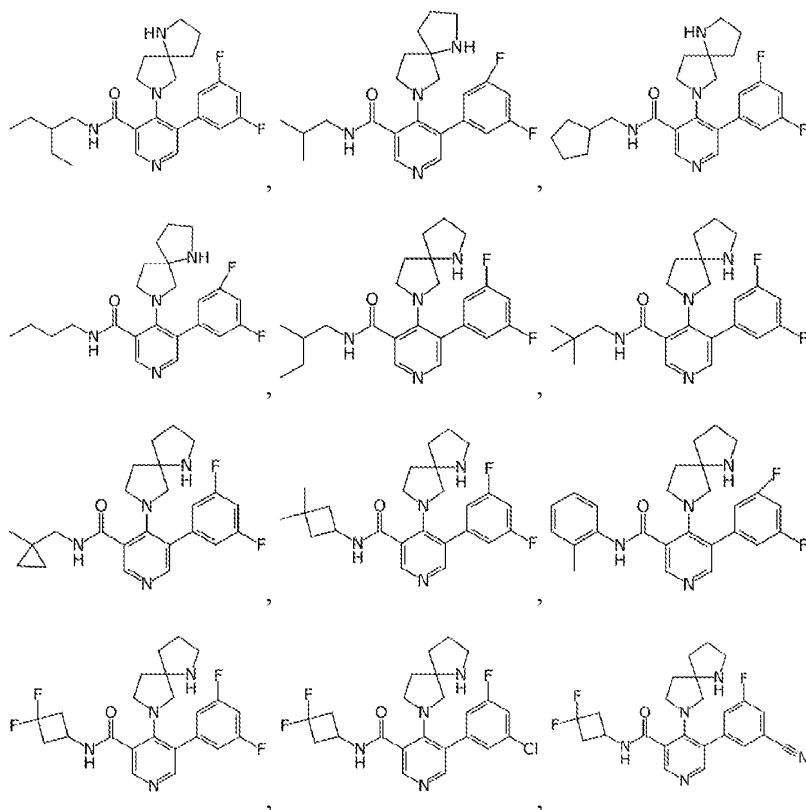


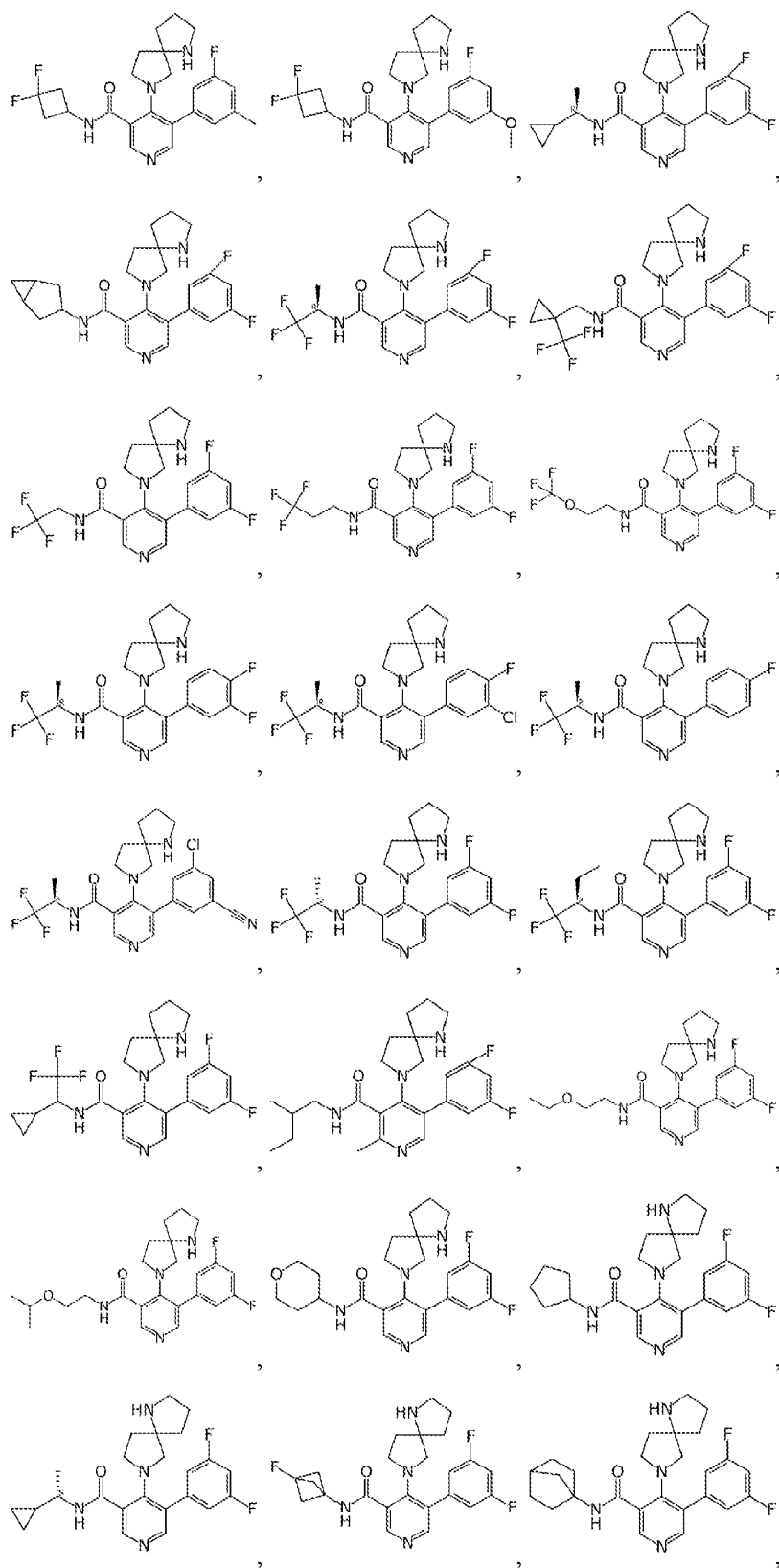
[0029] In one aspect, Z is . In some embodiments, R_4 and R_6 are fluoro.

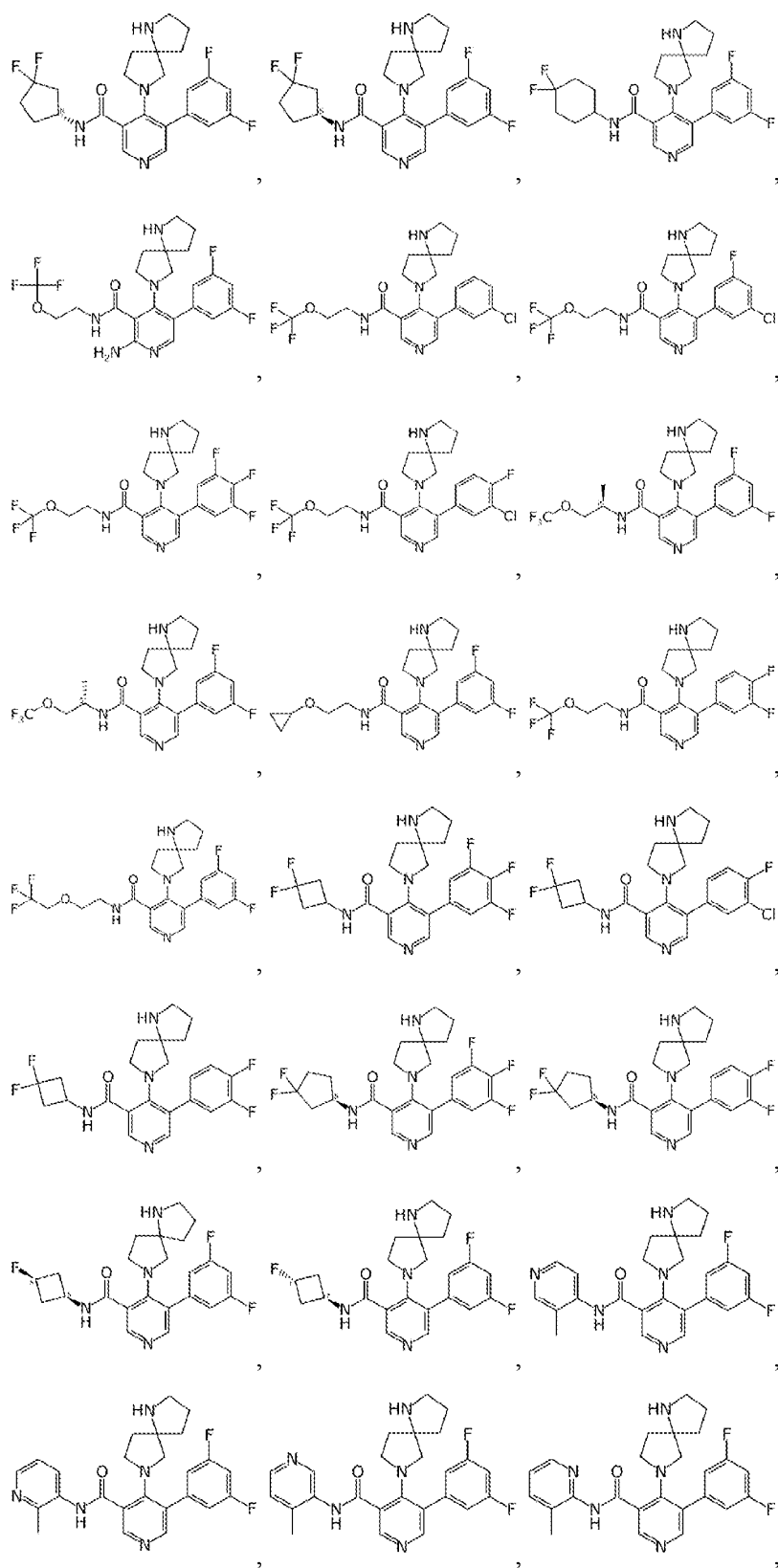


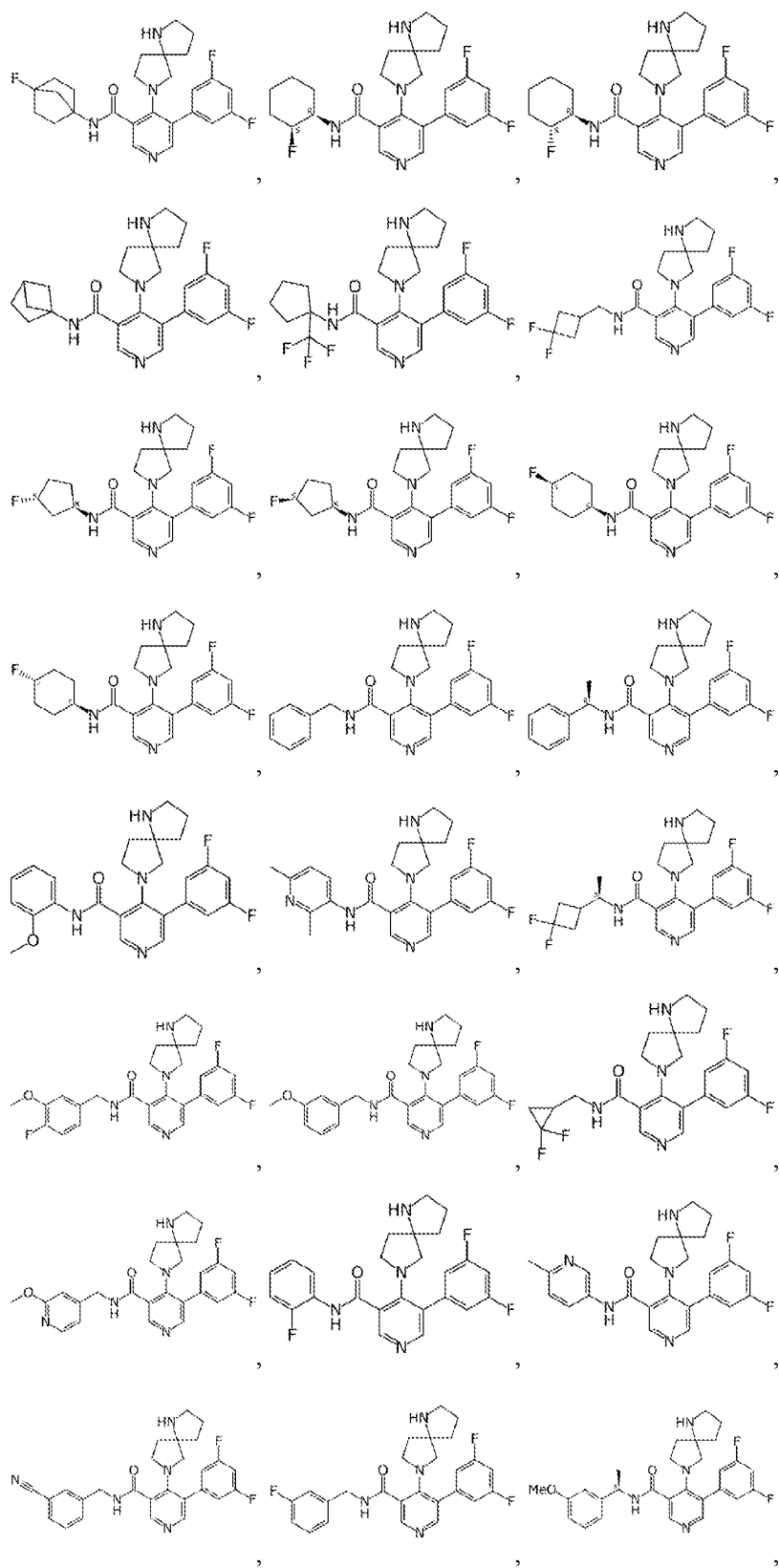
[0030] In one aspect, Z is .

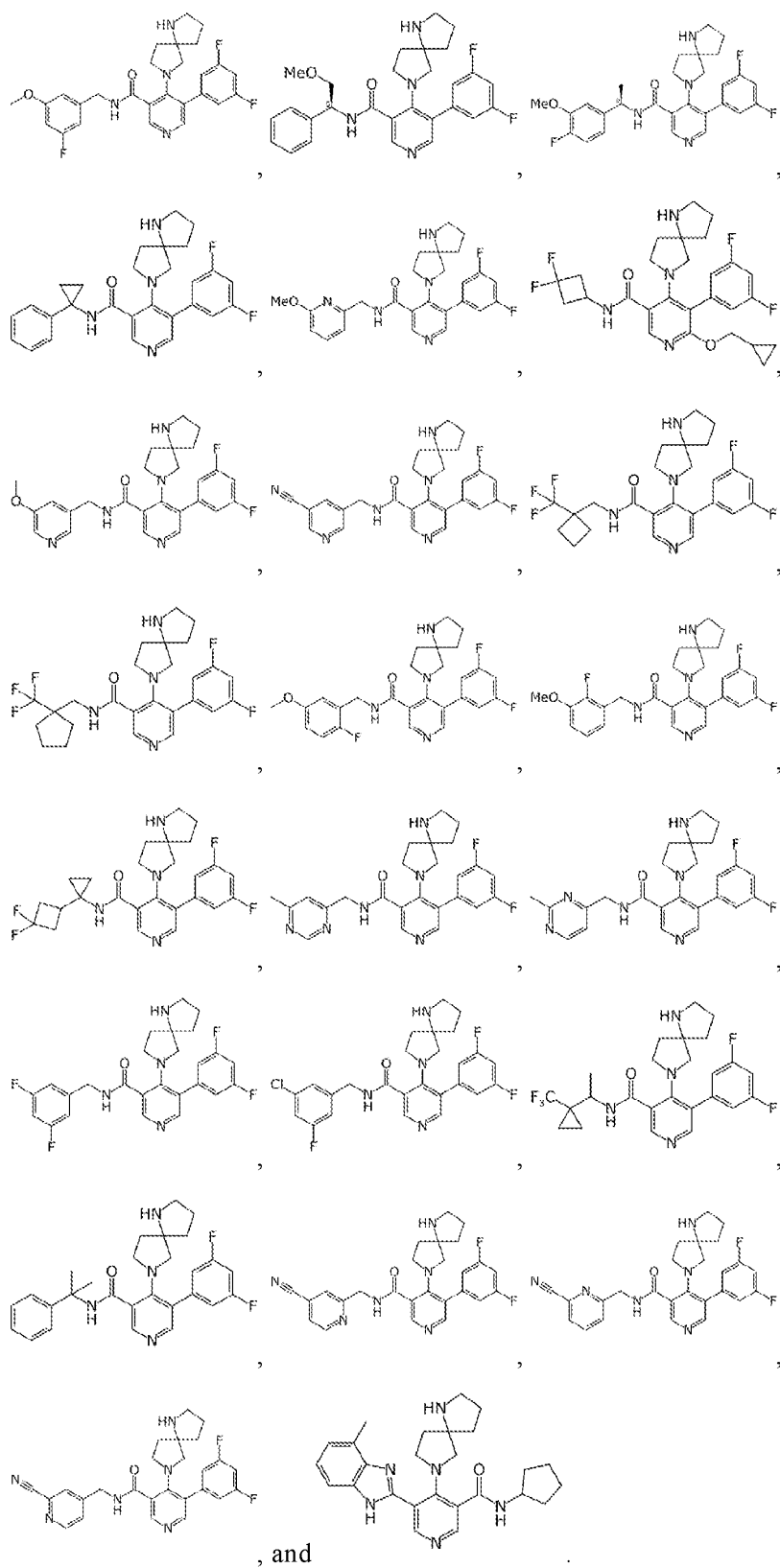
[0031] In one aspect, the compound is selected from:



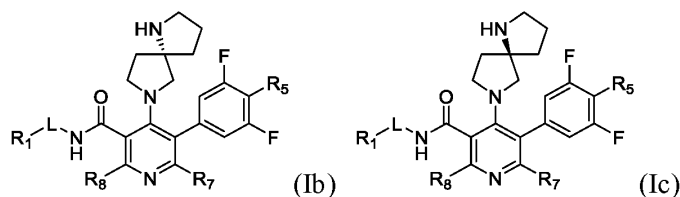








[0032] In another aspect, described herein is a compound of Formula (Ib) or Formula (Ic), or a pharmaceutically acceptable salt thereof:



wherein:

R_1 is unsubstituted or substituted C_{1-3} alkyl, unsubstituted or substituted C_{3-4} cycloalkyl, unsubstituted or substituted C_5 bicycloalkyl, or unsubstituted or substituted 6-membered heteroaryl, wherein if R_1 is substituted then R_1 is substituted with 1-2 X, wherein each X is independently selected from F, methyl, difluoromethyl, trifluoromethyl, methoxy, difluoromethoxy, trifluoromethoxy, CN, and OH;

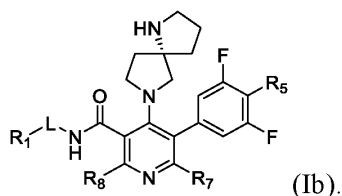
L is a bond or CR_2R_3 , wherein R_2 is H, and R_3 is H, methyl, or $-CH_2OCH_3$;

R_5 is H or F;

R_7 is H or CN; and

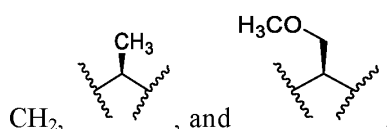
R_8 is H, D, OH, methoxy, or $-NH(CH_2)_2OH$.

[0033] In one aspect, the compound is a compound of Formula (Ib), or pharmaceutically acceptable salt thereof:

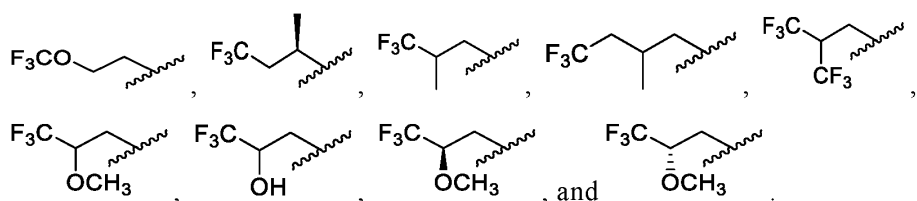


[0034] In one aspect, L is a bond.

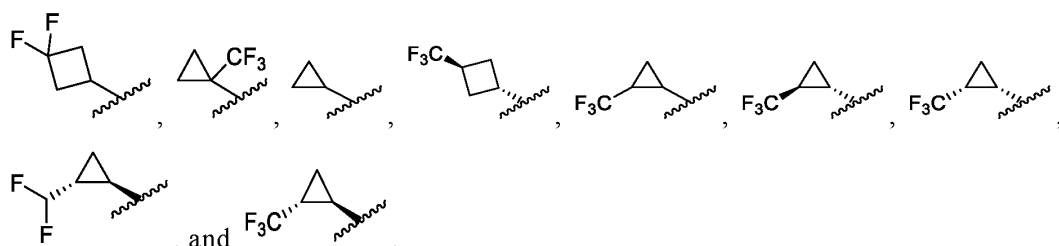
[0035] In one aspect, L is CR_2R_3 . In some embodiments, L is selected from:



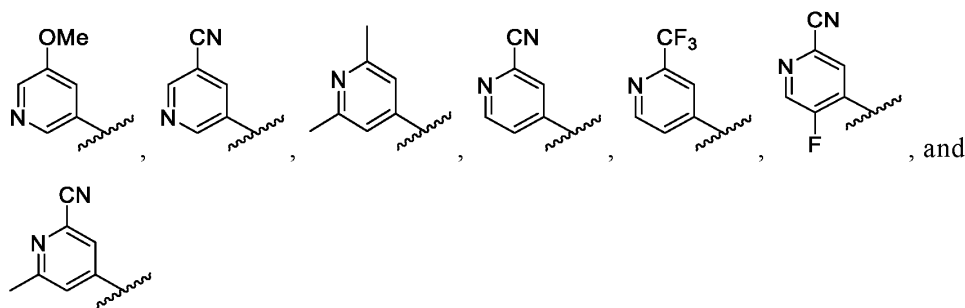
[0036] In one aspect, R_1 is unsubstituted or substituted C_{1-3} alkyl. In some embodiments, if R_1 is substituted then R_1 is substituted with 1-2 X, wherein each X is independently selected from the group consisting of methyl, trifluoromethyl, methoxy, trifluoromethoxy, and OH. In some embodiments, R_1 is selected from:



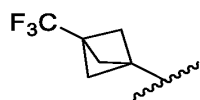
[0037] In one aspect, R₁ is unsubstituted or substituted C₃₋₄ cycloalkyl. In some embodiments, if R₁ is substituted then R₁ is substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro and trifluoromethyl. In some embodiments, R₁ is selected from:



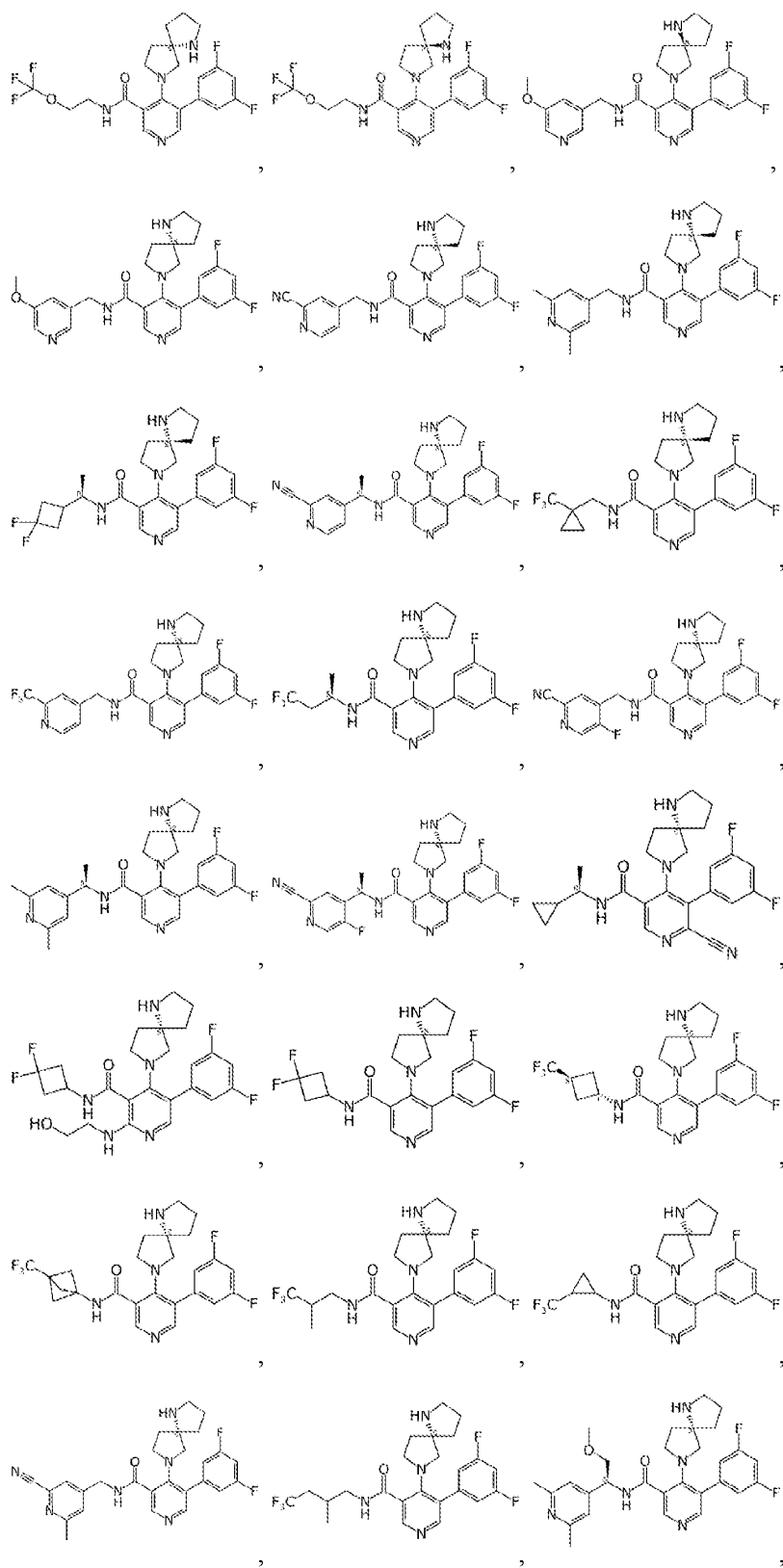
[0038] In one aspect, R₁ is unsubstituted or substituted pyridinyl. In some embodiments, if R₁ is substituted then R₁ is substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro, methyl, trifluoromethyl, methoxy, and CN. In some embodiments, R₁ is selected from:

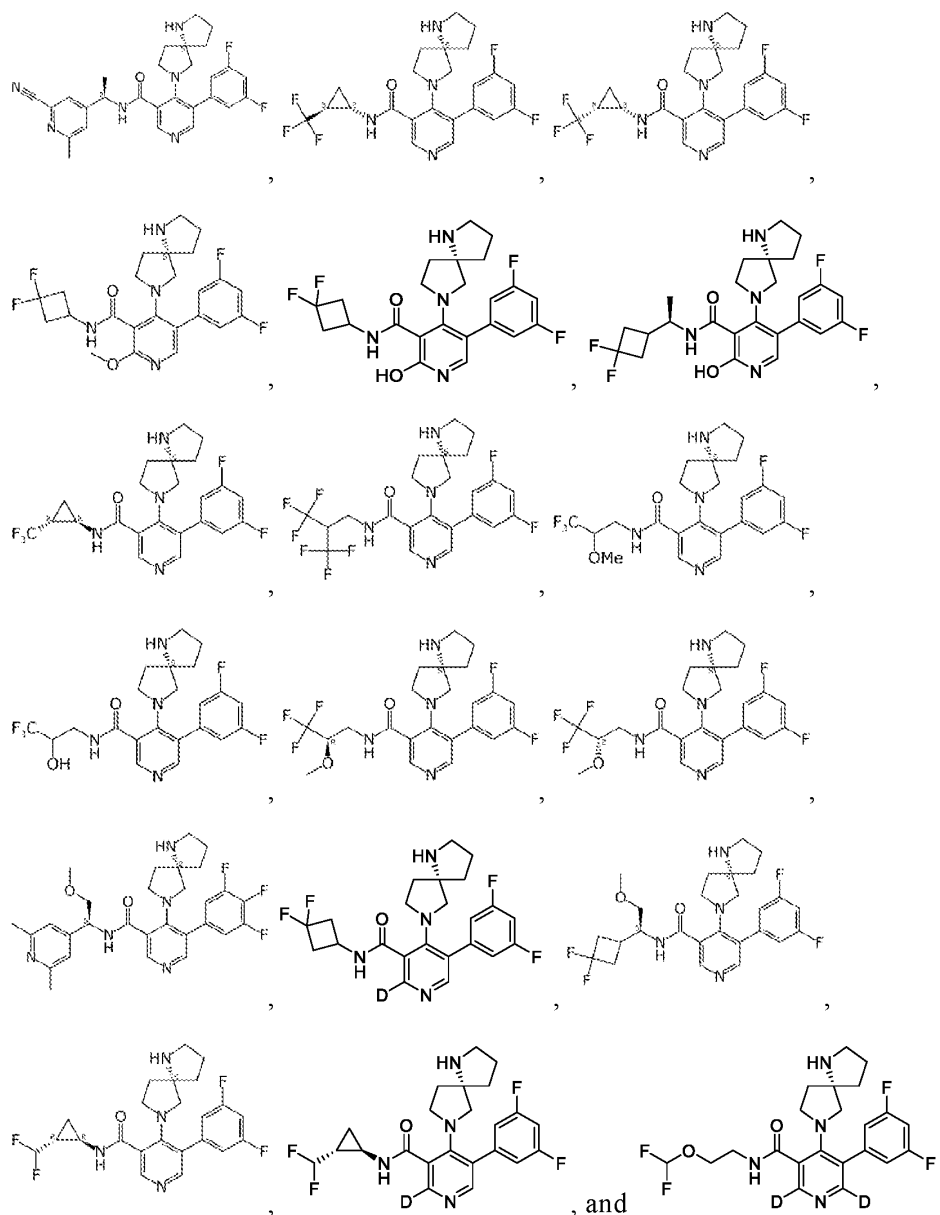


[0039] In one aspect, R₁ is unsubstituted or substituted C₅ bicycloalkyl. In some embodiments, one or more of the carbon atoms of the C₅ bicycloalkyl is a bridging carbon. In some embodiments, if R₁ is substituted then R₁ is substituted with trifluoromethyl. In some embodiments, R₁ is:



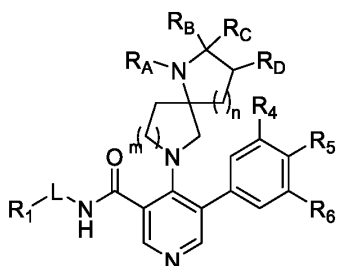
[0040] In one aspect, the compound is selected from:





[0041] In one aspect, R_7 is H and R_8 is H.

[0042] In another aspect, described herein is a compound of Formula (Id), or a pharmaceutically acceptable salt thereof:



wherein:

R₁ is unsubstituted or substituted C₁₋₄ alkyl, unsubstituted or substituted C₃₋₅ cycloalkyl, unsubstituted or substituted aryl, or unsubstituted or substituted 6-membered heteroaryl, wherein if R₁ is substituted then R₁ is substituted with 1-3 X, wherein each X is independently selected from F, Cl, methyl, ethyl, trifluoromethoxy, and CN;

L is a bond or CR₂R₃, wherein R₂ is H, and R₃ is H or methyl;

R₄ is H, F, or Cl;

R₅ is H or F;

R₆ is H, F, or Cl;

R_A is H, C(O)OEt, or C(O)Me;

R_B is H, D, or methyl;

R_C is H or D;

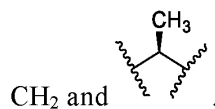
R_D is H or F;

m is an integer selected from 0 or 1; and

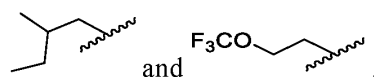
n is an integer selected from 0, 1, and 2.

[0043] In one aspect, L is a bond.

[0044] In one aspect, L is CR₂R₃. In some embodiments, L is selected from:

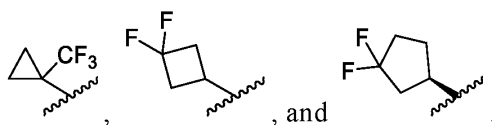


[0045] In one aspect, R₁ is unsubstituted or substituted C₁₋₄ alkyl. In some embodiments, if R₁ is substituted then R₁ is substituted with methyl or trifluoromethoxy. In some embodiments, R₁ is selected from:

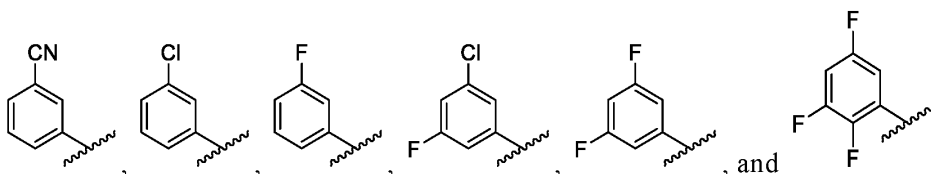


[0046] In one aspect, R₁ is unsubstituted or substituted C₃₋₅ cycloalkyl. In some embodiments, if R₁ is substituted then R₁ is substituted with 1-2 X, wherein each X is independently selected

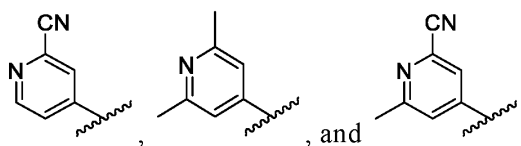
from the group consisting of fluoro and trifluoromethyl. In some embodiments, R_1 is selected from:



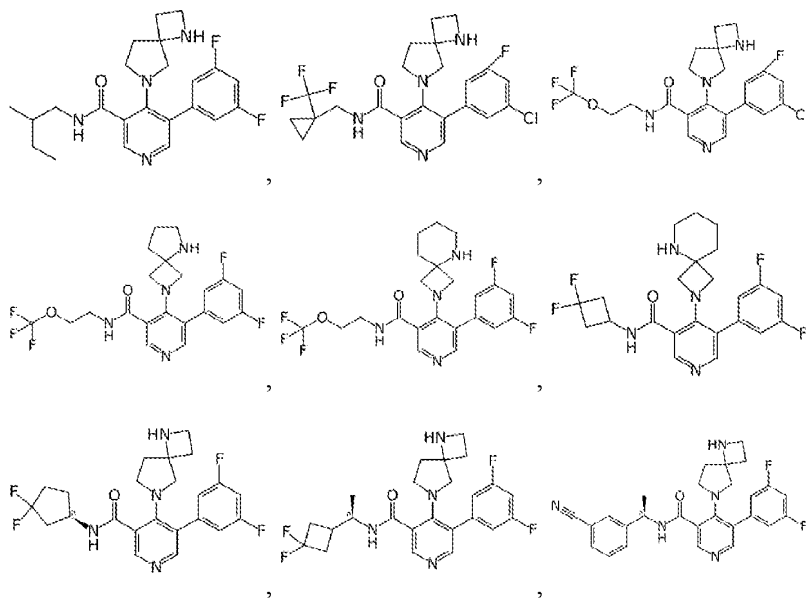
[0047] In one aspect, R_1 is unsubstituted or substituted phenyl. In some embodiments, if R_1 is substituted then R_1 is substituted with 1-3 X, wherein each X is independently selected from the group consisting of fluoro, chloro, and CN. In some embodiments, R_1 is selected from:

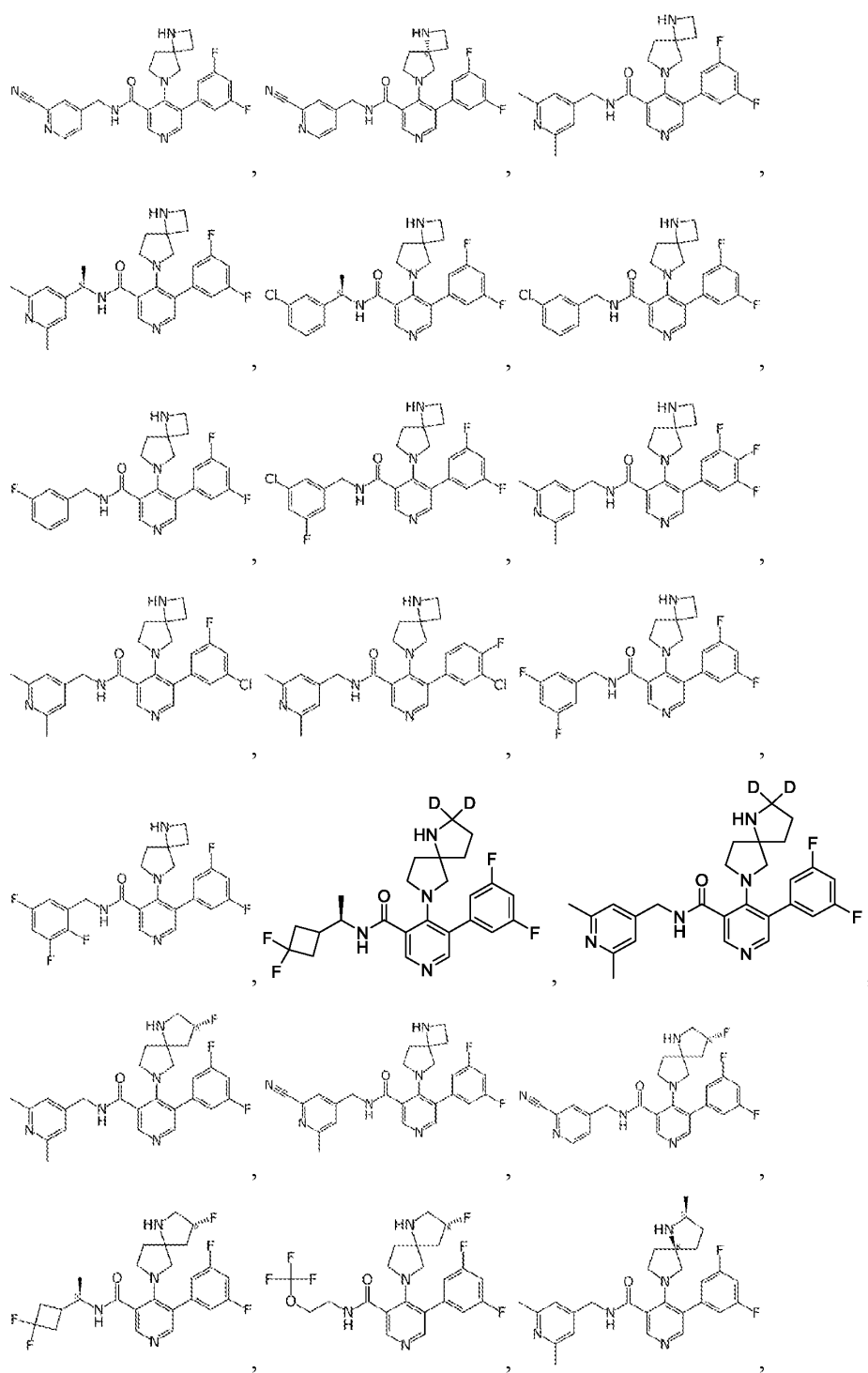


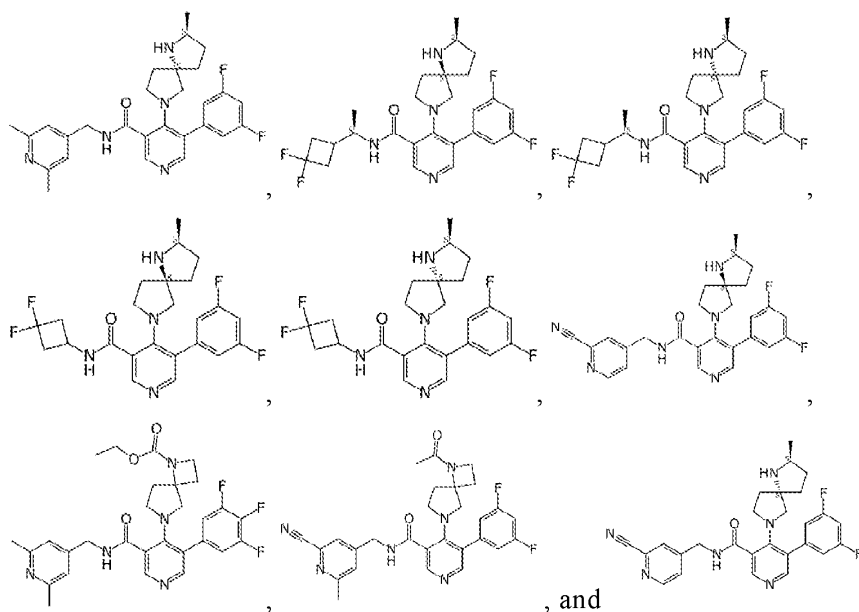
[0048] In one aspect, R_1 is unsubstituted or substituted pyridinyl. In some embodiments, if R_1 is substituted then R_1 is substituted with 1-2 X, wherein each X is independently selected from the group consisting of methyl and CN. In some embodiments, R_1 is selected from:



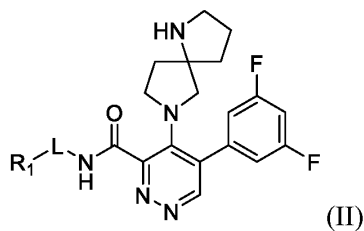
[0049] In one aspect, the compound is selected from:







[0050] In another aspect, described herein is a compound of Formula (II), or a pharmaceutically acceptable salt thereof:

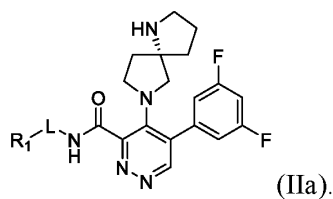


wherein:

R₁ is unsubstituted or substituted C₁₋₆ alkyl, unsubstituted or substituted C₃₋₆ cycloalkyl, unsubstituted or substituted aryl, or unsubstituted or substituted 6-membered heteroaryl, wherein if R₁ is substituted then R₁ is substituted with 1-2 X, wherein each X is independently selected from the group consisting of halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ fluoroalkyl, C₁₋₆ fluoroalkoxy, and CN; and

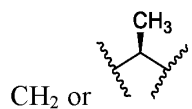
L is a bond or CR₂R₃, wherein R₂ is H, and R₃ is H or methyl.

[0051] In one aspect, the compound is a compound of Formula (IIa), or a pharmaceutically acceptable salt thereof:

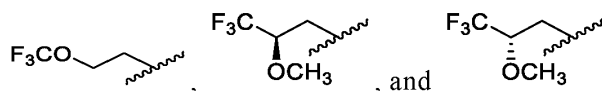


[0052] In one aspect, L is a bond.

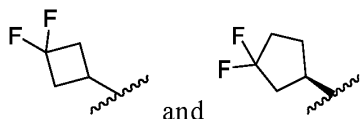
[0053] In one aspect, L is selected from:



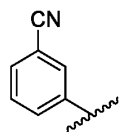
[0054] In one aspect, R₁ is unsubstituted or substituted ethyl. In some embodiments, if R₁ is substituted then R₁ is substituted with 1-2 X, wherein each X is independently selected from the group methoxy and trifluoromethoxy. In some embodiments, R₁ is selected from:



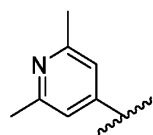
[0055] In one aspect, R₁ is unsubstituted or substituted C₄₋₅ cycloalkyl. In some embodiments, if R₁ is substituted then R₁ is substituted with fluoro. In some embodiments, R₁ is selected from:



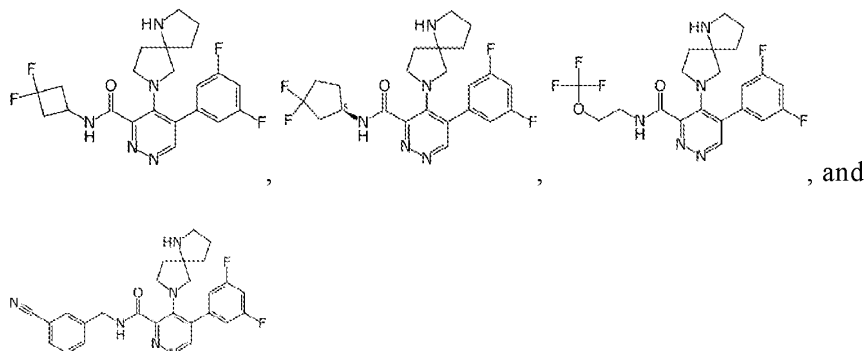
[0056] In one aspect, R₁ is unsubstituted or substituted phenyl. In some embodiments, if R₁ is substituted then R₁ is substituted with CN. In some embodiments, R₁ is:



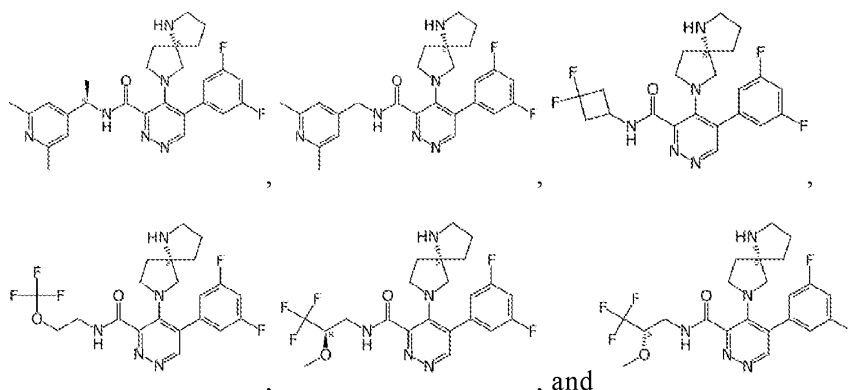
[0057] In one aspect, R₁ is unsubstituted or substituted pyridinyl. In some embodiments, if R₁ is substituted then R₁ is substituted with methyl. In some embodiments, R₁ is:



[0058] In one aspect, the compound is selected from:



[0059] In one aspect, the compound is selected from:



[0060] In another aspect, also disclosed herein, is a method of treating a disorder selected from polycystic kidney disease, polycystic liver disease, and ciliopathies, comprising administering to a subject in need thereof a compound of any one Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (II), or Formula (IIa), or a pharmaceutically acceptable salt thereof. In some embodiments, the disorder is polycystic kidney disease. In some embodiments, the polycystic kidney disease is autosomal dominant polycystic kidney disease (ADPKD).

