SUBSTITUTED 3-(5-(4-HYDROXYPIPERIDIN-4-YL)-1-OXOISOINDOLIN-2-YL)PIPERIDINE-2,6-DIONE DERIVATIVES AND 3-(2-(4-HYDROXYPIPERIDIN-4-YL)-5-OXO-5,7-DIHYDRO-6H-PYRROLO[3,4-B]PYRIDIN-6-YL)PIPERIDINE-2,6-DIONE DERIVATIVES AND USES THEREOF

CLAIM OF PRIORITY

This application claims priority to U.S. Application No. 63/547,061, filed November 2, 2023, and U.S. Application No. 63/547,063, filed November 2, 2023. The contents of the foregoing applications are incorporated herein by reference in their entirety.

FIELD OF THE DISCLOSURE

The present disclosure relates to substituted 3-(5-(4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione compounds and substituted 3-(2-(4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione compounds and compositions for modulation of hypoxia inducible factor 1 beta (HIF-1β) and their use for the treatment of HIF-1β-dependent diseases or disorders or where reduction of HIF-1β protein levels can ameliorate a disease or disorder.

BACKGROUND OF THE DISCLOSURE

The HIF transcription factors are master regulators of the cellular response to hypoxia. The HIF transcriptional regulator acts as a heterodimeric complex consisting of the constitutively expressed hypoxia inducible factor 1 beta (HIF-1β, also known as ARNT) and either of the two HIF-α isoforms, HIF-1α or HIF-2α. HIF-1β is a key player in both the hypoxic-response pathway and the aryl hydrocarbon receptor (AHR) pathway. The first evidence provided that the HIF heterodimer not only activates the erythropoietin gene but is also part of a widespread oxygen-sensing and signal transduction mechanism was demonstrated when HIF activity was detected in various non-erythropoietin-producing cell lines cultured under hypoxic conditions (Wang and Semenza, *Proc. Natl. Acad. Sci. USA*, 1993, 90, 4304-4308; Maxwell et al., *Proc. Natl. Acad. Sci. USA*, 1993, 90, 2423-2427).

Oxygen supply to tissues is essential in maintaining mammalian cell function and physiology and a deficiency in oxygen supply to tissues is a characteristic of a number of conditions in which there is insufficient blood flow to provide adequate oxygenation. Examples of diseases affected by inadequate oxygen supply include ischemic disorders, cancer, and atherosclerosis. Activation of a signaling cascade occurs in response to this hypoxic environment in tissues which drives the induction or repression of the transcription of a multitude of genes implicated in events such as angiogenesis (neo-vascularization),

glucose metabolism, and cell survival/death. A key to this hypoxic transcriptional response lies in the transcription factors, the hypoxia inducible factors (HIF).

It has been shown that both HIF-α isoforms are rapidly degraded under normoxic conditions due to the oxygen-dependent hydroxylation of specific proline residues that mark the proteins for proteasomal degradation (Jewell, et al., *Faseb. J.*. 2001, 15, 1312-1314; Gorlach, et al., *Biochim. BioPhase. Acta*, 2000, 1493, 125-134) and that under hypoxic conditions this hydroxylation is reversed, and the protein is further stabilized by phosphorylation (Wang et al., *Biochip. Biophys. Res. Commun*, 1995, 216, 669-675). Consequently, the HIF-α proteins are then translocated to the nucleus, where they interact with HIF-1β to form a heterodimeric transcription factor (Kallio et al., *Embo* J, 1998, 17, 6573-65, 86). The dimerization step has been shown in HIF-1β deficient cells to be an absolute requirement for the transcriptional activation of hypoxia response element genes (Wood et al., *J. Biol. Chem.*, 1996, 271, 15117-15123). As a result, there are categories of genes that are activated by the HIF dimer which include oxygen transport genes, such as erythropoietin (Semenza, et al., *J. Biol. Chem.*, 1994, 269, 23757- 23763) and transferrin (Rolfs et al., *J. Biol. Chem.*, 1997, 272, 20055-20062); as well as genes involved in angiogenesis, such as VEGF (Levy et al., *J. Biol. Chem.*, 1995, 270, 13333-13340); and genes involved in anaerobic metabolism, such as glucose transporter 1 (Ebert et al., *J. Biol. Chem.*, 1995, 270, 29083-29089). It is thought that hypoxia-induced genes such as VEGF play a role in promoting angiogenesis and subsequent tumor growth (Harris, *Nat. Rev. Cancer*, 2002, 2, 38-47).

Cellular oxygen concentration precisely regulates HIF transcriptional activity. While changes in oxygen levels do not affect HIF-1β protein levels, the abundance of the HIF-α subunits is markedly increased upon exposure of cells to hypoxia, primarily due to stabilization of the alpha subunits (Safran and Kaelin, *J. Clin. Invest.*, 2003, 111, 779-783). The HIF-2α/HIF-1β heterodimer protein, which contains the core recognition sequence 5'-TACGTG-3', binds to the hypoxic response element and is found in the cis-regulatory regions of hypoxia-regulated genes (Ema, et al., *Proc. Natl. Acad. Sci. U.S.A.*, 1997, 94, 4273-4278; Hogenesch, et al., *J. Biol. Chem.*, 1997, 272, 8581-8593). It has been shown that binding of the heterodimer to the hypoxia-responsive element (HRE) induces gene expression (Wiesener, et al., *Blood*, 1998, 92, 2260-2268).

A range of other genes regulated by the dioxin response element (DRE) can also be activated by HIF dimers resulting in some of the toxic and carcinogenic effects associated with many of the AHR ligands, such as immunotoxicity, developmental and reproductive toxicity, disruption of endocrine pathways, wasting syndrome, and tumor promotion (*Safe Toxicol. Lett.*, 2001, 120, 1-7). It has been demonstrated that the AHR/HIF-1β heterodimer directly associates with the estrogen receptors ER-α and ER-β and that this association results in the recruitment of unliganded estrogen receptor and coactivator

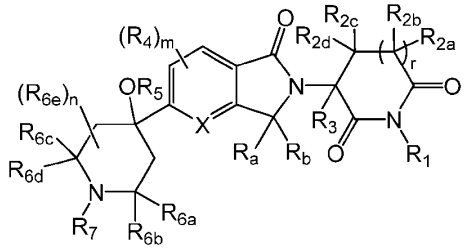
p300 to estrogen-responsive gene promoters. This association has been shown to lead the activation of transcription and estrogenic effects and to give rise to the adverse estrogen-related actions of dioxin-type environmental contaminants (Ohtake et al., *Nature*, 2003, 423, 545-550).

In summary, HIF-1β plays an important role in both the hypoxia-induced and AHR signaling pathways, which have been linked to various forms of malignancies (Harris, *Nat. Rev. Cancer*, 2002, 2, 8-47; *Safe Toxicol. Lett.*, 2001, 120, 1-7). The angiogenic promoting capabilities of HIF-1β also it a potential therapeutic target for a variety of angiogenic disorders, such as arthritis, cardiovascular diseases, skin conditions, aberrant wound healing and ocular conditions (*e.g.*, macular degeneration, diabetic retinopathy, diabetic macular edema and retinopathy of prematurity). Reduction of HIF-1β levels with small molecule modulators therefore has the potential to be a treatment for a range of diseases, including cancers, von Hippel-Lindau (VHL) disease, iron overload disorders, cardiovascular diseases, pulmonary arterial hypertension (PAH), autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, bacterial infections, fungal infections, parasitic infections, metabolic diseases, allergic and genetic diseases and other HIF-related diseases. For this reason, there remains a considerable need for novel and potent small molecule modulators of HIF-1β.

SUMMARY OF THE DISCLOSURE

The compounds of the disclosure have use as therapeutic agents, particularly for cancers, von Hippel-Lindau (VHL) disease, iron overload disorders, cardiovascular diseases, pulmonary diseases (e.g., pulmonary arterial hypertension (PAH)), autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, bacterial infections, fungal infections, parasitic infections, metabolic diseases, allergic and genetic diseases, and other HIF-1β-related diseases. In one aspect, the compounds of the disclosure have HIF-1β degrader activity, preferably having such activity at or below the 50 μM level, and more preferably having such activity at or below the 10 μM level. The compounds of the disclosure have usefulness in treating cancer, von Hippel-Lindau (VHL) disease, iron overload disorders, cardiovascular diseases, pulmonary arterial hypertension (PAH), autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, bacterial infections, fungal infections, parasitic infections, metabolic diseases, allergic and genetic diseases, and other diseases for which such degrader activity would be beneficial.

In one aspect, the present disclosure features a compound of Formula (I):



(I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R_a and R_b are each independently H, D, or (C_1-C_6)alkyl; R_1 is H, D, -C(O)R_{11}, -$CH_2OC(O)R_{11}$, -$CH_2OC(O)NHR_{12}$, -$CH_2OC(O)OR_{12}$, -$P(O)(OR_{12})_2$, -$CH_2OP(O)(OR_{12})_2$, -$CH_2OP(O)(OH)OR_{12}$, -$CH_2OP(O)(R_{12})_2$, -$CH_2OC(O)CH_2NHC(O)CH_2NH_2$, -$CH_2OC(O)CH(R_{12'})NHR_{12'}$, -$CH_2OC(O)(CH_2)_qC(O)OR_{12'}$, or -$CH_2OC(O)$-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S); R_{2a}, R_{2b}, R_{2c}, and R_{2d} are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, halogen, or -OH, wherein two of R_{2a}, R_{2b}, R_{2c}, and R_{2d} may be taken together with the carbon atom to which they are attached form a (C_3-C_7)carbocyclyl or (C_3-C_7)spirocarbocyclyl; R_3 is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, or halogen, wherein R_3 may be taken together with one of R_{2a}, R_{2b}, R_{2c}, and R_{2d} with the carbon atom to which they are attached to form a (C_3-C_7)carbocyclyl or (C_3-C_7)spirocarbocyclyl; each R_4 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)halohalkyl, or halogen; each $R_{4'}$ is independently at each occurrence H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)deuteroalkoxy, (C_1-C_6)haloalkoxy, (C_3-C_7)carbocyclyl, O(C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$; R_5 is H, D, (C_2-C_6)alkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)aminoalkyl, (C_1-C_6)alkyl-O-(C_1-C_6)hydroxyalkyl, -C(O)R_{12}, -$CH_2OC(O)R_{12}$, -$CH_2OC(O)N(R_{12})_2$, -$CH_2OC(O)_2R_{12}$, -$P(O)(OR_{12})_2$, -$CH_2OP(O)(OH)OR_{12}$, or -$CH_2OP(O)(R_{12})_2$; R_{6a}, R_{6b}, R_{6c}, and R_{6d} are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy,, or (C_3-C_7)carbocyclyl; or two of R_{6a}, R_{6b}, R_{6c}, and R_{6d} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl, (C_3-C_7)spirocarbocyclyl, 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl, heterocyclyl, and spiroheterocyclyl are optionally substituted

with one or more R_{10}; each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, -(C_1-C_6)alkylene-O-(C_1-C_6)alkyl, (C_6-C_{10})aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one or more R_{13}, the aryl and heteroaryl are optionally substituted with one or more R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{23}; or two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)carbocyclyl, (C_3-C_7)spirocarbocyclyl, a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl, heterocyclyl, and spiroheterocyclyl are optionally substituted with one or more R_{15}; or one R_{6e} is taken together with any one of R_{6a}, R_{6b}, R_{6c}, and R_{6d} and the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{15}; R_7 is (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_3-C_7)carbocyclyl, wherein alkyl, haloalkyl, hydroxyalkyl, halohydroxyalkyl, and carbocyclyl are optionally substituted with one or more substituents independently selected from R_{21}, D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$,-C(O)$NR_{32}R_{33}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$; when $R_{4'}$ is H, m is 1, n is 0 and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are all simultaneously H, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)alkyl, or (C_3-C_7)carbocyclyl optionally substituted with one or more substituents independently selected from R_{41}, D, (C_1-C_6)alkoxy, -OR_{16a}, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one or more R_8, the heteroaryl is optionally substituted with one or

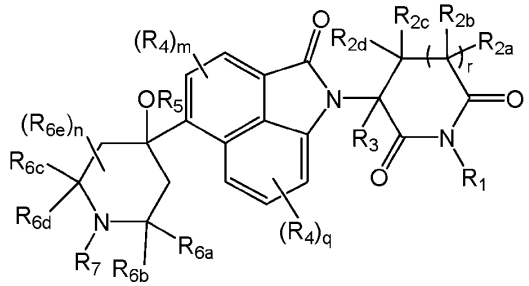
more R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$; when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)alkyl, or (C_3-C_7)carbocyclyl optionally substituted with one or more substituents independently selected from R_{41}, D, (C_1-C_6)alkoxy, -OR_{16a}, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$;when $R_{4'}$ is (C_1)alkyl, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one or more R_8, the heteroaryl is optionally substituted with one or more R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$; when $R_{4'}$ is D, (C_2-C_4)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)alkyl, or (C_3-C_7)carbocyclyl optionally substituted with one or more substituents independently selected from R_{41}, D, (C_1-C_6)alkoxy, -OR_{16a}, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$; R_8 and $R_{8'}$ are each independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -$C(O)NR_{32}R_{33}$, -$C(O)OR_{32}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms

selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the alkyl, deuteroalkyl, haloalkyl, alkoxy, haloalkoxy, hydroalkyl, phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more substituents selected from (C_1-C_6)alkyl, (C_3-C_7)carbocyclyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -$C(O)NR_{37}R_{38}$, -$C(O)R_{37}$, -$C(O)OR_{37}$, -SF_5, -SR_{40}, and -CN, and R_{13}; or two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R_{10}; two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{10}; or two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{10}; or two $R_{8'}$ when on the same carbon atom form C=(O); each R_9 and $R_{9'}$ are each independently at each occurrence H or (C_1-C_6)alkyl; R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, C(O)OR_9, -$C(O)R_9$, and -$C(O)NR_9R_{9'}$; R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN; R_{12} is independently at each occurrence H, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN; $R_{12'}$ is independently at each occurrence H or (C_1-C_6)alkyl; each R_{13} is independently at

each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{14}R_{14'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein carbocyclyl and heterocyclyl are optionally substituted with one or more R_{20} and the aryl and heteroaryl are optionally substituted with one or more R_{21}; or two R_{13} when on the same carbon atom may be taken together to form C=(O); R_{14} and $R_{14'}$ are each independently at each occurrence H or (C_1-C_6)alkyl; each R_{15} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$ optionally substituted with one or more R_{20}; R_{16} and $R_{16'}$ are each independently at each occurrence H or (C_1-C_6)alkyl; R_{16a} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{17} is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{18} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{19} is (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{20} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; each R_{22} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{28}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{22}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; each R_{23} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-

C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{29}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{23} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{30} and R_{31} are each independently at each occurrence H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_3-C_7)carbocyclyl, -C(O)R_{34}, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl or heteroaryl can be substituted with one or more R_{17}; R_{32}, R_{33}, and R_{34} are each independently at each occurrence H or (C_1-C_6)alkyl; R_{35} and R_{36} are each independently at each occurrence H, (C_1-C_6)alkyl, or -C(O)R_{39}; R_{37}, R_{38}, and R_{39} are each independently at each occurrence H or (C_1-C_6)alkyl; R_{40} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; two R_{41}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{10}; or two R_{41} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{10}; or m and p are each independently 0, 1, or 2; q is 1, 2, or 3; n is 0, 1, 2, 3 or 4; and r is 0 or 1.

In another aspect, the present disclosure features a Compound of Formula (II):



(II), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R_1 is H, D, -C(O)R_{11}, -$CH_2OC(O)R_{11}$, -$CH_2OC(O)NHR_{12}$, -$CH_2OC(O)OR_{12}$, -P(O)(OR_{12})$_2$, -$CH_2OP(O)(OR_{12})_2$, -$CH_2OP(O)(OH)OR_{12}$, -$CH_2OP(O)(R_{12})_2$, -$CH_2OC(O)CH_2NHC(O)CH_2NH_2$, -$CH_2OC(O)CH(R_{12'})NHR_{12'}$, -$CH_2OC(O)$-$(CH_2)_qC(O)OR_{12'}$, or -$CH_2OC(O)$-(5- or 6-membered

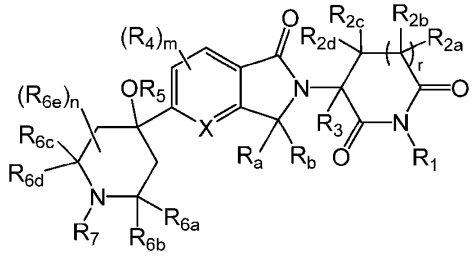
heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S); R_{2a}, R_{2b}, R_{2c}, and R_{2d} are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, halogen, or -OH, wherein two of R_{2a}, R_{2b}, R_{2c}, and R_{2d} may be taken together with the carbon atom to which they are attached form a (C_3-C_7)carbocyclyl or (C_3-C_7)spirocarbocyclyl; R_3 is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, or halogen, wherein R_3 may be taken together with one of R_{2a}, R_{2b}, R_{2c}, and R_{2d} with the carbon atom to which they are attached to form a (C_3-C_7)carbocyclyl or (C_3-C_7)spirocarbocyclyl; each R_4 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)halohalkyl, or halogen; R_5 is H, D, (C_2-C_6)alkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)aminoalkyl, (C_1-C_6)alkyl-O-(C_1-C_6)hydroxyalkyl, -C(O)R_{12}, -$CH_2OC(O)R_{12}$, -$CH_2OC(O)N(R_{12})_2$, -$CH_2OC(O)_2R_{12}$, -P(O)$(OR_{12})_2$, -$CH_2OP(O)(OH)OR_{12}$, or -$CH_2OP(O)(R_{12})_2$; R_{6a}, R_{6b}, R_{6c}, and R_{6d} are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy,, or (C_3-C_7)carbocyclyl; or two of R_{6a}, R_{6b}, R_{6c}, and R_{6d} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl, (C_3-C_7)spirocarbocyclyl, 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl, heterocyclyl, and spiroheterocyclyl are optionally substituted with one or more R_{10}; each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, -(C_1-C_6)alkylene-O-(C_1-C_6)alkyl, (C_6-C_{10})aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one or more R_{13}, the aryl and heteroaryl are optionally substituted with one or more R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{23}; or two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)carbocyclyl, (C_3-C_7)spirocarbocyclyl, a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl, heterocyclyl, and spiroheterocyclyl are optionally substituted with one or more R_{15}; or one R_{6e} is taken together with any one of R_{6a}, R_{6b}, R_{6c}, and R_{6d} and the atoms to which they are attached

form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{15}; R_7 is (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_3-C_7)carbocyclyl, wherein alkyl, haloalkyl, hydroxyalkyl, halohydroxyalkyl, and carbocyclyl are optionally substituted with one or more substituents independently selected from R_{21}, D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$,-C(O)$NR_{32}R_{33}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$; R_8 and $R_{8'}$ are each independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -C(O)$NR_{32}R_{33}$, -C(O)OR_{32}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the alkyl, deuteroalkyl, haloalkyl, alkoxy, haloalkoxy, hydroalkyl, phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more substituents selected from (C_1-C_6)alkyl, (C_3-C_7)carbocyclyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -C(O)$NR_{37}R_{38}$, -C(O)R_{37}, -C(O)OR_{37}, -SF_5, -SR_{40}, and -CN, and R_{13}; or two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R_{10}; two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{10}; or two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4

heteroatoms selected from O, NH, N, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{10}; or two $R_{8'}$ when on the same carbon atom form C=(O); each R_9 and $R_{9'}$ are each independently is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{13}R_{13'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein carbocyclyl and heterocyclyl are optionally substituted with one or more R_{20} and the aryl and heteroaryl are optionally substituted with one or more R_{21}; R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, - OH, -NH_2, -SF_5, -SR_{25}, -CN, C(O)OR_9, -C(O)R_9, and -C(O)NR_9R_9; R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN; R_{12} is independently at each occurrence H, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN; $R_{12'}$ is independently at each occurrence H or (C_1-C_6)alkyl; R_{13} and $R_{13'}$ are each independently at each occurrence H or (C_1-C_6)alkyl; each R_{14} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$; R_{15} and $R_{15'}$ are each independently at each occurrence H or (C_1-C_6)alkyl; R_{15a} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; each R_{16} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{16}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected

from O, N, NH, and S; R_{17} is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;R_{18} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{19} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{20} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, and R_{27} are each independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{30} and R_{31} are each independently at each occurrence H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_3-C_7)carbocyclyl, -C(O)R_{32}, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl or heteroaryl can be substituted with one or more R_{17}; R_{30}, R_{31}, and R_{32} are each independently at each occurrence H or (C_1-C_6)alkyl; R_{33} and R_{34} are each independently at each occurrence H, (C_1-C_6)alkyl, or -C(O)R_{37}; R_{35}, R_{36}, and R_{37} are each independently at each occurrence H or (C_1-C_6)alkyl; R_{38} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; m is 0, 1, or 2; q is 1, 2, or 3; n is 0, 1, 2, 3, or 4; and r is 0 or 1.

In another aspect, the present disclosure features a Compound of Formula (III):



(III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein X is N or N(O); R_a and R_b are each independently H, D, or (C_1-C_6)alkyl; R_1 is H, D, -C(O)R_{11}, -$CH_2OC(O)R_{11}$, -$CH_2OC(O)NHR_{12}$, -$CH_2OC(O)OR_{12}$, -P(O)(OR_{12})$_2$, -$CH_2OP(O)(OR_{12})_2$, -$CH_2OP(O)(OH)OR_{12}$, -$CH_2OP(O)(R_{12})_2$, -$CH_2OC(O)CH_2NHC(O)CH_2NH_2$, -$CH_2OC(O)CH(R_{12'})NHR_{12'}$, -$CH_2OC(O)(CH_2)_qC(O)OR_{12'}$, or -$CH_2OC(O)$-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S); R_{2a}, R_{2b}, R_{2c}, and R_{2d} are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, halogen, or -OH, wherein two of R_{2a}, R_{2b}, R_{2c}, and R_{2d} may be taken together with the carbon atom to which they are attached form a (C_3-C_7)carbocyclyl or (C_3-C_7)spirocarbocyclyl; R_3 is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, or halogen, wherein R_3 may be taken together with one of R_{2a}, R_{2b}, R_{2c}, and R_{2d} with the carbon atom to which they are attached to form a (C_3-C_7)carbocyclyl or (C_3-C_7)spirocarbocyclyl; each R_4 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, or halogen; R_5 is H, D, (C_2-C_6)alkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)aminoalkyl, (C_1-C_6)alkyl-O-(C_1-C_6)hydroxyalkyl, -C(O)R_{12}, -$CH_2OC(O)R_{12}$, -$CH_2OC(O)N(R_{12})_2$, -$CH_2OC(O)_2R_{12}$, -P(O)(OR_{12})$_2$, -$CH_2OP(O)(OH)OR_{12}$, or -$CH_2OP(O)(R_{12})_2$; R_{6a}, R_{6b}, R_{6c}, and R_{6d} are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy,, or (C_3-C_7)carbocyclyl; or two of R_{6a}, R_{6b}, R_{6c}, and R_{6d} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl, (C_3-C_7)spirocarbocyclyl, 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl, heterocyclyl, and spiroheterocyclyl are optionally substituted with one or more R_{10}; each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, -(C_1-C_6)alkylene-O-(C_1-C_6)alkyl, (C_6-C_{10})aryl, 5- or 6-membered heteroaryl comprising 1 to 4

heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one or more R_{13}, the aryl and heteroaryl are optionally substituted with one or more R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{23}; or two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)carbocyclyl, (C_3-C_7)spirocarbocyclyl, a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl, heterocyclyl, and spiroheterocyclyl are optionally substituted with one or more R_{15}; or one R_{6e} is taken together with any one of R_{6a}, R_{6b}, R_{6c}, and R_{6d} and the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{15}; R_7 is (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_3-C_7)carbocyclyl, wherein alkyl, haloalkyl, hydroxyalkyl, halohydroxyalkyl, and carbocyclyl are optionally substituted with one or more substituents independently selected from R_{21}, D, (C_1-C_6)alkoxy, -SF_5, -SR_{14a}, -$NR_{14}R_{14'}$,-C(O)$NR_{29}R_{30}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$; R_8 and $R_{8'}$ are each independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -C(O)$NR_{29}R_{30}$, -C(O)OR_{29}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more substituents selected from (C_1-C_6)alkyl, (C_3-C_7)carbocyclyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl,

halogen, –OH, -$NR_{32}R_{33}$, -$C(O)NR_{34}R_{35}$, -$C(O)R_{34}$, -$C(O)OR_{34}$, -SF_5, -SR_{37}, and -CN; or two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R_{10}; two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{10}; or two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{10}; or two $R_{8'}$ when on the same carbon atom form C=(O); R_9 is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, or -CN; R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN; R_{12} is independently at each occurrence H, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN; $R_{12'}$ is independently at each occurrence H or (C_1-C_6)alkyl; each R_{13} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -$C(O)OR_{15'}$, -$C(O)R_{15}$, or -$C(O)NR_{15'}R_{15''}$; R_{14} and $R_{14'}$ are each independently at each occurrence H or (C_1-C_6)alkyl; R_{14a} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{15} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; $R_{15'}$ is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; each R_{16} is independently at each occurrence (C_1-C_6)alkoxy,

(C_1-C_6)haloalkoxy, -$NR_{17}R_{17'}$, -CN,(C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein carbocyclyl and heterocyclyl are optionally substituted with one or more R_{22} and the aryl and heteroaryl are optionally substituted with one or more R_{23}; R_{17} and $R_{17'}$ are each independently at each occurrence H or (C_1-C_6)alkyl; each R_{18} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{20}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{18}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{21}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{19} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; R_{20} and R_{21} are each independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; each R_{22} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{22} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; each R_{23} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; R_{24}, R_{25} and R_{26} are each independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{27} and R_{28} are each independently at each

occurrence H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_3-C_7)carbocyclyl, -C(O)R_{31}, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl or heteroaryl can be substituted with one or more R_{17}; R_{29}, R_{30}, and R_{31} are each independently at each occurrence H or (C_1-C_6)alkyl; R_{32} and R_{33} are each independently at each occurrence H, (C_1-C_6)alkyl, or -C(O)R_{36}; R_{34}, R_{35}, and R_{36} are each independently at each occurrence H or (C_1-C_6)alkyl; R_{37} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; q is 1, 2, or 3; m is 0, 1 or 2; n is 0, 1, 2, 3 or 4; r is 0 or 1.

In one aspect of the disclosure, the hydrogens in the Compound of Formula (I), (II), or (III) are present in the normal isotopic abundances. In a preferred aspect of the disclosure, the hydrogens are isotopically enriched in deuterium (D), as discussed in more detail concerning isotopes and isotopic enrichment below.

Another aspect of the present disclosure relates to a pharmaceutical composition comprising a therapeutically effective amount of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier or excipient. The pharmaceutical composition is useful in the treatment of HIF-1β-dependent diseases or disorders. The pharmaceutical composition may further comprise at least one additional pharmaceutical agent.

In another aspect, the present disclosure relates to a pharmaceutical composition comprising a therapeutically effective amount of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier or excipient for use in the treatment of an HIF-1β-dependent disease or disorder by reducing HIF-1β protein levels wherein reduction of HIF-1β protein levels treats the HIF-1β-dependent disease or disorder. The pharmaceutical composition is useful in the treatment of HIF-1β-dependent diseases or disorders. The pharmaceutical composition may further comprise at least one additional pharmaceutical agent.

Another aspect of the present disclosure relates to a pharmaceutical composition comprising a therapeutically effective amount of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier or excipient. The pharmaceutical composition is useful in the treatment of diseases or disorders affected by the reduction of HIF-1β protein levels. The pharmaceutical composition may further comprise at least one additional pharmaceutical agent.

In another aspect, the present disclosure relates to a method of degrading HIF-1β, comprising administering to a patient in need thereof an effective amount of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Another aspect of the present disclosure relates to a method of modulating HIF-1β levels comprising administering to a patient in need thereof an effective amount of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

In another aspect, the present disclosure relates to an *in vitro* method of reducing the proliferation of a cell, comprising contacting the cell with an effective amount of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Another aspect of the present disclosure relates to a method of treating a disease or disorder that is affected by the modulation of HIF-1β levels, comprising administering to a patient in need thereof a therapeutically effective amount of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. In one embodiment, the disease or disorder is selected from cancer, von Hippel-Lindau (VHL) disease, iron overload disorders, cardiovascular diseases, pulmonary arterial hypertension (PAH), autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, metabolic diseases, and allergic and genetic diseases. In another embodiment, the disease or disorder is selected from renal cell carcinoma (RCC), von Hippel-Lindau disease (VHL), pulmonary arterial hypertension (PAH), glioblastoma, colitis, Crohn's disease, ulcerative colitis, T cell leukemia or T cell lymphoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), melanoma, triple-negative breast cancer (TNBC), nasopharyngeal cancer (NPC), microsatellite stable colorectal cancer (mssCRC), thymoma, carcinoid, gastrointestinal stromal tumor (GIST), myeloid leukemia, and coronary heart disease.

In another aspect, the present disclosure relates to a method of treating cancer, comprising administering to a patient in need thereof a therapeutically effective amount of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. In one embodiment, the cancer is VHL-deficient cancer. In another embodiment, the cancer is selected from renal cell carcinoma (RCC), glioblastoma, T cell leukemia or T cell lymphoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), melanoma, triple-negative breast cancer (TNBC), nasopharyngeal cancer (NPC), microsatellite stable colorectal cancer (mssCRC), thymoma, carcinoid, gastrointestinal stromal tumor (GIST), and myeloid leukemia.

Another aspect of the present disclosure relates to a method for reducing HIF-1β levels, comprising administering to a subject in need thereof a therapeutically effective amount of a Compound of Formula

(I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

In another aspect, the present disclosure relates to a method of treating von Hippel-Lindau (VHL) disease, comprising administering to a patient in need thereof a therapeutically effective amount of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Another aspect of the present disclosure relates to a method of treating a neoplastic condition, comprising administering to a patient in need thereof a therapeutically effective amount of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

In another aspect, the present disclosure relates to a method of treating renal cell carcinoma (RCC), comprising administering to a patient in need thereof a therapeutically effective amount of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. In one embodiment, the renal cell carcinoma is clear cell renal cell carcinoma (ccRCC).

The present disclosure provides degraders of HIF-1β that are therapeutic agents in the treatment of diseases such as cancer, von Hippel-Lindau (VHL) disease, iron overload disorders, cardiovascular diseases, pulmonary arterial hypertension (PAH), autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, metabolic diseases, and allergic and genetic diseases, in the treatment of diseases affected by the modulation of HIF-1β protein levels, and in the treatment HIF-1β-dependent diseases or disorders.

In one embodiment, the disease or disorder that can be treated by the compounds of the present disclosure is selected from cancer, von Hippel-Lindau (VHL) disease, iron overload disorders, cardiovascular diseases, pulmonary arterial hypertension (PAH), autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, metabolic diseases, and allergic and genetic diseases, including but not limited to, renal cell carcinoma (RCC), von Hippel-Lindau disease (VHL), pulmonary arterial hypertension (PAH), glioblastoma, colitis, Crohn's disease, ulcerative colitis, T cell leukemia or T cell lymphoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), melanoma, triple-negative breast cancer (TNBC), nasopharyngeal cancer (NPC), microsatellite stable colorectal cancer (mssCRC), thymoma, carcinoid, gastrointestinal stromal tumor (GIST), myeloid leukemia, and coronary heart disease.

The present disclosure provides agents with novel mechanisms of action toward HIF-1β proteins in the treatment of various types of diseases including cancer von Hippel-Lindau (VHL) disease, iron overload disorders, cardiovascular diseases, pulmonary arterial hypertension (PAH), autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, metabolic

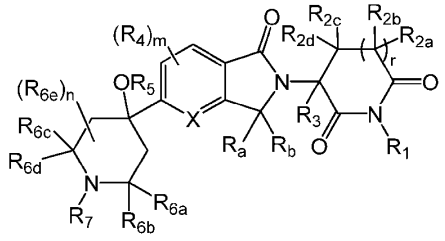
diseases, and allergic and genetic diseases, in the treatment of diseases affected by the modulation of HIF-1β protein levels, and in the treatment HIF-1β-dependent diseases or disorders. Ultimately the present disclosure provides the medical community with a novel pharmacological strategy for the treatment of diseases and disorders associated with HIF-1β proteins.

DETAILED DESCRIPTION OF THE DISCLOSURE

The present disclosure relates to compounds and compositions that are capable of modulating HIF-1β protein levels. The disclosure features methods of treating, preventing, or ameliorating a disease or disorder in which HIF-1β plays a role by administering to a patient in need thereof a therapeutically effective amount of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereo isomer, or tautomer thereof. The methods of the present disclosure can be used in the treatment of a variety of HIF-1β-dependent diseases and disorders by modulating HIF-1β protein levels. Modulation of HIF-1β protein levels through degradation provides a novel approach to the treatment, prevention, or amelioration of diseases including, but not limited to, cancer and metastasis, and other HIF-1β-dependent diseases or disorders.

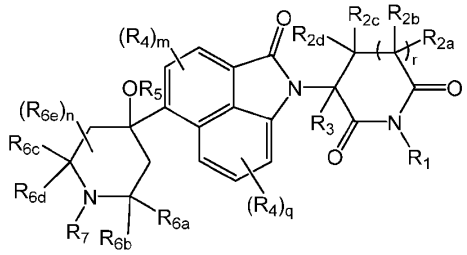
In one aspect, the compounds of the disclosure have use as therapeutic agents, particularly for cancers, von Hippel-Lindau (VHL) disease, iron overload disorders, cardiovascular diseases, pulmonary arterial hypertension (PAH), autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, bacterial infections, fungal infections, parasitic infections, metabolic diseases, allergic and genetic diseases and other HIF-1β-related diseases. In one aspect, the compounds of the disclosure have HIF-1β degradation activity, preferably having such activity at or below the 50 μM level, and more preferably having such activity at or below the 10 μM level. The compounds of the disclosure have usefulness in treating cancer and other diseases for which such degradation activity would be beneficial for the patient. In summary, the present disclosure provides novel HIF-1β degraders useful for the treatment of cancer, von Hippel-Lindau (VHL) disease, iron overload disorders, cardiovascular diseases, pulmonary arterial hypertension (PAH), autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, bacterial infections, fungal infections, parasitic infections, metabolic diseases, allergic and genetic diseases and other disease related to the modulation of HIF-1β-related diseases.

In a first aspect of the disclosure, the compounds of Formula (I) are described:



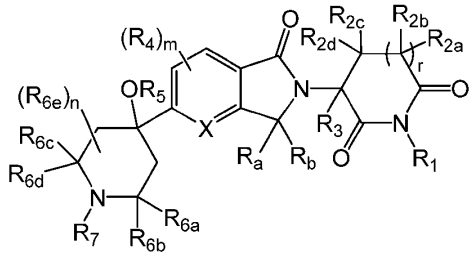
(I), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof, wherein R_a, R_b, R_1, R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, R_4, $R_{4'}$, R_5, R_{6a}, R_{6b}, R_{6c}, R_{6d}, R_{6e}, R_7, m, n, r and subvariables thereof are as defined herein.

In a second aspect of the disclosure, the compounds of Formula (II) are described:



(II), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof, wherein R_1, R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, R_4, R_5, R_{6a}, R_{6b}, R_{6c}, R_{6d}, R_{6e}, R_7, m, n, r and subvariables thereof are as defined herein.

In a second aspect of the disclosure, the compounds of Formula (III) are described:



(III), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof, wherein R_1, R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, R_4, R_5, R_{6a}, R_{6b}, R_{6c}, R_{6d}, R_{6e}, R_7, m, n, r and subvariables thereof are as defined herein.

The details of the disclosure are set forth in the accompanying description below. Although methods and materials similar or equivalent to those described herein can be used in the practice or of the present disclosure, illustrative methods and materials are now described. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning

as commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents and publications cited in this specification are incorporated herein by reference in their entireties.

Definition of Terms and Conventions Used

Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. As used in the specification and appended claims, however, unless specified to the contrary, the following terms have the meaning indicated and the following conventions are adhered to.

A. Chemical Nomenclature, Terms, and Conventions

In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, (C_1-C_{10})alkyl means an alkyl group or radical having 1 to 10 carbon atoms. In general, for groups comprising two or more subgroups, the last named group is the radical attachment point, for example, "alkylaryl" means a monovalent radical of the formula alkyl-aryl-, while "arylalkyl" means a monovalent radical of the formula aryl-alkyl-. Furthermore, the use of a term designating a monovalent radical where a divalent radical is appropriate shall be construed to designate the respective divalent radical and vice versa. Unless otherwise specified, conventional definitions of terms control and conventional stable atom valences are presumed and achieved in all formulas and groups. The articles "a" and "an" refer to one or more than one (*e.g.*, to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

The term "and/or" means either "and" or "or" unless indicated otherwise.

The term "optionally substituted" means that a given chemical moiety (*e.g.*, an alkyl group) can (but is not required to) be bonded other substituents (*e.g.*, heteroatoms). For instance, an alkyl group that is optionally substituted can be a fully saturated alkyl chain (*e.g.*, a pure hydrocarbon). Alternatively, the same optionally substituted alkyl group can have substituents different from hydrogen. For instance, it can, at any point along the chain be bounded to a halogen atom, a hydroxyl group, or any other substituent described herein. Thus, the term "optionally substituted" means that a given chemical moiety has the potential to contain other functional groups but does not necessarily have any further functional groups. Suitable substituents used in the optional substitution of the described groups include, without limitation, halogen, oxo, -OH, -CN, -COOH, -CH_2CN, -O-(C_1-C_6)alkyl, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, -O-(C_2-C_6)alkenyl, -O-(C_2-C_6)alkynyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, -OH, -OP(O)$(OH)_2$, -OC(O)(C_1-C_6)alkyl, -C(O)(C_1-C_6)alkyl, -OC(O)O(C_1-C_6)alkyl, -NH_2, -NH((C_1-C_6)alkyl), -N((C_1-C_6)alkyl)$_2$, -NHC(O)(C_1-C_6)alkyl, -C(O)NH(C_1-C_6)alkyl, -S(O)$_2$(C_1-C_6)alkyl,

-S(O)NH(C_1-C_6)alkyl, and S(O)N((C_1-C_6)alkyl)$_2$. The substituents can themselves be optionally substituted. "Optionally substituted" as used herein also refers to substituted or unsubstituted whose meaning is described below.

The term "substituted" means that the specified group or moiety bears one or more suitable substituents wherein the substituents may connect to the specified group or moiety at one or more positions. For example, an aryl substituted with a cycloalkyl may indicate that the cycloalkyl connects to one atom of the aryl with a bond or by fusing with the aryl and sharing two or more common atoms.

The term "unsubstituted" means that the specified group bears no substituents.

Unless otherwise specifically defined, "aryl" means a cyclic, aromatic hydrocarbon group having 1 to 3 aromatic rings, including monocyclic or bicyclic groups such as phenyl, biphenyl, or naphthyl. When containing two aromatic rings (bicyclic, etc.), the aromatic rings of the aryl group are optionally joined at a single point (*e.g.*, biphenyl), or fused (*e.g.*, naphthyl). The aryl group is optionally substituted by one or more substituents, *e.g.*, 1 to 5 substituents, at any point of attachment. Exemplary substituents include, but are not limited to, -H, -halogen, -CN, -O-(C_1-C_6)alkyl, (C1-C5)alkyl, -O-(C_2-C_5)alkenyl, -O-(C_2-C_6)alkynyl, (C_2-C_5)alkenyl, (C_2-C_6)alkynyl, -OH, -OP(O)(OH)$_2$, -OC(O)(C_1-C_5)alkyl, -C(O)(C_1-C_6)alkyl, -OC(O)O(C_1-C_6) alkyl, NH_2, NH((C_1-C_6)alkyl), N((C_1-C_6)alkyl)$_2$, -S(O)$_2$-(C_1-C_6)alkyl, -S(O)NH(C_1-C_6)alkyl, and S(O)N((C_1-C_6)alkyl)$_2$. The substituents are themselves optionally substituted. Furthermore, when containing two fused rings, the aryl groups optionally have an unsaturated or partially saturated ring fused with a fully saturated ring. Exemplary ring systems of these aryl groups include, but are not limited to, phenyl, biphenyl, naphthyl, anthracenyl, phenalenyl, phenanthrenyl, indanyl, indenyl, tetrahydronaphthalenyl, tetrahydrobenzoannulenyl, and the like.

Unless otherwise specifically defined, "heteroaryl" means a monovalent monocyclic aromatic radical of 5 to 24 ring atoms or a polycyclic aromatic radical, containing one or more ring heteroatoms selected from N, O, or S, the remaining ring atoms being C. Heteroaryl as herein defined also means a bicyclic heteroaromatic group wherein the heteroatom is selected from N, O, or S. The aromatic radical is optionally substituted independently with one or more substituents described herein. Examples include, but are not limited to, furyl, thienyl, pyrrolyl, pyridyl, pyrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, imidazolyl, isoxazolyl, oxazolyl, oxadiazolyl, pyrazinyl, indolyl, thiophen-2-yl, quinolyl, benzopyranyl, isothiazolyl, thiazolyl, thiadiazole, indazole, benzimidazolyl, thieno [3,2-b]thiophene, triazolyl, triazinyl, imidazo[1,2-b]pyrazolyl, furo[2,3-c]pyridinyl, imidazo[1,2-a]pyridinyl, indazolyl, pyrrolo[2,3-c]pyridinyl, pyrrolo[3,2-c]pyridinyl, pyrazolo[3,4-c]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-c]pyridinyl, thieno[2,3-b]pyridinyl, benzothiazolyl, indolyl, indolinyl, indolinonyl, dihydrobenzothiophenyl, dihydrobenzofuranyl, benzofuran, chromanyl, thiochromanyl, tetrahydroquinolinyl, dihydrobenzothiazine, dihydrobenzoxanyl, quinolinyl, isoquinolinyl, 1,6-naphthyridinyl, benzo[de]isoquinolinyl, pyrido[4,3-b

][1,6]naphthyridinyl, thieno[2,3-b]pyrazinyl, quinazolinyl, tetrazolo[1,5-a]pyridinyl, [1,2,4]triazolo[4,3-a]pyridinyl, isoindolyl, pyrrolo[2,3-b]pyridinyl, pyrrolo[3,4-b]pyridinyl, pyrrolo[3,2-b]pyridinyl, imidazo[5,4-b]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, tetrahydropyrrolo[1,2-a]pyrimidinyl, 3,4-dihydro-2H-1Δ^2-pyrrolo[2,1-b]pyrimidine, dibenzo[b,d]thiophene, pyridin-2-one, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, 1H-pyrido[3,4-b][l,4]thiazinyl, benzooxazolyl, benzoisoxazolyl, furo[2,3-b]pyridinyl, benzothiophenyl, 1,5-naphthyridinyl, furo[3,2-b]pyridine, [1,2,4]triazolo[l,5-a]pyridinyl, benzo[1,2,3]triazolyl, imidazo[1,2a]pyrimidinyl, [1,2,4]triazolo[4,3-b]pyridazinyl, benzo[c] [1,2,5]thiadiazoly1, benzo[c] [l,2,5]oxadiazole, 1,3-dihydro-2H-benzo[d]imidazol-2-one, 3,4-dihydro-2H-pyrazolo [1,5-b] [1,2]oxazinyl,4,5,6, 7-tetrahydropyrazolo [1,5-a]pyridinyl, thiazolo[5,4d]thiazolyl, imidazo[2,1-b] [1,3,4]thiadiazolyl, thieno[2,3-b]pyrrolyl, 3H-indolyl, and derivatives thereof. Furthermore, when containing two fused rings the aryl groups herein defined may have an unsaturated or partially saturated ring fused with a fully saturated ring. Exemplary ring systems of these heteroaryl groups include indolinyl, indolinonyl, dihydrobenzothiophenyl, dihydrobenzofuran, chromanyl, thiochromanyl, tetrahydroquinolinyl, dihydrobenzothiazine, 3,4-dihydro-1H-isoquinolinyl, 2,3-dihydrobenzofuran, indolinyl, indolyl, and dihydrobenzoxanyl.

Halogen or "halo" means fluorine, chlorine, bromine, or iodine.

"Alkyl" means a straight or branched chain saturated hydrocarbon containing 1-12 carbon atoms. Examples of a (C_1-C_6)alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl, isobutyl, sec-butyl, tert-butyl, isopentyl, neopentyl, and isohexyl.

"Alkoxy" means a straight or branched chain saturated hydrocarbon containing 1-12 carbon atoms containing a terminal "O" in the chain, *e.g.*, -O(alkyl). Examples of alkoxy groups include, without limitation, methoxy, ethoxy, propoxy, butoxy, t-butoxy, or pentoxy groups.

"Alkenyl" means a straight or branched chain unsaturated hydrocarbon containing 2-12 carbon atoms. The "alkenyl" group contains at least one double bond in the chain. The double bond of an alkenyl group can be unconjugated or conjugated to another unsaturated group. Examples of alkenyl groups include ethenyl, propenyl, n-butenyl, iso-butenyl, pentenyl, or hexenyl. An alkenyl group can be unsubstituted or substituted and may be straight or branched.

"Alkynyl" means a straight or branched chain unsaturated hydrocarbon containing 2-12 carbon atoms. The "alkynyl" group contains at least one triple bond in the chain. Examples of alkenyl groups include ethynyl, propargyl, n-butynyl, iso-butynyl, pentynyl, or hexynyl. An alkynyl group can be unsubstituted or substituted.

"Alkylene" or "alkylenyl" means a divalent alkyl radical. Any of the above-mentioned monovalent alkyl groups may be an alkylene by abstraction of a second hydrogen atom from the alkyl. As herein defined, alkylene may also be a (C_1-C_5)alkylene. An alkylene may further be a (C_1-C_4)alkylene. Typical

alkylene groups include, but are not limited to, -CH_2-, -$CH(CH_3)$-, -$C(CH_3)_2$-, -CH_2CH_2-, -$CH_2CH(CH_3)$-, -$CH_2C(CH_3)_2$-, -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH$-, and the like.

"Cycloalkyl" or "carbocyclyl" means a monocyclic or polycyclic saturated or partially unsaturated non-aromatic carbon ring containing 3-18 carbon atoms. Examples of cycloalkyl groups include, without limitations, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptanyl, cyclooctanyl, norboranyl, norborenyl, bicyclo[2.2.2]octanyl, or bicyclo[2.2.2]octenyl and derivatives thereof. A (C_3-C_8)cycloalkyl is a cycloalkyl group containing between 3 and 8 carbon atoms. A cycloalkyl group can be fused (*e.g.*, decalin) or bridged (*e.g.*, norbornane).

"Deuteroalkyl" means an alkyl group substituted with one or more deuterium ("D"). Examples of deuteroalkyl groups include -CDH_2, -CD_3, -CHD_2, -CD_2CH_3, -CD_2CD_3, CH_2CD_3, -$CHDCH_3$, -$CD_2CH_2CD_3$, etc.

"Heterocyclyl" or "heterocycloalkyl" means a saturated or partially saturated monocyclic or polycyclic ring containing carbon and at least one heteroatom selected from oxygen, nitrogen, or sulfur (O, N, or S) and wherein there is not delocalized n electrons (aromaticity) shared among the ring carbon or heteroatoms. The heterocycloalkyl ring structure may be substituted by one or more substituents. The substituents can themselves be optionally substituted. Examples of heterocycloalkyl rings include, but are not limited to, oxetanyl, azetadinyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, oxazolinyl, oxazolidinyl, thiazolinyl, thiazolidinyl, pyranyl, thiopyranyl, tetrahydropyranyl, dioxalinyl, piperidinyl, morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S-dioxide, piperazinyl, azepinyl, oxepinyl, diazepinyl, tropanyl, oxazolidinonyl, 1,4-dioxanyl, dihydrofuranyl, 1,3-dioxolanyl, imidazolidinyl, imidazolinyl, dithiolanyl, and homotropanyl.

"Hydroxyalkyl" means an alkyl group substituted with one or more -OH groups. Examples of hydroxyalkyl groups include HO-CH_2-, HO-CH_2CH_2-, and CH_3-CH(OH)-.

"Haloalkyl" means an alkyl group substituted with one or more halogens. Examples of haloalkyl groups include, but are not limited to, trifluoromethyl, difluoromethyl, pentafluoroethyl, trichloromethyl, etc.

"Haloalkoxy" means an alkoxy group substituted with one or more halogens. Examples of haloalkyl groups include, but are not limited to, trifluoromethoxy, difluoromethoxy, pentafluoroethoxy, trichloromethoxy, etc.