[0061] In another aspect, also disclosed herein, is a pharmaceutical composition including a compound of any one Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (II), or Formula (IIa), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

BRIEF DESCRIPTION OF THE DRAWINGS

[0062] FIG. 1 depicts how abnormal primary cilia function triggers cystogenesis in autosomal dominant polycystic kidney disease (ADPKD).

[0063] FIG. 2 depicts interplay of calcium ions and cAMP ciliary signaling pathways in renal tissue of (A) healthy individuals and (B) individuals with ADPKD.

[0064] FIG. 3 depicts the mechanism of action by which SSTR3 activation can inhibit adenylyl cyclase activity and decrease cilio-plasma cAMP levels.

[0065] FIG. 4 depicts an analysis of the mRNA expression of SSTR2, SSTR3, SSTR5, and vasopressin receptor 2 (AVPR2) in healthy and cystic tissue.

[0066] FIG. 5 depicts the effect of (A) compound 105 and (B) compound 108 in an *in vitro* 3D cystogenesis model.

[0067] FIG. 6 depicts the effect of oral administration of compound 108 on (A) left kidney weight and (B) kidney cystic index in ADPKD mice.

DETAILED DESCRIPTION OF THE INVENTION

[0068] Somatostatin (SSTR), also known as somatotropin release inhibiting factor (SRIF) was initially isolated as a 14-amino acid peptide from ovine hypothalami (Brazeau *et al.*, *Science* 179, 77-79, 1973). An *N*-terminal extended 28-amino acid peptide with similar biological activity to 14-amino acid somatostatin was subsequently isolated (Pradayrol *et al.*, *FEBS Letters*, 109, 55-58, 1980; Esch *et al.*, *Proc. Natl. Acad. Sci. U S A*, 77, 6827-6831, 1980). SSTR is a regulatory peptide produced by several cell types in response to other neuropeptides, neurotransmitters, hormones, cytokines, and growth factors. SSTR acts through both endocrine and paracrine pathways to affect its target cells. Many of these effects are related to the inhibition of secretion of other hormones, most notably growth hormone (GH). They are produced by a wide variety of cell types in the central nervous system (CNS) and gut and have multiple functions including modulation of secretion of growth hormone (GH), insulin, glucagon, as well as many other hormones that are anti-proliferative.

[0069] These pleiotropic actions of somatostatins are mediated by six somatostatin receptor proteins (SSTR1, SSTR2a, SSTR2b, SSTR3, SSTR4, SSTR5). The six somatostatin receptor proteins are encoded by five different somatostatin receptor genes (Reisine and Bell, *Endocr Rev.* 16, 427-442, 1995; Patel and Srikant, *Trends Endocrinol Metab* 8, 398-405, 1997). All the receptors are members of the class-A subgroup of the GPCR superfamily.

[0070] It is possible to selectively modulate any one of the somatostatin receptor subtypes, or combination thereof. Selectively modulating any one of the somatostatin receptor subtypes relative to other somatostatin receptor subtypes reduces unwanted side effects in a variety of clinical applications.

[0071] In some embodiments, the SSTR3 agonists described herein are used in the treatment of a variety of diseases or conditions such as, but not limited to, ciliopathic diseases, including, but not limited to, polycystic kidney disease and polycystic liver disease. In some embodiments, SSTR3 agonists described herein are used in the treatment of a variety of diseases or conditions associated with dysfunction of cilia such as, but not limited to, polycystic kidney disease (PKD), autosomal dominant polycystic kidney disease (ADPKD), autosomal recessive polycystic kidney disease (ARPKD), and combinations thereof. In some embodiments, SSTR3 agonists described herein are used in the treatment of polycystic kidney disease (PKD). In some embodiments, the SSTR3 agonist described herein are used in the treatment of autosomal dominant polycystic kidney disease (ADPKD). In some embodiments, somatostatin receptor modulators described herein are used in the treatment of polycystic kidney disease (PKD) in a mammal.

Ciliopathies

[0072] Ciliopathies are a class of developmental and degenerative single-gene disorders characterized by dysfunction of a hairlike cellular organelle called the cilium. Cilia are microtubule-based structures found on almost all vertebrate cells. They originate from a basal body, a modified centrosome, which is the organelle that forms the spindle poles during mitosis. Most of the proteins that are altered in the single-gene disorders that make up ciliopathies function at the cilium-centrosome complex, which represents nature's universal system for cellular detection and management of external signals. The important role that the cilium-centrosome complex plays in the normal function of most tissues accounts for the involvement of multiple organ systems in ciliopathies. The dysfunction of cilia can cause a variety of ciliopathic diseases and conditions, including, but not limited to, polycystic liver disease, polycystic kidney disease (PKD), autosomal dominant polycystic kidney disease (ADPKD), autosomal recessive polycystic kidney disease (ARPKD), and combinations thereof.

Polycystic Kidney Disease

[0073] Polycystic kidney disease (PKD), also known as polycystic kidney syndrome) is a genetic disorder in which the renal tubules become structurally abnormal, resulting in the development and growth of multiple cysts, non-functioning tubules filled with fluid pumped into them, within the kidney. Cysts range in size from microscopic to enormous, crushing adjacent normal tubules and eventually rendering them non-functional as well. There are two types of PKD, each having their own pathology and genetic cause: autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD). The mutated gene is expressed in all cells in the body; as a result, cysts may also occur in the liver.

[0074] Tissue levels of cAMP are increased in numerous animal models of ciliopathies, including those for polycystic kidney disease (PKD). In general, tissue levels of cAMP are determined by the activities of membrane-bound and soluble adenylyl cyclases (ACs) and cAMP phosphodiesterases (PDEs), which are subject to complex regulatory mechanisms. For example, in some instances, ACs can be under the positive or negative control of G protein-coupled receptors (GPCRs) and extracellular ligands. For example, somatostatin acts on the five somatostatin receptors (SSTR 1 to 5), which in turn inhibits ACs and decreases intracellular cAMP levels.

[0075] Increased cAMP levels disrupt tubulogenesis, stimulate chloride and fluid secretion within the cyst cavity, and activate proliferative signaling pathways, including mitogen-activated protein kinase/extracellularly-regulated kinase, mTOR, and β -catenin signaling. Activated mTOR transcriptionally stimulates aerobic glycolysis, increasing ATP synthesis and lowering AMP levels, which together with B-Raf-dependent activation of LKB1, inhibits

AMPK, further enhancing mTOR activity and CFTR-driven chloride and fluid secretion. Increased PKA signaling, due to increased cAMP levels, also activates a number of transcription factors, including STAT3 and cAMP response element-binding protein (CREB). Activated STAT3 induces the transcription of cytokines, chemokines, and growth factors that, in turn, activates STAT3 on interstitial alternatively activated (M2) macrophages, which results in a feed forward loop between cyst-lining cells and M2 macrophages. Aberrant integrin–extracellular membrane interaction and cAMP signaling within focal adhesion complexes may also contribute to the increased adhesion of cyst-derived cells to laminin-322 and collagen. Hyperactive CREB in ADPKD mediates cAMP-dependent gene regulation that can govern a wide range of cellular processes, including metabolism, cell survival and proliferation, differentiation, apoptosis, and immune responses. The central role of cAMP in the pathogenesis of PKD provides a strong rationale for strategies to lower its levels in cystic tissues.

[0076] ADPKD is the most common genetic cause of kidney disease, affecting about 1:1000 individuals (Clin. Med. (Lond) 2009 Jun; 9(3): 278-283). The disease is characterized by slow and gradual bilateral kidney cyst formation, which often results in renal insufficiency usually around the fifth or sixth decade of life. The cysts that are formed in the ADPKD patient kidney originate in renal tubules where mutation in PKD1 or PKD2, genes which encode the polycystin-1 or polycystin-2 protein, respectively, impairs cilia functions in epithelial cells (J. Nephrol. 1997 Nov-Dec; 10(6): 295-310; AIMS Mol. Sci. 2014; 1(1): 27-46). Abnormal ciliary signaling results in incomplete differentiation and persistent proliferation of epithelial cells which leads to cyst formation (see, e.g., FIG. 1) (Int. J. Mol. Sci. 2022 Mar 19; 23(6): 3317). The cysts then grow and expand, owing to increased fluid transport into the lumen as a result of excess chloride ion secretion in the cavity. Eventually the cyst branches off from the main nephron and imposes continuous stress on the surrounding tissue, resulting in local injury. While replacement of normal renal tissue with cysts starts early in life, reductions in total nephron mass are masked by compensatory changes in glomerular filtration rate (i.e., GFR) such that total GFR remains apparently normal for many years until compensation fails years later, at which time ADPKD patients typically also experience flank pain, haematuria, urine infections, or renal colic. ADPKD often results in chronic kidney disease and end-stage renal disease (ESRD) that requires dialysis or kidney transplantation for patient survival.

[0077] The biological function of polycystins remains poorly understood. However increasing evidences point toward a model where loss of the inhibitory roles of polycystins in ciliary pathway activation might be the driver of cystogenesis observed in ADPKD. In healthy individuals, the polycystin-1 and polycystin-2 (PC1/2) proteins directly associate to form a

calcium permeable channel that is localized on primary cilia in renal epithelia (Nature Reviews Nephrology 2019; 15: 412-422). See FIG. 2(A).

[0078] Cilia are nonmotile plasma membrane appendages that serve as a mechanosensor that detect changes in fluid flow in the lumen of renal tubules and transduces them into a Ca^{2+} signaling response. This allows the cilium to be a specialized signaling hub that holds a much higher calcium concentration than the cytoplasm (Int. J. Mol. Sci. 2020 Sept 26; 21(19): 7109). High calcium levels directly inhibit ciliary adenylyl cyclase 5 and 6 (AC5/6) which convert ATP in cAMP and stimulate phosphodiesterase (i.e., PDE), an enzyme that catalyzes the hydrolysis of cAMP. As such, functional polycystin protein complexes maintain low ciliary levels of cAMP, a second messenger that plays a role in multiple cellular processes, including cell growth and differentiation. See FIG. 2(A).

[0079] In ADPKD patients, mutation in polycystin-1 or 2 leads to the formation of non-functional or hypofunctional channels and causes a significant decrease in ciliary calcium levels (World J. Nephrol. 2016 Jan 6; 5(1): 76-83). Consequently, calcium-inhibitable AC5/6 activity is increased, and calcium-dependent PDE4 activity is reduced. AC5/6 and PDE4 activity dysregulation result in a significant increase in intra-ciliary cAMP levels. See FIG. 2(B).

[0080] High levels of cAMP then triggers cyst formation by stimulating the expression of cAMP dependent genes involved in proliferation as well as cyst expansion by driving chloride ions and fluid secretion in the cyst cavity via protein kinase A (PKA)-stimulated cystic fibrosis transmembrane conductance regulator (CFTR) activation. Thus, in ADPKD, dysregulated cross-talk between intraciliary calcium and the cAMP signaling pathway seems to play a critical role in cystogenesis. Therefore, the inventors hypothesize that cyst formation observed in ADPKD should be inhibited/reduced by blocking adenylyl cyclase activity selectively within the cilia.

[0081] SSTR3 is a prototypical ciliary GPCR (Neuroscience 1999 Mar; 89(3): 909-26). SSTR3 trafficking to the cilia requires a series of highly regulated processes that include the translocation of the receptor from the cytoplasm to the axoneme through the transition zone owing to a particular amino acid sequence located in the third transmembrane domain (J. Cell. Biol. 2018 May 7; 217(5): 1847-1868). As a G_i coupled receptor, SSTR3 activation can inhibit adenylyl cyclase activity (Murthy et al., J. Biol. Chem. 1996; 271(38): 23458-23463) and decrease cilio-plasma cAMP levels, which is central to the establishment of ADPKD. See FIG. 3.

[0082] Public data set (GSE7869) from a global gene profiling study on renal cysts was reported by Song et al. (Hum. Mol. Genet. 2009; 18: 2328-2343). The data set comprises microarray expression data from cysts of different sizes from five PKD1-patients and from three kidneys of healthy patients. The inventors performed a reanalysis of the data using a

Transcriptome Analysis Console (Thermo Fisher). Inspecting the probe covering SSTRR3 (SSTR3), SSTRR3-mRNA expression was found in healthy and cystic tissue at higher levels when compared to somatostatin receptor 2 and 5 (SSTR2, SSTR5), or the vasopressin receptor 2 (AVPR2) (See FIG. 4). Thus, the inventors determined that the cellular localization and signaling capability of SSTR3 makes it an attractive target for the treatment of ADPKD.

[0083] Autosomal recessive polycystic kidney disease (ARPKD), an important cause of ESRD and mortality in infants and children, is caused by mutations in PKHD1 (encoding fibrocystin). As with ADPKD, in ARPKD cyst formation is caused by disruption of mechanisms controlling cellular differentiation, leading to excessive cell proliferation and fluid secretion, and pathogenic interactions of mutated epithelial cells with an abnormal extracellular matrix and alternatively activated interstitial macrophages. Dysregulation of the crosstalk between ciliary calcium and cyclic adenosine monophosphate (cAMP) signaling play central roles in the development of PKD. In some instances, the compounds described herein are somatostatin agonists that selectively activate somatostatin receptor subtype 3 (SSTR3) that in turn reduce cAMP levels and cAMP dependent signaling.

[0084] In some embodiments, somatostatin receptor modulators described herein are used to treat ciliopathies in a mammal. In some embodiments, somatostatin receptor modulators described herein lead to a decrease in cAMP levels, which is useful for the treatment of ciliopathies described herein. In some embodiments, the ciliopathic disease or condition is selected from polycystic kidney disease (PKD), autosomal dominant polycystic kidney disease (ADPKD), autosomal recessive polycystic kidney disease (ARPKD), polycystic liver disease, and combinations thereof. In some embodiments, the ciliopathic disease or condition is selected from polycystic kidney disease (PKD), autosomal dominant polycystic kidney disease (ADPKD), and autosomal recessive polycystic kidney disease (ARPKD). In some embodiments, the ciliopathic disease or condition is polycystic kidney disease (PKD). In some embodiments, the ciliopathic disease or condition is autosomal dominant polycystic kidney disease (ADPKD). In some embodiments, the ciliopathic disease or condition is autosomal recessive polycystic kidney disease (ARPKD).

[0085] Also described herein is a method of treating a disease or condition in a mammal that would benefit from the modulation of somatostatin receptor subtype 3 (SSTR3) activity comprising administering to the mammal in need thereof a selective small molecule SSTR3 agonist compound.

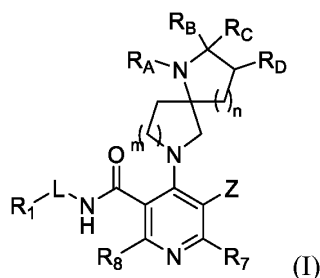
[0086] In some embodiments, the disease or condition is any one of the diseases or conditions described herein, or combinations thereof. In some embodiments, the disease or condition is

associated with dysfunction of cilia. In some embodiments, the disease or condition is a ciliopathic disease or condition. In some embodiments, the selective small molecule SSTR3 agonist is a compound described herein.

Compounds

[0087] Provided are compounds of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (II), and Formula (IIa), including pharmaceutically acceptable salts thereof, which are somatostatin subtype 3 receptor (SSTR3) agonists.

[0088] In certain embodiments, the compound is a compound of Formula (I):

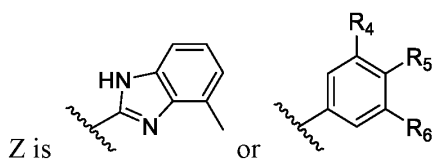


or a pharmaceutically acceptable salt thereof, wherein:

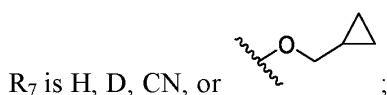
R₁ is unsubstituted or substituted C₁₋₆ alkyl, unsubstituted or substituted C₃₋₆ cycloalkyl, unsubstituted or substituted 6-membered heterocycloalkyl, unsubstituted or substituted C₅₋₇ bicycloalkyl, unsubstituted or substituted aryl, or unsubstituted or substituted 6-membered heteroaryl;

wherein if R₁ is substituted then R₁ is substituted with 1-3 X, wherein each X is independently selected from the group consisting of halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ fluoroalkyl, C₁₋₆ fluoroalkoxy, C₃₋₆ cycloalkoxy, CN, and OH;

L is a bond or CR₂R₃, wherein R₂ is H or C₁₋₆ alkyl, and R₃ is H, C₁₋₆ alkyl, C₁₋₆ alkoxy, CH₂OCH₃, or C₁₋₆ fluoroalkyl; or R₂ and R₃ together with the carbon to which they are attached form a C₃₋₆ cycloalkyl;



wherein R₄ is H or halogen; R₅ is H or halogen; and R₆ is H, halogen, CN, C₁₋₆ alkyl, or C₁₋₆ alkoxy;



R₇ is H, D, CN, or

R₈ is H, D, OH, C₁₋₆ alkyl, C₁₋₆ alkoxy, NH₂, or -NH(CH₂)₂OH;

R_A is H, $C(O)OC_{1-6}$ alkyl, or $C(O)C_{1-6}$ alkyl;

R_B is H, D, or C_{1-6} alkyl;

R_C is H or D;

R_D is H or halogen;

m is an integer selected from 0 and 1; and

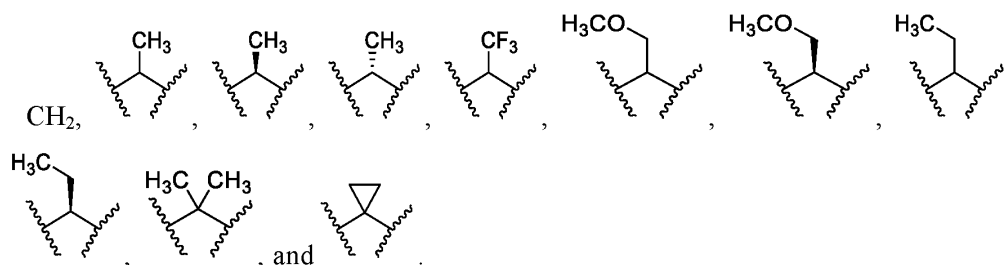
n is an integer selected from 0, 1, and 2.

[0089] In certain embodiments, L is a bond.

[0090] In certain embodiments, L is CR_2R_3 . In certain embodiments, L is CR_2R_3 and R_2 is H or methyl. In certain embodiments, L is CR_2R_3 and R_2 is H. In certain embodiments, L is CR_2R_3 and R_2 is methyl. In certain embodiments, L is CR_2R_3 and R_3 is H, methyl, ethyl, trifluoromethyl, or CH_2OCH_3 . In certain embodiments, L is CR_2R_3 and R_3 is H. In certain embodiments, L is CR_2R_3 and R_3 is methyl. In certain embodiments, L is CR_2R_3 and R_3 is ethyl. In certain embodiments, L is CR_2R_3 and R_3 is trifluoromethyl. In certain embodiments, L is CR_2R_3 and R_3 is CH_2OCH_3 . In certain embodiments, L is CR_2R_3 and R_2 is H and R_3 is H. In certain embodiments, L is CR_2R_3 and R_2 is H and R_3 is methyl.

[0091] In certain embodiments, L is CR_2R_3 and R_2 and R_3 together with the carbon to which they are attached form a C_{3-6} cycloalkyl. In certain embodiments, L is CR_2R_3 and R_2 and R_3 together with the carbon to which they are attached form a cyclopropyl moiety.

[0092] In certain embodiments, L is selected from:



[0093] In certain embodiments, R_1 is unsubstituted or substituted C_{1-4} alkyl. In certain embodiments, R_1 is unsubstituted C_{1-4} alkyl. In certain embodiments, R_1 is substituted C_{1-4} alkyl. In certain embodiments, R_1 is C_{1-4} alkyl substituted with 1-2 X, wherein each X is independently selected from methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH. In certain embodiments, R_1 is C_{1-4} alkyl substituted with X, wherein X is selected from methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH. In certain embodiments, R_1 is C_{1-4} alkyl substituted with 2 X, wherein each X is independently

selected from methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH.

[0094] In certain embodiments, R₁ is unsubstituted or substituted methyl. In certain embodiments, R₁ is unsubstituted methyl. In certain embodiments, R₁ is substituted methyl. In certain embodiments, R₁ is methyl substituted with 1-2 X, wherein each X is independently selected from trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH. In certain embodiments, R₁ is methyl substituted with X, wherein X is selected from trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH. In certain embodiments, R₁ is methyl substituted with 2 X, wherein each X is independently selected from trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH.

[0095] In certain embodiments, R₁ is unsubstituted or substituted ethyl. In certain embodiments, R₁ is unsubstituted ethyl. In certain embodiments, R₁ is substituted ethyl. In certain embodiments, R₁ is ethyl substituted with 1-2 X, wherein each X is independently selected from methyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH. In certain embodiments, R₁ is ethyl substituted with X, wherein X is selected from methyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH. In certain embodiments, R₁ is ethyl substituted with 2 X, wherein each X is independently selected from methyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH.

[0096] In certain embodiments, R₁ is unsubstituted or substituted n-propyl. In certain embodiments, R₁ is unsubstituted n-propyl. In certain embodiments, R₁ is substituted n-propyl. In certain embodiments, R₁ is n-propyl substituted with 1-2 X, wherein each X is independently selected from methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH. In certain embodiments, R₁ is n-propyl substituted with X, wherein X is selected from methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH. In certain embodiments, R₁ is n-propyl substituted with 2 X, wherein each X is independently selected from methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH.

[0097] In certain embodiments, R₁ is unsubstituted or substituted isopropyl. In certain embodiments, R₁ is unsubstituted isopropyl. In certain embodiments, R₁ is substituted isopropyl. In certain embodiments, R₁ is isopropyl substituted with 1-2 X, wherein each X is independently

selected from methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH. In certain embodiments, R₁ is isopropyl substituted with X, wherein X is selected from methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH. In certain embodiments, R₁ is isopropyl substituted with 2 X, wherein each X is independently selected from methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH.

[0098] In certain embodiments, R₁ is unsubstituted or substituted n-butyl. In certain embodiments, R₁ is unsubstituted n-butyl. In certain embodiments, R₁ is substituted n-butyl. In certain embodiments, R₁ is n-butyl substituted with 1-2 X, wherein each X is independently selected from methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH. In certain embodiments, R₁ is n-butyl substituted with X, wherein X is selected from methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH. In certain embodiments, R₁ is n-butyl substituted with 2 X, wherein each X is independently selected from methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH.

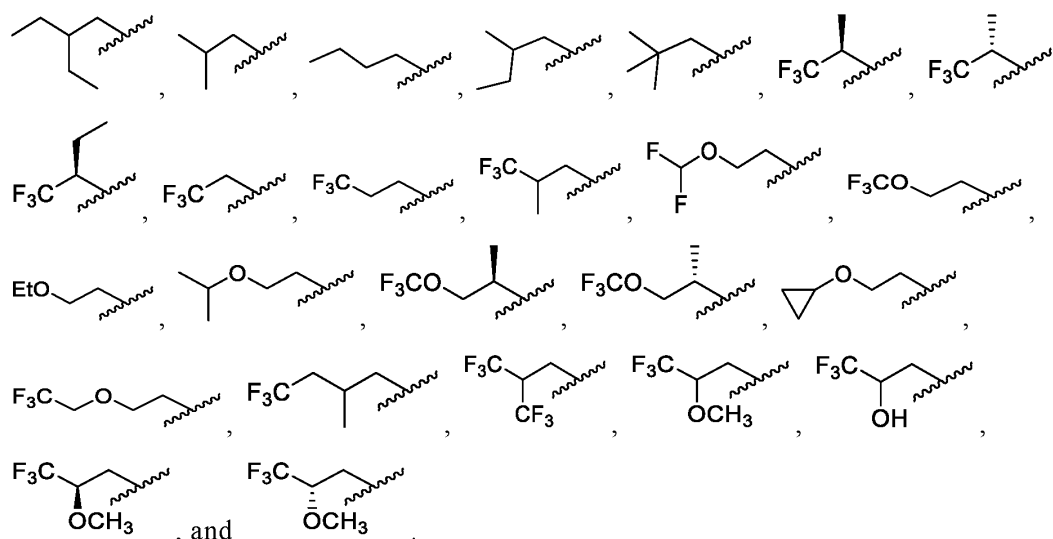
[0099] In certain embodiments, R₁ is unsubstituted or substituted isobutyl. In certain embodiments, R₁ is unsubstituted isobutyl. In certain embodiments, R₁ is substituted isobutyl. In certain embodiments, R₁ is isobutyl substituted with 1-2 X, wherein each X is independently selected from methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH. In certain embodiments, R₁ is isobutyl substituted with X, wherein X is selected from methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH. In certain embodiments, R₁ is isobutyl substituted with 2 X, wherein each X is independently selected from methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH.

[00100] In certain embodiments, R₁ is unsubstituted or substituted sec-butyl. In certain embodiments, R₁ is unsubstituted sec-butyl. In certain embodiments, R₁ is substituted sec-butyl. In certain embodiments, R₁ is sec-butyl substituted with 1-2 X, wherein each X is independently selected from methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH. In certain embodiments, R₁ is sec-butyl substituted with X, wherein X is selected from methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH.

In certain embodiments, R_1 is sec-butyl substituted with 2 X, wherein each X is independently selected from methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH.

[00101] In certain embodiments, R_1 is unsubstituted or substituted tert-butyl. In certain embodiments, R_1 is unsubstituted tert-butyl. In certain embodiments, R_1 is substituted tert-butyl. In certain embodiments, R_1 is tert-butyl substituted with 1-2 X, wherein each X is independently selected from methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH. In certain embodiments, R_1 is tert-butyl substituted with X, wherein X is selected from methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH. In certain embodiments, R_1 is tert-butyl substituted with 2 X, wherein each X is independently selected from methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH.

[00102] In certain embodiments, R_1 is selected from:



[00103] In certain embodiments, R_1 is unsubstituted or substituted C₃₋₆ cycloalkyl. In certain embodiments, R_1 is unsubstituted C₃₋₆ cycloalkyl. In certain embodiments, R_1 is substituted C₃₋₆ cycloalkyl. In certain embodiments, R_1 is C₃₋₆ cycloalkyl substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro, methyl, difluoromethyl, and trifluoromethyl. In certain embodiments, R_1 is C₃₋₆ cycloalkyl substituted with X, wherein X is selected from fluoro, methyl, difluoromethyl, and trifluoromethyl. In certain embodiments, R_1 is C₃₋₆ cycloalkyl substituted with 2 X, wherein each X is independently selected from fluoro, methyl, difluoromethyl, and trifluoromethyl.

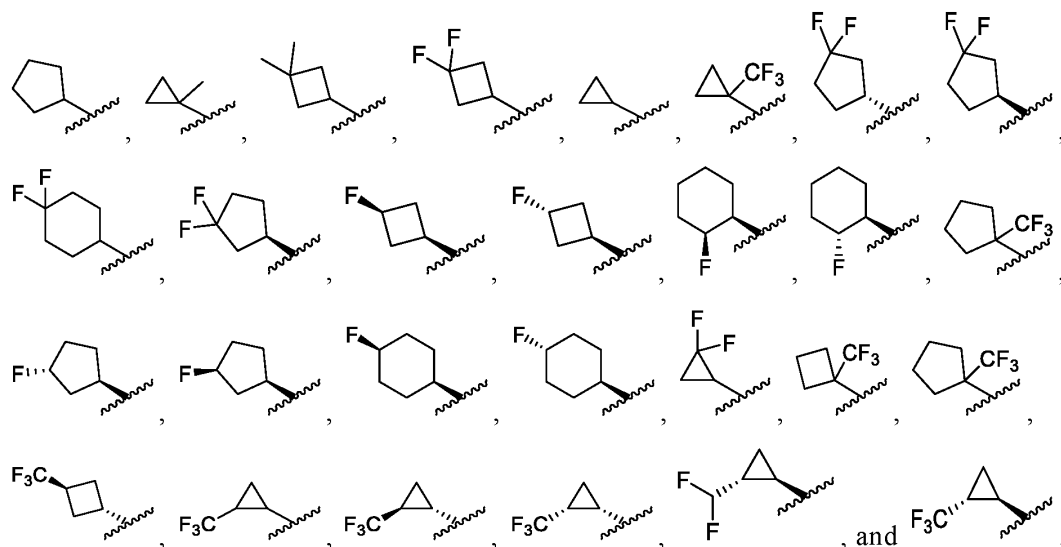
[00104] In certain embodiments, R₁ is unsubstituted or substituted cyclopropyl. In certain embodiments, R₁ is unsubstituted cyclopropyl. In certain embodiments, R₁ is substituted cyclopropyl. In certain embodiments, R₁ is cyclopropyl substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro, methyl, difluoromethyl, and trifluoromethyl. In certain embodiments, R₁ is cyclopropyl substituted with X, wherein X is selected from fluoro, methyl, difluoromethyl, and trifluoromethyl. In certain embodiments, R₁ is cyclopropyl substituted with 2 X, wherein each X is independently selected from fluoro, methyl, difluoromethyl, and trifluoromethyl.

[00105] In certain embodiments, R₁ is unsubstituted or substituted cyclobutyl. In certain embodiments, R₁ is unsubstituted cyclobutyl. In certain embodiments, R₁ is substituted cyclobutyl. In certain embodiments, R₁ is cyclobutyl substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro, methyl, difluoromethyl, and trifluoromethyl. In certain embodiments, R₁ is cyclobutyl substituted with X, wherein X is selected from fluoro, methyl, difluoromethyl, and trifluoromethyl. In certain embodiments, R₁ is cyclobutyl substituted with 2 X, wherein each X is independently selected from fluoro, methyl, difluoromethyl, and trifluoromethyl.

[00106] In certain embodiments, R₁ is unsubstituted or substituted cyclopentyl. In certain embodiments, R₁ is unsubstituted cyclopentyl. In certain embodiments, R₁ is substituted cyclopentyl. In certain embodiments, R₁ is cyclopentyl substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro, methyl, difluoromethyl, and trifluoromethyl. In certain embodiments, R₁ is cyclopentyl substituted with X, wherein X is selected from fluoro, methyl, difluoromethyl, and trifluoromethyl. In certain embodiments, R₁ is cyclopentyl substituted with 2 X, wherein each X is independently selected from fluoro, methyl, difluoromethyl, and trifluoromethyl.

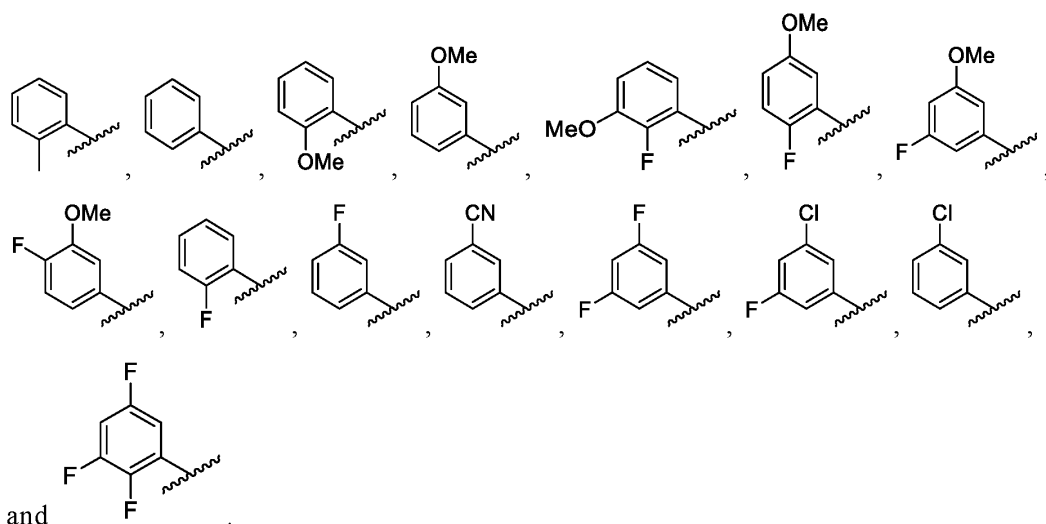
[00107] In certain embodiments, R₁ is unsubstituted or substituted cyclohexyl. In certain embodiments, R₁ is unsubstituted cyclohexyl. In certain embodiments, R₁ is substituted cyclohexyl. In certain embodiments, R₁ is cyclohexyl substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro, methyl, difluoromethyl, and trifluoromethyl. In certain embodiments, R₁ is cyclohexyl substituted with X, wherein X is selected from fluoro, methyl, difluoromethyl, and trifluoromethyl. In certain embodiments, R₁ is cyclohexyl substituted with 2 X, wherein each X is independently selected from fluoro, methyl, difluoromethyl, and trifluoromethyl.

[00108] In certain embodiments, R₁ is selected from:

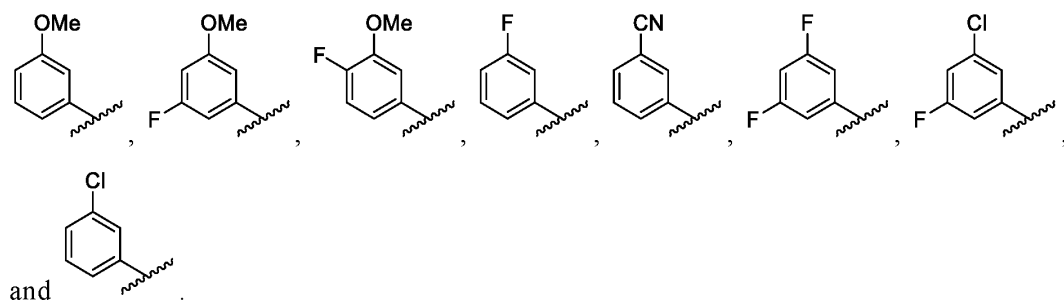


[00109] In certain embodiments, R_1 is unsubstituted or substituted phenyl. In certain embodiments, R_1 is unsubstituted phenyl. In certain embodiments, R_1 is substituted phenyl. In certain embodiments, R_1 is phenyl substituted with 1-3 X, wherein each X is independently selected from fluoro, chloro, methyl, methoxy, and CN. In certain embodiments, R_1 is phenyl substituted with X, wherein X is selected from fluoro, chloro, methyl, methoxy, and CN. In certain embodiments, R_1 is phenyl substituted with 2 X, wherein each X is independently selected from fluoro, chloro, methyl, methoxy, and CN. In certain embodiments, R_1 is phenyl substituted with 3 X, wherein each X is independently selected from fluoro, chloro, methyl, methoxy, and CN.

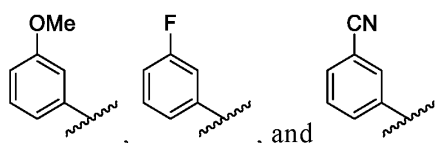
[00110] In certain embodiments, R_1 is selected from:



[00111] In certain embodiments, R_1 is selected from:



[00112] In certain embodiments, R_1 is selected from:

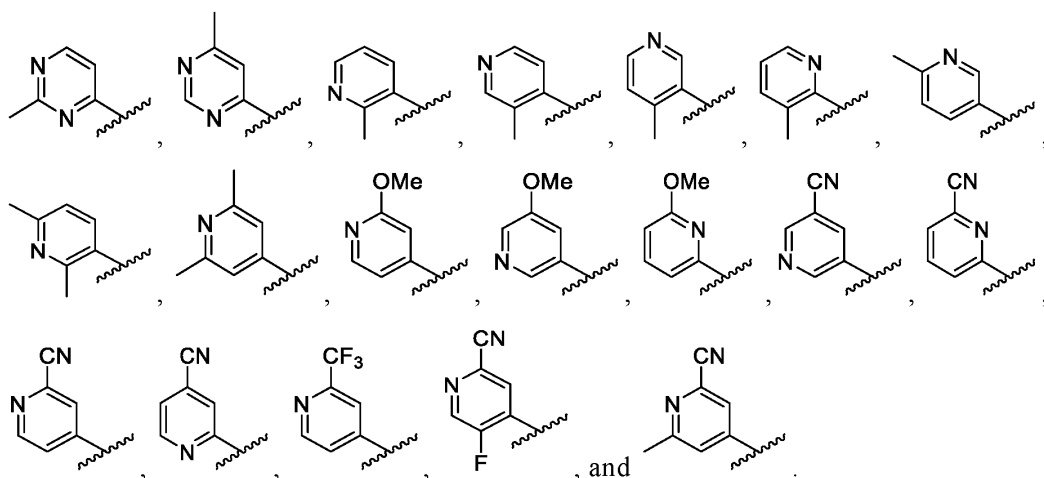


[00113] In certain embodiments, R_1 is unsubstituted or substituted pyridinyl or unsubstituted or substituted pyrimidinyl.

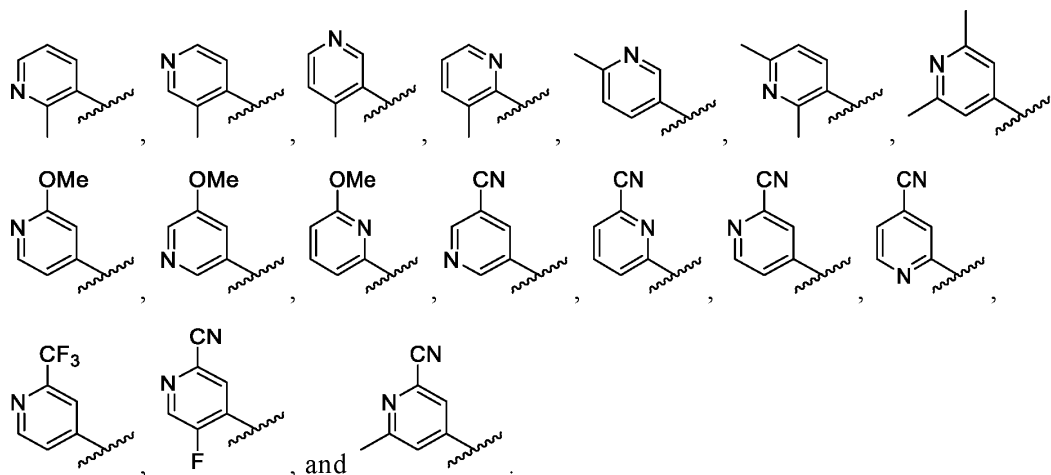
[00114] In certain embodiments, R_1 is unsubstituted or substituted pyridinyl. In certain embodiments, R_1 is unsubstituted pyridinyl. In certain embodiments, R_1 is pyridinyl substituted with 1-2 X, wherein each X is independently selected from fluoro, methyl, trifluoromethyl, methoxy, and CN. In certain embodiments, R_1 is pyridinyl substituted with X, wherein X is selected from fluoro, methyl, trifluoromethyl, methoxy, and CN. In certain embodiments, R_1 is pyridinyl substituted with 2 X, wherein each X is independently selected from fluoro, methyl, trifluoromethyl, methoxy, and CN.

[00115] In certain embodiments, R_1 is unsubstituted or substituted pyrimidinyl. In certain embodiments, R_1 is unsubstituted pyrimidinyl. In certain embodiments, R_1 is pyrimidinyl substituted with X, wherein X is methyl.

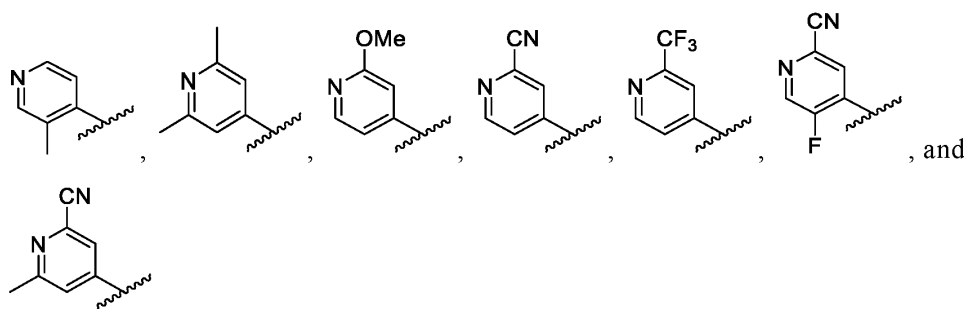
[00116] In certain embodiments, R_1 is selected from:



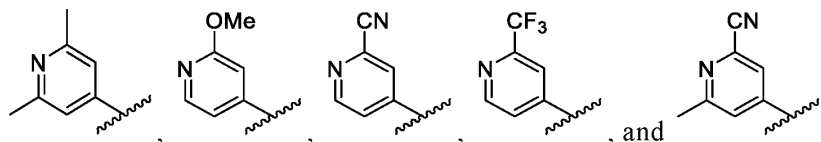
[00117] In certain embodiments, R₁ is selected from:



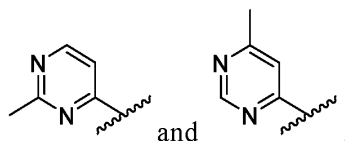
[00118] In certain embodiments, R₁ is selected from:



[00119] In certain embodiments, R₁ is selected from:



[00120] In certain embodiments, R₁ is selected from:



[00121] In certain embodiments, R₁ is unsubstituted or substituted C₅₋₇ bicycloalkyl. In certain embodiments, R₁ is unsubstituted C₅₋₇ bicycloalkyl. In certain embodiments, R₁ is substituted C₅₋₇ bicycloalkyl. In certain embodiments, R₁ is C₅₋₇ bicycloalkyl substituted with fluoro or trifluoromethyl. In certain embodiments, R₁ is C₅₋₇ bicycloalkyl substituted with fluoro. In certain embodiments, R₁ is C₅₋₇ bicycloalkyl substituted with trifluoromethyl. In certain embodiments,

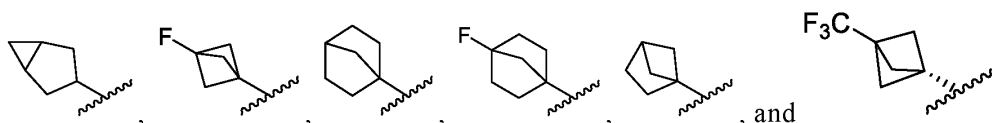
one or more of the carbon atoms of the C₅₋₇ bicycloalkyl is a bridging carbon. In certain embodiments, one of the carbon atoms of the C₅₋₇ bicycloalkyl is a bridging carbon.

[00122] In certain embodiments, R₁ is unsubstituted or substituted C₅ bicycloalkyl. In certain embodiments, R₁ is unsubstituted C₅ bicycloalkyl. In certain embodiments, R₁ is substituted C₅ bicycloalkyl. In certain embodiments, R₁ is C₅ bicycloalkyl substituted with fluoro or trifluoromethyl. In certain embodiments, R₁ is C₅ bicycloalkyl substituted with fluoro. In certain embodiments, R₁ is C₅ bicycloalkyl substituted with trifluoromethyl. In certain embodiments, one or more of the carbon atoms of the C₅ bicycloalkyl is a bridging carbon. In certain embodiments, one of the carbon atoms of the C₅ bicycloalkyl is a bridging carbon.

[00123] In certain embodiments, R₁ is unsubstituted or substituted C₆ bicycloalkyl. In certain embodiments, R₁ is unsubstituted C₆ bicycloalkyl. In certain embodiments, R₁ is substituted C₆ bicycloalkyl. In certain embodiments, R₁ is C₆ bicycloalkyl substituted with fluoro or trifluoromethyl. In certain embodiments, R₁ is C₆ bicycloalkyl substituted with fluoro. In certain embodiments, R₁ is C₆ bicycloalkyl substituted with trifluoromethyl. In certain embodiments, one or more of the carbon atoms of the C₆ bicycloalkyl is a bridging carbon. In certain embodiments, one of the carbon atoms of the C₆ bicycloalkyl is a bridging carbon.

[00124] In certain embodiments, R₁ is unsubstituted or substituted C₇ bicycloalkyl. In certain embodiments, R₁ is unsubstituted C₇ bicycloalkyl. In certain embodiments, R₁ is substituted C₇ bicycloalkyl. In certain embodiments, R₁ is C₇ bicycloalkyl substituted with fluoro or trifluoromethyl. In certain embodiments, R₁ is C₇ bicycloalkyl substituted with fluoro. In certain embodiments, R₁ is C₇ bicycloalkyl substituted with trifluoromethyl. In certain embodiments, one or more of the carbon atoms of the C₇ bicycloalkyl is a bridging carbon. In certain embodiments, one of the carbon atoms of the C₇ bicycloalkyl is a bridging carbon.

[00125] In certain embodiments, R₁ is selected from:



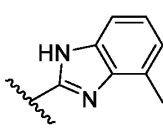
[00126] In certain embodiments, R₁ is tetrahydropyran.

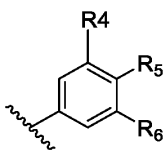
[00127] In certain embodiments, m is 1 and n is 1. In some embodiments m is 0 and n is 2.

[00128] In certain embodiments, R_A is hydrogen.

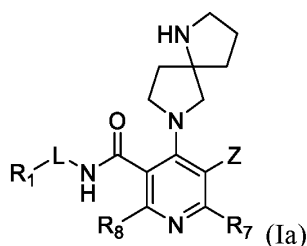
[00129] In certain embodiments, R_B is hydrogen; R_C is hydrogen; and R_D is hydrogen.

[00130] In certain embodiments, R_A is hydrogen, R_B is hydrogen, R_C is hydrogen, and R_D is hydrogen.