"Halohydroxyalkyl" means an alkyl group substituted with at least one halogen and at least one -OH group. Examples of halohydroxyalkyl groups include, but are not limited to, HO-C(H)F-, HO-CH(F)-CH_2-, CF_3-CH(OH)-CH_2-, and CH_3-CH(OH)-, etc.

"Cyano" means a substituent having a carbon atom joined to a nitrogen atom by a triple bond, *i.e.*, $C{\equiv}N$.

"Amino" means a substituent containing at least one nitrogen atom (*e.g.*, NH_2).

"Spirocarbocyclyl " or "spirocycloalkyl" means carbogenic bicyclic ring systems with both rings connected through a single atom. The rings can be different in size and nature, or identical in size and nature. Examples include spiropentane, spirohexane, spiroheptane, spirooctane, spirononane, or spirodecane. One or both of the rings in a spirocycle can be fused to another ring carbocyclic, heterocyclic, aromatic, or heteroaromatic ring. A (C_3-C_{12})spirocarbocyclyl is a spirocycle containing between 3 and 12 carbon atoms.

"Spiroheterocyclyl" or "spiroheterocycloalkyl" means a spirocycle wherein at least one of the rings is a heterocycle one or more of the carbon atoms can be substituted with a heteroatom (*e.g.*, one or more of the carbon atoms can be substituted with a heteroatom in at least one of the rings). One or both of the rings in a spiroheterocyclyl can be fused to another ring, *e.g.*, carbocyclic, heterocyclic, aromatic, or heteroaromatic ring.

B. Salt, Prodrug, Derivative, and Solvate Terms and Conventions

"Prodrug" or "prodrug derivative" means a covalently-bonded derivative or carrier of the parent compound or active drug substance which undergoes at least some biotransformation prior to exhibiting its pharmacological effect(s). In general, such prodrugs have metabolically cleavable groups and are rapidly transformed *in vivo* to yield the parent compound, for example, by hydrolysis in blood, and generally include esters and amide analogs of the parent compounds. The prodrug is formulated with the objectives of improved chemical stability, improved patient acceptance and compliance, improved bioavailability, prolonged duration of action, improved organ selectivity, improved formulation (*e.g.*, increased aqueous solubility), and/or decreased side effects (*e.g.*, toxicity). In general, prodrugs themselves have weak or no biological activity and are stable under ordinary conditions. Prodrugs can be readily prepared from the parent compounds using methods known in the art, such as those described in A Textbook of Drug Design and Development, Krogsgaard-Larsen and H. Bundgaard (eds.), Gordon & Breach, 1991, particularly Chapter 5: "Design and Applications of Prodrugs"; Design of Prodrugs, H. Bundgaard (ed.), Elsevier, 1985; Prodrugs: Topical and Ocular Drug Delivery, K.B. Sloan (ed.), Marcel Dekker, 1998; Methods in Enzymology, K. Widder et al. (eds.), Vol. 42, Academic Press, 1985, particularly pp. 309-396; Burger's Medicinal Chemistry and Drug Discovery, 5th Ed., M. Wolff (ed.), John Wiley & Sons, 1995, particularly Vol. 1 and pp. 172-178 and pp. 949-982; Pro-Drugs as Novel Delivery Systems, T. Higuchi and V. Stella (eds.), Am. Chem. Soc., 1975; Bioreversible Carriers in Drug Design, E.B. Roche (ed.), Elsevier, 1987, each of which is incorporated herein by reference in their entireties.

"Pharmaceutically acceptable prodrug" as used herein means a prodrug of a compound of the disclosure which is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like,

commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible.

"Salt" means an ionic form of the parent compound or the product of the reaction between the parent compound with a suitable acid or base to make the acid salt or base salt of the parent compound. Salts of the compounds of the present disclosure can be synthesized from the parent compounds which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid parent compound with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

"Pharmaceutically acceptable salt" means a salt of a compound of the disclosure which is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, generally water or oil-soluble or dispersible, and effective for their intended use. The term includes pharmaceutically acceptable acid addition salts and pharmaceutically acceptable base addition salts. As the compounds of the present disclosure are useful in both free base and salt form, in practice, the use of the salt form amounts to use of the base form. Lists of suitable salts are found in, *e.g.*, S.M. Birge et al., *J. Pharm. Sci.*, 1977, 66, pp. 1-19, which is hereby incorporated by reference in its entirety.

"Pharmaceutically-acceptable acid addition salt" means those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, nitric acid, phosphoric acid, and the like, and organic acids such as acetic acid, trichloroacetic acid, trifluoroacetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, 2-acetoxybenzoic acid, butyric acid, camphoric acid, camphorsulfonic acid, cinnamic acid, citric acid, digluconic acid, ethanesulfonic acid, glutamic acid, glycolic acid, glycerophosphoric acid, hemisulfic acid, heptanoic acid, hexanoic acid, formic acid, fumaric acid, 2-hydroxyethanesulfonic acid (isethionic acid), lactic acid, maleic acid, hydroxymaleic acid, malic acid, malonic acid, mandelic acid, mesitylenesulfonic acid, methanesulfonic acid, naphthalenesulfonic acid, nicotinic acid, 2-naphthalenesulfonic acid, oxalic acid, pamoic acid, pectinic acid, phenylacetic acid, 3-phenylpropionic acid, picric acid, pivalic acid, propionic acid, pyruvic acid, pyruvic acid, salicylic acid, stearic acid, succinic acid, sulfanilic acid, tartaric acid, p-toluenesulfonic acid, undecanoic acid, and the like.

"Pharmaceutically-acceptable base addition salt" means those salts which retain the biological effectiveness and properties of the free acids and which are not biologically or otherwise undesirable, formed with inorganic bases such as ammonia or hydroxide, carbonate, or bicarbonate of ammonium or a metal cation such as sodium, potassium, lithium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Particularly preferred are the ammonium, potassium, sodium, calcium, and

magnesium salts. Salts derived from pharmaceutically-acceptable organic nontoxic bases include salts of primary, secondary, and tertiary amines, quaternary amine compounds, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion-exchange resins, such as methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, triethylamine, isopropylamine, tripropylamine, tributylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, tetramethylammonium compounds, tetraethylammonium compounds, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, dibenzylamine, N,N-dibenzylphenethylamine, 1-ephenamine, N,N'-dibenzylethylenediamine, polyamine resins, and the like. Particularly preferred organic nontoxic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine.

"Solvate" means a complex of variable stoichiometry formed by a solute, for example, a Compound of Formula (I), (II), or (III)) and solvent, for example, water, ethanol, or acetic acid. This physical association may involve varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances, the solvate will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. In general, such solvents selected for the purpose of the disclosure do not interfere with the biological activity of the solute. Solvates encompasses both solution-phase and isolatable solvates. Representative solvates include hydrates, ethanolates, methanolates, and the like.

"Hydrate" means a solvate wherein the solvent molecule(s) is/are water.

The compounds of the present disclosure as discussed below include the free base or acid thereof, their salts, solvates, and prodrugs and may include oxidized sulfur atoms or quaternized nitrogen atoms in their structure, although not explicitly stated or shown, particularly the pharmaceutically acceptable forms thereof Such forms, particularly the pharmaceutically acceptable forms, are intended to be embraced by the appended claims.

C. Isomer Terms and Conventions

"Isomers" means compounds having the same number and kind of atoms, and hence the same molecular weight, but differing with respect to the arrangement or configuration of the atoms in space. The term includes stereoisomers and geometric isomers.

"Stereoisomer" or "optical isomer" means a stable isomer that has at least one chiral atom or restricted rotation giving rise to perpendicular dissymmetric planes (*e.g.*, certain biphenyls, allenes, and spiro compounds) and can rotate plane-polarized light. Because asymmetric centers and other chemical

structures exist in the compounds of the disclosure which may give rise to stereoisomerism, the disclosure contemplates stereoisomers and mixtures thereof. The compounds of the disclosure and their salts include asymmetric carbon atoms and may therefore exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. Typically, such compounds will be prepared as a racemic mixture. If desired, however, such compounds can be prepared or isolated as pure stereo isomers, i.e., as individual enantiomers or diastereomers, or as stereoisomer-enriched mixtures. As discussed in more detail below, individual stereoisomers of compounds are prepared by synthesis from optically active starting materials containing the desired chiral centers or by preparation of mixtures of enantiomeric products followed by separation or resolution, such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, use of chiral resolving agents, or direct separation of the enantiomers on chiral chromatographic columns. Starting compounds of particular stereochemistry are either commercially available or are made by the methods described below and resolved by techniques well known in the art.

"Enantiomers" means a pair of stereoisomers that are non-superimposable mirror images of each other.

"Diastereoisomers" or "diastereomers" mean optical isomers, which are not mirror images of each other.

"Racemic mixture" or "racemate" means a mixture containing equal parts of individual enantiomers. "Non-racemic mixture" means a mixture containing unequal parts of individual enantiomers.

"Geometrical isomer" means a stable isomer, which results from restricted freedom of rotation about double bonds (*e.g.*, cis-2-butene and trans-2-butene) or in a cyclic structure (*e.g.*, cis-1,3-dichlorocyclobutane and trans-1,3-dichlorocyclobutane). Because carbon-carbon double (olefinic) bonds, C=N double bonds, cyclic structures, and the like may be present in the compounds of the disclosure, the disclosure contemplates each of the various stable geometric isomers and mixtures thereof resulting from the arrangement of substituents around these double bonds and in these cyclic structures. The substituents and the isomers are designated using the cis/trans convention or using the E or Z system, wherein the term "E" means higher order substituents on opposite sides of the double bond, and the term "Z" means higher order substituents on the same side of the double bond. A thorough discussion of E and Z isomerism is provided in J. March, Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 4th ed., John Wiley & Sons, 1992, which is hereby incorporated by reference in its entirety. Several of the following examples represent single E isomers, single Z isomers, and mixtures of E/Z isomers. Determination of the E and Z isomers can be done by analytical methods such as x-ray crystallography, ^{1}H NMR, and ^{13}C NMR.

Some of the compounds of the disclosure can exist in more than one tautomeric form. As mentioned above, the compounds of the disclosure include all such tautomers.

It is well known in the art that the biological and pharmacological activity of a compound is sensitive to the stereochemistry of the compound. Thus, for example, enantiomers often exhibit strikingly different biological activity including differences in pharmacokinetic properties, including metabolism, protein binding, and the like, and pharmacological properties, including the type of activity displayed, the degree of activity, toxicity, and the like. Thus, one skilled in the art will appreciate that one enantiomer may be more active or may exhibit beneficial effects when enriched relative to the other enantiomer or when separated from the other enantiomer. Additionally, one skilled in the art would know how to separate, enrich, or selectively prepare the enantiomers of the compounds of the disclosure from this disclosure and the knowledge of the prior art.

Thus, although the racemic form of drug may be used, it is often less effective than administering an equal amount of enantiomerically pure drug; indeed, in some cases, one enantiomer may be pharmacologically inactive and would merely serve as a simple diluent. For example, although ibuprofen had been previously administered as a racemate, it has been shown that only the S-isomer of ibuprofen is effective as an anti-inflammatory agent (in the case of ibuprofen, however, although the R-isomer is it is converted *in vivo* to the S-isomer, thus, the rapidity of action of the racemic form of the drug is less than that of the pure S-isomer). Furthermore, the pharmacological activities of enantiomers may have distinct biological activity. For example, S-penicillamine is a therapeutic agent for chronic arthritis, while inactive, R-penicillamine is toxic. Indeed, some purified enantiomers have advantages over the racemates, as it has been reported that purified individual isomers have faster transdermal penetration rates compared to the racemic mixture. See U.S. Pat. Nos. 5,114,946 and 4,818,541.

Thus, if one enantiomer is pharmacologically more active, less toxic, or has a preferred disposition in the body than the other enantiomer, it would be therapeutically more beneficial to administer that enantiomer preferentially. In this way, the patient undergoing treatment would be exposed to a lower total dose of the drug and to a lower dose of an enantiomer that is possibly toxic or an inhibitor of the other enantiomer.

Preparation of pure enantiomers or mixtures of desired enantiomeric excess (ee) or enantiomeric purity are accomplished by one or more of the many methods of (a) separation or resolution of enantiomers, or (b) enantioselective synthesis known to those of skill in the art, or a combination thereof. These resolution methods generally rely on chiral recognition and include, for example, chromatography using chiral stationary phases, enantioselective host-guest complexation, resolution or synthesis using chiral auxiliaries, enantioselective synthesis, enzymatic and nonenzymatic kinetic resolution, or spontaneous enantioselective crystallization. Such methods are disclosed generally in Chiral Separation Techniques: A Practical Approach (2nd Ed.), G. Subramanian (ed.), Wiley-VCH, 2000; T.E. Beesley and R.P.W. Scott, Chiral Chromatography, John Wiley & Sons, 1999; and Satinder Ahuja, Chiral Separations by Chromatography,

Am. Chem. Soc., 2000. Furthermore, there are equally well-known methods for the quantitation of enantiomeric excess or purity, for example, GC, HPLC, CE, or NMR, and assignment of absolute configuration and conformation, for example, CD ORD, X-ray crystallography, or NMR.

In general, all tautomeric forms and isomeric forms and mixtures, whether individual geometric isomers or stereoisomers or racemic or non-racemic mixtures, of a chemical structure or compound is intended, unless the specific stereochemistry or isomeric form is specifically indicated in the compound name or structure.

D. Pharmaceutical Administration and Treatment Terms and Conventions

A "patient" or "subject" is a mammal, *e.g.*, a human, mouse, rat, guinea pig, dog, cat, horse, cow, pig, or nonhuman primate, such as a monkey, chimpanzee, baboon or, rhesus. In certain embodiments, the subject is a primate. In yet other embodiments, the subject is a human.

An "effective amount" or "therapeutically effective amount" when used in connection with a compound means an amount of a compound of the present disclosure that (i) treats or prevents the particular disease, condition, or disorder, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition, or disorder described herein.

The terms "pharmaceutically effective amount" or "therapeutically effective amount" means an amount of a compound according to the disclosure which, when administered to a patient in need thereof, is sufficient to effect treatment for disease-states, conditions, or disorders for which the compounds have utility. Such an amount would be sufficient to elicit the biological or medical response of a tissue, system, or patient that is sought by a researcher or clinician. The amount of a compound of according to the disclosure which constitutes a therapeutically effective amount will vary depending on such factors as the compound and its biological activity, the composition used for administration, the time of administration, the route of administration, the rate of excretion of the compound, the duration of treatment, the type of disease-state or disorder being treated and its severity, drugs used in combination with or coincidentally with the compounds of the disclosure, and the age, body weight, general health, sex, and diet of the patient. Such a therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own knowledge, the prior art, and this disclosure.

As used herein, the term "pharmaceutical composition" refers to a compound of the disclosure, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, together with at least one pharmaceutically acceptable carrier, in a form suitable for oral or parenteral administration.

"Carrier" encompasses carriers, excipients, and diluents and means a material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a pharmaceutical agent from one organ, or portion of the body, to another organ,

or portion of the body of a subject. A subject is "in need of" a treatment if such subject would benefit biologically, medically, or in quality of life from such treatment (preferably, a human).

As used herein, the term "inhibit", "inhibition", or "inhibiting" refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

As used herein, the term "treat", "treating", or "treatment" of any disease or disorder refers to alleviating or ameliorating the disease or disorder (i.e., slowing or arresting the development of the disease or at least one of the clinical symptoms thereof); or alleviating or ameliorating at least one physical parameter or biomarker associated with the disease or disorder, including those which may not be discernible to the patient.

As used herein, the term "prevent", "preventing", or "prevention" of any disease or disorder refers to the prophylactic treatment of the disease or disorder; or delaying the onset or progression of the disease or disorder.

"Pharmaceutically acceptable" means that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

"Disorder" means, and is used interchangeably with, the terms disease, condition, or illness, unless otherwise indicated.

"Administer", "administering", or "administration" means to either directly administering a disclosed compound or pharmaceutically acceptable salt of the disclosed compound or a composition to a subject, or administering a prodrug derivative or analog of the compound or pharmaceutically acceptable salt of the compound or composition to the subject, which can form an equivalent amount of active compound within the subject's body.

"Prodrug" means a compound which is convertible *in vivo* by metabolic means (*e.g.*, by hydrolysis) to a disclosed compound. "Compounds of the present disclosure", "compounds of the disclosure", and equivalent expressions (unless specifically identified otherwise) refer to compounds of Formulae (I), (II), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik), (Il), (Im), (Io), (Ip), (Iq), (Ir), (Iu), (Iv), (Iw), (Ix), (Iy), (Iz), (Iaa), (Ibb), (Icc), (Idd), (Iee), (Iff), (Igg), (Ihh), (Iii), (Ijj), (Ikk), (Imm), (Ioo), (Ipp), (Iqq), (Irr), (Iss), (Itt), (Iuu), (Ivv), (Iww), (Ixx), (Iyy), (Izz), (Iab), (Iac), (IIa), (IIb), (IIc), (IId), (IIe), and (IIf) as herein described including the tautomers, the prodrugs, salts particularly the pharmaceutically acceptable salts, and the solvates and hydrates thereof, where the context so permits thereof, as well as all stereoisomers (including diastereoisomers and enantiomers), rotamers, tautomers, and isotopically labelled compounds (including deuterium substitutions), as well as inherently formed moieties (*e.g.*, polymorphs, solvates and/or hydrates). For the purposes of this disclosure, solvates and hydrates are generally considered

compositions. In general and preferably, the compounds of the disclosure and the formula designating the compounds of the disclosure are understood to only include stable compounds thereof and exclude unstable compounds, even if an unstable compound might be considered to be literally embraced by the compound formula. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts and solvates, where the context so permits. For the sake of clarity, particular instances when the context so permits are sometimes indicated in the text, but these instances are purely illustrative, and it is not intended to exclude other instances when the context so permits.

"Stable compound" or "stable structure" means a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic or diagnostic agent. For example, a compound, which would have a "dangling valency" or is a carbanion is not a compound contemplated by the disclosure.

In a specific embodiment, the term "about" or "approximately" means within 20%, preferably within 10%, and more preferably within 5% of a given value or range.

The yield of each of the reactions described herein is expressed as a percentage of the theoretical yield.

"Simultaneously" or "simultaneous" when referring to a method of treating or a therapeutic use means with a combination of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and one or more second agent(s) means administration of the compound and the one or more second agent(s) by the same route and at the same time.

"Separately" or "separate" when referring to a method of treating or a therapeutic use means with a combination of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and one or more second agent(s) means administration of the compound and the one or more second agent(s) by different routes and at approximately the same time.

By therapeutic administration "over a period of time" means, when referring to a method of treating or a therapeutic use with a combination of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and one or more second agent(s), administration of the compound and the one or more second agent(s) by the same or different routes and at different times. In some embodiments, the administration of the compound or the one or more second agent(s) occurs before the administration of the other begins. In this way, it is possible to administer a one of the active ingredients (i.e., a compound of the Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or one or more second agent(s)) for several months before administering the other active ingredient or ingredients. In this case, no

simultaneous administration occurs. Another therapeutic administration over a period of time consists of the administration over time of the two or more active ingredients of the combination using different frequencies of administration for each of the active ingredients, whereby at certain time points in time simultaneous administration of all of the active ingredients takes place whereas at other time points in time only a part of the active ingredients of the combination may be administered (*e.g.*, for example. a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and the one or more second agents the therapeutic administration over a period of time could be such that a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, is administered once a day and the one or more second agent(s) is administered once every four weeks).

The compounds can be administered simultaneously (as a single preparation or separate preparation), sequentially, separately, or over a period of time to the other drug therapy or treatment modality. In general, a combination therapy envisions administration of two or more drugs during a single cycle or course of therapy.

"HIF-1β-dependent disease or disorder" means any disease or disorder which is directly or indirectly affected by the modulation of HIF-1β protein levels.

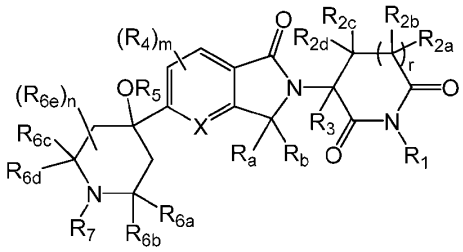
The term "von Hippel-Lindau disease" or "VHL disease" or "VHL syndrome" or "von Hippel-Lindau syndrome", as used herein, refers to a rare disease caused by a mutation in the von Hippel-Lindau (VHL) tumor suppressor leading to an aberrant non-functional VHL protein and to an absence of VHL protein. VHL gene mutations associated with this condition either prevent the production of any VHL protein or lead to the production of an abnormal version of the protein, with more than 370 inherited mutations in the VHL gene having been identified in people with von Hippel-Lindau disease (http://www.umd.be/VHL/). VHL disease is characterized by the formation of multiple benign and malignant tumors and fluid-filled sacs (cysts) in many different parts of the body, including: retinal hemangioblastoma, CNS hemangioblastoma, clear cell renal cell carcinoma (CCRCC), pheochromocytoma, pancreatic islet tumor, endolymphatic sac tumors and cysts in testes and broad ligament.

"Colitis" is an inflammation of the colon. The colitis may be acute or chronic. As used herein, colitis includes ulcerative colitis, microscopic colitis, lymphocytic colitis, collagenous colitis, diversion colitis, chemical colitis, ischemic colitis, infections colitis, pancolitis, left-sided colitis, extensive colitis, segmental colitis, microscopic colitis, radiation-induced colitis, medication-induced colitis and proctitis.

E. Compounds

The present disclosure relates to compounds or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, or tautomers thereof, capable of modulating HIF-1β protein levels, which are useful for the treatment of diseases and disorders associated with modulation of HIF-1β protein levels. The disclosure further relates to compounds, or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, or tautomers thereof, which are useful for reducing or decreasing HIF-1β protein levels.

A first aspect of the present disclosure relates to Compounds of Formula (I):



(I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R_a and R_b are each independently H, D, or (C_1-C_6)alkyl; R_1 is H, D, -C(O)R_{11}, -$CH_2OC(O)R_{11}$, -$CH_2OC(O)NHR_{12}$, -$CH_2OC(O)OR_{12}$, -P(O)$(OR_{12})_2$, -$CH_2OP(O)(OR_{12})_2$, -$CH_2OP(O)(OH)OR_{12}$, -$CH_2OP(O)(R_{12})_2$, -$CH_2OC(O)CH_2NHC(O)CH_2NH_2$, -$CH_2OC(O)CH(R_{12'})NHR_{12'}$, -$CH_2OC(O)(CH_2)_qC(O)OR_{12'}$, or -$CH_2OC(O)$-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S); R_{2a}, R_{2b}, R_{2c}, and R_{2d} are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, halogen, or -OH, wherein two of R_{2a}, R_{2b}, R_{2c}, and R_{2d} may be taken together with the carbon atom to which they are attached form a (C_3-C_7)carbocyclyl or (C_3-C_7)spirocarbocyclyl; R_3 is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, or halogen, wherein R_3 may be taken together with one of R_{2a}, R_{2b}, R_{2c}, and R_{2d} with the carbon atom to which they are attached to form a (C_3-C_7)carbocyclyl or (C_3-C_7)spirocarbocyclyl; each R_4 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)halohalkyl, or halogen; each $R_{4'}$ is independently at each occurrence H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)deuteroalkoxy, (C_1-C_6)haloalkoxy, (C_3-C_7)carbocyclyl, O(C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$; R_5 is H, D, (C_2-C_6)alkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)aminoalkyl, (C_1-C_6)alkyl-O-(C_1-C_6)hydroxyalkyl, -C(O)R_{12}, -$CH_2OC(O)R_{12}$, -$CH_2OC(O)N(R_{12})_2$, -$CH_2OC(O)_2R_{12}$, -P(O)$(OR_{12})_2$, -$CH_2OP(O)(OH)OR_{12}$, or -$CH_2OP(O)(R_{12})_2$; R_{6a}, R_{6b}, R_{6c}, and R_{6d} are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy,, or (C_3-C_7)carbocyclyl; or two of R_{6a}, R_{6b}, R_{6c}, and R_{6d} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl, (C_3-C_7)spirocarbocyclyl, 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O,

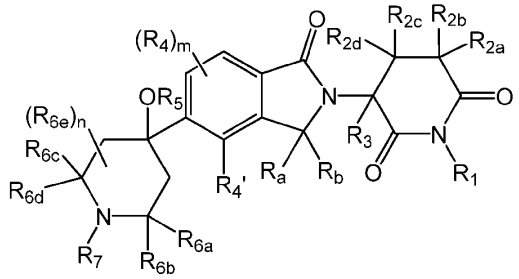
N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl, heterocyclyl, and spiroheterocyclyl are optionally substituted with one or more R_{10}; each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, -(C_1-C_6)alkylene-O-(C_1-C_6)alkyl, (C_6-C_{10})aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one or more R_{13}, the aryl and heteroaryl are optionally substituted with one or more R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{23}; or two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)carbocyclyl, (C_3-C_7)spirocarbocyclyl, a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl, heterocyclyl, and spiroheterocyclyl are optionally substituted with one or more R_{15}; or one R_{6e} is taken together with any one of R_{6a}, R_{6b}, R_{6c}, and R_{6d} and the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{15}; R_7 is (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_3-C_7)carbocyclyl, wherein alkyl, haloalkyl, hydroxyalkyl, halohydroxyalkyl, and carbocyclyl are optionally substituted with one or more substituents independently selected from R_{21}, D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$,-C(O)$NR_{32}R_{33}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$; when $R_{4'}$ is H, m is 1, n is 0 and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are all simultaneously H, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)alkyl, or (C_3-C_7)carbocyclyl optionally substituted with one or more substituents independently selected from R_{41}, D, (C_1-C_6)alkoxy, -OR_{16a}, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one or more R_8, the heteroaryl is optionally substituted with one or more R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$, when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)alkyl, or (C_3-C_7)carbocyclyl optionally substituted with one or more substituents independently selected from R_{41}, D, (C_1-C_6)alkoxy, -OR_{16a}, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl,

5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$;when $R_{4'}$ is (C_1)alkyl, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one or more R_8, the heteroaryl is optionally substituted with one or more R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$; when $R_{4'}$ is D, (C_2-C_4)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)alkyl, or (C_3-C_7)carbocyclyl optionally substituted with one or more substituents independently selected from R_{41}, D, (C_1-C_6)alkoxy, -OR_{16a}, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$; R_8 and $R_{8'}$ are each independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -$C(O)NR_{32}R_{33}$, -$C(O)OR_{32}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the alkyl, deuteroalkyl, haloalkyl, alkoxy, haloalkoxy, hydroalkyl, phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more substituents selected from (C_1-C_6)alkyl, (C_3-C_7)carbocyclyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -$C(O)NR_{37}R_{38}$, -$C(O)R_{37}$, -$C(O)OR_{37}$, -SF_5, -SR_{40}, and -CN, and R_{13}; or two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R_{10}; two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-

membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{10}; or two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{10}; or two $R_{8'}$ when on the same carbon atom form C=(O); each R_9 and $R_{9'}$ are each independently at each occurrence H or (C_1-C_6)alkyl; R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, C(O)OR_9, -C(O)R_9, and -C(O)$NR_9R_{9'}$; R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN; R_{12} is independently at each occurrence H, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN; $R_{12'}$ is independently at each occurrence H or (C_1-C_6)alkyl; each R_{13} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{14}R_{14'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein carbocyclyl and heterocyclyl are optionally substituted with one or more R_{20} and the aryl and heteroaryl are optionally substituted with one or more R_{21}; or two R_{13} when on the same carbon atom may be taken together to form C=(O); R_{14} and $R_{14'}$ are each independently at each occurrence H or (C_1-C_6)alkyl; each R_{15} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$ optionally substituted with one or more R_{20}; R_{16} and $R_{16'}$ are each independently at each occurrence H or (C_1-C_6)alkyl; R_{16a} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{17} is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{18} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{19} is (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{20} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a

4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; each R_{22} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{28}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{22}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; each R_{23} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{29}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{23} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{30} and R_{31} are each independently at each occurrence H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_3-C_7)carbocyclyl, -C(O)R_{34}, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl or heteroaryl can be substituted with one or more R_{17}; R_{32}, R_{33}, and R_{34} are each independently at each occurrence H or (C_1-C_6)alkyl; R_{35} and R_{36} are each independently at each occurrence H, (C_1-C_6)alkyl, or -C(O)R_{39}; R_{37}, R_{38}, and R_{39} are each independently at each occurrence H or (C_1-C_6)alkyl; R_{40} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; two R_{41}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{10}; or two R_{41} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{10}; or m and p are each independently 0, 1, or 2; q is 1, 2, or 3; n is 0, 1, 2, 3 or 4; and r is 0 or 1.

In some embodiments, the compound of Formula (I) is a compound of Formula (I'):



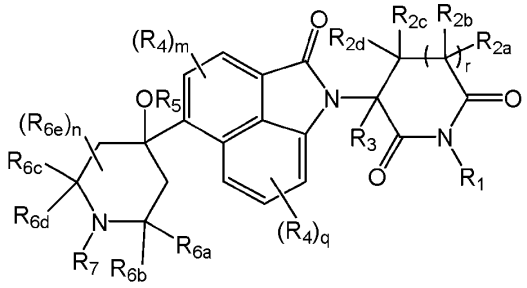
(I'), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereo isomer, or tautomer thereof, wherein R_a and R_b are each independently H, D, or $(C_1$-$C_6)$alkyl; R_1 is H, D, $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, $-CH_2OP(O)(R_{12})_2$, $-CH_2OC(O)CH_2NHC(O)CH_2NH_2$, $-CH_2OC(O)CH(R_{12'})NHR_{12'}$, $-CH_2OC(O)(CH_2)_qC(O)OR_{12'}$, or $-CH_2OC(O)$-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S); R_{2a}, R_{2b}, R_{2c}, and R_{2d} are each independently H or D; R_3 is H, D, $(C_1$-$C_3)$alkyl, or $(C_1$-$C_3)$deuteroalkyl; each R_4 is independently at each occurrence D or halogen;each $R_{4'}$ is independently at each occurrence H, D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$; R_5 is H, D, $(C_2$-$C_6)$alkyl, $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, $-CH_2OC(O)_2R_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$; R_{6a}, R_{6b}, R_{6c}, and R_{6d} are each independently H, D, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl; each R_{6e} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, $(C_1$-$C_6)$hydroxyalkyl, -CN, -OH, -O-$(C_1$-$C_6)$hydroxyalkyl, $(C_6$-$C_{10})$aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one or more R_{13}, the aryl and heteroaryl are optionally substituted with one or more R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{23}; or two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a $(C_3$-$C_7)$spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one or more R_{15}; when $R_{4'}$ is H, m is 1, n is 0 and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are all simultaneously H, then R_7 is $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$halohydroxyalkyl, or $(C_1$-$C_6)$alkyl optionally substituted with one or more substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one or more R_8, the heteroaryl is optionally substituted with one or more R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$; when $R_{4'}$ is H, m is 0,

n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$; when $R_{4'}$ is (C_1)alkyl, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one or more R_8, the heteroaryl is optionally substituted with one or more R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$; when $R_{4'}$ is D, (C_2-C_4)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$; R_8 and $R_{8'}$ are each independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -$C(O)NR_{32}R_{33}$, -$C(O)OR_{32}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -$C(O)NR_{37}R_{38}$, -$C(O)R_{37}$, -$C(O)OR_{37}$, -SF_5, -SR_{40}, and -CN; or two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R_{10};

two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{10}; or two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{10}; or two $R_{8'}$ when on the same carbon atom form C=(O); each R_9 and $R_{9'}$ are each independently at each occurrence H or (C_1-C_6)alkyl; R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{25}$, or -CN; R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, $-NH_2$, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, $-NH_2$, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, $-NH_2$, and -CN; R_{12} is independently at each occurrence H, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, $-NH_2$, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, $-NH_2$, and -CN; $R_{12'}$ is independently at each occurrence H or (C_1-C_6)alkyl; each R_{13} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, $-NR_{14}R_{14'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein carbocyclyl and heterocyclyl are optionally substituted with one or more R_{20} and the aryl and heteroaryl are optionally substituted with one or more R_{21}; R_{14} and $R_{14'}$ are each independently at each occurrence H or (C_1-C_6)alkyl; each R_{15} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, $-C(O)OR_{17}$, $-C(O)R_{18}$, or $-C(O)NR_{17}R_{17}$; R_{16} and $R_{16'}$ are each independently at each occurrence H or (C_1-C_6)alkyl; R_{16a} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{17} is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{18} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{19} is (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{26}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{20} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl

comprising 1 to 4 heteroatoms selected from O, N, NH, and S; each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; each R_{22} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{28}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{22}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; each R_{23} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{29}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{23} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{30} and R_{31} are each independently at each occurrence H, (C_1-C_6)alkyl, or -C(O)R_{34}; R_{32}, R_{33}, and R_{34} are each independently at each occurrence H or (C_1-C_6)alkyl; R_{35} and R_{36} are each independently at each occurrence H, (C_1-C_6)alkyl, or -C(O)R_{39}; R_{37}, R_{38}, and R_{39} are each independently at each occurrence H or (C_1-C_6)alkyl; R_{40} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; m and p are each independently 0, 1, or 2; q is 1, 2, or 3; and n is 0, 1, 2, 3 or 4.

In another aspect of the present disclosure relates to Compounds of Formula (II):



(II), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R_1 is H, D, -C(O)R_{11}, -CH_2OC(O)R_{11}, -CH_2OC(O)NHR_{12}, -CH_2OC(O)OR_{12}, -P(O)(OR_{12})$_2$, -CH_2OP(O)(OR_{12})$_2$, -CH_2OP(O)(OH)OR_{12}, -CH_2OP(O)(R_{12})$_2$, -CH_2OC(O)CH_2NHC(O)CH_2NH_2, -CH_2OC(O)CH($R_{12'}$)N$HR_{12'}$, -CH_2OC(O)-(CH_2)$_q$C(O)O$R_{12'}$, or -CH_2OC(O)-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S); R_{2a}, R_{2b}, R_{2c}, and R_{2d} are each independently H, D, (C_1-C_6)alkyl, (C_1-

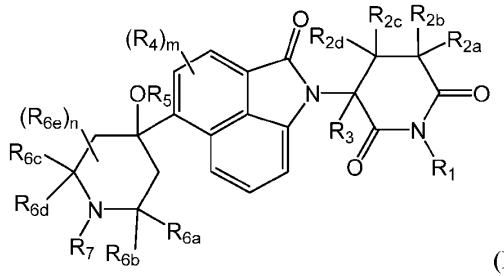
C_6)deuteroalkyl, halogen, or -OH, wherein two of R_{2a}, R_{2b}, R_{2c}, and R_{2d} may be taken together with the carbon atom to which they are attached form a (C_3-C_7)carbocyclyl or (C_3-C_7)spirocarbocyclyl; R_3 is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, or halogen, wherein R_3 may be taken together with one of R_{2a}, R_{2b}, R_{2c}, and R_{2d} with the carbon atom to which they are attached to form a (C_3-C_7)carbocyclyl or (C_3-C_7)spirocarbocyclyl; each R_4 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)halohalkyl, or halogen; R_5 is H, D, (C_2-C_6)alkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)aminoalkyl, (C_1-C_6)alkyl-O-(C_1-C_6)hydroxyalkyl, -C(O)R_{12}, -CH_2OC(O)R_{12}, -CH_2OC(O)N(R_{12})$_2$, -CH_2OC(O)$_2R_{12}$, -P(O)(OR_{12})$_2$, -CH_2OP(O)(OH)OR_{12}, or -CH_2OP(O)(R_{12})$_2$; R_{6a}, R_{6b}, R_{6c}, and R_{6d} are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy,, or (C_3-C_7)carbocyclyl; or two of R_{6a}, R_{6b}, R_{6c}, and R_{6d} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl, (C_3-C_7)spirocarbocyclyl, 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl, heterocyclyl, and spiroheterocyclyl are optionally substituted with one or more R_{10}; each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, -(C_1-C_6)alkylene-O-(C_1-C_6)alkyl, (C_6-C_{10})aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one or more R_{13}, the aryl and heteroaryl are optionally substituted with one or more R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{23}; or two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)carbocyclyl, (C_3-C_7)spirocarbocyclyl, a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl, heterocyclyl, and spiroheterocyclyl are optionally substituted with one or more R_{15}; or one R_{6e} is taken together with any one of R_{6a}, R_{6b}, R_{6c}, and R_{6d} and the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{15}; R_7 is (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_3-C_7)carbocyclyl, wherein alkyl, haloalkyl, hydroxyalkyl, halohydroxyalkyl, and carbocyclyl are optionally substituted with one or more substituents independently selected from R_{21}, D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$,-C(O)$NR_{32}R_{33}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted

with one or more R_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$; R_8 and $R_{8'}$ are each independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -C(O)$NR_{32}R_{33}$, -C(O)OR_{32}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the alkyl, deuteroalkyl, haloalkyl, alkoxy, haloalkoxy, hydroalkyl, phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more substituents selected from (C_1-C_6)alkyl, (C_3-C_7)carbocyclyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -C(O)$NR_{37}R_{38}$, -C(O)R_{37}, -C(O)OR_{37}, -SF_5, -SR_{40}, and -CN, and R_{13}; or two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R_{10}; two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{10}; or two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, NH, N, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{10}; or two $R_{8'}$ when on the same carbon atom form C=(O); each R_9 and $R_{9'}$ are each independently is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{13}R_{13'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein carbocyclyl and heterocyclyl are optionally substituted with one or more R_{20} and the aryl and heteroaryl are optionally substituted with one or more R_{21}; R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, - OH, -NH_2, -SF_5, -SR_{25}, -CN, C(O)OR_9, -C(O)R_9, and -C(O)NR_9R_9; R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-

C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN; R_{12} is independently at each occurrence H, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN; $R_{12'}$ is independently at each occurrence H or (C_1-C_6)alkyl; R_{13} and $R_{13'}$ are each independently at each occurrence H or (C_1-C_6)alkyl; each R_{14} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$; R_{15} and $R_{15'}$ are each independently at each occurrence H or (C_1-C_6)alkyl; R_{15a} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; each R_{16} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{16}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; R_{17} is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;R_{18} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{19} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{20} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, and R_{27} are each independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{30} and R_{31} are each independently at each occurrence H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_3-C_7)carbocyclyl, -C(O)R_{32}, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4

heteroatoms selected from O, N, NH, and S, wherein the phenyl or heteroaryl can be substituted with one or more R_{17}; R_{30}, R_{31}, and R_{32} are each independently at each occurrence H or $(C_1$-$C_6)$alkyl; R_{33} and R_{34} are each independently at each occurrence H, $(C_1$-$C_6)$alkyl, or -C(O)R_{37}; R_{35}, R_{36}, and R_{37} are each independently at each occurrence H or $(C_1$-$C_6)$alkyl; R_{38} is H, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl; m is 0, 1, or 2; q is 1, 2, or 3; n is 0, 1, 2, 3, or 4; and r is 0 or 1.

In some embodiments, the compound of Formula (II) is a compound of Formula (II'):



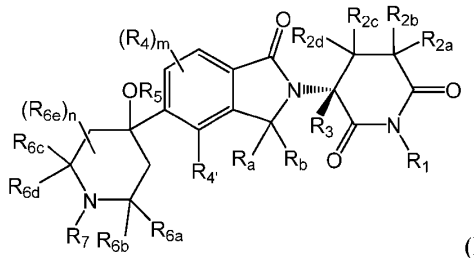
(II'), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereo isomer, or tautomer thereof, R_1 is H, D, -C(O)R_{11}, -CH_2OC(O)R_{11}, -CH_2OC(O)NHR_{12}, -CH_2OC(O)OR_{12}, -P(O)$(OR_{12})_2$, -CH_2OP(O)$(OR_{12})_2$, -CH_2OP(O)(OH)OR_{12}, -CH_2OP(O)$(R_{12})_2$, -CH_2OC(O)CH_2NHC(O)CH_2NH_2, -CH_2OC(O)$CH(R_{12'})NHR_{12'}$, -CH_2OC(O)$(CH_2)_q$C(O)O$R_{12'}$, or -CH_2OC(O)-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S); R_{2a}, R_{2b}, R_{2c}, and R_{2d} are each independently H or D; R_3 is H, D, $(C_1$-$C_3)$alkyl, or $(C_1$-$C_3)$deuteroalkyl; each R_4 is independently at each occurrence D; R_5 is H, D, $(C_1$-$C_6)$alkyl, -C(O)R_{12}, -CH_2OC(O)R_{12}, -CH_2OC(O)N$(R_{12})_2$, -CH_2OC(O)$_2R_{12}$, -P(O)$(OR_{12})_2$, -CH_2OP(O)(OH)OR_{12}, or -CH_2OP(O)$(R_{12})_2$; R_{6a}, R_{6b}, R_{6c}, and R_{6d} are each independently H, D, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl; each R_{6e} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, $(C_1$-$C_6)$hydroxyalkyl, -CN, -OH, -O-$(C_1$-$C_6)$hydroxyalkyl, $(C_6$-$C_{10})$aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one or more R_9, the aryl and heteroaryl are optionally substituted with one or more R_{16}, and the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{19}; or two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a $(C_3$-$C_7)$spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one or more R_{14}; R_7 is $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$halohydroxyalkyl, or $(C_1$-$C_6)$alkyl optionally substituted with one or more substituents independently selected from D, $(C_1$-$C_6)$alkoxy, -SF_5, -SR_{15a}, -$NR_{15}R_{15'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-

C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$; R_8 and $R_{8'}$ are each independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -$C(O)NR_{30}R_{31}$, -$C(O)OR_{30}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -$C(O)NR_{35}R_{36}$, -$C(O)R_{35}$, -$C(O)OR_{35}$, -SF_5, -SR_{38}, and -CN; or two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R_{10}; two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{10}; or two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{10}; or two $R_{8'}$ when on the same carbon atom form C=(O); each R_9 is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{13}R_{13'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein carbocyclyl and heterocyclyl are optionally substituted with one or more R_{20} and the aryl and heteroaryl are optionally substituted with one or more R_{21}; R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{23}, or -CN; R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2,

and -CN; R_{12} is independently at each occurrence H, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN; $R_{12'}$ is independently at each occurrence H or (C_1-C_6)alkyl; R_{13} and $R_{13'}$ are each independently at each occurrence H or (C_1-C_6)alkyl; each R_{14} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$; R_{15} and $R_{15'}$ are each independently at each occurrence H or (C_1-C_6)alkyl; R_{15a} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; each R_{16} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{16}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; R_{17} is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{18} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{19} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{20} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, and R_{27} are each independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{28} and R_{29} are each independently at each occurrence H, (C_1-C_6)alkyl, or -C(O)R_{32}; R_{30}, R_{31}, and R_{32} are each independently at each occurrence H or (C_1-C_6)alkyl; R_{33} and R_{34} are each independently at each occurrence

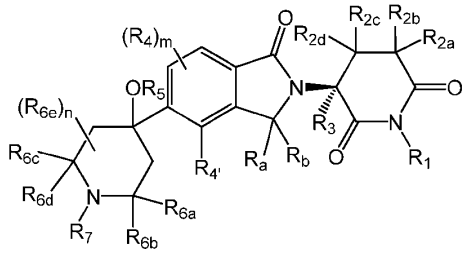
H, (C_1-C_6)alkyl, or -C(O)R_{37};R_{35}, R_{36}, and R_{37} are each independently at each occurrence H or (C_1-C_6)alkyl; R_{38} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; m is 0, 1, or 2; q is 1, 2, or 3; and n is 0, 1, 2, 3, or 4.