[00131] In certain embodiments, Z is .

[00132] In certain embodiments, Z is: .

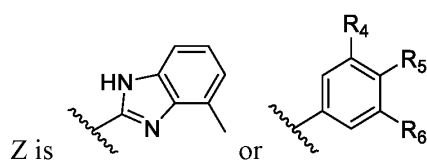
[00133] In certain embodiments, the compound is a compound of Formula (Ia):



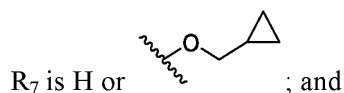
or a pharmaceutically acceptable salt thereof, wherein:

R_1 is unsubstituted or substituted C_{1-4} alkyl, unsubstituted or substituted C_{3-6} cycloalkyl, tetrahydropyran, unsubstituted or substituted C_{5-7} bicycloalkyl, unsubstituted or substituted aryl, or unsubstituted or substituted 6-membered heteroaryl, wherein if R_1 is substituted then R_1 is substituted with 1-2 X, wherein each X is independently selected from F, Cl, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, trifluoromethoxy, cyclopropoxy, OCH_2CF_3 , CN, and OH;

L is a bond or CR_2R_3 , wherein R_2 is H or methyl, and R_3 is H, methyl, ethyl, trifluoromethyl, or $-CH_2OCH_3$; or R_2 and R_3 together with the carbon to which they are attached form a cyclopropyl group;



wherein R_4 is H, F, or Cl; R_5 is H or F; and R_6 is H, F, Cl, CN, methyl, or methoxy;



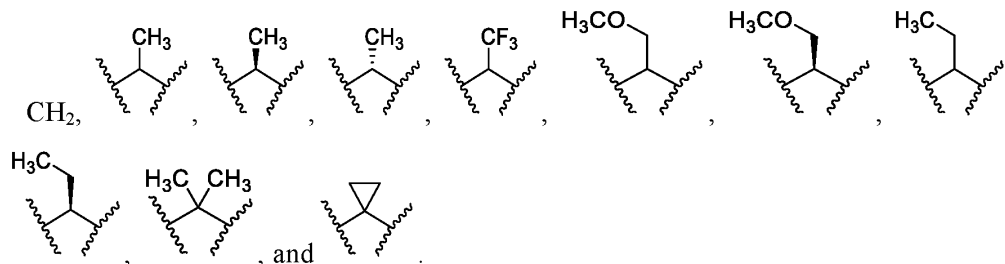
R_8 is H, NH_2 , or methyl.

[00134] In certain embodiments, L is a bond.

[00135] In certain embodiments, L is CR_2R_3 . In certain embodiments, L is CR_2R_3 and R_2 is H or methyl. In certain embodiments, L is CR_2R_3 and R_2 is H. In certain embodiments, L is CR_2R_3 and

R_2 is methyl. In certain embodiments, L is CR_2R_3 and R_3 is H, methyl, ethyl, trifluoromethyl, or $-CH_2OCH_3$. In certain embodiments, L is CR_2R_3 and R_2 is H and R_3 is H. In certain embodiments, L is CR_2R_3 and R_2 is H and R_3 is methyl. In certain embodiments, L is CR_2R_3 and R_2 and R_3 together with the carbon to which they are attached form a cyclopropyl moiety.

[00136] In certain embodiments, L is selected from:



[00137] In certain embodiments, R_1 is unsubstituted or substituted C_{1-4} alkyl. In certain embodiments, R_1 is unsubstituted C_{1-4} alkyl. In certain embodiments, R_1 is substituted C_{1-4} alkyl. In certain embodiments, R_1 is C_{1-4} alkyl substituted with 1-2 X, wherein each X is independently selected from methyl, ethyl, trifluoromethyl, ethoxy, isopropoxy, trifluoromethoxy, trifluoroethoxy, and cyclopropoxy. In certain embodiments, R_1 is C_{1-4} alkyl substituted with X, wherein X is selected from methyl, ethyl, trifluoromethyl, ethoxy, isopropoxy, trifluoromethoxy, trifluoroethoxy, and cyclopropoxy. In certain embodiments, R_1 is C_{1-4} alkyl substituted with 2 X, wherein each X is independently selected from methyl, ethyl, trifluoromethyl, ethoxy, isopropoxy, trifluoromethoxy, trifluoroethoxy, and cyclopropoxy.

[00138] In certain embodiments, R_1 is unsubstituted or substituted methyl. In certain embodiments, R_1 is unsubstituted methyl. In certain embodiments, R_1 is substituted methyl. In certain embodiments, R_1 is methyl substituted trifluoromethoxy.

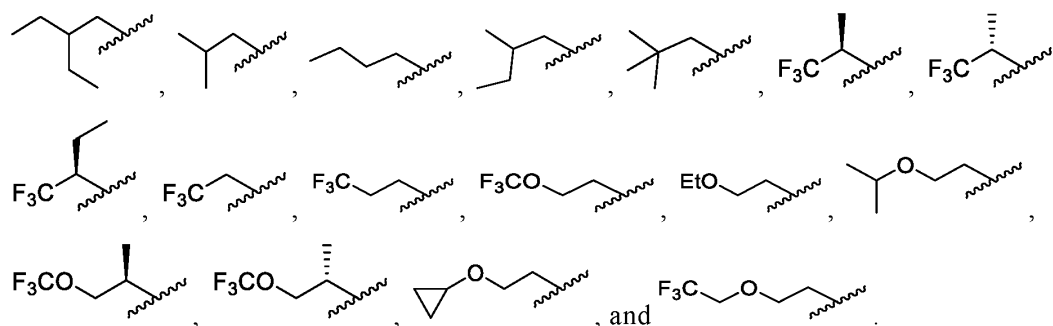
[00139] In certain embodiments, R_1 is unsubstituted or substituted ethyl. In certain embodiments, R_1 is unsubstituted ethyl. In certain embodiments, R_1 is substituted ethyl. In certain embodiments, R_1 is ethyl substituted with 1-2 X, wherein each X is independently selected from methyl, trifluoromethyl, ethoxy, isopropoxy, trifluoromethoxy, trifluoroethoxy, and cyclopropoxy. In certain embodiments, R_1 is ethyl substituted with X, wherein X is selected from trifluoromethyl, ethoxy, isopropoxy, trifluoromethoxy, trifluoroethoxy, and cyclopropoxy. In certain embodiments, R_1 is ethyl substituted with 2 X, wherein each X is independently selected from methyl and trifluoromethoxy.

[00140] In certain embodiments, R_1 is unsubstituted or substituted n-propyl. In certain embodiments, R_1 is unsubstituted n-propyl. In certain embodiments, R_1 is substituted n-propyl. In certain embodiments, R_1 is n-propyl substituted with 1-2 X, wherein each X is independently

selected from methyl and trifluoromethyl. In certain embodiments, R_1 is n-propyl substituted with X, wherein X is selected from methyl and trifluoromethyl. In certain embodiments, R_1 is n-propyl substituted with 2 X, wherein each X is methyl.

[00141] In certain embodiments, R_1 is unsubstituted or substituted n-butyl. In certain embodiments, R_1 is unsubstituted n-butyl. In certain embodiments, R_1 is substituted n-butyl. In certain embodiments, R_1 is n-butyl substituted with X, wherein X is selected from methyl and ethyl.

[00142] In certain embodiments, R_1 is selected from:



[00143] In certain embodiments, R_1 is unsubstituted or substituted C_{3-6} cycloalkyl. In certain embodiments, R_1 is unsubstituted C_{3-6} cycloalkyl. In certain embodiments, R_1 is unsubstituted or substituted C_{3-6} cycloalkyl. In certain embodiments, R_1 is C_{3-6} cycloalkyl substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro, methyl, and trifluoromethyl. In certain embodiments, R_1 is C_{3-6} cycloalkyl substituted with X, wherein X is selected from the group consisting of fluoro, methyl, and trifluoromethyl. In certain embodiments, R_1 is C_{3-6} cycloalkyl substituted with 2 X, wherein each X is independently selected from the group consisting of fluoro, methyl, and trifluoromethyl.

[00144] In certain embodiments, R_1 is unsubstituted or substituted cyclopropyl. In certain embodiments, R_1 is unsubstituted cyclopropyl. In certain embodiments, R_1 is substituted cyclopropyl. In certain embodiments, R_1 is cyclopropyl substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro, methyl, and trifluoromethyl. In certain embodiments, R_1 is cyclopropyl substituted with X, wherein X is selected from methyl and trifluoromethyl. In certain embodiments, R_1 is cyclopropyl substituted with 2 X, wherein each X is fluoro.

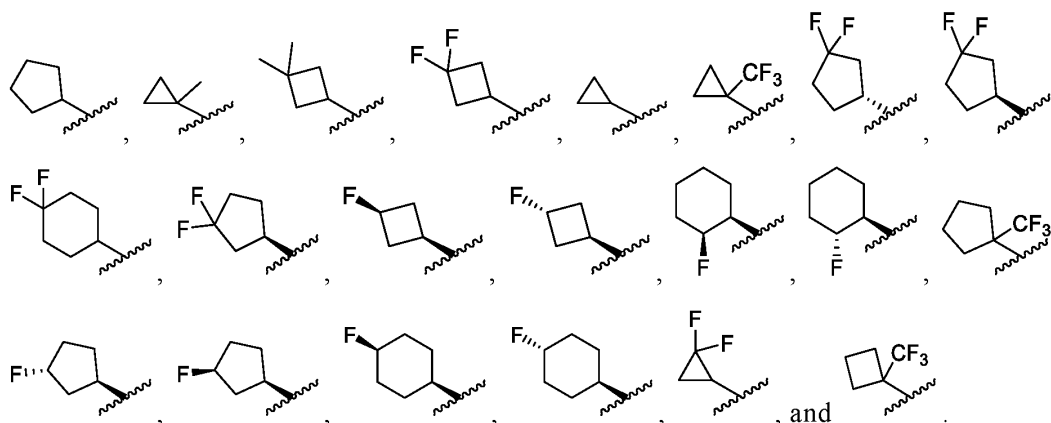
[00145] In certain embodiments, R_1 is unsubstituted or substituted cyclobutyl. In certain embodiments, R_1 is unsubstituted cyclobutyl. In certain embodiments, R_1 is substituted cyclobutyl. In certain embodiments, R_1 is cyclobutyl substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro, methyl, and trifluoromethyl. In

certain embodiments, R_1 is cyclobutyl substituted with X, wherein X is selected from fluoro and trifluoromethyl. In certain embodiments, R_1 is cyclobutyl substituted with 2 X, wherein each X is independently selected from fluoro and methyl.

[00146] In certain embodiments, R_1 is unsubstituted or substituted cyclopentyl. In certain embodiments, R_1 is unsubstituted cyclopentyl. In certain embodiments, R_1 is substituted cyclopentyl. In certain embodiments, R_1 is cyclopentyl substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro and trifluoromethyl. In certain embodiments, R_1 is cyclopentyl substituted with X, wherein X is selected from fluoro and trifluoromethyl. In certain embodiments, R_1 is cyclopentyl substituted with 2 X, wherein each X is fluoro.

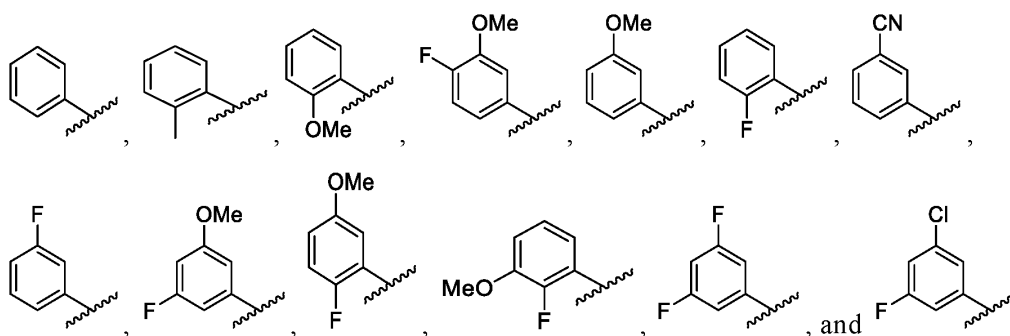
[00147] In certain embodiments, R_1 is unsubstituted or substituted cyclohexyl. In certain embodiments, R_1 is unsubstituted cyclohexyl. In certain embodiments, R_1 is substituted cyclohexyl. In certain embodiments, R_1 is cyclohexyl substituted with 1-2 X, wherein X is fluoro. In certain embodiments, R_1 is cyclohexyl substituted with X, wherein X is fluoro. In certain embodiments, R_1 is cyclohexyl substituted with 2 X, wherein X is fluoro.

[00148] In certain embodiments, R_1 is selected from:

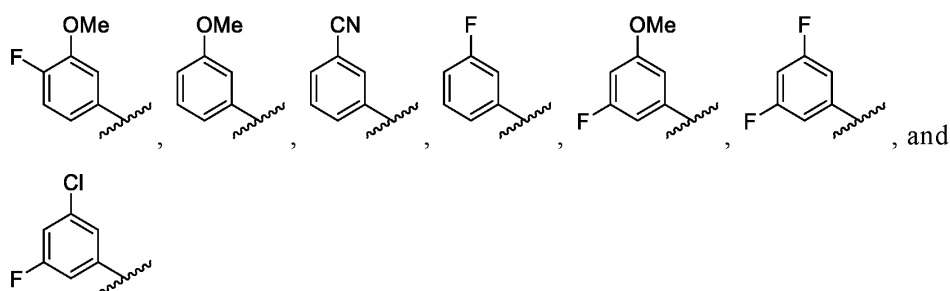


[00149] In certain embodiments, R_1 is unsubstituted or substituted phenyl. In certain embodiments, R_1 is unsubstituted phenyl. In certain embodiments, R_1 is substituted phenyl. In certain embodiments, R_1 is phenyl substituted with 1-2 X, wherein each X is independently selected from fluoro, chloro, methyl, methoxy, and CN. In certain embodiments, R_1 is phenyl substituted with X, wherein X is selected from fluoro, methyl, methoxy, and CN. In certain embodiments, R_1 is phenyl substituted with 2 X, wherein each X is independently selected from fluoro, chloro, methyl, methoxy, and CN.

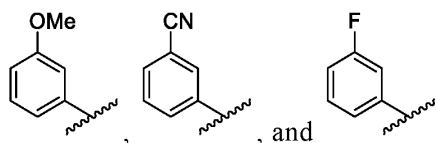
[00150] In certain embodiments, R_1 is selected from:



[00151] In certain embodiments, R_1 is selected from:



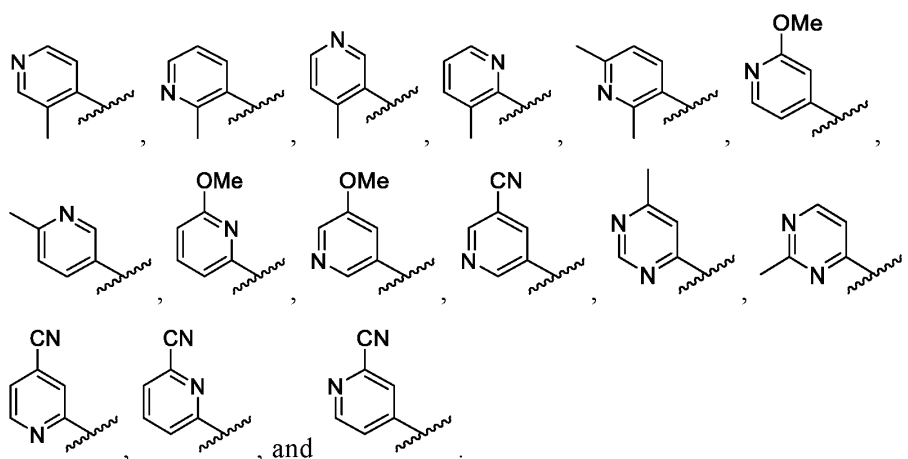
[00152] In certain embodiments, R₁ is selected from:



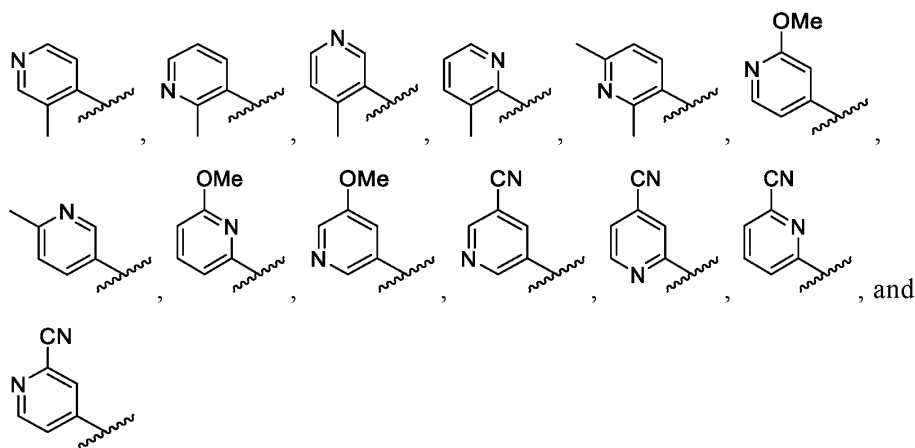
[00153] In certain embodiments, R₁ is unsubstituted or substituted pyridinyl. In certain embodiments, R₁ is unsubstituted pyridinyl. In certain embodiments, R₁ is pyridinyl substituted with 1-2 X, wherein each X is independently selected from methyl, methoxy, and CN. In certain embodiments, R₁ is pyridinyl substituted with X, wherein X is selected from methyl, methoxy, and CN. In certain embodiments, R₁ is pyridinyl substituted with 2 X, wherein each X is methyl.

[00154] In certain embodiments, R₁ is unsubstituted or substituted pyrimidinyl. In certain embodiments, R₁ is unsubstituted pyrimidinyl. In certain embodiments, R₁ is pyrimidinyl substituted with X, wherein X is methyl.

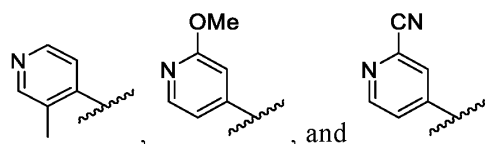
[00155] In certain embodiments, R_1 is selected from:



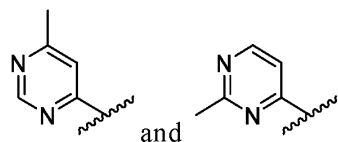
[00156] In certain embodiments, R₁ is selected from:



[00157] In certain embodiments, R_1 is selected from:



[00158] In certain embodiments, R_1 is selected from:



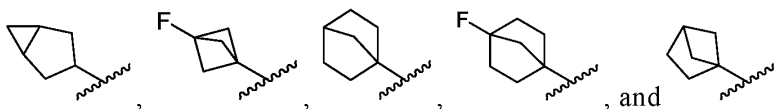
[00159] In certain embodiments, R₁ is unsubstituted or substituted C₅₋₇ bicycloalkyl. In certain embodiments, R₁ is unsubstituted C₅₋₇ bicycloalkyl. In certain embodiments, R₁ is substituted C₅₋₇ bicycloalkyl. In certain embodiments, R₁ is C₅₋₇ bicycloalkyl substituted with fluoro. In certain embodiments, one or more of the carbon atoms of the C₅₋₇ bicycloalkyl is a bridging carbon. In certain embodiments, one of the carbon atoms of the C₅₋₇ bicycloalkyl is a bridging carbon.

[00160] In certain embodiments, R_1 is unsubstituted or substituted C_5 bicycloalkyl. In certain embodiments, R_1 is unsubstituted C_5 bicycloalkyl. In certain embodiments, R_1 is substituted C_5 bicycloalkyl. In certain embodiments, R_1 is C_5 bicycloalkyl substituted with X, wherein X is fluoro. In certain embodiments, one or more of the carbon atoms of the C_5 bicycloalkyl is a bridging carbon. In certain embodiments, one of the carbon atoms of the C_5 bicycloalkyl is a bridging carbon.

[00161] In certain embodiments, R_1 is unsubstituted or substituted C_6 bicycloalkyl. In certain embodiments, R_1 is unsubstituted C_6 bicycloalkyl. In certain embodiments, one or more of the carbon atoms of the C_6 bicycloalkyl is a bridging carbon. In certain embodiments, one of the carbon atoms of the C_6 bicycloalkyl is a bridging carbon.

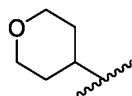
[00162] In certain embodiments, R_1 is unsubstituted or substituted C_7 bicycloalkyl. In certain embodiments, R_1 is unsubstituted C_7 bicycloalkyl. In certain embodiments, R_1 is substituted C_7 bicycloalkyl. In certain embodiments, R_1 is C_7 bicycloalkyl substituted with X, wherein X is fluoro. In certain embodiments, one or more of the carbon atoms of the C_7 bicycloalkyl is a bridging carbon. In certain embodiments, one of the carbon atoms of the C_7 bicycloalkyl is a bridging carbon.

[00163] In certain embodiments, R_1 is selected from:

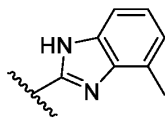


[00164] In certain embodiments, R_1 is tetrahydropyran.

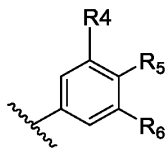
[00165] In certain embodiments, R_1 is:



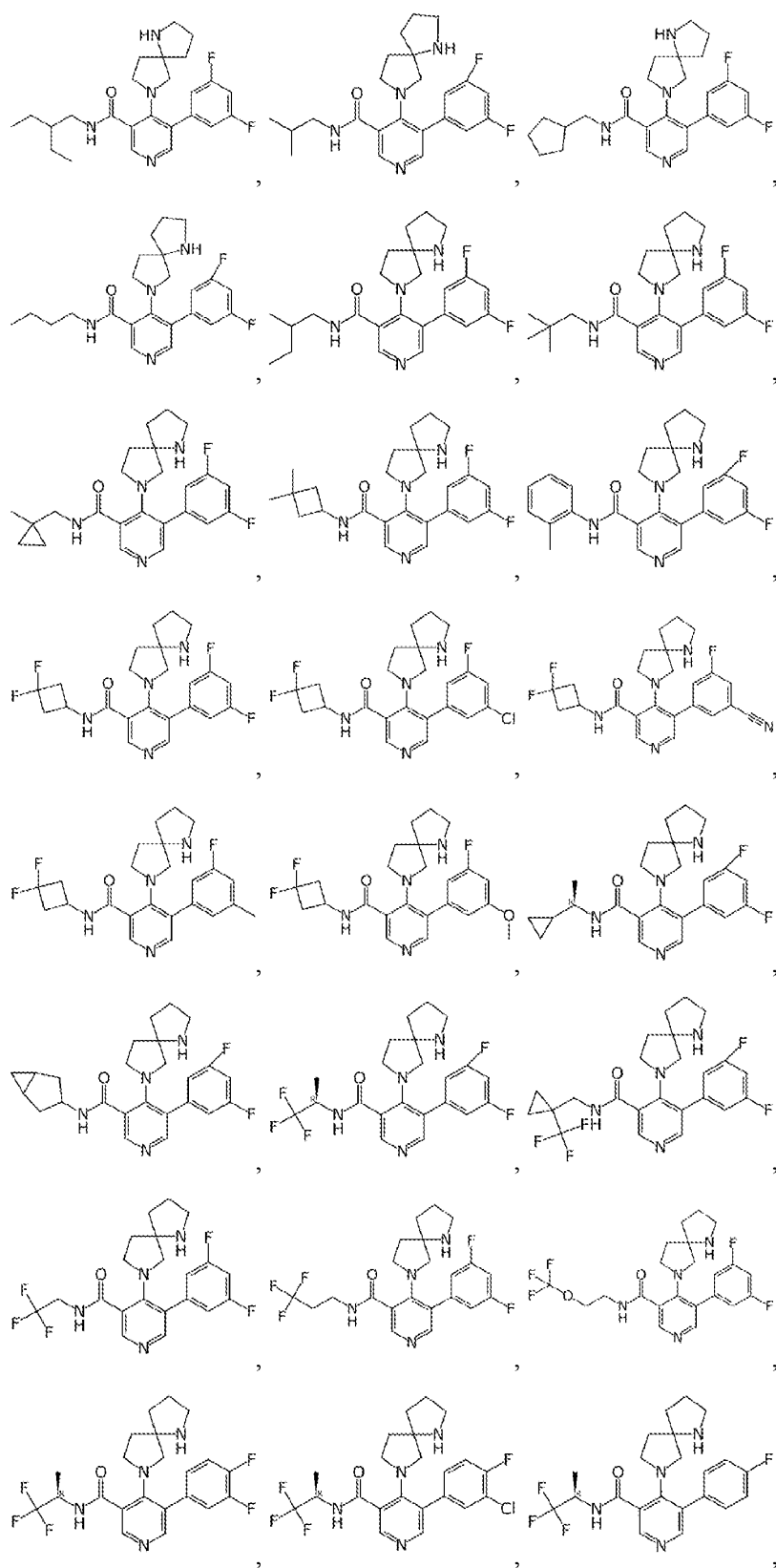
[00166] In certain embodiments, Z is

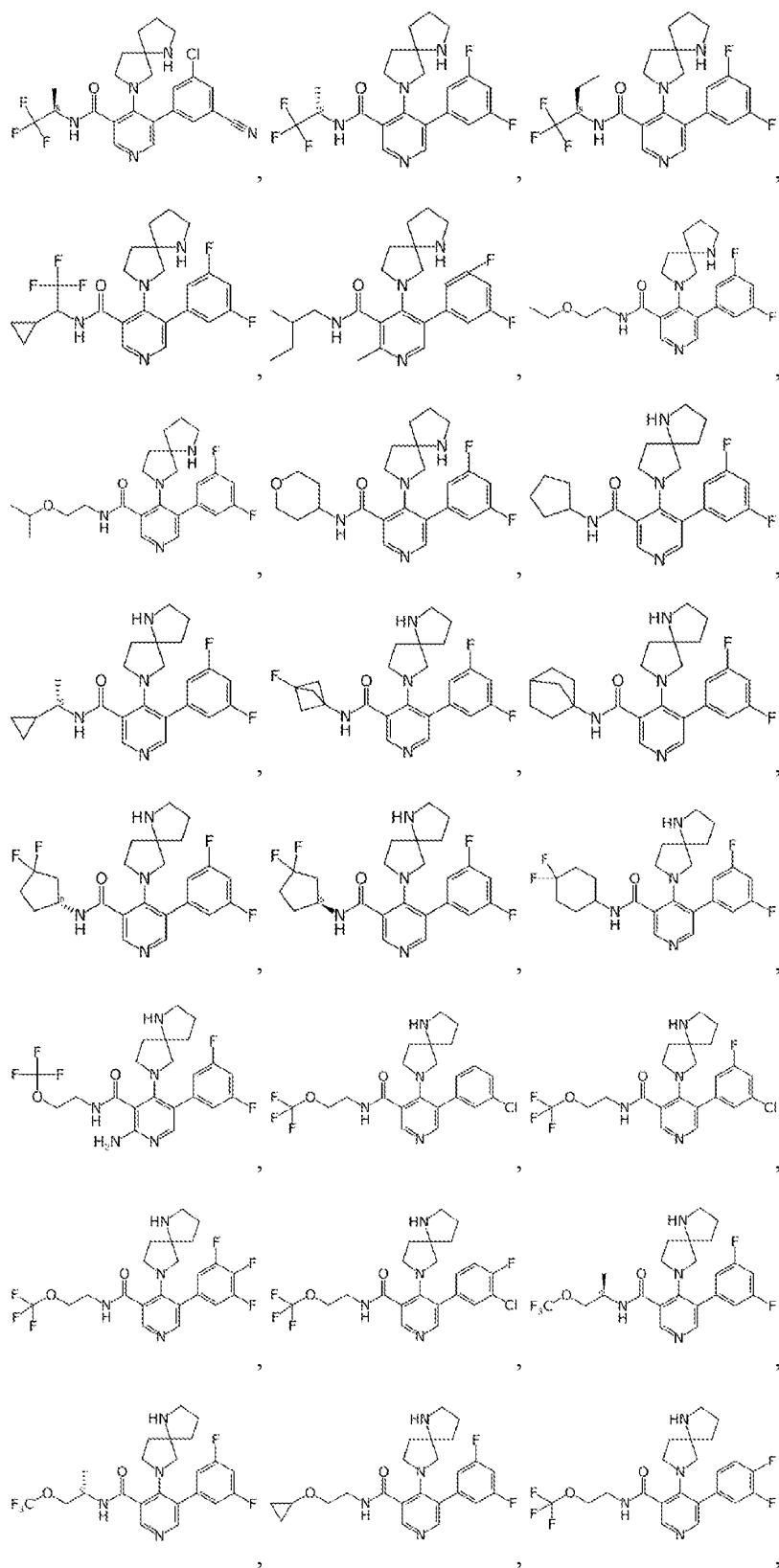


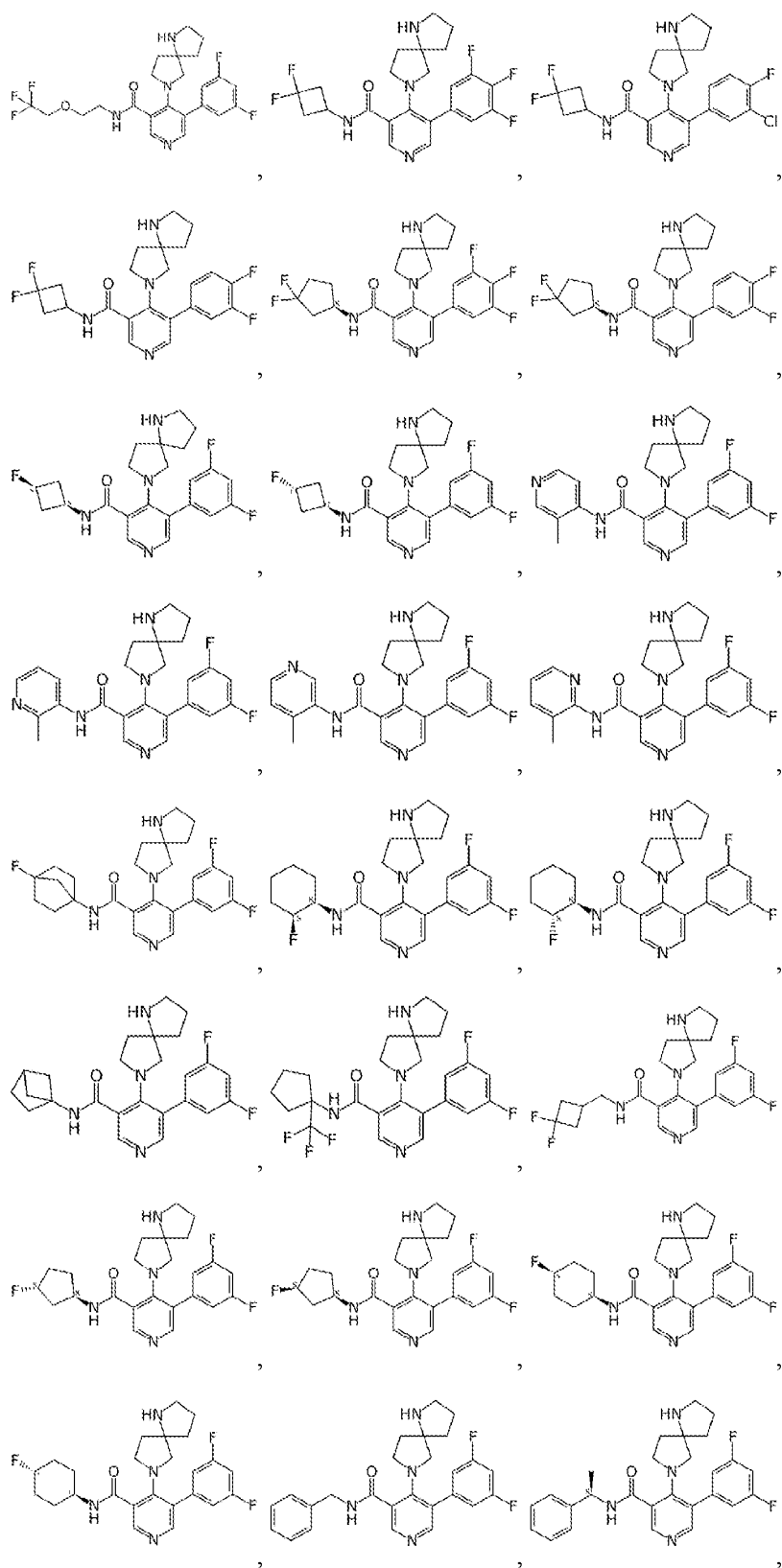
[00167] In certain embodiments, Z is:

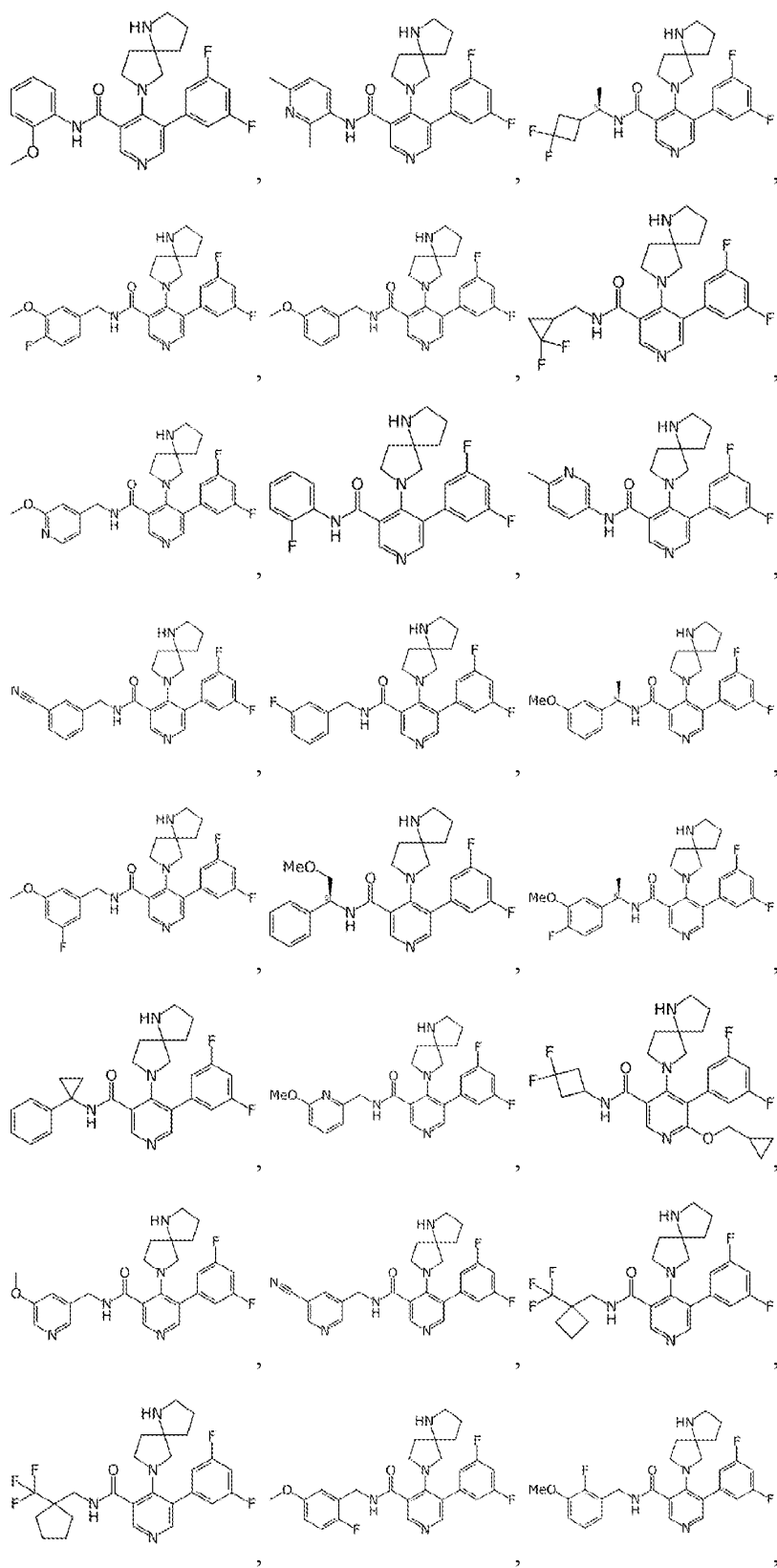


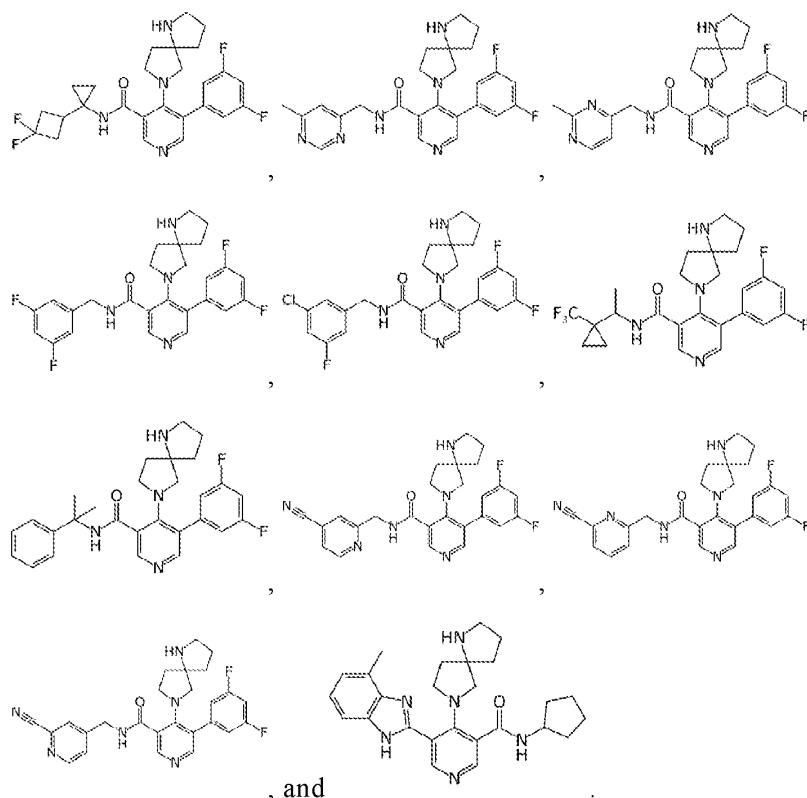
[00168] In certain embodiments, the compound of Formula (Ia) is selected from:











[00169] In certain embodiments, the compound of Formula (Ia) is a compound set forth in Table 1.

[00170] In certain embodiments, the compound of Formula (Ia) is compound 1.

[00171] In certain embodiments, the compound of Formula (Ia) is compound 2.

[00172] In certain embodiments, the compound of Formula (Ia) is compound 3.

[00173] In certain embodiments, the compound of Formula (Ia) is compound 4.

[00174] In certain embodiments, the compound of Formula (Ia) is compound 5.

[00175] In certain embodiments, the compound of Formula (Ia) is compound 6.

[00176] In certain embodiments, the compound of Formula (Ia) is compound 7.

[00177] In certain embodiments, the compound of Formula (Ia) is compound 8.

[00178] In certain embodiments, the compound of Formula (Ia) is compound 9.

[00179] In certain embodiments, the compound of Formula (Ia) is compound 10.

[00180] In certain embodiments, the compound of Formula (Ia) is compound 11.

[00181] In certain embodiments, the compound of Formula (Ia) is compound 12.

[00182] In certain embodiments, the compound of Formula (Ia) is compound 13.

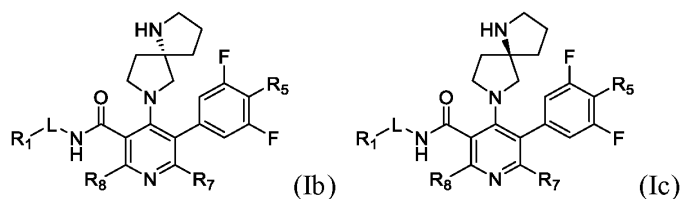
[00183] In certain embodiments, the compound of Formula (Ia) is compound 14.

[00184] In certain embodiments, the compound of Formula (Ia) is compound 15.

- [00185] In certain embodiments, the compound of Formula (Ia) is compound **16**.
- [00186] In certain embodiments, the compound of Formula (Ia) is compound **17**.
- [00187] In certain embodiments, the compound of Formula (Ia) is compound **18**.
- [00188] In certain embodiments, the compound of Formula (Ia) is compound **19**.
- [00189] In certain embodiments, the compound of Formula (Ia) is compound **20**.
- [00190] In certain embodiments, the compound of Formula (Ia) is compound **21**.
- [00191] In certain embodiments, the compound of Formula (Ia) is compound **22**.
- [00192] In certain embodiments, the compound of Formula (Ia) is compound **23**.
- [00193] In certain embodiments, the compound of Formula (Ia) is compound **24**.
- [00194] In certain embodiments, the compound of Formula (Ia) is compound **25**.
- [00195] In certain embodiments, the compound of Formula (Ia) is compound **26**.
- [00196] In certain embodiments, the compound of Formula (Ia) is compound **27**.
- [00197] In certain embodiments, the compound of Formula (Ia) is compound **28**.
- [00198] In certain embodiments, the compound of Formula (Ia) is compound **29**.
- [00199] In certain embodiments, the compound of Formula (Ia) is compound **30**.
- [00200] In certain embodiments, the compound of Formula (Ia) is compound **31**.
- [00201] In certain embodiments, the compound of Formula (Ia) is compound **32**.
- [00202] In certain embodiments, the compound of Formula (Ia) is compound **33**.
- [00203] In certain embodiments, the compound of Formula (Ia) is compound **34**.
- [00204] In certain embodiments, the compound of Formula (Ia) is compound **35**.
- [00205] In certain embodiments, the compound of Formula (Ia) is compound **36**.
- [00206] In certain embodiments, the compound of Formula (Ia) is compound **37**.
- [00207] In certain embodiments, the compound of Formula (Ia) is compound **38**.
- [00208] In certain embodiments, the compound of Formula (Ia) is compound **39**.
- [00209] In certain embodiments, the compound of Formula (Ia) is compound **40**.
- [00210] In certain embodiments, the compound of Formula (Ia) is compound **41**.
- [00211] In certain embodiments, the compound of Formula (Ia) is compound **42**.
- [00212] In certain embodiments, the compound of Formula (Ia) is compound **43**.
- [00213] In certain embodiments, the compound of Formula (Ia) is compound **44**.
- [00214] In certain embodiments, the compound of Formula (Ia) is compound **45**.
- [00215] In certain embodiments, the compound of Formula (Ia) is compound **46**.
- [00216] In certain embodiments, the compound of Formula (Ia) is compound **47**.
- [00217] In certain embodiments, the compound of Formula (Ia) is compound **48**.
- [00218] In certain embodiments, the compound of Formula (Ia) is compound **49**.

- [00219] In certain embodiments, the compound of Formula (Ia) is compound 50.
- [00220] In certain embodiments, the compound of Formula (Ia) is compound 51.
- [00221] In certain embodiments, the compound of Formula (Ia) is compound 52.
- [00222] In certain embodiments, the compound of Formula (Ia) is compound 53.
- [00223] In certain embodiments, the compound of Formula (Ia) is compound 54.
- [00224] In certain embodiments, the compound of Formula (Ia) is compound 55.
- [00225] In certain embodiments, the compound of Formula (Ia) is compound 56.
- [00226] In certain embodiments, the compound of Formula (Ia) is compound 57.
- [00227] In certain embodiments, the compound of Formula (Ia) is compound 58.
- [00228] In certain embodiments, the compound of Formula (Ia) is compound 59.
- [00229] In certain embodiments, the compound of Formula (Ia) is compound 60.
- [00230] In certain embodiments, the compound of Formula (Ia) is compound 61.
- [00231] In certain embodiments, the compound of Formula (Ia) is compound 62.
- [00232] In certain embodiments, the compound of Formula (Ia) is compound 63.
- [00233] In certain embodiments, the compound of Formula (Ia) is compound 64.
- [00234] In certain embodiments, the compound of Formula (Ia) is compound 65.
- [00235] In certain embodiments, the compound of Formula (Ia) is compound 66.
- [00236] In certain embodiments, the compound of Formula (Ia) is compound 67.
- [00237] In certain embodiments, the compound of Formula (Ia) is compound 68.
- [00238] In certain embodiments, the compound of Formula (Ia) is compound 69.
- [00239] In certain embodiments, the compound of Formula (Ia) is compound 70.
- [00240] In certain embodiments, the compound of Formula (Ia) is compound 71.
- [00241] In certain embodiments, the compound of Formula (Ia) is compound 72.
- [00242] In certain embodiments, the compound of Formula (Ia) is compound 73.
- [00243] In certain embodiments, the compound of Formula (Ia) is compound 74.
- [00244] In certain embodiments, the compound of Formula (Ia) is compound 75.
- [00245] In certain embodiments, the compound of Formula (Ia) is compound 76.
- [00246] In certain embodiments, the compound of Formula (Ia) is compound 77.
- [00247] In certain embodiments, the compound of Formula (Ia) is compound 78.
- [00248] In certain embodiments, the compound of Formula (Ia) is compound 79.
- [00249] In certain embodiments, the compound of Formula (Ia) is compound 80.
- [00250] In certain embodiments, the compound of Formula (Ia) is compound 81.
- [00251] In certain embodiments, the compound of Formula (Ia) is compound 82.
- [00252] In certain embodiments, the compound of Formula (Ia) is compound 83.