In one embodiment, the compounds of Formula (I) have the structure of Formula (Ia):



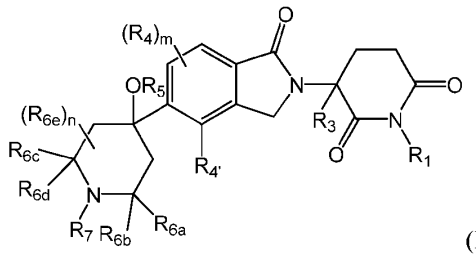
(Ia), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Ib):



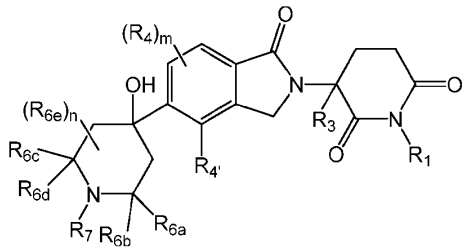
(Ib), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Ic):



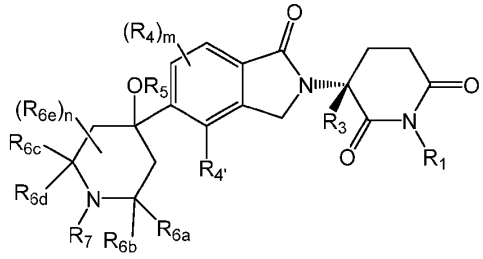
(Ic), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Id):



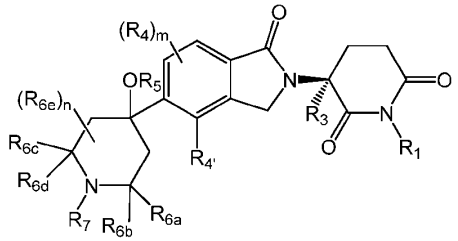
(Id), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Ie):



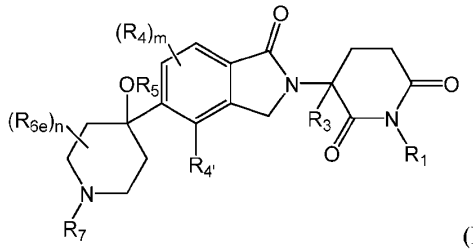
(Ic), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (If):



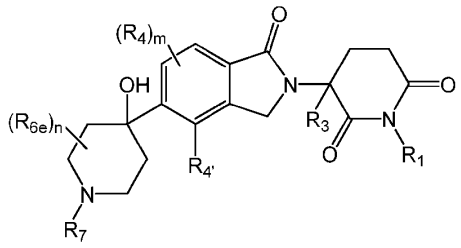
(If), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Ig):



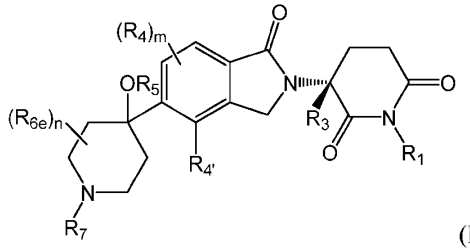
(Ig), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Ih):



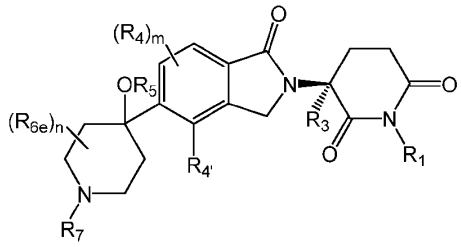
(Ih), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Ii):



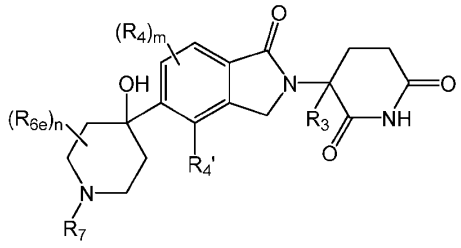
(Ii), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Ij):



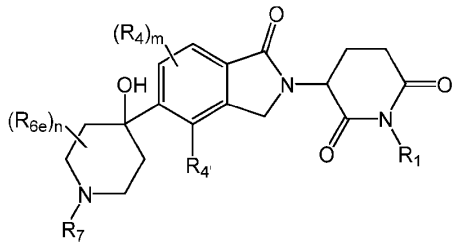
(Ij), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Ik):



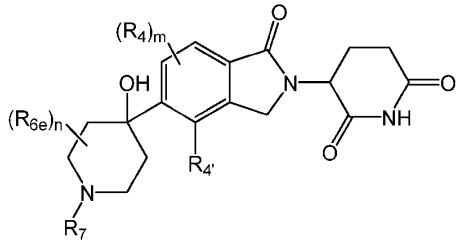
(Ik), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Il):



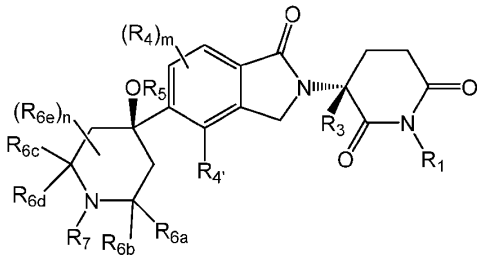
(II), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Im):

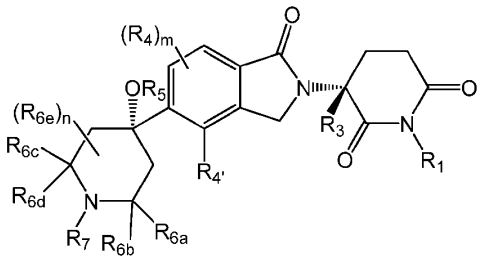


(Im), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Io):

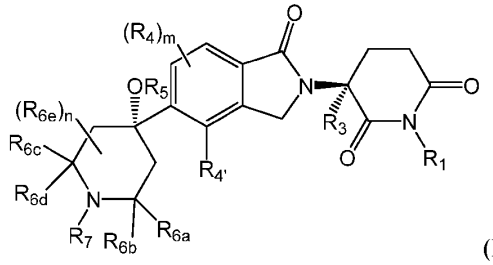


(Io), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Ip):

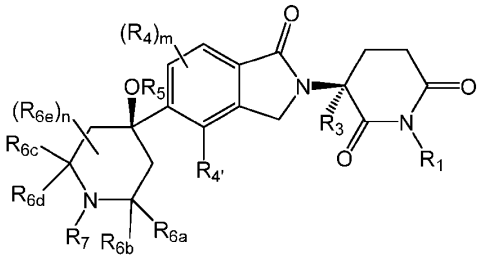


(Ip), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Iq):

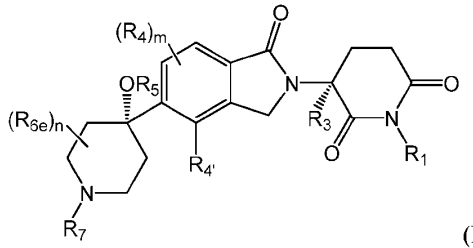


(Iq), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Ir):

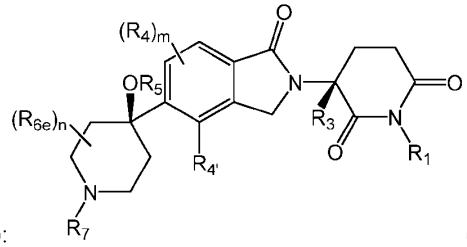


(Ir), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Iu):

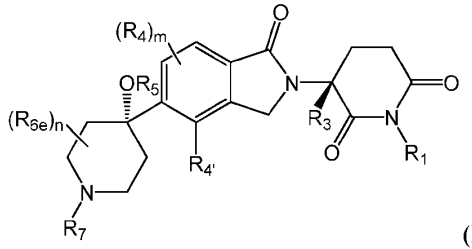


(Iu), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Iv):

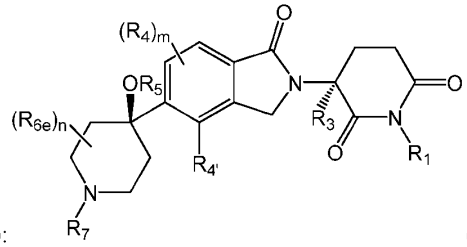


(Iv), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Iw):

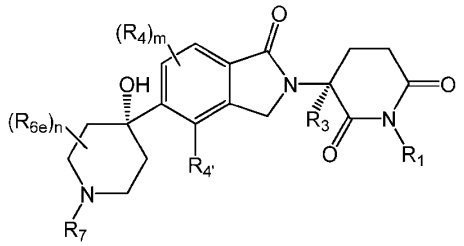


(Iw), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Ix):

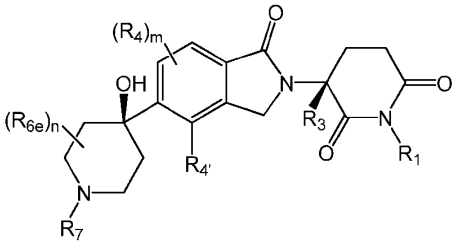


(Ix), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Iy):

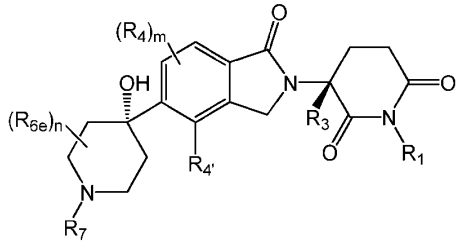


(Iy), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Iz):

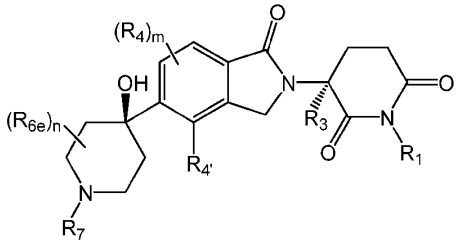


(Iz), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Iaa):

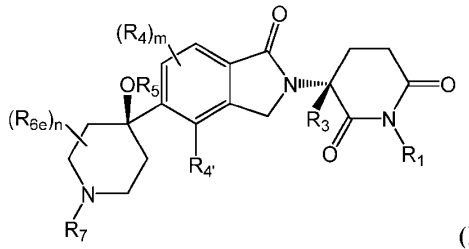


(Iaa), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Ibb):

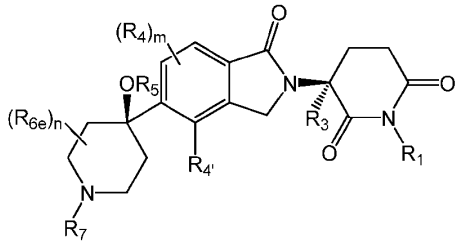


(Ibb), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Icc):

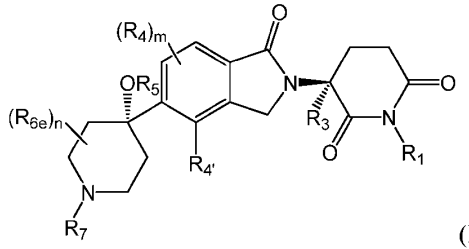


(Icc), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Idd):

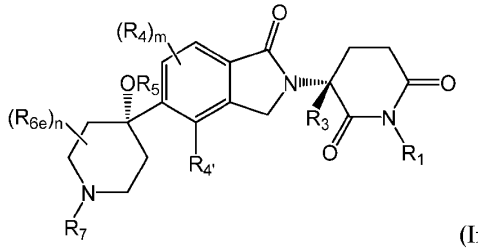


(Idd), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Iee):

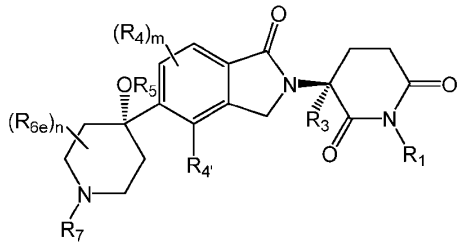


(Iee), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Iff):

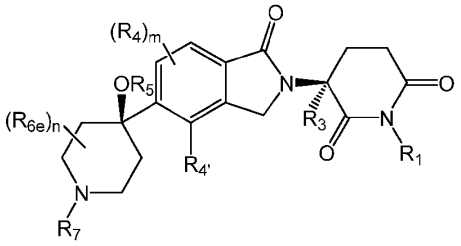


(Iff), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Igg):

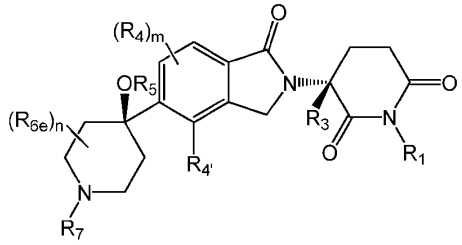


(Igg), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Ihh):

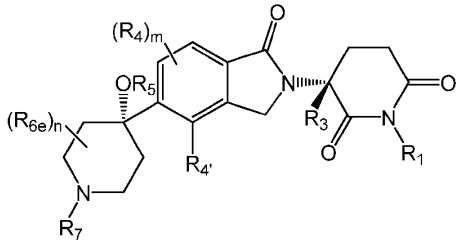


(Ihh), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Iii):

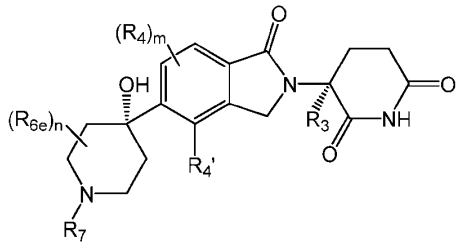


(Iii), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Ijj):

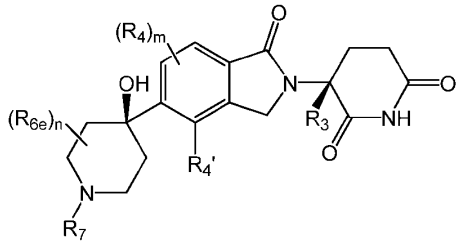


(Ijj), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Ikk):

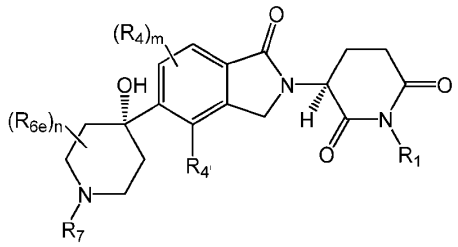


(Ikk), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Imm):

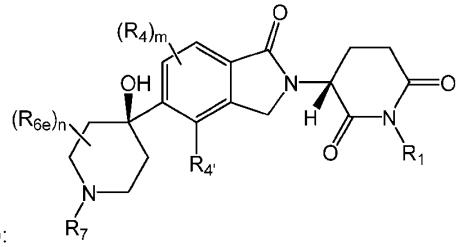


(Imm), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Ioo):

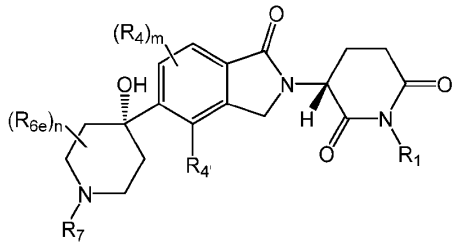


(Ioo), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Ipp):

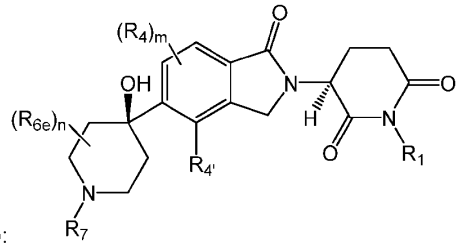


(Ipp), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Iqq):

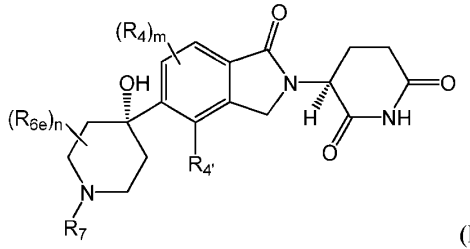


(Iqq), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Irr):

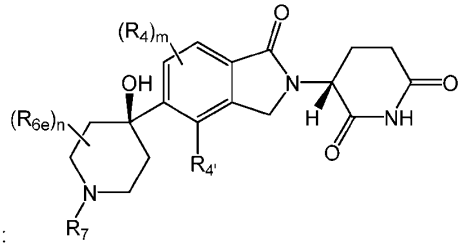


(Irr), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Iss):

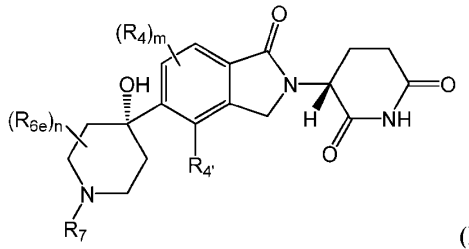


(Iss), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Itt):

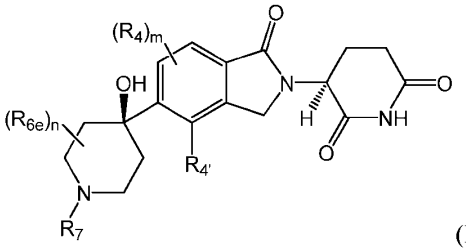


(Itt), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Iuu):

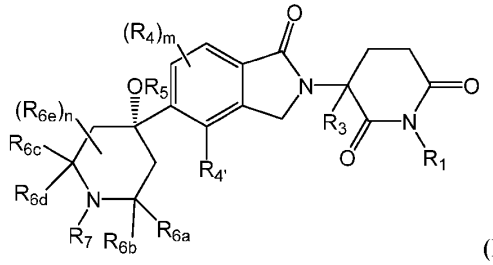


(Iuu), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Ivv):

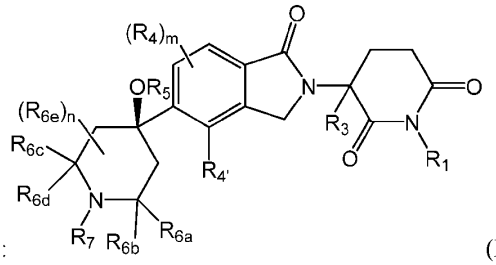


(Ivv), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Iww):

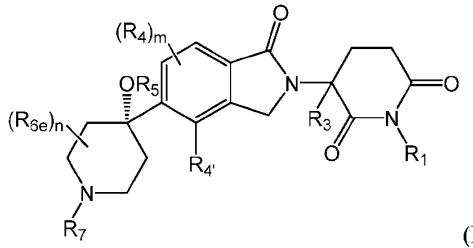


(Iww), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Ixx):

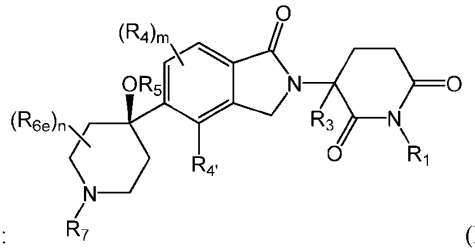


(Ixx), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Iyy):

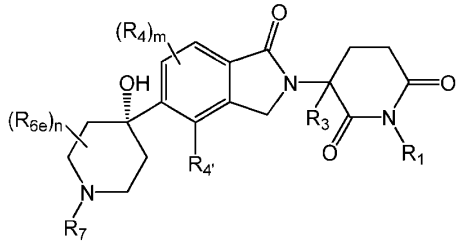


(Iyy), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Izz):

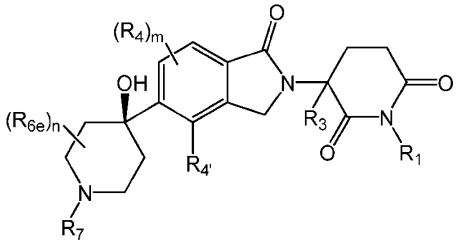


(Izz), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Iab):

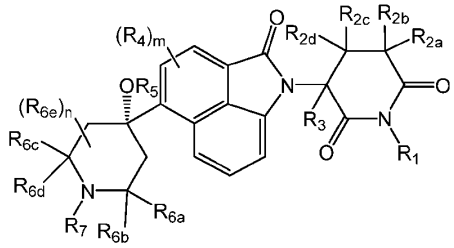


(Iab), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Iac):

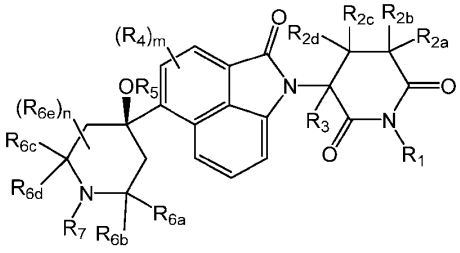


(Iac), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (II) have the structure of Formula (IIa):

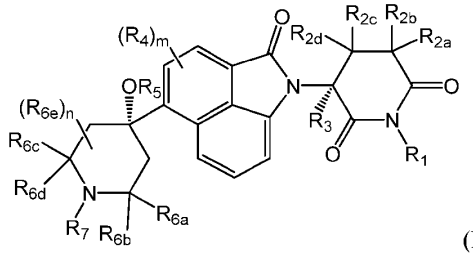


(IIa). In another embodiment, the compounds of Formula (II) have the structure of Formula (IIb):

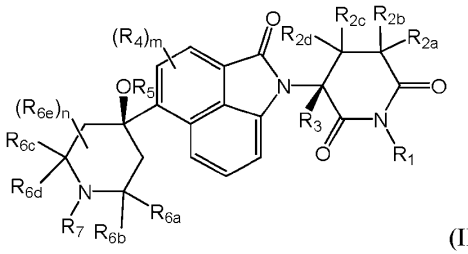


(IIb).

In another embodiment, the compounds of Formula (II) have the structure of Formula (IIc):

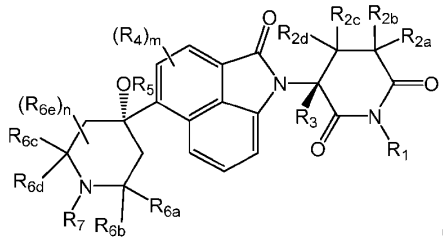


(IIc). In another embodiment, the compounds of Formula (II) have the structure of Formula (IId):

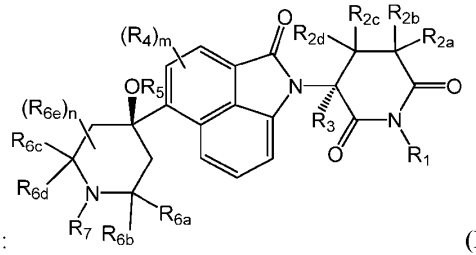


(IId).

In another embodiment, the compounds of Formula (II) have the structure of Formula (IIe):



(IIe). In another embodiment, the compounds of Formula (II) have the structure of Formula (IIf):



(IIf).

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac):

R_a and R_b are each independently H, D, or (C_1-C_6)alkyl;

R_1 is H, D, -C(O)R_{11}, -$CH_2OC(O)R_{11}$, -$CH_2OC(O)NHR_{12}$, -$CH_2OC(O)OR_{12}$, -$P(O)(OR_{12})_2$, -$CH_2OP(O)(OR_{12})_2$, -$CH_2OP(O)(OH)OR_{12}$, -$CH_2OP(O)(R_{12})_2$, -$CH_2OC(O)CH_2NHC(O)CH_2NH_2$, -$CH_2OC(O)CH(R_{12'})NHR_{12'}$, -$CH_2OC(O)(CH_2)_qC(O)OR_{12'}$, or -$CH_2OC(O)$-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S);

R_{2a}, R_{2b}, R_{2c}, and R_{2d} are each independently H or D;

R_3 is H, D, (C_1-C_3)alkyl, or (C_1-C_3)deuteroalkyl;

each R_4 is independently at each occurrence D or halogen;

each $R_{4'}$ is independently at each occurrence H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$;

R_5 is H, D, (C_2-C_6)alkyl, -C(O)R_{12}, -$CH_2OC(O)R_{12}$, -$CH_2OC(O)N(R_{12})_2$, -$CH_2OC(O)_2R_{12}$, -$P(O)(OR_{12})_2$, -$CH_2OP(O)(OH)OR_{12}$, or -$CH_2OP(O)(R_{12})_2$;

R_{6a}, R_{6b}, R_{6c}, and R_{6d} are each independently H, D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl;

each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10})aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to four R_{13}, the aryl and heteroaryl are optionally substituted with one to four R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{23}; or

two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one to four R_{15};

when $R_{4'}$ is H, m is 1, n is 0 and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are all simultaneously H, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one to four R_8, the heteroaryl is optionally substituted with one to four R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$

when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently

selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$;

when $R_{4'}$ is (C_1)alkyl, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one to four R_8, the heteroaryl is optionally substituted with one to four R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$;

when $R_{4'}$ is D, (C_2-C_4)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$;

R_8 and $R_{8'}$ are each independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -$C(O)NR_{32}R_{33}$, -$C(O)OR_{32}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -$C(O)NR_{37}R_{38}$, -$C(O)R_{37}$, -$C(O)OR_{37}$, -SF_5, -SR_{40}, and -CN; or

two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH,

and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four R_{10};

two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_{10}; or

two $R_{8'}$ together with the atoms to which they are attached form a $(C_3$-$C_7)$carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{10}; or

two $R_{8'}$ when on the same carbon atom form C=(O);

each R_9 and $R_{9'}$ are each independently at each occurrence H or $(C_1$-$C_6)$alkyl;

R_{10} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{25}$, or -CN;

R_{11} is independently at each occurrence H, $(C_1$-$C_6)$alkoxy, $-NH_2$, $-N(H)(C_1$-$C_6)$alkyl, $-N((C_1$-$C_6)alkyl)_2$, $(C_1$-$C_6)$alkyl optionally substituted with one to four substituents independently selected from $(C_6$-$C_{10})$aryl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$haloalkyl, halogen, -OH, $-NH_2$, and -CN, or $(C_6$-$C_{10})$aryl optionally substituted with one to four substituents independently selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$haloalkyl, halogen, -OH, $-NH_2$, and -CN;

R_{12} is independently at each occurrence H, $(C_1$-$C_6)$alkyl optionally substituted with one to four substituents independently selected from $(C_6$-$C_{10})$aryl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$haloalkyl, halogen, -OH, $-NH_2$, and -CN, or $(C_6$-$C_{10})$aryl optionally substituted with one to four substituents independently selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$haloalkyl, halogen, -OH, $-NH_2$, and -CN;

$R_{12'}$ is independently at each occurrence H or $(C_1$-$C_6)$alkyl;

each R_{13} is independently at each occurrence $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $-NR_{14}R_{14'}$, -CN, $(C_3$-$C_7)$carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_6$-$C_{10})$ aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20} and the aryl and heteroaryl are optionally substituted with one to four R_{21};

R_{14} and $R_{14'}$ are each independently at each occurrence H or $(C_1$-$C_6)$alkyl;

each R_{15} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, $-C(O)OR_{17}$, $-C(O)R_{18}$, or $-C(O)NR_{17}R_{17}$;

R_{16} and $R_{16'}$ are each independently at each occurrence H or $(C_1$-$C_6)$alkyl;

R_{16a} is H, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl;

R_{17} is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{18} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{19} is (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{20} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{22} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{28}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{22}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{23} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{29}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{23} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{30} and R_{31} are each independently at each occurrence H, (C_1-C_6)alkyl, or -C(O)R_{34};

R_{32}, R_{33}, and R_{34} are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{35} and R_{36} are each independently at each occurrence H, (C_1-C_6)alkyl, or -C(O)R_{39};

R_{37}, R_{38}, and R_{39} are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{40} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

m and p are each independently 0, 1, or 2;

q is 1, 2, or 3; and

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

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_a is H, D, or (C_1-C_6)alkyl. In another embodiment, R_a is H, D, or (C_1-C_3)alkyl. In another embodiment, R_a is H or (C_1-C_6)alkyl. In another embodiment, R_a is D or (C_1-C_6)alkyl. In another embodiment, R_a is H or D. In another embodiment, R_a is (C_1-C_6)alkyl. In another embodiment, R_a is (C_1-C_3)alkyl. In another embodiment, R_a is D. In yet another embodiment, R_a is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_b is H, D, or (C_1-C_6)alkyl. In another embodiment, R_b is H, D, or (C_1-C_3)alkyl. In another embodiment, R_b is H or (C_1-C_6)alkyl. In another embodiment, R_b is D or (C_1-C_6)alkyl. In another embodiment, R_b is H or D. In another embodiment, R_b is (C_1-C_6)alkyl. In another embodiment, R_b is (C_1-C_3)alkyl. In another embodiment, R_b is D. In yet another embodiment, R_b is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is H, D, -C(O)R_{11}, -CH_2OC(O)R_{11}, -CH_2OC(O)NHR_{12}, -CH_2OC(O)OR_{12}, -P(O)(OR_{12})$_2$, -CH_2OP(O)(OR_{12})$_2$, -CH_2OP(O)(OH)OR_{12}, -CH_2OP(O)(R_{12})$_2$, -

$CH_2OC(O)CH_2NHC(O)CH_2NH_2$, $-CH_2OC(O)CH(R_{12'})NHR_{12'}$, $-CH_2OC(O)(CH_2)_qC(O)OR_{12'}$, or -$CH_2OC(O)$-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S). In another embodiment, R_1 is H, D, $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In yet another embodiment, R_1 is H, D, $-CH_2OC(O)CH_2NHC(O)CH_2NH_2$, $-CH_2OC(O)CH(R_{12'})NHR_{12'}$, $-CH_2OC(O)(CH_2)_qC(O)OR_{12'}$, or -$CH_2OC(O)$-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S).

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, $-CH_2OP(O)(R_{12})_2$, $-CH_2OC(O)CH_2NHC(O)CH_2NH_2$, $-CH_2OC(O)CH(R_{12'})NHR_{12'}$, $-CH_2OC(O)(CH_2)_qC(O)OR_{12'}$, or -$CH_2OC(O)$-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S). In yet another embodiment, R_1 is $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$, In another embodiment, R_1 is $-CH_2OC(O)CH_2NHC(O)CH_2NH_2$, $-CH_2OC(O)CH(R_{12'})NHR_{12'}$, $-CH_2OC(O)(CH_2)_qC(O)OR_{12'}$, or -$CH_2OC(O)$-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S). In another embodiment, R_1 is H or D. In yet another embodiment, R_1 is D. In another embodiment, R_1 is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{2a} is H or D. In another embodiment, R_{2a} is D. In yet another embodiment, R_{2a} is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula

(Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{2b} is H or D. In another embodiment, R_{2b} is D. In yet another embodiment, R_{2b} is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{2c} is H or D. In another embodiment, R_{2c} is D. In yet another embodiment, R_{2c} is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{2d} is H or D. In another embodiment, R_{2d} is D. In yet another embodiment, R_{2d} is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_3 is H, D, $(C_1\text{-}C_3)$alkyl, or $(C_1\text{-}C_3)$deuteroalkyl. In another embodiment, R_3 is D, $(C_1\text{-}C_3)$alkyl, or $(C_1\text{-}C_3)$deuteroalkyl. In yet another embodiment, R_3 is H, $(C_1\text{-}$

C_3)alkyl, or (C_1-C_3)deuteroalkyl. In another embodiment, R_3 is H, D, or (C_1-C_3)alkyl. In yet another embodiment, R_3 is H, D, or (C_1-C_3)deuteroalkyl. In another embodiment, R_3 is (C_1-C_3)alkyl or (C_1-C_3)deuteroalkyl. In another embodiment, R_3 is D or (C_1-C_3)deuteroalkyl. In another embodiment, R_3 is H or (C_1-C_3)deuteroalkyl. In another embodiment, R_3 is D or (C_1-C_3)alkyl. In another embodiment, R_3 is H or (C_1-C_3)alkyl. In another embodiment, R_3 is H or D. In yet another embodiment, R_3 is D. In another embodiment, R_3 is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_4 is D. In another embodiment, R_4 is halogen.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), $R_{4'}$ is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$. In another embodiment, $R_{4'}$ is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, or $-NR_9R_9$. In yet another embodiment, $R_{4'}$ is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, or $-S(O)_pR_{19}$. In another embodiment, $R_{4'}$ is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$. In yet another embodiment, $R_{4'}$ is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$. In another embodiment, $R_{4'}$ is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ic), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv),

Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), $R_{4'}$ is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$. In another embodiment, $R_{4'}$ is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$. In yet another embodiment, $R_{4'}$ is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$. In another embodiment, $R_{4'}$ is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$. In yet another embodiment, $R_{4'}$ is H, D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$. In another embodiment, $R_{4'}$ is H, D, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$. In yet another embodiment, $R_{4'}$ is H, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$. In another embodiment, $R_{4'}$ is D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), $R_{4'}$ is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, or halogen. In yet another embodiment, $R_{4'}$ is H, D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, or halogen. In another embodiment, $R_{4'}$ is D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$. In yet another embodiment, $R_{4'}$ is D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$. In another embodiment, $R_{4'}$ is (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$. In yet another embodiment, $R_{4'}$ is (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$. In another embodiment, $R_{4'}$ is H, D, (C_1-C_3)alkyl, (C_1-C_3)deuteroalkyl, (C_1-C_3)haloalkyl, (C_1-C_3)alkoxy, (C_1-C_3)haloalkoxy, halogen, -

OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$. In yet another embodiment, $R_{4'}$ is H, D, $(C_1$-$C_3)$alkyl, $(C_1$-$C_3)$haloalkyl, $(C_1$-$C_3)$alkoxy, $(C_1$-$C_3)$haloalkoxy, halogen, -OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), $R_{4'}$ is H, D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, halogen, or $-NR_9R_{9'}$. In another embodiment, $R_{4'}$ is H, D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, halogen, or $-NR_9R_{9'}$. In yet another embodiment, $R_{4'}$ is H, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, halogen, or $-NR_9R_{9'}$. In another embodiment, $R_{4'}$ is H, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, halogen, or $-NR_9R_{9'}$. In yet another embodiment, $R_{4'}$ is H, D, $(C_1$-$C_3)$alkyl, $(C_1$-$C_3)$deuteroalkyl, $(C_1$-$C_3)$haloalkyl, $(C_1$-$C_3)$alkoxy, $(C_1$-$C_3)$haloalkoxy, -OH, -CN, halogen, or $-NR_9R_{9'}$. In another embodiment, $R_{4'}$ is H, D, $(C_1$-$C_3)$alkyl, $(C_1$-$C_3)$haloalkyl, $(C_1$-$C_3)$alkoxy, $(C_1$-$C_3)$haloalkoxy, -OH, -CN, halogen, or $-NR_9R_{9'}$. In yet another embodiment, $R_{4'}$ is H, $(C_1$-$C_3)$alkyl, $(C_1$-$C_3)$deuteroalkyl, $(C_1$-$C_3)$haloalkyl, $(C_1$-$C_3)$alkoxy, $(C_1$-$C_3)$haloalkoxy, -OH, -CN, halogen, or $-NR_9R_{9'}$. In another embodiment, $R_{4'}$ is H, $(C_1$-$C_3)$alkyl, $(C_1$-$C_3)$haloalkyl, $(C_1$-$C_3)$alkoxy, $(C_1$-$C_3)$haloalkoxy, -OH, -CN, halogen, or $-NR_9R_{9'}$ In yet another embodiment, $R_{4'}$ is H, D, $(C_1$-$C_3)$alkyl, $(C_1$-$C_3)$deuteroalkyl, $(C_1$-$C_3)$haloalkyl, $(C_1$-$C_3)$alkoxy, halogen, or $-NR_9R_{9'}$. In another embodiment, $R_{4'}$ is H, D, $(C_1$-$C_3)$alkyl, $(C_1$-$C_3)$haloalkyl, $(C_1$-$C_3)$alkoxy, halogen, or $-NR_9R_{9'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_5 is H, D, $(C_2$-$C_6)$alkyl, $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, $-CH_2OC(O)_2R_{12}$, $-P(O)(OR_{12})_2$, or, $-CH_2OP(O)(OH)OR_{12}$. In another embodiment, R_5 is H, D, $(C_2$-$C_6)$alkyl, $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, $-CH_2OC(O)_2R_{12}$, $-P(O)(OR_{12})_2$, or $-CH_2OP(O)(R_{12})_2$. In yet another embodiment, R_5 is H, D, $(C_2$-$C_6)$alkyl, $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, $-CH_2OC(O)_2R_{12}$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In another embodiment,

R_5 is H, D, $(C_2$-$C_6)$alkyl, $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In yet another embodiment, R_5 is H, D, $(C_2$-$C_6)$alkyl, $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)_2R_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In another embodiment, R_5 is H, D, $(C_2$-$C_6)$alkyl, $-C(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, $-CH_2OC(O)_2R_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In yet another embodiment, R_5 is H, D, $(C_2$-$C_6)$alkyl, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, $-CH_2OC(O)_2R_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In another embodiment, R_5 is H, D, $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, $-CH_2OC(O)_2R_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In yet another embodiment, R_5 is H, $(C_2$-$C_6)$alkyl, $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, $-CH_2OC(O)_2R_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In another embodiment, R_5 is D, $(C_2$-$C_6)$alkyl, $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, $-CH_2OC(O)_2R_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In yet another embodiment, R_5 is H, D, $(C_2$-$C_6)$alkyl, $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, or $-CH_2OC(O)_2R_{12}$. In another embodiment, R_5 is H, D, $(C_2$-$C_6)$alkyl, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In yet another embodiment, R_5 is $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, $-CH_2OC(O)_2R_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In another embodiment, R_5 is H, D, or $(C_2$-$C_6)$alkyl. In yet another embodiment, R_5 is H or D. In yet another embodiment, R_5 is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{6a} is H, D, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl. In another embodiment, R_{6a} is H, D, $(C_1$-$C_2)$alkyl, or $(C_1$-$C_2)$deuteroalkyl. In yet another embodiment, R_{6a} is H, D, $(C_1$-$C_2)$alkyl, or $(C_1$-$C_2)$haloalkyl. In another embodiment, R_{6a} is H, D, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl. In yet another embodiment, R_{6a} is H, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl. In another embodiment, R_{6a} is D, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl. In yet another embodiment, R_{6a} is H, D, or $(C_1$-$C_2)$alkyl. In another embodiment, R_{6a} is H, D, or $(C_1$-$C_2)$deuteroalkyl. In yet another embodiment, R_{6a} is H, D, or $(C_1$-$C_2)$haloalkyl. In another embodiment, R_{6a} is H, $(C_1$-$C_2)$alkyl, or $(C_1$-$C_2)$haloalkyl. In yet another embodiment, R_{6a} is D, $(C_1$-$C_2)$alkyl, or $(C_1$-$C_2)$haloalkyl. In yet another embodiment, R_{6a} is $(C_1$-$C_2)$alkyl or $(C_1$-$C_2)$haloalkyl. In another embodiment, R_{6a} is H or D. In yet another embodiment, R_{6a} is D. In another embodiment, R_{6a} is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{6b} is H, D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{6b} is H, D, (C_1-C_2)alkyl, or (C_1-C_2)deuteroalkyl. In yet another embodiment, R_{6b} is H, D, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{6b} is H, D, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6b} is H, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{6b} is D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6b} is H, D, or (C_1-C_2)alkyl. In another embodiment, R_{6b} is H, D, or (C_1-C_2)deuteroalkyl. In yet another embodiment, R_{6b} is H, D, or (C_1-C_2)haloalkyl. In another embodiment, R_{6b} is H, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6b} is D, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6b} is (C_1-C_2)alkyl or (C_1-C_2)haloalkyl. In another embodiment, R_{6b} is H or D. In yet another embodiment, R_{6b} is D. In another embodiment, R_{6b} is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{6c} is H, D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{6c} is H, D, (C_1-C_2)alkyl, or (C_1-C_2)deuteroalkyl. In yet another embodiment, R_{6c} is H, D, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{6c} is H, D, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6c} is H, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{6c} is D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6c} is H, D, or (C_1-C_2)alkyl. In another embodiment, R_{6c} is H, D, or (C_1-C_2)deuteroalkyl. In yet another embodiment, R_{6c} is H, D, or (C_1-C_2)haloalkyl. In another embodiment, R_{6c} is H, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6c} is D, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6c} is (C_1-C_2)alkyl or (C_1-C_2)haloalkyl. In another embodiment, R_{6c} is H or D. In yet another embodiment, R_{6c} is D. In another embodiment, R_{6c} is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{6d} is H, D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{6d} is H, D, (C_1-C_2)alkyl, or (C_1-C_2)deuteroalkyl. In yet another embodiment, R_{6d} is H, D, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{6d} is H, D, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6d} is H, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{6d} is D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6d} is H, D, or (C_1-C_2)alkyl. In another embodiment, R_{6d} is H, D, or (C_1-C_2)deuteroalkyl. In yet another embodiment, R_{6d} is H, D, or (C_1-C_2)haloalkyl. In another embodiment, R_{6d} is H, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6d} is D, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6d} is (C_1-C_2)alkyl or (C_1-C_2)haloalkyl. In another embodiment, R_{6d} is H or D. In yet another embodiment, R_{6d} is D. In another embodiment, R_{6d} is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_{13}, the aryl and heteroaryl are optionally substituted with one to six R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{23}. In another embodiment, each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or (C_3-C_7)carbocyclyl, wherein

the alkyl is optionally substituted with one to six R_{13}, the aryl and heteroaryl are optionally substituted with one to six R_{22}, and the carbocyclyl is optionally substituted with one to four R_{23}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{6e} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, $(C_1$-$C_6)$hydroxyalkyl, -CN, -OH, -O-$(C_1$-$C_6)$hydroxyalkyl, $(C_6$-$C_{10})$ aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to four R_{13}, the aryl and heteroaryl are optionally substituted with one to six R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{23}. In another embodiment, each R_{6e} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, $(C_1$-$C_6)$hydroxyalkyl, -CN, -OH, -O-$(C_1$-$C_6)$hydroxyalkyl, $(C_6$-$C_{10})$ aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_{13}, the aryl and heteroaryl are optionally substituted with one to six R_{22}, and the heterocyclyl is optionally substituted with one to four R_{23}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{6e} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, $(C_1$-$C_6)$hydroxyalkyl, -CN, -OH, -O-$(C_1$-$C_6)$hydroxyalkyl, $(C_6$-$C_{10})$ aryl, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to four R_{13}, the aryl is optionally substituted with one to six R_{22}, and the carbocyclyl and

heterocyclyl are optionally substituted with one to four R_{23}. In yet another embodiment, each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_{13}, the heteroaryl is optionally substituted with one to six R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{23}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_{13}, the aryl and heteroaryl are optionally substituted with one to six R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{23}. In yet another embodiment, each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_{13}, the aryl and heteroaryl are optionally substituted with one to six R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{23}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz),

Formula (Iab), and/or Formula (Iac), each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_{13}, the aryl and heteroaryl are optionally substituted with one to six R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{23}. In yet another embodiment, each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_{13}, the aryl and heteroaryl are optionally substituted with one to six R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{23}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_{13}, the aryl and heteroaryl are optionally substituted with one to six R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{23}. In yet another embodiment, each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_{13}, the aryl and heteroaryl are optionally substituted with one to six R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{23}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{6c} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_{13}, the aryl and heteroaryl are optionally substituted with one to six R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{23}. In yet another embodiment, each R_{6c} is independently at each occurrence D, (C_1-C_6)deuteroalkyl, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one six R_{13}, the aryl and heteroaryl are optionally substituted with one to six R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{23}. In another embodiment, each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one six R_{13}, the aryl and heteroaryl are optionally substituted with one to six R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{23}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{6e} is independently at each occurrence D, (C_1-C_6)deuteroalkyl,

(C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the aryl and heteroaryl are optionally substituted with one to four R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{23}. In yet another embodiment, each R_{6e} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_{13}, the aryl and heteroaryl are optionally substituted with one to six R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{23}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, wherein the alkyl is optionally substituted with one to six R_{13}. In another embodiment, each R_{6e} is independently at each occurrence (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the aryl and heteroaryl are optionally substituted with one to six R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{23}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz),

Formula (Iab), and/or Formula (Iac), each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, halogen, (C_1-C_6)hydroxyalkyl, -OH, (C_6-C_{10}) aryl, or (C_3-C_7)carbocyclyl, wherein the alkyl is optionally substituted with one to six R_{13}, the aryl is optionally substituted with one to six R_{22}, and the carbocyclyl is optionally substituted with one to four R_{23}. In yet another embodiment, each R_{6e} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, halogen, (C_1-C_6)hydroxyalkyl, -OH, (C_6-C_{10}) aryl, or (C_3-C_7)carbocyclyl, wherein the alkyl is optionally substituted with one to six R_{13}, the aryl is optionally substituted with one to six R_{22}, and the carbocyclyl is optionally substituted with one to four R_{23}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one to four R_{15}. In another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are substituted with one to four R_{15}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl is optionally substituted with one to four R_{15}. In another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spiroheterocyclyl is optionally substituted with one to four R_{15}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ic), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv),

Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 6-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one to four R_{15}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 6-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are substituted with one to four R_{15}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- or 5-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one to four R_{15}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- or 5-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are substituted with one to four R_{15}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 5- to 7-membered spiroheterocyclyl

comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one to four R_{15}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 5- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are substituted with one to four R_{15}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 5- or 6-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one to four R_{15}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 5- or 6-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are substituted with one to four R_{15}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 6- or 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one to four R_{15}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 6- or 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are substituted with one to four R_{15}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl, wherein the spirocarbocyclyl is optionally substituted with one to four R_{15}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl, wherein the spirocarbocyclyl is substituted with one to four R_{15}. In another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a 5- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spiroheterocyclyl is optionally substituted with one to four R_{15}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a 5- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spiroheterocyclyl is substituted with one to four R_{15}. In another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a 5- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss),

Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is H, m is 1, n is 0 and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are all simultaneously H, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one or more R_8, the heteroaryl is optionally substituted with one or more R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$. In another embodiment, when $R_{4'}$ is H, m is 1, n is 0 and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are all simultaneously H, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl substituted with one or more substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one or more R_8, the heteroaryl is optionally substituted with one or more R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is H, m is 1, n is 0 and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are all simultaneously H, then R_7 is (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one or more R_8, the heteroaryl is optionally substituted with one or more R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$. In another embodiment, when $R_{4'}$ is H, m is 1, n is 0 and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are all simultaneously H, then R_7 is (C_1-C_6)alkyl substituted with one or more substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O,

N, NH, and S, wherein the phenyl is substituted with one or more R_8, the heteroaryl is optionally substituted with one or more R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is H, m is 1, n is 0 and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are all simultaneously H, then R_7 is $(C_1$-$C_6)$alkyl optionally substituted with one or more substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one or more R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$. In another embodiment, when $R_{4'}$ is H, m is 1, n is 0 and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are all simultaneously H, then R_7 is $(C_1$-$C_6)$alkyl substituted with one or more substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one or more R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is H, m is 1, n is 0 and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are all simultaneously H, then R_7 is $(C_1$-$C_6)$alkyl optionally substituted with one or more substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl

and heteroaryl are substituted with one or more R_8, and the carbocyclyl and heterocyclyl are substituted with one or more $R_{8'}$.In another embodiment, when $R_{4'}$ is H, m is 1, n is 0 and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are all simultaneously H, then R_7 is $(C_1$-$C_6)$alkyl substituted with one or more substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one or more R_8, and the carbocyclyl and heterocyclyl are substituted with one or more $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is H, m is 1, n is 0 and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are all simultaneously H, then R_7 is $(C_1$-$C_6)$alkyl optionally substituted with one or more substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one or more R_8, the heteroaryl is optionally substituted with one or more R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$. In another embodiment, when $R_{4'}$ is H, m is 1, n is 0 and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are all simultaneously H, then R_7 is $(C_1$-$C_6)$alkyl substituted with one or more substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one or more R_8, the heteroaryl is optionally substituted with one or more R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz),

Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is H, m is 1, n is 0 and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are all simultaneously H, then R_7 is (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one or more R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$. In another embodiment, when $R_{4'}$ is H, m is 1, n is 0 and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are all simultaneously H, then R_7 is (C_1-C_6)alkyl substituted with one or more substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one or more R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is H, m is 1, n is 0 and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are all simultaneously H, then R_7 is (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one or more R_8, and the carbocyclyl and heterocyclyl are substituted with one or more $R_{8'}$.In another embodiment, when $R_{4'}$ is H, m is 1, n is 0 and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are all simultaneously H, then R_7 is (C_1-C_6)alkyl substituted with one or more substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one or more R_8, and the carbocyclyl and heterocyclyl are substituted with one or more $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ic), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv),

Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac),when $R_{4'}$ is H, m is 1, n is 0 and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are all simultaneously H, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, or (C_1-C_6)halohydroxyalkyl,. In another embodiment, when $R_{4'}$ is H, m is 1, n is 0 and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are all simultaneously H, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, and -$NR_{16}R_{16'}$. In another embodiment, when $R_{4'}$ is H, m is 1, n is 0 and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are all simultaneously H, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, or (C_1-C_6)alkyl substituted with one or more substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, and -$NR_{16}R_{16'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl,

and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.In another embodiment, when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)alkyl substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ic), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv),

Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is $(C_1$-$C_6)$alkyl optionally substituted with one to four substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one to four R_8, the heteroaryl is optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In another embodiment, when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is $(C_1$-$C_6)$alkyl substituted with one to four substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one to four R_8, the heteroaryl is optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is $(C_1$-$C_6)$alkyl optionally substituted with one to four substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is $(C_1$-$C_6)$alkyl substituted with one to four substituents independently selected

from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8, the carbocyclyl is substituted with one to four $R_{8'}$ and heterocyclyl is optionally substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)alkyl substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8, the carbocyclyl is substituted with one to four $R_{8'}$ and heterocyclyl is optionally substituted with one to four $R_{8'}$.In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1,

and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)alkyl substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)alkyl substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula

(Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one to four R_8, heteroaryl is optionally substituted with one to four R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)alkyl substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one to four R_8, heteroaryl is optionally substituted with one to four R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)alkyl substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl

comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)alkyl substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, or (C_1-C_6)halohydroxyalkyl,. In another embodiment, is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected

from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$. In another embodiment, is $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$hydroxyalkyl, or $(C_1$-$C_6)$alkyl substituted with one to four substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is (C_1)alkyl, then R_7 is $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$halohydroxyalkyl, or $(C_1$-$C_6)$alkyl optionally substituted with one to four substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one to four R_8, the heteroaryl is optionally substituted with one to four R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is (C_1)alkyl, then R_7 is $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$halohydroxyalkyl, or $(C_1$-$C_6)$alkyl substituted with one to four substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one to four R_8, the heteroaryl is optionally substituted with one to four R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is (C_1)alkyl, then R_7 is $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$halohydroxyalkyl, or $(C_1$-$C_6)$alkyl optionally substituted with one to four substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-

membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and the heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is (C_1)alkyl, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and the heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is (C_1)alkyl, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and the heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is (C_1)alkyl, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and the heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc),

Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is (C_1)alkyl, then R_7 is $(C_1$-$C_6)$alkyl optionally substituted with one to four substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one to four R_8, the heteroaryl is optionally substituted with one to four R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is (C_1)alkyl, then R_7 is $(C_1$-$C_6)$alkyl substituted with one to four substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one to four R_8, the heteroaryl is optionally substituted with one to four R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is (C_1)alkyl, then R_7 is $(C_1$-$C_6)$alkyl optionally substituted with one to four substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and the heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is (C_1)alkyl, then R_7 is $(C_1$-$C_6)$alkyl substituted with one to four substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and the heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is (C_1)alkyl, then R_7 is $(C_1$-$C_6)$alkyl optionally substituted with one to four substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and the heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is (C_1)alkyl, then R_7 is $(C_1$-$C_6)$alkyl substituted with one to four substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and the heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is (C_1)alkyl, then R_7 is $(C_1$-$C_6)$alkyl optionally substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one to four R_8, the heteroaryl is optionally substituted with one to four R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is (C_1)alkyl, then R_7 is $(C_1$-$C_6)$alkyl substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein

the phenyl is substituted with one to four R_8, the heteroaryl is optionally substituted with one to four R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is (C_1)alkyl, then R_7 is $(C_1$-$C_6)$alkyl optionally substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and the heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is (C_1)alkyl, then R_7 is $(C_1$-$C_6)$alkyl substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and the heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is (C_1)alkyl, then R_7 is $(C_1$-$C_6)$alkyl optionally substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and the heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is (C_1)alkyl, then R_7 is $(C_1$-$C_6)$alkyl substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected

from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and the heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is (C_1)alkyl, when $R_{4'}$ is (C_1)alkyl, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, or (C_1-C_6)halohydroxyalkyl,. In another embodiment, when $R_{4'}$ is (C_1)alkyl, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$. In another embodiment, when $R_{4'}$ is (C_1)alkyl, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is D, (C_2-C_4)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is D, (C_2-C_4)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl substituted with one to

four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is D, (C_2-C_4)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one to four R_8, the heteroaryl is optionally substituted with one to four R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is D, (C_2-C_4)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one to four R_8, the heteroaryl is optionally substituted with one to four R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss),

Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is D, $(C_2$-$C_4)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$, then R_7 is $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$halohydroxyalkyl, or $(C_1$-$C_6)$alkyl optionally substituted with one to four substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and the heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is D, $(C_2$-$C_4)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$, then R_7 is $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$halohydroxyalkyl, or $(C_1$-$C_6)$alkyl substituted with one to four substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S wherein the phenyl and the heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is D, $(C_2$-$C_4)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$, then R_7 is $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$halohydroxyalkyl, or $(C_1$-$C_6)$alkyl optionally substituted with one to four substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and the heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is D, $(C_2$-$C_4)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$, then R_7 is $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$halohydroxyalkyl, or $(C_1$-$C_6)$alkyl substituted with one to four substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered

heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S wherein the phenyl and the heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is D, (C_2-C_4)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$, then R_7 is (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is D, (C_2-C_4)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$, then R_7 is (C_1-C_6)alkyl substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is D, (C_2-C_4)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$, then R_7 is (C_1-C_6)alkyl optionally

substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one to four R_8, the heteroaryl is optionally substituted with one to four R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is D, (C_2-C_4)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$, then R_7 is (C_1-C_6)alkyl substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one to four R_8, the heteroaryl is optionally substituted with one to four R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is D, (C_2-C_4)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$, then R_7 is (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and the heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is D, (C_2-C_4)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$, then R_7 is (C_1-C_6)alkyl substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S wherein the phenyl and the heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il),

Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is D, $(C_2$-$C_4)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$, then R_7 is $(C_1$-$C_6)$alkyl optionally substituted with one to four substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and the heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is D, $(C_2$-$C_4)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$, then R_7 is $(C_1$-$C_6)$alkyl substituted with one to four substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S wherein the phenyl and the heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is D, $(C_2$-$C_4)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$, then R_7 is $(C_1$-$C_6)$alkyl optionally substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is D, $(C_2$-$C_4)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$, then R_7 is $(C_1$-$C_6)$alkyl substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl

comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is D, (C_2-C_4)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$, then R_7 is (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one to four R_8, the heteroaryl is optionally substituted with one to four R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is D, (C_2-C_4)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$, then R_7 is (C_1-C_6)alkyl substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one to four R_8, the heteroaryl is optionally substituted with one to four R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is D, (C_2-C_4)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$, then R_7 is (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl

comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and the heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is D, (C_2-C_4)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$, then R_7 is (C_1-C_6)alkyl substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S wherein the phenyl and the heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is D, (C_2-C_4)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$, then R_7 is (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and the heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In another embodiment, when $R_{4'}$ is D, (C_2-C_4)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$, then R_7 is (C_1-C_6)alkyl substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S wherein the phenyl and the heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj),

Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), when $R_{4'}$ is D, $(C_2$-$C_4)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$, then R_7 is $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$hydroxyalkyl, or $(C_1$-$C_6)$halohydroxyalkyl,. In another embodiment, when $R_{4'}$ is D, $(C_2$-$C_4)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$, then R_7 is $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$halohydroxyalkyl, or $(C_1$-$C_6)$alkyl optionally substituted with one to four substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16}$. In another embodiment, when $R_{4'}$ is D, $(C_2$-$C_4)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$, then R_7 is $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$halohydroxyalkyl, or $(C_1$-$C_6)$alkyl substituted with one to four substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{40}$, and -CN. In another embodiment, R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4

heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -$C(O)NR_{37}R_{38}$, -$C(O)R_{37}$, -$C(O)OR_{37}$, -SF_5, -SR_{40}, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -$C(O)NR_{32}R_{33}$, -$C(O)OR_{32}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -$C(O)NR_{37}R_{38}$, -$C(O)R_{37}$, -$C(O)OR_{37}$, -SF_5, -SR_{40}, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -$C(O)NR_{32}R_{33}$, -$C(O)OR_{32}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -$C(O)NR_{37}R_{38}$, -$C(O)R_{37}$, -$C(O)OR_{37}$, -SF_5, -SR_{40}, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv),

Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{40}$, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{40}$, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms

selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -$C(O)NR_{37}R_{38}$, -$C(O)R_{37}$, -$C(O)OR_{37}$, -SF_5, -SR_{40}, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -$C(O)NR_{32}R_{33}$, -$C(O)OR_{32}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -$C(O)NR_{37}R_{38}$, -$C(O)R_{37}$, -$C(O)OR_{37}$, -SF_5, -SR_{40}, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -$C(O)NR_{32}R_{33}$, -$C(O)OR_{32}$, (C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -$C(O)NR_{37}R_{38}$, -$C(O)R_{37}$, -$C(O)OR_{37}$, -SF_5, -SR_{40}, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-

C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -C(O)$NR_{32}R_{33}$, -C(O)OR_{32}, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -C(O)$NR_{37}R_{38}$, -C(O)R_{37}, -C(O)OR_{37}, -SF_5, -SR_{40}, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -C(O)$NR_{32}R_{33}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -C(O)$NR_{37}R_{38}$, -C(O)R_{37}, -C(O)OR_{37}, -SF_5, -SR_{40}, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -C(O)OR_{32}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted

with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -$C(O)NR_{37}R_{38}$, -$C(O)R_{37}$, -$C(O)OR_{37}$, -SF_5, -SR_{40}, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -$C(O)NR_{32}R_{33}$, -$C(O)OR_{32}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -$C(O)NR_{37}R_{38}$, -$C(O)R_{37}$, -$C(O)OR_{37}$, -SF_5, -SR_{40}, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -CN, -$C(O)NR_{32}R_{33}$, -$C(O)OR_{32}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -$C(O)NR_{37}R_{38}$, -$C(O)R_{37}$, -$C(O)OR_{37}$, -SF_5, -SR_{40}, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv),

Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{30}R_{31}$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{40}$, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-SF_5$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{40}$, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -

$NR_{30}R_{31}$, $-SF_5$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, (C_3-C_7)carbocyclyl, $-O(C_3-C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{40}$, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, (C_3-C_7)carbocyclyl, $-O(C_3-C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{40}$, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, (C_3-C_7)carbocyclyl, $-O(C_3-C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted

with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -$C(O)NR_{37}R_{38}$, -$C(O)R_{37}$, -$C(O)OR_{37}$, -SF_5, -SR_{40}, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -$C(O)NR_{32}R_{33}$, -$C(O)OR_{32}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -$C(O)NR_{37}R_{38}$, -$C(O)R_{37}$, -$C(O)OR_{37}$, -SF_5, -SR_{40}, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -$C(O)NR_{32}R_{33}$, -$C(O)OR_{32}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -$C(O)NR_{37}R_{38}$, -$C(O)R_{37}$, -$C(O)OR_{37}$, -SF_5, -SR_{40}, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -$C(O)NR_{32}R_{33}$, -$C(O)OR_{32}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N,

NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{40}$, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{40}$, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-

C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -C(O)$NR_{37}R_{38}$, -C(O)R_{37}, -C(O)OR_{37}, -SF_5, -SR_{40}, and -CN.

In another embodiment, R_8 is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -C(O)$NR_{32}R_{33}$, -C(O)OR_{32}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -C(O)$NR_{37}R_{38}$, -C(O)R_{37}, -C(O)OR_{37}, -SF_5, -SR_{40}, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -C(O)$NR_{32}R_{33}$, or -C(O)OR_{32}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_8 is independently at each occurrence (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -C(O)$NR_{37}R_{38}$, -C(O)R_{37}, -C(O)OR_{37}, -SF_5, -SR_{40}, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv),

Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_8 is independently at each occurrence (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -$C(O)NR_{37}R_{38}$, -$C(O)R_{37}$, -$C(O)OR_{37}$, -SF_5, -SR_{40}, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -$C(O)NR_{32}R_{33}$, -$C(O)OR_{32}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -$C(O)NR_{37}R_{38}$, -$C(O)R_{37}$, -$C(O)OR_{37}$, -SF_5, -SR_{40}, and -CN. In another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -$C(O)NR_{32}R_{33}$, -$C(O)OR_{32}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected

from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{40}$, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{40}$, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{40}$, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula

(Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{40}$, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{40}$, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N,

NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{40}$, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{40}$, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, $(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{40}$, and -CN. In

yet another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -C(O)$NR_{32}R_{33}$, -C(O)OR_{32}, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -C(O)$NR_{37}R_{38}$, -C(O)R_{37}, -C(O)OR_{37}, -SF_5, -SR_{40}, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -C(O)$NR_{32}R_{33}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -C(O)$NR_{37}R_{38}$, -C(O)R_{37}, -C(O)OR_{37}, -SF_5, -SR_{40}, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -C(O)OR_{32}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from

O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -$C(O)NR_{37}R_{38}$, -$C(O)R_{37}$, -$C(O)OR_{37}$, -SF_5, -SR_{40}, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -$C(O)NR_{32}R_{33}$, -$C(O)OR_{32}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -$C(O)NR_{37}R_{38}$, -$C(O)R_{37}$, -$C(O)OR_{37}$, -SF_5, -SR_{40}, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -CN, -$C(O)NR_{32}R_{33}$, -$C(O)OR_{32}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -$C(O)NR_{37}R_{38}$, -$C(O)R_{37}$, -$C(O)OR_{37}$, -SF_5, -SR_{40}, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula

(Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NR_{30}R_{31}$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{40}$, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-SF_5$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{40}$, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-

C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -C(O)$NR_{32}R_{33}$, -C(O)OR_{32}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -C(O)$NR_{37}R_{38}$, -C(O)R_{37}, -C(O)OR_{37}, -SF_5, -SR_{40}, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -C(O)$NR_{32}R_{33}$, -C(O)OR_{32}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -C(O)$NR_{37}R_{38}$, -C(O)R_{37}, -C(O)OR_{37}, -SF_5, -SR_{40}, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -C(O)$NR_{32}R_{33}$, -C(O)OR_{32}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from

O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{40}$, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{40}$, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{40}$, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl,

monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -$C(O)NR_{37}R_{38}$, -$C(O)R_{37}$, -$C(O)OR_{37}$, -SF_5, -SR_{40}, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -$C(O)NR_{32}R_{33}$, -$C(O)OR_{32}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -$C(O)NR_{37}R_{38}$, -$C(O)R_{37}$, -$C(O)OR_{37}$, -SF_5, -SR_{40}, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -$C(O)NR_{32}R_{33}$, -$C(O)OR_{32}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-

C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -C(O)$NR_{37}R_{38}$, -C(O)R_{37}, -C(O)OR_{37}, -SF_5, -SR_{40}, and -CN.

In another embodiment, $R_{8'}$ is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -C(O)$NR_{32}R_{33}$, -C(O)OR_{32}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -C(O)$NR_{37}R_{38}$, -C(O)R_{37}, -C(O)OR_{37}, -SF_5, -SR_{40}, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -C(O)$NR_{32}R_{33}$, or -C(O)OR_{32}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), $R_{8'}$ is independently at each occurrence (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -C(O)$NR_{37}R_{38}$, -C(O)R_{37}, -C(O)OR_{37}, -SF_5, -SR_{40}, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv),

Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), $R_{8'}$ is independently at each occurrence (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -$C(O)NR_{37}R_{38}$, -$C(O)R_{37}$, -$C(O)OR_{37}$, -SF_5, -SR_{40}, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four R_{10}. In another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are substituted with one to four R_{10}. In another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or (C_3-C_7)carbocyclyl, wherein the phenyl, heteroaryl, and carbocyclyl are optionally substituted with one to four R_{10}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula

(Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, and heterocyclyl are optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, carbocyclyl, and heterocyclyl are optionally substituted with one to four R_{10}. In another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four R_{10}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{10}. In another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or (C_3-C_7)carbocyclyl, wherein the phenyl and carbocyclyl are optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms

selected from O, N, NH, and S or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heteroaryl and heterocyclyl are optionally substituted with one to four R_{10}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, wherein the phenyl is optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heteroaryl is optionally substituted with one to four R_{10}. In another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{10}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-

membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is optionally substituted with one to four R_{10} and the heteroaryl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one to four R_{10} and the heteroaryl is optionally substituted with one to four R_{10}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, wherein the phenyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heteroaryl is optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, wherein the phenyl is substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heteroaryl is substituted with one to four R_{10}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein

the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- or 5-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 5- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 6- or 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- or 5-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 5- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms

selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 6- or 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- or 5-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 5- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 6- or 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- or 5-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 5- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and

the heterocyclyl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 6- or 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_5)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_4)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_4-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two $R_{8'}$ together with the atoms to which they are attached form a (C_5-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_6-C_7)carbocyclyl or 4- to

7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_5-C_6)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_5)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_4)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_4-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two $R_{8'}$ together with the atoms to which they are attached form a (C_5-

C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two R_8 together with the atoms to which they are attached form a (C_6-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In another embodiment, two R_8 together with the atoms to which they are attached form a (C_5-C_6)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two R_8 together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}. In yet another embodiment, two R_8 together with the atoms to which they are attached form a (C_3-C_5)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}. In another embodiment, two R_8 together with the atoms to which they are attached form a (C_3-C_4)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}. In yet another embodiment, two R_8 together with the atoms to which they are attached form a (C_4-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj),

Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two $R_{8'}$ together with the atoms to which they are attached form a (C_5-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_6-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_5-C_6)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two $R_{8'}$ together with the atoms to which they are attached form a (C_3-

C_5)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, together with the atoms to which they are attached form a (C_3-C_5)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}. In another embodiment, two R_8, together with the atoms to which they are attached form a (C_3-C_4)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, together with the atoms to which they are attached form a (C_3-C_4)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two R_8, together with the atoms to which they are attached form a (C_4-C_7)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, together with the atoms to which they are attached form a (C_4-C_7)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}. In another embodiment, two R_8, together with the atoms to which they are attached form a (C_5-C_7)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, together with the atoms to which they are attached form a (C_5-C_7)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two R_8, together with the atoms to which they are attached form a (C_6-C_7)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, together with the atoms to which they are attached form a (C_6-C_7)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}. In another embodiment, two R_8, together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}. In another embodiment,

two $R_{8'}$ together with the atoms to which they are attached form a (C_4-C_6)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_4-C_6)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two $R_{8'}$ together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a 5- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a 5- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is substituted with one to four R_{10}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two $R_{8'}$ together with the atoms to which they are attached form a 6- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a 6- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a 4- to 6-membered

heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a 4- to 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is substituted with one to four R_{10}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two $R_{8'}$ together with the atoms to which they are attached form a 4- to 5-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a 4- to 5-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is substituted with one to four R_{10}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two $R_{8'}$ when on the same carbon atom form C=(O).

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj),

Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_9 is independently at each occurrence H or (C_1-C_6)alkyl. In another embodiment, R_9 is independently at each occurrence H or (C_1-C_3)alkyl. In yet another embodiment, R_9 is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, R_9 is independently at each occurrence (C_1-C_3)alkyl. In yet another embodiment, R_9 is independently at each occurrence H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), $R_{9'}$ is independently at each occurrence H or (C_1-C_6)alkyl. In another embodiment, $R_{9'}$ is independently at each occurrence H or (C_1-C_3)alkyl. In yet another embodiment, $R_{9'}$ is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, $R_{9'}$ is independently at each occurrence (C_1-C_3)alkyl. In yet another embodiment, $R_{9'}$ is independently at each occurrence H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, or -CN. In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, or -SR_{25}. In yet another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, or -CN. In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SR_{25}, or -CN. In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-

C_6)hydroxyalkyl, halogen, -OH, -SF_5, -SR_{25}, or -CN. In yet another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -NH_2, -SF_5, -SR_{25}, or -CN. In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl,-OH, -NH_2, -SF_5, -SR_{25}, or -CN. In yet another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -NH_2, -SF_5, -SR_{25}, or -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, or -CN. In yet another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, or -CN. In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, or -CN. In yet another embodiment, R_{10} is independently at each occurrence (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, or -CN.

In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, or -CN. In yet another embodiment, R_{10} is independently at each occurrence (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, or -CN. In yet another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, or -CN. In yet another embodiment, R_{10} is independently at each occurrence (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, or -CN. In another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, or -CN. In yet another embodiment, R_{10} is independently at each occurrence (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, or -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, or halogen. In yet another embodiment, R_{10} is independently at each occurrence halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{25}$, or -CN. In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{25}$, or -CN. In yet another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{25}$, or -CN. In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, or -CN. In yet another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, halogen, or -CN. In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, halogen, or -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, or halogen. In yet another embodiment, R_{10} is independently at each occurrence halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{25}$, or -CN. In another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{25}$, or -CN. In yet another embodiment, R_{10} is independently at each occurrence (C_1-C_6)haloalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{25}$, or -CN. In another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, or -CN. In yet another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-

C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, halogen, or -CN. In another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, halogen, or -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In another embodiment, R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In another embodiment, R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In yet

another embodiment, R_{11} is independently at each occurrence H, $(C_1$-$C_6)$alkoxy, $-NH_2$, $-N((C_1$-$C_6)$alkyl$)_2$, $(C_1$-$C_6)$alkyl optionally substituted with one to four substituents independently selected from $(C_6$-$C_{10})$aryl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$haloalkyl, halogen, -OH, $-NH_2$, and -CN, or $(C_6$-$C_{10})$aryl optionally substituted with one to four substituents independently selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$haloalkyl, halogen, -OH, $-NH_2$, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{11} is independently at each occurrence H, $(C_1$-$C_6)$alkoxy, $-N(H)(C_1$-$C_6)$alkyl, $-N((C_1$-$C_6)$alkyl$)_2$, $(C_1$-$C_6)$alkyl optionally substituted with one to four substituents independently selected from $(C_6$-$C_{10})$aryl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$haloalkyl, halogen, -OH, $-NH_2$, and -CN, or $(C_6$-$C_{10})$aryl optionally substituted with one to four substituents independently selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$haloalkyl, halogen, -OH, $-NH_2$, and -CN. In yet another embodiment, R_{11} is independently at each occurrence H, $-NH_2$, $-N(H)(C_1$-$C_6)$alkyl, $-N((C_1$-$C_6)$alkyl$)_2$, $(C_1$-$C_6)$alkyl optionally substituted with one to four substituents independently selected from $(C_6$-$C_{10})$aryl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$haloalkyl, halogen, -OH, $-NH_2$, and -CN, or $(C_6$-$C_{10})$aryl optionally substituted with one to four substituents independently selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$haloalkyl, halogen, -OH, $-NH_2$, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{11} is independently at each occurrence $(C_1$-$C_6)$alkoxy, $-NH_2$, $-N(H)(C_1$-$C_6)$alkyl, $-N((C_1$-$C_6)$alkyl$)_2$, $(C_1$-$C_6)$alkyl optionally substituted with one to four substituents independently selected from $(C_6$-$C_{10})$aryl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$haloalkyl, halogen, -OH, $-NH_2$, and -CN, or $(C_6$-$C_{10})$aryl optionally substituted with one to four substituents independently selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$haloalkyl, halogen, -OH, $-NH_2$,

and -CN. In yet another embodiment, R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{12} is independently at each occurrence H, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In yet another embodiment, R_{12} is independently at each occurrence H, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, or (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In another embodiment, R_{12} is independently at each occurrence H, (C_1-C_6)alkyl substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{12} is independently at each occurrence H, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In yet another embodiment, R_{12} is

independently at each occurrence H. In another embodiment, R_{12} is independently at each occurrence (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In another embodiment, R_{12} is independently at each occurrence (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{12} is independently at each occurrence (C_1-C_6)alkyl substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In yet another embodiment, R_{12} is independently at each occurrence (C_6-C_{10})aryl substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), $R_{12'}$ is independently at each occurrence H or (C_1-C_6)alkyl. In another embodiment, $R_{12'}$ is independently at each occurrence H or (C_1-C_3)alkyl. In another embodiment, $R_{12'}$ is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, $R_{12'}$ is independently at each occurrence H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj),

Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{13} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{14}R_{14'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20} and the aryl and heteroaryl are optionally substituted with one to four R_{21}. In another embodiment, each R_{13} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{14}R_{14'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{20} and the aryl and heteroaryl are optionally substituted with one to four R_{21}. In yet another embodiment, each R_{13} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{14}R_{14'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20} and the aryl and heteroaryl are substituted with one to four R_{21}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{13} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{14}R_{14'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or (C_6-C_{10}) aryl, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20} and the aryl is optionally substituted with one to four R_{21}. In yet another embodiment, each R_{13} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{14}R_{14'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20} and the heteroaryl is optionally substituted with one to four R_{21}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{13} is independently at each occurrence $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $-NR_{14}R_{14'}$, -CN, $(C_3$-$C_7)$carbocyclyl, $(C_6$-$C_{10})$ aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein carbocyclyl is optionally substituted with one to four R_{20} and the aryl and heteroaryl are optionally substituted with one to four R_{21}. In yet another embodiment, each R_{13} is independently at each occurrence $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $-NR_{14}R_{14'}$, -CN, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_6$-$C_{10})$ aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{20} and the aryl and heteroaryl are optionally substituted with one to four R_{21}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{13} is independently at each occurrence $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, -CN, $(C_3$-$C_7)$carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_6$-$C_{10})$ aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20} and the aryl and heteroaryl are optionally substituted with one to four R_{21}. In another embodiment, each R_{13} is independently at each occurrence $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $-NR_{14}R_{14'}$, $(C_3$-$C_7)$carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_6$-$C_{10})$ aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20} and the aryl and heteroaryl are optionally substituted with one to four R_{21}. In yet another embodiment, each R_{13} is independently at each occurrence

(C_1-C_6)alkoxy, -$NR_{14}R_{14'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20} and the aryl and heteroaryl are optionally substituted with one to four R_{21}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{13} is independently at each occurrence (C_1-C_6)haloalkoxy, -$NR_{14}R_{14'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20} and the aryl and heteroaryl are optionally substituted with one to four R_{21}. In yet another embodiment, each R_{13} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{14}R_{14'}$, or -CN. In yet another embodiment, each R_{13} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, or -$NR_{14}R_{14'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{13} is independently at each occurrence (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20} and the aryl and heteroaryl are optionally substituted with one to four R_{21}. In yet another embodiment, each R_{13} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{14}R_{14'}$, -CN, (C_3-C_7)carbocyclyl,

or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}), wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{13} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{14}R_{14'}$, -CN, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the aryl and heteroaryl are optionally substituted with one to four R_{21}. In yet another embodiment, each R_{13} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{14}R_{14'}$, -CN, (C_3-C_7)carbocyclyl, or (C_6-C_{10}) aryl, wherein the carbocyclyl is optionally substituted with one to four R_{20} and the aryl is optionally substituted with one to four R_{21}. In another embodiment, each R_{13} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{14}R_{14'}$, -CN, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{20} and the heteroaryl is optionally substituted with one to four R_{21}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{13} is independently at each occurrence (C_1-C_6)alkoxy, -$NR_{14}R_{14'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20} and the aryl and heteroaryl are optionally substituted with one to four R_{21}. In yet another embodiment, each R_{13} is independently at each occurrence (C_1-C_6)alkoxy, -$NR_{14}R_{14'}$, -CN,

(C_3-C_7)carbocyclyl, or (C_6-C_{10}) aryl, wherein the carbocyclyl is substituted with one to four R_{20} and the aryl is optionally substituted with one to four R_{21}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{13} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{14}R_{14'}$, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the aryl and heteroaryl are optionally substituted with one to four R_{21}. In yet another embodiment, each R_{13} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{14}R_{14'}$, (C_3-C_7)carbocyclyl, or (C_6-C_{10}) aryl, wherein the carbocyclyl is optionally substituted with one to four R_{20} and the aryl is optionally substituted with one to four R_{21}. In another embodiment, each R_{13} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{14}R_{14'}$, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{20} and the heteroaryl is optionally substituted with one to four R_{21}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{13} is independently at each occurrence (C_1-C_6)alkoxy, -$NR_{14}R_{14'}$, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20} and the aryl and heteroaryl are optionally substituted with one to four R_{21}. In yet another embodiment, each R_{13} is independently at each occurrence (C_1-C_6)alkoxy, -$NR_{14}R_{14'}$, (C_3-

C_7)carbocyclyl, or (C_6-C_{10}) aryl, wherein the carbocyclyl is substituted with one to four R_{20} and the aryl is optionally substituted with one to four R_{21}.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{14} is independently at each occurrence H or (C_1-C_6)alkyl. In another embodiment, R_{14} is independently at each occurrence H or (C_1-C_3)alkyl. In yet another embodiment, R_{14} is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, R_{14} is independently at each occurrence (C_1-C_3)alkyl. In yet another embodiment, R_{14} is independently at each occurrence H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), $R_{14'}$ is independently at each occurrence H or (C_1-C_6)alkyl. In another embodiment, $R_{14'}$ is independently at each occurrence H or (C_1-C_3)alkyl. In yet another embodiment, $R_{14'}$ is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, $R_{14'}$ is independently at each occurrence (C_1-C_3)alkyl. In yet another embodiment, $R_{14'}$ is independently at each occurrence H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{15} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)N$R_{17}R_{17}$. In another embodiment, each R_{15} is independently at each

occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, or -C(O)R_{18}. In yet another embodiment, each R_{15} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, or -C(O)$NR_{17}R_{17}$. In another embodiment, each R_{15} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{15} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$. In yet another embodiment, each R_{15} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$. In another embodiment, each R_{15} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$. In yet another embodiment, each R_{15} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{15} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$. In yet another embodiment, each R_{15} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$. In another embodiment, each R_{15} is independently at each occurrence D, (C_1-

C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$. In yet another embodiment, each R_{15} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$.

In another embodiment, each R_{15} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, or halogen. In yet another embodiment, each R_{15} is independently at each occurrence halogen, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$. In another embodiment, each R_{15} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, or halogen. In another embodiment, each R_{15} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, or halogen. In yet another embodiment, each R_{15} is independently at each occurrence halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$. In another embodiment, each R_{15} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, or halogen.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{16} is independently at each occurrence H or (C_1-C_6)alkyl. In another embodiment, R_{16} is independently at each occurrence H or (C_1-C_3)alkyl. In yet another embodiment, R_{16} is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, R_{16} is independently at each occurrence (C_1-C_3)alkyl. In another embodiment, R_{16} is independently at each occurrence H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), $R_{16'}$ is independently at each occurrence H or (C_1-C_6)alkyl. In another embodiment, $R_{16'}$ is independently at each occurrence H or (C_1-C_3)alkyl. In yet another embodiment, $R_{16'}$

is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, $R_{16'}$ is independently at each occurrence (C_1-C_3)alkyl. In another embodiment, $R_{16'}$ is independently at each occurrence H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{16a} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{16a} is H, (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{16a} is H or (C_1-C_6)alkyl. In another embodiment, R_{16a} is H or (C_1-C_6)haloalkyl. In yet another embodiment, R_{16a} is (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{16a} is (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{16a} is (C_1-C_6)alkyl. In another embodiment, R_{16a} is (C_1-C_3)alkyl. In another embodiment, R_{16a} is (C_1-C_6)haloalkyl. In another embodiment, R_{16a} is (C_1-C_3)haloalkyl. In another embodiment, R_{16a} is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{17} is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{17} is independently at each occurrence H, (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{17} is independently at each occurrence H or (C_1-C_6)alkyl. In another embodiment, R_{17} is independently at each occurrence H or (C_1-C_6)haloalkyl. In yet another embodiment, R_{17} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{17} is independently at each occurrence (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{17} is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, R_{17} is independently at each occurrence (C_1-C_3)alkyl. In another embodiment, R_{17} is independently at each occurrence (C_1-C_6)haloalkyl. In another embodiment, R_{17} is independently at each occurrence (C_1-C_3)haloalkyl. In another embodiment, R_{17} is independently at each occurrence H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula

(Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{18} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{18} is independently at each occurrence (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In another embodiment, R_{18} is independently at each occurrence (C_1-C_6)haloalkyl. In another embodiment, R_{18} is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, R_{18} is independently at each occurrence (C_1-C_3)haloalkyl. In another embodiment, R_{18} is independently at each occurrence (C_1-C_3)alkyl.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{19} is (C_1-C_3)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{19} is (C_1-C_6)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{19} is (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In another embodiment, R_{19} is (C_1-C_6)alkyl. In yet another embodiment, R_{19} is (C_1-C_6)haloalkyl. In another embodiment, R_{19} is (C_1-C_3)alkyl. In yet another embodiment, R_{19} is (C_1-C_3)haloalkyl.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-

C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or (C_3-C_7)carbocyclyl. In yet another embodiment, each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-

C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula

(Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{20} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{26}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{20} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{26}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{20} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{26}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{20} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{26}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{20} is independently at each occurrence D, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{26}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{20} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{26}$, -CN, phenyl, 5- or 6-membered

heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, or -CN. In yet another embodiment, each R_{20} is independently at each occurrence halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{20} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, or

-CN. In yet another embodiment, each R_{20} is independently at each occurrence halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{26}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{20} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{26}$, -CN, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{20} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{26}$, -CN, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{20} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two R_{20} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, two R_{20} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl. In another embodiment, two R_{20} together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl. In yet another embodiment, two R_{20} together with the atoms to which they are attached form a (C_3-C_5)carbocyclyl. In another embodiment, two R_{20} together with the atoms to which they are attached form a (C_3-C_4)carbocyclyl. In yet another embodiment, two R_{20} together with the atoms to which they are attached form a (C_4-C_7)carbocyclyl. In another embodiment, two R_{20} together with the atoms to which they are attached form a (C_5-C_7)carbocyclyl. In yet another embodiment, two R_{20} together with the atoms to which they are attached form a (C_6-C_7)carbocyclyl.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc),

Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two R_{20} together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, two R_{20} together with the atoms to which they are attached form a 4- to 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, two R_{20} together with the atoms to which they are attached form a 4- or 5-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, two R_{20} together with the atoms to which they are attached form a 5- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, two R_{20} together with the atoms to which they are attached form a 6- or 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or (C_3-C_7)carbocyclyl. In yet another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula

(Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -SF_5, -SR_{27}, -CN,

phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, $-NH_2$, $-SF_5$, $-SR_{27}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl,-OH, $-NH_2$, $-SF_5$, $-SR_{27}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{27}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{27}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-

C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{21} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, or -CN. In yet another embodiment, each R_{21} is independently at each occurrence halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-

C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{21} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, or -CN. In yet another embodiment, each R_{21} is independently at each occurrence halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{21} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{21} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{21} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{22} is independently at each occurrence (C_1-C_6)alkyl, (C_1-

C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{28}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{22} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{28}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or (C_3-C_7)carbocyclyl. In yet another embodiment, each R_{22} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{28}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{22} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{28}, -CN, phenyl, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{22} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{28}, -CN, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{22} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{28}, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc),

Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{22} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{22} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SR_{28}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{22} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-SF_5$, $-SR_{28}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{22} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, $-NH_2$, $-SF_5$, $-SR_{28}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{22} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, -OH, $-NH_2$, $-SF_5$, $-SR_{28}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{22} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{28}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{22} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{28}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{22} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{28}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{22} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{28}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{22} is independently at each occurrence (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{28}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{22} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{28}, or -CN. In yet another embodiment, each R_{22} is independently at each occurrence halogen, -OH, -NH_2, -SF_5, -SR_{28}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH,

and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{22} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{28}, -CN, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{22} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{28}, -CN, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{22} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two R_{22}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, two R_{22}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl. In yet another embodiment, two R_{22}, when on adjacent atoms, together with the atoms to which they are attached form a 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, two R_{22}, when on adjacent atoms, together with the atoms to which they are attached form a 5-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, two R_{22}, when on adjacent atoms, together with the atoms to which they are attached form a 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Icc), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss),

Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{23} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{29}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{23} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{29}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or $(C_3$-$C_7)$carbocyclyl. In yet another embodiment, each R_{23} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{29}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{23} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{29}$, -CN, phenyl, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{23} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{29}$, -CN, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{23} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{29}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula

(Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{23} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{23} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SR_{29}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{23} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-SF_5$, $-SR_{29}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{23} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, $-NH_2$, $-SF_5$, $-SR_{29}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{23} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, -OH, $-NH_2$, $-SF_5$, $-SR_{29}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{23} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{29}$, -CN, phenyl, 5- or 6-membered

heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{23} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{29}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{23} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{29}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{23} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{29}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{23} is independently at each occurrence (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{29}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), each R_{23} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{29}, or

-CN. In yet another embodiment, each R_{23} is independently at each occurrence halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{29}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{23} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{29}$, -CN, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{23} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{29}$, -CN, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{23} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two R_{23} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, two R_{23} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl. In another embodiment, two R_{23} together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl. In yet another embodiment, two R_{23} together with the atoms to which they are attached form a (C_3-C_5)carbocyclyl. In another embodiment, two R_{23} together with the atoms to which they are attached form a (C_3-C_4)carbocyclyl. In yet another embodiment, two R_{23} together with the atoms to which they are attached form a (C_4-C_7)carbocyclyl. In another embodiment, two R_{23} together with the atoms to which they are attached form a (C_5-C_7)carbocyclyl. In yet another embodiment, two R_{23} together with the atoms to which they are attached form a (C_6-C_7)carbocyclyl.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc),

Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), two R_{23} together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, two R_{23} together with the atoms to which they are attached form a 4- to 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, two R_{23} together with the atoms to which they are attached form a 4- or 5-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, two R_{23} together with the atoms to which they are attached form a 5- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, two R_{23} together with the atoms to which they are attached form a 6- or 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{24} is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{24} is independently at each occurrence H, (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{24} is independently at each occurrence H or (C_1-C_6)alkyl. In another embodiment, R_{24} is independently at each occurrence H or (C_1-C_6)haloalkyl. In yet another embodiment, R_{24} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{24} is independently at each occurrence (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{24} is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, R_{24} is independently at each occurrence (C_1-C_3)alkyl. In another embodiment, R_{24} is independently at each occurrence (C_1-C_6)haloalkyl. In another embodiment, R_{24} is independently at each occurrence (C_1-C_3)haloalkyl. In another embodiment, R_{24} is independently at each occurrence H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc),

Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{25} is independently at each occurrence H, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{25} is independently at each occurrence H, $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$haloalkyl. In yet another embodiment, R_{25} is independently at each occurrence H or $(C_1$-$C_6)$alkyl. In another embodiment, R_{25} is independently at each occurrence H or $(C_1$-$C_6)$haloalkyl. In yet another embodiment, R_{25} is independently at each occurrence $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{25} is independently at each occurrence $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$haloalkyl. In yet another embodiment, R_{25} is independently at each occurrence $(C_1$-$C_6)$alkyl. In another embodiment, R_{25} is independently at each occurrence $(C_1$-$C_3)$alkyl. In another embodiment, R_{25} is independently at each occurrence $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{25} is independently at each occurrence $(C_1$-$C_3)$haloalkyl. In another embodiment, R_{25} is independently at each occurrence H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{26} is independently at each occurrence H, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{26} is independently at each occurrence H, $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$haloalkyl. In yet another embodiment, R_{26} is independently at each occurrence H or $(C_1$-$C_6)$alkyl. In another embodiment, R_{26} is independently at each occurrence H or $(C_1$-$C_6)$haloalkyl. In yet another embodiment, R_{26} is independently at each occurrence $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{26} is independently at each occurrence $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$haloalkyl. In yet another embodiment, R_{26} is independently at each occurrence $(C_1$-$C_6)$alkyl. In another embodiment, R_{26} is independently at each occurrence $(C_1$-$C_3)$alkyl. In another embodiment, R_{26} is independently at each occurrence $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{26} is independently at each occurrence $(C_1$-$C_3)$haloalkyl. In another embodiment, R_{26} is independently at each occurrence H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc),

Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{27} is independently at each occurrence H, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{27} is independently at each occurrence H, $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$haloalkyl. In yet another embodiment, R_{27} is independently at each occurrence H or $(C_1$-$C_6)$alkyl. In another embodiment, R_{27} is independently at each occurrence H or $(C_1$-$C_6)$haloalkyl. In yet another embodiment, R_{27} is independently at each occurrence $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{27} is independently at each occurrence $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$haloalkyl. In yet another embodiment, R_{27} is independently at each occurrence $(C_1$-$C_6)$alkyl. In another embodiment, R_{27} is independently at each occurrence $(C_1$-$C_3)$alkyl. In another embodiment, R_{27} is independently at each occurrence $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{27} is independently at each occurrence $(C_1$-$C_3)$haloalkyl. In another embodiment, R_{27} is independently at each occurrence H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{28} is independently at each occurrence H, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{28} is independently at each occurrence H, $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$haloalkyl. In yet another embodiment, R_{28} is independently at each occurrence H or $(C_1$-$C_6)$alkyl. In another embodiment, R_{28} is independently at each occurrence H or $(C_1$-$C_6)$haloalkyl. In yet another embodiment, R_{28} is independently at each occurrence $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{28} is independently at each occurrence $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$haloalkyl. In yet another embodiment, R_{28} is independently at each occurrence $(C_1$-$C_6)$alkyl. In another embodiment, R_{28} is independently at each occurrence $(C_1$-$C_3)$alkyl. In another embodiment, R_{28} is independently at each occurrence $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{28} is independently at each occurrence $(C_1$-$C_3)$haloalkyl. In another embodiment, R_{28} is independently at each occurrence H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc),

Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{29} is independently at each occurrence H, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{29} is independently at each occurrence H, $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$haloalkyl. In yet another embodiment, R_{29} is independently at each occurrence H or $(C_1$-$C_6)$alkyl. In another embodiment, R_{29} is independently at each occurrence H or $(C_1$-$C_6)$haloalkyl. In yet another embodiment, R_{29} is independently at each occurrence $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{29} is independently at each occurrence $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$haloalkyl. In yet another embodiment, R_{29} is independently at each occurrence $(C_1$-$C_6)$alkyl. In another embodiment, R_{29} is independently at each occurrence $(C_1$-$C_3)$alkyl. In another embodiment, R_{29} is independently at each occurrence $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{29} is independently at each occurrence $(C_1$-$C_3)$haloalkyl. In another embodiment, R_{29} is independently at each occurrence H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{30} is H, $(C_1$-$C_6)$alkyl, or -C(O)R_{34}. In another embodiment, R_{30} is H, $(C_1$-$C_3)$alkyl, or -C(O)R_{34}. In yet another embodiment, R_{30} is H or $(C_1$-$C_6)$alkyl. In another embodiment, R_{30} is H or -C(O)R_{34}. In yet another embodiment, R_{30} is $(C_1$-$C_3)$alkyl or -C(O)R_{34}. In another embodiment, R_{30} is $(C_1$-$C_3)$alkyl. In yet another embodiment, R_{30} is -C(O)R_{34}. In another embodiment, R_{30} is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{31} is H, $(C_1$-$C_6)$alkyl, or -C(O)R_{34}. In another embodiment, R_{31} is H, $(C_1$-$C_3)$alkyl, or -C(O)R_{34}. In yet another embodiment, R_{31} is H or $(C_1$-$C_6)$alkyl. In another embodiment,

R_{31} is H or -C(O)R_{34}. In yet another embodiment, R_{31} is (C_1-C_3)alkyl or -C(O)R_{34}. In another embodiment, R_{31} is (C_1-C_3)alkyl. In yet another embodiment, R_{31} is -C(O)R_{34}. In another embodiment, R_{31} is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{32} is H or (C_1-C_6)alkyl. In another embodiment, R_{32} is H or (C_1-C_3)alkyl. In yet another embodiment, R_{32} is (C_1-C_6)alkyl. In another embodiment, R_{32} is (C_1-C_3)alkyl. In yet another embodiment, R_{32} is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{33} is H or (C_1-C_6)alkyl. In another embodiment, R_{33} is H or (C_1-C_3)alkyl. In yet another embodiment, R_{33} is (C_1-C_6)alkyl. In another embodiment, R_{33} is (C_1-C_3)alkyl. In yet another embodiment, R_{33} is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{34} is H or (C_1-C_6)alkyl. In another embodiment, R_{34} is H or (C_1-C_3)alkyl. In yet another embodiment, R_{34} is (C_1-C_6)alkyl. In another embodiment, R_{34} is (C_1-C_3)alkyl. In yet another embodiment, R_{34} is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula

(Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{35} is H, (C_1-C_3)alkyl, or -C(O)R_{39}. In yet another embodiment, R_{35} is H or (C_1-C_6)alkyl. In another embodiment, R_{35} is H or -C(O)R_{39}. In yet another embodiment, R_{35} is (C_1-C_3)alkyl or -C(O)R_{39}. In another embodiment, R_{35} is (C_1-C_3)alkyl. In yet another embodiment, R_{35} is -C(O)R_{39}. In another embodiment, R_{35} is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{36} is H, (C_1-C_6)alkyl, or -C(O)R_{39}. In another embodiment, R_{36} is H, (C_1-C_3)alkyl, or -C(O)R_{39}. In yet another embodiment, R_{36} is H or (C_1-C_6)alkyl. In another embodiment, R_{36} is H or -C(O)R_{39}. In yet another embodiment, R_{36} is (C_1-C_3)alkyl or -C(O)R_{39}. In another embodiment, R_{36} is (C_1-C_3)alkyl. In yet another embodiment, R_{36} is -C(O)R_{39}. In another embodiment, R_{36} is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{37} is H or (C_1-C_6)alkyl. In another embodiment, R_{37} is H or (C_1-C_3)alkyl. In yet another embodiment, R_{37} is (C_1-C_6)alkyl. In another embodiment, R_{37} is (C_1-C_3)alkyl. In yet another embodiment, R_{37} is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc),

Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{38} is H or (C_1-C_6)alkyl. In another embodiment, R_{38} is H or (C_1-C_3)alkyl. In yet another embodiment, R_{38} is (C_1-C_6)alkyl. In another embodiment, R_{38} is (C_1-C_3)alkyl. In yet another embodiment, R_{38} is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{39} is H or (C_1-C_6)alkyl. In another embodiment, R_{39} is H or (C_1-C_3)alkyl. In yet another embodiment, R_{39} is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, R_{39} is (C_1-C_3)alkyl. In yet another embodiment, R_{39} is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_{40} is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{40} is independently at each occurrence H, (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{40} is independently at each occurrence H or (C_1-C_6)alkyl. In another embodiment, R_{40} is independently at each occurrence H or (C_1-C_6)haloalkyl. In yet another embodiment, R_{40} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{40} is independently at each occurrence (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{40} is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, R_{40} is independently at each occurrence (C_1-C_3)alkyl. In another embodiment, R_{40} is independently at each occurrence (C_1-C_6)haloalkyl. In another embodiment, R_{40} is independently at each occurrence (C_1-C_3)haloalkyl. In another embodiment, R_{40} is independently at each occurrence H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), m is 0 or 1. In another embodiment, m is 1 or 2. In yet another embodiment, m is 0 or 2. In another embodiment, m is 0. In yet another embodiment, m is 1. In another embodiment, m is 2.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), p is 0 or 1. In another embodiment, p is 1 or 2. In yet another embodiment, p is 0 or 2. In another embodiment, p is 0. In yet another embodiment, p is 1. In another embodiment, p is 2.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), q is 1, 2, or 3. In another embodiment, q is 1 or 3. In yet another embodiment, q is 2 or 3. In another embodiment, q is 1 or 2. In yet another embodiment, q is 1. In another embodiment, q is 2. In yet another embodiment, q is 3.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc),

Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), n is 0, 1, 2, 3, or 4. In another embodiment, n is 0, 1, 2, or 3. In yet another embodiment, n is 0, 1, 2, or 4. In another embodiment, n is 0, 1, 3 or 4. In yet another embodiment, n is 0, 2, 3, or 4. In another embodiment, n is 1, 2, 3 or 4. In yet another embodiment, n is 0, 1, or 2. In another embodiment, n is 2, 3, or 4. In yet another embodiment, n is 1, 2, or 3. In another embodiment, n is 0 or 1. In yet another embodiment, n is 1 or 2. In another embodiment, n is 2 or 3. In yet another embodiment, n is 3 or 4. In another embodiment, n is 0 or 2. In yet another embodiment, n is 0 or 3. In another embodiment, n is 0 or 4. In yet another embodiment, n is 1 or 2. In another embodiment, n is 1 or 3. In yet another embodiment, n is 1 or 4. In another embodiment, n is 0 or 2. In yet another embodiment, n is 2 or 4. In another embodiment, n is 0. In yet another embodiment, n is 1. In another embodiment, n is 2. In yet another embodiment, n is 4.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is H or D and R_{2a} is H. In another embodiment, R_1 is H or D, R_{2a} is H, and R_{2b} is H. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H and R_{2c} is H. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H and R_{2d} is H. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, and R_3 is H or D. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, and m is 0.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, and R_{6a} is H. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D,

m is 0, R_{6a} is H, and R_{6b} is H. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, and R_{6c} is H. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, and R_{6d} is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, and R_5 is H. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 0. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and $R_{4'}$ is H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, halogen, -OH, -CN, or $-NR_9R_{9'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 1 or 2. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and $R_{4'}$ is H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, halogen, -OH, -CN, or $-NR_9R_{9'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Icc), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss),

Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, and R_{6a} is H. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, and R_{6b} is H. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, and R_{6c} is H. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, and R_{6d} is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, and R_5 is H. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 0. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and $R_{4'}$ is H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, halogen, -OH, -CN, or $-NR_9R_{9'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 1 or 2. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and $R_{4'}$ is H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, halogen, -OH, -CN, or $-NR_9R_{9'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc),

Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and $R_{4'}$ is H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, halogen, -OH, -CN, or $-NR_9R_{9'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and $R_{4'}$ is H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, halogen, -OH, -CN, or $-NR_9R_{9'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, and R_{6a} is H. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, and R_{6b} is H. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, and R_{6c} is H. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, and R_{6d} is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Icc), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss),

Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, and R_5 is H. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 0. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and $R_{4'}$ is H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, or -$NR_9R_{9'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 1 or 2. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and $R_{4'}$ is H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, or -$NR_9R_{9'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is H and R_{2a} is H. In another embodiment, R_1 is H, R_{2a} is H, and R_{2b} is H. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H and R_{2c} is H. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H and R_{2d} is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, and R_3 is H or D. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, and m is 0.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc),

Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, and R_{6a} is H. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, and R_{6b} is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, and R_{6c} is H. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, and R_{6d} is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, and R_5 is H. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 0. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and $R_{4'}$ is H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, or -$NR_9R_{9'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 1 or 2. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and $R_{4'}$ is H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, or -$NR_9R_{9'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula

(Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, and R_{6a} is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, and R_{6b} is H. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, and R_{6c} is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, and R_{6d} is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, and R_5 is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 0. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and $R_{4'}$ is H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, or -$NR_9R_{9'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 1 or 2. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and $R_{4'}$ is H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, or -$NR_9R_{9'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, and R_3 is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H and m is 0. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, and R_{6a} is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, and R_{6b} is H. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, and R_{6c} is H.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, and R_{6a} is H, R_{6b} is H, R_{6c} is H, and R_{6d} is H. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, and R_5 is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 0. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and $R_{4'}$ is H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, or -$NR_9R_{9'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H,

R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 1 or 2. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and $R_{4'}$ is H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, or -$NR_9R_{9'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, and R_{6a} is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, and R_{6b} is H. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, and R_{6c} is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, and R_{6d} is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, and R_5 is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 0. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and $R_{4'}$ is H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, or -$NR_9R_{9'}$.

In some embodiments of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id) Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), and/or Formula (Iac), R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 1 or 2. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and $R_{4'}$ is H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, or -$NR_9R_{9'}$.

In some embodiments of the Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf):

R_1 is H, D, -$C(O)R_{11}$, -$CH_2OC(O)R_{11}$, -$CH_2OC(O)NHR_{12}$, -$CH_2OC(O)OR_{12}$, -$P(O)(OR_{12})_2$, -$CH_2OP(O)(OR_{12})_2$, -$CH_2OP(O)(OH)OR_{12}$, -$CH_2OP(O)(R_{12})_2$, -$CH_2OC(O)CH_2NHC(O)CH_2NH_2$,

$-CH_2OC(O)CH(R_{12'})NHR_{12'}$, $-CH_2OC(O)(CH_2)_qC(O)OR_{12'}$, or $-CH_2OC(O)$-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S);

R_{2a}, R_{2b}, R_{2c}, and R_{2d} are each independently H or D;

R_3 is H, D, $(C_1$-$C_3)$alkyl, or $(C_1$-$C_3)$deuteroalkyl;

each R_4 is independently at each occurrence D;

R_5 is H, D, $(C_1$-$C_6)$alkyl, $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, $-CH_2OC(O)_2R_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$;

R_{6a}, R_{6b}, R_{6c}, and R_{6d} are each independently H, D, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl;

each R_{6e} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, $(C_1$-$C_6)$hydroxyalkyl, -CN, -OH, -O-$(C_1$-$C_6)$hydroxyalkyl, $(C_6$-$C_{10})$aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to four R_9, the aryl and heteroaryl are optionally substituted with one to four R_{16}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}; or

two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a $(C_3$-$C_7)$spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one to four R_{14};

R_7 is $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$halohydroxyalkyl, or $(C_1$-$C_6)$alkyl optionally substituted with one to four substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{15a}$, $-NR_{15}R_{15'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$;

R_8 and $R_{8'}$ are each independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{28}R_{29}$, $-SF_5$, $-SR_{22}$, -CN, $-C(O)NR_{30}R_{31}$, $-C(O)OR_{30}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted

with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -$C(O)NR_{35}R_{36}$, -$C(O)R_{35}$, -$C(O)OR_{35}$, -SF_5, -SR_{38}, and -CN; or

two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four R_{10};

two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_{10}; or

two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{10}; or

two $R_{8'}$ when on the same carbon atom form C=(O);

each R_9 is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{13}R_{13'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20} and the aryl and heteroaryl are optionally substituted with one to four R_{21};

R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{23}, or -CN;

R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN;

R_{12} is independently at each occurrence H, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN;

$R_{12'}$ is independently at each occurrence H or (C_1-C_6)alkyl;

R_{13} and $R_{13'}$ are each independently at each occurrence H or (C_1-C_6)alkyl;

each R_{14} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$;

R_{15} and $R_{15'}$ are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{15a} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

each R_{16} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{16}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

R_{17} is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{18} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{19} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{20} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, and R_{27} are each independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{28} and R_{29} are each independently at each occurrence H, (C_1-C_6)alkyl, or -C(O)R_{32};

R_{30}, R_{31}, and R_{32} are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{33} and R_{34} are each independently at each occurrence H, (C_1-C_6)alkyl, or -C(O)R_{37};

R_{35}, R_{36}, and R_{37} are each independently at each occurrence H or $(C_1$-$C_6)$alkyl;

R_{38} is H, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl;

m is 0, 1, or 2;

q is 1, 2, or 3; and

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

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H, D, $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, $-CH_2OP(O)(R_{12})_2$, $-CH_2OC(O)CH_2NHC(O)CH_2NH_2$, $-CH_2OC(O)CH(R_{12'})NHR_{12'}$, $-CH_2OC(O)(CH_2)_qC(O)OR_{12'}$, or $-CH_2OC(O)$-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S). In another embodiment, R_1 is H, D, $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In yet another embodiment, R_1 is H, D, $-CH_2OC(O)CH_2NHC(O)CH_2NH_2$, $-CH_2OC(O)CH(R_{12'})NHR_{12'}$, $-CH_2OC(O)(CH_2)_qC(O)OR_{12'}$, or $-CH_2OC(O)$-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S).