- [00253] In certain embodiments, the compound of Formula (Ia) is compound **84**.
- [00254] In certain embodiments, the compound of Formula (Ia) is compound **85**.
- [00255] In certain embodiments, the compound of Formula (Ia) is compound **86**.
- [00256] In certain embodiments, the compound of Formula (Ia) is compound **87**.
- [00257] In certain embodiments, the compound of Formula (Ia) is compound **88**.
- [00258] In certain embodiments, the compound of Formula (Ia) is compound **89**.
- [00259] In certain embodiments, the compound of Formula (Ia) is compound **90**.
- [00260] In certain embodiments, the compound of Formula (Ia) is compound **100**.
- [00261] In certain embodiments, the compound of Formula (Ia) is compound **101**.
- [00262] In certain embodiments, the compound of Formula (Ia) is compound **102**.
- [00263] In certain embodiments, the compound of Formula (Ia) is compound **103**.
- [00264] In certain embodiments, the compound of Formula (Ia) is compound **104**.
- [00265] In certain embodiments, the compound of Formula (Ia) is compound **105**.
- [00266] In certain embodiments, the compound of Formula (Ia) is compound **106**.
- [00267] In certain embodiments, the compound of Formula (Ia) is compound **107**.
- [00268] In certain embodiments, R_4 , R_5 , and R_6 are halogen.
- [00269] In certain embodiments, R_4 and R_6 are halogen. In certain embodiments, R_4 and R_6 are halogen, and R_5 is hydrogen.
- [00270] In certain embodiments, R_4 and R_6 are fluoro. In certain embodiments, R_4 and R_6 are fluoro, and R_5 is hydrogen.
- [00271] In certain embodiments, the compound is a compound of Formula (Ib) or Formula (Ic), or a pharmaceutically acceptable salt thereof:



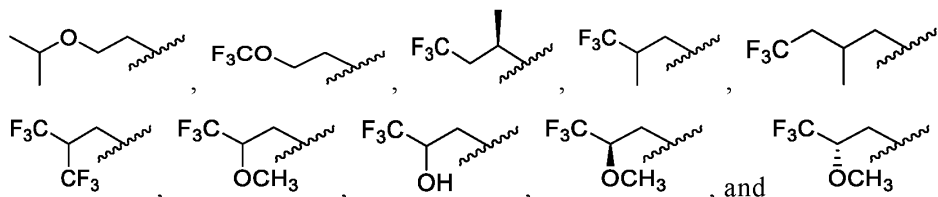
wherein:

R_1 is unsubstituted or substituted C_{1-3} alkyl, unsubstituted or substituted C_{3-4} cycloalkyl, unsubstituted or substituted C_5 bicycloalkyl, or unsubstituted or substituted 6-membered heteroaryl, wherein if R_1 is substituted then R_1 is substituted with 1-2 X, wherein each X is independently selected from F, methyl, difluoromethyl, trifluoromethyl, methoxy, difluoromethoxy, trifluoromethoxy, CN, and OH;

L is a bond or CR_2R_3 , wherein R_2 is H, and R_3 is H, methyl, or $-CH_2OCH_3$;

[00278] In certain embodiments, R_1 is unsubstituted or substituted n-propyl. In certain embodiments, R_1 is unsubstituted n-propyl. In certain embodiments, R_1 is substituted n-propyl. In certain embodiments, R_1 is n-propyl substituted with 1-2 X, wherein each X is independently selected from methyl and trifluoromethyl. In certain embodiments, R_1 is n-propyl substituted with X, wherein X is trifluoromethyl. In certain embodiments, R_1 is n-propyl substituted with 2 X, wherein each X is independently selected from methyl and trifluoromethyl.

[00279] In certain embodiments, R_1 is selected from:

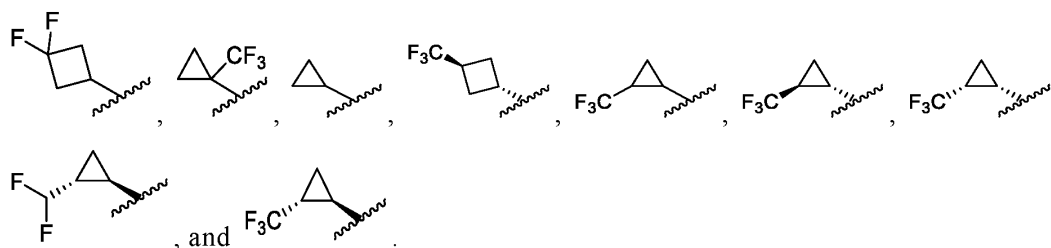


[00280] In certain embodiments, R_1 is unsubstituted or substituted C_{3-4} cycloalkyl. In certain embodiments, R_1 is unsubstituted C_{3-4} cycloalkyl. In certain embodiments, R_1 is substituted C_{3-6} cycloalkyl. In certain embodiments, R_1 is C_{3-4} cycloalkyl substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro, difluoromethyl, and trifluoromethyl. In certain embodiments, R_1 is C_{3-4} cycloalkyl substituted with X, wherein X is selected from fluoro, difluoromethyl, and trifluoromethyl. In certain embodiments, R_1 is C_{3-4} cycloalkyl substituted with 2 X, wherein each X is independently selected from fluoro, difluoromethyl, and trifluoromethyl.

[00281] In certain embodiments, R_1 is unsubstituted or substituted cyclopropyl. In certain embodiments, R_1 is unsubstituted cyclopropyl. In certain embodiments, R_1 is substituted cyclopropyl. In certain embodiments, R_1 is cyclopropyl substituted with X, wherein X is selected from difluoromethyl or trifluoromethyl.

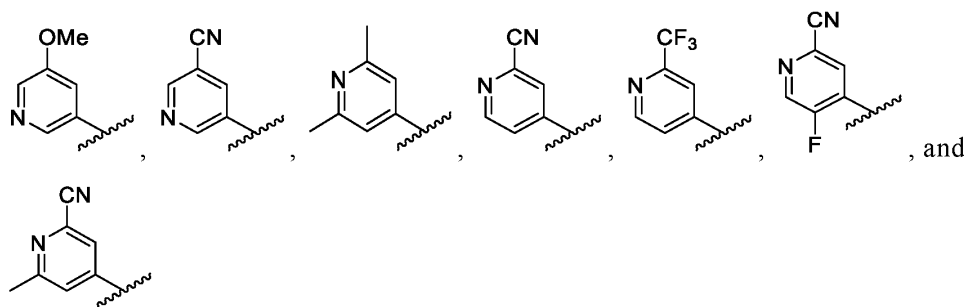
[00282] In certain embodiments, R_1 is unsubstituted or substituted cyclobutyl. In certain embodiments, R_1 is unsubstituted cyclobutyl. In certain embodiments, R_1 is substituted cyclobutyl. In certain embodiments, R_1 is cyclobutyl substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro and trifluoromethyl. In certain embodiments, R_1 is cyclobutyl substituted with X, wherein X is trifluoromethyl. In certain embodiments, R_1 is cyclobutyl substituted with 2 X, wherein X is fluoro.

[00283] In certain embodiments, R_1 is selected from:

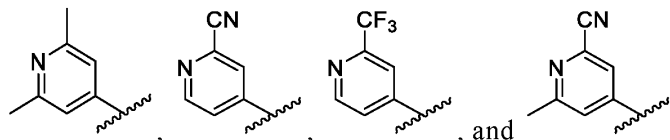


[00284] In certain embodiments, R_1 is unsubstituted or substituted pyridinyl. In certain embodiments, R_1 is unsubstituted pyridinyl. In certain embodiments, R_1 is pyridinyl substituted with 1-2 X, wherein each X is independently selected from fluoro, methyl, trifluoromethyl, methoxy, and CN. In certain embodiments, R_1 is pyridinyl substituted with X, wherein X is selected from trifluoromethyl, methoxy, and CN. In certain embodiments, R_1 is pyridinyl substituted with 2 X, wherein each X is independently selected from fluoro, methyl, and CN.

[00285] In certain embodiments, R_1 is selected from:

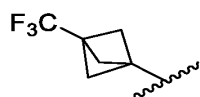


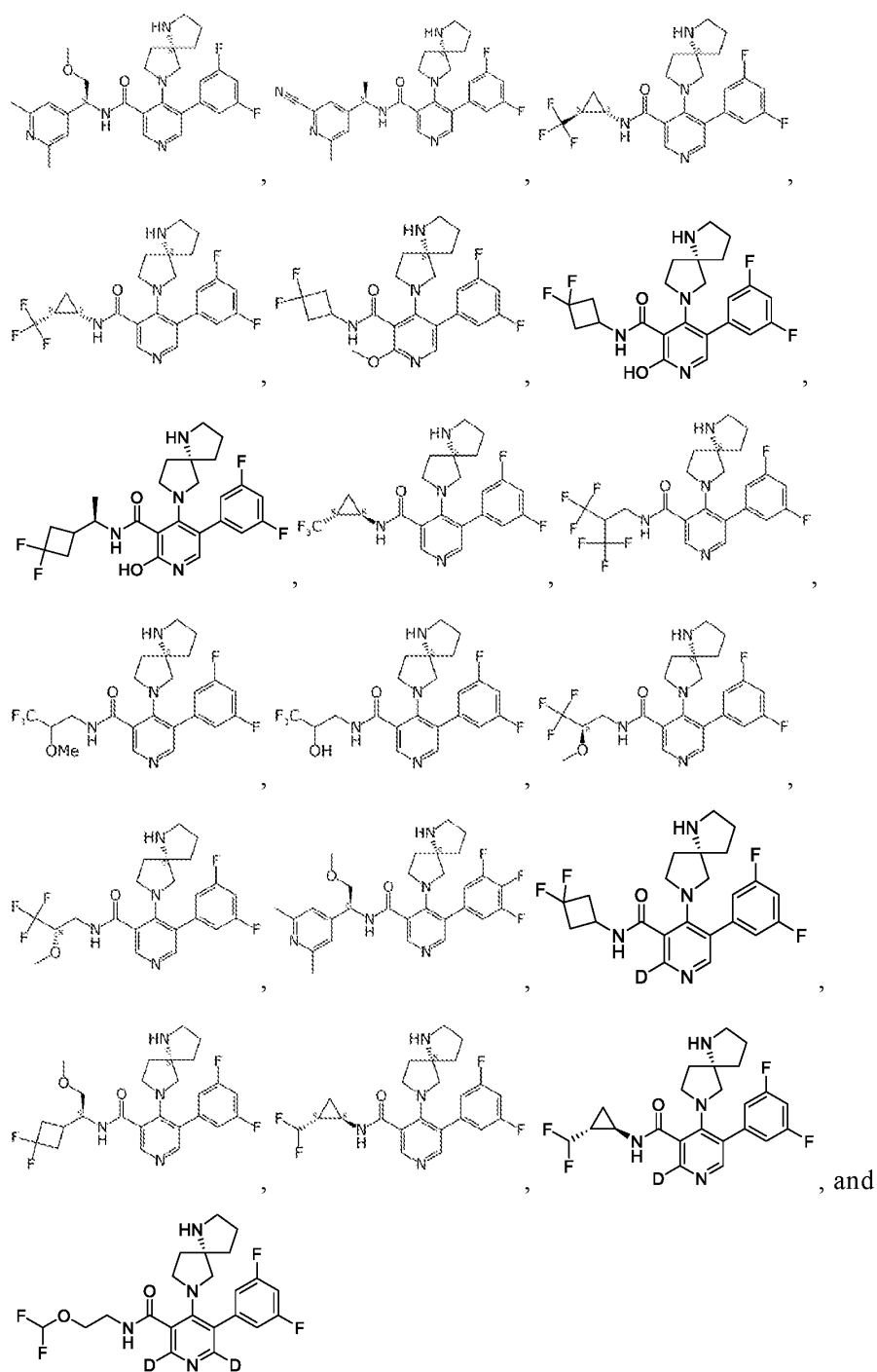
[00286] In certain embodiments, R_1 is selected from:



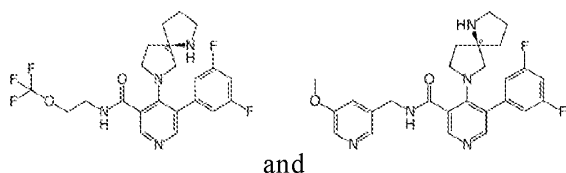
[00287] In certain embodiments, R_1 is unsubstituted or substituted C_5 bicycloalkyl. In certain embodiments, R_1 is unsubstituted C_5 bicycloalkyl. In certain embodiments, R_1 is substituted C_5 bicycloalkyl. In certain embodiments, R_1 is C_5 bicycloalkyl substituted with X, wherein X is trifluoromethyl. In certain embodiments, one or more of the carbon atoms of the C_5 bicycloalkyl is a bridging carbon. In certain embodiments, one of the carbon atoms of the C_5 bicycloalkyl is a bridging carbon.

[00288] In certain embodiments, R_1 is selected from:





[00291] In certain embodiments, the compound of Formula (Ic) is selected from:



[00292] In certain embodiments, the compound of Formula (Ib) is compound **108**.

[00293] In certain embodiments, the compound of Formula (Ic) is compound **109**.

[00294] In certain embodiments, the compound of Formula (Ic) is compound **110**.

[00295] In certain embodiments, the compound of Formula (Ib) is compound **111**.

[00296] In certain embodiments, the compound of Formula (Ib) is compound **112**.

[00297] In certain embodiments, the compound of Formula (Ib) is compound **113**.

[00298] In certain embodiments, the compound of Formula (Ib) is compound **114**.

[00299] In certain embodiments, the compound of Formula (Ib) is compound **115**.

[00300] In certain embodiments, the compound of Formula (Ib) is compound **116**.

[00301] In certain embodiments, the compound of Formula (Ib) is compound **117**.

[00302] In certain embodiments, the compound of Formula (Ib) is compound **118**.

[00303] In certain embodiments, the compound of Formula (Ib) is compound **119**.

[00304] In certain embodiments, the compound of Formula (Ib) is compound **120**.

[00305] In certain embodiments, the compound of Formula (Ib) is compound **121**.

[00306] In certain embodiments, the compound of Formula (Ib) is compound **122**.

[00307] In certain embodiments, the compound of Formula (Ib) is compound **123**.

[00308] In certain embodiments, the compound of Formula (Ib) is compound **124**.

[00309] In certain embodiments, the compound of Formula (Ib) is compound **125**.

[00310] In certain embodiments, the compound of Formula (Ib) is compound **126**.

[00311] In certain embodiments, the compound of Formula (Ib) is compound **127**.

[00312] In certain embodiments, the compound of Formula (Ib) is compound **128**.

[00313] In certain embodiments, the compound of Formula (Ib) is compound **129**.

[00314] In certain embodiments, the compound of Formula (Ib) is compound **130**.

[00315] In certain embodiments, the compound of Formula (Ib) is compound **131**.

[00316] In certain embodiments, the compound of Formula (Ib) is compound **132**.

[00317] In certain embodiments, the compound of Formula (Ib) is compound **133**.

[00318] In certain embodiments, the compound of Formula (Ib) is compound **134**.

[00319] In certain embodiments, the compound of Formula (Ib) is compound **135**.

[00320] In certain embodiments, the compound of Formula (Ib) is compound **136**.

[00321] In certain embodiments, the compound of Formula (Ib) is compound **137**.

[00322] In certain embodiments, the compound of Formula (Ib) is compound **138**.

[00323] In certain embodiments, the compound of Formula (Ib) is compound **139**.

[00324] In certain embodiments, the compound of Formula (Ib) is compound **140**.

[00325] In certain embodiments, the compound of Formula (Ib) is compound **141**.

[00326] In certain embodiments, the compound of Formula (Ib) is compound **142**.

[00327] In certain embodiments, the compound of Formula (Ib) is compound **143**.

[00328] In certain embodiments, the compound of Formula (Ib) is compound **144**.

[00329] In certain embodiments, the compound of Formula (Ib) is compound **145**.

[00330] In certain embodiments, the compound of Formula (Ib) is compound **146**.

[00331] In certain embodiments, the compound of Formula (Ib) is compound **147**.

[00332] In certain embodiments, the compound of Formula (Ib) is compound **148**.

[00333] In certain embodiments, the compound of Formula (Ib) is compound **149**.

[00334] In certain embodiments, the compound of Formula (Ib) is compound **150**.

[00335] In certain embodiments, the compound of Formula (Ib) is compound **151**.

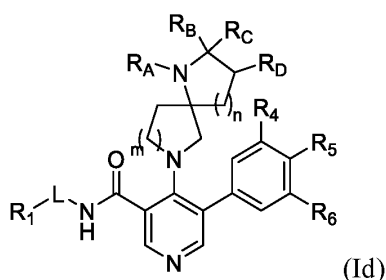
[00336] In certain embodiments, the compound of Formula (Ib) is compound **152**.

[00337] In certain embodiments, R₅ is hydrogen.

[00338] In certain embodiments, R₇ is hydrogen and R₈ is hydrogen.

[00339] In certain embodiments, R₅ is hydrogen, R₇ is hydrogen, and R₈ is hydrogen.

[00340] In certain embodiments, the compound is a compound of Formula (Id), or a pharmaceutically acceptable salt thereof:



wherein:

R₁ is unsubstituted or substituted C₁₋₄ alkyl, unsubstituted or substituted C₃₋₅ cycloalkyl, unsubstituted or substituted aryl, or unsubstituted or substituted 6-membered heteroaryl, wherein if R₁ is substituted then R₁ is substituted with 1-3 X, wherein each X is independently selected from F, Cl, methyl, ethyl, trifluoromethoxy, and CN;

L is a bond or CR₂R₃, wherein R₂ is H, and R₃ is H or methyl;

R_4 is H, F, or Cl;

R_5 is H or F;

R_6 is H, F, or Cl;

R_A is H, C(O)OEt, or C(O)Me;

R_B is H, D, or methyl;

R_C is H or D;

R_D is H or F;

m is an integer selected from 0 or 1; and

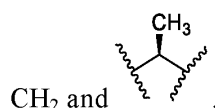
n is an integer selected from 0, 1, and 2.

[00341] In certain embodiments, L is a bond.

[00342] In certain embodiments, L is CR_2R_3 . In certain embodiments, L is CR_2R_3 and R_3 is H.

In certain embodiments, L is CR_2R_3 and R_3 is methyl.

[00343] In certain embodiments, L is selected from:

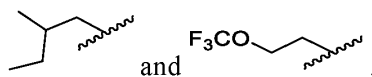


[00344] In certain embodiments, R_1 is unsubstituted or substituted C_{1-4} alkyl. In certain embodiments, R_1 is unsubstituted C_{1-4} alkyl. In certain embodiments, R_1 is substituted C_{1-4} alkyl. In certain embodiments, R_1 is C_{1-4} alkyl substituted with X, wherein X is methyl or trifluoromethoxy.

[00345] In certain embodiments, R_1 is unsubstituted or substituted ethyl. In certain embodiments, R_1 is unsubstituted ethyl. In certain embodiments, R_1 is substituted ethyl. In certain embodiments, R_1 is ethyl substituted with X, wherein X is trifluoromethoxy.

[00346] In certain embodiments, R_1 is unsubstituted or substituted n-butyl. In certain embodiments, R_1 is unsubstituted n-butyl. In certain embodiments, R_1 is substituted n-butyl. In certain embodiments, R_1 is n-butyl substituted with X, wherein X is methyl.

[00347] In certain embodiments, R_1 is selected from:



[00348] In certain embodiments, R_1 is unsubstituted or substituted C_{3-5} cycloalkyl. In certain embodiments, R_1 is unsubstituted C_{3-5} cycloalkyl. In certain embodiments, R_1 is substituted C_{3-5} cycloalkyl. In certain embodiments, R_1 is C_{3-5} cycloalkyl substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro and trifluoromethyl. In certain embodiments, R_1 is C_{3-5} cycloalkyl substituted with X, wherein X is selected from fluoro and

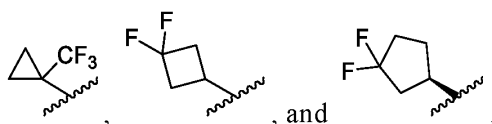
trifluoromethyl. In certain embodiments, R_1 is C_{3-5} cycloalkyl substituted with 2 X, wherein each X is independently selected from fluoro and trifluoromethyl.

[00349] In certain embodiments, R_1 is unsubstituted or substituted cyclopropyl. In certain embodiments, R_1 is unsubstituted cyclopropyl. In certain embodiments, R_1 is substituted cyclopropyl. In certain embodiments, R_1 is cyclopropyl substituted with X, wherein X is trifluoromethyl.

[00350] In certain embodiments, R_1 is unsubstituted or substituted cyclobutyl. In certain embodiments, R_1 is unsubstituted cyclobutyl. In certain embodiments, R_1 is substituted cyclobutyl. In certain embodiments, R_1 is cyclobutyl substituted with 2 X, wherein X is fluoro.

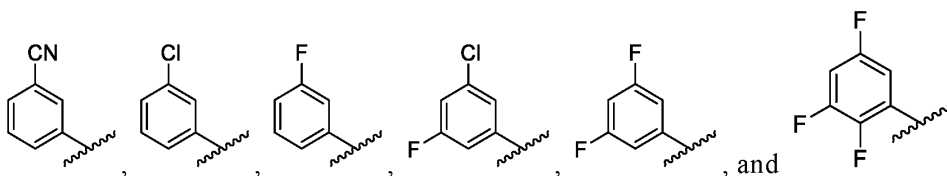
[00351] In certain embodiments, R_1 is unsubstituted or substituted cyclopentyl. In certain embodiments, R_1 is unsubstituted cyclopentyl. In certain embodiments, R_1 is substituted cyclopentyl. In certain embodiments, R_1 is cyclopentyl substituted with 2 X, wherein X is fluoro.

[00352] In certain embodiments, R_1 is selected from:

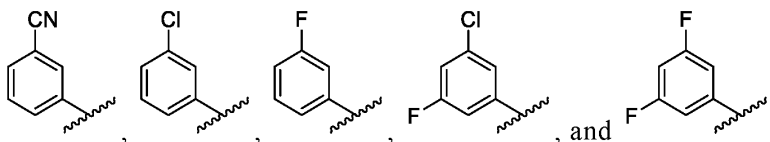


[00353] In certain embodiments, R_1 is unsubstituted or substituted phenyl. In certain embodiments, R_1 is unsubstituted phenyl. In certain embodiments, R_1 is substituted phenyl. In certain embodiments, R_1 is phenyl substituted with 1-3 X, wherein each X is independently selected from fluoro, chloro, and CN. In certain embodiments, R_1 is phenyl substituted with X, wherein X is selected from fluoro, chloro, and CN. In certain embodiments, R_1 is phenyl substituted with 2 X, wherein each X is independently selected from fluoro and chloro. In certain embodiments, R_1 is phenyl substituted with 3 X, wherein each X is fluoro.

[00354] In certain embodiments, R_1 is selected from:

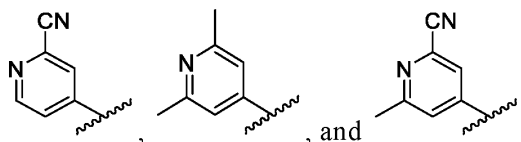


[00355] In certain embodiments, R_1 is selected from:



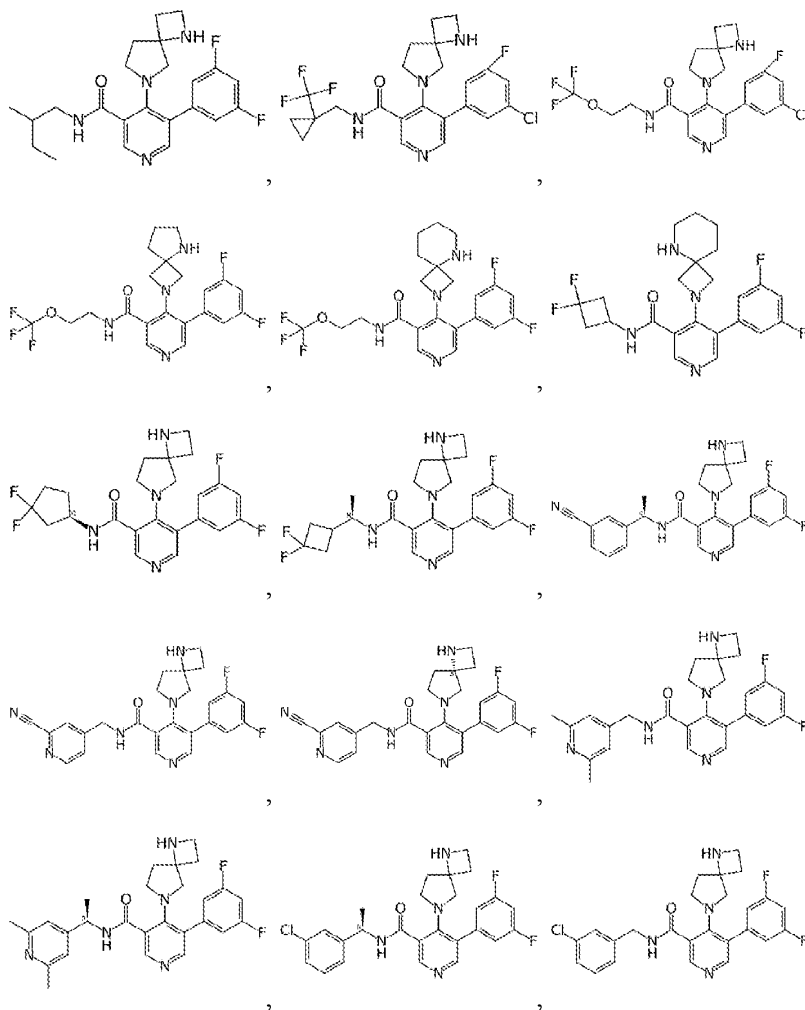
[00356] In certain embodiments, R_1 is unsubstituted or substituted pyridinyl. In certain embodiments, R_1 is unsubstituted pyridinyl. In certain embodiments, R_1 is pyridinyl substituted with 1-2 X, wherein each X is independently selected from methyl and CN. In certain embodiments, R_1 is pyridinyl substituted with X, wherein X is CN. In certain embodiments, R_1 is pyridinyl substituted with 2 X, wherein each X is independently selected from methyl and CN.

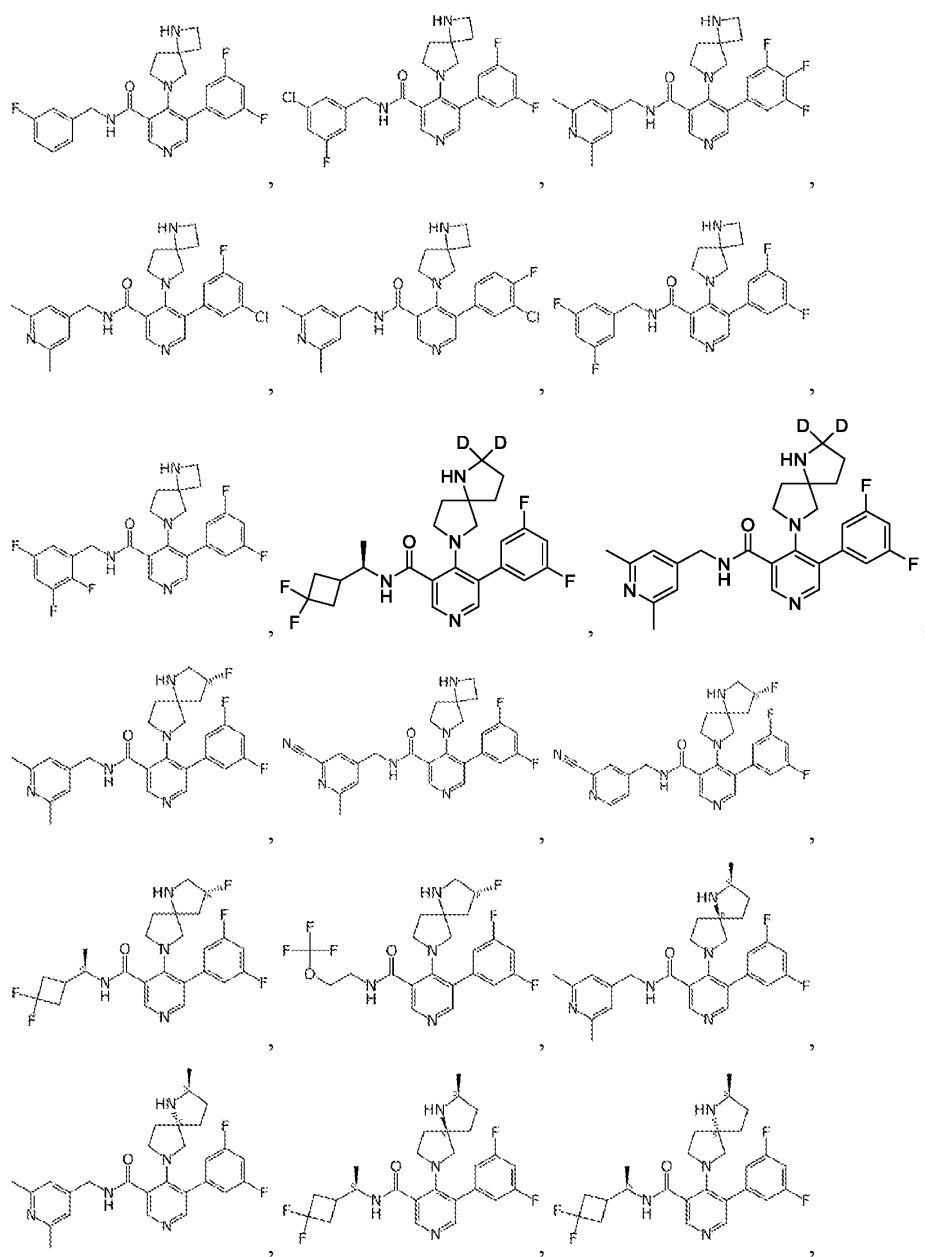
[00357] In certain embodiments, R_1 is selected from:

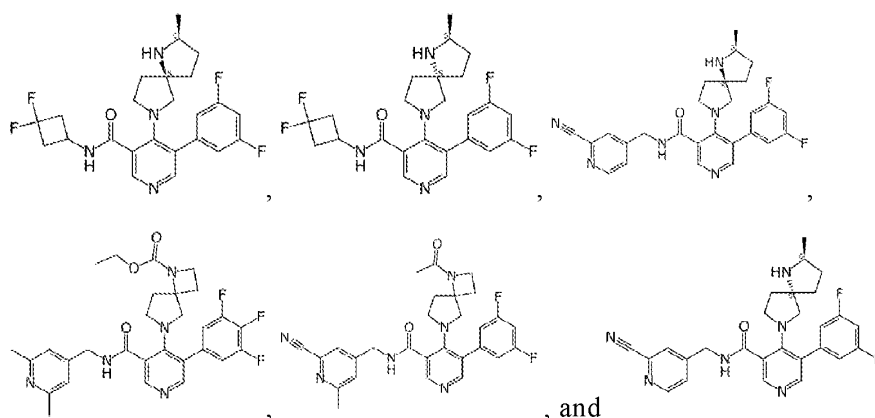


[00358] In certain embodiments, the compound of Formula (Id) is a compound set forth in Table 3.

[00359] In certain embodiments, the compound of Formula (Id) is selected from:







[00360] In certain embodiments, the compound of Formula (Id) is compound **153**.

[00361] In certain embodiments, the compound of Formula (Id) is compound **154**.

[00362] In certain embodiments, the compound of Formula (Id) is compound **155**.

[00363] In certain embodiments, the compound of Formula (Id) is compound **156**.

[00364] In certain embodiments, the compound of Formula (Id) is compound **157**.

[00365] In certain embodiments, the compound of Formula (Id) is compound **158**.

[00366] In certain embodiments, the compound of Formula (Id) is compound **159**.

[00367] In certain embodiments, the compound of Formula (Id) is compound **160**.

[00368] In certain embodiments, the compound of Formula (Id) is compound **161**.

[00369] In certain embodiments, the compound of Formula (Id) is compound **162**.

[00370] In certain embodiments, the compound of Formula (Id) is compound **163**.

[00371] In certain embodiments, the compound of Formula (Id) is compound **164**.

[00372] In certain embodiments, the compound of Formula (Id) is compound **165**.

[00373] In certain embodiments, the compound of Formula (Id) is compound **166**.

[00374] In certain embodiments, the compound of Formula (Id) is compound **167**.

[00375] In certain embodiments, the compound of Formula (Id) is compound **168**.

[00376] In certain embodiments, the compound of Formula (Id) is compound **169**.

[00377] In certain embodiments, the compound of Formula (Id) is compound **170**.

[00378] In certain embodiments, the compound of Formula (Id) is compound **171**.

[00379] In certain embodiments, the compound of Formula (Id) is compound **172**.

[00380] In certain embodiments, the compound of Formula (Id) is compound **173**.

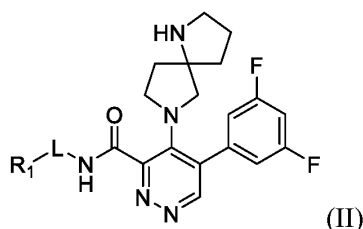
[00381] In certain embodiments, the compound of Formula (Id) is compound **174**.

[00382] In certain embodiments, the compound of Formula (Id) is compound **175**.

[00383] In certain embodiments, the compound of Formula (Id) is compound **176**.

[00384] In certain embodiments, the compound of Formula (Id) is compound **177**.

- [00385] In certain embodiments, the compound of Formula (Id) is compound **178**.
 [00386] In certain embodiments, the compound of Formula (Id) is compound **179**.
 [00387] In certain embodiments, the compound of Formula (Id) is compound **180**.
 [00388] In certain embodiments, the compound of Formula (Id) is compound **181**.
 [00389] In certain embodiments, the compound of Formula (Id) is compound **182**.
 [00390] In certain embodiments, the compound of Formula (Id) is compound **183**.
 [00391] In certain embodiments, the compound of Formula (Id) is compound **184**.
 [00392] In certain embodiments, the compound of Formula (Id) is compound **185**.
 [00393] In certain embodiments, the compound of Formula (Id) is compound **186**.
 [00394] In certain embodiments, the compound of Formula (Id) is compound **187**.
 [00395] In certain embodiments, the compound of Formula (Id) is compound **188**.
 [00396] In certain embodiments, the compound of Formula (Id) is compound **189**.
 [00397] In certain embodiments, the compound of Formula (Id) is compound **190**.
 [00398] In certain embodiments, the compound of Formula (Id) is compound **191**.
 [00399] In certain embodiments, the compound is a compound of Formula (II), or a pharmaceutically acceptable salt thereof:

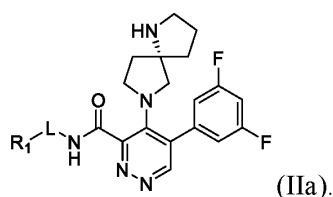


wherein:

R_1 is unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted aryl, or unsubstituted or substituted 6-membered heteroaryl, wherein if R_1 is substituted then R_1 is substituted with 1-2 X, wherein each X is independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} fluoroalkyl, C_{1-6} fluoroalkoxy, and CN; and

L is a bond or CR_2R_3 , wherein R_2 is H, and R_3 is H or methyl.

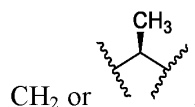
- [00400] In certain embodiments, the compound is a compound of Formula (IIa), or a pharmaceutically acceptable salt thereof:



[00401] In certain embodiments, L is a bond.

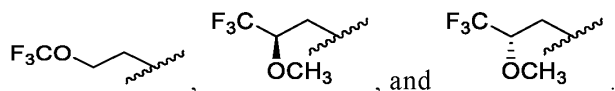
[00402] In certain embodiments, L is CR_2R_3 . In certain embodiments, L is CR_2R_3 and R_3 is H. In certain embodiments, L is CR_2R_3 and R_3 is methyl.

[00403] In certain embodiments, L is selected from:



[00404] In certain embodiments, R_1 is unsubstituted or substituted ethyl. In certain embodiments, R_1 is unsubstituted ethyl. In certain embodiments, R_1 is substituted ethyl. In certain embodiments, R_1 is ethyl substituted with 1-2 X, wherein each X is independently selected from methoxy and trifluoromethoxy. In certain embodiments, R_1 is ethyl substituted with X, wherein X is trifluoromethoxy. In certain embodiments, R_1 is ethyl substituted with 2 X, wherein each X is independently selected methoxy and trifluoromethoxy.

[00405] In certain embodiments, R_1 is selected from:

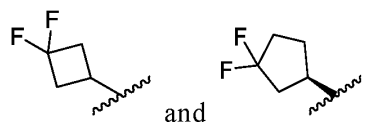


[00406] In certain embodiments, R_1 is unsubstituted or substituted C_{4-5} cycloalkyl. In certain embodiments, R_1 is unsubstituted C_{4-5} cycloalkyl. In certain embodiments, R_1 is substituted C_{4-5} cycloalkyl. In certain embodiments, R_1 is C_{4-5} cycloalkyl substituted with fluoro.

[00407] In certain embodiments, R_1 is unsubstituted or substituted cyclobutyl. In certain embodiments, R_1 is unsubstituted cyclobutyl. In certain embodiments, R_1 is substituted cyclobutyl. In certain embodiments, R_1 is cyclobutyl substituted with 2 X, wherein X is fluoro.

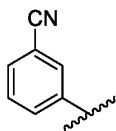
[00408] In certain embodiments, R_1 is unsubstituted or substituted cyclopentyl. In certain embodiments, R_1 is unsubstituted cyclopentyl. In certain embodiments, R_1 is substituted cyclopentyl. In certain embodiments, R_1 is cyclopentyl substituted with 2 X, wherein X is fluoro.

[00409] In certain embodiments, R_1 is selected from:



[00410] In certain embodiments, R_1 is unsubstituted or substituted phenyl. In certain embodiments, R_1 is unsubstituted phenyl. In certain embodiments, R_1 is substituted phenyl. In certain embodiments, R_1 is phenyl substituted with X, wherein X is CN.

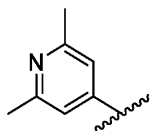
[00411] In certain embodiments, R_1 is:



[00412] In certain embodiments, R_1 is unsubstituted or substituted pyridinyl.

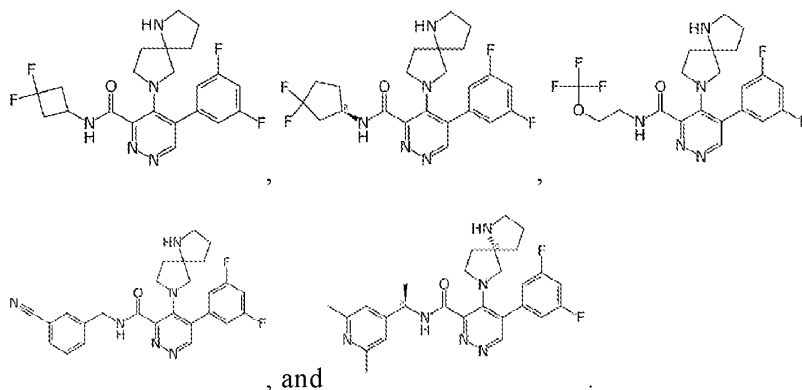
[00413] In certain embodiments, R_1 is unsubstituted or substituted pyridinyl. In certain embodiments, R_1 is unsubstituted pyridinyl. In certain embodiments, R_1 is pyridinyl substituted with 2 X, wherein X is methyl.

[00414] In certain embodiments, R_1 is :

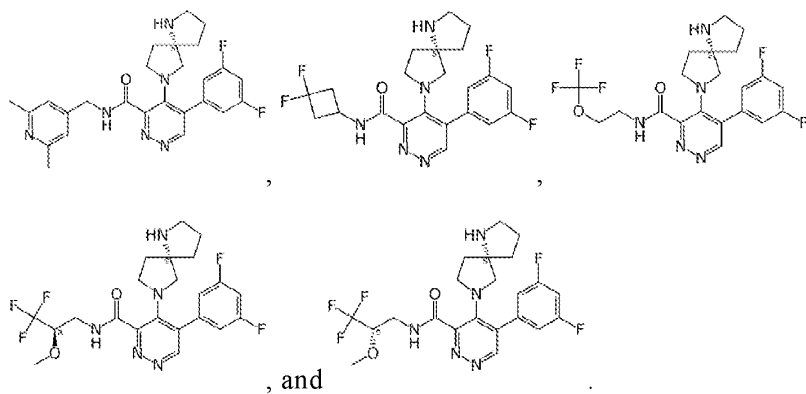


[00415] In certain embodiments, the compound of Formula (II) or Formula (IIa) is a compound as set forth in Table 4.

[00416] In certain embodiments, the compound of Formula (II) is selected from:



[00417] In certain embodiments, the compound of Formula (IIa) is selected from:



- [00418] In certain embodiments, the compound of Formula (II) is compound **192**.
[00419] In certain embodiments, the compound of Formula (II) is compound **193**.
[00420] In certain embodiments, the compound of Formula (II) is compound **194**.
[00421] In certain embodiments, the compound of Formula (II) is compound **195**.
[00422] In certain embodiments, the compound of Formula (IIa) is compound **196**.
[00423] In certain embodiments, the compound of Formula (IIa) is compound **197**.
[00424] In certain embodiments, the compound of Formula (IIa) is compound **198**.
[00425] In certain embodiments, the compound of Formula (IIa) is compound **199**.
[00426] In certain embodiments, the compound of Formula (IIa) is compound **200**.
[00427] In certain embodiments, the compound of Formula (IIa) is compound **201**.
[00428] Exemplary compounds described herein include the compounds described in the following Tables:

[00429] **Table 1: Compounds of formula (Ia):**

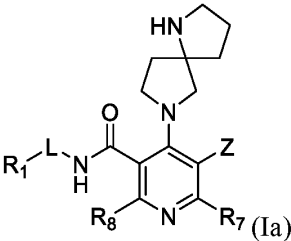


Table 1: Compounds of Formula (Ia)								
Compound	L	R1	Z	R4	R5	R6	R7	R8
1	Bond			F	H	F	H	H

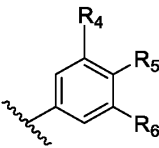
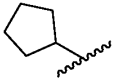
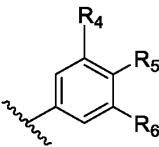
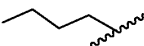
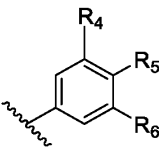
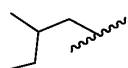
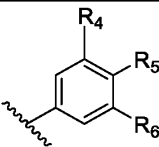
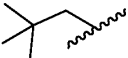
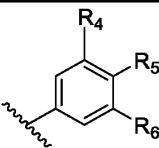
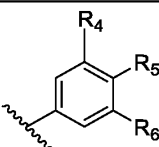
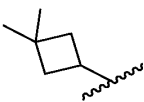
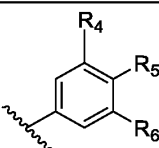
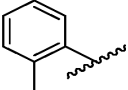
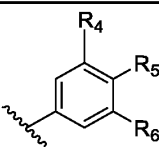
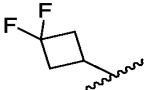
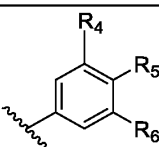
Table 1: Compounds of Formula (Ia)								
Compound	L	R1	Z	R4	R5	R6	R7	R8
2	Bond			F	H	F	H	H
3	CH ₂			F	H	F	H	H
4	Bond			F	H	F	H	H
5	Bond			F	H	F	H	H
6	Bond			F	H	F	H	H
7	CH ₂			F	H	F	H	H
8	Bond			F	H	F	H	H
9	Bond			F	H	F	H	H
10	Bond			F	H	F	H	H

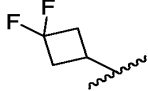
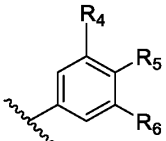
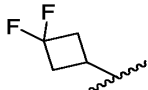
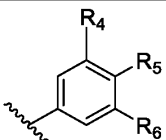
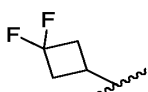
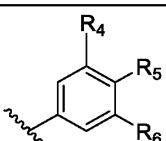
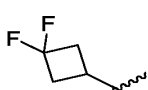
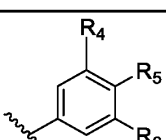
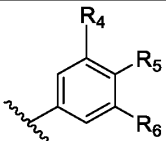
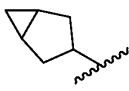
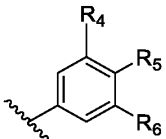
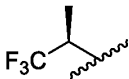
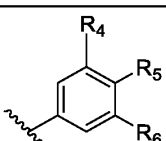
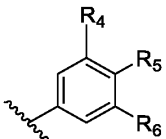
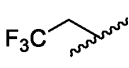
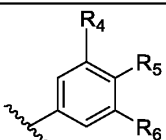
Table 1: Compounds of Formula (Ia)								
Compound	L	R1	Z	R4	R5	R6	R7	R8
11	Bond			F	H	Cl	H	H
12	Bond			F	H	CN	H	H
13	Bond			F	H	CH3	H	H
14	Bond			F	H	OCH3	H	H
15				F	H	F	H	H
16	Bond			F	H	F	H	H
17	Bond			F	H	F	H	H
18	CH2			F	H	F	H	H
19	Bond			F	H	F	H	H

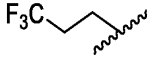
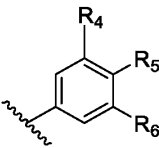
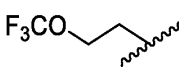
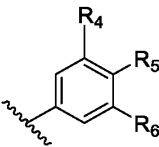
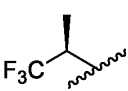
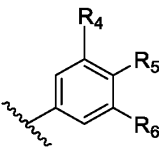
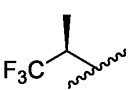
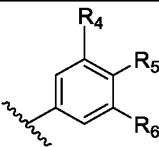
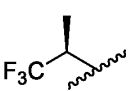
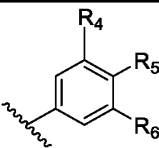
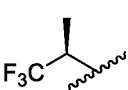
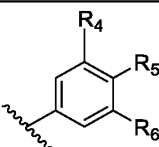
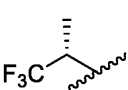
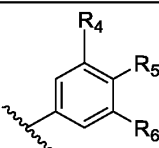
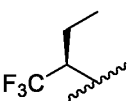
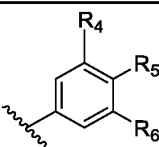
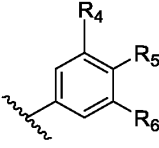
Table 1: Compounds of Formula (Ia)								
Compound	L	R1	Z	R4	R5	R6	R7	R8
20	Bond			F	H	F	H	H
21	Bond			F	H	F	H	H
22	Bond			F	F	H	H	H
23	Bond			Cl	F	H	H	H
24	Bond			H	F	H	H	H
25	Bond			Cl	H	CN	H	H
26	Bond			F	H	F	H	H
27	Bond			F	H	F	H	H
28				F	H	F	H	H

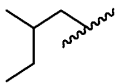
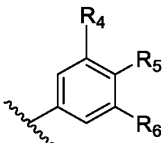
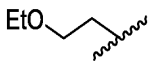
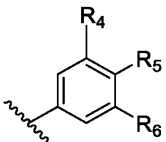
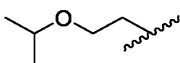
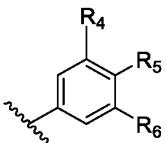
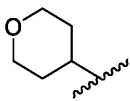
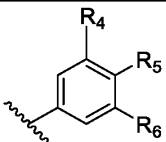
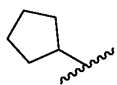
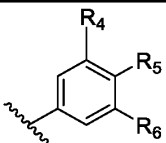
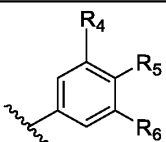
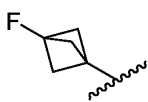
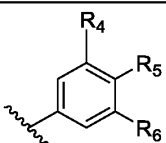
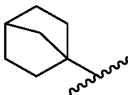
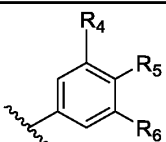
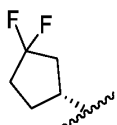
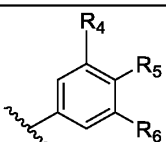
Table 1: Compounds of Formula (Ia)								
Compound	L	R1	Z	R4	R5	R6	R7	R8
29	Bond			F	H	F	H	CH ₃
30	Bond			F	H	F	H	H
31	Bond			F	H	F	H	H
32	Bond			F	H	F	H	H
33	Bond			F	H	F	H	H
34				F	H	F	H	H
35	Bond			F	H	F	H	H
36	Bond			F	H	F	H	H
37	Bond			F	H	F	H	H

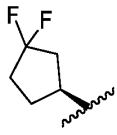
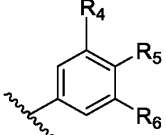
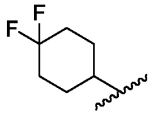
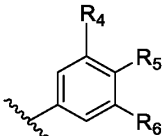
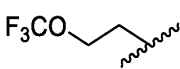
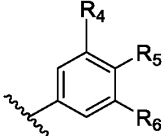
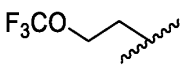
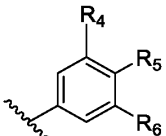
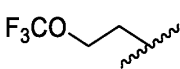
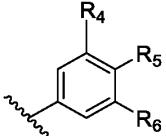
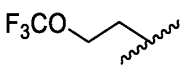
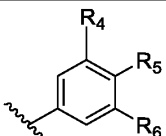
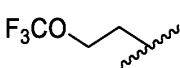
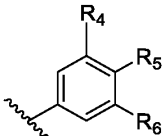
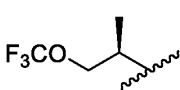
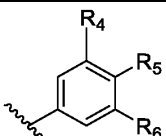
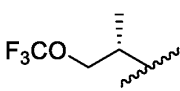
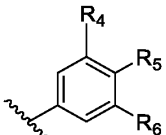
Table 1: Compounds of Formula (Ia)								
Compound	L	R1	Z	R4	R5	R6	R7	R8
38	Bond			F	H	F	H	H
39	Bond			F	H	F	H	H
40	Bond			F	H	F	H	NH ₂
41	Bond			Cl	H	H	H	H
42	Bond			Cl	H	F	H	H
43	Bond			F	F	F	H	H
44	Bond			Cl	F	H	H	H
45	Bond			F	H	F	H	H
46	Bond			F	H	F	H	H

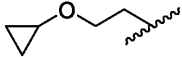
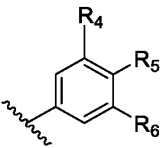
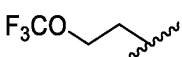
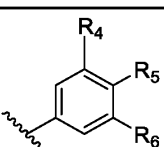
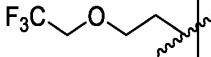
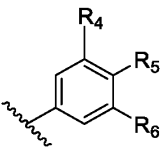
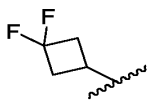
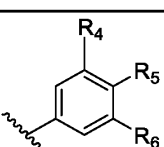
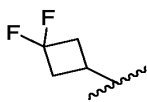
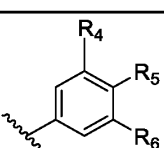
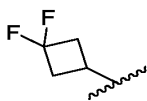
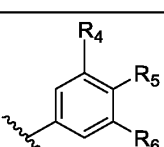
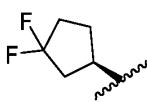
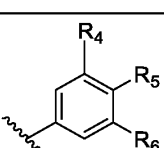
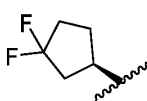
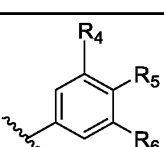
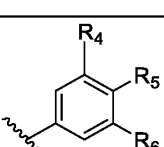
Table 1: Compounds of Formula (Ia)								
Compound	L	R1	Z	R4	R5	R6	R7	R8
47	Bond			F	H	F	H	H
48	Bond			F	F	H	H	H
49	Bond			F	H	F	H	H
50	Bond			F	F	F	H	H
51	Bond			Cl	F	H	H	H
52	Bond			F	F	H	H	H
53	Bond			F	F	F	H	H
54	Bond			F	F	H	H	H
55	Bond			F	H	F	H	H

Table 1: Compounds of Formula (Ia)								
Compound	L	R1	Z	R4	R5	R6	R7	R8
56	Bond			F	H	F	H	H
57	Bond			F	H	F	H	H
58	Bond			F	H	F	H	H
59	Bond			F	H	F	H	H
60	Bond			F	H	F	H	H
61	Bond			F	H	F	H	H
62	Bond			F	H	F	H	H
63	Bond			F	H	F	H	H
64	Bond			F	H	F	H	H

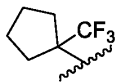
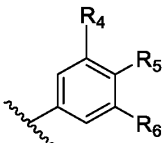
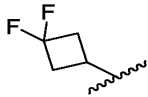
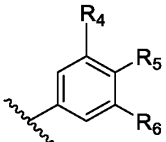
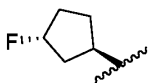
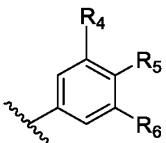
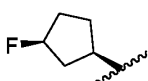
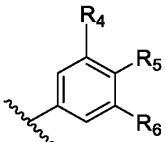
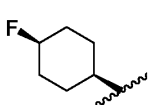
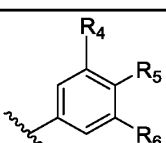
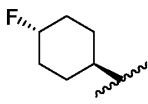
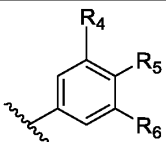
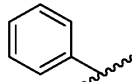
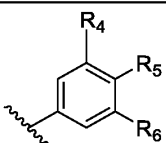
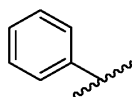
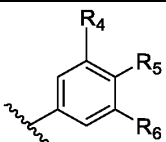
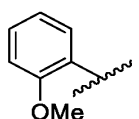
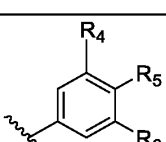
Table 1: Compounds of Formula (Ia)								
Compound	L	R1	Z	R4	R5	R6	R7	R8
65	Bond			F	H	F	H	H
66	CH ₂			F	H	F	H	H
67	Bond			F	H	F	H	H
68	Bond			F	H	F	H	H
69	Bond			F	H	F	H	H
70	Bond			F	H	F	H	H
71	CH ₂			F	H	F	H	H
72				F	H	F	H	H
73	Bond			F	H	F	H	H

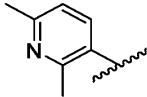
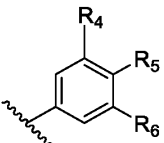
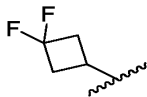
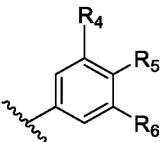
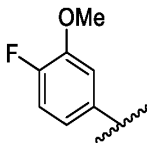
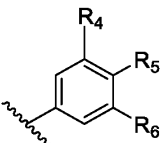
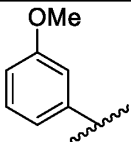
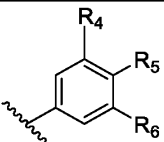
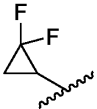
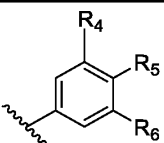
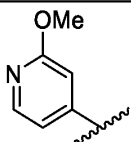
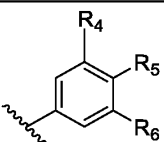
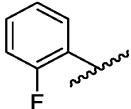
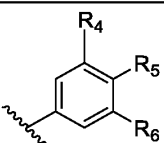
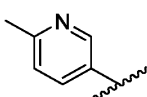
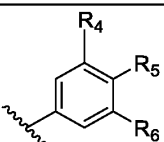
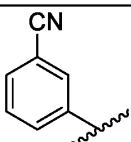
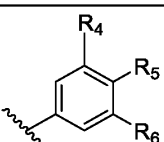
Table 1: Compounds of Formula (Ia)								
Compound	L	R1	Z	R4	R5	R6	R7	R8
74	Bond			F	H	F	H	H
75				F	H	F	H	H
76	CH ₂			F	H	F	H	H
77	CH ₂			F	H	F	H	H
78	CH ₂			F	H	F	H	H
79	CH ₂			F	H	F	H	H
80	Bond			F	H	F	H	H
81	Bond			F	H	F	H	H
82	CH ₂			F	H	F	H	H

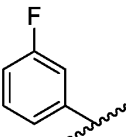
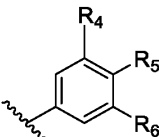
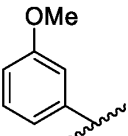
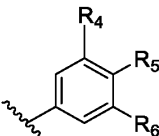
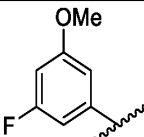
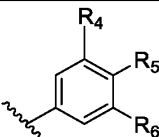
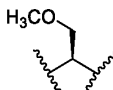
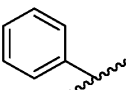
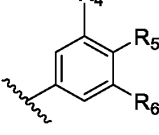
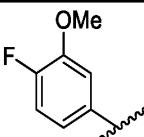
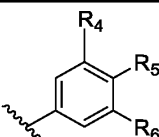
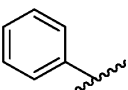
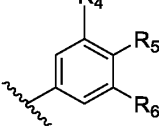
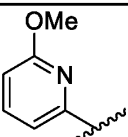
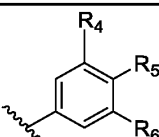
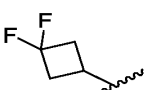
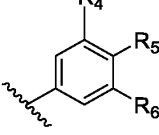
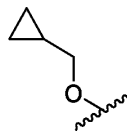
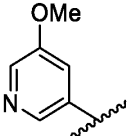
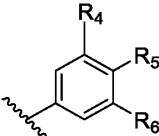
Table 1: Compounds of Formula (Ia)								
Compound	L	R1	Z	R4	R5	R6	R7	R8
83	CH ₂			F	H	F	H	H
84				F	H	F	H	H
85	CH ₂			F	H	F	H	H
86				F	H	F	H	H
87				F	H	F	H	H
88				F	H	F	H	H
89	CH ₂			F	H	F	H	H
90	Bond			F	H	F		H
91	CH ₂			F	H	F	H	H

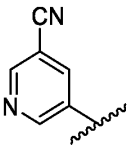
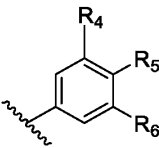
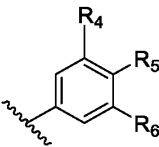
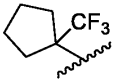
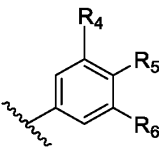
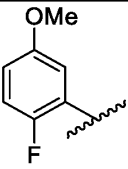
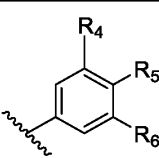
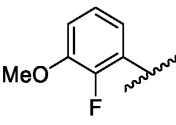
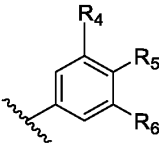
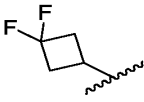
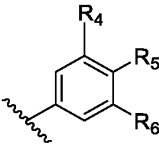
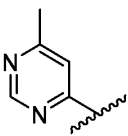
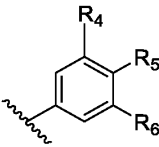
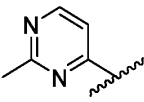
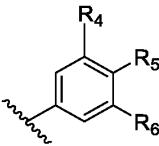
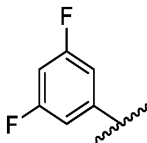
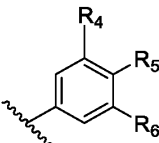
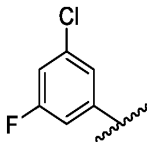
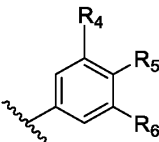
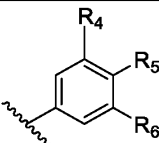
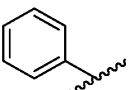
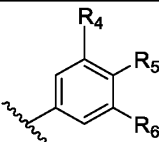
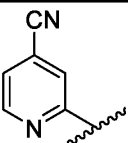
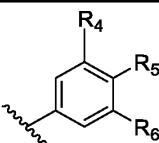
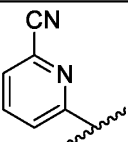
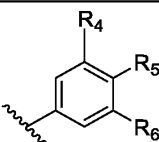
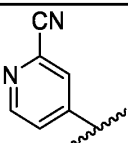
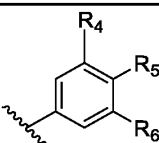
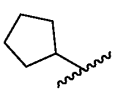
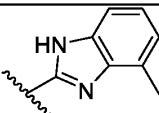
Table 1: Compounds of Formula (Ia)								
Compound	L	R1	Z	R4	R5	R6	R7	R8
92	CH ₂			F	H	F	H	H
93	CH ₂			F	H	F	H	H
94	CH ₂			F	H	F	H	H
95	CH ₂			F	H	F	H	H
96	CH ₂			F	H	F	H	H
97				F	H	F	H	H
98	CH ₂			F	H	F	H	H
99	CH ₂			F	H	F	H	H

Table 1: Compounds of Formula (Ia)								
Compound	L	R1	Z	R4	R5	R6	R7	R8
100	CH ₂			F	H	F	H	H
101	CH ₂			F	H	F	H	H
102				F	H	F	H	H
103				F	H	F	H	H
104	CH ₂			F	H	F	H	H
105	CH ₂			F	H	F	H	H
106	CH ₂			F	H	F	H	H
107	Bond			-	-	-	H	H

[00430] Names of the compounds in Table 1 are as follows:

- 1: N-2-ethylbutyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 2: N-isobutyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;

- 3: N-cyclopentylmethyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 4: N-butyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 5: N-2-methylbutyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 6: N-neopentyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 7: N-(1-methylcyclopropyl)methyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 8: N-3,3-dimethylcyclobutyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 9: N-o-tolyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 10: N-3,3-difluorocyclobutyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 11: N-3,3-difluorocyclobutyl-5-(3-chloro-5-fluorophenyl)-4-(1,7-diaza-7-spiro[4.4]nonyl)nicotinamide;
- 12: N-3,3-difluorocyclobutyl-5-(3-cyano-5-fluorophenyl)-4-(1,7-diaza-7-spiro[4.4]nonyl)nicotinamide;
- 13: N-3,3-difluorocyclobutyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3-fluoro-5-tolyl)nicotinamide;
- 14: N-3,3-difluorocyclobutyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3-fluoro-5-methoxyphenyl)nicotinamide;
- 15: N-[(R)-1-cyclopropylethyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 16: N-(bicyclo[3.1.0]hex-3-yl)-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 17: N-[(R)-2,2,2-trifluoro-1-methylethyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 18: N-[1-(trifluoromethyl)cyclopropyl]methyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 19: N-2,2,2-trifluoroethyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 20: N-3,3,3-trifluoropropyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 21: N-2-trifluoromethoxyethyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 22: N-[(R)-2,2,2-trifluoro-1-methylethyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,4-difluorophenyl)nicotinamide;
- 23: N-[(R)-2,2,2-trifluoro-1-methylethyl]-5-(3-chloro-4-fluorophenyl)-4-(1,7-diaza-7-spiro[4.4]nonyl)nicotinamide;

- 24:** N-[(R)-2,2,2-trifluoro-1-methylethyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(p-fluorophenyl)nicotinamide;
- 25:** N-[(R)-2,2,2-trifluoro-1-methylethyl]-5-(3-chloro-5-cyanophenyl)-4-(1,7-diaza-7-spiro[4.4]nonyl)nicotinamide;
- 26:** N-[(S)-2,2,2-trifluoro-1-methylethyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 27:** N-[(R)-1-(trifluoromethyl)propyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 28:** N-(1-cyclopropyl-2,2,2-trifluoroethyl)-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 29:** N-2-methylbutyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)-2-methylnicotinamide;
- 30:** N-2-ethoxyethyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 31:** N-2-isopropoxyethyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 32:** N-(tetrahydro-2H-pyran-4-yl)-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 33:** N-cyclopentyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 34:** N-[(S)-1-cyclopropylethyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 35:** N-(3-fluorobicyclo[1.1.1]pent-1-yl)-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 36:** N-1-norbornanyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 37:** N-[(R)-3,3-difluorocyclopentyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 38:** N-[(S)-3,3-difluorocyclopentyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 39:** N-4,4-difluorocyclohexyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 40:** N-2-trifluoromethoxyethyl-2-amino-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 41:** N-2-trifluoromethoxyethyl-5-(m-chlorophenyl)-4-(1,7-diaza-7-spiro[4.4]nonyl)nicotinamide;
- 42:** N-2-trifluoromethoxyethyl-5-(3-chloro-5-fluorophenyl)-4-(1,7-diaza-7-spiro[4.4]nonyl)nicotinamide;

- 43:** N-2-trifluoromethoxyethyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,4,5-trifluorophenyl)nicotinamide;
- 44:** N-2-trifluoromethoxyethyl-5-(3-chloro-4-fluorophenyl)-4-(1,7-diaza-7-spiro[4.4]nonyl)nicotinamide;
- 45:** N-[(R)-1-methyl-2-trifluoromethoxyethyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 46:** N-[(S)-1-methyl-2-trifluoromethoxyethyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 47:** N-2-cyclopropoxyethyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 48:** N-2-trifluoromethoxyethyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,4-difluorophenyl)nicotinamide;
- 49:** N-[2-(2,2,2-trifluoroethoxy)ethyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 50:** N-3,3-difluorocyclobutyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,4,5-trifluorophenyl)nicotinamide;
- 51:** N-3,3-difluorocyclobutyl-5-(3-chloro-4-fluorophenyl)-4-(1,7-diaza-7-spiro[4.4]nonyl)nicotinamide;
- 52:** N-3,3-difluorocyclobutyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,4-difluorophenyl)nicotinamide;
- 53:** N-[(R)-3,3-difluorocyclopentyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,4,5-trifluorophenyl)nicotinamide;
- 54:** N-[(R)-3,3-difluorocyclopentyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,4-difluorophenyl)nicotinamide;
- 55:** N-[(1s,3s)-3-fluorocyclobutyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 56:** N-[(1r,3r)-3-fluorocyclobutyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 57:** N-(3-methyl-4-pyridyl)-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 58:** N-(2-methyl-3-pyridyl)-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 59:** N-(4-methyl-3-pyridyl)-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 60:** N-(3-methyl-2-pyridyl)-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 61:** N-(4-fluoro-1-norbornanyl)-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;

- 62:** N-[(1R,2S)-2-fluorocyclohexyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 63:** N-[(1R,2R)-2-fluorocyclohexyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 64:** N-(bicyclo[2.1.1]hex-1-yl)-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 65:** N-1-(trifluoromethyl)cyclopentyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 66:** N-(3,3-difluorocyclobutyl)methyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 67:** N-[(1R,3R)-3-fluorocyclopentyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 68:** N-[(1R,3S)-3-fluorocyclopentyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 69:** N-[(1s,4s)-4-fluorocyclohexyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 70:** N-[(1r,4r)-4-fluorocyclohexyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 71:** N-benzyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 72:** N-[(R)-1-phenylethyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 73:** N-o-methoxyphenyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 74:** N-(2,6-dimethyl-3-pyridyl)-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 75:** N-[(R)-1-(3,3-difluorocyclobutyl)ethyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 76:** N-[(4-fluoro-3-methoxyphenyl)methyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 77:** N-(m-methoxyphenyl)methyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 78:** N-(2,2-difluorocyclopropyl)methyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 79:** N-[(2-methoxy-4-pyridyl)methyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 80:** N-o-fluorophenyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;

- 81:** N-(6-methyl-3-pyridyl)-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 82:** N-(m-cyanophenyl)methyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 83:** N-(m-fluorophenyl)methyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 84:** N-[(R)-1-(m-methoxyphenyl)ethyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 85:** N-[(3-fluoro-5-methoxyphenyl)methyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 86:** N-[(S)-2-methoxy-1-phenylethyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 87:** N-[(R)-1-(4-fluoro-3-methoxyphenyl)ethyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 88:** N-1-phenylcyclopropyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 89:** N-[(6-methoxy-2-pyridyl)methyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 90:** N-3,3-difluorocyclobutyl-6-(cyclopropylmethoxy)-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 91:** N-[(5-methoxy-3-pyridyl)methyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 92:** N-[(5-cyano-3-pyridyl)methyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 93:** N-[1-(trifluoromethyl)cyclobutyl]methyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 94:** N-[1-(trifluoromethyl)cyclopentyl]methyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 95:** N-[(2-fluoro-5-methoxyphenyl)methyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 96:** N-[(2-fluoro-3-methoxyphenyl)methyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 97:** N-[1-(3,3-difluorocyclobutyl)cyclopropyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 98:** N-[(6-methyl-4-pyrimidinyl)methyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;

- 99:** N-[(2-methyl-4-pyrimidinyl)methyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 100:** N-(3,5-difluorophenyl)methyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 101:** N-[(3-chloro-5-fluorophenyl)methyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 102:** N-{1-[1-(trifluoromethyl)cyclopropyl]ethyl}-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 103:** N-(1-methyl-1-phenylethyl)-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 104:** N-[(4-cyano-2-pyridyl)methyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 105:** N-[(6-cyano-2-pyridyl)methyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide;
- 106:** N-[(2-cyano-4-pyridyl)methyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide; and
- 107:** N-cyclopentyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(4-methyl-1H-1,3-benzimidazol-2-yl)nicotinamide.

[00431] In some embodiments, provided herein is a pharmaceutically acceptable salt of a compound that is described in Table 1.

[00432] Table 2: Compounds of Formulas (Ib) and (Ic):

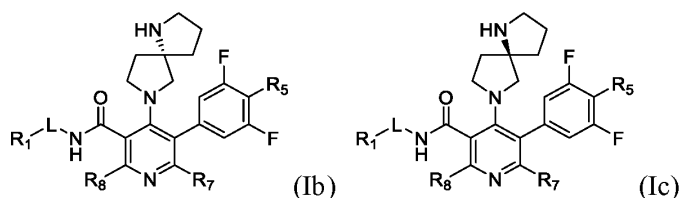


Table 2: Compounds of Formulas (Ib) and (Ic)						
Compound	Formula	L	R ₁	R ₅	R ₇	R ₈
108	Ib	Bond		H	H	H
109	Ic	Bond		H	H	H
110	Ic	CH ₂		H	H	H

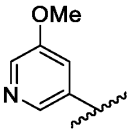
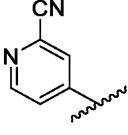
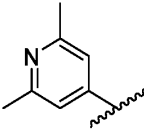
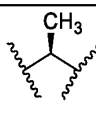
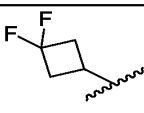
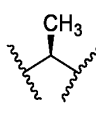
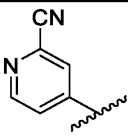
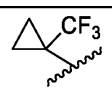
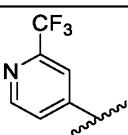
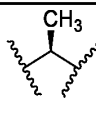
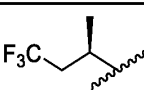
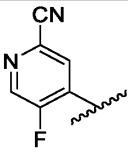
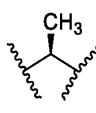
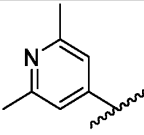
Table 2: Compounds of Formulas (Ib) and (Ic)						
Compound	Formula	L	R ₁	R ₅	R ₇	R ₈
111	Ib	CH ₂		H	H	H
112	Ib	CH ₂		H	H	H
113	Ib	CH ₂		H	H	H
114	Ib			H	H	H
115	Ib			H	H	H
116	Ib	CH ₂		H	H	H
117	Ib	CH ₂		H	H	H
118	Ib			H	H	H
119	Ib	CH ₂		H	H	H
120	Ib			H	H	H

Table 2: Compounds of Formulas (Ib) and (Ic)

Compound	Formula	L	R ₁	R ₅	R ₇	R ₈
121	Ib			H	H	H
122	Ib			H	CN	H
123	Ib	Bond		H	H	
124	Ib	Bond		H	H	H
125	Ib	Bond		H	H	H
126	Ib	Bond		H	H	H
127	Ib	Bond		H	H	H
128	Ib	Bond		H	H	H
129	Ib	CH ₂		H	H	H
130	Ib	Bond		H	H	H
131	Ib			H	H	H
132	Ib			H	H	H

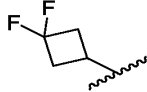
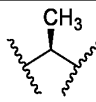
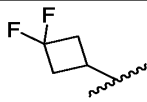
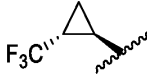
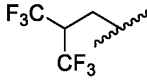
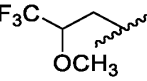
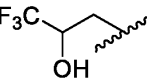
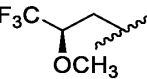
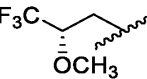
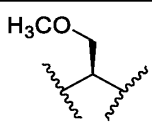
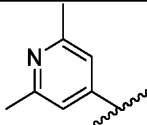
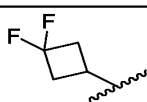
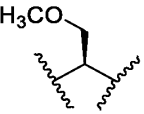
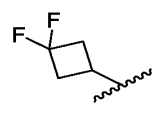
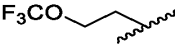
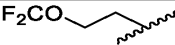
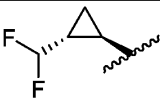
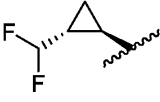
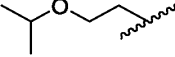
Table 2: Compounds of Formulas (Ib) and (Ic)						
Compound	Formula	L	R ₁	R ₅	R ₇	R ₈
133	Ib	Bond		H	H	H
134	Ib	Bond		H	H	H
135	Ib	Bond		H	H	OCH ₃
136	Ib	Bond		H	H	OH
137	Ib			H	H	OH
138	Ib	Bond		H	H	H
139	Ib	Bond		H	H	H
140	Ib	Bond		H	H	H
141	Ib	Bond		H	H	H
142	Ib	Bond		H	H	H
143	Ib	Bond		H	H	H
144	Ib			F	H	H
145	Ib	Bond		H	H	D

Table 2: Compounds of Formulas (Ib) and (Ic)						
Compound	Formula	L	R ₁	R ₅	R ₇	R ₈
146	Ib			H	H	H
147	Ib	Bond		H	H	D
148	Ib	Bond		H	H	D
149	Ib	Bond		H	H	D
150	Ib	Bond		H	H	H
151	Ib	Bond		H	D	H
152	Ib	Bond		H	D	D

*single enantiomer, absolute stereochemistry not determined

[00433] Names of the compounds in Table 2 are as follows:

108: N-2-trifluoromethoxyethyl-4-{(S)-1,7-diaza-7-spiro[4.4]nonyl}-5-(3,5-difluorophenyl)nicotinamide;

109: N-2-trifluoromethoxyethyl-4-{(R)-1,7-diaza-7-spiro[4.4]nonyl}-5-(3,5-difluorophenyl)nicotinamide;

110: N-[(5-methoxy-3-pyridyl)methyl]-4-{(R)-1,7-diaza-7-spiro[4.4]nonyl}-5-(3,5-difluorophenyl)nicotinamide;

111: N-[(5-methoxy-3-pyridyl)methyl]-4-{(S)-1,7-diaza-7-spiro[4.4]nonyl}-5-(3,5-difluorophenyl)nicotinamide;

112: N-[(2-cyano-4-pyridyl)methyl]-4-{(S)-1,7-diaza-7-spiro[4.4]nonyl}-5-(3,5-difluorophenyl)nicotinamide;

113: N-[(2,6-dimethyl-4-pyridyl)methyl]-4-{(S)-1,7-diaza-7-spiro[4.4]nonyl}-5-(3,5-difluorophenyl)nicotinamide;

114: N-[(R)-1-(3,3-difluorocyclobutyl)ethyl]-4-{(S)-1,7-diaza-7-spiro[4.4]nonyl}-5-(3,5-difluorophenyl)nicotinamide;

- 115:** N-[(R)-1-(2-cyano-4-pyridyl)ethyl]-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 116:** N-[1-(trifluoromethyl)cyclopropyl]methyl-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 117:** N-[[2-(trifluoromethyl)-4-pyridyl]methyl]-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 118:** N-[(R)-3,3,3-trifluoro-1-methylpropyl]-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 119:** N-[(2-cyano-5-fluoro-4-pyridyl)methyl]-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 120:** N-[(R)-1-(2,6-dimethyl-4-pyridyl)ethyl]-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 121:** N-[(R)-1-(2-cyano-5-fluoro-4-pyridyl)ethyl]-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 122:** N-[(R)-1-cyclopropylethyl]-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-6-cyano-5-(3,5-difluorophenyl)nicotinamide;
- 123:** N-3,3-difluorocyclobutyl-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)-2-(2-hydroxyethylamino)nicotinamide;
- 124:** N-3,3-difluorocyclobutyl-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 125:** N-[(1R,3S)-3-(trifluoromethyl)cyclobutyl]-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 126:** N-{3-(trifluoromethyl)bicyclo[1.1.1]pent-1-yl}-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 127:** N-(3,3,3-trifluoro-2-methylpropyl)-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 128:** N-2-(trifluoromethyl)cyclopropyl-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 129:** N-[(2-cyano-6-methyl-4-pyridyl)methyl]-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 130:** N-(4,4,4-trifluoro-2-methylbutyl)-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 131:** N-[(S)-1-(2,6-dimethyl-4-pyridyl)-2-methoxyethyl]-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;

- 132:** N-[(R)-1-(2-cyano-6-methyl-4-pyridyl)ethyl]-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 133:** N-[(1S,2S)-2-(trifluoromethyl)cyclopropyl]-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 134:** N-[(1S,2R)-2-(trifluoromethyl)cyclopropyl]-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 135:** N-3,3-difluorocyclobutyl-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)-2-methoxynicotinamide;
- 136:** N-3,3-difluorocyclobutyl-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)-2-oxo-1,2-dihydronicotinamide;
- 137:** N-[(R)-1-(3,3-difluorocyclobutyl)ethyl]-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)-2-oxo-1,2-dihydronicotinamide;
- 138:** N-[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 139:** N-[3,3,3-trifluoro-2-(trifluoromethyl)propyl]-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 140:** N-(3,3,3-trifluoro-2-methoxypropyl)-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 141:** N-(3,3,3-trifluoro-2-hydroxypropyl)-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 142:** N-[(R)-3,3,3-trifluoro-2-methoxypropyl]-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 143:** N-[(S)-3,3,3-trifluoro-2-methoxypropyl]-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 144:** N-[(S)-1-(2,6-dimethyl-4-pyridyl)-2-methoxyethyl]-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,4,5-trifluorophenyl)nicotinamide;
- 145:** N-3,3-difluorocyclobutyl-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)(2-²H)nicotinamide;
- 146:** N-[(S)-1-(3,3-difluorocyclobutyl)-2-methoxyethyl]-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide.
- 147:** N-2-trifluoromethoxyethyl-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)(2-²H)nicotinamide;
- 148:** N-[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)(2-²H)nicotinamide;

149: N-2-difluoromethoxyethyl-4-{(S)-1,7-diaza-7-spiro[4.4]nonyl}-5-(3,5-difluorophenyl)(2-²H)nicotinamide;

150: N-[(1R,2R)-2-(difluoromethyl)cyclopropyl]-4-{(S)-1,7-diaza-7-spiro[4.4]nonyl}-5-(3,5-difluorophenyl)nicotinamide;

151: N-[(1R,2R)-2-(difluoromethyl)cyclopropyl]-4-{(S)-1,7-diaza-7-spiro[4.4]nonyl}-5-(3,5-difluorophenyl)(2-²H)nicotinamide; and

152: N-2-difluoromethoxyethyl-4-{(S)-1,7-diaza-7-spiro[4.4]nonyl}-5-(3,5-difluorophenyl)(2,6-²H₂)nicotinamide.

[00434] In some embodiments, provided herein is a pharmaceutically acceptable salt of a compound that is described in Table 2.

[00435] **Table 3: Compounds of Formula (Id):**

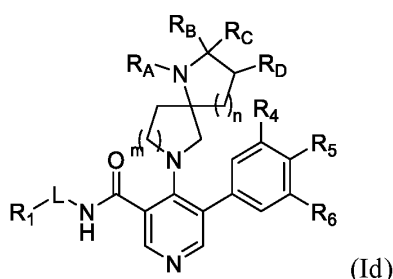


Table 3: Compounds of Formula (Id)											
Compound	L	R ₁	R ₄	R ₅	R ₆	R _A	R _B	R _C	R _D	m	n
153	Bond		F	H	F	H	H	H	H	1	0
154	CH ₂		F	H	Cl	H	H	H	H	1	0
155	Bond		F	H	Cl	H	H	H	H	1	0
156	Bond		F	H	F	H	H	H	H	0	1
157	Bond		F	H	F	H	H	H	H	0	2
158	Bond		F	H	F	H	H	H	H	0	2
159	Bond		F	H	F	H	H	H	H	1	0

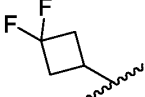
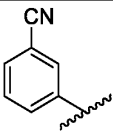
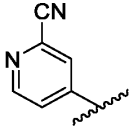
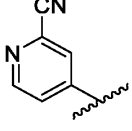
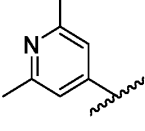
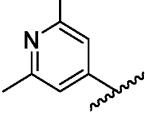
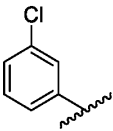
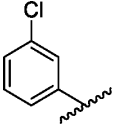
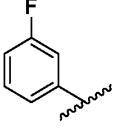
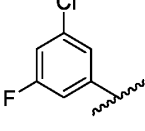
Table 3: Compounds of Formula (Id)											
Compound	L	R ₁	R ₄	R ₅	R ₆	R _A	R _B	R _C	R _D	m	n
160			F	H	F	H	H	H	H	1	0
161			F	H	F	H	H	H	H	1	0
162	CH ₂		F	H	F	H	H	H	H	1	0
163	CH ₂		F	H	F	H	H	H	H	1	0
164	CH ₂		F	H	F	H	H	H	H	1	0
165			F	H	F	H	H	H	H	1	0
166			F	H	F	H	H	H	H	1	0
167	CH ₂		F	H	F	H	H	H	H	1	0
168	CH ₂		F	H	F	H	H	H	H	1	0
169	CH ₂		F	H	F	H	H	H	H	1	0

Table 3: Compounds of Formula (Id)											
Compound	L	R ₁	R ₄	R ₅	R ₆	R _A	R _B	R _C	R _D	m	n
170	CH ₂		F	F	F	H	H	H	H	1	0
171	CH ₂		F	H	Cl	H	H	H	H	1	0
172	CH ₂		H	F	Cl	H	H	H	H	1	0
173	CH ₂		F	H	F	H	H	H	H	1	0
174	CH ₂		F	H	F	H	H	H	H	1	0
175			F	H	F	H	D	D	H	1	1
176	CH ₂		F	H	F	H	D	D	H	1	1
177	CH ₂		F	H	F	H	H	H	F	1	1
178	CH ₂		F	H	F	H	H	H	H	1	0

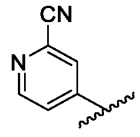
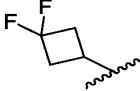
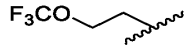
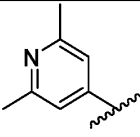
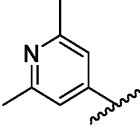
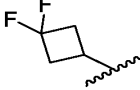
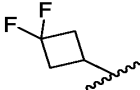
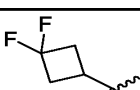
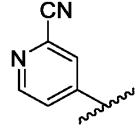
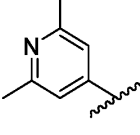
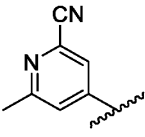
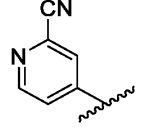
Table 3: Compounds of Formula (Id)											
Compound	L	R ₁	R ₄	R ₅	R ₆	R _A	R _B	R _C	R _D	m	n
179	CH ₂		F	H	F	H	H	H	F	1	1
180			F	H	F	H	H	H	F	1	1
181	Bond		F	H	F	H	H	H	F	1	1
182	CH ₂		F	H	F	H	CH ₃	H	H	1	1
183	CH ₂		F	H	F	H	CH ₃	H	H	1	1
184			F	H	F	H	CH ₃	H	H	1	1
185			F	H	F	H	CH ₃	H	H	1	1
186	Bond		F	H	F	H	CH ₃	H	H	1	1
187	Bond		F	H	F	H	CH ₃	H	H	1	1
188	CH ₂		F	H	F	H	CH ₃	H	H	1	1
189	CH ₂		F	F	F	C(O)OEt	H	H	H	1	0

Table 3: Compounds of Formula (Id)											
Compound	L	R ₁	R ₄	R ₅	R ₆	R _A	R _B	R _C	R _D	m	n
190	CH ₂		F	H	F	C(O)Me	H	H	H	1	0
191	CH ₂		F	H	F	H	CH ₃	H	H	1	1

[00436] Names of the compounds in Table 3 are as follows:

153: N-2-methylbutyl-4-(1,6-diaza-6-spiro[3.4]octyl)-5-(3,5-difluorophenyl)nicotinamide;

154: N-[1-(trifluoromethyl)cyclopropyl]methyl-5-(3-chloro-5-fluorophenyl)-4-(1,6-diaza-6-spiro[3.4]octyl)nicotinamide;

155: N-2-trifluoromethoxyethyl-5-(3-chloro-5-fluorophenyl)-4-(1,6-diaza-6-spiro[3.4]octyl)nicotinamide;

156: N-2-trifluoromethoxyethyl-4-(2,5-diaza-2-spiro[3.4]octyl)-5-(3,5-difluorophenyl)nicotinamide;

157: N-2-trifluoromethoxyethyl-4-(2,5-diaza-2-spiro[3.5]nonyl)-5-(3,5-difluorophenyl)nicotinamide;

158: N-3,3-difluorocyclobutyl-4-(2,5-diaza-2-spiro[3.5]nonyl)-5-(3,5-difluorophenyl)nicotinamide;

159: N-[(R)-3,3-difluorocyclopentyl]-4-(1,6-diaza-6-spiro[3.4]octyl)-5-(3,5-difluorophenyl)nicotinamide;

160: N-[(R)-1-(3,3-difluorocyclobutyl)ethyl]-4-(1,6-diaza-6-spiro[3.4]octyl)-5-(3,5-difluorophenyl)nicotinamide;

161: N-[(R)-1-(m-cyanophenyl)ethyl]-4-(1,6-diaza-6-spiro[3.4]octyl)-5-(3,5-difluorophenyl)nicotinamide;

162: N-[(2-cyano-4-pyridyl)methyl]-4-(1,6-diaza-6-spiro[3.4]octyl)-5-(3,5-difluorophenyl)nicotinamide;

163: N-[(2-cyano-4-pyridyl)methyl]-4-[(S)-1,6-diaza-6-spiro[3.4]octyl]-5-(3,5-difluorophenyl)nicotinamide;

164: N-[(2,6-dimethyl-4-pyridyl)methyl]-4-(1,6-diaza-6-spiro[3.4]octyl)-5-(3,5-difluorophenyl)nicotinamide;

- 165:** N-[(R)-1-(2,6-dimethyl-4-pyridyl)ethyl]-4-(1,6-diaza-6-spiro[3.4]octyl)-5-(3,5-difluorophenyl)nicotinamide;
- 166:** N-[(R)-1-(m-chlorophenyl)ethyl]-4-(1,6-diaza-6-spiro[3.4]octyl)-5-(3,5-difluorophenyl)nicotinamide;
- 167:** N-(m-chlorophenyl)methyl-4-(1,6-diaza-6-spiro[3.4]octyl)-5-(3,5-difluorophenyl)nicotinamide;
- 168:** N-(m-fluorophenyl)methyl-4-(1,6-diaza-6-spiro[3.4]octyl)-5-(3,5-difluorophenyl)nicotinamide;
- 169:** N-[(3-chloro-5-fluorophenyl)methyl]-4-(1,6-diaza-6-spiro[3.4]octyl)-5-(3,5-difluorophenyl)nicotinamide;
- 170:** N-[(2,6-dimethyl-4-pyridyl)methyl]-4-(1,6-diaza-6-spiro[3.4]octyl)-5-(3,4,5-trifluorophenyl)nicotinamide;
- 171:** N-[(2,6-dimethyl-4-pyridyl)methyl]-5-(3-chloro-5-fluorophenyl)-4-(1,6-diaza-6-spiro[3.4]octyl)nicotinamide;
- 172:** N-[(2,6-dimethyl-4-pyridyl)methyl]-5-(3-chloro-4-fluorophenyl)-4-(1,6-diaza-6-spiro[3.4]octyl)nicotinamide;
- 173:** N-(3,5-difluorophenyl)methyl-4-(1,6-diaza-6-spiro[3.4]octyl)-5-(3,5-difluorophenyl)nicotinamide;
- 174:** N-(2,3,5-trifluorophenyl)methyl-4-(1,6-diaza-6-spiro[3.4]octyl)-5-(3,5-difluorophenyl)nicotinamide;
- 175:** N-[(R)-1-(3,3-difluorocyclobutyl)ethyl]-4-[(2,2-²H₂)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 176:** N-[(2,6-dimethyl-4-pyridyl)methyl]-4-[(2,2-²H₂)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 177:** N-[(2,6-dimethyl-4-pyridyl)methyl]-4-[(3R)-3-fluoro-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 178:** N-[(2-cyano-6-methyl-4-pyridyl)methyl]-4-(1,6-diaza-6-spiro[3.4]octyl)-5-(3,5-difluorophenyl)nicotinamide;
- 179:** N-[(2-cyano-4-pyridyl)methyl]-4-[(3R)-3-fluoro-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 180:** N-[(R)-1-(3,3-difluorocyclobutyl)ethyl]-4-[(3R)-3-fluoro-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;
- 181:** N-2-trifluoromethoxyethyl-4-[(3R)-3-fluoro-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;

182: N-[(2,6-dimethyl-4-pyridyl)methyl]-4-[(2S,5R)-2-methyl-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;

183: N-[(2,6-dimethyl-4-pyridyl)methyl]-4-[(2S,5S)-2-methyl-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;

184: N-[(R)-1-(3,3-difluorocyclobutyl)ethyl]-4-[(2S,5R)-2-methyl-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;

185: N-[(R)-1-(3,3-difluorocyclobutyl)ethyl]-4-[(2S,5S)-2-methyl-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;

186: N-3,3-difluorocyclobutyl-4-[(2S,5R)-2-methyl-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;

187: N-3,3-difluorocyclobutyl-4-[(2S,5S)-2-methyl-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;

188: N-[(2-cyano-4-pyridyl)methyl]-4-[(2S,5R)-2-methyl-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide;

189: ethyl 6-(5-[(2,6-dimethyl-4-pyridyl)methyl]carbamoyl)-3-(3,4,5-trifluorophenyl)-4-pyridyl)-1,6-diaza-1-spiro[3.4]octanecarboxylate;

190: N-[(2-cyano-6-methyl-4-pyridyl)methyl]-4-(1-acetyl-1,6-diaza-6-spiro[3.4]octyl)-5-(3,5-difluorophenyl)nicotinamide; and

191: N-[(2-cyano-4-pyridyl)methyl]-4-[(2S,5S)-2-methyl-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)nicotinamide.

[00437] In some embodiments, provided herein is a pharmaceutically acceptable salt of a compound that is described in Table 3.