In some embodiments of Formula (II), R_1 is $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, $-CH_2OP(O)(R_{12})_2$, $-CH_2OC(O)CH_2NHC(O)CH_2NH_2$, $-CH_2OC(O)CH(R_{12'})NHR_{12'}$, $-CH_2OC(O)(CH_2)_qC(O)OR_{12'}$, or $-CH_2OC(O)$-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S). In yet another embodiment, R_1 is $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$, In another embodiment, R_1 is $-CH_2OC(O)CH_2NHC(O)CH_2NH_2$, $-CH_2OC(O)CH(R_{12'})NHR_{12'}$, $-CH_2OC(O)(CH_2)_qC(O)OR_{12'}$, or $-CH_2OC(O)$-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S). In another embodiment, R_1 is H or D. In yet another embodiment, R_1 is D. In another embodiment, R_1 is H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{2a} is H or D. In another embodiment, R_{2a} is D. In yet another embodiment, R_{2a} is H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{2b} is H or D. In another embodiment, R_{2b} is D. In yet another embodiment, R_{2b} is H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{2c} is H or D. In another embodiment, R_{2c} is D. In yet another embodiment, R_{2c} is H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{2d} is H or D. In another embodiment, R_{2d} is D. In yet another embodiment, R_{2d} is H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_3 is H, D, (C_1-C_3)alkyl, or (C_1-C_3)deuteroalkyl. In another embodiment, R_3 is D, (C_1-C_3)alkyl, or (C_1-C_3)deuteroalkyl. In yet another embodiment, R_3 is H, (C_1-C_3)alkyl, or (C_1-C_3)deuteroalkyl. In another embodiment, R_3 is H, D, or (C_1-C_3)alkyl. In yet another embodiment, R_3 is H, D, or (C_1-C_3)deuteroalkyl. In another embodiment, R_3 is (C_1-C_3)alkyl or (C_1-C_3)deuteroalkyl. In another embodiment, R_3 is D or (C_1-C_3)deuteroalkyl. In another embodiment, R_3 is H or (C_1-C_3)deuteroalkyl. In another embodiment, R_3 is D or (C_1-C_3)alkyl. In another embodiment, R_3 is H or (C_1-C_3)alkyl. In another embodiment, R_3 is H or D. In yet another embodiment, R_3 is D. In another embodiment, R_3 is H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_4 is D.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_5 is H, D, (C_1-C_6)alkyl, $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, $-CH_2OC(O)_2R_{12}$, $-P(O)(OR_{12})_2$, or, $-CH_2OP(O)(OH)OR_{12}$. In another embodiment, R_5 is H, D, (C_1-C_6)alkyl, $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, $-CH_2OC(O)_2R_{12}$, $-P(O)(OR_{12})_2$, or $-CH_2OP(O)(R_{12})_2$. In yet another embodiment, R_5 is H, D, (C_1-C_6)alkyl, $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, $-CH_2OC(O)_2R_{12}$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In another embodiment, R_5 is H, D, (C_1-C_6)alkyl, $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In yet another embodiment, R_5 is H, D, (C_1-C_6)alkyl, $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)_2R_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In another embodiment, R_5 is H, D, (C_1-C_6)alkyl, $-C(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, $-CH_2OC(O)_2R_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In yet another embodiment, R_5 is H, D, (C_1-C_6)alkyl, $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, $-CH_2OC(O)_2R_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In another embodiment, R_5 is H, D, $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, $-CH_2OC(O)_2R_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In yet another embodiment, R_5 is H, (C_1-C_6)alkyl, $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, $-CH_2OC(O)_2R_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In another embodiment, R_5 is D, (C_1-C_6)alkyl, $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, $-CH_2OC(O)_2R_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In yet another embodiment, R_5 is H, D, (C_1-C_6)alkyl, $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, or $-CH_2OC(O)_2R_{12}$. In another embodiment, R_5 is H, D, (C_1-C_6)alkyl, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In yet another embodiment, R_5 is $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, -

$CH_2OC(O)N(R_{12})_2$, $-CH_2OC(O)_2R_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In another embodiment, R_5 is H, D, or $(C_1$-$C_6)$alkyl. In yet another embodiment, R_5 is H or D. In yet another embodiment, R_5 is H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{6a} is H, D, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl. In another embodiment, R_{6a} is H, D, $(C_1$-$C_2)$alkyl, or $(C_1$-$C_2)$deuteroalkyl. In yet another embodiment, R_{6a} is H, D, $(C_1$-$C_2)$alkyl, or $(C_1$-$C_2)$haloalkyl. In another embodiment, R_{6a} is H, D, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl. In yet another embodiment, R_{6a} is H, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl. In another embodiment, R_{6a} is D, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl. In yet another embodiment, R_{6a} is H, D, or $(C_1$-$C_2)$alkyl. In another embodiment, R_{6a} is H, D, or $(C_1$-$C_2)$deuteroalkyl. In yet another embodiment, R_{6a} is H, D, or $(C_1$-$C_2)$haloalkyl. In another embodiment, R_{6a} is H, $(C_1$-$C_2)$alkyl, or $(C_1$-$C_2)$haloalkyl. In yet another embodiment, R_{6a} is D, $(C_1$-$C_2)$alkyl, or $(C_1$-$C_2)$haloalkyl. In yet another embodiment, R_{6a} is $(C_1$-$C_2)$alkyl or $(C_1$-$C_2)$haloalkyl. In another embodiment, R_{6a} is H or D. In yet another embodiment, R_{6a} is D. In another embodiment, R_{6a} is H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{6b} is H, D, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl. In another embodiment, R_{6b} is H, D, $(C_1$-$C_2)$alkyl, or $(C_1$-$C_2)$deuteroalkyl. In yet another embodiment, R_{6b} is H, D, $(C_1$-$C_2)$alkyl, or $(C_1$-$C_2)$haloalkyl. In another embodiment, R_{6b} is H, D, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl. In yet another embodiment, R_{6b} is H, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl. In another embodiment, R_{6b} is D, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl. In yet another embodiment, R_{6b} is H, D, or $(C_1$-$C_2)$alkyl. In another embodiment, R_{6b} is H, D, or $(C_1$-$C_2)$deuteroalkyl. In yet another embodiment, R_{6b} is H, D, or $(C_1$-$C_2)$haloalkyl. In another embodiment, R_{6b} is H, $(C_1$-$C_2)$alkyl, or $(C_1$-$C_2)$haloalkyl. In yet another embodiment, R_{6b} is D, $(C_1$-$C_2)$alkyl, or $(C_1$-$C_2)$haloalkyl. In yet another embodiment, R_{6b} is $(C_1$-$C_2)$alkyl or $(C_1$-$C_2)$haloalkyl. In another embodiment, R_{6b} is H or D. In yet another embodiment, R_{6b} is D. In another embodiment, R_{6b} is H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{6c} is H, D, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl. In another embodiment, R_{6c} is H, D, $(C_1$-$C_2)$alkyl, or $(C_1$-$C_2)$deuteroalkyl. In yet another embodiment, R_{6c} is H, D, $(C_1$-$C_2)$alkyl, or $(C_1$-$C_2)$haloalkyl. In another embodiment, R_{6c} is H, D, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl. In yet another embodiment, R_{6c} is H, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl. In another embodiment, R_{6c} is D, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl. In yet another embodiment, R_{6c} is H, D, or $(C_1$-$C_2)$alkyl. In another embodiment, R_{6c} is H, D, or $(C_1$-$C_2)$deuteroalkyl. In yet another embodiment, R_{6c} is H, D, or $(C_1$-$C_2)$haloalkyl. In another embodiment, R_{6c} is H, $(C_1$-$C_2)$alkyl, or $(C_1$-$C_2)$haloalkyl. In yet another embodiment, R_{6c} is D, $(C_1$-$C_2)$alkyl, or $(C_1$-$C_2)$haloalkyl. In yet another

embodiment, R_{6c} is $(C_1$-$C_2)$alkyl or $(C_1$-$C_2)$haloalkyl. In another embodiment, R_{6c} is H or D. In yet another embodiment, R_{6c} is D. In another embodiment, R_{6c} is H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{6d} is H, D, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl. In another embodiment, R_{6d} is H, D, $(C_1$-$C_2)$alkyl, or $(C_1$-$C_2)$deuteroalkyl. In yet another embodiment, R_{6d} is H, D, $(C_1$-$C_2)$alkyl, or $(C_1$-$C_2)$haloalkyl. In another embodiment, R_{6d} is H, D, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl. In yet another embodiment, R_{6d} is H, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl. In another embodiment, R_{6d} is D, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl. In yet another embodiment, R_{6d} is H, D, or $(C_1$-$C_2)$alkyl. In another embodiment, R_{6d} is H, D, or $(C_1$-$C_2)$deuteroalkyl. In yet another embodiment, R_{6d} is H, D, or $(C_1$-$C_2)$haloalkyl. In another embodiment, R_{6d} is H, $(C_1$-$C_2)$alkyl, or $(C_1$-$C_2)$haloalkyl. In yet another embodiment, R_{6d} is D, $(C_1$-$C_2)$alkyl, or $(C_1$-$C_2)$haloalkyl. In yet another embodiment, R_{6d} is $(C_1$-$C_2)$alkyl or $(C_1$-$C_2)$haloalkyl. In another embodiment, R_{6d} is H or D. In yet another embodiment, R_{6d} is D. In another embodiment, R_{6d} is H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{6e} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, $(C_1$-$C_6)$hydroxyalkyl, -CN, -OH, -O-$(C_1$-$C_6)$hydroxyalkyl, $(C_6$-$C_{10})$ aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_9, the aryl and heteroaryl are optionally substituted with one to six R_{16}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}. In another embodiment, each R_{6e} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, $(C_1$-$C_6)$hydroxyalkyl, -CN, -OH, -O-$(C_1$-$C_6)$hydroxyalkyl, $(C_6$-$C_{10})$ aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or $(C_3$-$C_7)$carbocyclyl, wherein the alkyl is optionally substituted with one to six R_9, the aryl and heteroaryl are optionally substituted with one to six R_{16}, and the carbocyclyl is optionally substituted with one to four R_{19}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{6e} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, $(C_1$-$C_6)$hydroxyalkyl, -CN, -OH, -O-$(C_1$-$C_6)$hydroxyalkyl, $(C_6$-$C_{10})$ aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to four R_9, the aryl and heteroaryl are optionally substituted with one to six R_{16}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}. In another embodiment, each R_{6e} is independently at each

occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_9, the aryl and heteroaryl are optionally substituted with one to six R_{16}, and the heterocyclyl is optionally substituted with one to four R_{19}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{6c} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to four R_9, the aryl is optionally substituted with one to six R_{16}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}. In yet another embodiment, each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_9, the heteroaryl is optionally substituted with one to six R_{16}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_9, the aryl and heteroaryl are optionally substituted with one to six R_{16}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}. In yet another embodiment, each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_9, the aryl and heteroaryl are optionally substituted with one to six R_{16}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_9, the aryl and heteroaryl are optionally substituted with one to six R_{16}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}. In yet another embodiment, each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_9, the aryl and heteroaryl are optionally substituted with one to six R_{16}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_9, the aryl and heteroaryl are optionally substituted with one to six R_{16}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}. In yet another embodiment, each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_9, the aryl and heteroaryl are optionally substituted with one to six R_{16}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_9, the aryl and

heteroaryl are optionally substituted with one to six R_{16}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}. In yet another embodiment, each R_{6e} is independently at each occurrence D, (C_1-C_6)deuteroalkyl, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one six R_9, the aryl and heteroaryl are optionally substituted with one to six R_{16}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}. In another embodiment, each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one six R_9, the aryl and heteroaryl are optionally substituted with one to six R_{16}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{6e} is independently at each occurrence D, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the aryl and heteroaryl are optionally substituted with one to four R_{16}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}. In yet another embodiment, each R_{6e} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_9, the aryl and heteroaryl are optionally substituted with one to six R_{16}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, wherein the alkyl is optionally substituted with one to six R_9. In another embodiment, each R_{6e} is independently at each occurrence (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered

heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the aryl and heteroaryl are optionally substituted with one to six R_{16}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, halogen, (C_1-C_6)hydroxyalkyl, -OH, (C_6-C_{10}) aryl, or (C_3-C_7)carbocyclyl, wherein the alkyl is optionally substituted with one to six R_9, the aryl is optionally substituted with one to six R_{16}, and the carbocyclyl is optionally substituted with one to four R_{19}. In yet another embodiment, each R_{6e} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, halogen, (C_1-C_6)hydroxyalkyl, -OH, (C_6-C_{10}) aryl, or (C_3-C_7)carbocyclyl, wherein the alkyl is optionally substituted with one to six R_9, the aryl is optionally substituted with one to six R_{16}, and the carbocyclyl is optionally substituted with one to four R_{19}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one to four R_{14}. In another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are substituted with one to four R_{14}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl is optionally substituted with one to four R_{14}. In another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spiroheterocyclyl is optionally substituted with one to four R_{14}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 6-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one to four R_{14}. In yet another embodiment, two R_{6e}, when

on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 6-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are substituted with one to four R_{14}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- or 5-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one to four R_{14}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- or 5-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are substituted with one to four R_{14}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 5- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one to four R_{14}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 5- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are substituted with one to four R_{14}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 5- or 6-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one to four R_{14}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 5- or 6-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are substituted with one to four R_{14}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 6- or 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one to four R_{14}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-

C_7)spirocarbocyclyl or a 6- or 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are substituted with one to four R_{14}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl, wherein the spirocarbocyclyl is optionally substituted with one to four R_{14}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl, wherein the spirocarbocyclyl is substituted with one to four R_{14}. In another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a 5- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spiroheterocyclyl is optionally substituted with one to four R_{14}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a 5- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spiroheterocyclyl is substituted with one to four R_{14}. In another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a 5- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{15a}, -$NR_{15}R_{15'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{15a}, -$NR_{15}R_{15'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -

SF_5, $-SR_{15a}$, $-NR_{15}R_{15'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, or (C_1-C_6)halohydroxyalkyl. In another embodiment, R_7 is (C_1-C_6)haloalkyl or (C_1-C_6)hydroxyalkyl. In yet another embodiment, R_7 is (C_1-C_6)haloalkyl or (C_1-C_6)halohydroxyalkyl. In another embodiment, R_7 is (C_1-C_6)hydroxyalkyl or (C_1-C_6)halohydroxyalkyl.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_7 is (C_1-C_6)haloalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, $-SF_5$, $-SR_{15a}$, $-NR_{15}R_{15'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_7 is (C_1-C_6)hydroxyalkyl or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, $-SF_5$, $-SR_{15a}$, $-NR_{15}R_{15'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_7 is (C_1-C_6)hydroxyalkyl or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkoxy, $-SF_5$, $-SR_{15a}$, $-NR_{15}R_{15'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, $-SF_5$, $-SR_{15a}$, $-NR_{15}R_{15'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally

substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SR_{15a}, -$NR_{15}R_{15'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -$NR_{15}R_{15'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{15a}, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{15a}, -$NR_{15}R_{15'}$, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heteroaryl is optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{15a}, -$NR_{15}R_{15'}$, phenyl, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heteroaryl is optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{15a}, -$NR_{15}R_{15'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms

selected from O, N, NH, and S, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the heterocyclyl is optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{15a}, -$NR_{15}R_{15'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, and (C_3-C_7)carbocyclyl, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl is optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_7 is (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_7 is (C_1-C_6)haloalkyl or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_7 is (C_1-C_6)hydroxyalkyl or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, R_7 is (C_1-C_6)halohydroxyalkyl or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -C(O)$NR_{30}R_{31}$, -C(O)OR_{30}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -C(O)$NR_{35}R_{36}$, -C(O)R_{35}, -C(O)OR_{35}, -SF_5, -SR_{38}, and -CN. In another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -C(O)$NR_{30}R_{31}$, -C(O)OR_{30}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms

selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -$C(O)NR_{35}R_{36}$, -$C(O)R_{35}$, -$C(O)OR_{35}$, -SF_5, -SR_{38}, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -$C(O)NR_{30}R_{31}$, -$C(O)OR_{30}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -$C(O)NR_{35}R_{36}$, -$C(O)R_{35}$, -$C(O)OR_{35}$, -SF_5, -SR_{38}, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -$C(O)NR_{30}R_{31}$, -$C(O)OR_{30}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -$C(O)NR_{35}R_{36}$, -$C(O)R_{35}$, -$C(O)OR_{35}$, -SF_5, -SR_{38}, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -$C(O)NR_{30}R_{31}$, -$C(O)OR_{30}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -$C(O)NR_{35}R_{36}$, -$C(O)R_{35}$, -$C(O)OR_{35}$, -SF_5, -SR_{38}, and -CN. In

yet another embodiment, R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{28}R_{29}$, $-SF_5$, $-SR_{22}$, -CN, $-C(O)NR_{30}R_{31}$, $-C(O)OR_{30}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{33}R_{34}$, $-C(O)NR_{35}R_{36}$, $-C(O)R_{35}$, $-C(O)OR_{35}$, $-SF_5$, $-SR_{38}$, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{28}R_{29}$, $-SF_5$, $-SR_{22}$, -CN, $-C(O)NR_{30}R_{31}$, $-C(O)OR_{30}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{33}R_{34}$, $-C(O)NR_{35}R_{36}$, $-C(O)R_{35}$, $-C(O)OR_{35}$, $-SF_5$, $-SR_{38}$, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{28}R_{29}$, $-SF_5$, $-SR_{22}$, -CN, $-C(O)NR_{30}R_{31}$, $-C(O)OR_{30}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{33}R_{34}$, $-C(O)NR_{35}R_{36}$, $-C(O)R_{35}$, $-C(O)OR_{35}$, $-SF_5$, $-SR_{38}$, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH,

-$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -C(O)$NR_{30}R_{31}$, -C(O)OR_{30}, (C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -C(O)$NR_{35}R_{36}$, -C(O)R_{35}, -C(O)OR_{35}, -SF_5, -SR_{38}, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -C(O)$NR_{30}R_{31}$, -C(O)OR_{30}, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -C(O)$NR_{35}R_{36}$, -C(O)R_{35}, -C(O)OR_{35}, -SF_5, -SR_{38}, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -C(O)$NR_{30}R_{31}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -C(O)$NR_{35}R_{36}$, -C(O)R_{35}, -C(O)OR_{35}, -SF_5, -SR_{38}, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -C(O)OR_{30}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms

selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -$C(O)NR_{35}R_{36}$, -$C(O)R_{35}$, -$C(O)OR_{35}$, -SF_5, -SR_{38}, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -$C(O)NR_{30}R_{31}$, -$C(O)OR_{30}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -$C(O)NR_{35}R_{36}$, -$C(O)R_{35}$, -$C(O)OR_{35}$, -SF_5, -SR_{38}, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -CN, -$C(O)NR_{30}R_{31}$, -$C(O)OR_{30}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -$C(O)NR_{35}R_{36}$, -$C(O)R_{35}$, -$C(O)OR_{35}$, -SF_5, -SR_{38}, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SR_{22}, -CN, -$C(O)NR_{30}R_{31}$, -$C(O)OR_{30}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms

selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -$C(O)NR_{35}R_{36}$, -$C(O)R_{35}$, -$C(O)OR_{35}$, -SF_5, -SR_{38}, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -SF_5, -SR_{22}, -CN, -$C(O)NR_{30}R_{31}$, -$C(O)OR_{30}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -$C(O)NR_{35}R_{36}$, -$C(O)R_{35}$, -$C(O)OR_{35}$, -SF_5, -SR_{38}, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -$C(O)NR_{30}R_{31}$, -$C(O)OR_{30}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -$C(O)NR_{35}R_{36}$, -$C(O)R_{35}$, -$C(O)OR_{35}$, -SF_5, -SR_{38}, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -$C(O)NR_{30}R_{31}$, -$C(O)OR_{30}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected

from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -$C(O)NR_{35}R_{36}$, -$C(O)R_{35}$, -$C(O)OR_{35}$, -SF_5, -SR_{38}, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -$C(O)NR_{30}R_{31}$, -$C(O)OR_{30}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -$C(O)NR_{35}R_{36}$, -$C(O)R_{35}$, -$C(O)OR_{35}$, -SF_5, -SR_{38}, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -$C(O)NR_{30}R_{31}$, -$C(O)OR_{30}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -$C(O)NR_{35}R_{36}$, -$C(O)R_{35}$, -$C(O)OR_{35}$, -SF_5, -SR_{38}, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -$C(O)NR_{30}R_{31}$, -$C(O)OR_{30}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from

O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{33}R_{34}$, $-C(O)NR_{35}R_{36}$, $-C(O)R_{35}$, $-C(O)OR_{35}$, $-SF_5$, $-SR_{38}$, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{28}R_{29}$, $-SF_5$, $-SR_{22}$, -CN, $-C(O)NR_{30}R_{31}$, $-C(O)OR_{30}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{33}R_{34}$, $-C(O)NR_{35}R_{36}$, $-C(O)R_{35}$, $-C(O)OR_{35}$, $-SF_5$, $-SR_{38}$, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{28}R_{29}$, $-SF_5$, $-SR_{22}$, -CN, $-C(O)NR_{30}R_{31}$, $-C(O)OR_{30}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{33}R_{34}$, $-C(O)NR_{35}R_{36}$, $-C(O)R_{35}$, $-C(O)OR_{35}$, $-SF_5$, $-SR_{38}$, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{28}R_{29}$, $-SF_5$, $-SR_{22}$, -CN, $-C(O)NR_{30}R_{31}$, $-C(O)OR_{30}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-

C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -C(O)$NR_{35}R_{36}$, -C(O)R_{35}, -C(O)OR_{35}, -SF_5, -SR_{38}, and -CN.

In another embodiment, R_8 is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -C(O)$NR_{30}R_{31}$, -C(O)OR_{30}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -C(O)$NR_{35}R_{36}$, -C(O)R_{35}, -C(O)OR_{35}, -SF_5, -SR_{38}, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -C(O)$NR_{30}R_{31}$, or -C(O)OR_{30}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_8 is independently at each occurrence (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -C(O)$NR_{35}R_{36}$, -C(O)R_{35}, -C(O)OR_{35}, -SF_5, -SR_{38}, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_8 is independently at each occurrence (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy,

(C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -C(O)$NR_{35}R_{36}$, -C(O)R_{35}, -C(O)OR_{35}, -SF_5, -SR_{38}, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -C(O)$NR_{30}R_{31}$, -C(O)OR_{30}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -C(O)$NR_{35}R_{36}$, -C(O)R_{35}, -C(O)OR_{35}, -SF_5, -SR_{38}, and -CN. In another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -C(O)$NR_{30}R_{31}$, -C(O)OR_{30}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -C(O)$NR_{35}R_{36}$, -C(O)R_{35}, -C(O)OR_{35}, -SF_5, -SR_{38}, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -C(O)$NR_{30}R_{31}$, -C(O)OR_{30}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -C(O)$NR_{35}R_{36}$, -C(O)R_{35}, -

$C(O)OR_{35}$, $-SF_5$, $-SR_{38}$, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NR_{28}R_{29}$, $-SF_5$, $-SR_{22}$, -CN, $-C(O)NR_{30}R_{31}$, $-C(O)OR_{30}$, (C_3-C_7)carbocyclyl, $-O(C_3-C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, $-NR_{33}R_{34}$, $-C(O)NR_{35}R_{36}$, $-C(O)R_{35}$, $-C(O)OR_{35}$, $-SF_5$, $-SR_{38}$, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NR_{28}R_{29}$, $-SF_5$, $-SR_{22}$, -CN, $-C(O)NR_{30}R_{31}$, $-C(O)OR_{30}$, (C_3-C_7)carbocyclyl, $-O(C_3-C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, $-NR_{33}R_{34}$, $-C(O)NR_{35}R_{36}$, $-C(O)R_{35}$, $-C(O)OR_{35}$, $-SF_5$, $-SR_{38}$, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NR_{28}R_{29}$, $-SF_5$, $-SR_{22}$, -CN, $-C(O)NR_{30}R_{31}$, $-C(O)OR_{30}$, (C_3-C_7)carbocyclyl, $-O(C_3-C_7)$carbocyclyl, phenyl, -O-phenyl, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, $-NR_{33}R_{34}$, $-C(O)NR_{35}R_{36}$, $-C(O)R_{35}$, $-C(O)OR_{35}$, $-SF_5$, $-SR_{38}$, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NR_{28}R_{29}$, $-SF_5$, $-SR_{22}$, -CN, $-C(O)NR_{30}R_{31}$, $-C(O)OR_{30}$, (C_3-C_7)carbocyclyl, $-O(C_3-C_7)$carbocyclyl, phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N,

NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{33}R_{34}$, $-C(O)NR_{35}R_{36}$, $-C(O)R_{35}$, $-C(O)OR_{35}$, $-SF_5$, $-SR_{38}$, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{28}R_{29}$, $-SF_5$, $-SR_{22}$, -CN, $-C(O)NR_{30}R_{31}$, $-C(O)OR_{30}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{33}R_{34}$, $-C(O)NR_{35}R_{36}$, $-C(O)R_{35}$, $-C(O)OR_{35}$, $-SF_5$, $-SR_{38}$, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{28}R_{29}$, $-SF_5$, $-SR_{22}$, -CN, $-C(O)NR_{30}R_{31}$, $-C(O)OR_{30}$, $(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{33}R_{34}$, $-C(O)NR_{35}R_{36}$, $-C(O)R_{35}$, $-C(O)OR_{35}$, $-SF_5$, $-SR_{38}$, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{28}R_{29}$, $-SF_5$, $-SR_{22}$, -CN, $-C(O)NR_{30}R_{31}$, $-C(O)OR_{30}$, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S

or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -$C(O)NR_{35}R_{36}$, -$C(O)R_{35}$, -$C(O)OR_{35}$, -SF_5, -SR_{38}, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -$C(O)NR_{30}R_{31}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -$C(O)NR_{35}R_{36}$, -$C(O)R_{35}$, -$C(O)OR_{35}$, -SF_5, -SR_{38}, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -$C(O)OR_{30}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -$C(O)NR_{35}R_{36}$, -$C(O)R_{35}$, -$C(O)OR_{35}$, -SF_5, -SR_{38}, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -$C(O)NR_{30}R_{31}$, -$C(O)OR_{30}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from

O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{33}R_{34}$, $-C(O)NR_{35}R_{36}$, $-C(O)R_{35}$, $-C(O)OR_{35}$, $-SF_5$, $-SR_{38}$, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{28}R_{29}$, $-SF_5$, -CN, $-C(O)NR_{30}R_{31}$, $-C(O)OR_{30}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{33}R_{34}$, $-C(O)NR_{35}R_{36}$, $-C(O)R_{35}$, $-C(O)OR_{35}$, $-SF_5$, $-SR_{38}$, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{28}R_{29}$, $-SR_{22}$, -CN, $-C(O)NR_{30}R_{31}$, $-C(O)OR_{30}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{33}R_{34}$, $-C(O)NR_{35}R_{36}$, $-C(O)R_{35}$, $-C(O)OR_{35}$, $-SF_5$, $-SR_{38}$, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-SF_5$, $-SR_{22}$, -CN, $-C(O)NR_{30}R_{31}$, $-C(O)OR_{30}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-

C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -C(O)$NR_{35}R_{36}$, -C(O)R_{35}, -C(O)OR_{35}, -SF_5, -SR_{38}, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -C(O)$NR_{30}R_{31}$, -C(O)OR_{30}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -C(O)$NR_{35}R_{36}$, -C(O)R_{35}, -C(O)OR_{35}, -SF_5, -SR_{38}, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -C(O)$NR_{30}R_{31}$, -C(O)OR_{30}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -C(O)$NR_{35}R_{36}$, -C(O)R_{35}, -C(O)OR_{35}, -SF_5, -SR_{38}, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -C(O)$NR_{30}R_{31}$, -C(O)OR_{30}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-

C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -C(O)$NR_{35}R_{36}$, -C(O)R_{35}, -C(O)OR_{35}, -SF_5, -SR_{38}, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -C(O)$NR_{30}R_{31}$, -C(O)OR_{30}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -C(O)$NR_{35}R_{36}$, -C(O)R_{35}, -C(O)OR_{35}, -SF_5, -SR_{38}, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -C(O)$NR_{30}R_{31}$, -C(O)OR_{30}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -C(O)$NR_{35}R_{36}$, -C(O)R_{35}, -C(O)OR_{35}, -SF_5, -SR_{38}, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -C(O)$NR_{30}R_{31}$, -C(O)OR_{30}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -C(O)$NR_{35}R_{36}$, -C(O)R_{35}, -C(O)OR_{35}, -SF_5, -SR_{38}, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{28}R_{29}$, $-SF_5$, $-SR_{22}$, -CN, $-C(O)NR_{30}R_{31}$, $-C(O)OR_{30}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{33}R_{34}$, $-C(O)NR_{35}R_{36}$, $-C(O)R_{35}$, $-C(O)OR_{35}$, $-SF_5$, $-SR_{38}$, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{28}R_{29}$, $-SF_5$, $-SR_{22}$, -CN, $-C(O)NR_{30}R_{31}$, $-C(O)OR_{30}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{33}R_{34}$, $-C(O)NR_{35}R_{36}$, $-C(O)R_{35}$, $-C(O)OR_{35}$, $-SF_5$, $-SR_{38}$, and -CN.

In another embodiment, $R_{8'}$ is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{28}R_{29}$, $-SF_5$, $-SR_{22}$, -CN, $-C(O)NR_{30}R_{31}$, $-C(O)OR_{30}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{33}R_{34}$, $-C(O)NR_{35}R_{36}$, $-C(O)R_{35}$, $-C(O)OR_{35}$, $-SF_5$, $-SR_{38}$, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-

C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -C(O)$NR_{30}R_{31}$, or -C(O)OR_{30}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), $R_{8'}$ is independently at each occurrence (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -C(O)$NR_{35}R_{36}$, -C(O)R_{35}, -C(O)OR_{35}, -SF_5, -SR_{38}, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), $R_{8'}$ is independently at each occurrence (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -C(O)$NR_{35}R_{36}$, -C(O)R_{35}, -C(O)OR_{35}, -SF_5, -SR_{38}, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four R_{10}. In another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are substituted with one to four R_{10}. In another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4

heteroatoms selected from O, N, NH, and S, or (C_3-C_7)carbocyclyl, wherein the phenyl, heteroaryl, and carbocyclyl are optionally substituted with one to four R_{10}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, and heterocyclyl are optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, carbocyclyl, and heterocyclyl are optionally substituted with one to four R_{10}. In another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four R_{10}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{10}. In another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or (C_3-C_7)carbocyclyl, wherein the phenyl and carbocyclyl are optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heteroaryl and heterocyclyl are optionally substituted with one to four R_{10}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, wherein the phenyl is optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heteroaryl is optionally substituted with one to four R_{10}. In another embodiment, two R_8, when on adjacent

atoms, together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{10}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is optionally substituted with one to four R_{10} and the heteroaryl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one to four R_{10} and the heteroaryl is optionally substituted with one to four R_{10}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, wherein the phenyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heteroaryl is optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, wherein the phenyl is substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heteroaryl is substituted with one to four R_{10}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl

or 4- to 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- or 5-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 5- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 6- or 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- or 5-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 5- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 6- or 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- or 5-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 5- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 6- or 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- or 5-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 5- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 6- or 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_5)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_4)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_4-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4

heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two $R_{8'}$ together with the atoms to which they are attached form a (C_5-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_6-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_5-C_6)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_5)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_4)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_4-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two $R_{8'}$ together with the atoms to which they are attached form a (C_5-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_6-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the

heterocyclyl is optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_5-C_6)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_5)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_4)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_4-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two $R_{8'}$ together with the atoms to which they are attached form a (C_5-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_6-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_5-C_6)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms

to which they are attached form a (C_3-C_6)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_5)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_5)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_4)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_4)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two $R_{8'}$ together with the atoms to which they are attached form a (C_4-C_7)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_4-C_7)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_5-C_7)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_5-C_7)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two $R_{8'}$ together with the atoms to which they are attached form a (C_6-C_7)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_6-C_7)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_4-C_6)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_4-C_6)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two $R_{8'}$ together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the

heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is substituted with one to four R_{10}. In another embodiment, two R_8, together with the atoms to which they are attached form a 5- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, together with the atoms to which they are attached form a 5- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is substituted with one to four R_{10}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two R_8, together with the atoms to which they are attached form a 6- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, together with the atoms to which they are attached form a 6- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is substituted with one to four R_{10}. In another embodiment, two R_8, together with the atoms to which they are attached form a 4- to 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, together with the atoms to which they are attached form a 4- to 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is substituted with one to four R_{10}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two R_8, together with the atoms to which they are attached form a 4- to 5-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, together with the atoms to which they are attached form a 4- to 5-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is substituted with one to four R_{10}. In another embodiment, two R_8, together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is substituted with one to four R_{10}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two R_8, when on the same carbon atom form C=(O).

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_9 is independently at each occurrence (C_1-C_6)alkoxy, (C_1-

C_6)haloalkoxy, -$NR_{13}R_{13'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20} and the aryl and heteroaryl are optionally substituted with one to four R_{21}. In another embodiment, each R_9 is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{13}R_{13'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{20} and the aryl and heteroaryl are optionally substituted with one to four R_{21}. In yet another embodiment, each R_9 is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{13}R_{13'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20} and the aryl and heteroaryl are substituted with one to four R_{21}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_9 is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{13}R_{13'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or (C_6-C_{10}) aryl, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20} and the aryl is optionally substituted with one to four R_{21}. In yet another embodiment, each R_9 is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{13}R_{13'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20} and the heteroaryl is optionally substituted with one to four R_{21}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_9 is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{13}R_{13'}$, -CN, (C_3-C_7)carbocyclyl, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein carbocyclyl is optionally substituted with one to four R_{20} and the aryl and heteroaryl are optionally substituted with one to four R_{21}. In yet another embodiment, each R_9 is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{13}R_{13'}$, -CN, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4

heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{20} and the aryl and heteroaryl are optionally substituted with one to four R_{21}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_9 is independently at each occurrence $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, -CN, $(C_3$-$C_7)$carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_6$-$C_{10})$ aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20} and the aryl and heteroaryl are optionally substituted with one to four R_{21}. In another embodiment, each R_9 is independently at each occurrence $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $-NR_{13}R_{13'}$, $(C_3$-$C_7)$carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_6$-$C_{10})$ aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20} and the aryl and heteroaryl are optionally substituted with one to four R_{21}. In yet another embodiment, each R_9 is independently at each occurrence $(C_1$-$C_6)$alkoxy, $-NR_{13}R_{13'}$, -CN, $(C_3$-$C_7)$carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_6$-$C_{10})$ aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20} and the aryl and heteroaryl are optionally substituted with one to four R_{21}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_9 is independently at each occurrence $(C_1$-$C_6)$haloalkoxy, $-NR_{13}R_{13'}$, -CN, $(C_3$-$C_7)$carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_6$-$C_{10})$ aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20} and the aryl and heteroaryl are optionally substituted with one to four R_{21}. In yet another embodiment, each R_9 is independently at each occurrence $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $-NR_{13}R_{13'}$, or -CN. In yet another embodiment, each R_9 is independently at each occurrence $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, or $-NR_{13}R_{13'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_9 is independently at each occurrence $(C_3$-$C_7)$carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_6$-$C_{10})$ aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20} and the aryl and heteroaryl are optionally substituted with one to four R_{21}. In yet another embodiment, each R_9 is

independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{13}R_{13'}$, -CN, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}), wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_9 is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{13}R_{13'}$, -CN, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the aryl and heteroaryl are optionally substituted with one to four R_{21}. In yet another embodiment, each R_9 is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{13}R_{13'}$, -CN, (C_3-C_7)carbocyclyl, or (C_6-C_{10}) aryl, wherein the carbocyclyl is optionally substituted with one to four R_{20} and the aryl is optionally substituted with one to four R_{21}. In another embodiment, each R_9 is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{13}R_{13'}$, -CN, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{20} and the heteroaryl is optionally substituted with one to four R_{21}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_9 is independently at each occurrence (C_1-C_6)alkoxy, -$NR_{13}R_{13'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20} and the aryl and heteroaryl are optionally substituted with one to four R_{21}. In yet another embodiment, each R_9 is independently at each occurrence (C_1-C_6)alkoxy, -$NR_{13}R_{13'}$, -CN, (C_3-C_7)carbocyclyl, or (C_6-C_{10}) aryl, wherein the carbocyclyl is substituted with one to four R_{20} and the aryl is optionally substituted with one to four R_{21}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_9 is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{13}R_{13'}$, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the aryl and heteroaryl are optionally substituted with one to four R_{21}. In yet another embodiment, each R_9 is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{13}R_{13'}$, (C_3-C_7)carbocyclyl, or (C_6-C_{10}) aryl, wherein the carbocyclyl is optionally substituted with one to four R_{20} and the aryl is optionally substituted with one to four R_{21}. In another embodiment, each R_9 is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{13}R_{13'}$, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N,

NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{20} and the heteroaryl is optionally substituted with one to four R_{21}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_9 is independently at each occurrence $(C_1$-$C_6)$alkoxy, $-NR_{13}R_{13'}$, $(C_3$-$C_7)$carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_6$-$C_{10})$ aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{20} and the aryl and heteroaryl are optionally substituted with one to four R_{21}. In yet another embodiment, each R_9 is independently at each occurrence $(C_1$-$C_6)$alkoxy, $-NR_{13}R_{20'}$, $(C_3$-$C_7)$carbocyclyl, or $(C_6$-$C_{10})$ aryl, wherein the carbocyclyl is substituted with one to four R_{20} and the aryl is optionally substituted with one to four R_{21}.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{10} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{23}$, or -CN. In another embodiment, R_{10} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, or $-SR_{23}$. In yet another embodiment, R_{10} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, or -CN. In another embodiment, R_{10} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SR_{23}$, or -CN. In another embodiment, R_{10} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-SF_5$, $-SR_{23}$, or -CN. In yet another embodiment, R_{10} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, $-NH_2$, $-SF_5$, $-SR_{23}$, or -CN. In another embodiment, R_{10} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl,-OH, $-NH_2$, $-SF_5$, $-SR_{23}$, or -CN. In yet another embodiment, R_{10} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{23}$, or -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{10} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{23}$, or -CN. In yet another embodiment, R_{10} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, -

SR_{23}, or -CN. In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{23}$, or -CN. In yet another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{23}$, or -CN. In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{23}$, or -CN. In yet another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{23}$, or -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, or halogen. In yet another embodiment, R_{10} is independently at each occurrence halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{23}$, or -CN. In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{23}$, or -CN. In yet another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{23}$, or -CN. In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, or -CN. In yet another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, halogen, or -CN. In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, halogen, or -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{23}$, or -CN. In another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, or $-SR_{23}$. In yet another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, or -CN. In another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SR_{23}$, or -CN. In another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-SF_5$, $-SR_{23}$, or -CN. In yet another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, $-NH_2$, $-SF_5$, $-SR_{23}$, or -CN. In another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-

C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl,-OH, -NH_2, -SF_5, -SR_{23}, or -CN. In yet another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -NH_2, -SF_5, -SR_{23}, or -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{23}, or -CN. In yet another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{23}, or -CN. In another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{23}, or -CN. In yet another embodiment, R_{10} is independently at each occurrence (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{23}, or -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, or halogen. In yet another embodiment, R_{10} is independently at each occurrence halogen, -OH, -NH_2, -SF_5, -SR_{23}, or -CN. In another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{23}, or -CN. In yet another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{23}, or -CN. In another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, or -CN. In yet another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, halogen, or -CN. In another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, halogen, or -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In another embodiment, R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In another embodiment, R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one to four

substituents independently selected from (C_6-C_{10})aryl, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In yet another embodiment, R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In yet another embodiment, R_{11} is independently at each occurrence H, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{11} is independently at each occurrence (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In yet another embodiment, R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl

optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{12} is independently at each occurrence H, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In yet another embodiment, R_{12} is independently at each occurrence H, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, or (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In another embodiment, R_{12} is independently at each occurrence H, (C_1-C_6)alkyl substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{12} is independently at each occurrence H, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In yet another embodiment, R_{12} is independently at each occurrence H. In another embodiment, R_{12} is independently at each occurrence (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In another embodiment, R_{12} is independently at each occurrence (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{12} is independently at each occurrence (C_1-C_6)alkyl substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In yet another embodiment, R_{12} is independently at each occurrence (C_6-C_{10})aryl substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), $R_{12'}$ is independently at each occurrence H or (C_1-C_6)alkyl. In another embodiment, $R_{12'}$ is independently at each occurrence H or (C_1-C_3)alkyl. In another embodiment, $R_{12'}$ is

independently at each occurrence (C_1-C_6)alkyl. In another embodiment, $R_{12'}$ is independently at each occurrence H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{13} is independently at each occurrence H or (C_1-C_6)alkyl. In another embodiment, R_{13} is independently at each occurrence H or (C_1-C_3)alkyl. In yet another embodiment, R_{13} is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, R_{13} is independently at each occurrence (C_1-C_3)alkyl. In yet another embodiment, R_{13} is independently at each occurrence H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), $R_{13'}$ is independently at each occurrence H or (C_1-C_6)alkyl. In another embodiment, $R_{13'}$ is independently at each occurrence H or (C_1-C_3)alkyl. In yet another embodiment, $R_{13'}$ is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, $R_{13'}$ is independently at each occurrence (C_1-C_3)alkyl. In yet another embodiment, $R_{13'}$ is independently at each occurrence H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{14} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$. In another embodiment, each R_{14} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, or -C(O)R_{18}. In yet another embodiment, each R_{14} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, or -C(O)$NR_{17}R_{17}$. In another embodiment, each R_{14} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{14} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$. In yet another embodiment, each R_{14} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$. In another embodiment, each R_{14} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$. In yet another embodiment, each R_{14} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{14} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-

C_6)deuteroalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$. In yet another embodiment, each R_{14} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$. In another embodiment, each R_{14} is independently at each occurrence D, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$. In yet another embodiment, each R_{14} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$.

In another embodiment, each R_{14} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, or halogen. In yet another embodiment, each R_{14} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$. In another embodiment, each R_{14} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, or halogen. In another embodiment, each R_{14} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, or halogen. In yet another embodiment, each R_{14} is independently at each occurrence halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$. In another embodiment, each R_{14} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, or halogen.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{15} is independently at each occurrence H or (C_1-C_6)alkyl. In another embodiment, R_{15} is independently at each occurrence H or (C_1-C_3)alkyl. In yet another embodiment, R_{15} is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, R_{15} is independently at each occurrence (C_1-C_3)alkyl. In another embodiment, R_{15} is independently at each occurrence H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), $R_{15'}$ is independently at each occurrence H or (C_1-C_6)alkyl. In another embodiment, $R_{15'}$ is independently at each occurrence H or (C_1-C_3)alkyl. In yet another embodiment, $R_{15'}$ is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, $R_{15'}$ is independently at each occurrence (C_1-C_3)alkyl. In another embodiment, $R_{15'}$ is independently at each occurrence H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{15a} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{15a} is H, (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{15a} is H or (C_1-C_6)alkyl. In another embodiment, R_{15a} is H or (C_1-C_6)haloalkyl. In yet another embodiment, R_{15a} is (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{15a} is (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment,

R_{15a} is $(C_1$-$C_6)$alkyl. In another embodiment, R_{15a} is $(C_1$-$C_3)$alkyl. In another embodiment, R_{15a} is $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{15a} is $(C_1$-$C_3)$haloalkyl. In another embodiment, R_{15a} is H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{16} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{24}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{16} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{24}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or $(C_3$-$C_7)$carbocyclyl. In yet another embodiment, each R_{16} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{24}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{16} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{24}$, -CN, phenyl, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{16} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{24}$, -CN, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{16} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{24}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{16} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{16} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-

C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{16} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{16} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-

C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{16} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, or -CN. In yet another embodiment, each R_{16} is independently at each occurrence halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two R_{16}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, two R_{16}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl. In yet another embodiment, two R_{16}, when on adjacent atoms, together with the atoms to which they are attached form a 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, two R_{16}, when on adjacent atoms, together with the atoms to which they are attached form a 5-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, two R_{16}, when on adjacent atoms, together with the atoms to which they are attached form a 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{17} is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{17} is independently at each occurrence H, (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{17} is independently at each occurrence H or (C_1-C_6)alkyl. In

another embodiment, R_{17} is independently at each occurrence H or $(C_1$-$C_6)$haloalkyl. In yet another embodiment, R_{17} is independently at each occurrence $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{17} is independently at each occurrence $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$haloalkyl. In yet another embodiment, R_{17} is independently at each occurrence $(C_1$-$C_6)$alkyl. In another embodiment, R_{17} is independently at each occurrence $(C_1$-$C_3)$alkyl. In another embodiment, R_{17} is independently at each occurrence $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{17} is independently at each occurrence $(C_1$-$C_3)$haloalkyl. In another embodiment, R_{17} is independently at each occurrence H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{18} is independently at each occurrence $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{18} is independently at each occurrence $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$haloalkyl. In another embodiment, R_{18} is independently at each occurrence $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{18} is independently at each occurrence $(C_1$-$C_6)$alkyl. In another embodiment, R_{18} is independently at each occurrence $(C_1$-$C_3)$haloalkyl. In another embodiment, R_{18} is independently at each occurrence $(C_1$-$C_3)$alkyl.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{19} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{25}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{19} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{25}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or $(C_3$-$C_7)$carbocyclyl. In yet another embodiment, each R_{19} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{25}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{19} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{25}$, -CN, phenyl, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{19} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{25}$, -CN, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and

S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-

C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, or -CN. In yet another embodiment, each R_{19} is independently at each occurrence halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two R_{19} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH,

and S. In another embodiment, two R_{19} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl. In another embodiment, two R_{19} together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl. In yet another embodiment, two R_{19} together with the atoms to which they are attached form a (C_3-C_5)carbocyclyl. In another embodiment, two R_{19} together with the atoms to which they are attached form a (C_3-C_4)carbocyclyl. In yet another embodiment, two R_{19} together with the atoms to which they are attached form a (C_4-C_7)carbocyclyl. In another embodiment, two R_{19} together with the atoms to which they are attached form a (C_5-C_7)carbocyclyl. In yet another embodiment, two R_{19} together with the atoms to which they are attached form a (C_6-C_7)carbocyclyl.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two R_{19} together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, two R_{19} together with the atoms to which they are attached form a 4- to 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, two R_{19} together with the atoms to which they are attached form a 4- or 5-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, two R_{19} together with the atoms to which they are attached form a 5- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, two R_{19} together with the atoms to which they are attached form a 6- or 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or (C_3-C_7)carbocyclyl. In yet another embodiment, each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-

C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH,

and S. In another embodiment, each R_{20} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, -OH, $-NH_2$, $-SF_5$, $-SR_{26}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{20} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{26}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{20} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{26}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{20} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{26}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{20} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{26}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{20} is independently at each occurrence D, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{26}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{20} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{26}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{20} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{26}$, or

-CN. In yet another embodiment, each R_{20} is independently at each occurrence halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{20} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, or -CN. In yet another embodiment, each R_{20} is independently at each occurrence halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{20} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{20} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{20} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two R_{20} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, two R_{20} together with the atoms to which they are attached form a (C_3-

C_7)carbocyclyl. In another embodiment, two R_{20} together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl. In yet another embodiment, two R_{20} together with the atoms to which they are attached form a (C_3-C_5)carbocyclyl. In another embodiment, two R_{20} together with the atoms to which they are attached form a (C_3-C_4)carbocyclyl. In yet another embodiment, two R_{20} together with the atoms to which they are attached form a (C_4-C_7)carbocyclyl. In another embodiment, two R_{20} together with the atoms to which they are attached form a (C_5-C_7)carbocyclyl. In yet another embodiment, two R_{20} together with the atoms to which they are attached form a (C_6-C_7)carbocyclyl.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), two R_{20} together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, two R_{20} together with the atoms to which they are attached form a 4- to 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, two R_{20} together with the atoms to which they are attached form a 4- or 5-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, two R_{20} together with the atoms to which they are attached form a 5- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, two R_{20} together with the atoms to which they are attached form a 6- or 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or (C_3-C_7)carbocyclyl. In yet another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -

CN, phenyl, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl,-OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-

C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{21} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, or -CN. In yet another embodiment, each R_{21} is independently at each occurrence halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-

C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), each R_{21} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, or -CN. In yet another embodiment, each R_{21} is independently at each occurrence halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{21} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{21} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{21} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{22} is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{22} is independently at each occurrence H, (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{22} is independently at each occurrence H or (C_1-C_6)alkyl. In another embodiment, R_{22} is independently at each occurrence H or (C_1-C_6)haloalkyl. In yet another embodiment, R_{22} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{22} is independently at each occurrence (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{22} is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, R_{22} is independently at each occurrence (C_1-C_3)alkyl. In another embodiment, R_{22} is independently at each occurrence (C_1-C_6)haloalkyl. In another embodiment, R_{22} is independently at each occurrence (C_1-C_3)haloalkyl. In another embodiment, R_{22} is independently at each occurrence H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{23} is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{23} is independently at each occurrence H, (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{23} is independently at each occurrence H or (C_1-C_6)alkyl. In another embodiment, R_{23} is independently at each occurrence H or (C_1-C_6)haloalkyl. In yet another embodiment, R_{23} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{23} is independently at each occurrence (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{23} is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, R_{23} is independently at each occurrence (C_1-C_3)alkyl. In another embodiment, R_{23} is independently at each occurrence (C_1-C_6)haloalkyl. In another embodiment, R_{23} is independently at each occurrence (C_1-C_3)haloalkyl. In another embodiment, R_{23} is independently at each occurrence H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{24} is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{24} is independently at each occurrence H, (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{24} is independently at each occurrence H or (C_1-C_6)alkyl. In another embodiment, R_{24} is independently at each occurrence H or (C_1-C_6)haloalkyl. In yet another embodiment, R_{24} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{24} is independently at each occurrence (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{24} is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, R_{24} is independently at each occurrence (C_1-C_3)alkyl. In another embodiment, R_{24} is independently at each occurrence (C_1-C_6)haloalkyl. In another embodiment, R_{24} is independently at each occurrence (C_1-C_3)haloalkyl. In another embodiment, R_{24} is independently at each occurrence H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{25} is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{25} is independently at each occurrence H, (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{25} is independently at each occurrence H or (C_1-C_6)alkyl. In another embodiment, R_{25} is independently at each occurrence H or (C_1-C_6)haloalkyl. In yet another embodiment, R_{25} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{25} is independently at each occurrence (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{25} is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, R_{25} is independently at each occurrence (C_1-C_3)alkyl. In another embodiment, R_{25} is independently at each occurrence (C_1-C_6)haloalkyl. In another embodiment, R_{25} is independently at each occurrence (C_1-C_3)haloalkyl. In another embodiment, R_{25} is independently at each occurrence H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{26} is independently at each occurrence H, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{26} is independently at each occurrence H, $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$haloalkyl. In yet another embodiment, R_{26} is independently at each occurrence H or $(C_1$-$C_6)$alkyl. In another embodiment, R_{26} is independently at each occurrence H or $(C_1$-$C_6)$haloalkyl. In yet another embodiment, R_{26} is independently at each occurrence $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{26} is independently at each occurrence $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$haloalkyl. In yet another embodiment, R_{26} is independently at each occurrence $(C_1$-$C_6)$alkyl. In another embodiment, R_{26} is independently at each occurrence $(C_1$-$C_3)$alkyl. In another embodiment, R_{26} is independently at each occurrence $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{26} is independently at each occurrence $(C_1$-$C_3)$haloalkyl. In another embodiment, R_{26} is independently at each occurrence H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{27} is independently at each occurrence H, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{27} is independently at each occurrence H, $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$haloalkyl. In yet another embodiment, R_{27} is independently at each occurrence H or $(C_1$-$C_6)$alkyl. In another embodiment, R_{27} is independently at each occurrence H or $(C_1$-$C_6)$haloalkyl. In yet another embodiment, R_{27} is independently at each occurrence $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{27} is independently at each occurrence $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$haloalkyl. In yet another embodiment, R_{27} is independently at each occurrence $(C_1$-$C_6)$alkyl. In another embodiment, R_{27} is independently at each occurrence $(C_1$-$C_3)$alkyl. In another embodiment, R_{27} is independently at each occurrence $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{27} is independently at each occurrence $(C_1$-$C_3)$haloalkyl. In another embodiment, R_{27} is independently at each occurrence H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{28} is H, $(C_1$-$C_6)$alkyl, or $-C(O)R_{32}$. In another embodiment, R_{28} is H, $(C_1$-$C_3)$alkyl, or $-C(O)R_{32}$. In yet another embodiment, R_{28} is H or $(C_1$-$C_6)$alkyl. In another embodiment, R_{28} is H or $-C(O)R_{32}$. In yet another embodiment, R_{28} is $(C_1$-$C_3)$alkyl or $-C(O)R_{32}$. In another embodiment, R_{28} is $(C_1$-$C_3)$alkyl. In yet another embodiment, R_{28} is $-C(O)R_{32}$. In another embodiment, R_{28} is H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{29} is H, $(C_1$-$C_6)$alkyl, or $-C(O)R_{32}$. In another embodiment, R_{29} is H, $(C_1$-$C_3)$alkyl, or $-C(O)R_{32}$. In yet another embodiment, R_{29} is H or $(C_1$-$C_6)$alkyl. In another embodiment, R_{29} is H or $-C(O)R_{32}$. In yet another embodiment, R_{29} is $(C_1$-$C_3)$alkyl or $-C(O)R_{32}$. In another embodiment, R_{29} is $(C_1$-$C_3)$alkyl. In yet another embodiment, R_{29} is $-C(O)R_{32}$. In another embodiment, R_{29} is H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{30} is H or $(C_1$-$C_6)$alkyl. In another embodiment, R_{30} is H or $(C_1$-

C_3)alkyl. In yet another embodiment, R_{30} is (C_1-C_6)alkyl. In another embodiment, R_{30} is (C_1-C_3)alkyl. In yet another embodiment, R_{30} is H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{31} is H or (C_1-C_6)alkyl. In another embodiment, R_{31} is H or (C_1-C_3)alkyl. In yet another embodiment, R_{31} is (C_1-C_6)alkyl. In another embodiment, R_{31} is (C_1-C_3)alkyl. In yet another embodiment, R_{31} is H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{32} is H or (C_1-C_6)alkyl. In another embodiment, R_{32} is H or (C_1-C_3)alkyl. In yet another embodiment, R_{32} is (C_1-C_6)alkyl. In another embodiment, R_{32} is (C_1-C_3)alkyl. In yet another embodiment, R_{32} is H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{33} is H, (C_1-C_6)alkyl, or -C(O)R_{37}. In another embodiment, R_{33} is H, (C_1-C_3)alkyl, or -C(O)R_{37}. In yet another embodiment, R_{33} is H or (C_1-C_6)alkyl. In another embodiment, R_{33} is H or -C(O)R_{37}. In yet another embodiment, R_{33} is (C_1-C_3)alkyl or -C(O)R_{37}. In another embodiment, R_{33} is (C_1-C_3)alkyl. In yet another embodiment, R_{33} is -C(O)R_{37}. In another embodiment, R_{33} is H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{34} is H, (C_1-C_6)alkyl, or -C(O)R_{37}. In another embodiment, R_{34} is H, (C_1-C_3)alkyl, or -C(O)R_{37}. In yet another embodiment, R_{34} is H or (C_1-C_6)alkyl. In another embodiment, R_{34} is H or -C(O)R_{37}. In yet another embodiment, R_{34} is (C_1-C_3)alkyl or -C(O)R_{37}. In another embodiment, R_{34} is (C_1-C_3)alkyl. In yet another embodiment, R_{34} is -C(O)R_{37}. In another embodiment, R_{34} is H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{35} is H or (C_1-C_6)alkyl. In another embodiment, R_{35} is H or (C_1-C_3)alkyl. In yet another embodiment, R_{35} is (C_1-C_6)alkyl. In another embodiment, R_{35} is (C_1-C_3)alkyl. In yet another embodiment, R_{35} is H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{36} is H or (C_1-C_6)alkyl. In another embodiment, R_{36} is H or (C_1-C_3)alkyl. In yet another embodiment, R_{36} is (C_1-C_6)alkyl. In another embodiment, R_{36} is (C_1-C_3)alkyl. In yet another embodiment, R_{36} is H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{37} is H or (C_1-C_6)alkyl. In another embodiment, R_{37} is H or (C_1-C_3)alkyl. In yet another embodiment, R_{37} is (C_1-C_6)alkyl. In another embodiment, R_{37} is (C_1-C_3)alkyl. In yet another embodiment, R_{37} is H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_{38} is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-

C_6)haloalkyl. In another embodiment, R_{38} is independently at each occurrence H, (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{38} is independently at each occurrence H or (C_1-C_6)alkyl. In another embodiment, R_{38} is independently at each occurrence H or (C_1-C_6)haloalkyl. In yet another embodiment, R_{38} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{38} is independently at each occurrence (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{38} is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, R_{38} is independently at each occurrence (C_1-C_3)alkyl. In another embodiment, R_{38} is independently at each occurrence (C_1-C_6)haloalkyl. In another embodiment, R_{38} is independently at each occurrence (C_1-C_3)haloalkyl. In another embodiment, R_{38} is independently at each occurrence H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), m is 0 or 1. In another embodiment, m is 1 or 2. In yet another embodiment, m is 0 or 2. In another embodiment, m is 0. In yet another embodiment, m is 1. In another embodiment, m is 2.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), q is 1, 2, or 3. In another embodiment, q is 1 or 3. In yet another embodiment, q is 2 or 3. In another embodiment, q is 1 or 2. In yet another embodiment, q is 1. In another embodiment, q is 2. In yet another embodiment, q is 3.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), n is 0, 1, 2, 3, or 4. In another embodiment, n is 0, 1, 2, or 3. In yet another embodiment, n is 0, 1, 2, or 4. In another embodiment, n is 0, 1, 3 or 4. In yet another embodiment, n is 0, 2, 3, or 4. In another embodiment, n is 1, 2, 3 or 4. In yet another embodiment, n is 0, 1, or 2. In another embodiment, n is 2, 3, or 4. In yet another embodiment, n is 1, 2, or 3. In another embodiment, n is 0 or 1. In yet another embodiment, n is 1 or 2. In another embodiment, n is 2 or 3. In yet another embodiment, n is 3 or 4. In another embodiment, n is 0 or 2. In yet another embodiment, n is 0 or 3. In another embodiment, n is 0 or 4. In yet another embodiment, n is 1 or 2. In another embodiment, n is 1 or 3. In yet another embodiment, n is 1 or 4. In another embodiment, n is 0 or 2. In yet another embodiment, n is 2 or 4. In another embodiment, n is 0. In yet another embodiment, n is 1. In another embodiment, n is 2. In yet another embodiment, n is 4.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H or D and R_{2a} is H. In another embodiment, R_1 is H or D, R_{2a} is H, and R_{2b} is H. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H and R_{2c} is H. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H and R_{2d} is H. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, and R_3 is H or D. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, and m is 0. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is

H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, and R_{6a} is H. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, and R_{6b} is H. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, and R_{6c} is H. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, and R_{6d} is H. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, and R_5 is H. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 0.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 1 or 2. In another embodiment, R_1 is H or D, R_{2a} is H,

R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, and R_{6a} is H. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, and R_{6b} is H. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, and R_{6c} is H. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, and R_{6d} is H.In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, and R_5 is H. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_5 is H, and n is 0. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl,

or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is $(C_1$-$C_6)$alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is $(C_1$-$C_6)$alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is $(C_1$-$C_6)$alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_5 is H, and n is 1 or 2. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is $(C_1$-$C_6)$alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is $(C_1$-$C_6)$alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH,

and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, and R_{6a} is H. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, and R_{6b} is H. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, and R_{6c} is H. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, and R_{6d} is H.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, and R_5 is H. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_5 is H, and n is 0. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from

O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_5 is H, and n is 1 or 2. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_5 is H, n is 1 or 2 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are

substituted with one to four $R_{8'}$. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H and R_{2a} is H. In another embodiment, R_1 is H, R_{2a} is H, and R_{2b} is H. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H and R_{2c} is H. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H and R_{2d} is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, and R_3 is H or D. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, and m is 0. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, and R_{6a} is H. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, aR_{6a} is H, and R_{6b} is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, and R_{6c} is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, and R_{6d} is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, and R_5 is H. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 0. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-

membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 1 or 2. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf),R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4

heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, and R_5 is H. In another embodiment R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, and R_{6a} is H. In yet another embodiment R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, and R_{6b} is H. In another embodiment R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, and R_{6c} is H. In yet another embodiment R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, and R_{6d} is H. In another embodiment R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, and R_5 is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 0. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is $(C_1$-$C_6)$alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is $(C_1$-$C_6)$alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is $(C_1$-$C_6)$alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is $(C_1$-$C_6)$alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered

comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 1 or 2. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_5 is H, n is 1 or 2 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, and R_3 is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, and R_{6a} is H. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, $R_{6a,}$ is H, and R_{6b} is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, $R_{6a,}$ is H, R_{6b} is H, and R_{6c} is H. In another embodiment, R_1

is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, a R_3 is H, $R_{6a,}$ is H, R_{6b} is H, R_{6c} is H, and R_{6d} is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H and m is 0. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, and R_5 is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 0. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is $(C_1\text{-}C_6)$alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3\text{-}C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is $(C_1\text{-}C_6)$alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3\text{-}C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is $(C_1\text{-}C_6)$alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3\text{-}C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is $(C_1\text{-}C_6)$alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3\text{-}C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 1 or 2. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is $(C_1\text{-}C_6)$alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising

1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, and R_{6a} is H. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, and R_{6b} is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, and R_{6c} is H. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, and R_{6d} is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, and R_5 is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 0. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_5 is H, n is 0 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to

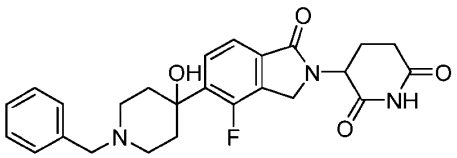
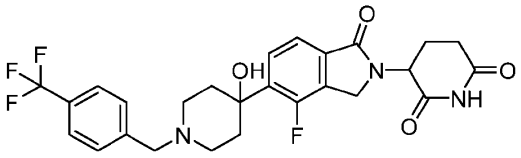
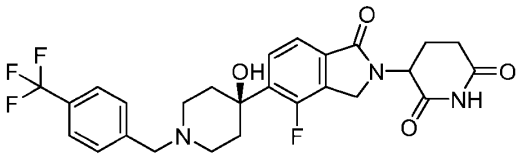
four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is $(C_1$-$C_6)$alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

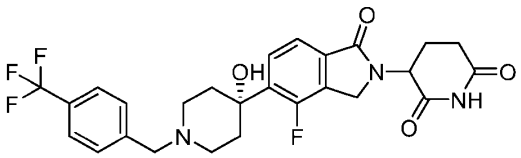
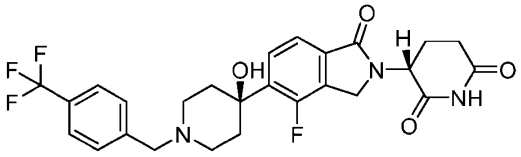
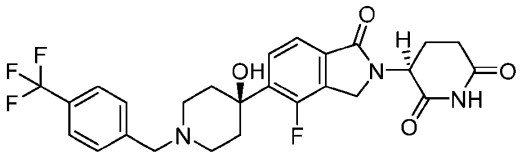
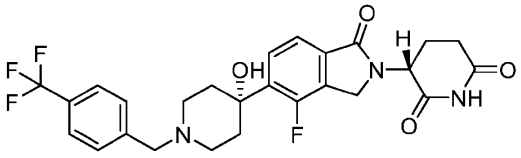
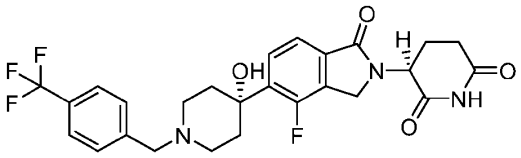
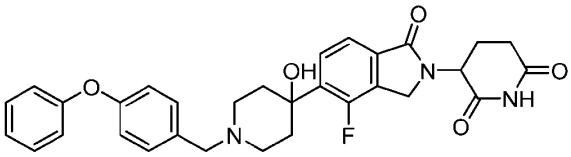
In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is $(C_1$-$C_6)$alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0 and R_7 is $(C_1$-$C_6)$alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

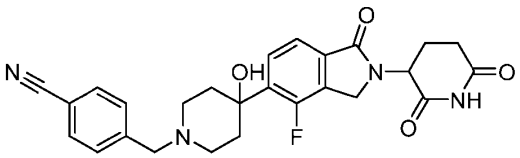
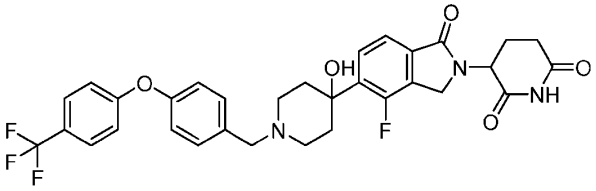
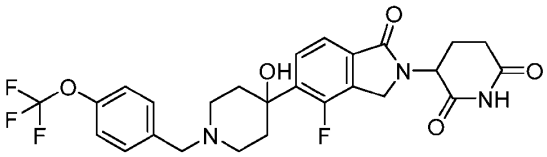
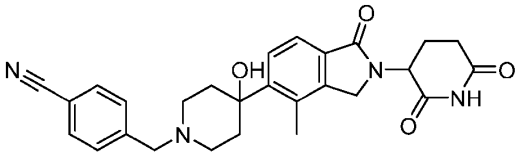
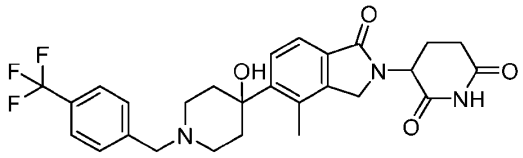
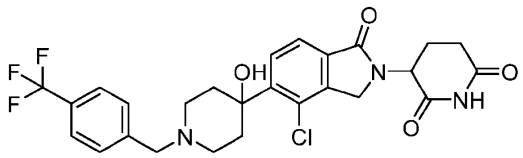
In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 1 or 2. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is $(C_1$-$C_6)$alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is $(C_1$-$C_6)$alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

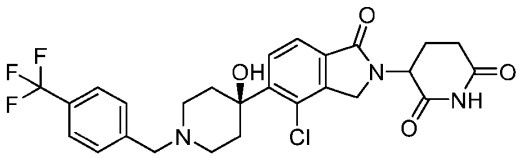
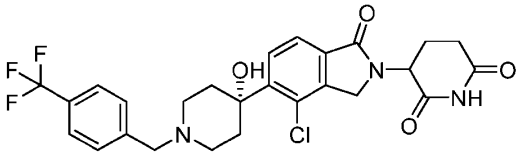
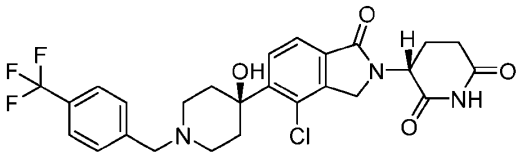
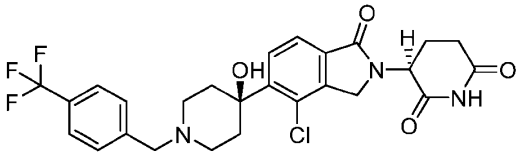
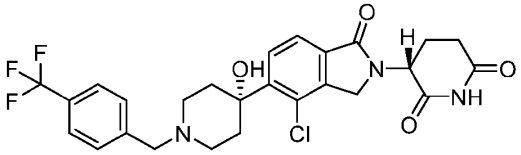
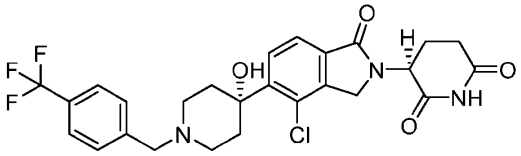
In some embodiments of Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2 and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. Non-limiting illustrative compounds of a compound of Formula (I) and (II) include the compounds in Table 1.

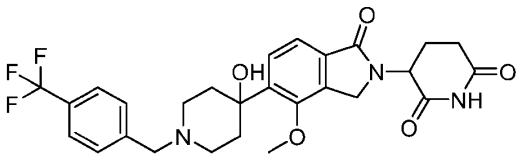
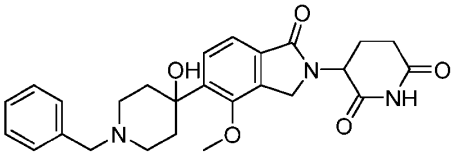
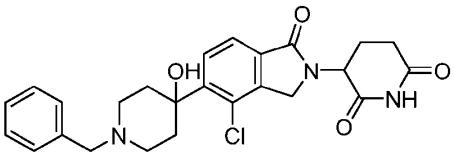
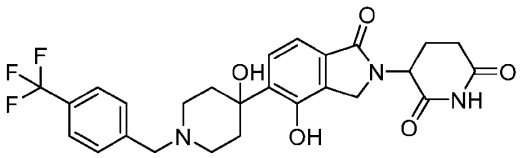
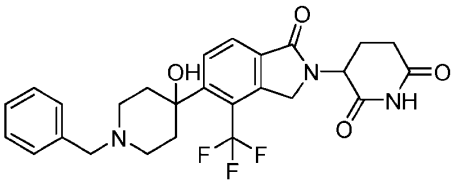
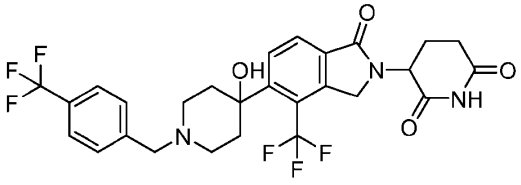
Table 1: Exemplary compounds of the disclosure

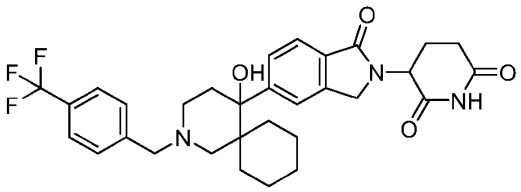
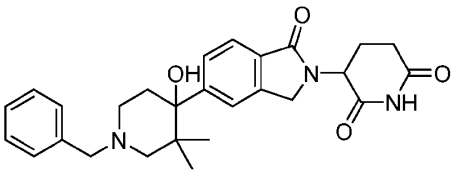
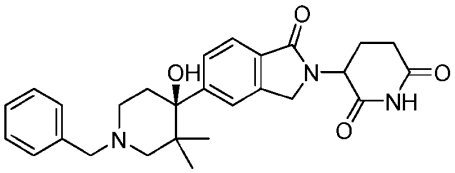
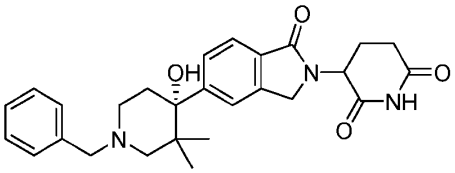
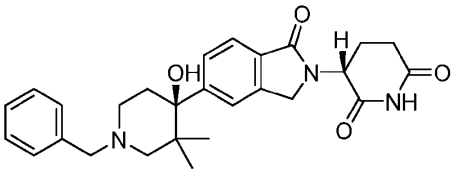
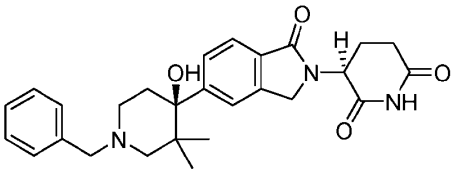
Cmpd No.	Compound Structure
I-1	
I-2	
I-3	

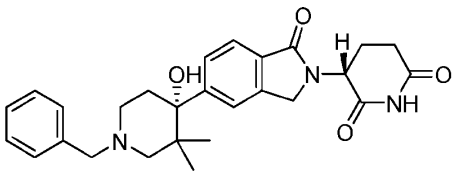
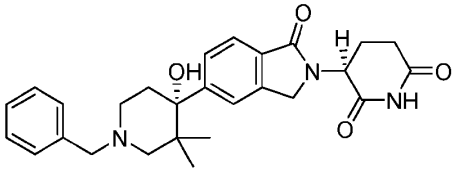
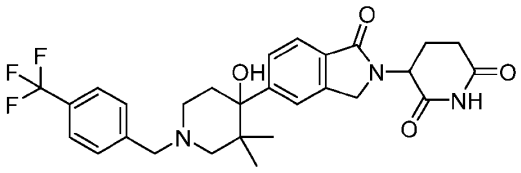
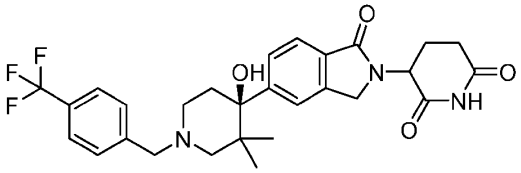
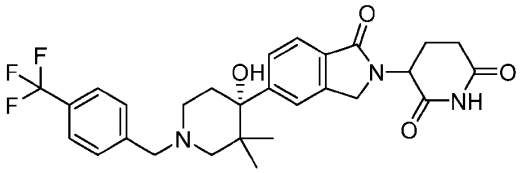
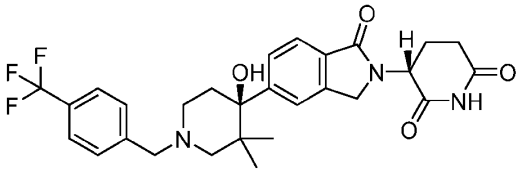
Cmpd No.	Compound Structure
I-4	
I-5	
I-6	
I-7	
I-8	
I-9	

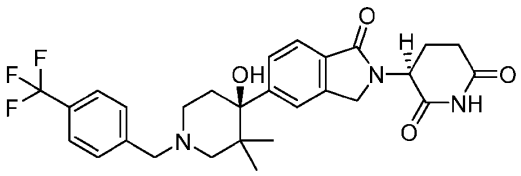
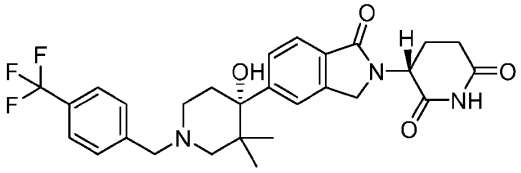
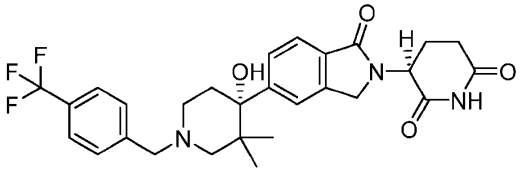
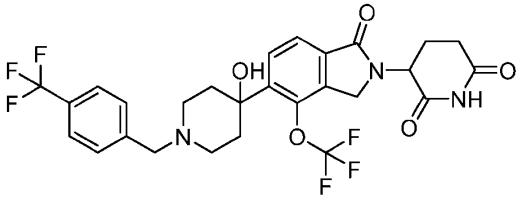
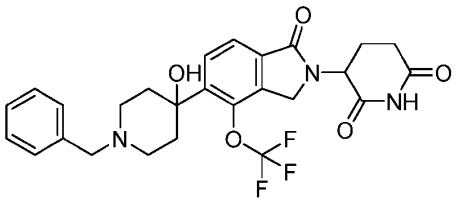
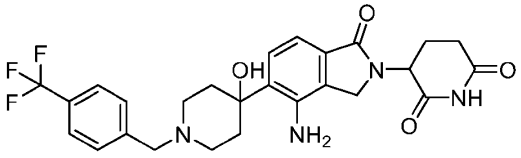
Cmpd No.	Compound Structure
I-10	
I-11	
I-12	
I-13	
I-14	
I-15	

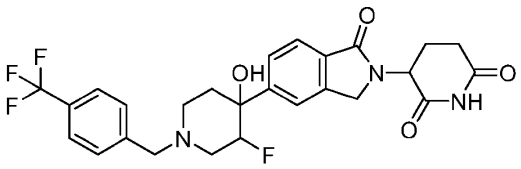
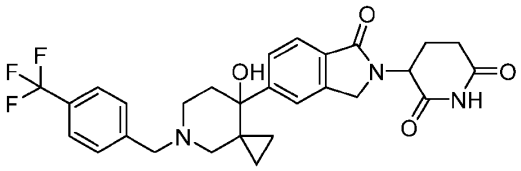
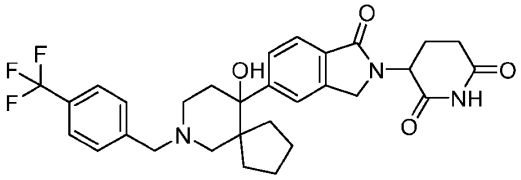
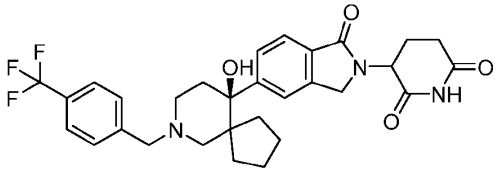
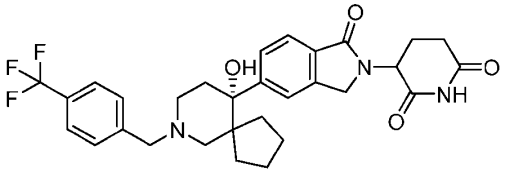
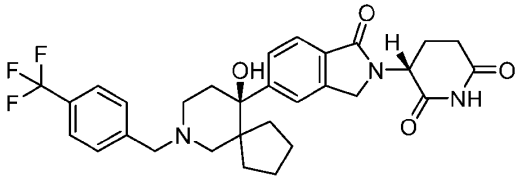
Cmpd No.	Compound Structure
I-16	
I-17	
I-18	
I-19	
I-20	
I-21	

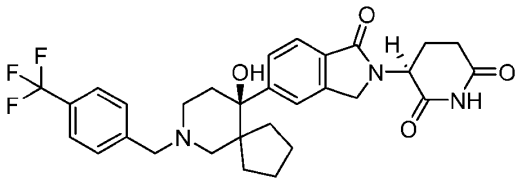
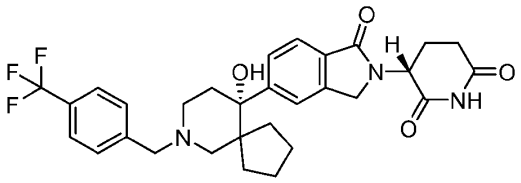
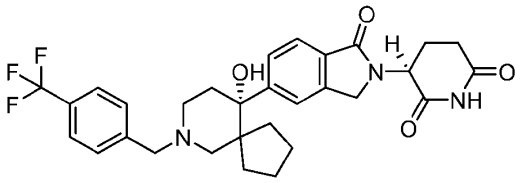
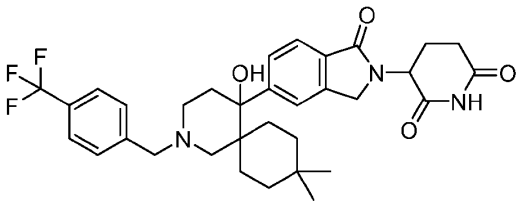
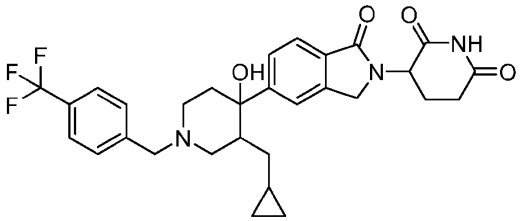
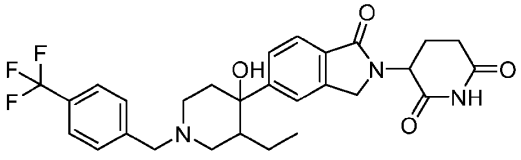
Cmpd No.	Compound Structure
I-22	
I-23	
I-24	
I-25	
I-26	
I-27	

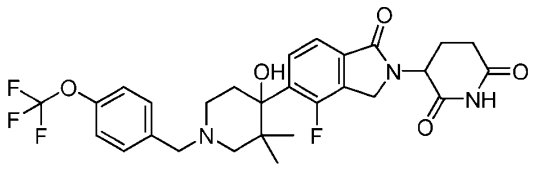
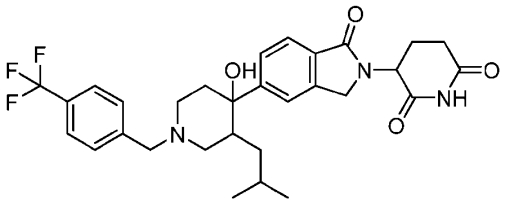
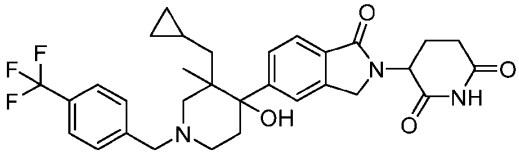
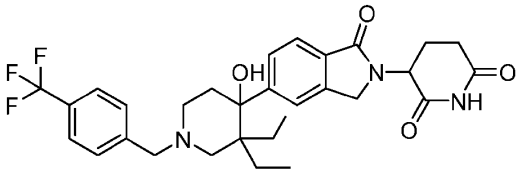
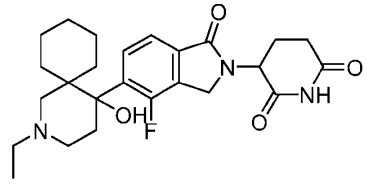
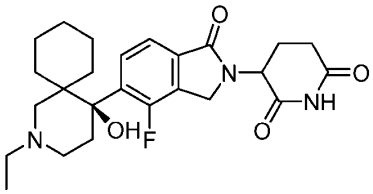
Cmpd No.	Compound Structure
I-28	
I-29	
I-30	
I-31	
I-32	
I-33	

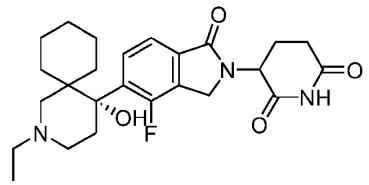
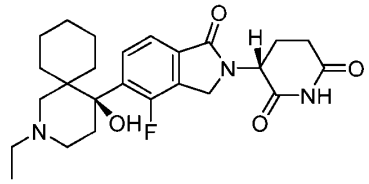
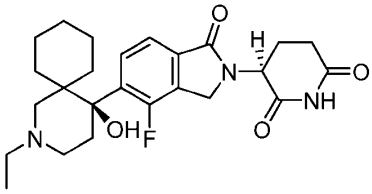
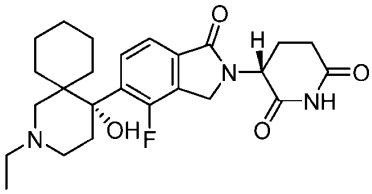
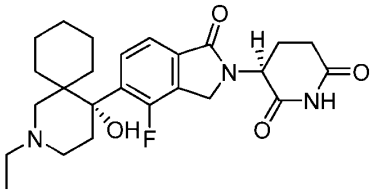
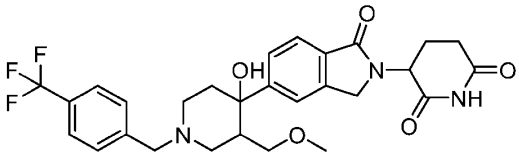
Cmpd No.	Compound Structure
I-34	
I-35	
I-36	
I-37	
I-38	
I-39	

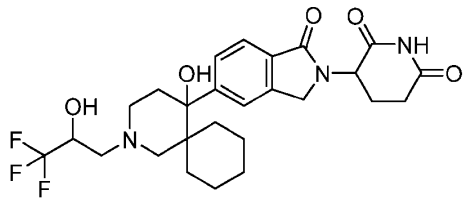
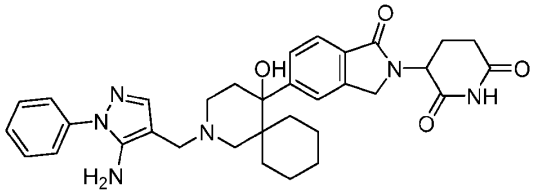
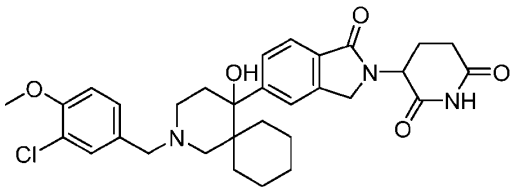
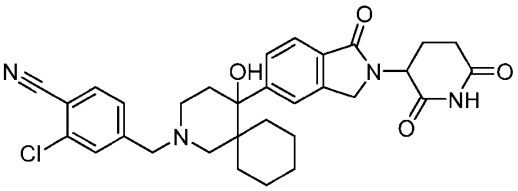
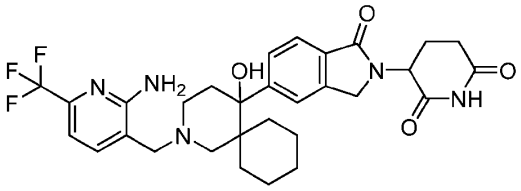
Cmpd No.	Compound Structure
I-40	
I-41	
I-42	
I-43	
I-44	
I-45	

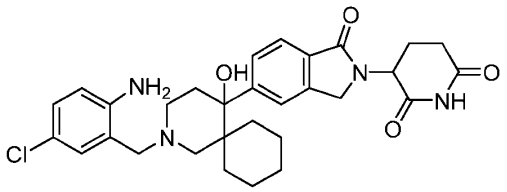
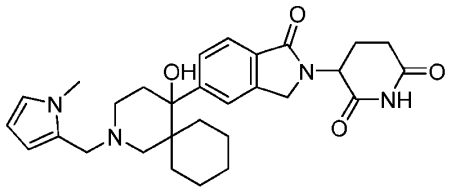
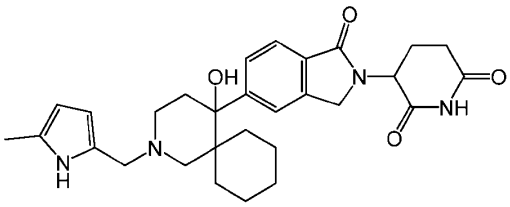
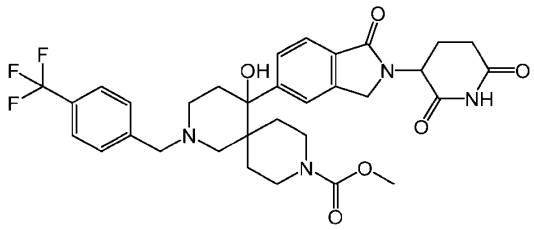
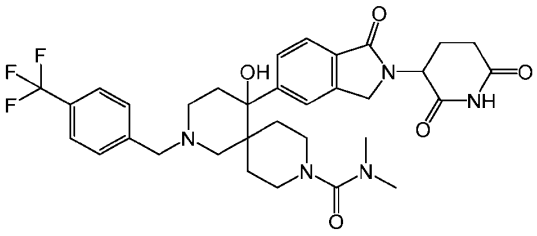
Cmpd No.	Compound Structure
I-46	
I-47	
I-48	
I-49	
I-50	
I-51	

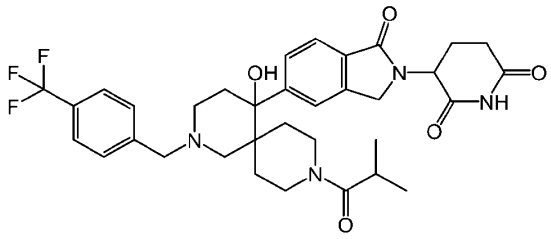
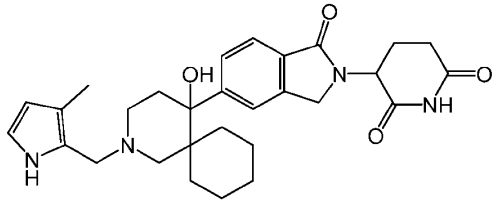
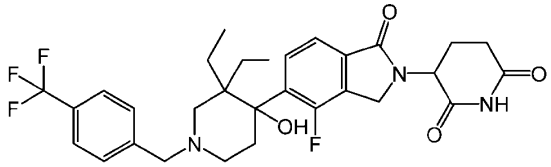
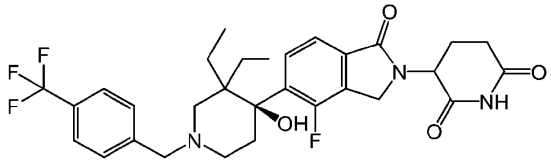
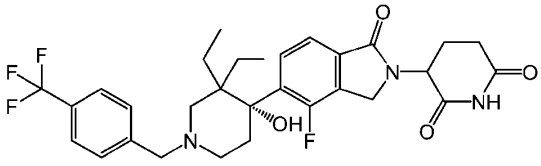
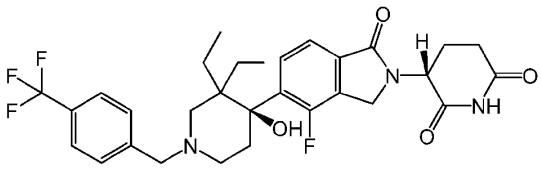
Cmpd No.	Compound Structure
I-52	
I-53	
I-54	
I-55	
I-56	
I-57	

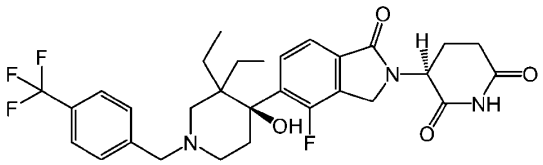
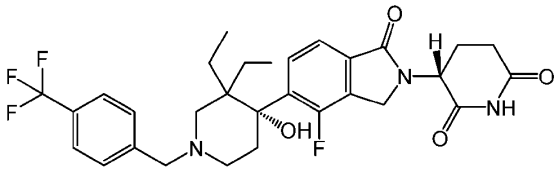
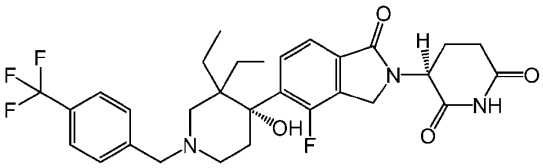
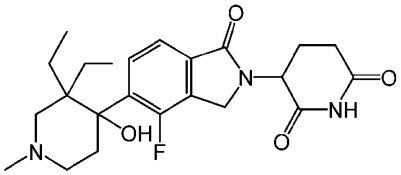
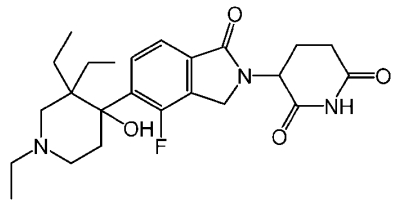
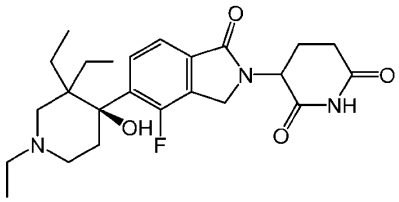
Cmpd No.	Compound Structure
I-58	
I-59	
I-60	
I-61	
I-62	
I-63	

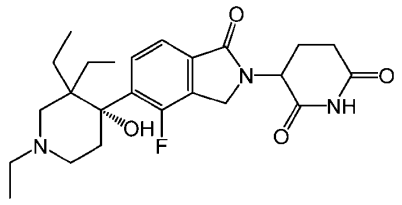
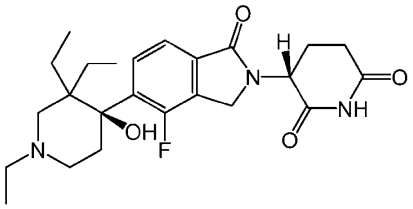
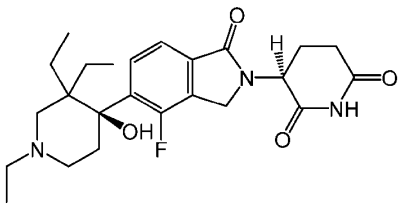
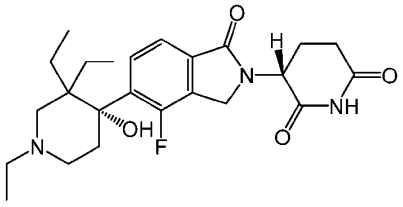
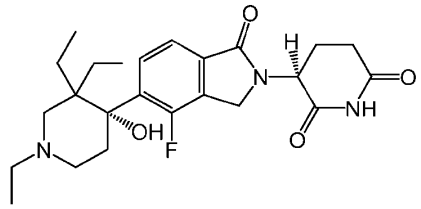
Cmpd No.	Compound Structure
I-64	
I-65	
I-66	
I-67	
I-68	
I-69	

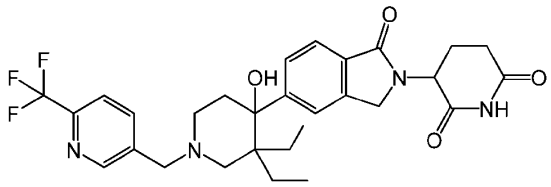
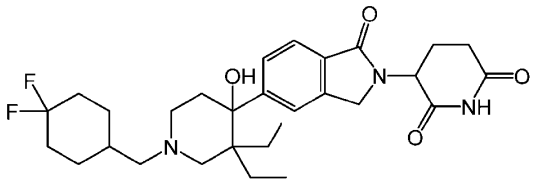
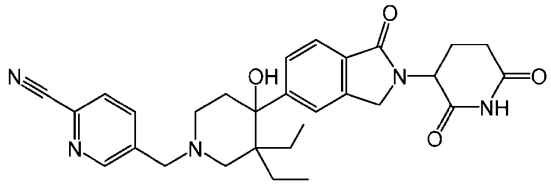
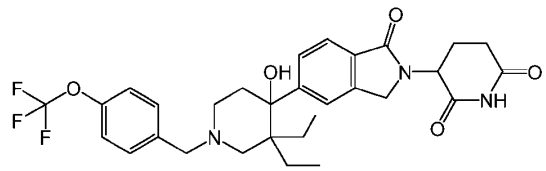
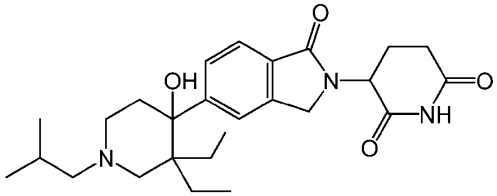
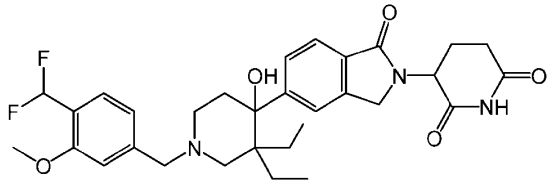
Cmpd No.	Compound Structure
I-70	
I-71	
I-72	
I-73	
I-74	