[00438] Table 4: Compounds of Formula (II) and (IIa):

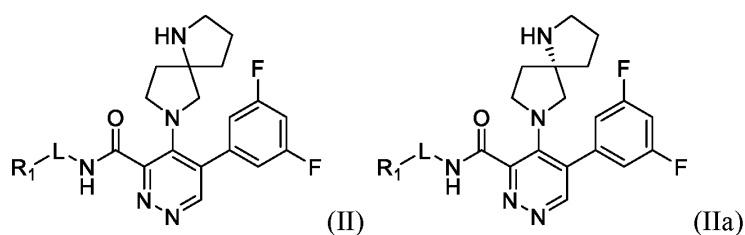
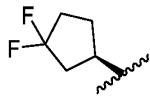
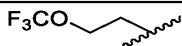
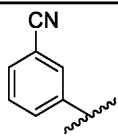
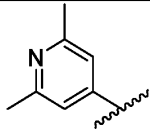
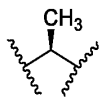
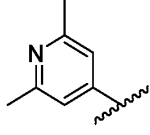
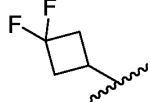
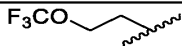
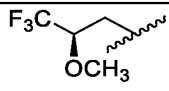
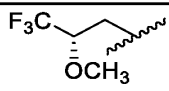


Table 4: Compounds of Formulas (II) and (IIa)			
Compound	Formula	L	R ₁
192	II	Bond	

Table 4: Compounds of Formulas (II) and (IIa)			
Compound	Formula	L	R ₁
193	II	Bond	
194	II	Bond	
195	II	CH ₂	
196	IIa	CH ₂	
197	IIa		
198	IIa	Bond	
199	IIa	Bond	
200	IIa	Bond	
201	IIa	Bond	

[00439] Names of the compounds in Table 4 are as follows:

192: N-3,3-difluorocyclobutyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)-3-pyridazinecarboxamide;

193: N-[(R)-3,3-difluorocyclopentyl]-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)-3-pyridazinecarboxamide;

194: N-2-trifluoromethoxyethyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)-3-pyridazinecarboxamide;

195: N-(m-cyanophenyl)methyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)-3-pyridazinecarboxamide;

196: N-[(2,6-dimethyl-4-pyridyl)methyl]-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)-3-pyridazinecarboxamide;

197: N-[(R)-1-(2,6-dimethyl-4-pyridyl)ethyl]-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)-3-pyridazinecarboxamide;

198: N-3,3-difluorocyclobutyl-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)-3-pyridazinecarboxamide;

199: N-2-trifluoromethoxyethyl-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)-3-pyridazinecarboxamide;

200: N-[(R)-3,3,3-trifluoro-2-methoxypropyl]-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)-3-pyridazinecarboxamide; and

201: N-[(S)-3,3,3-trifluoro-2-methoxypropyl]-4-[(S)-1,7-diaza-7-spiro[4.4]nonyl]-5-(3,5-difluorophenyl)-3-pyridazinecarboxamide.

[00440] In some embodiments, provided herein is a pharmaceutically acceptable salt of a compound that is described in Table 4.

[00441] “Pharmaceutically acceptable,” as used herein, refers a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively nontoxic, i.e., the material is administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[00442] The term “pharmaceutically acceptable salt” refers to a form of a therapeutically active agent that consists of a cationic form of the therapeutically active agent in combination with a suitable anion, or in alternative embodiments, an anionic form of the therapeutically active agent in combination with a suitable cation.

[00443] In some embodiments, pharmaceutically acceptable salts are obtained by reacting a compound of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (II), or Formula (IIa) with an acid. In some embodiments, the free base form of the compound of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (II), or Formula (IIa) is basic and is reacted with an organic acid or an inorganic acid.

[00444] In some embodiments, pharmaceutically acceptable salts are obtained by reacting a compound of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (II), or Formula (IIa) with a base. In some embodiments, the compound of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (II), or Formula (IIa) is acidic and is reacted with a base.

[00445] In some embodiments, the compounds of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (II), or Formula (IIa) possess one or more stereocenters and each stereocenter exists independently in either the R or S configuration. In some embodiments, the compound of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (II), or Formula (IIa) exists in the R configuration. In some embodiments, the compound of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (II), or Formula (IIa) exists in the S configuration. The compounds presented herein include all diastereomeric, individual enantiomers, atropisomers, epimeric, and tautomeric forms, as well as the appropriate mixtures thereof. The compounds and methods provided herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof.

[00446] Individual stereoisomers are obtained, if desired, by methods such as, stereoselective synthesis and/or the separation of stereoisomers by chiral chromatographic columns or the separation of diastereomers by either non-chiral or chiral chromatographic columns or crystallization and recrystallization in a proper solvent or a mixture of solvents. In certain embodiments, compounds of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (II), or Formula (IIa) are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds/salts, separating the diastereomers and recovering the optically pure individual enantiomers. In some embodiments, resolution of individual enantiomers is carried out using covalent diastereomeric derivatives of the compounds described herein. In another embodiment, diastereomers are separated by separation/resolution techniques based upon differences in solubility. In other embodiments, separation of stereoisomers is performed by chromatography or by the forming diastereomeric salts and separation by recrystallization, or chromatography, or any combination thereof.

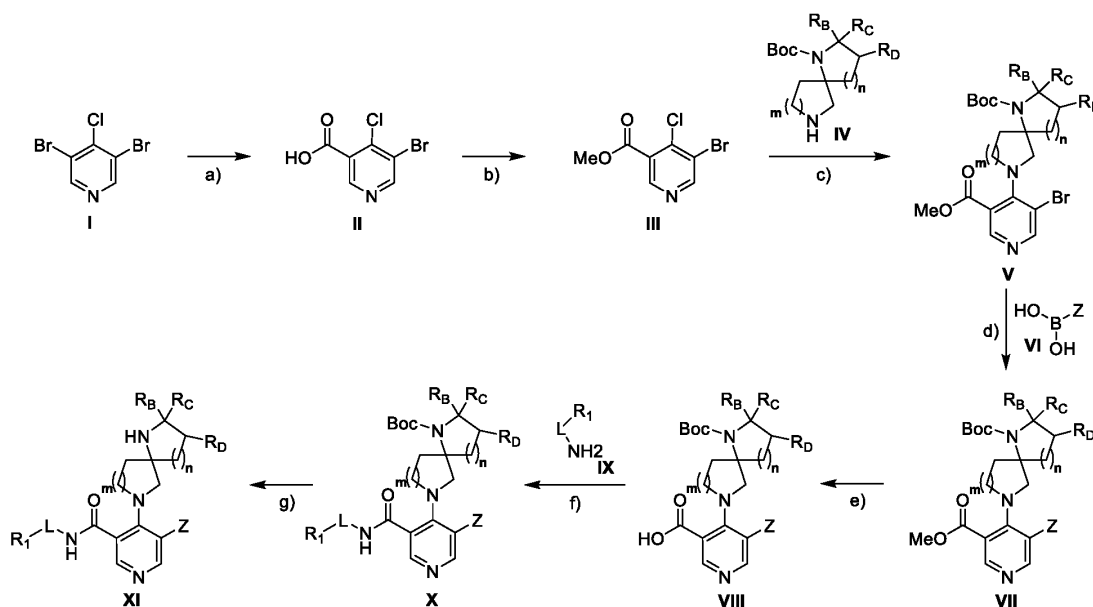
Synthesis of Compounds

[00447] Compounds of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (II), or Formula (IIa) described herein are synthesized using standard synthetic techniques or using methods known in the art in combination with methods described herein.

[00448] Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC are employed.

[00449] Compounds are prepared using standard organic chemistry techniques. Alternative reaction conditions for the synthetic transformations described herein may be employed such as variation of solvent, reaction temperature, reaction time, as well as different chemical reagents and other reaction conditions.

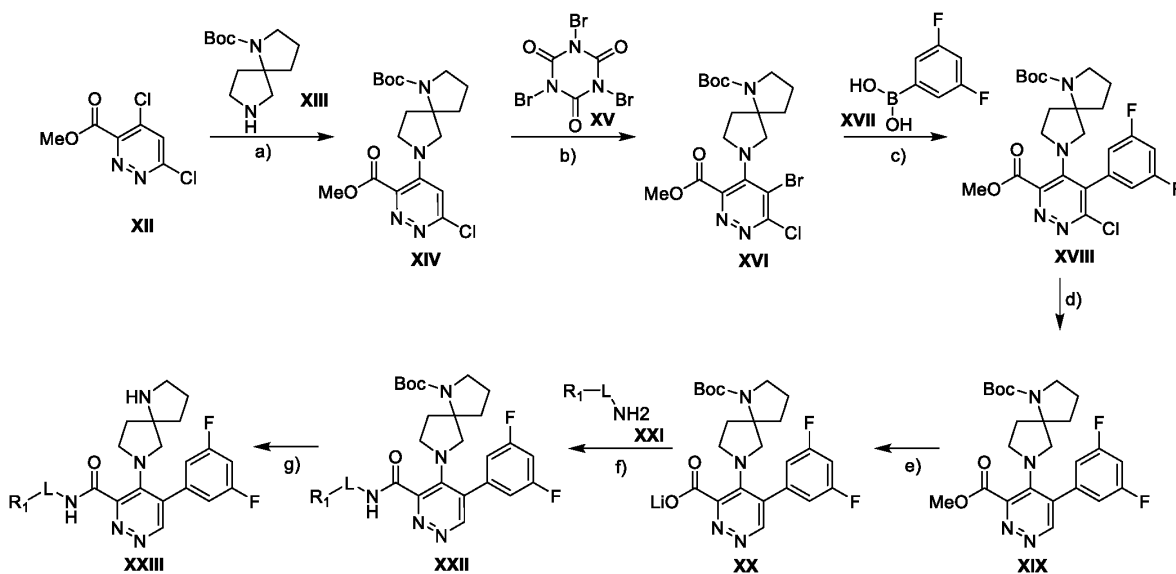
[00450] In some embodiments, compounds of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), and Formula (Id) described herein are prepared as described in **Scheme A**.



Scheme A

a) i) $i\text{PrMgCl}$, THF, $-40^\circ\text{C} \sim \text{RT}$; ii) Dry ice, 6 h; b) MeI , K_2CO_3 , DMF, RT, 1 h; c) **IV**, MeCN, DIEA, 100°C , 2 h; d) **VI**, $\text{Pd}(\text{dtbpf})\text{Cl}_2$, K_3PO_4 , toluene/ H_2O = 10:1, 70°C , 1 h; e) $\text{LiOH} \cdot \text{H}_2\text{O}$, $\text{MeOH}/\text{H}_2\text{O}$ = 2:1, 60°C , 16 h; f) **IX**, HATU, DIEA, DMF, RT, 30 min; g) TFA, DCM, RT, 30 min.

[00451] In some other embodiments, compounds of Formula (II) or Formula (IIa) described herein are prepared as described in **Scheme B**.



Scheme B

a) **XIII**, DIEA, MeCN, RT, 2 h; b) **XV**, AcOH, DCM, RT, 30 min; c) **XVII**, Pd(dppf)Cl₂, K₂CO₃, toluene/H₂O (5:1), 70°C, 3 h; d) Pd/C, MeOH, RT, 2 h; e) LiOH·H₂O, MeOH/H₂O= 2:1, 60°C, 1 h; f) **XXI**, HATU, DIEA, NMP, RT, 1 h; g) TFA, DCM, RT, 1 h

[00452] In some embodiments, compounds are prepared as described in the Examples.

Certain Terminology

[00453] Unless otherwise stated, the following terms used in this application have the definitions given below. The use of the term “including” as well as other forms, such as “include”, “includes,” and “included,” is not limiting. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[00454] As used herein, C₁-C_x includes C₁-C₂, C₁-C₃ . . . C₁-C_x. By way of example only, a group designated as “C₁-C₆” indicates that there are one to six carbon atoms in the moiety, i.e. groups containing 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, or 6 carbon atoms. Thus, by way of example only, “C₁-C₄ alkyl” indicates that there are one to four carbon atoms in the alkyl group, *i.e.*, the alkyl group is selected from among methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl.

[00455] An “alkyl” group refers to an aliphatic hydrocarbon group. The alkyl group is branched or straight chain. In some embodiments, the “alkyl” group has 1 to 6 carbon atoms, i.e. a C₁-C₆ alkyl. Whenever it appears herein, a numerical range such as “1 to 6” refers to each integer in the given range; *e.g.*, “1 to 6 carbon atoms” means that the alkyl group consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 6 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated. In some embodiments, an alkyl is a C₁-C₆ alkyl. In one aspect the alkyl is methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, or t-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tertiary butyl, pentyl, neopentyl, or hexyl.

[00456] An “alkoxy” group refers to an (alkyl)O- group, where alkyl is as defined herein.

[00457] The term “aromatic” refers to a planar ring having a delocalized π -electron system containing $4n+2$ π electrons, where n is an integer. The term “aromatic” includes both carbocyclic aryl (“aryl”, *e.g.*, phenyl) and heterocyclic aryl (or “heteroaryl” or “heteroaromatic”) groups (*e.g.*, pyridine, pyrimidine). The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of carbon atoms) groups.

[00458] The term “carbocyclic” or “carbocycle” refers to a ring or ring system where the atoms forming the backbone of the ring are all carbon atoms. The term thus distinguishes carbocyclic from “heterocyclic” rings or “heterocycles” in which the ring backbone contains at least one

atom which is different from carbon. In some embodiments, at least one of the two rings of a bicyclic carbocycle is aromatic. In some embodiments, both rings of a bicyclic carbocycle are aromatic. Carbocycles include aryls and cycloalkyls.

[00459] As used herein, the term “aryl” refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. In some embodiments, an aryl is a phenyl. Depending on the structure, an aryl group is a monoradical or a diradical (i.e., an arylene group).

[00460] The term “cycloalkyl” refers to a monocyclic or polycyclic aliphatic, non-aromatic radical, wherein each of the atoms forming the ring (i.e. skeletal atoms) is a carbon atom. Cycloalkyl groups include groups having from 3 to 7 ring atoms. In some embodiments, cycloalkyl groups are selected from among cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl. In some embodiments, a cycloalkyl is a C₃-C₇cycloalkyl. In some embodiments, a cycloalkyl is a C₃-C₆ cycloalkyl. In some embodiments, a cycloalkyl is a bicyclic cycloalkyl, or a “bicycloalkyl.” In some embodiments, cycloalkyls or bicycloalkyls are spirocyclic or bridged compounds.

[00461] A “cycloalkoxy” group refers to a (cycloalkyl)O- group, where cycloalkyl is as defined herein.

[00462] The term “halo” or, alternatively, “halogen” or “halide” means fluoro, chloro, bromo or iodo. In some embodiments, halo is fluoro, chloro, or bromo.

[00463] The term “fluoroalkyl” refers to an alkyl in which one or more hydrogen atoms are replaced by a fluorine atom. In one aspect, a fluoroalkyl is a C₁-C₆ fluoroalkyl.

[00464] A “fluoroalkoxy” group refers to a (fluoroalkyl)O- group, where fluoroalkyl is as defined herein.

[00465] The term “heterocycle” or “heterocyclic” refers to heteroaromatic rings (also known as heteroaryls) and heterocycloalkyl rings containing one to two heteroatoms in the ring(s), where each heteroatom in the ring(s) is selected from O, S, and N, wherein each heterocyclic group has from 3 to 6 atoms in its ring system, and with the proviso that any ring does not contain two adjacent O or S atoms. Non-aromatic heterocyclic groups (also known as heterocycloalkyls) include rings having 3 to 6 atoms in its ring system and aromatic heterocyclic groups include rings having 5 to 6 atoms in its ring system. Examples of non-aromatic heterocyclic groups include, but are not limited to, tetrahydropyranyl. Examples of aromatic heterocyclic groups include, but are not limited to, pyridinyl and pyrimidinyl.

[00466] The terms “heteroaryl” or, alternatively, “heteroaromatic” refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen, and sulfur. Illustrative examples of heteroaryl groups include monocyclic heteroaryls, such as pyridinyl and pyrimidinyl

[00467] A “heterocycloalkyl” group refers to a cycloalkyl group that includes at least one heteroatom selected from nitrogen, oxygen and sulfur. Illustrative examples of heterocycloalkyl groups include monocyclic heterocycloalkyls, such as tetrahydropyranyl.

[00468] The term “bond” refers to a chemical bond between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. In one aspect, when a group described herein is a bond, the referenced group is absent thereby allowing a bond to be formed between the remaining identified groups.

[00469] The term “moiety” refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[00470] The term “acceptable” with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

[00471] The term “modulate” as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the target.

[00472] The term “modulator” as used herein, refers to a molecule that interacts with a target either directly or indirectly. The interactions include, but are not limited to, the interactions of an agonist, partial agonist, an inverse agonist, antagonist, degrader, or combinations thereof. In some embodiments, a modulator is an agonist.

[00473] The terms “administer,” “administering,” “administration,” and the like, as used herein, refer to the methods that may be used to enable delivery of compounds or compositions to the desired site of biological action.

[00474] The terms “effective amount” and “therapeutically effective amount,” as used herein, refer to a sufficient amount of an agent or a compound being administered, which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result includes reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an “effective amount” for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate “effective” amount in any individual case is optionally determined using techniques, such as a dose escalation study.

[00475] The term “subject” or “patient” encompasses mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such

as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. In one aspect, the mammal is a human.

[00476] The terms “treat,” “treating” or “treatment,” as used herein, include alleviating, abating or ameliorating at least one symptom of a disease or condition, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

Pharmaceutical Compositions

[00477] In some embodiments, the compounds described herein are formulated into pharmaceutical compositions. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable inactive ingredients that facilitate processing of the active compounds into preparations that are used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein is found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999), herein incorporated by reference for such disclosure.

[00478] In some embodiments, the compounds described herein are administered either alone or in combination with one or more pharmaceutically acceptable carriers, excipients and/or diluents, in a pharmaceutical composition. Administration of the compounds and compositions described herein can be effected by any method that enables delivery of the compounds to the site of action.

[00479] In some embodiments, disclosed herein is a pharmaceutical composition including a compound of any one Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (II), or Formula (IIa), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some embodiments, disclosed herein is a pharmaceutical composition including a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some embodiments, disclosed herein is a pharmaceutical composition including a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some embodiments, disclosed herein is a pharmaceutical composition including a compound of

Formula (Ib) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some embodiments, disclosed herein is a pharmaceutical composition including a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some embodiments, disclosed herein is a pharmaceutical composition including a compound of Formula (Id), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some embodiments, disclosed herein is a pharmaceutical composition including a compound of Formula (II), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some embodiments, disclosed herein is a pharmaceutical composition including a compound of Formula (IIa), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

Methods of Dosing and Treatment Regimens

[00480] In some embodiments, the compounds of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (II), or Formula (IIa), or a pharmaceutically acceptable salt thereof, are used in the preparation of medicaments for the treatment of diseases or conditions in a mammal that would benefit from SSTR3 agonist. Methods for treating any of the diseases or conditions described herein in a mammal in need of such treatment involve administration of pharmaceutical compositions that include at least one compound of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (II), or Formula (IIa), or a pharmaceutically acceptable salt thereof, in therapeutically effective amounts to said mammal.

[00481] In certain embodiments, the compositions containing the compound(s) described herein are administered for therapeutic treatments. In certain therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to at least partially arrest at least one of the symptoms of the disease or condition. Amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation and/or dose ranging clinical trial.

[00482] The amount of a given compound of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (II), or Formula (IIa), or a pharmaceutically acceptable salt thereof that corresponds to a therapeutically effective amount varies depending upon factors such as the particular compound, disease condition and its severity, the identity (*e.g.*, weight, sex) of the subject or host in need of treatment, but nevertheless is determined according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated.

[00483] Toxicity and therapeutic efficacy of such therapeutic regimens are determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD₅₀ and the ED₅₀. The dose ratio between the toxic and therapeutic effects is the therapeutic index and it is expressed as the ratio between LD₅₀ and ED₅₀. In certain embodiments, the data obtained from cell culture assays and animal studies are used in formulating the therapeutically effective daily dosage range and/or the therapeutically effective unit dosage amount for use in mammals, including humans. In some embodiments, the daily dosage amount of the compounds described herein lies within a range of circulating concentrations that include the ED₅₀ with minimal toxicity. In certain embodiments, the daily dosage range and/or the unit dosage amount varies within this range depending upon the dosage form employed and the route of administration utilized.

[00484] As used above, and throughout the description of the invention, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

Abbreviations:

LCMS: liquid chromatography–mass spectrometry;

HPLC: high performance liquid chromatography;

Prep-HPLC: preparative high performance liquid chromatography;

Chiral-SFC: chiral supercritical fluid chromatography;

POCl₃: phosphoryl chloride;

DIEA: N,N-diisopropylethylamine or N-ethyl-N-isopropylpropan-2-amine;

DCM: dichloromethane;

PE: petroleum ether;

EtOAc or EA: ethyl acetate;

MeCN: acetonitrile;

Pd(dtbpf)Cl₂: [1,1'-Bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II);

HCl: hydrochloric acid;

Na₂CO₃: sodium carbonate;

THF: tetrahydrofuran;

H₂O: water;

DMF: dimethylformamide;

N₂: nitrogen gas;

NaHCO₃: sodium bicarbonate;

MgSO₄: magnesium sulfate;

HATU: 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate;

TFA: trifluoroacetic acid or 2,2,2-trifluoroacetic acid;

Zn(CN)₂: zinc cyanide;

Pd₂(dba)₃·CHCl₃: tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct;

NMP: N-methylpyrrolidone;

K₂CO₃: potassium carbonate;

NaOH: sodium hydroxide;

MeOH: methanol;

NaHSO₄: sodium bisulfate;

FA: formic acid;

NH₃·H₂O: aqueous ammonia;

Boc₂O: di-tert-butyl dicarbonate;

AcOH: acetic acid;

NaHSO₃: sodium bisulfite;

Na₂SO₄: sodium sulfate;

K₃PO₄: potassium phosphate;

Pd-C: palladium on carbon;

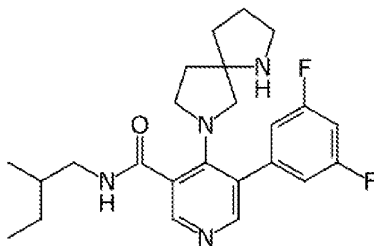
H₂: hydrogen gas;

LiOH: lithium hydroxide.

[00485] The following examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

Synthesis of Compounds

Example A-1. Preparation of N-2-methylbutyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide (Compound 5)



[00486] Step 1-1, preparation of 5-bromo-4-chloronicotinoyl chloride: Into a 50-mL round-bottom-flask was placed a mixture of 5-bromo-4-chloronicotinic acid (2.50 g, 1 Eq, 10.6 mmol;

prepared as disclosed in Example 2, step 2-1) and POCl₃ (25 g, 15 mL, 15 Eq, 0.16 mol). The resulting reaction mixture was stirred at 100 °C for 1 hour. The crude product was concentrated under reduced pressure to afford 5-bromo-4-chloronicotinoyl chloride (2.85 g, 10 mmol, 95%, 90% Purity).

[00487] Step 1-2, preparation of 5-bromo-4-chloro-N-(2-methylbutyl)nicotinamide: Into a 100-mL round-bottom flask was placed 2-methylbutan-1-amine (1.71 g, 2.00 Eq, 19.6 mmol), DIEA (10.0 g, 13.5 mL, 7.88 Eq, 77.4 mmol), and DCM (50 mL). Then 5-bromo-4-chloronicotinoyl chloride (2.78 g, 90% Wt, 1 Eq, 9.82 mmol) in DCM (10 mL) was added and the reaction mixture was stirred at 0 °C for 1 hour. The mixture was purified by silica gel column (PE/EtOAc system, with the amount of EtOAc increased from 0% to 65% over 20 min). This afforded 5-bromo-4-chloro-N-(2-methylbutyl)nicotinamide (1.60 g, 5.24 mmol, 53.3%); LCMS (M+H)⁺ = 305.0, 307.0.

[00488] Step 1-3, preparation of tert-butyl 7-(3-bromo-5-((2-methylbutyl)carbamoyl)pyridin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate: Into a 50-mL round-bottom flask was placed 5-bromo-4-chloro-N-(2-methylbutyl)nicotinamide (1.60 g, 1.18 Eq, 5.24 mmol), tert-butyl 1,7-diazaspiro[4.4]nonane-1-carboxylate (1.00 g, 1 Eq, 4.42 mmol), DIEA (1.50 g, 2.02 mL, 2.63 Eq, 11.6 mmol), and MeCN (20 mL). The resulting reaction mixture was stirred at 70 °C for 2 hours. The mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was purified by silica gel column eluted with PE/EtOAc (1:1) to afford tert-butyl 7-(3-bromo-5-((2-methylbutyl)carbamoyl)pyridin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate (1.88 g, 3.79 mmol, 85.9%); LCMS (M+H)⁺ = 495.2, 497.2.

[00489] Step 1-4, preparation of tert-butyl 7-(3-(3,5-difluorophenyl)-5-((2-methylbutyl)carbamoyl)pyridin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate: Into a 50-mL round-bottom-flask was added tert-butyl 7-(3-bromo-5-((2-methylbutyl)carbamoyl)pyridin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate (1.88 g, 1 Eq, 3.79 mmol), (3,5-difluorophenyl)boronic acid (3.00 g, 5.01 Eq, 19.0 mmol), Pd(dtbpf)Cl₂ (124 mg, 0.0501 Eq, 190 μmol), and potassium phosphate (4.00 g, 4.97 Eq, 18.8 mmol) in toluene (30 mL) and water (3 mL). The resulting mixture was stirred at 70 °C for 5 hours under a nitrogen atmosphere. The mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was purified by silica gel column eluted with PE/EtOAc (1:1 to 1:5) to afford tert-butyl 7-(3-(3,5-difluorophenyl)-5-((2-methylbutyl)carbamoyl)pyridin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate (1.80 g, 3.40 mmol, 89.7%); LCMS (M+H)⁺ = 529.3.

[00490] Step 1-5, preparation of N-2-methylbutyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide dihydrochloride: Into an 8-mL of vial was placed a mixture of tert-butyl 7-(3-(3,5-difluorophenyl)-5-((2-methylbutyl)carbamoyl)pyridin-4-yl)-1,7-

[00491] diazaspiro[4.4]nonane-1-carboxylate (100 mg, 1 Eq, 189 μ mol) and HCl/ether (2.0 M HCl in ether; 2 mL). The reaction mixture was stirred at 25 °C for 2 hours. The mixture was concentrated under reduced pressure and dried by lyophilization to afford N-2-methylbutyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide dihydrochloride (80 mg, 0.16 mmol, 84%); LCMS (M+H)⁺ = 429.3.

[00492] Step 1-6, preparation of N-2-methylbutyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide: Into a 8-mL vial was placed N-2-methylbutyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide dihydrochloride (30 mg, 1 Eq, 60 μ mol), which was dissolved in water (5 mL) and the pH value adjusted to 9 with Na₂CO₃, and extracted with DCM (2 x 7 mL). The organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum to afford 5-(3,5-difluorophenyl)-N-(2-methylbutyl)-4-(1,7-diazaspiro[4.4]nonan-7-yl)nicotinamide (20 mg, 47 μ mol, 78%); LCMS (M+H)⁺ = 429.3.

[00493] The following compounds were prepared similarly to **Example 1** with appropriate substitution of reagents and/or substrates and/or functional group modifications via well-known chemistry with appropriate reagents.

Compound No.	MS (M+H) ⁺
1	443.3
2	415.2
3	441.3
4	415.2
6	429.3
7	427.3
8	441.3
9	449.3
10	449.3
11	465.2
12	456.3
13	445.3
14	461.3

Compound No.	MS (M+H) ⁺
15	427.2
16	439.3
17	455.2
18	481.2
19	441.2
20	455.3
21	471.2
22	455.2
23	471.2
24	437.2
25	478.2
26	455.2
27	469.2

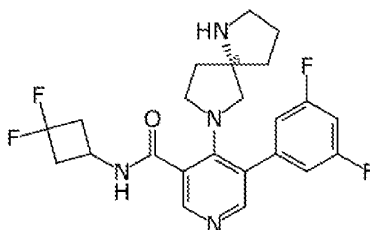
Compound No.	MS (M+H) ⁺
28	481.2
29	443.3
30	431.3
31	445.3
32	443.2
33	427.3
34	427.3
35	443.4
36	453.3
37	463.4
38	462.9
39	477.1
40	486.2
41	469.2
42	487.2
43	489.3
44	487.4
45	485.5
46	485.3
47	443.6
48	471.3
49	485.4
50	467.3
51	465.4
52	449.2
53	481.3
54	463.3
55	431.4
56	431.3
57	450.3
58	450.3

Compound No.	MS (M+H) ⁺
59	450.3
60	450.3
61	471.3
62	459.4
63	459.5
64	439.4
65	495.5
66	463.2
67	445.4
68	445.3
69	459.4
70	459.4
71	449.4
72	463.2
73	465.4
74	464.5
75	477.1
76	497.5
77	479.2
78	449.2
79	480.3
80	453.2
81	450.2
82	474.2
83	467.4
84	493.3
85	497.5
86	493.4
87	511.4
88	475.1
89	480.3

Compound No.	MS (M+H) ⁺
90	519.3
91	480.3
92	475.2
93	495.4
94	509.4
95	497.3
96	497.3
97	489.3
98	465.4

Compound No.	MS (M+H) ⁺
99	465.4
100	485.4
101	501.2
102	495.4
103	477.4
104	475.2
105	475.2
106	475.2
107	445.3

Example A-2. Preparation of N-3,3-difluorocyclobutyl-4-((S)-1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide (Compound 124)



[00494] Step 2-1, preparation of 5-bromo-4-chloronicotinic acid: Into a 500 mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed THF (150 mL) and 3,5-dibromo-4-chloropyridine (15.0 g, 1 Eq, 55.3 mmol). This was followed by the addition of isopropylmagnesium chloride (6.82 g, 30 mL, 2M, 1.2 Eq, 66.3 mmol) dropwise with stirring at -40 °C. The temperature was increased to 20 °C naturally. The resulting reaction solution was stirred for 30 min at 20 °C. Dry ice (300 g) was washed with THF (200ml) and then the THF was decanted. The reaction solution was poured onto the dry ice immediately and stirred for 3 hours. The reaction was then quenched by H₂O (150 ml). The resulting solution was extracted ethyl acetate (2 x 100 mL). The aqueous phase was adjusted to a pH of 1-2 and extracted with ethyl acetate (3 x 100 mL). The organic phases were combined and washed with 200 ml of brine. The resulting mixture was concentrated under vacuum to afford 5-bromo-4-chloronicotinic acid (9.6 g, 32 mmol, 59%, 80% Purity).

[00495] Step 2-2, preparation of methyl 5-bromo-4-chloronicotinate: Into a 40-mL vial was placed 5-bromo-4-chloronicotinic acid (1 g, 1 Eq, 4 mmol) and DMF (10 mL). This was followed

by the addition of potassium carbonate (2 g, 3 Eq, 0.01 mol). The resulting reaction mixture was stirred for 3 h at 25 °C to afford methyl 5-bromo-4-chloronicotinate (800 mg, 3.19 mmol, 80%).

[00496] Step 2-3, preparation of tert-butyl (S)-7-(3-bromo-5-(methoxycarbonyl)pyridin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate: To a solution of methyl 5-bromo-4-chloronicotinate (503.2 mg, 1 Eq, 2.009 mmol) and tert-butyl (S)-1,7-diazaspiro[4.4]nonane-1-carboxylate (500.1 mg, 1.1 Eq, 2.210 mmol) in MeCN (5 mL) was added N-ethyl-N-isopropylpropan-2-amine (519.3 mg, 700 µL, 2 Eq, 4.018 mmol). The mixture was heated at 100 °C for 16 hour. The mixture was concentrated in vacuo to dryness, and the residue was purified by silica gel column chromatography (eluted at 40% ethyl acetate in hexanes). Pure fractions were combined, concentrated in vacuo to dryness, and dried under a high vacuum to afford tert-butyl (S)-7-(3-bromo-5-(methoxycarbonyl)pyridin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate (866.0 mg, 1.967 mmol, 97.90 %); LCMS (M+H)⁺ = 440.1, 442.4.

[00497] Step 2-4, preparation of tert-butyl (S)-7-(3-(3,5-difluorophenyl)-5-(methoxycarbonyl)pyridin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate: To a mixture of tert-butyl (S)-7-(3-bromo-5-(methoxycarbonyl)pyridin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate (866.0 mg, 1 Eq, 1.967 mmol), (3,5-difluorophenyl)boronic acid (465.8 mg, 1.5 Eq, 2.950 mmol), Pd(dtbpf)Cl₂ (256.4 mg, 0.2 Eq, 393.3 µmol), and potassium phosphate (1.252 g, 3 Eq, 5.900 mmol) in a sealed tube was added toluene (10 mL) and water (1.0 mL). N₂ (g) was bubbled through the mixture for 5 min. The resulting mixture was heated at 70 °C for 1 hour. The mixture was concentrated in vacuo, and the residue was purified by reverse-phase column chromatography. Pure fractions were combined, neutralized with saturated NaHCO₃ (aq), and concentrated to remove MeCN. The aqueous residue was extracted with ethyl acetate (two times), and the combined organics were dried over anhydrous MgSO₄ and concentrated in vacuo to dryness to afford tert-butyl (S)-7-(3-(3,5-difluorophenyl)-5-(methoxycarbonyl)pyridin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate (706.5 mg, 1.492 mmol, 75.87%); LCMS (M+H)⁺ = 474.1.

[00498] Step 2-5, preparation of (S)-4-(1-(tert-butoxycarbonyl)-1,7-diazaspiro[4.4]nonan-7-yl)-5-(3,5-difluorophenyl)nicotinic acid: To a solution of tert-butyl (S)-7-(3-(3,5-difluorophenyl)-5-(methoxycarbonyl)pyridin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate (649.0 mg, 1 Eq, 1.371 mmol) in a mixed solvent of methanol (10 mL) and water (5.0 mL) was added lithium hydroxide hydrate (575.1 mg, 10 Eq, 13.71 mmol). The mixture was heated at 60 °C for 5 hours. The mixture was concentrated in vacuo to remove methanol. To the aqueous residue was added ice water and neutralized with 1N HCl (aq) to pH 6-7. The solution was extracted with ethyl acetate (3X) and 20% isopropyl alcohol/dichloromethane (1X). The combined organics were dried over

anhydrous MgSO_4 and concentrated in vacuo to dryness to afford (S)-4-(1-(tert-butoxycarbonyl)-1,7-diazaspiro[4.4]nonan-7-yl)-5-(3,5-difluorophenyl)nicotinic acid (564.2 mg, 1.228 mmol, 89.59 %); LCMS ($\text{M}+\text{H}$)⁺ = 460.2.

[00499] Step 2-6, preparation of tert-butyl (S)-7-(3-((3,3-difluorocyclobutyl)carbamoyl)-5-(3,5-difluorophenyl)pyridin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate: To a solution of (S)-4-(1-(tert-butoxycarbonyl)-1,7-diazaspiro[4.4]nonan-7-yl)-5-(3,5-difluorophenyl)nicotinic acid (564.2 mg, 1 Eq, 1.228 mmol) and 3-((dimethylamino)(dimethyliminio)methyl)-3H-[1,2,3]triazolo[4,5-b]pyridine 1-oxide hexafluorophosphate(V) (887.1 mg, 1.9 Eq, 2.333 mmol) in DMF (1 mL) was added N-ethyl-N-isopropylpropan-2-amine (793.5 mg, 1.07 mL, 5 Eq, 6.139 mmol). The mixture was stirred at 25 °C for 5 min. To this HATU-activated solution was added 3,3-difluorocyclobutan-1-amine hydrochloride (352.5 mg, 2 Eq, 2.456 mmol). The mixture was stirred at 25 °C for 10 min. The crude mixture was directly purified by reverse-phase column chromatography. Pure fractions were combined, neutralized with saturated NaHCO_3 (aq), and concentrated in vacuo to remove MeCN. The aqueous residue was extracted with ethyl acetate (2X). The combined organics were dried over anhydrous MgSO_4 , filtered, and concentrated in vacuo to dryness to afford tert-butyl (S)-7-(3-((3,3-difluorocyclobutyl)carbamoyl)-5-(3,5-difluorophenyl)pyridin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate (487.5 mg, 888.7 μmol , 72.37 %); LCMS ($\text{M}+\text{H}$)⁺ = 549.6.

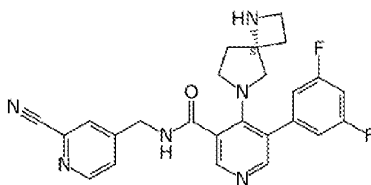
[00500] Step 2-7, preparation of N-3,3-difluorocyclobutyl-4-((S)-1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide: To a solution of tert-butyl (S)-7-(3-((3,3-difluorocyclobutyl)carbamoyl)-5-(3,5-difluorophenyl)pyridin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate (487.5 mg, 1 Eq, 888.7 μmol) in dichloromethane (1 mL) was added 2,2,2-trifluoroacetic acid (2.026 g, 1.360 mL, 20 Eq, 17.77 mmol). The mixture was stirred at 25 °C for 30 min. The mixture was concentrated in vacuo to dryness, and the residue was purified by reverse-phase column chromatography. Pure fractions were combined, neutralized with saturated NaHCO_3 (aq), and concentrated in vacuo to remove MeCN. The aqueous residue was extracted with ethyl acetate (2X), and the combined organics were dried over anhydrous MgSO_4 , concentrated in vacuo to dryness, and dried under a high vacuum to afford N-3,3-difluorocyclobutyl-4-((S)-1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)nicotinamide (331.17 mg, 738.44 μmol , 83.10 %); LCMS ($\text{M}+\text{H}$)⁺ = 449.4.

[00501] The following compounds were prepared similarly to **Example 2** with appropriate substitution of reagents and/or substrates and/or functional group modifications via well-known chemistry with appropriate reagents.

Compound No.	MS (M+H) ⁺
108	471.2
109	471.2
110	480.3
111	480.2
112	474.9
113	478.3
114	477.4
115	489.2
116	481.2
117	518.1
118	469.5
119	493.2
120	492.3
121	507.3
122	452.4
123	508.3
125	481.4
126	493.5
127	469.4
128	467.4
129	489.3
130	483.1

Compound No.	MS (M+H) ⁺
131	522.3
132	503.2
133	467.2
134	467.3
135	479.2
136	465.2
137	493.2
138	467.2
139	523.2
140	485.4
141	471.3
142	485.2
143	485.2
144	540.3
145	450.2
146	507.3
147	472.2
148	468.2
149	454.2
150	449.1
151	450.2
152	455.2

Example A-3. Preparation of N-[(2-cyano-4-pyridyl)methyl]-4-[(S)-1,6-diaza-6-spiro[3.4]octyl]-5-(3,5-difluorophenyl)nicotinamide (Compound 163)



[00502] Step 3-1, preparation of tert-butyl ((2-cyanopyridin-4-yl)methyl)carbamate: Into a 250mL flask maintained with an inert atmosphere of nitrogen were added tert-butyl ((2-bromopyridin-4-yl)methyl)carbamate (5.0 g, 1 Eq, 17 mmol), $\text{Zn}(\text{CN})_2$ (5.0 g, 2.4 Eq, 43 mmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CH}_3\text{Cl}$ (1.8 g, 0.10 Eq, 1.7 mmol), and xantphos (2.0 g, 0.20 Eq, 3.5 mmol) in NMP (100 mL). The mixture was stirred for 2 hours at 120 °C. Then the mixture was concentrated under reduced pressure, and the residue purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford tert-butyl ((2-cyanopyridin-4-yl)methyl)carbamate (3.0 g, 13 mmol, 74%); LCMS ($\text{M}+\text{H}$)⁺ = 234.1.

[00503] Step 3-2, preparation of 4-(aminomethyl)picolinonitrile hydrochloride: Into a 100 mL flask were added tert-butyl ((2-cyanopyridin-4-yl)methyl)carbamate (3.0 g, 1 Eq, 13 mmol) and 4-(aminomethyl)picolinonitrile hydrochloride (2.0 g, 12 mmol, 92%). The mixture was stirred 1 hour at 25 °C. The solution was concentrated under reduced pressure. Water and MeCN were added and the mixture freeze dried under vacuum to afford 4-(aminomethyl)picolinonitrile hydrochloride (2.0 g, 12 mmol, 92%).

[00504] Step 3-3, preparation of tert-butyl 6-(3-bromo-5-(methoxycarbonyl)pyridin-4-yl)-1,6-diazaspiro[3.4]octane-1-carboxylate: Into a 250 mL flask were added methyl 5-bromo-4-chloronicotinate (3.0 g, 1 Eq, 12 mmol; prepared as disclosed in Example 2, steps 2-1 to 2-2), tert-butyl 1,6-diazaspiro[3.4]octane-1-carboxylate oxalate (3.0 g, 0.83 Eq, 9.9 mmol), and DIEA (6.0 g, 8.1 mL, 3.9 Eq, 46 mmol) in MeCN (40 mL). The mixture was stirred for 5 hours at 60 °C. The solution was concentrated under vacuum, and the residue applied on a silica gel column and eluted with ethyl acetate/PE (1:3) to afford tert-butyl 6-(3-bromo-5-(methoxycarbonyl)pyridin-4-yl)-1,6-diazaspiro[3.4]octane-1-carboxylate (3.5 g, 8.2 mmol, 69%); LCMS ($\text{M}+\text{H}$)⁺ = 426.1, 428.1.

[00505] Step 3-4, preparation of tert-butyl 6-(3-(3,5-difluorophenyl)-5-(methoxycarbonyl)pyridin-4-yl)-1,6-diazaspiro[3.4]octane-1-carboxylate: Into a 250 mL flask maintained with an inert atmosphere of nitrogen were added tert-butyl 6-(3-bromo-5-(methoxycarbonyl)pyridin-4-yl)-1,6-diazaspiro[3.4]octane-1-carboxylate (3.5 g, 1 Eq, 8.2 mmol), $\text{Pd}(\text{dtbpf})\text{Cl}_2$ (500 mg, 0.093 Eq, 767 μmol), (3,5-difluorophenyl)boronic acid (2.6 g, 2.0 Eq, 16 mmol), and K_2CO_3 (3.5 g, 3.1 Eq, 25 mmol) in 1,4-dioxane (60 mL) and water (6 mL). The mixture was stirred for 1 hour at 80 °C. The mixture was concentrated under reduced pressure, and the residue applied on a silica gel column and eluted with ethyl acetate/PE (2:1) to afford tert-butyl 6-(3-(3,5-difluorophenyl)-5-(methoxycarbonyl)pyridin-4-yl)-1,6-diazaspiro[3.4]octane-1-carboxylate (3.5 g, 7.6 mmol, 93%); LCMS ($\text{M}+\text{H}$)⁺ = 461.1.

[00506] Step 3-5, preparation of 4-(1-(tert-butoxycarbonyl)-1,6-diazaspiro[3.4]octan-6-yl)-5-(3,5-difluorophenyl)nicotinic acid: Into a 250 mL flask were added tert-butyl 6-(3-(3,5-difluorophenyl)-5-(methoxycarbonyl)pyridin-4-yl)-1,6-diazaspiro[3.4]octane-1-carboxylate (3.5 g, 1 Eq, 7.6 mmol) and NaOH (3.0 g, 9.8 Eq, 75 mmol) in MeOH (60 mL) and water (6 mL). The mixture was stirred 1 hour at 80 °C. The mixture solution was concentrated under vacuum and diluted with water. The pH value of the solution was adjusted to 5-6 with saturated aqueous NaHSO₄. The resulting solution was extracted with DCM (3 x 40 mL). The organic layers were combined, washed with brine, dried, and concentrated under vacuum to afford 4-(1-(tert-butoxycarbonyl)-1,6-diazaspiro[3.4]octan-6-yl)-5-(3,5-difluorophenyl)nicotinic acid (3.0 g, 6.7 mmol, 88%); LCMS (M+H)⁺ = 446.1.

[00507] Step 3-6, preparation of tert-butyl (R)-6-(3-(((2-cyanopyridin-4-yl)methyl)carbamoyl)-5-(3,5-difluorophenyl)pyridin-4-yl)-1,6-diazaspiro[3.4]octane-1-carboxylate: Into a 100 mL flask were added 4-(1-(tert-butoxycarbonyl)-1,6-diazaspiro[3.4]octan-6-yl)-5-(3,5-difluorophenyl)nicotinic acid (2.5 g, 1 Eq, 5.6 mmol), DIEA (3.0 g, 4.0 mL, 4.1 Eq, 23 mmol), and HATU (2.5 g, 1.2 Eq, 6.6 mmol) in DMF (40 mL). The mixture was stirred for 10 min at room temperature, then 4-(aminomethyl)picolinonitrile hydrochloride (2.0 g, 2.1 Eq, 12 mmol; from step 3-2) was added. The mixture was stirred 1 hour at 25 °C. The crude product was purified by Prep-HPLC with the following conditions (2#-analyse-HPLC-SHIMADZU (HPLC-01)): Column, SunFine prep OBD 19*150mm 5um C-01; mobile phase, water (0.05% FA) and MeCN (27% MeCN up to 47% in 7 min); Detector 254 nm & 220 nm. The flow rate was set at 80 mL/min. The purified solution was concentrated under vacuum to afford 1.8 g of product. The product was purified by Chiral-SFC and two diastereomers were obtained. The first peak (t = 2.69 min) was identified as tert-butyl (S)-6-(3-(((2-cyanopyridin-4-yl)methyl)carbamoyl)-5-(3,5-difluorophenyl)pyridin-4-yl)-1,6-diazaspiro[3.4]octane-1-carboxylate (830 mg, 1.48 mmol, 26%); LCMS (M+H)⁺ = 561.4. The second peak (t = 3.35 min) was identified as tert-butyl (R)-6-(3-(((2-cyanopyridin-4-yl)methyl)carbamoyl)-5-(3,5-difluorophenyl)pyridin-4-yl)-1,6-diazaspiro[3.4]octane-1-carboxylate (740 mg, 1.32 mmol, 24 %); LCMS (M+H)⁺ = 561.3.