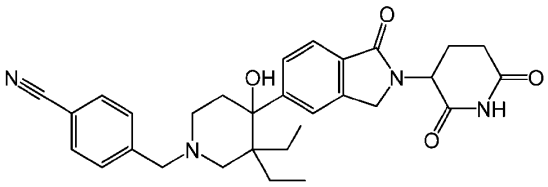
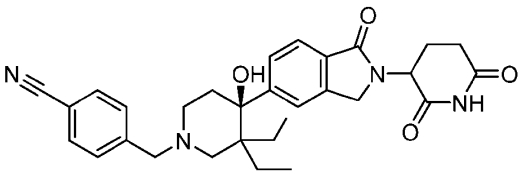
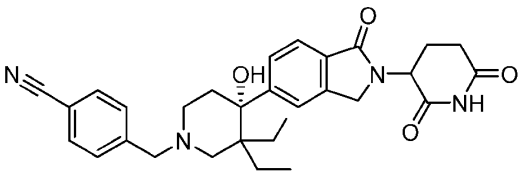
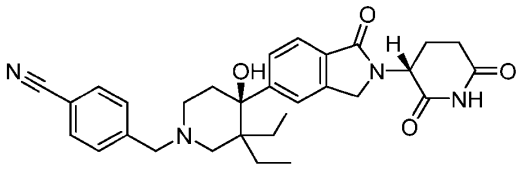
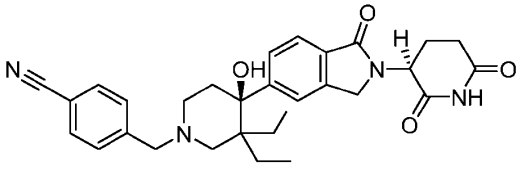
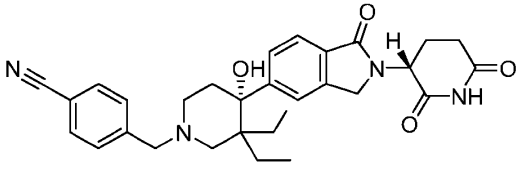
Cmpd No.	Compound Structure
I-75	
I-76	
I-77	
I-78	
I-79	

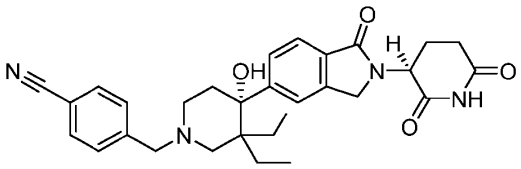
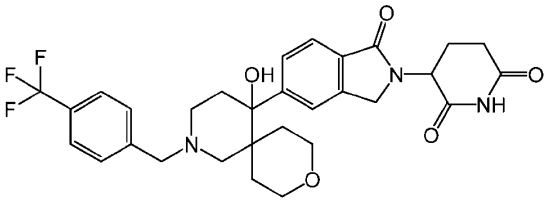
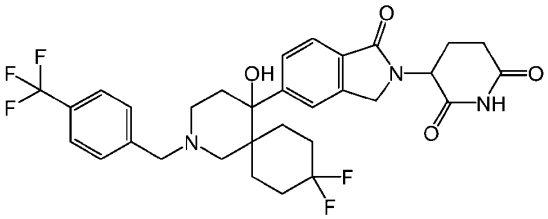
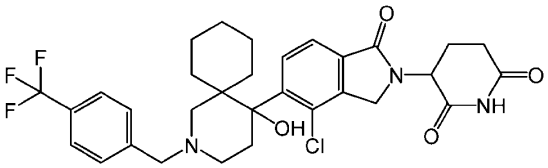
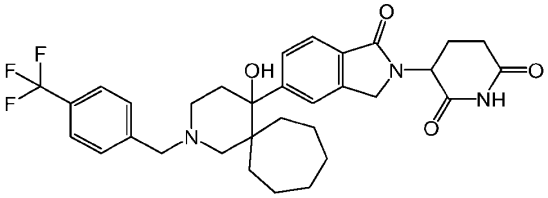
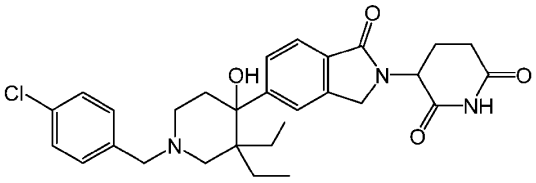
Cmpd No.	Compound Structure
I-80	
I-81	
I-82	
I-83	
I-84	
I-85	

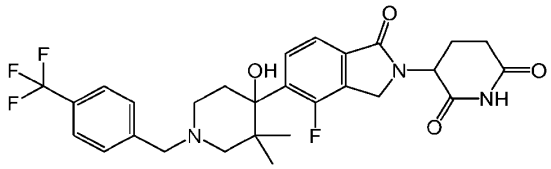
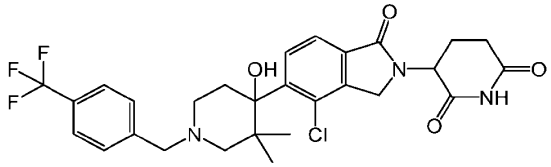
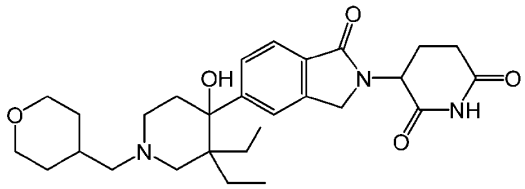
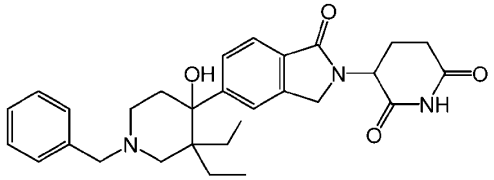
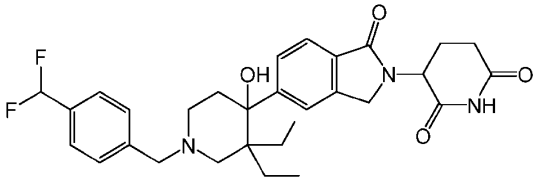
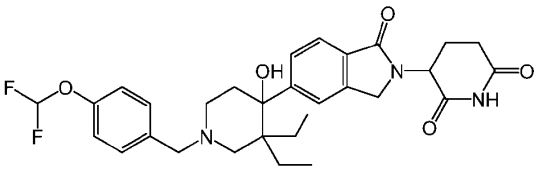
Cmpd No.	Compound Structure
I-86	
I-87	
I-88	
I-89	
I-90	
I-91	

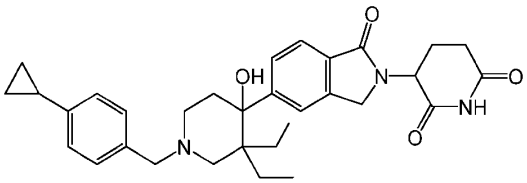
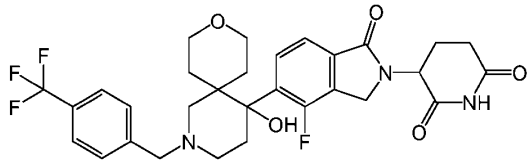
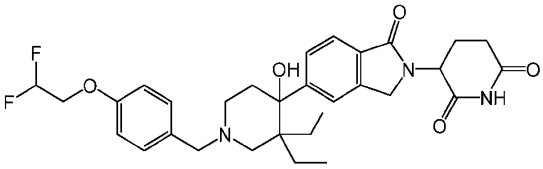
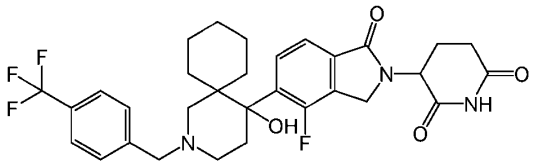
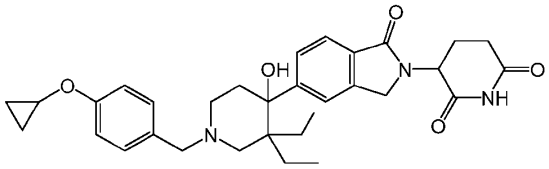
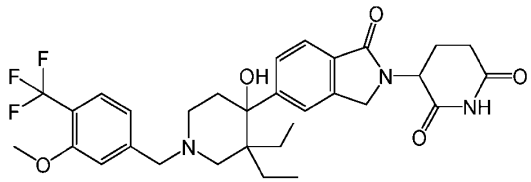
Cmpd No.	Compound Structure
I-92	
I-93	
I-94	
I-95	
I-96	

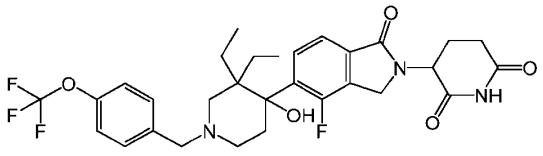
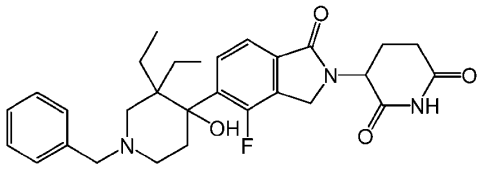
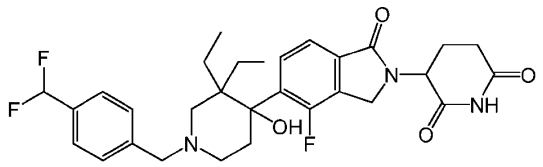
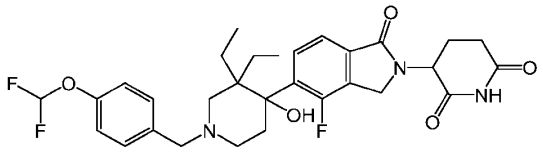
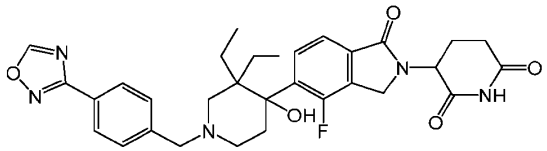
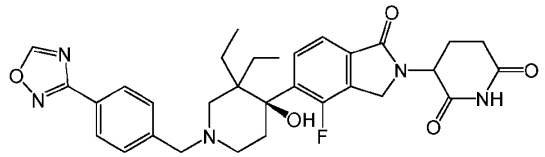
Cmpd No.	Compound Structure
I-97	
I-98	
I-99	
I-100	
I-101	
I-102	

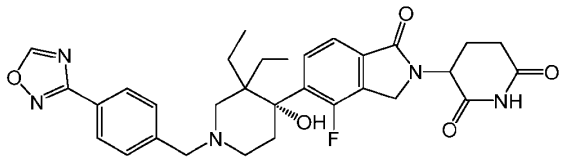
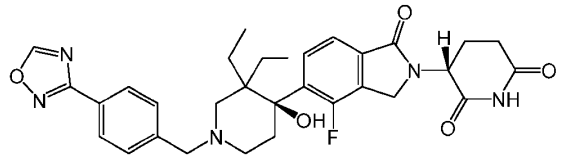
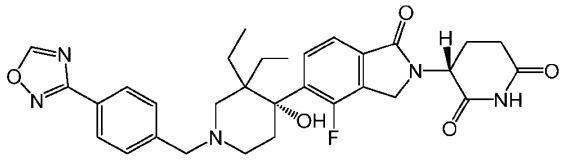
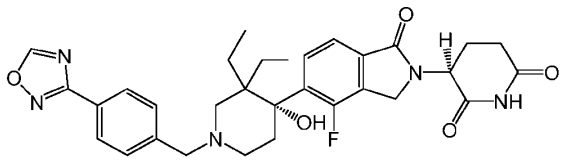
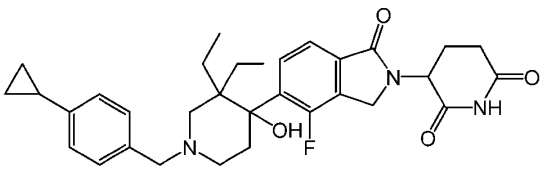
Cmpd No.	Compound Structure
I-103	
I-104	
I-105	
I-106	
I-107	
I-108	

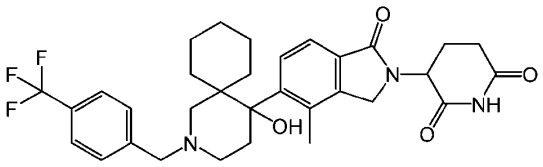
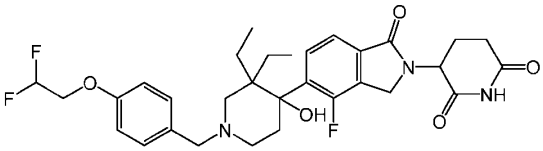
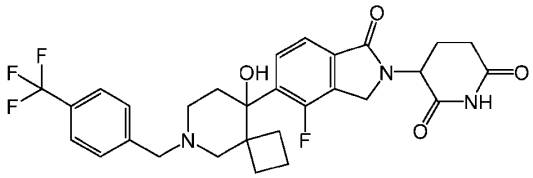
Cmpd No.	Compound Structure
I-109	
I-110	
I-111	
I-112	
I-113	
I-114	

Cmpd No.	Compound Structure
I-115	
I-116	
I-117	
I-118	
I-119	
I-120	

Cmpd No.	Compound Structure
I-121	
I-122	
I-123	
I-124	
I-125	
I-126	

Cmpd No.	Compound Structure
I-127	
I-128	
I-129	
I-130	
I-131	
I-132	

Cmpd No.	Compound Structure
I-133	
I-134	
I-135	
I-136	
I-137	
I-138	

Cmpd No.	Compound Structure
I-139	
I-140	
I-141	
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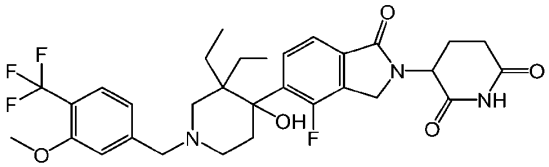
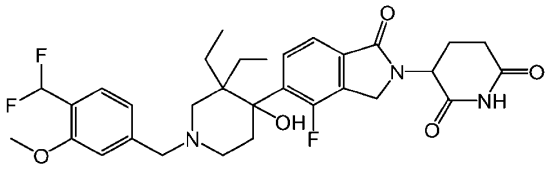
I-143	
I-144	

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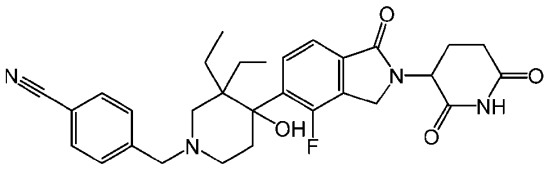
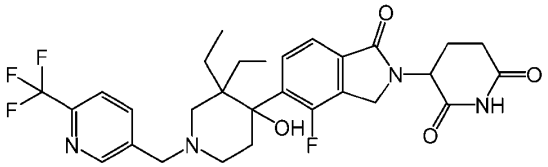
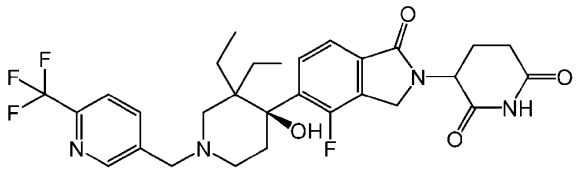
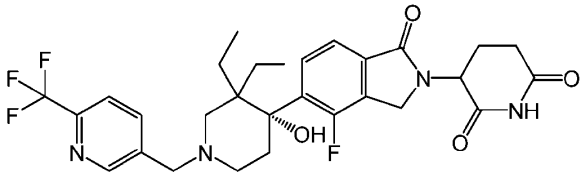
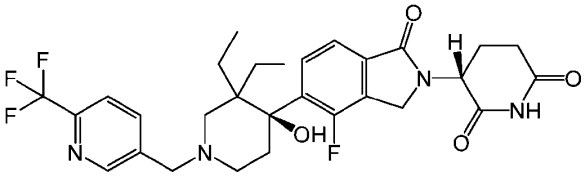
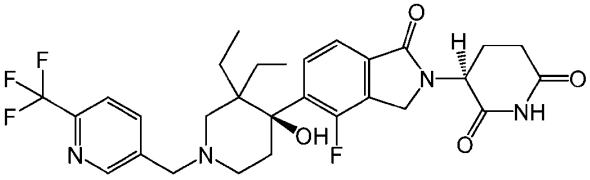
I-145	
I-146	
I-147	
I-148	
I-149	
I-150	

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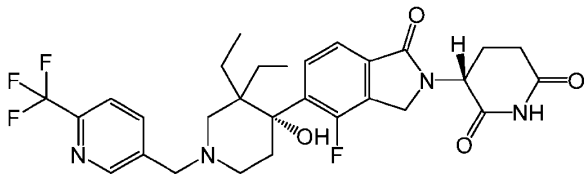
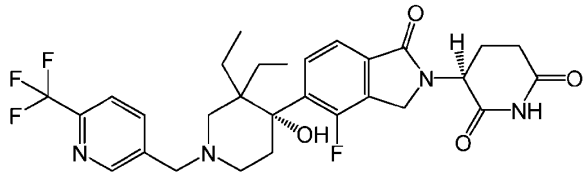
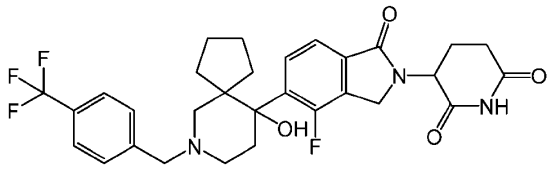
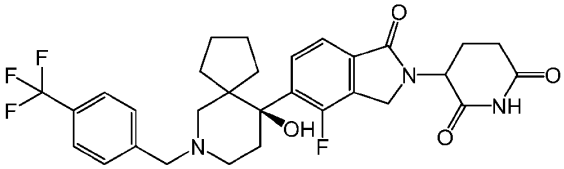
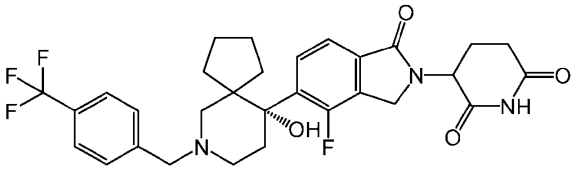
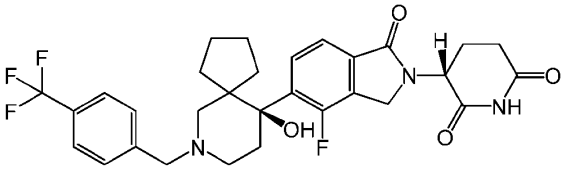
I-151	
I-152	
I-153	
I-154	
I-155	
I-156	

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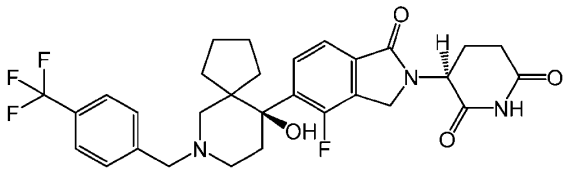
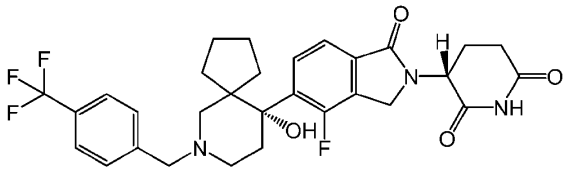
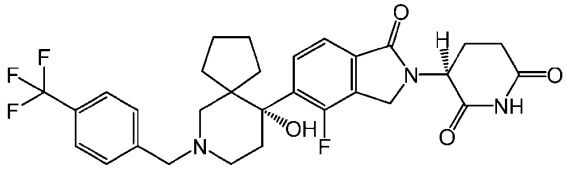
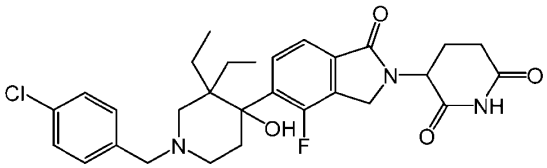
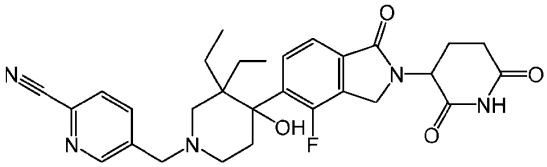
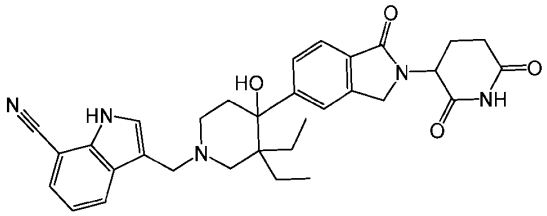
I-157	
I-158	
I-159	
I-160	
I-161	
I-162	

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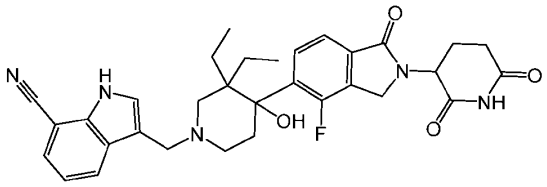
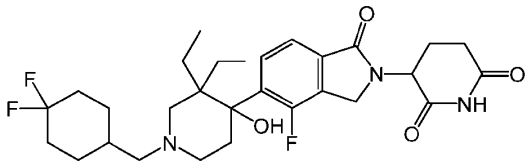
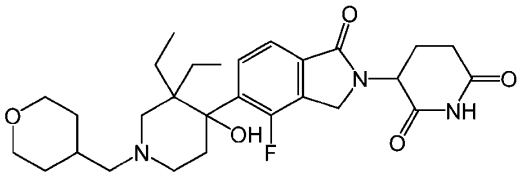
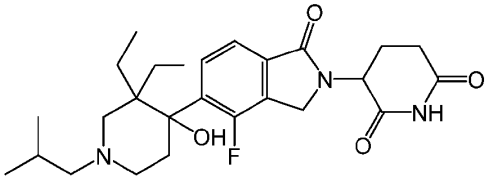
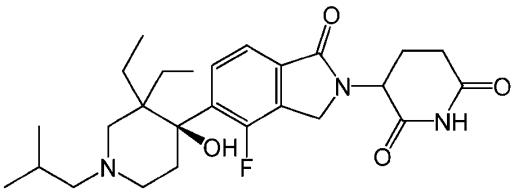
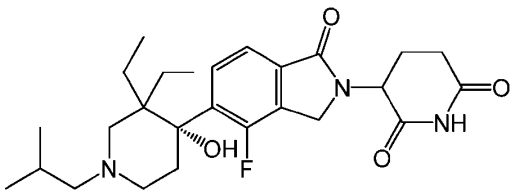
I-163	
I-164	
I-165	
I-166	
I-167	
I-168	

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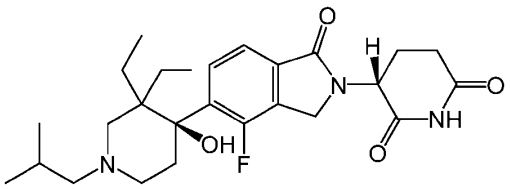
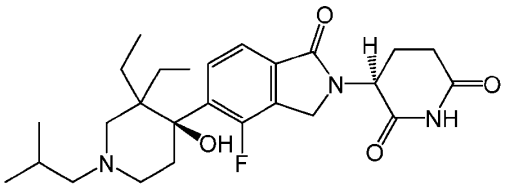
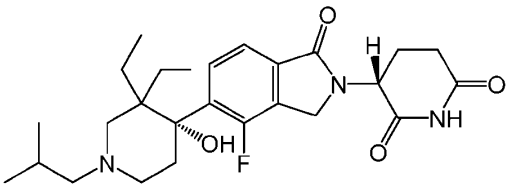
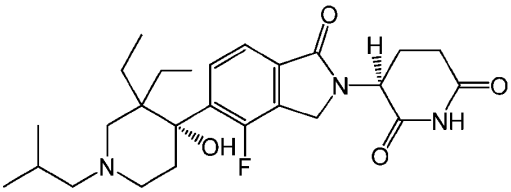
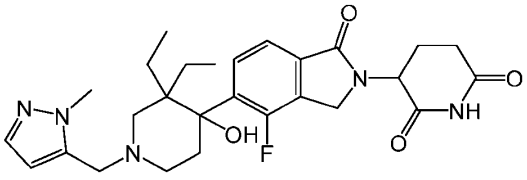
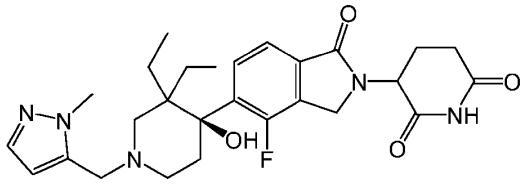
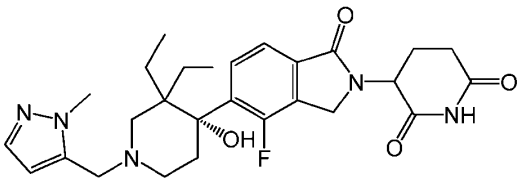
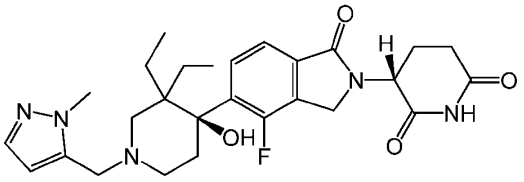
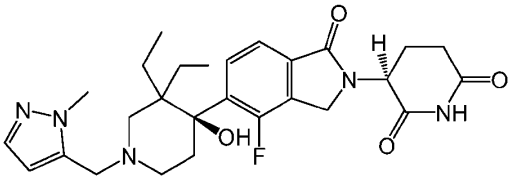
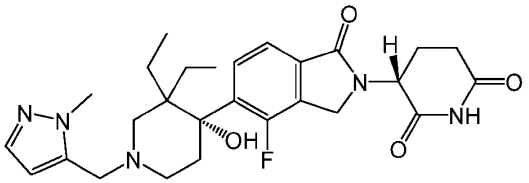
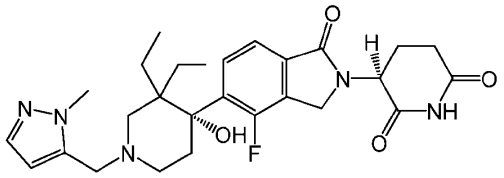
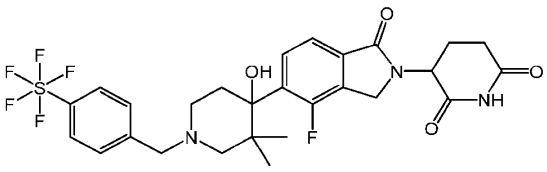
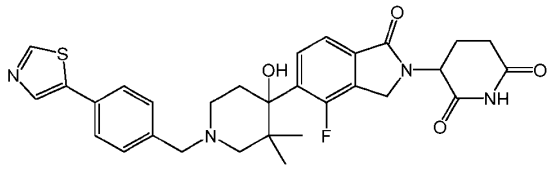
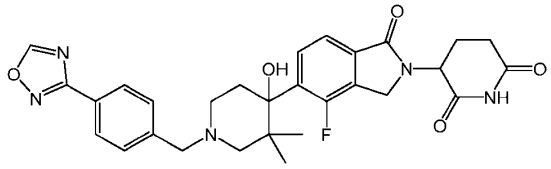
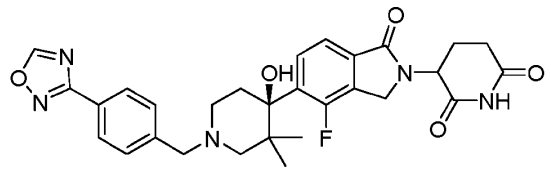
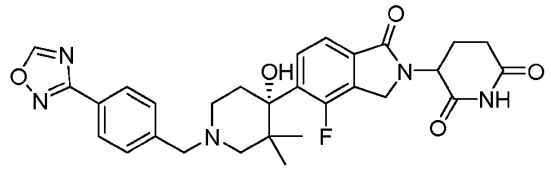
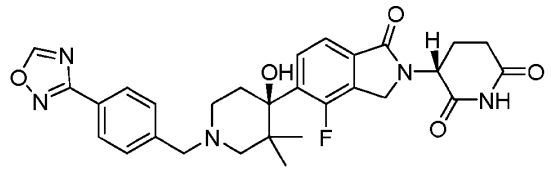
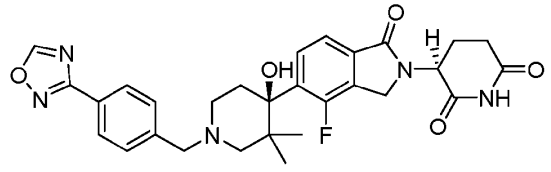
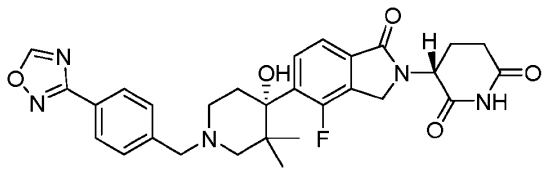
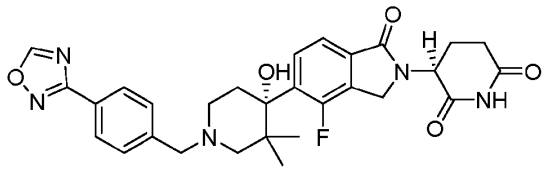
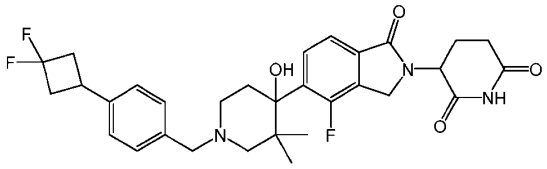
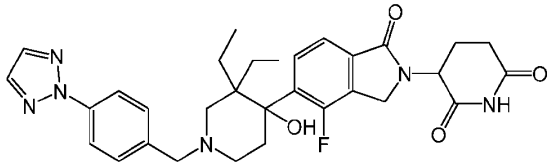
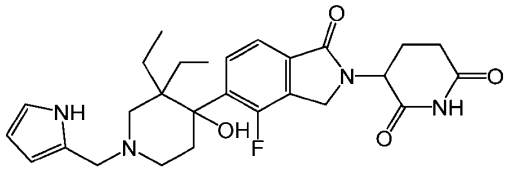
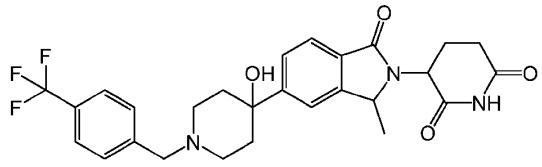
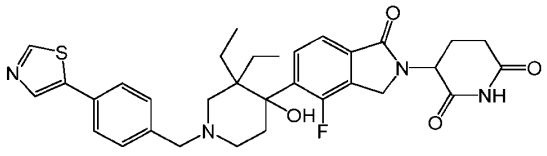
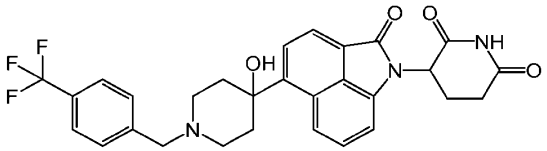
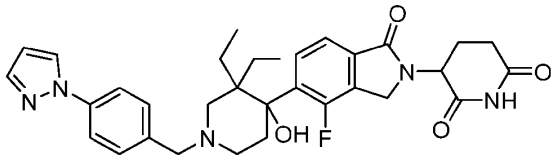
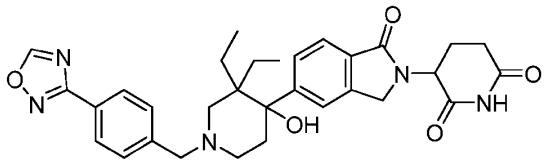
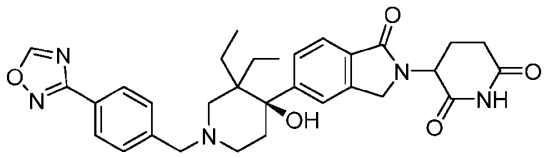
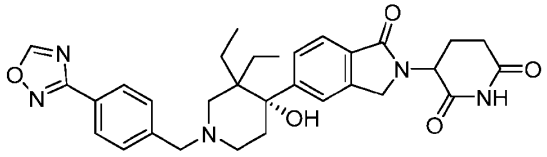
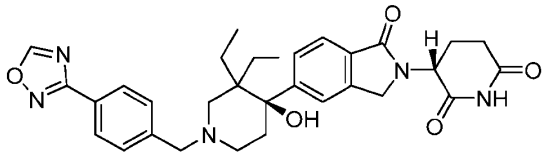
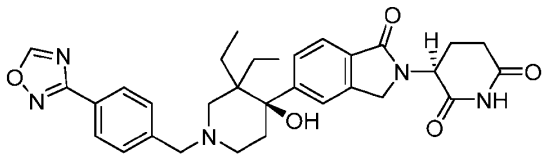
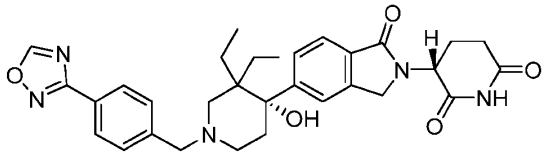
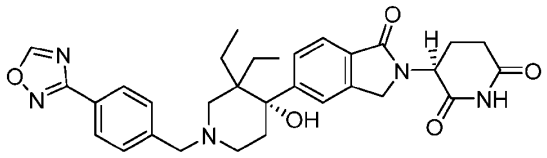
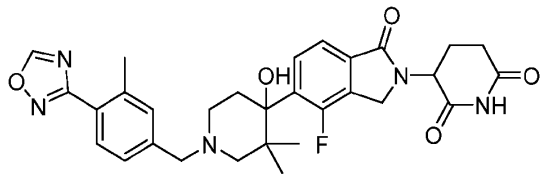
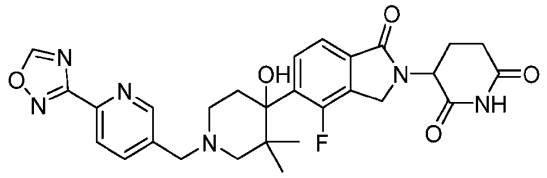
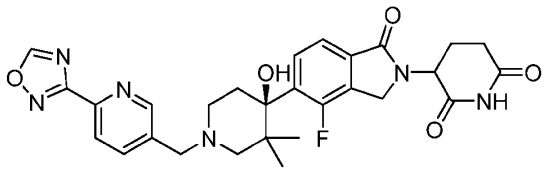
I-169	
I-170	
I-171	
I-172	
I-173	
I-174	

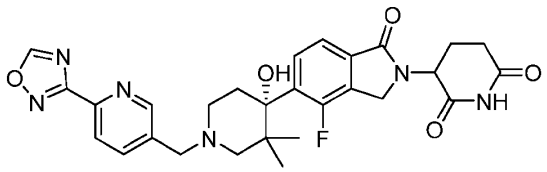
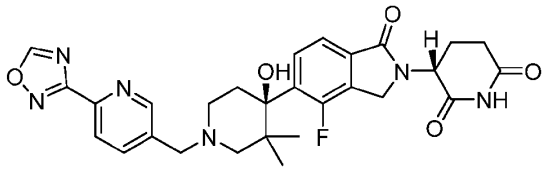
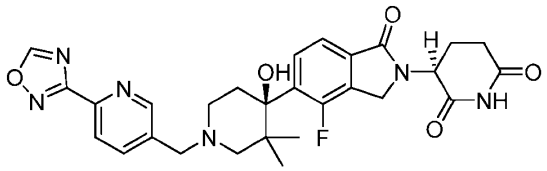
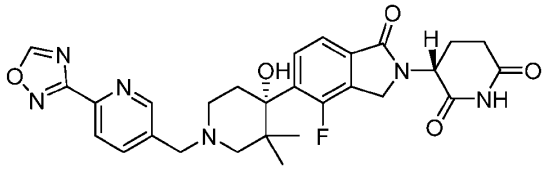
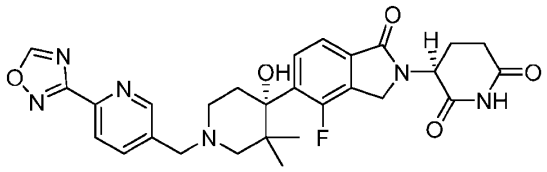
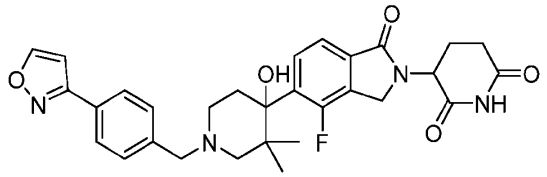
Cmpd No.	Compound Structure
I-175	
I-176	
I-177	
I-178	
I-179	
I-180	

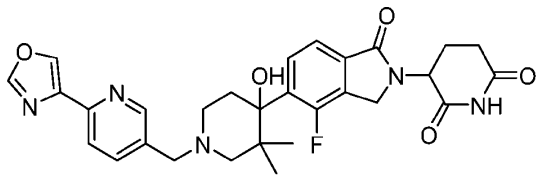
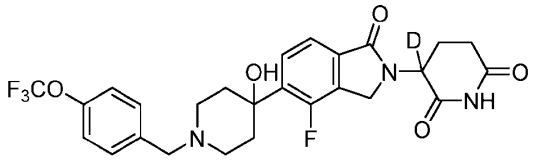
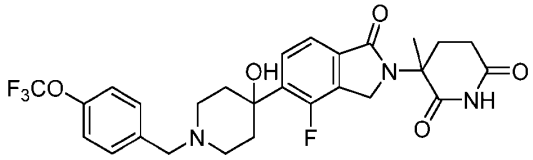
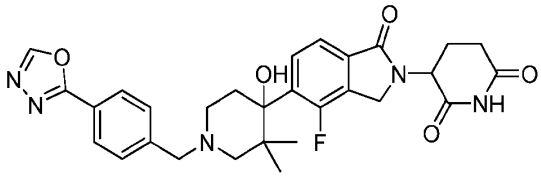
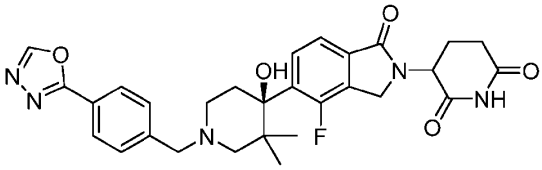
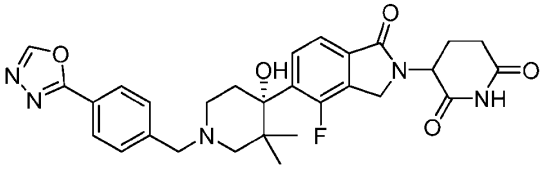
Cmpd No.	Compound Structure
I-181	
I-182	
I-183	
I-184	
I-185	
I-186	

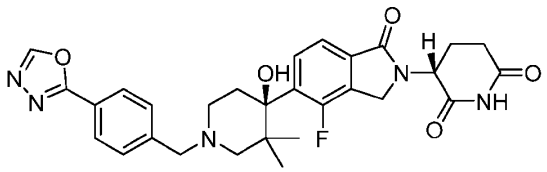
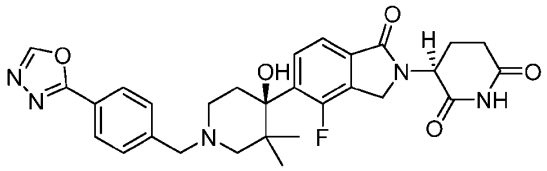
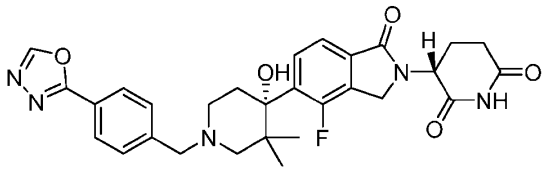
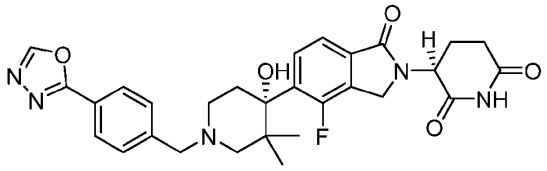
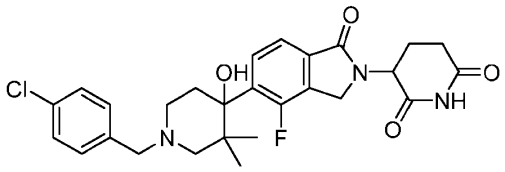
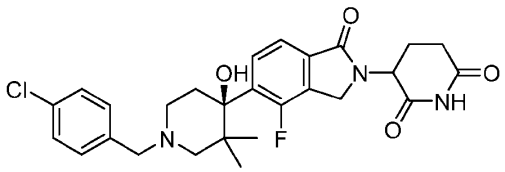
Cmpd No.	Compound Structure
I-187	
I-188	
I-189	
I-190	
I-191	
I-192	

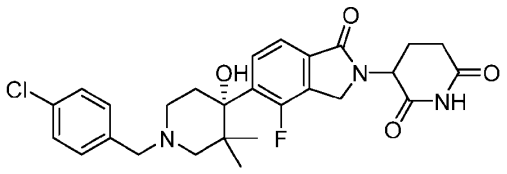
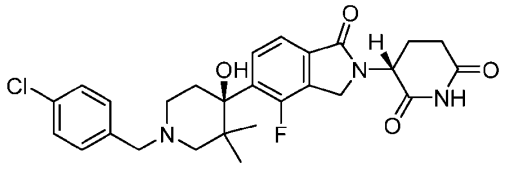
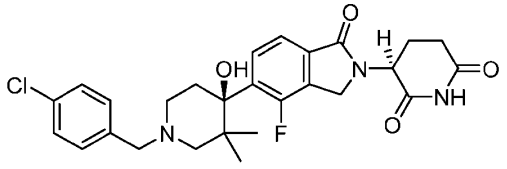
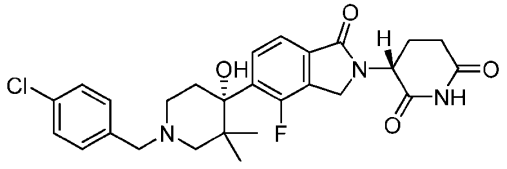
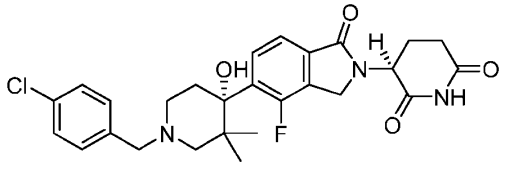
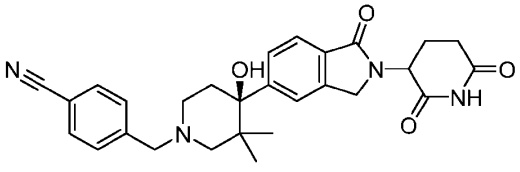
Cmpd No.	Compound Structure
I-193	
I-194	
I-195	
I-196	
I-197	
I-198	
I-199	

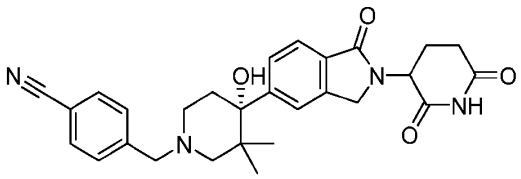
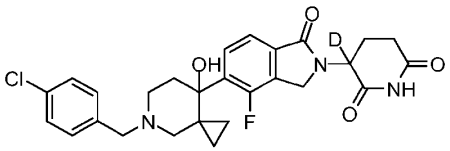
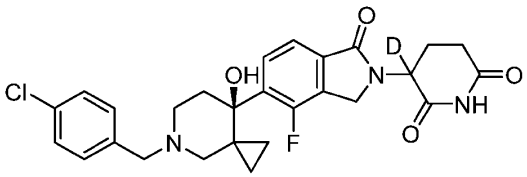
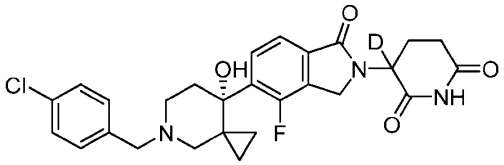
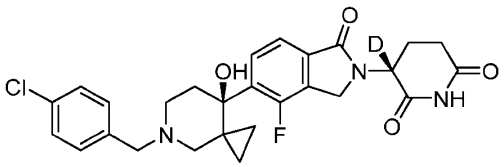
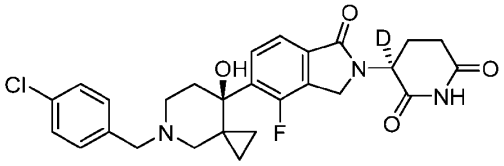
Cmpd No.	Compound Structure
I-200	
I-201	
I-202	
I-203	
I-204	
I-205	

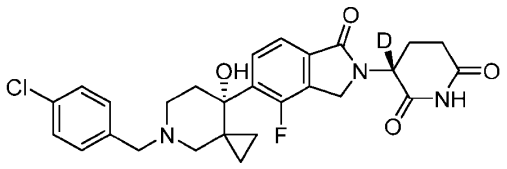
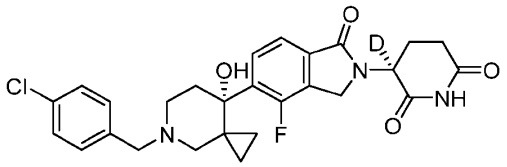
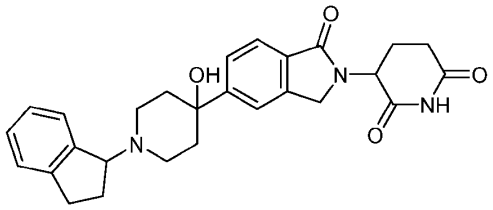
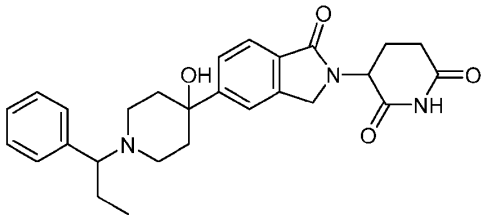
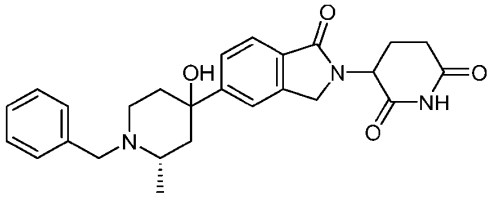
Cmpd No.	Compound Structure
I-206	
I-207	
I-208	
I-209	
I-210	
I-211	

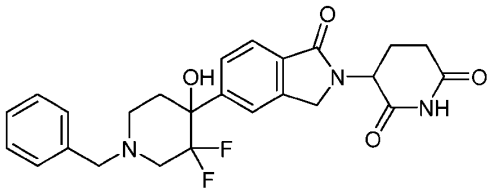
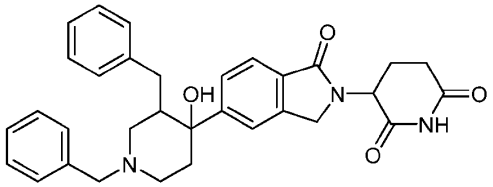
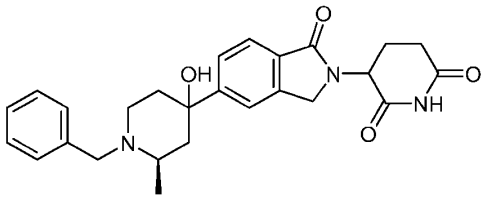
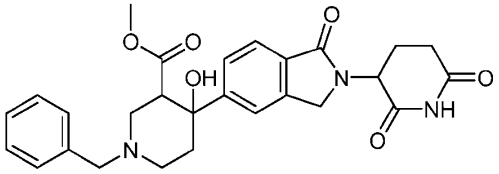
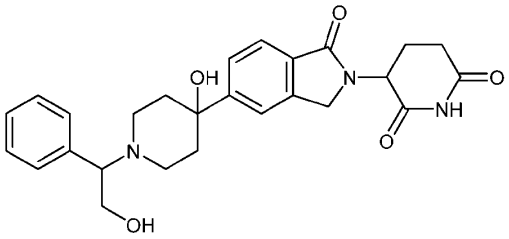
Cmpd No.	Compound Structure
I-212	
I-213	
I-214	
I-215	
I-216	
I-217	