[00508] Step 3-7, preparation of N-[(2-cyano-4-pyridyl)methyl]-4-{(S)-1,6-diaza-6-spiro[3.4]octyl}-5-(3,5-difluorophenyl)nicotinamide: Into a 100 mL flask were added tert-butyl (R)-6-(3-(((2-cyanopyridin-4-yl)methyl)carbamoyl)-5-(3,5-difluorophenyl)pyridin-4-yl)-1,6-diazaspiro[3.4]octane-1-carboxylate (740 mg, 1 Eq, 1.32 mmol) in a mixture of TFA (2 mL) and DCM (10 mL). The mixture was stirred for 1 hour at 25 °C. The solution was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (2#-analyse-HPLC SHIMADZU(HPLC-01)): Column, XBridge prep OBD 19*150mm 5um C-

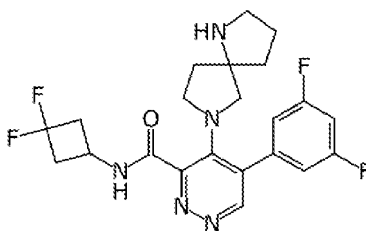
01; mobile phase, water (0.05% NH₃.H₂O) and MeCN (26% MeCN up to 48% in 7 min); Detector, 254 nm & 220 nm. The flow rate was 80 mL/min. This resulted in N-[(2-cyano-4-pyridyl)methyl]-4-[(S)-1,6-diaza-6-spiro[3.4]octyl]-5-(3,5-difluorophenyl)nicotinamide (367.4 mg, 797.8 μmol, 60.4%); LCMS (M+H)⁺ = 461.3.

[00509] The following compounds were prepared similarly to **Example 3** with appropriate substitution of reagents and/or substrates and/or functional group modifications via well-known chemistry with appropriate reagents.

Compound No.	MS (M+H) ⁺
153	415.3
154	483.2
155	473.2
156	457.4
157	471.2
158	449.1
159	449.2
160	463.3
161	474.2
162	461.3
164	464.6
165	478.3
166	483.4
167	469.5
168	453.0
169	487.0
170	482.3
171	480.2
172	480.5

Compound No.	MS (M+H) ⁺
173	470.9
174	489.3
175	479.0
176	480.1
177	496.3
178	475.2
179	493.1
180	495.2
181	489.2
182	492.2
183	492.3
184	491.2
185	491.2
186	463.2
187	463.2
188	489.3
189	554.2
190	517.3
191	489.2

Example A-4. Preparation of N-3,3-difluorocyclobutyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)-3-pyridazinecarboxamide (Compound 192)



[00510] Step 4-1, preparation of tert-butyl 7-(6-chloro-3-(methoxycarbonyl)pyridazin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate: Into a 40-mL vial were placed methyl 4,6-dichloropyridazine-3-carboxylate (1.0 g, 1 Eq, 4.8 mmol), 1,7-diazaspiro[4.4]nonane dihydrochloride (1.4 g, 1 Eq, 7.0 mmol), and DIEA (3.1 g, 4.2 mL, 5 Eq, 24 mmol) in MeCN (10 mL). The resulting solution was stirred for 2 hours at 25 °C. Then Boc₂O (1.6 g, 1.7 mL, 1.8 Eq, 7.3 mmol) was added and the resulting solution was stirred for 1 hour at 25 °C. The resulting solution was concentrated under reduced pressure and purified by silica gel column chromatography, eluted with PE/EtOAc (3:1) to afford tert-butyl 7-(6-chloro-3-(methoxycarbonyl)pyridazin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate (1.5 g, 3.8 mmol, 93%); LCMS (M+H)⁺ = 397.2.

[00511] Step 4-2, preparation of tert-butyl 7-(5-bromo-6-chloro-3-(methoxycarbonyl)pyridazin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate: Into a 40-mL vial were placed tert-butyl 7-(6-chloro-3-(methoxycarbonyl)pyridazin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate (1.5 g, 1 Eq, 3.8 mmol), DCM (2.8 mL), and AcOH (14 mL). Then 1,3,5-tribromo-1,3,5-triazinane-2,4,6-trione (1.4 g, 1.0 Eq, 3.8 mmol) was added at 0 °C and the solution was stirred for 30 minutes at 25 °C. The resulting solution was quenched with NaHSO₃ (10 mL) and the pH adjusted to 7 with NaHCO₃. The reaction mixture was extracted with ethyl acetate (3 x 30 mL) and the organic layers were combined, washed with brine (2 x 100 mL), and dried over anhydrous Na₂SO₄. After filtration the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5:1) to afford tert-butyl 7-(5-bromo-6-chloro-3-(methoxycarbonyl)pyridazin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate (1.4 g, 2.9 mmol, 78%); LCMS (M+H)⁺ = 475.1, 477.1.

[00512] Step 4-3, preparation of tert-butyl 7-(6-chloro-5-(3,5-difluorophenyl)-3-(methoxycarbonyl)pyridazin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate: Into a 40 mL vial were added tert-butyl 7-(5-bromo-6-chloro-3-(methoxycarbonyl)pyridazin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate (750 mg, 1 Eq, 1.58 mmol), (3,5-difluorophenyl)boronic acid (300 mg, 1.21 Eq, 1.90 mmol), Pd(dtbpf)Cl₂ (103 mg, 0.100 Eq, 158 μmol), and K₃PO₄

(1.00 g, 2.99 Eq, 4.71 mmol) in 1,4-dioxane (7 mL) and water (0.7 mL). The resulting mixture was stirred for 1 hour at 70 °C under nitrogen atmosphere. The resulting mixture was quenched by water (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (2 x 100 mL), and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:3) to afford tert-butyl 7-(6-chloro-5-(3,5-difluorophenyl)-3-(methoxycarbonyl)pyridazin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate (350 mg, 688 μmol, 43.6%); LCMS (M+H)⁺ = 509.4, 511.4.

[00513] Step 4-4, preparation of tert-butyl 7-(5-(3,5-difluorophenyl)-3-(methoxycarbonyl)pyridazin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate: Into a 50 mL round-bottom flask were added tert-butyl 7-(6-chloro-5-(3,5-difluorophenyl)-3-(methoxycarbonyl)pyridazin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate (350 mg, 1 Eq, 688 μmol) and Pd-C (35 mg, 0.48 Eq, 0.33 mmol; 10 wt.%) in MeOH (10 mL). The reaction mixture was stirred for 1 hour at 25 °C under H₂ (3 bar). Then the mixture was filtered, and the filtrate was concentrated in vacuo to afford tert-butyl 7-(5-(3,5-difluorophenyl)-3-(methoxycarbonyl)pyridazin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate (250 mg, 527 μmol, 76.6 %); LCMS (M+H)⁺ = 475.2.

[00514] Step 4-5, preparation of lithium 4-(1-(tert-butoxycarbonyl)-1,7-diazaspiro[4.4]nonan-7-yl)-5-(3,5-difluorophenyl)pyridazine-3-carboxylate: Into a 8 mL vial were added tert-butyl 7-(5-(3,5-difluorophenyl)-3-(methoxycarbonyl)pyridazin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate (50 mg, 1 Eq, 0.11 mmol), MeOH (0.2 mL), and water (0.04 mL), followed by LiOH (4 mg, 2 Eq, 0.2 mmol). The mixture was stirred for 1 hour at 60 °C. The resulting mixture was concentrated in vacuum to afford lithium 4-(1-(tert-butoxycarbonyl)-1,7-diazaspiro[4.4]nonan-7-yl)-5-(3,5-difluorophenyl)pyridazine-3-carboxylate (50 mg, 92 μmol, 87%, 86% Purity).

[00515] Step 4-6, preparation of tert-butyl 7-(3-((3,3-difluorocyclobutyl)carbamoyl)-5-(3,5-difluorophenyl)pyridazin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate: Into a 8-mL vial was placed lithium 4-(1-(tert-butoxycarbonyl)-1,7-diazaspiro[4.4]nonan-7-yl)-5-(3,5-difluorophenyl)pyridazine-3-carboxylate (50 mg, 1 Eq, 0.11 mmol), HATU (49 mg, 1.2 Eq, 0.13 mmol), and DIEA (70 mg, 94 μL, 5.1 Eq, 0.54 mmol) in DMF (1 mL). The resulting reaction mixture was stirred for 10 minutes at 25 °C. Then 3,3-difluorocyclobutan-1-amine hydrochloride (23 mg, 1.5 Eq, 0.16 mmol) was added. The resulting reaction mixture was stirred for 1 h at 25 °C. The mixture was purified by Prep-HPLC with the following conditions: Column, SunFire Prep C18 OBD Column, 19*150mm, 5μm; mobile phase, water (0.1% TFA) and MeCN (30% MeCN up to 75% in 7 min); Total flow rate, 20 mL/min; Detector, UV 220 nm. This afforded

tert-butyl 7-(3-((3,3-difluorocyclobutyl)carbamoyl)-5-(3,5-difluorophenyl)pyridazin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate (30 mg, 55 μ mol, 51%); LCMS (M+H)⁺ = 550.4.

[00516] Step 4-7, preparation of N-3,3-difluorocyclobutyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)-3-pyridazinecarboxamide: Into a 50 mL round-bottom flask were added tert-butyl 7-(3-((3,3-difluorocyclobutyl)carbamoyl)-5-(3,5-difluorophenyl)pyridazin-4-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate (30 mg, 1 Eq, 55 μ mol), DCM (3 mL), and TFA (1 mL). The mixture was stirred for 1 hour at room temperature. The resulting mixture was concentrated under reduced pressure and the crude product was purified by Prep-HPLC with the following conditions (2#-analyse-HPLC-SHIMADZU(HPLC-0013)): Column, Kinetex EVO 21.2*150mm 5 μ m; mobile phase, water (0.1% TFA) and MeCN (25% MeCN up to 55.0% in 15 min); Detector, 220 nm. This afforded N-3,3-difluorocyclobutyl-4-(1,7-diaza-7-spiro[4.4]nonyl)-5-(3,5-difluorophenyl)-3-pyridazinecarboxamide bis(2,2,2-trifluoroacetate) (32.1 mg, 47.4 μ mol, 87%); LCMS (M+H)⁺ = 450.2.

[00517] The following compounds were prepared similarly to **Example 4** with appropriate substitution of reagents and/or substrates and/or functional group modifications via well-known chemistry with appropriate reagents.

Compound No.	MS (M+H) ⁺
193	464.2
194	472.2
195	475.2
196	479.3
197	493.3
198	450.2
199	472.2
200	486.2
201	486.1

Example B-1: SSTR assays

Functional Assays

[00518] General overview: All five SSTR subtypes are Gi coupled G-protein coupled receptors (GPCRs) that lead to decreases in intracellular cyclic AMP (cAMP) when activated by an agonist. Therefore, measurement of intracellular cAMP levels can be used to assess whether

compounds are agonists of SSTR subtypes. One example of an intracellular cAMP assay is described below.

cAMP assay protocol for SSTR3

[00519] Chinese hamster ovary cells (CHO-K1, ATCC #CCL-61) stably expressing the human somatostatin receptor subtype 3 are plated two or four days prior to the assay, at 6,000 or 2,000 cells per well, respectively in a 96-well tissue culture-treated plate in Ham's F12 growth media (ThermoFisher #10-080-CM) supplemented with 10% donor bovine serum (Gemini Bio-Products #100-506), 100 U/mL penicillin; 100 ug/mL streptomycin; 2 mM L-glutamine (Gemini Bio-Products #400-110) and 0.25 mg/mL G418 (GoldBio #G-418-5). The cells are cultured at 37 °C, 5% CO₂ and 95% humidity. cAMP is measured with HTRF dynamic cAMP assay (Cisbio, #62AM5PEJ) per manufacturer's instructions. On the day of the assay, the media is aspirated and the cells are treated with 50 µL of stimulation buffer supplemented with 10.2 mM 3-isobutyl-1-methylxanthine (IBMX, Millipore Sigma #I5879) and 1.6 µM NKH477 (Tocris #1603), plus various dilutions of compounds of the present invention. The cells are incubated for 20 minutes at 37 °C (the final concentration of the compounds of the invention are typically 0-10,000 nM). The cells are treated with 50 µL of lysis buffer (HTRF cAMP kit, Cisbio) and incubated at room temperature for 30 minutes with rotary shaking at 600 rpm, and then diluted with 150 µL of stimulation buffer and shaken for an additional five minutes at 300 rpm. The lysate is transferred to 384-well plates and incubated for 1-24 hours at room temperature, and cAMP accumulation is detected by d2-labeled cAMP and Anti-cAMP-Cryptate. The time-resolved fluorescent signal is read using a m1000 Pro (Tecan) or CLARIOStar (BMG Labtech) microplate reader, where the samples are excited with light at 340 nm and emission light is measured at 620 nm and 665 nm. The data is expressed as a calculation of the fluorescence ratio (665 nm/620 nm). The intracellular cAMP concentrations are calculated by regression to a standard curve and are plotted vs. the concentration of the compounds of the invention. The EC₅₀ of the compounds are calculated using standard methods. All data manipulations are in GraphPad Prism v9 (GraphPad, San Diego, CA).

[00520] Table A reports biological activity of compounds as evaluated by inhibition of cAMP activities via human SSTR3 receptor.

Table A: SSTR3 Activity	
Compound No.	SSTR3 (EC ₅₀ ; nM)
1	1.1
2	6.1

Table A: SSTR3 Activity	
Compound No.	SSTR3 (EC ₅₀ ; nM)
3	1.4
4	7.6

Table A: SSTR3 Activity	
Compound No.	SSTR3 (EC ₅₀ ; nM)
5	0.9
6	5.9
7	7
8	4.5
9	0.93
10	2.6
11	1
12	14
13	4.1
14	3.4
15	3.8
16	1.4
17	4.2
18	1.5
19	4.6
20	3.5
21	2.5
22	6.5
23	2.3
24	29
25	98
26	62
27	21
28	4.8
29	25
30	66
31	40
32	45
33	10
34	24

Table A: SSTR3 Activity	
Compound No.	SSTR3 (EC ₅₀ ; nM)
35	15
36	4.9
37	1.4
38	16
39	10
40	14
41	3.7
42	2.4
43	1.2
44	1.6
45	3.9
46	84
47	56
48	2.7
49	65
50	2.1
51	2.1
52	6.7
53	1.1
54	3.3
55	30
56	19
57	9.2
58	23
59	11
60	38
61	6.3
62	26
63	17
64	12

Table A: SSTR3 Activity	
Compound No.	SSTR3 (EC ₅₀ ; nM)
65	40
66	2.8
67	11
68	17
69	37
70	18
71	1.5
72	1.7
73	1
74	15
75	0.84
76	2.3
77	1
78	8.8
79	3.5
80	4
81	66
82	0.42
83	0.63
84	1.3
85	0.81
86	1.8
87	5.2
88	2.6
89	3
90	46
91	14
92	1.9
93	1.4
94	0.86

Table A: SSTR3 Activity	
Compound No.	SSTR3 (EC ₅₀ ; nM)
95	2.2
96	3.1
97	13
98	31
99	50
100	0.77
101	0.52
102	4.9
103	11
104	1.5
105	2.4
106	0.48
107	91
108	1.4
109	55
110	51
111	6.9
112	0.29
113	0.72
114	0.34
115	0.33
116	1.2
117	1.9
118	1.8
119	0.15
120	0.57
121	0.28
122	27
123	63
124	1.3

Table A: SSTR3 Activity	
Compound No.	SSTR3 (EC ₅₀ ; nM)
125	3.5
126	3
127	0.83
128	1.4
129	0.14
130	0.9
131	1.2
132	0.21
133	6.7
134	3.8
135	13
136	4.5
137	19
138	0.57
139	0.33
140	0.31
141	4
142	0.2
143	0.38
144	0.24
145	2
146	1.1
147	2.1
148	2.5
149	7.7
150	6.9
151	5.3
152	12
153	1.9
154	3.9

Table A: SSTR3 Activity	
Compound No.	SSTR3 (EC ₅₀ ; nM)
155	4.5
156	7
157	1.5
158	4.2
159	13
160	2.7
161	1.2
162	0.96
163	0.4
164	2.5
165	11
166	1.2
167	0.21
168	0.4
169	0.12
170	0.33
171	1.5
172	0.38
173	0.26
174	0.49
175	0.96
176	1.3
177	100
178	0.16
179	24
180	41
181	56
182	3.2
183	89
184	0.47

Table A: SSTR3 Activity	
Compound No.	SSTR3 (EC ₅₀ ; nM)
185	20
186	6.1
187	50
188	1.1
189	79
190	66
191	1.1
192	2.9
193	0.88

Table A: SSTR3 Activity	
Compound No.	SSTR3 (EC ₅₀ ; nM)
194	1.7
195	0.28
196	1.1
197	1
198	1.2
199	0.94
200	0.21
201	0.5

Example B-2: *In vitro* 3D cystogenesis model

[00521] Madin-Darby Canine Kidney (MDCK) cells were resuspended as a single-cell suspension in ice-cold collagen type-I (Sigma-Aldrich) in complete medium and plated at a density of 250 cells per well in a 96-well plate (five to eight wells per condition). The plates were incubated at 37 °C for 1 hour to polymerize the gel. To promote cyst growth, 100 μ M of the pan phosphodiesterase inhibitor IBMX (3-isobutyl-1-methylxanthine) was added in complete medium on plating day. At the same time Compound **5** or Compound **108** at varying concentrations were added to the wells. The medium was changed every 48-72 hours within the span of 9 days. On day 9, the effects of each treatment on cysts were evaluated. Random visual fields were chosen and, to account for all the cysts in the field of view, multiple z-planes were photographed using an inverted phase contrast microscope (Olympus CK2) at x40 magnification. Cyst areas of all captured cysts were measured with ImageJ V. 2.9.0 and data were analyzed using GraphPad Prism software. Data (mean $\pm$ SEM) were expressed as cyst area in μ m² for each culture condition. For each experiment was n = 2. Statistic by two-tailed *t*-test: **P*<0.05. See FIG. 5.

[00522] **Results.** MDCK cells originate from the dog renal collecting duct and are widely used to study cystogenesis *in vitro*. When seeded in collagen gel, MDCK cells spontaneously form cysts and retain their apical to basolateral polarity. Similarly, to what is observed in ADPKD patients, intracellular cAMP production drives cyst swelling in this system.

[00523] This system was used to develop a 3D culture system to test the potential efficacy of the SSTR3 agonists disclosed herein. In this assay, cells were seeded in collagen in a 96 well plate

and cyst growth was promoted by addition of IBMX, a pan PDE inhibitor. IBMX was used to increase cAMP level as this treatment was found to preferentially rise cAMP levels in the cilia rather than in the cytoplasm. As shown in FIG. 5, addition of IBMX resulted in a significant increase in cyst size. Importantly, cyst swelling induced by IBMX was attenuated by treatment with compound 5 (see FIG. 5(A)) and compound 108 (see FIG. 5(B)) in a concentration dependent manner.

[00524] These results support the hypothesis that SSTR3 receptor activation decreases ciliary cAMP levels and cyst expansion observed in ADPKD.

Example B-3: Evaluation of SSTR3 Agonists on Kidney Weight and Kidney Cystic Index in a Mouse Model of Autosomal Dominant Polycystic Kidney Disease (ADPKD)

[00525] The following experimental protocol was used to evaluate the efficacy of SSTR3 receptor agonists in attenuating kidney size and kidney cystic index (KCI) in an autosomal dominant polycystic kidney disease (ADPKD) mouse model.

[00526] **Generation of ADPKD Mouse Model.** The ADPKD mouse model was generated by selective inactivation of the *Pkd1* gene in the kidney of *Pax8 Tet-O-Cre/Pkd1 flox* mice (Piontek et al., *Clin J Am Soc Nephrol* 2004, 15 (12), 3035–3043; Piontek et al., *Nat Med* 2007, 13 (12), 1490–1495; Traykova-Brauch et al., *Nat Med* 2008, 14 (9), 979–984) which results in the renal cyst formation. Specifically, induction of *Pkd1* deletion in the kidney was performed by administration of doxycycline hyclate (50 mg/kg) intraperitoneally to *Pax8 Tet-O-Cre/Pkd1 flox* mice on postnatal days (PND) 11 and 12. By PND20, *Pax8 Tet-O-Cre/Pkd1 flox* mice treated with doxycycline hyclate (referred to as ADPKD mice) developed enlarged and cystic kidneys compared to control non-treated littermates.

[00527] **SSTR3 Agonists in the ADPKD mouse model.** To evaluate the ability of SSTR3 agonists to reduce kidney weight and KCI in the ADPKD mouse model, studies were performed in PND12 ADPKD male and female mice. Vehicle or SSTR3 agonists were administered once daily by oral gavage from PND12 to PND 20. Body weight and clinical signs were recorded daily. On PND20, 1-2 hours after treatment with vehicle or SSTR3 agonists, mice were anesthetized, and blood was collected by cardiac puncture to the left ventricle after performing thoracotomy using needles coated with ethylenediaminetetraacetic acid (EDTA). The blood was collected into EDTA tubes and stored on ice until processed to plasma. The plasma samples were frozen and stored. The heart was harvested, and weight recorded to obtain the kidney to heart weight ratio. The left kidney was harvested, weighed, bisected longitudinally and, placed in 4% paraformaldehyde overnight at 4°C to fix the tissue. Post fixing, the left kidney was processed and embedded in paraffin for histomorphometry. Transverse kidney sections including the

cortex, medulla, and papilla were collected on a slide and the slides are stained with hematoxylin and eosin stain. Images were taken at 1x and 4x, and total cystic area was measured from the images using Image J software. The kidney cystic index (KCI) was calculated using the total cystic area.

[00528] Compound 108. Vehicle or 10, 30, or 100 mg/kg/day Compound **108** was administered orally once daily to ADPKD mice from postnatal days (PND) 12 to 20. Left kidney weight (A) and kidney cystic index (%) (B) were measured and calculated post euthanasia on PND 20. Data are expressed as mean $\pm$ SEM (n=17 for the vehicle group, n=14 for 10 mg/kg/day, n=15 for 30 mg/kg/day, and n=13 for 100 mg/kg/day Compound **108** groups). All data were analyzed using one-way analysis of variance (ANOVA) followed by a post-hoc test (Dunnett's test) to compare the treatment groups to the vehicle group. *p<0.5, ns: not significant. See FIG 6.

[00529] Results. Compound **108** was tested in a mouse model of ADPKD to evaluate its ability to decrease kidney size and kidney cystic index in this model. Kidney cystic index (KCI) after 9-day treatment with Compound **108** is summarized in Table B below:

Table B: <i>In vivo</i> efficacy in mouse ADPKD model			
Compound	Dose (mg/kg/day)	KCI (Mean $\pm$ SD (%))	% Change in cystic index relative to vehicle
108	0	41.98 $\pm$ 4.30	NA
	10	40.89 $\pm$ 5.71	-2.6
	30	43.39 $\pm$ 6.24	+3.4
	100	36.41 $\pm$ 5.46**	-13.3

Abbreviations: KCI = kidney cystic index; SD = standard deviation.

Statistical significance was calculated using one-way ANOVA followed by post hoc Dunnett's test to compare treatment groups with the vehicle group. *p $\leq$ 0.5, **p $\leq$ 0.01.

[00530] Once daily oral administration of 100 mg/kg/day of compound 108 from postnatal day (PND) 12 to PND 20 in ADPKD model mice significantly decreased kidney cystic index with a 13.3% suppression compared to the vehicle group (see FIG. 6(B)) but had no significant effect on kidney weight (see FIG. 6(A)).

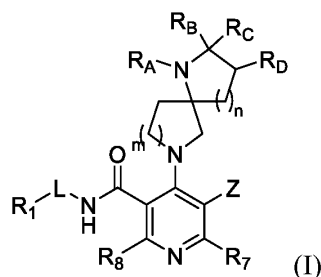
[00531] In view of these results, one would have a reasonable expectation of successfully treating PKD, including ADPKD, by administration of the SSTR3 agonists disclosed herein to a subject.

[00532] The examples and embodiments described herein are for illustrative purposes only and various modifications or changes suggested to persons skilled in the art are to be included within the spirit and purview of this application and scope of the appended claims.

CLAIMS

We Claim:

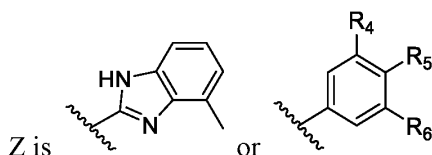
1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof:



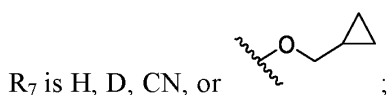
wherein:

R₁ is unsubstituted or substituted C₁₋₆ alkyl, unsubstituted or substituted C₃₋₆ cycloalkyl, unsubstituted or substituted 6-membered heterocycloalkyl, unsubstituted or substituted C₅₋₇ bicycloalkyl, unsubstituted or substituted aryl, or unsubstituted or substituted 6-membered heteroaryl; wherein if R₁ is substituted then R₁ is substituted with 1-3 X, wherein each X is independently selected from the group consisting of halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ fluoroalkyl, C₁₋₆ fluoroalkoxy, C₃₋₆ cycloalkoxy, CN, and OH;

L is a bond or CR₂R₃, wherein R₂ is H or C₁₋₆ alkyl, and R₃ is H, C₁₋₆ alkyl, C₁₋₆ alkoxy, CH₂OCH₃, or C₁₋₆ fluoroalkyl; or R₂ and R₃ together with the carbon to which they are attached form a C₃₋₆ cycloalkyl;



wherein R₄ is H or halogen; R₅ is H or halogen; and R₆ is H, halogen, CN, C₁₋₆ alkyl, or C₁₋₆ alkoxy;



R₈ is H, D, OH, C₁₋₆ alkyl, C₁₋₆ alkoxy, NH₂, or -NH(CH₂)₂OH;

R_A is H, C(O)OC₁₋₆ alkyl, or C(O)C₁₋₆ alkyl;

R_B is H, D, or C₁₋₆ alkyl;

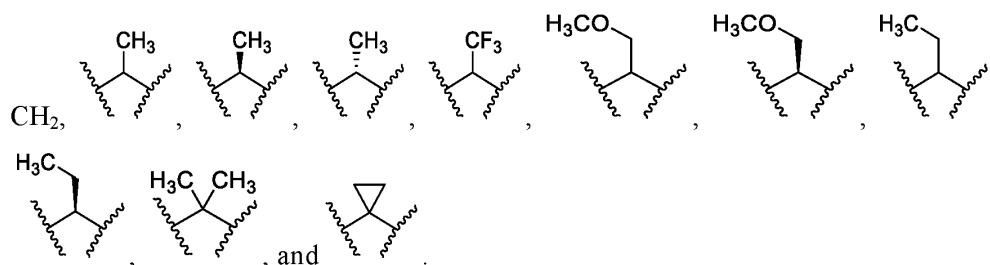
R_C is H or D;

R_D is H or halogen;

m is an integer selected from 0 and 1; and

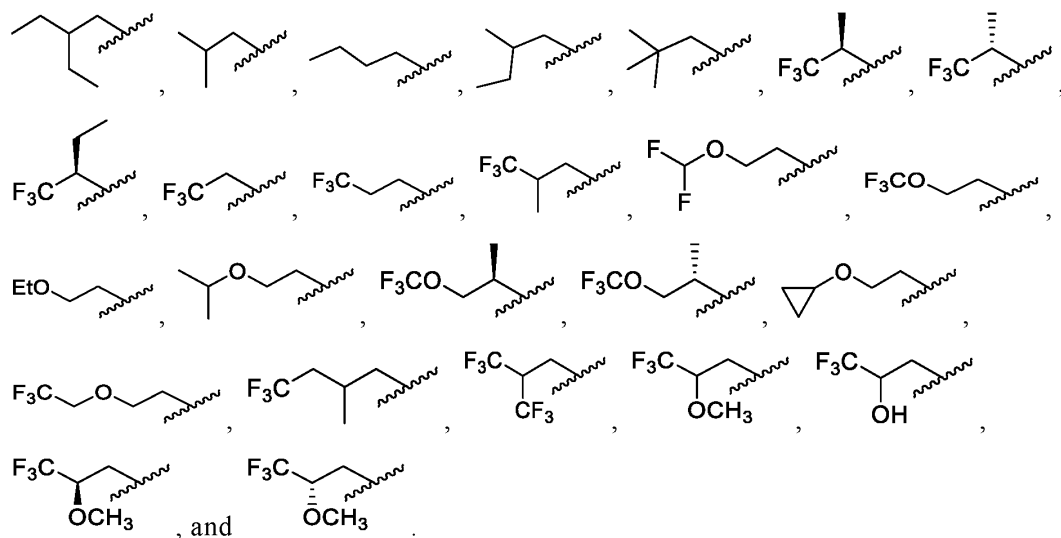
n is an integer selected from 0, 1, and 2.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L is a bond.
3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L is CR_2R_3 .
4. The compound of any one of claims 1 and 3, or a pharmaceutically acceptable salt thereof, wherein R_2 is H or methyl.
5. The compound of any one of claims 1, 3, and 4, or a pharmaceutically acceptable salt thereof, wherein R_3 is H, methyl, ethyl, trifluoromethyl, or CH_2OCH_3 .
6. The compound of any one of claims 1 and 3, or a pharmaceutically acceptable salt thereof, wherein R_2 and R_3 together with the carbon to which they are attached form a C_{3-6} cycloalkyl.
7. The compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein L is selected from the group consisting of:



8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R_1 is unsubstituted or substituted C_{1-4} alkyl.
9. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein if R_1 is substituted then R_1 is substituted with 1-2 X, wherein each X is independently selected from the group consisting of methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH.

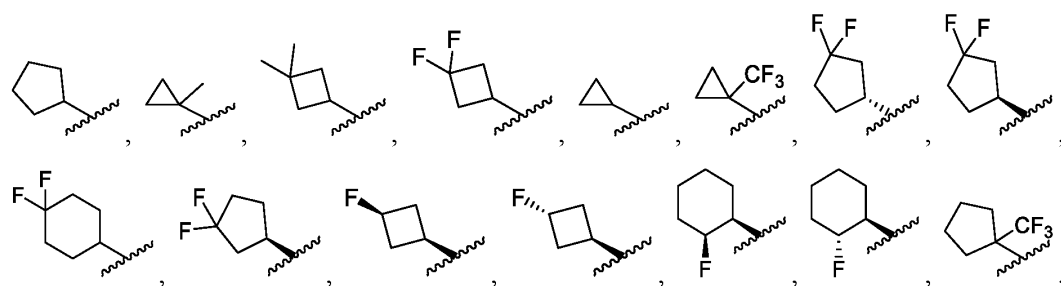
10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from the group consisting of:

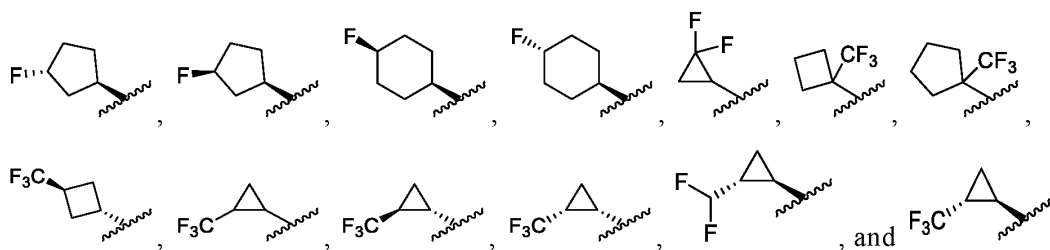


11. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R_1 is unsubstituted or substituted C_{3-6} cycloalkyl.

12. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein if R_1 is substituted then R_1 is substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro, methyl, difluoromethyl, and trifluoromethyl.

13. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from the group consisting of:

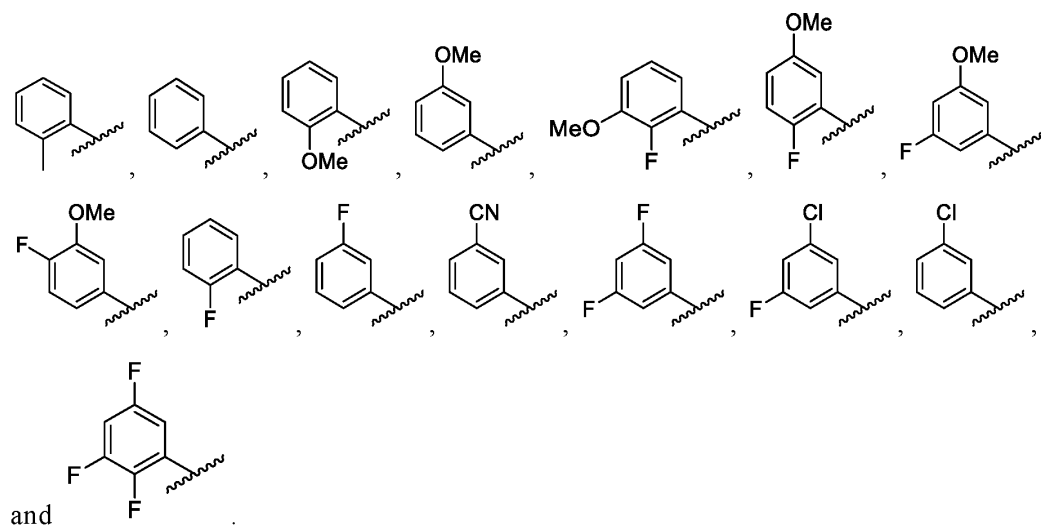




14. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R₁ is unsubstituted or substituted phenyl.

15. The compound of claim 14, or a pharmaceutically acceptable salt thereof, wherein if R₁ is substituted then R₁ is substituted with 1-3 X, wherein each X is independently selected from the group consisting of fluoro, chloro, methyl, methoxy, and CN.

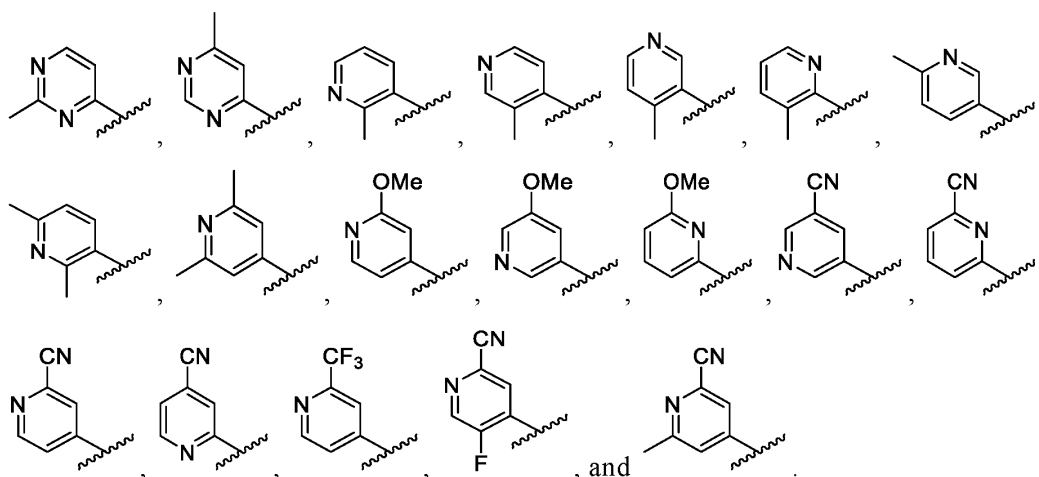
16. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R₁ is selected from the group consisting of:



17. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R₁ is unsubstituted or substituted pyridinyl, or unsubstituted or substituted pyrimidinyl.

18. The compound of claim 17, or a pharmaceutically acceptable salt thereof, wherein if R_1 is substituted then R_1 is substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro, methyl, trifluoromethyl, methoxy, and CN.

19. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from the group consisting of:

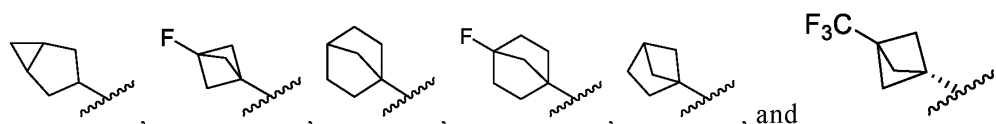


20. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R_1 is unsubstituted or substituted C_{5-7} bicycloalkyl.

21. The compound of claim 20, or a pharmaceutically acceptable salt thereof, wherein if R_1 is substituted then R_1 is substituted with fluoro or trifluoromethyl.

22. The compound of claim 20 or 21, or a pharmaceutically acceptable salt thereof, wherein one or more of the carbon atoms of the C_{5-7} bicycloalkyl is a bridging carbon.

23. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from the group consisting of:

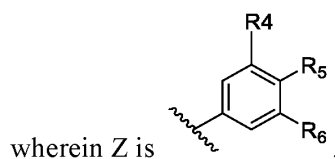


24. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, wherein m is 1 and n is 1.

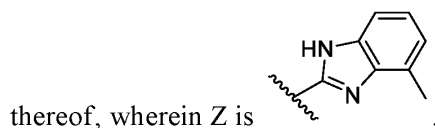
25. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof, wherein R_A is H.

26. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, wherein R_B is H; R_C is H; and R_D is H.

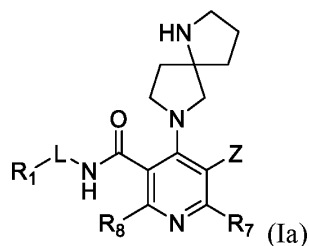
27. The compound of any one of claims 1-26, or a pharmaceutically acceptable salt thereof,



28. The compound of any one of claims 1-7 and 11-13, or a pharmaceutically acceptable salt thereof, wherein Z is

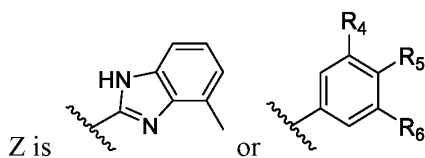


29. The compound of claim 1, wherein the compound is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof:

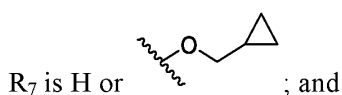


wherein:

- R_1 is unsubstituted or substituted C_{1-4} alkyl, unsubstituted or substituted C_{3-6} cycloalkyl, tetrahydropyran, unsubstituted or substituted C_{5-7} bicycloalkyl, unsubstituted or substituted aryl, or unsubstituted or substituted 6-membered heteroaryl, wherein if R_1 is substituted then R_1 is substituted with 1-2 X, wherein each X is independently selected from F, Cl, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, trifluoromethoxy, cyclopropoxy, OCH_2CF_3 , CN, and OH;
- L is a bond or CR_2R_3 , wherein R_2 is H or methyl, and R_3 is H, methyl, ethyl, trifluoromethyl, or $-CH_2OCH_3$; or R_2 and R_3 together with the carbon to which they are attached form a cyclopropyl group;



wherein R_4 is H, F, or Cl; R_5 is H or F; and R_6 is H, F, Cl, CN, methyl, or methoxy;

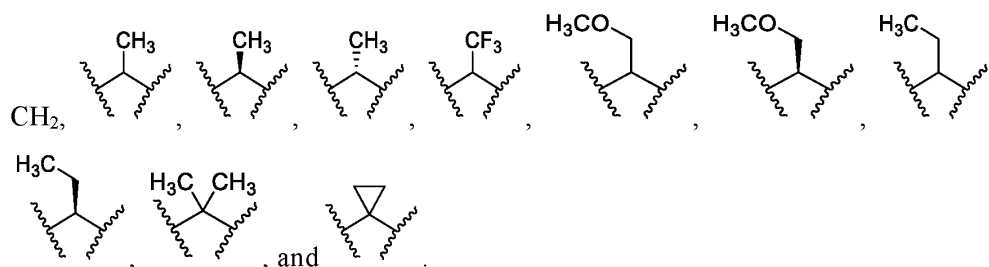


R_8 is H, NH_2 , or methyl.

30. The compound of claim 29, or a pharmaceutically acceptable salt thereof, wherein L is a bond.

31. The compound of claim 29, or a pharmaceutically acceptable salt thereof, wherein L is CR_2R_3 .

32. The compound of any one of claims 29 and 31, or a pharmaceutically acceptable salt thereof, wherein L is selected from the group consisting of:

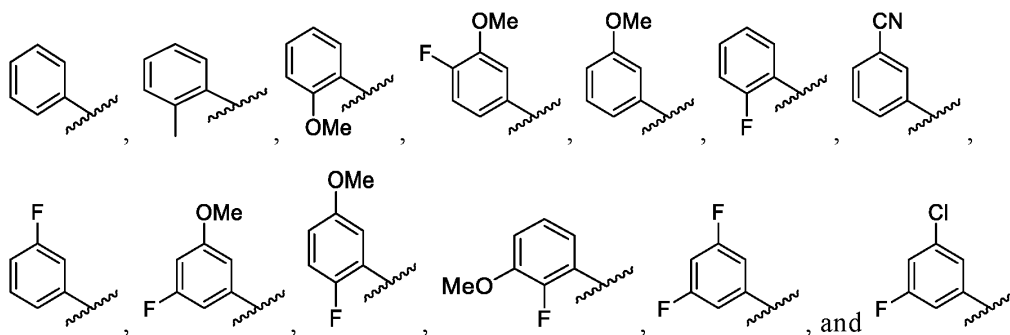


33. The compound of any one of claims 29-32, or a pharmaceutically acceptable salt thereof, wherein R_1 is unsubstituted or substituted C_{1-4} alkyl.

34. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein if R_1 is substituted then R_1 is substituted with 1-2 X, wherein each X is independently selected from the group consisting of methyl, ethyl, trifluoromethyl, ethoxy, isopropoxy, trifluoromethoxy, trifluoroethoxy, and cyclopropoxy.

40. The compound of claim 39, or a pharmaceutically acceptable salt thereof, wherein if R₁ is substituted then R₁ is substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro, chloro, methyl, methoxy, and CN.

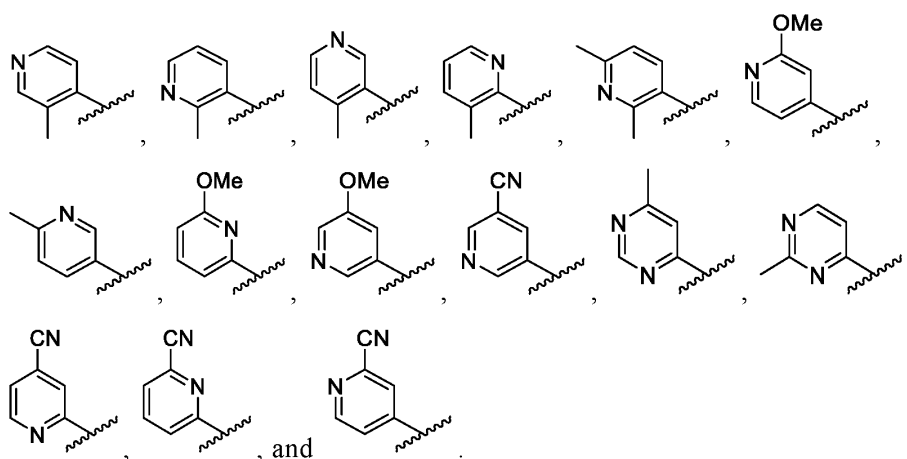
41. The compound of any one of claims 29-32 and 39-40, or a pharmaceutically acceptable salt thereof, wherein R₁ is selected from the group consisting of:



42. The compound of any one of claims 29-32, or a pharmaceutically acceptable salt thereof, wherein R₁ is unsubstituted or substituted pyridinyl, or unsubstituted or substituted pyrimidinyl.

43. The compound of claim 40, or a pharmaceutically acceptable salt thereof, wherein if R₁ is substituted then R₁ is substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro, methyl, trifluoromethyl, methoxy, and CN.

44. The compound of any one of claims 29-32, or a pharmaceutically acceptable salt thereof, wherein R₁ is selected from the group consisting of:

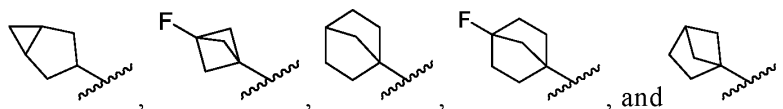


45. The compound of any one of claims 29-32, or a pharmaceutically acceptable salt thereof, wherein R₁ is unsubstituted or substituted C₅₋₇ bicycloalkyl.

46. The compound of claim 45, or a pharmaceutically acceptable salt thereof, wherein one or more of the carbon atoms of the C₅₋₇ bicycloalkyl is a bridging carbon.

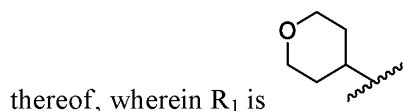
47. The compound of any one of claims 45-46, or a pharmaceutically acceptable salt thereof, wherein if R₁ is substituted then R₁ is substituted with fluoro.

48. The compound of any one of claims 29-32, or a pharmaceutically acceptable salt thereof, wherein R₁ is selected from the group consisting of:

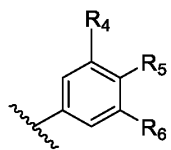


49. The compound of any one of claims 29-32, or a pharmaceutically acceptable salt thereof, wherein R₁ is tetrahydropyran.

50. The compound of any one of claims 29-32 and 49, or a pharmaceutically acceptable salt

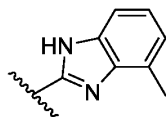


51. The compound of any one of claims 29-50, or a pharmaceutically acceptable salt thereof,



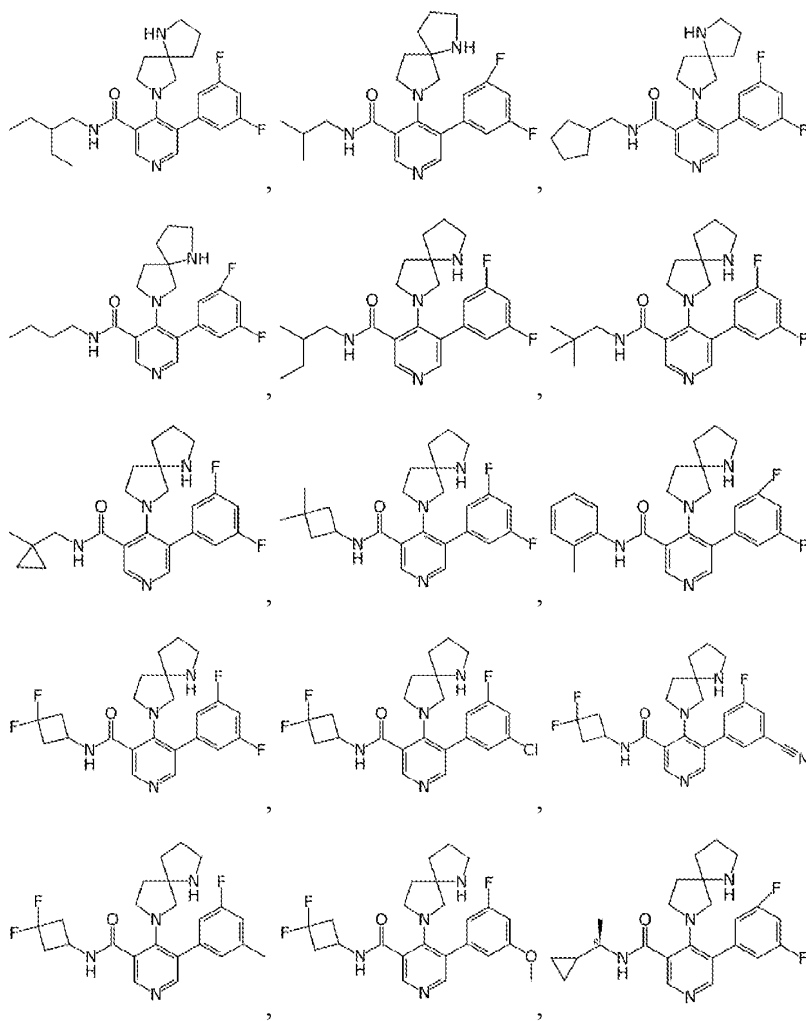
wherein Z is

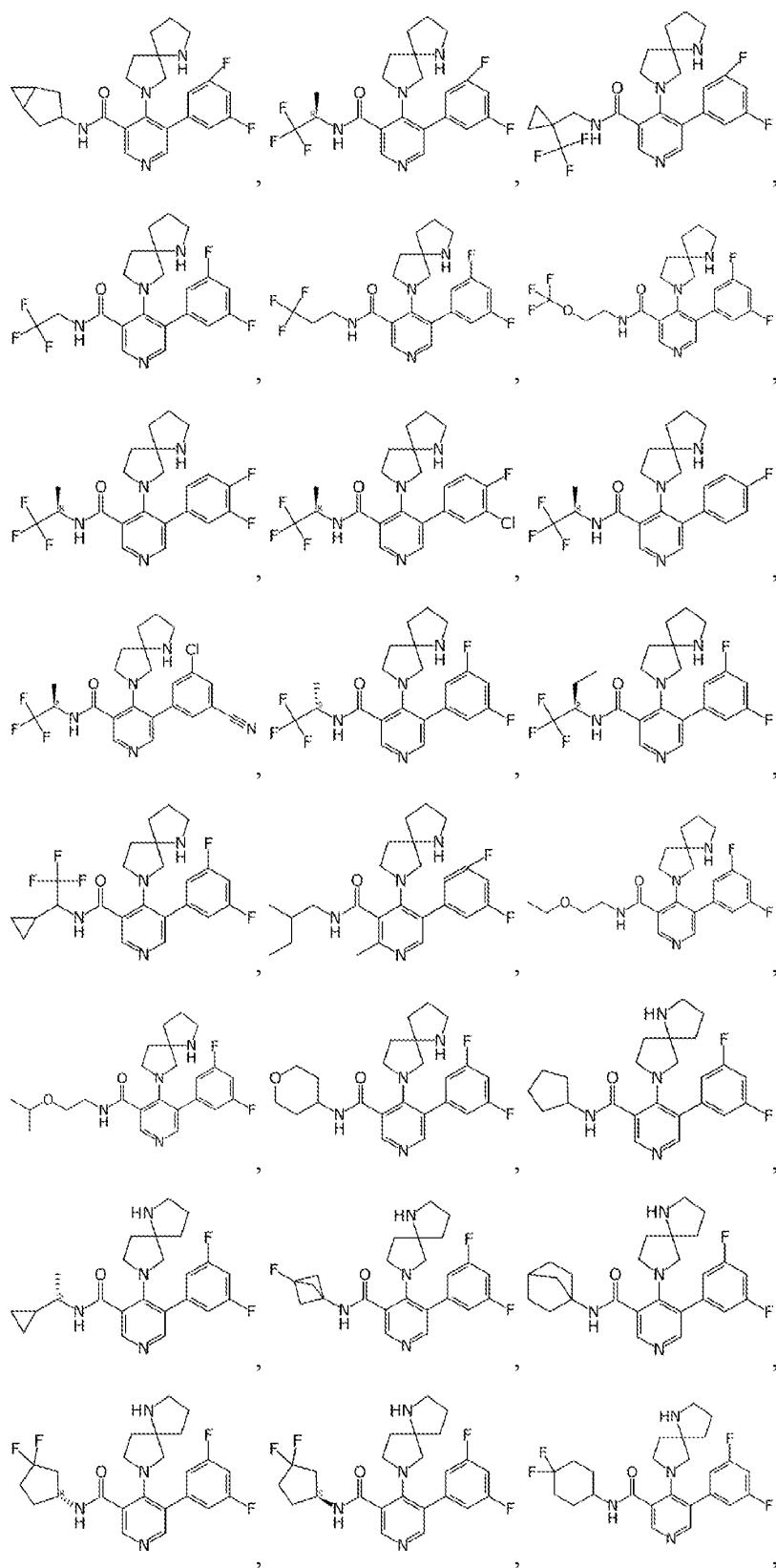
52. The compound of any one of claims 29-32 and 36-37, or a pharmaceutically acceptable

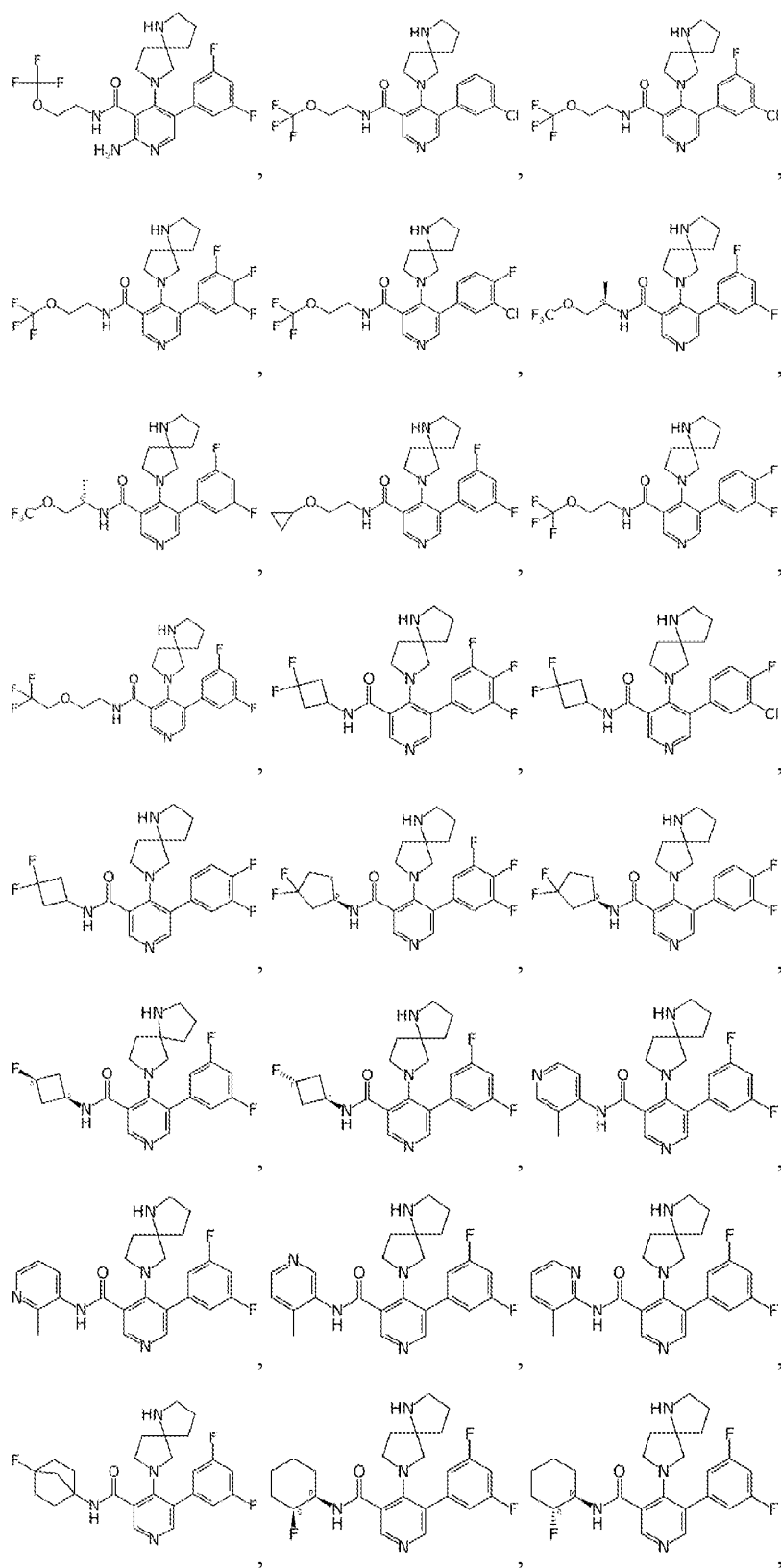


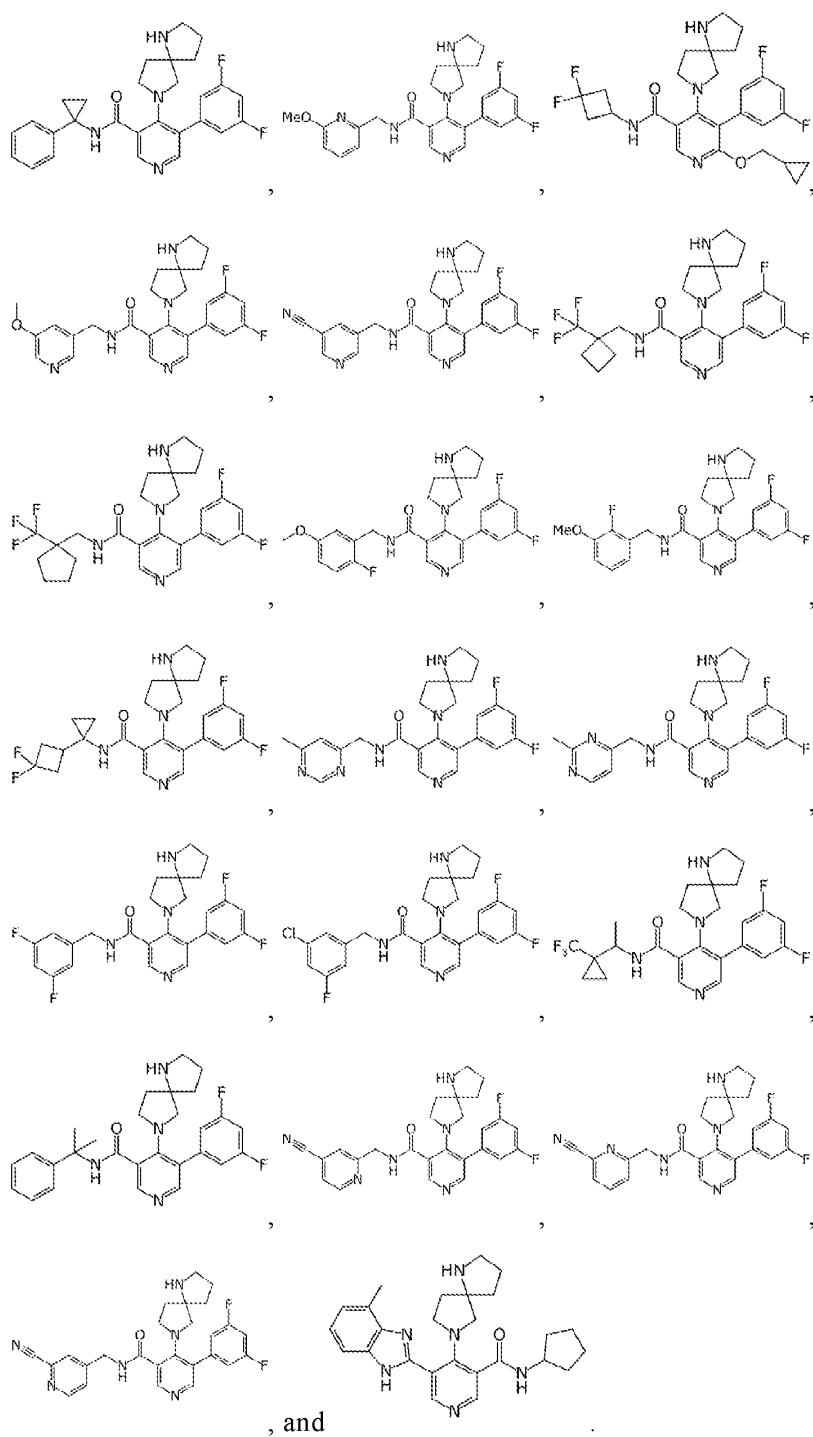
salt thereof, wherein Z is

53. The compound of claim 29, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:



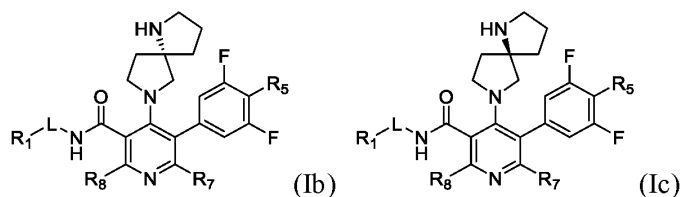






54. The compound of any one of claims 1-27 and 29-51, or a pharmaceutically acceptable salt thereof, wherein R₄ and R₆ are fluoro.

55. The compound of claim 1, wherein the compound is a compound of formula (Ib) or (Ic), or a pharmaceutically acceptable salt thereof:



wherein:

R_1 is unsubstituted or substituted C_{1-3} alkyl, unsubstituted or substituted C_{3-4} cycloalkyl, unsubstituted or substituted C_5 bicycloalkyl, or unsubstituted or substituted 6-membered heteroaryl, wherein if R_1 is substituted then R_1 is substituted with 1-2 X, wherein each X is independently selected from F, methyl, difluoromethyl, trifluoromethyl, methoxy, difluoromethoxy, trifluoromethoxy, CN, and OH;

L is a bond or CR_2R_3 , wherein R_2 is H, and R_3 is H, methyl, or $-CH_2OCH_3$;

R_5 is H or F;

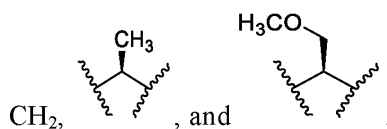
R_7 is H, D, or CN; and

R_8 is H, D, OH, methoxy, or $-NH(CH_2)_2OH$.

56. The compound of claim 55, or a pharmaceutically acceptable salt thereof, wherein L is a bond.

57. The compound of claim 55, or a pharmaceutically acceptable salt thereof, wherein L is CR_2R_3 .

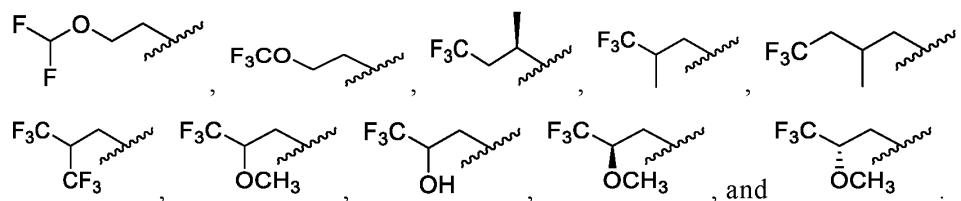
58. The compound of any one of claims 55 and 57, or a pharmaceutically acceptable salt thereof, wherein L is selected from the group consisting of:



59. The compound of any one of claims 55-58, or a pharmaceutically acceptable salt thereof, wherein R_1 is unsubstituted or substituted C_{1-3} alkyl.

60. The compound of claim 59, or a pharmaceutically acceptable salt thereof, wherein if R_1 is substituted then R_1 is substituted with 1-2 X, wherein each X is independently selected from the group consisting of methyl, trifluoromethyl, methoxy, difluoromethoxy, trifluoromethoxy, and OH.

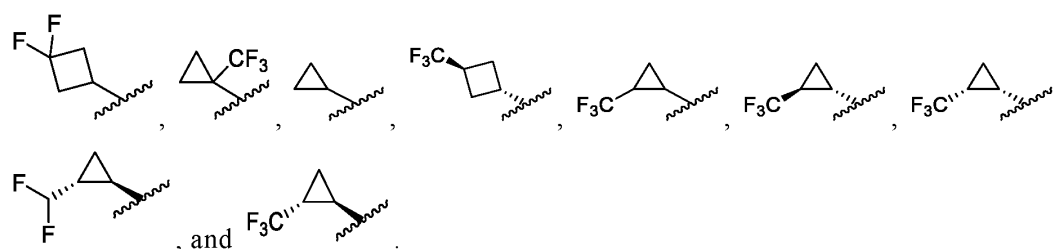
61. The compound of any one of claims 55-60, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from the group consisting of:



62. The compound of any one of claims 55-59, or a pharmaceutically acceptable salt thereof, wherein R_1 is unsubstituted or substituted C_{3-4} cycloalkyl.

63. The compound of claim 62, or a pharmaceutically acceptable salt thereof, wherein if R_1 is substituted then R_1 is substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro, difluoromethyl, and trifluoromethyl.

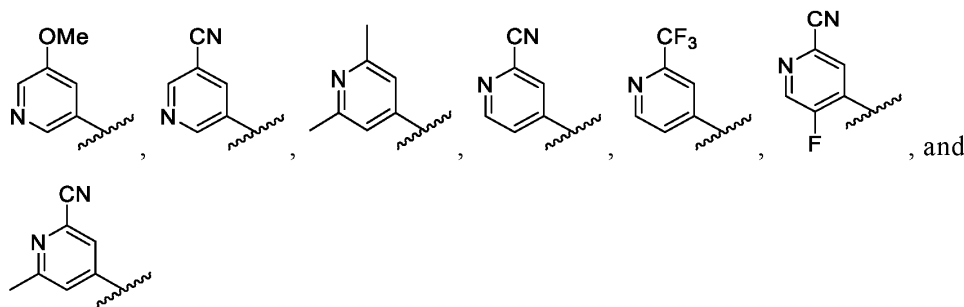
64. The compound of any one of claims 55-59, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from the group consisting of:



65. The compound of any one of claims 55-59, or a pharmaceutically acceptable salt thereof, wherein R_1 is unsubstituted or substituted pyridinyl.

66. The compound of claim 65, or a pharmaceutically acceptable salt thereof, wherein if R_1 is substituted then R_1 is substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro, methyl, trifluoromethyl, methoxy, and CN.

67. The compound of any one of claims 55-59, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from the group consisting of:



68. The compound of any one of claims 55-59, or a pharmaceutically acceptable salt thereof, wherein R_1 is unsubstituted or substituted C_5 bicycloalkyl.

69. The compound of claim 68, or a pharmaceutically acceptable salt thereof, wherein one or more of the carbon atoms of the C_5 bicycloalkyl is a bridging carbon.

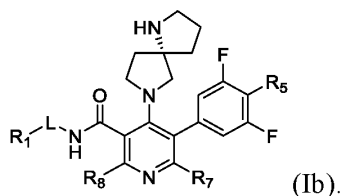
70. The compound of any one of claims 68-69, or a pharmaceutically acceptable salt thereof, wherein if R_1 is substituted then R_1 is substituted with trifluoromethyl.

71. The compound of any one of claims 55-59, or a pharmaceutically acceptable salt thereof,

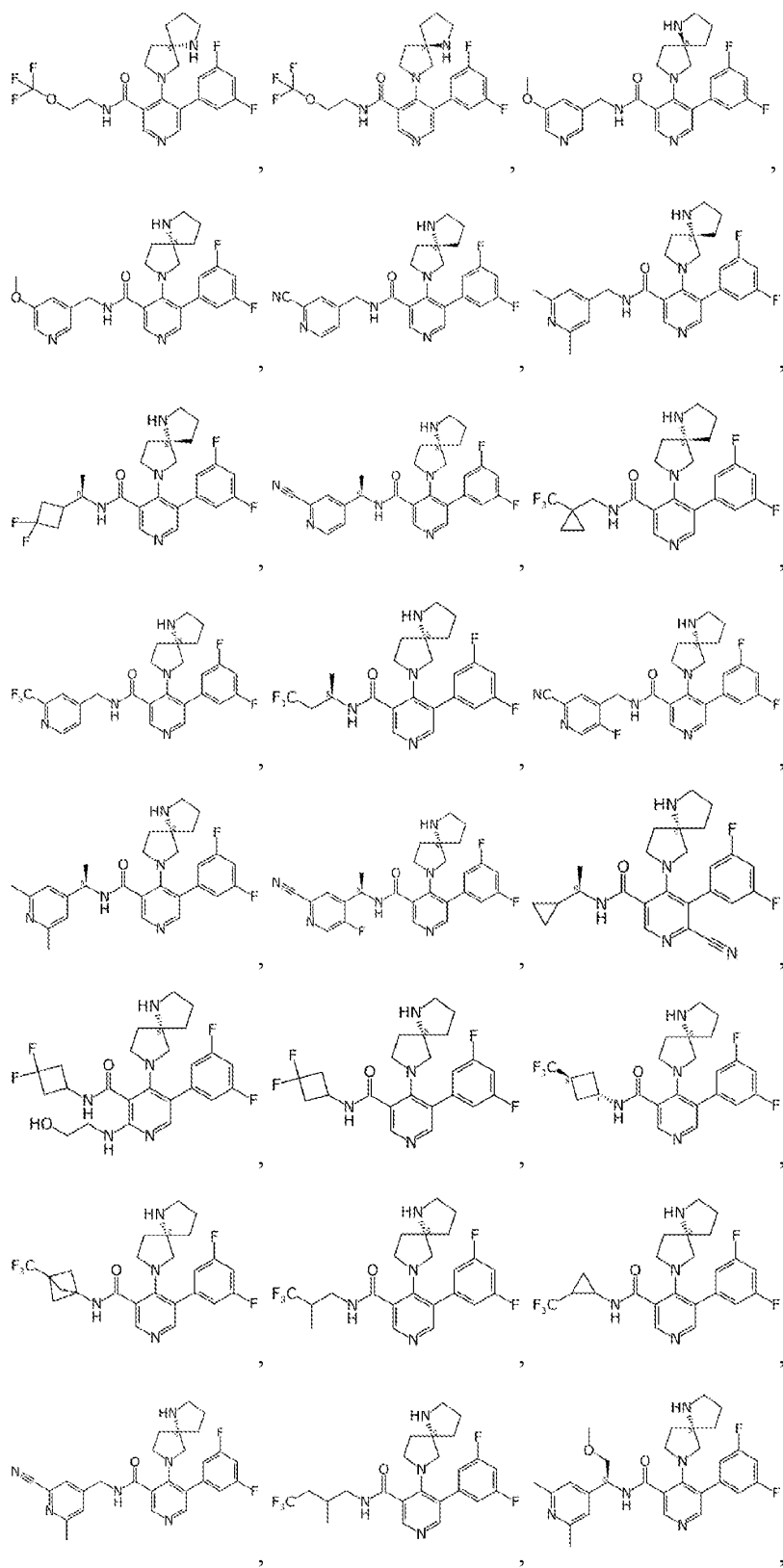


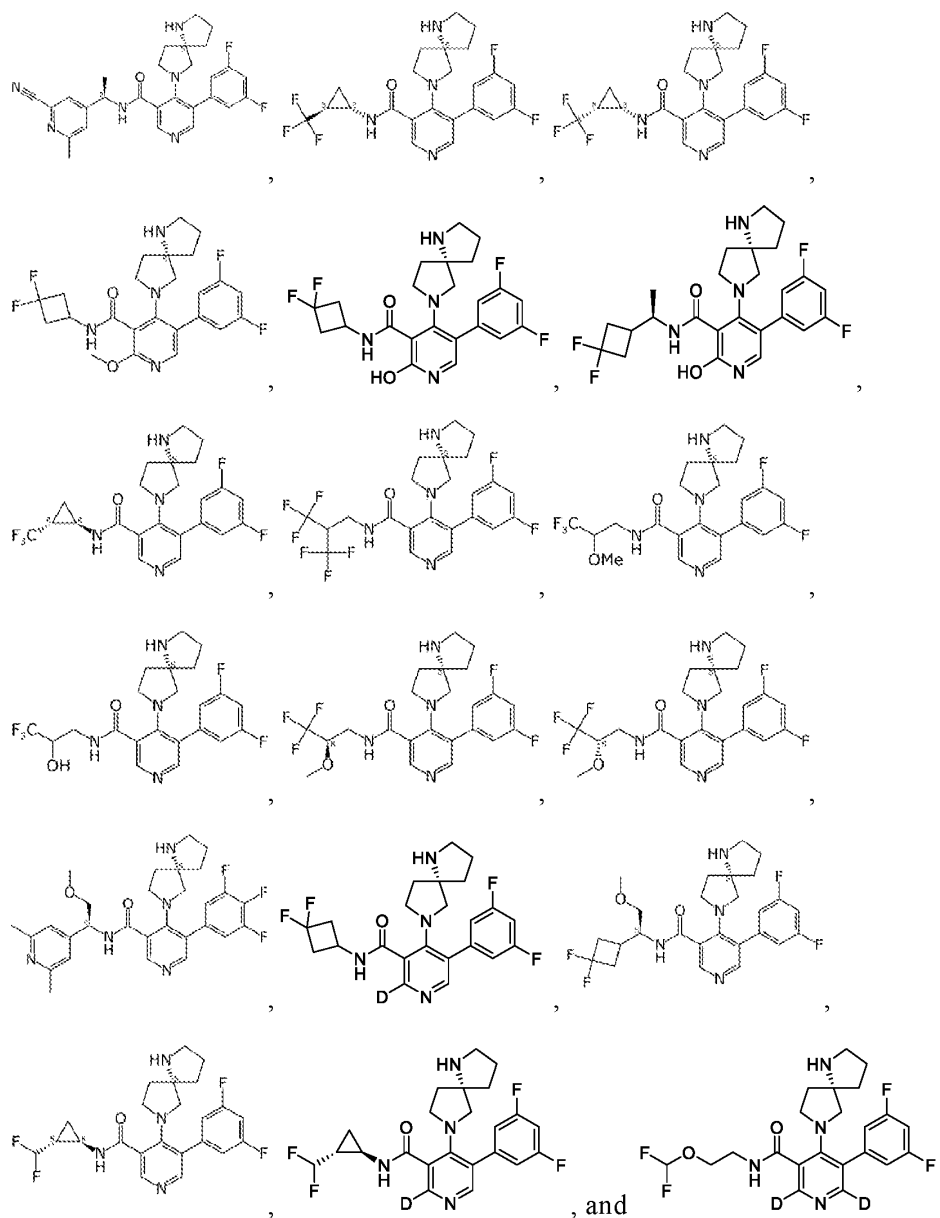
wherein R_1 is

72. The compound of any one of claims 55-71, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (Ib), or a pharmaceutically acceptable salt thereof:

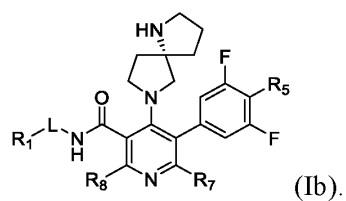


73. The compound of claim 55, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:



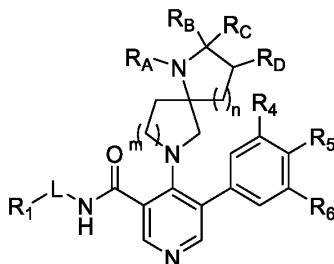


74. The compound of claim 73, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (Ib):



75. The compound of any one of claims 1-52, 54-72, and 74, or a pharmaceutically acceptable salt thereof, wherein R_7 is H and R_8 is H.

76. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of Formula (Id), or a pharmaceutically acceptable salt thereof:



wherein:

R_1 is unsubstituted or substituted C_{1-4} alkyl, unsubstituted or substituted C_{3-5} cycloalkyl, unsubstituted or substituted aryl, or unsubstituted or substituted 6-membered heteroaryl, wherein if R_1 is substituted then R_1 is substituted with 1-3 X, wherein each X is independently selected from F, Cl, methyl, ethyl, trifluoromethoxy, and CN;

L is a bond or CR_2R_3 , wherein R_2 is H, and R_3 is H or methyl;

R_4 is H, F, or Cl;

R_5 is H or F;

R_6 is H, F, or Cl;

R_A is H, $C(O)OEt$, or $C(O)Me$;

R_B is H, D, or methyl;

R_C is H or D;

R_D is H or F;

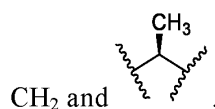
m is an integer selected from 0 or 1; and

n is an integer selected from 0, 1, and 2.

77. The compound of claim 76, or a pharmaceutically acceptable salt thereof, wherein L is a bond.

78. The compound of claim 76, or a pharmaceutically acceptable salt thereof, wherein L is CR_2R_3 .

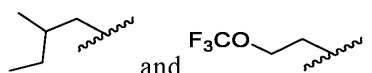
79. The compound of any one of claims 76 and 78, or a pharmaceutically acceptable salt thereof, wherein L is selected from the group consisting of:



80. The compound of any one of claims 76-79, or a pharmaceutically acceptable salt thereof, wherein R₁ is unsubstituted or substituted C₁₋₄ alkyl.

81. The compound of claim 80, or a pharmaceutically acceptable salt thereof, wherein if R₁ is substituted then R₁ is substituted with methyl or trifluoromethoxy.

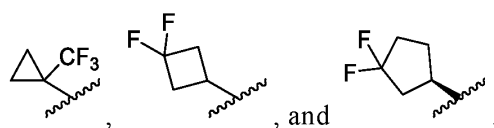
82. The compound of any one of claims 76-81, or a pharmaceutically acceptable salt thereof, wherein R₁ is selected from the group consisting of:



83. The compound of any one of claims 76-79, or a pharmaceutically acceptable salt thereof, wherein R₁ is unsubstituted or substituted C₃₋₅ cycloalkyl.

84. The compound of claim 83, or a pharmaceutically acceptable salt thereof, wherein if R₁ is substituted then R₁ is substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro and trifluoromethyl.

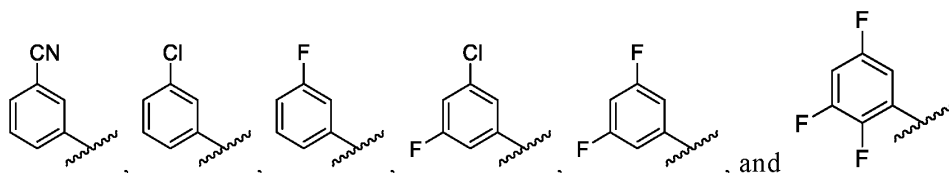
85. The compound of any one of claims 76-79, or a pharmaceutically acceptable salt thereof, wherein R₁ is selected from the group consisting of:



86. The compound of any one of claims 76-79, or a pharmaceutically acceptable salt thereof, wherein R₁ is unsubstituted or substituted phenyl.

87. The compound of claim 86, or a pharmaceutically acceptable salt thereof, wherein if R₁ is substituted then R₁ is substituted with 1-3 X, wherein each X is independently selected from the group consisting of fluoro, chloro, and CN.

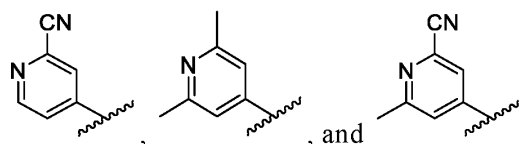
88. The compound of any one of claims 76-79, or a pharmaceutically acceptable salt thereof, wherein R₁ is selected from the group consisting of:



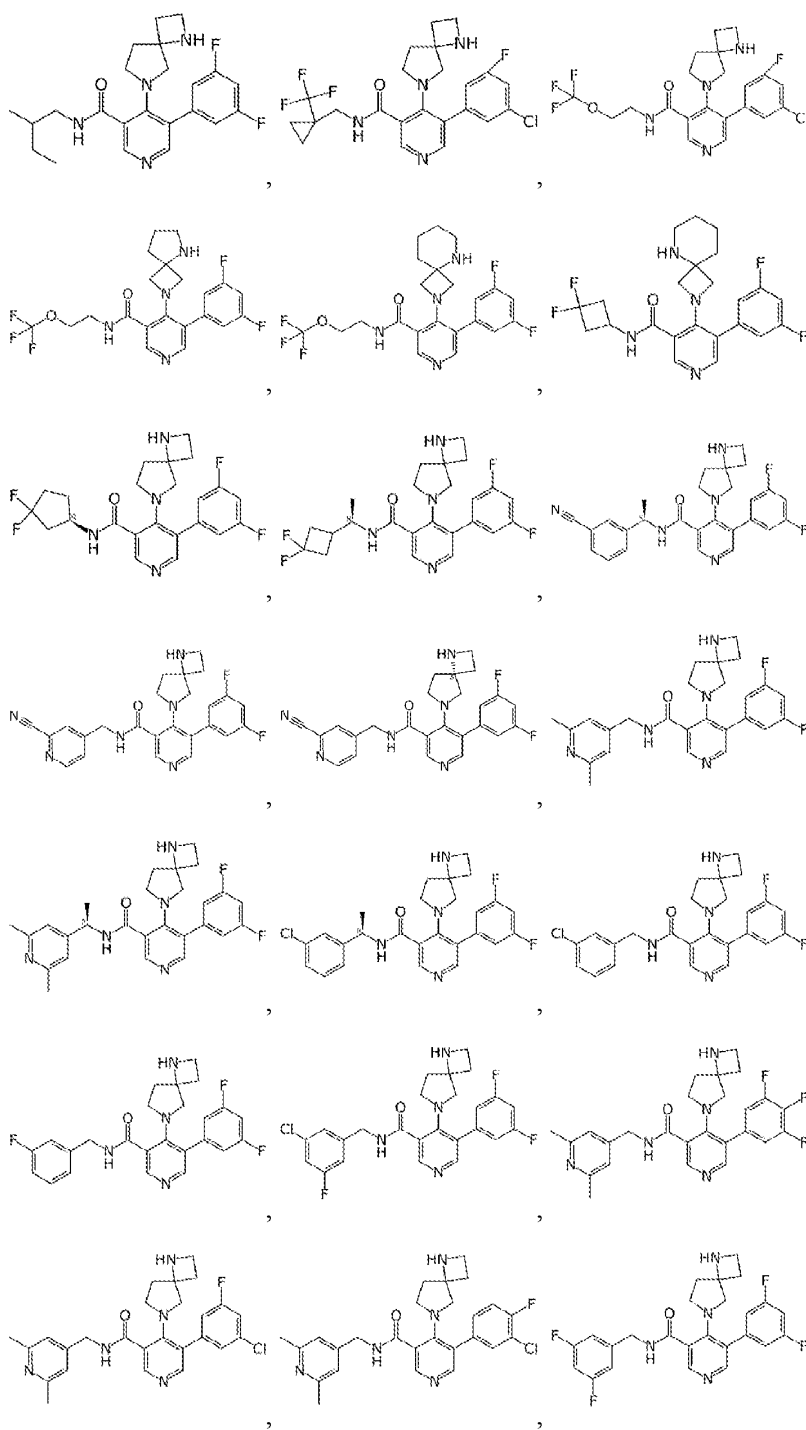
89. The compound of any one of claims 76-79, or a pharmaceutically acceptable salt thereof, wherein R₁ is unsubstituted or substituted pyridinyl.

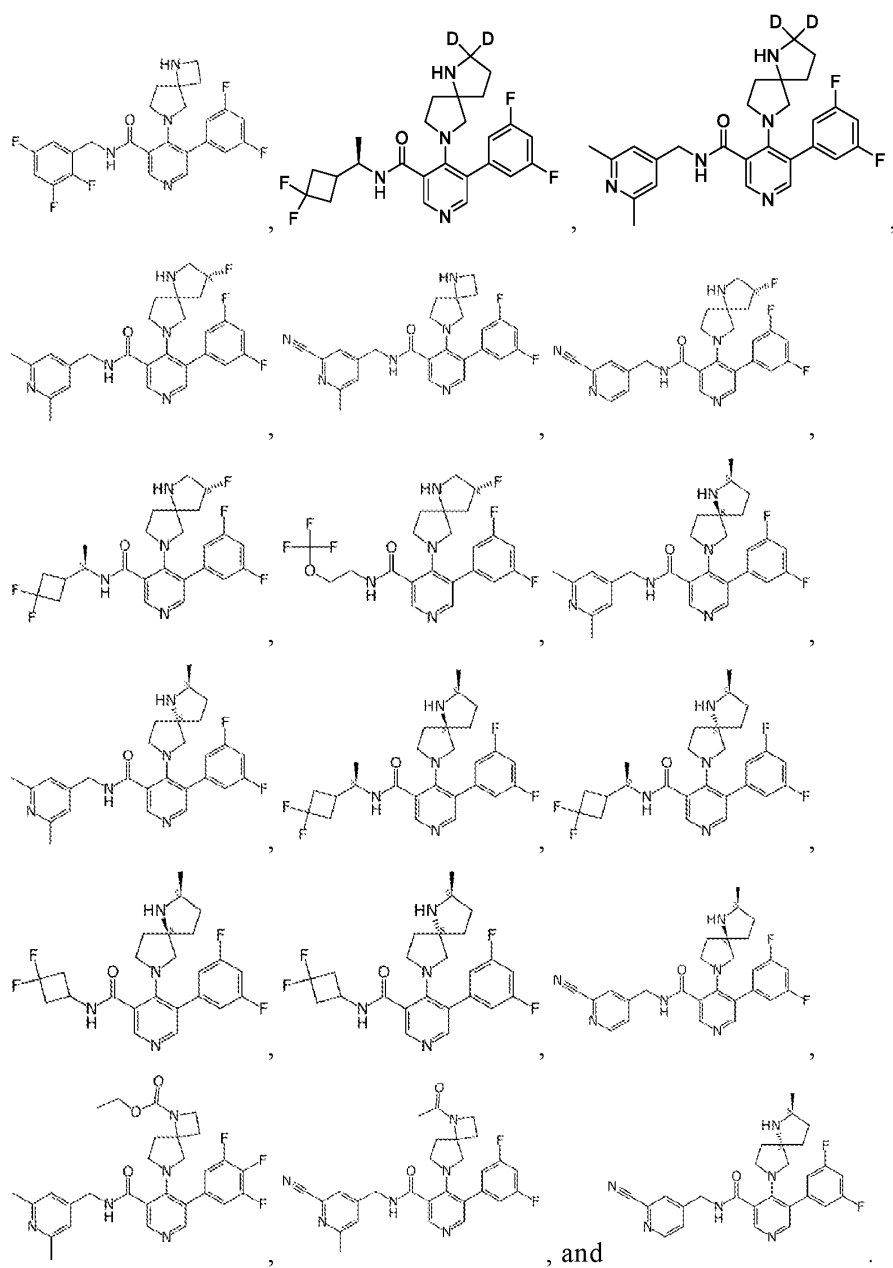
90. The compound of claim 89, or a pharmaceutically acceptable salt thereof, wherein if R₁ is substituted then R₁ is substituted with 1-2 X, wherein each X is independently selected from the group consisting of methyl and CN.

91. The compound of any one of claims 76-79, or a pharmaceutically acceptable salt thereof, wherein R₁ is selected from the group consisting of:

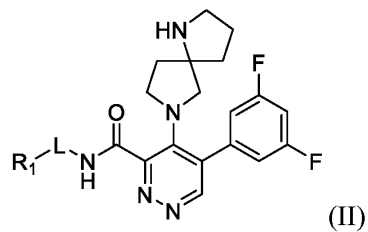


92. The compound of claim 76, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:





93. A compound of Formula (II), or a pharmaceutically acceptable salt thereof:

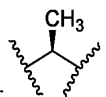


wherein:

R_1 is unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted aryl, or unsubstituted or substituted 6-membered heteroaryl, wherein if R_1 is substituted then R_1 is substituted with 1-2 X, wherein each X is independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} fluoroalkyl, C_{1-6} fluoroalkoxy, and CN; and
L is a bond or CR_2R_3 , wherein R_2 is H, and R_3 is H or methyl.

94. The compound of claim 93, or a pharmaceutically acceptable salt thereof, wherein L is a bond.

95. The compound of any one of claims 93, or a pharmaceutically acceptable salt thereof,

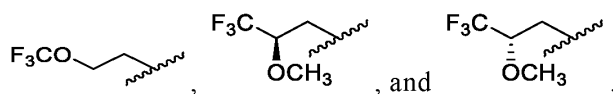


wherein L is CH_2 or

96. The compound of any one of claims 93-95, or a pharmaceutically acceptable salt thereof, wherein R_1 is unsubstituted or substituted ethyl.

97. The compound of claim 96, or a pharmaceutically acceptable salt thereof, wherein if R_1 is substituted then R_1 is substituted with 1-2 X, wherein each X is independently selected from the group methoxy and trifluoromethoxy.

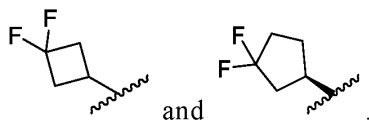
98. The compound of any one of claims 93-97, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from the group consisting of:



99. The compound of any one of claims 93-95, or a pharmaceutically acceptable salt thereof, wherein R_1 is unsubstituted or substituted C_{4-5} cycloalkyl.

100. The compound of claim 99, or a pharmaceutically acceptable salt thereof, wherein if R_1 is substituted then R_1 is substituted with fluoro.

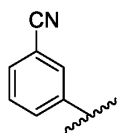
101. The compound of any one of claims 93-95, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from the group consisting of:



102. The compound of any one of claims 93-95, or a pharmaceutically acceptable salt thereof, wherein R_1 is unsubstituted or substituted phenyl.

103. The compound of claim 102, or a pharmaceutically acceptable salt thereof, wherein if R_1 is substituted then R_1 is substituted with CN.

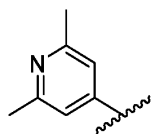
104. The compound of any one of claims 93-95, or a pharmaceutically acceptable salt thereof, wherein R_1 is:



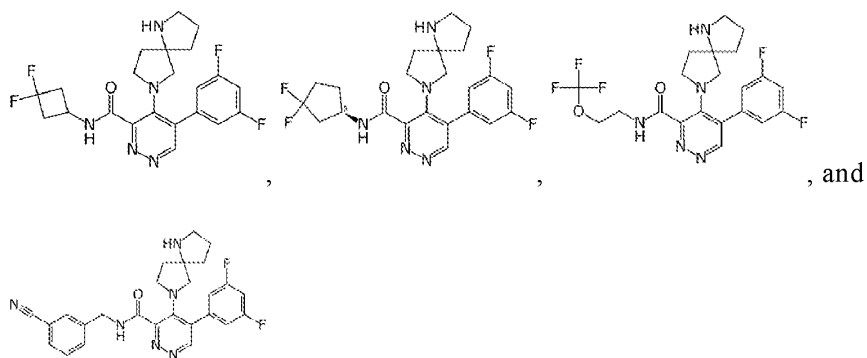
105. The compound of any one of claims 93-95, or a pharmaceutically acceptable salt thereof, wherein R_1 is unsubstituted or substituted pyridinyl.

106. The compound of claim 105, or a pharmaceutically acceptable salt thereof, wherein if R_1 is substituted then R_1 is substituted with methyl.

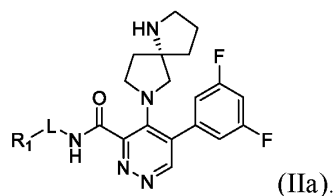
107. The compound of any one of claims 93-95, or a pharmaceutically acceptable salt thereof, wherein R_1 is:



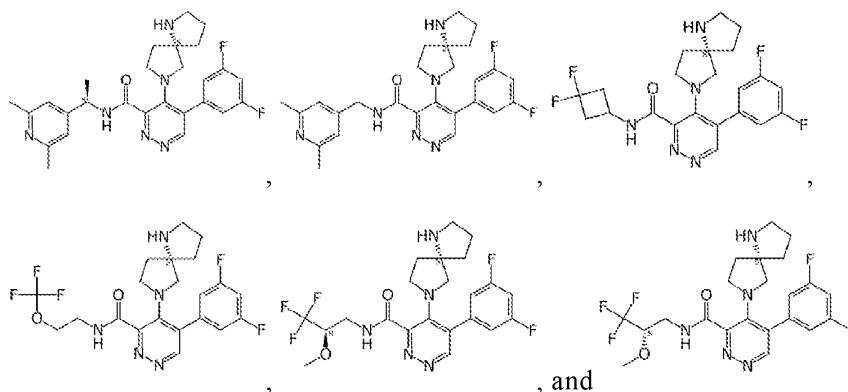
108. The compound of claim 93, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:



109. The compound of any one of claims 93-107, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (IIa):



110. The compound of claim 109, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:



111. A method of treating a disorder selected from the group consisting of polycystic kidney disease, polycystic liver disease, and ciliopathies, comprising administering to a subject in need thereof a compound of any one of claims 1-110, or a pharmaceutically acceptable salt thereof.

112. The method of claim 111, wherein the disorder is polycystic kidney disease.

113. The method of any one of claims 111-112, wherein the polycystic kidney disease is autosomal dominant polycystic kidney disease (ADPKD).

114. A pharmaceutical composition comprising a compound of any one of claims 1-110, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.