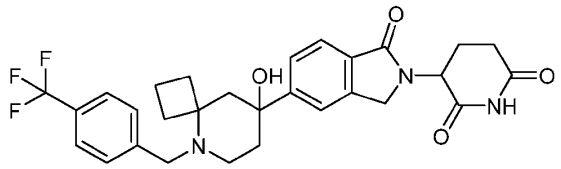
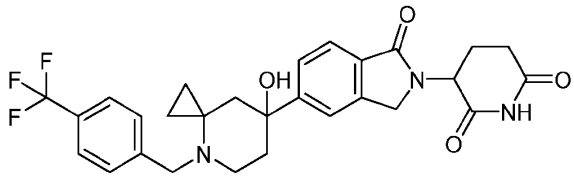
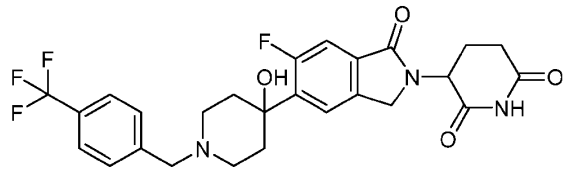
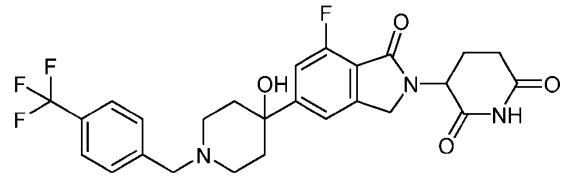
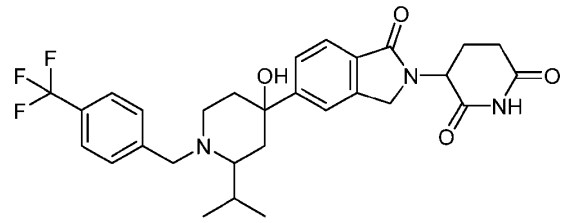
Cmpd No.	Compound Structure
I-218	
I-219	
I-220	
I-221	
I-222	
I-223	

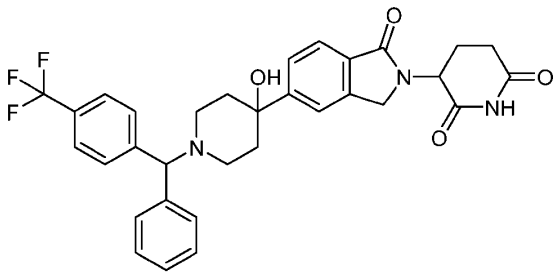
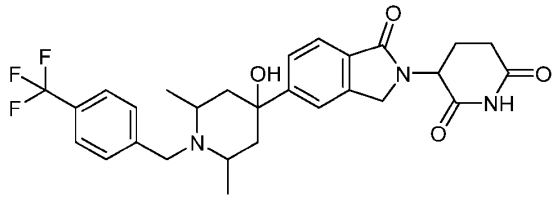
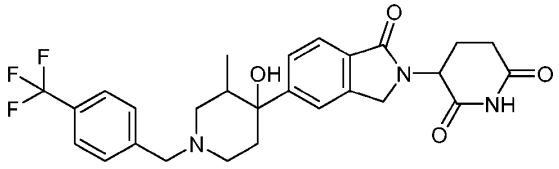
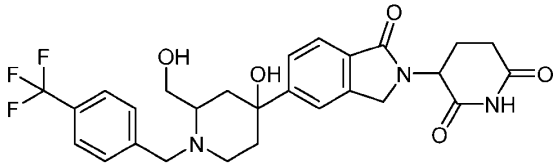
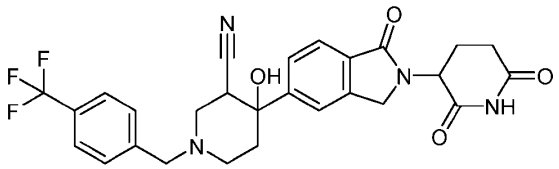
Cmpd No.	Compound Structure
I-224	
I-225	
I-226	
I-227	
I-228	
I-229	

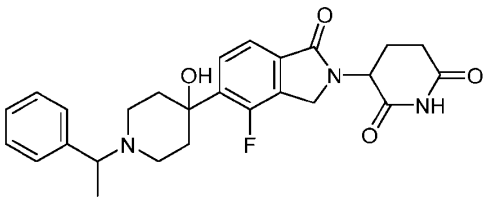
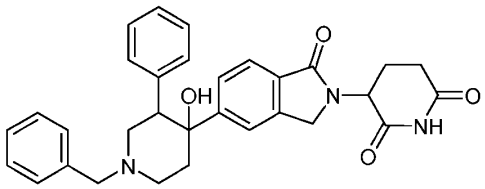
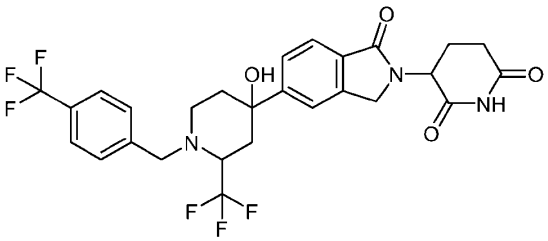
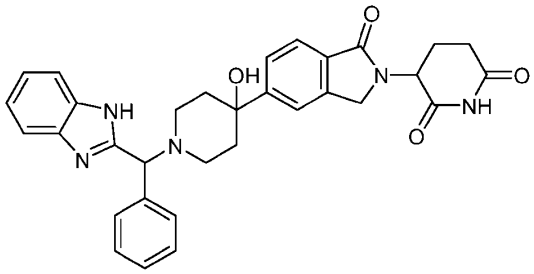
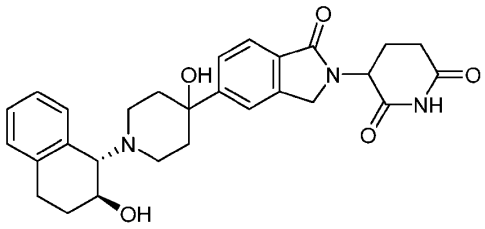
Cmpd No.	Compound Structure
I-230	
I-231	
I-232	
I-233	
I-234	
I-235	

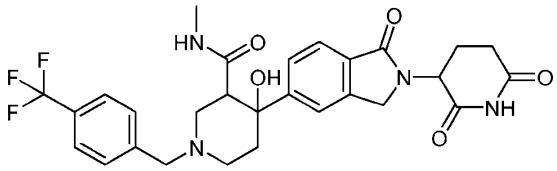
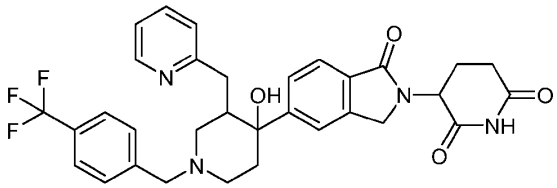
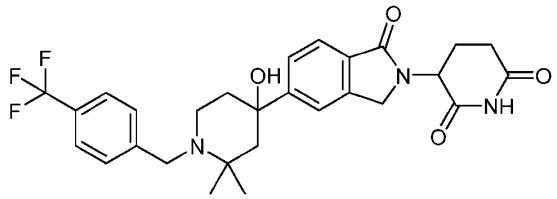
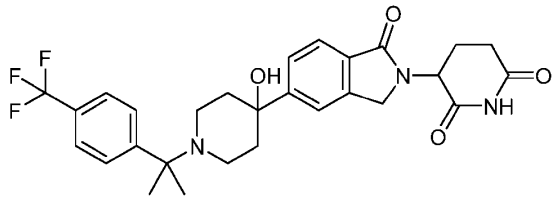
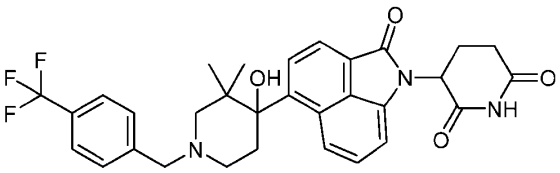
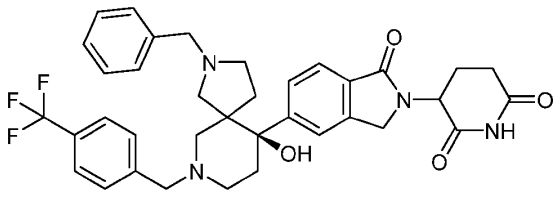
Cmpd No.	Compound Structure
I-236	
I-237	
I-238	
I-239	
I-240	

Cmpd No.	Compound Structure
I-241	
I-242	
I-243	
I-244	
I-245	

Cmpd No.	Compound Structure
I-246	
I-247	
I-248	
I-249	
I-250	

Cmpd No.	Compound Structure
I-251	
I-252	
I-253	
I-254	
I-255	

Cmpd No.	Compound Structure
I-256	
I-257	
I-258	
I-259	
I-260	

Cmpd No.	Compound Structure
I-261	
I-262	
I-263	
I-264	
I-265	
I-266	

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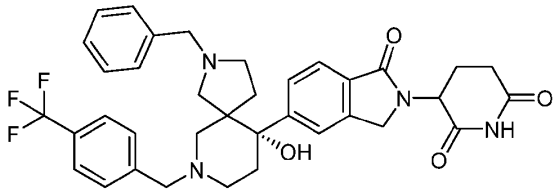
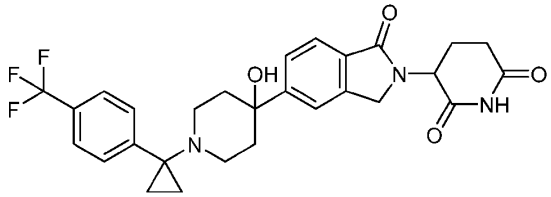
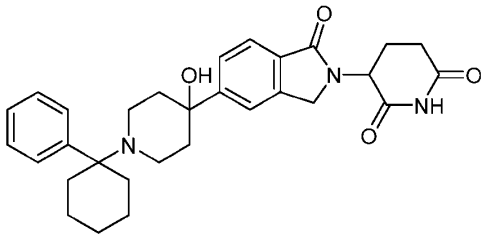
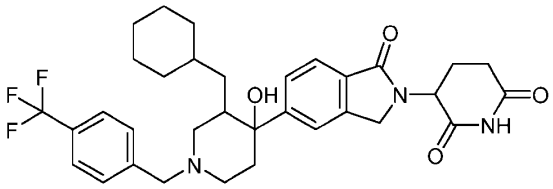
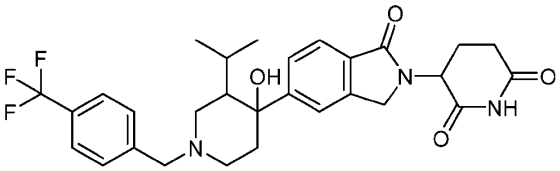
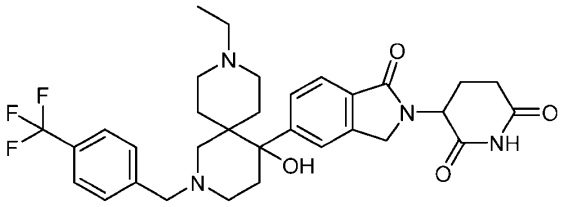
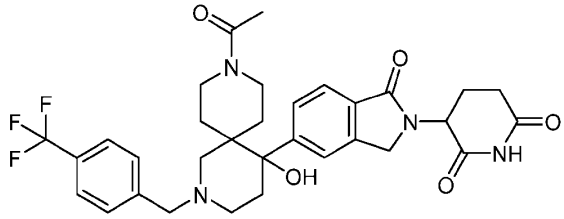
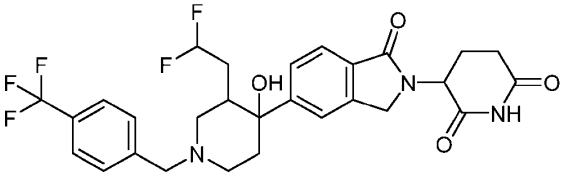
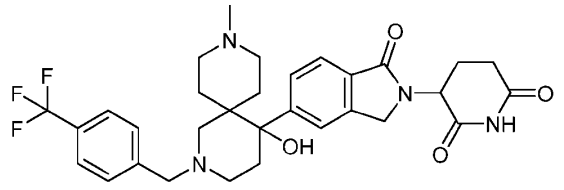
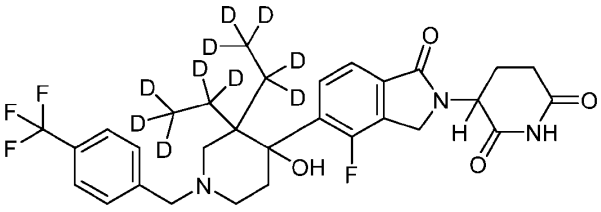
I-267	
I-268	
I-269	
I-270	
I-271	

Cmpd No.	Compound Structure
I-272	
I-273	
I-274	
I-275	
I-276	

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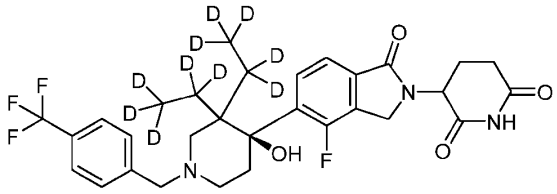
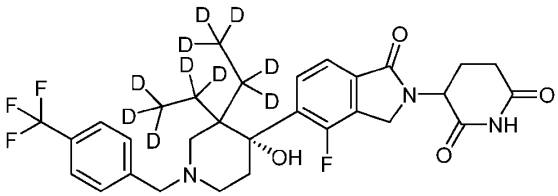
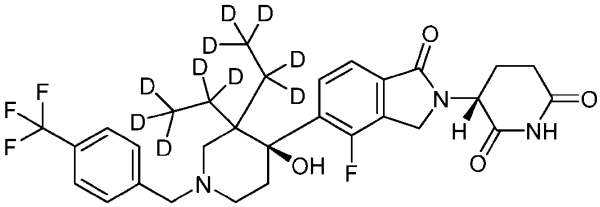
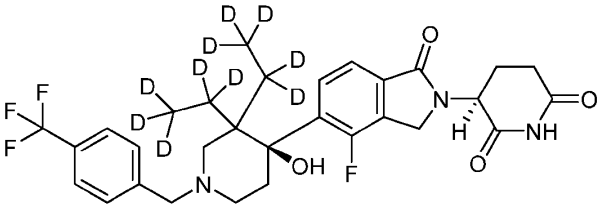
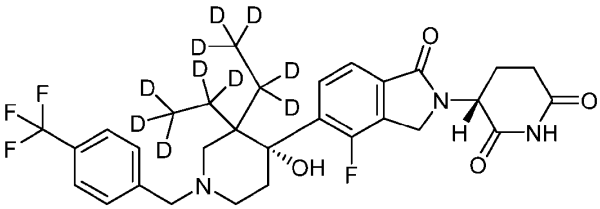
I-277	
I-278	
I-279	
I-280	
I-281	

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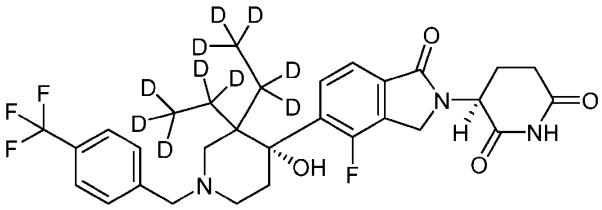
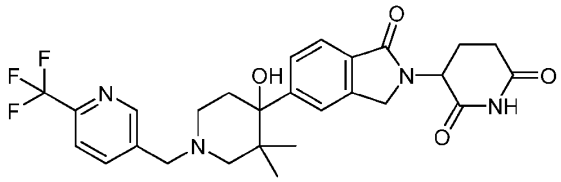
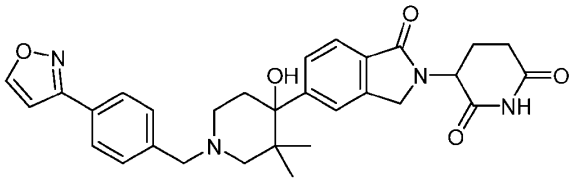
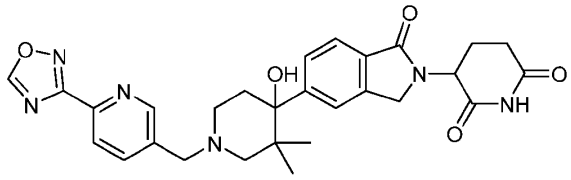
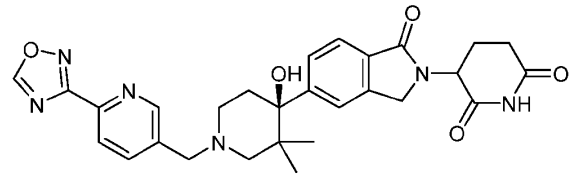
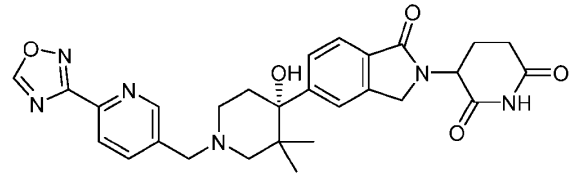
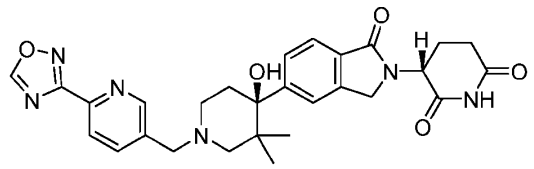
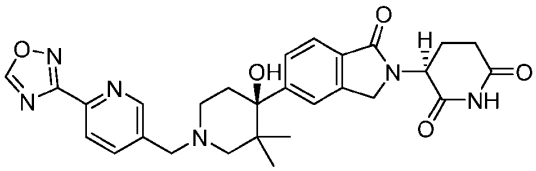
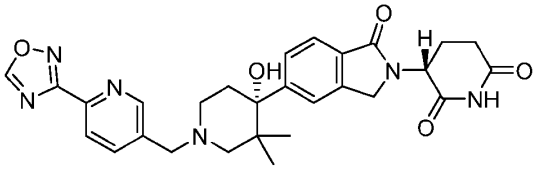
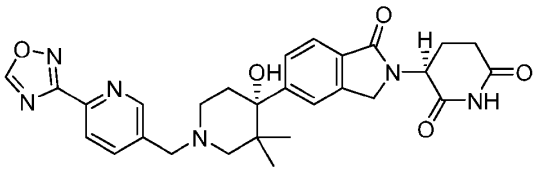
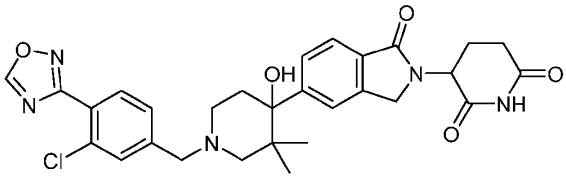
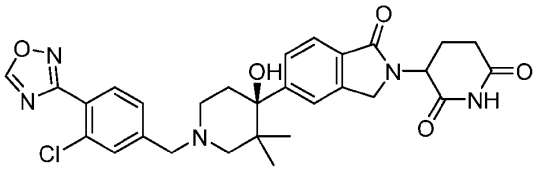
I-282	
I-283	
I-284	
I-285	
I-286	
I-287	

Cmpd No.	Compound Structure
I-288	
I-289	
I-290	
I-291	
I-292	
I-293	

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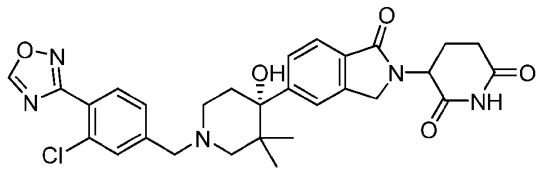
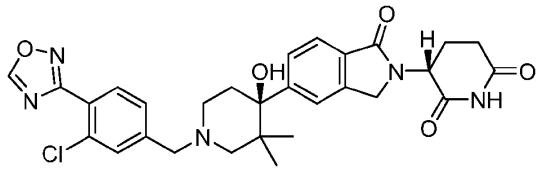
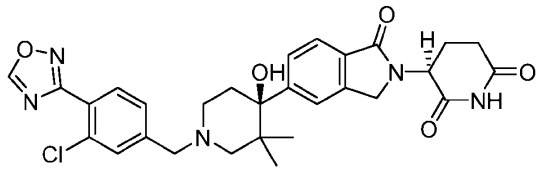
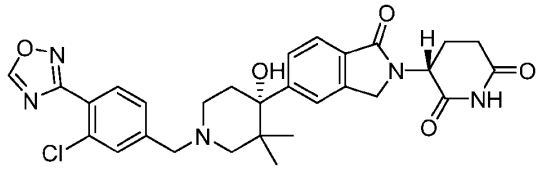
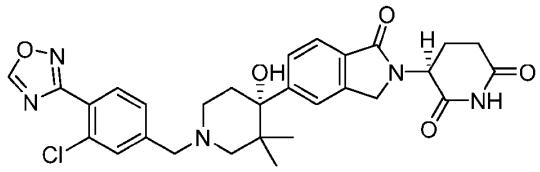
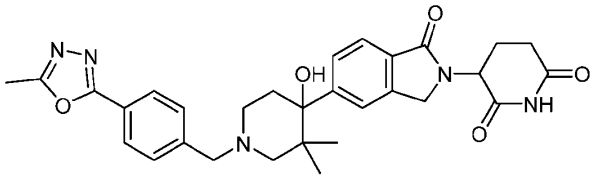
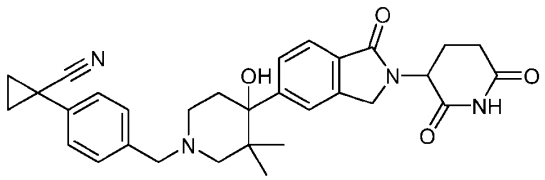
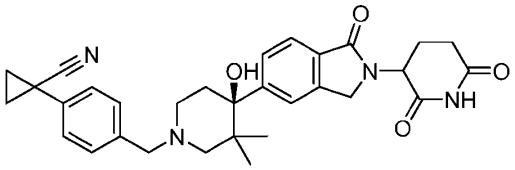
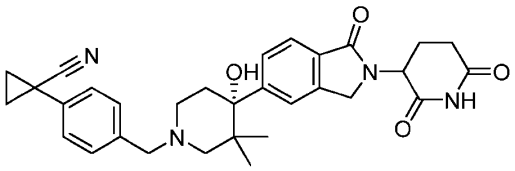
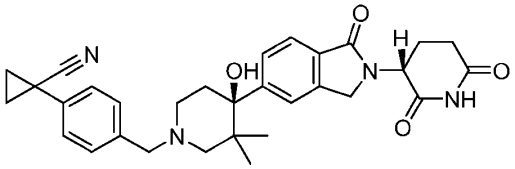
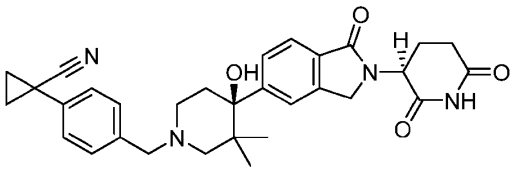
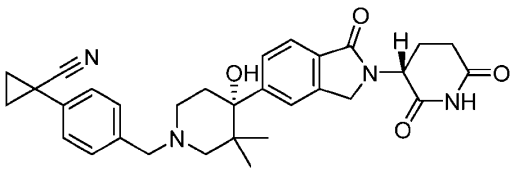
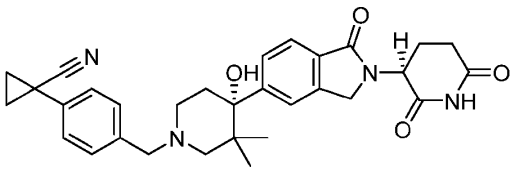
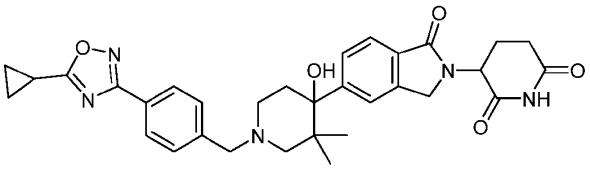
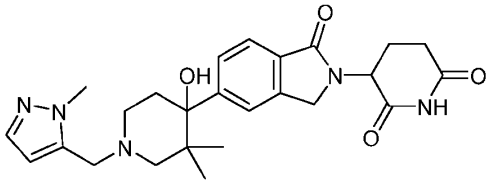
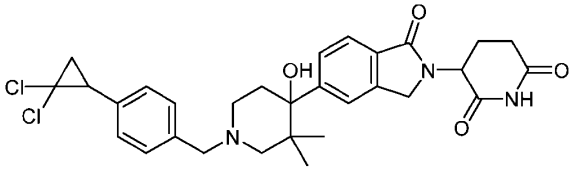
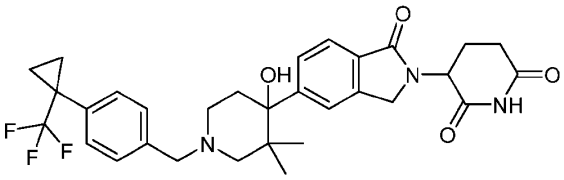
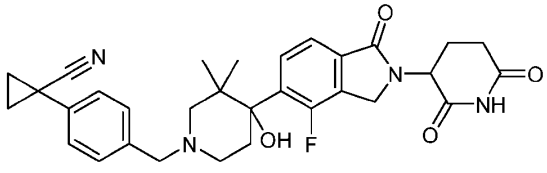
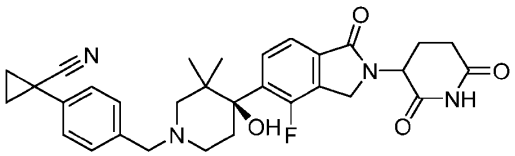
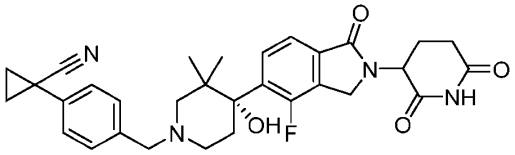
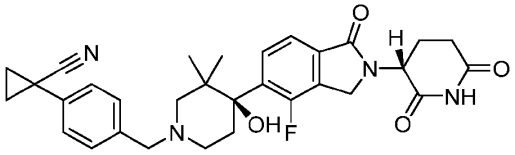
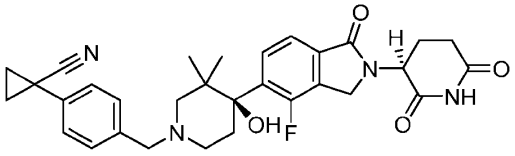
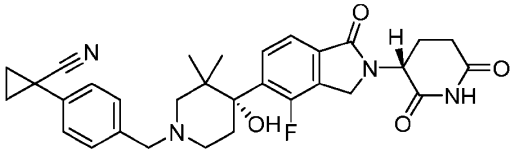
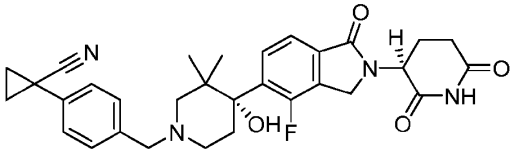
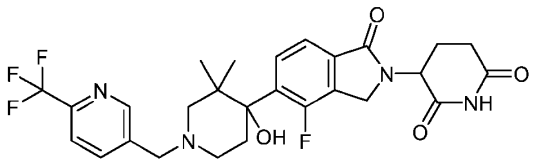
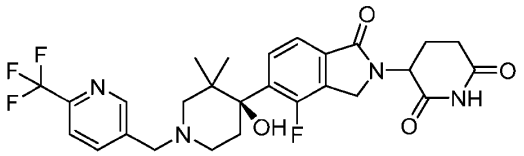
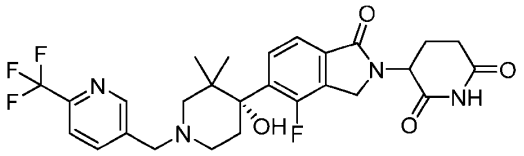
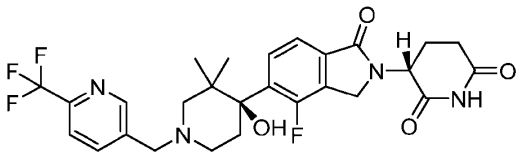
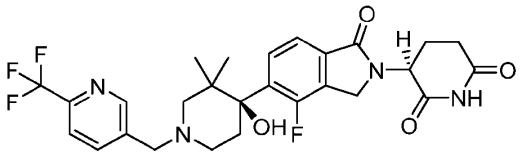
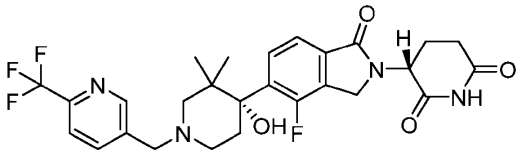
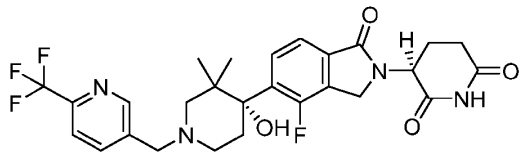
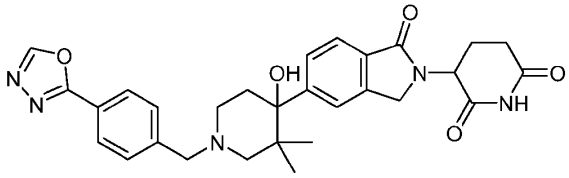
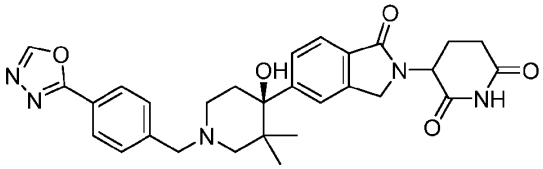
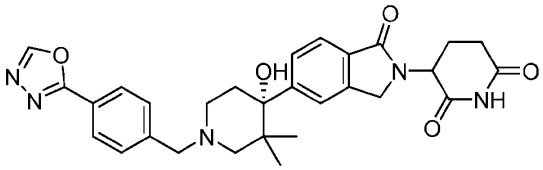
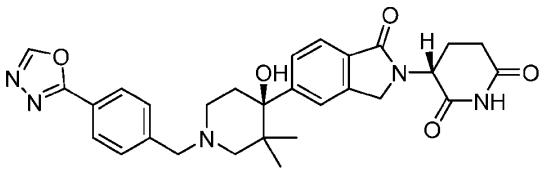
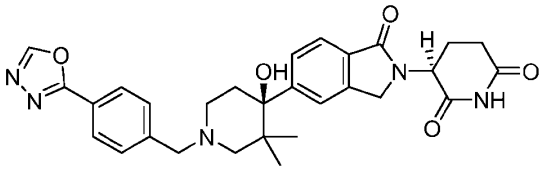
I-294	
I-295	
I-296	
I-297	
I-298	
I-299	

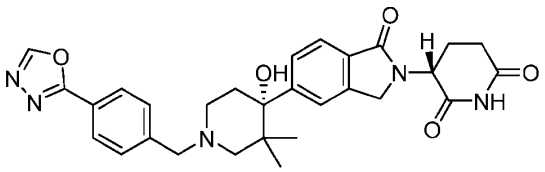
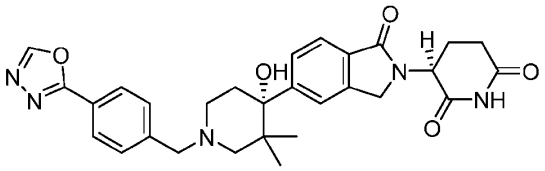
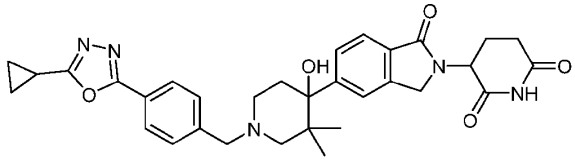
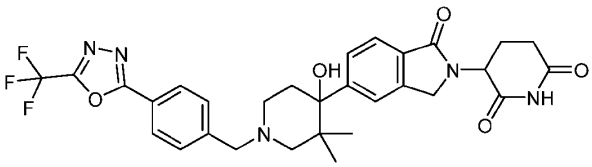
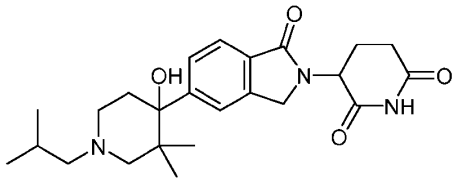
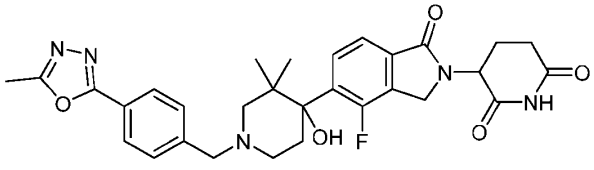
Cmpd No.	Compound Structure
I-300	
I-301	
I-302	
I-303	
I-304	
I-305	

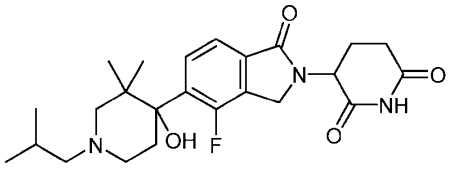
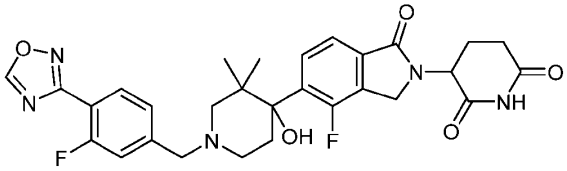
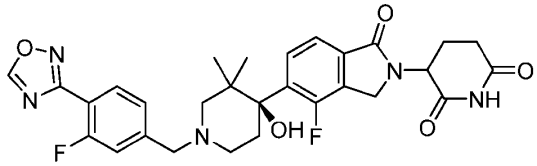
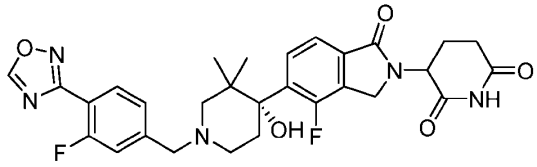
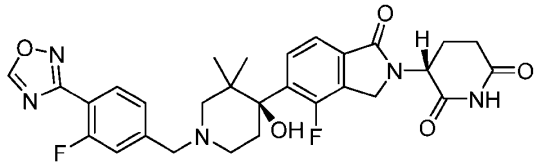
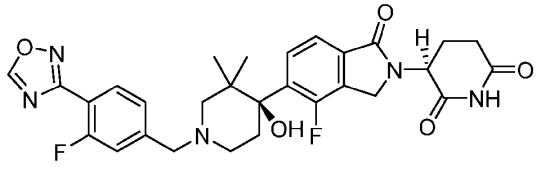
Cmpd No.	Compound Structure
I-306	
I-307	
I-308	
I-309	
I-310	
I-311	

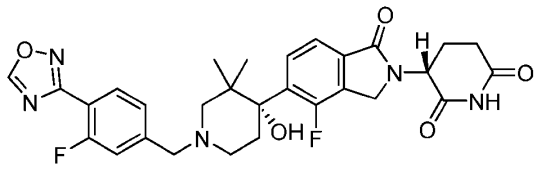
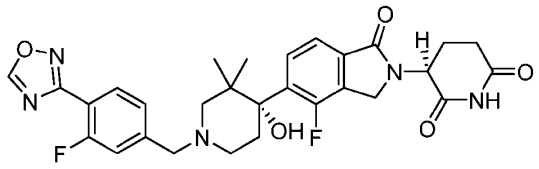
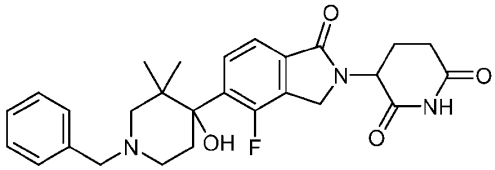
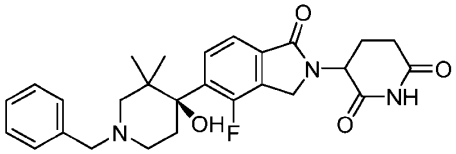
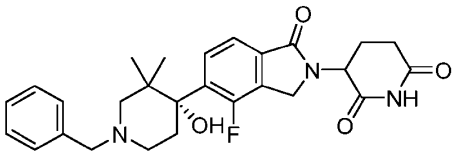
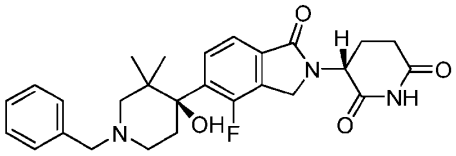
Cmpd No.	Compound Structure
I-312	
I-313	
I-314	
I-315	
I-316	
I-317	

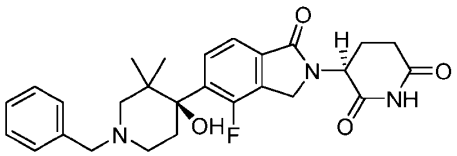
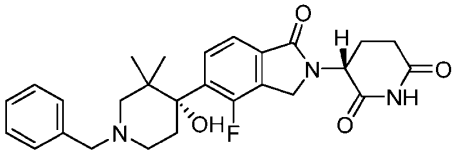
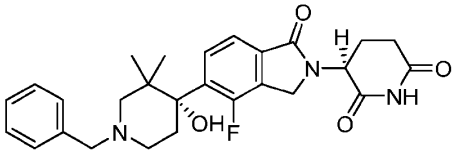
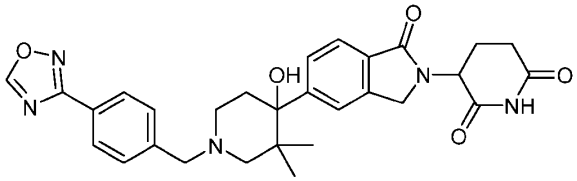
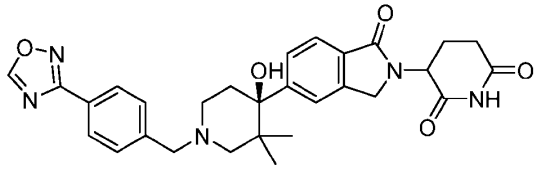
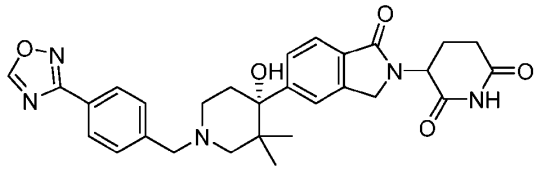
Cmpd No.	Compound Structure
I-318	
I-319	
I-320	
I-321	
I-322	
I-323	

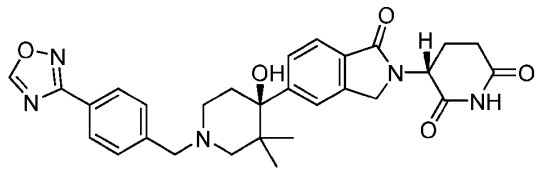
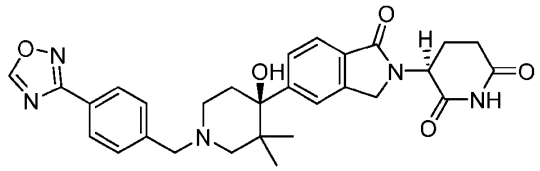
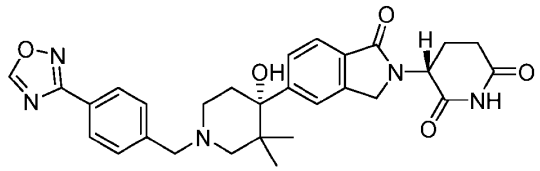
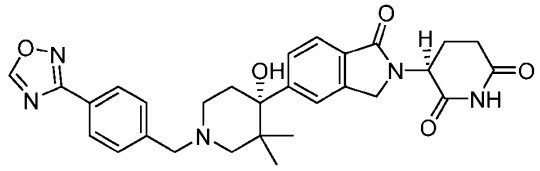
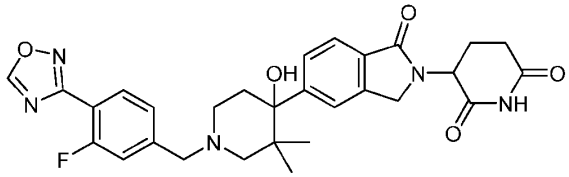
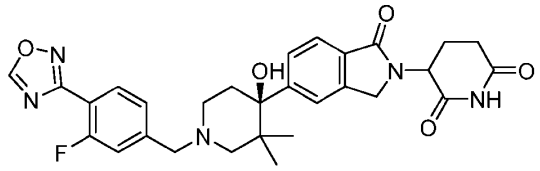
Cmpd No.	Compound Structure
I-324	
I-325	
I-326	
I-327	
I-328	
I-329	

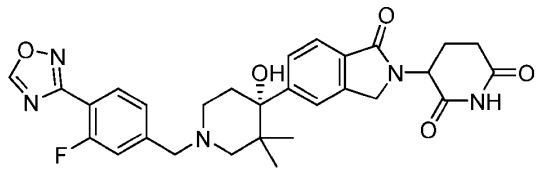
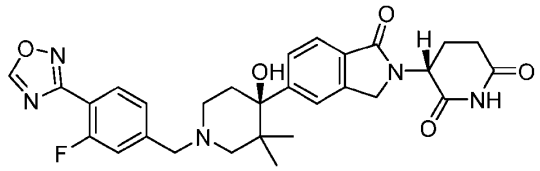
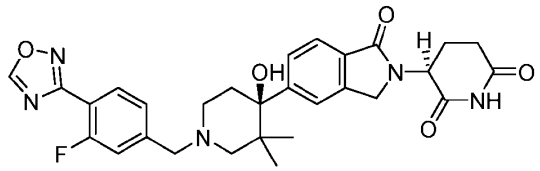
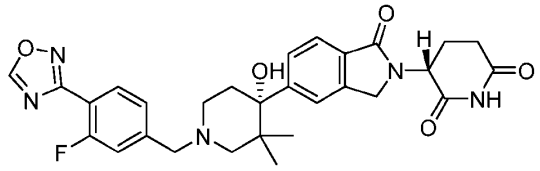
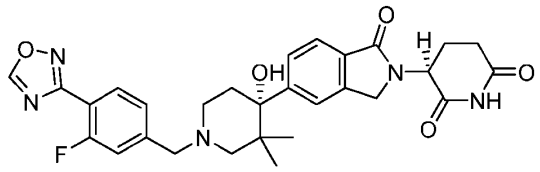
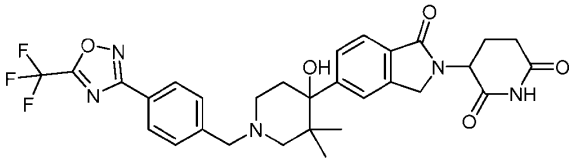
Cmpd No.	Compound Structure
I-330	
I-331	
I-332	
I-333	
I-334	
I-335	

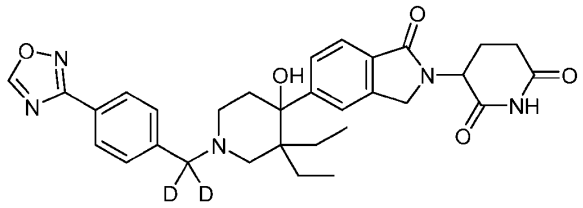
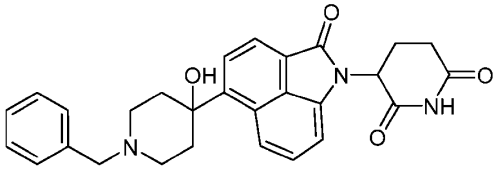
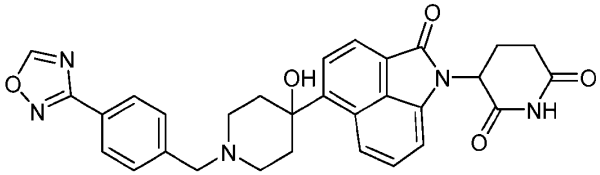
Cmpd No.	Compound Structure
I-336	
I-337	
I-338	
I-339	
I-340	
I-341	

Cmpd No.	Compound Structure
I-342	
I-343	
I-344	
I-345	
I-346	
I-347	

Cmpd No.	Compound Structure
I-348	
I-349	
I-350	
I-351	
I-352	
I-353	

Cmpd No.	Compound Structure
I-354	
I-355	
I-356	
I-357	
I-358	
I-359	

Cmpd No.	Compound Structure
I-360	
I-361	
I-362	
I-363	
I-364	
I-365	

Cmpd No.	Compound Structure
I-366	
I-367	
I-368	

* Absolute and relative stereochemistry was not assigned.

Embodiment 1: A compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereo isomer, or tautomer thereof, wherein:

R_a and R_b are each independently H, D, or $(C_1$-$C_6)$alkyl;

R_1 is H, D, $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, $-CH_2OP(O)(R_{12})_2$, $-CH_2OC(O)CH_2NHC(O)CH_2NH_2$, $-CH_2OC(O)CH(R_{12'})NHR_{12'}$, $-CH_2OC(O)(CH_2)_qC(O)OR_{12'}$, or $-CH_2OC(O)$-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S);

R_{2a}, R_{2b}, R_{2c}, and R_{2d} are each independently H or D;

R_3 is H, D, $(C_1$-$C_3)$alkyl, or $(C_1$-$C_3)$deuteroalkyl;

each R_4 is independently at each occurrence D or halogen;

each $R_{4'}$ is independently at each occurrence H, D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$;

R_5 is H, D, $(C_2$-$C_6)$alkyl, $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, $-CH_2OC(O)_2R_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$;

R_{6a}, R_{6b}, R_{6c}, and R_{6d} are each independently H, D, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl;

each R_{6e} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, $(C_1$-$C_6)$hydroxyalkyl, -CN, -OH, -O-$(C_1$-$C_6)$hydroxyalkyl, $(C_6$-$C_{10})$aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one or more R_{13}, the aryl and heteroaryl are optionally substituted with one or more R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{23}; or

two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a $(C_3$-$C_7)$spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one or more R_{15};

when $R_{4'}$ is H, m is 1, n is 0 and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are all simultaneously H, then R_7 is $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$halohydroxyalkyl, or $(C_1$-$C_6)$alkyl optionally substituted with one or more substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one or more R_8, the heteroaryl is optionally substituted with one or more R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$

when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$halohydroxyalkyl, or $(C_1$-$C_6)$alkyl optionally substituted with one or more substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$;

when $R_{4'}$ is (C_1)alkyl, then R_7 is $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$halohydroxyalkyl, or $(C_1$-$C_6)$alkyl optionally substituted with one or more substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4

heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one or more R_8, the heteroaryl is optionally substituted with one or more R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$;

when $R_{4'}$ is D, $(C_2$-$C_4)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$, then R_7 is $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$halohydroxyalkyl, or $(C_1$-$C_6)$alkyl optionally substituted with one or more substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$;

R_8 and $R_{8'}$ are each independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{40}$, and -CN; or

two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R_{10};

two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{10}; or

two $R_{8'}$ together with the atoms to which they are attached form a $(C_3$-$C_7)$carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{10}; or

two $R_{8'}$ when on the same carbon atom form C=(O);

each R_9 and $R_{9'}$ are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, or -CN;

R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN;

R_{12} is independently at each occurrence H, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN;

$R_{12'}$ is independently at each occurrence H or (C_1-C_6)alkyl;

each R_{13} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{14}R_{14'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein carbocyclyl and heterocyclyl are optionally substituted with one or more R_{20} and the aryl and heteroaryl are optionally substituted with one or more R_{21};

R_{14} and $R_{14'}$ are each independently at each occurrence H or (C_1-C_6)alkyl;

each R_{15} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$;

R_{16} and $R_{16'}$ are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{16a} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{17} is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{18} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{19} is (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{20} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{22} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{28}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{22}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{23} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{29}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{23} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{30} and R_{31} are each independently at each occurrence H, (C_1-C_6)alkyl, or -C(O)R_{34};

R_{32}, R_{33}, and R_{34} are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{35} and R_{36} are each independently at each occurrence H, (C_1-C_6)alkyl, or -C(O)R_{39};

R_{37}, R_{38}, and R_{39} are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{40} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

m and p are each independently 0, 1, or 2;

q is 1, 2, or 3; and

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

Embodiment 2: The compound according to Embodiment 1, having a Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (Ie), or Formula (If), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 3: The compound according to Embodiment 1 or 2, wherein R_5 is H.

Embodiment 4: The compound according to any one of Embodiments 1-3, wherein R_{6a} is H.

Embodiment 5: The compound according to any one of Embodiments 1-4, wherein R_{6b} is H.

Embodiment 6: The compound according to any one of Embodiments 1-5, wherein R_{6c} is H.

Embodiment 7: The compound according to any one of Embodiments 1-6, wherein R_{6d} is H.

Embodiment 8: The compound according to Embodiment 1 or 2, having a Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), or Formula (Im), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 9: The compound according to any one of Embodiments 1-8, wherein R_3 is H.

Embodiment 10: The compound according to any one of Embodiments 1-9, wherein $R_{4'}$ is (C_1)alkyl and R_7 is (C_1-C_6)alkyl optionally substituted with one to three phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one to three R_8, the heteroaryl is optionally substituted with one to three R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one to three $R_{8'}$.

Embodiment 11: The compound according to any one of Embodiments 1-9, wherein $R_{4'}$ is (C_2-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$ and R_7 is (C_1-C_6)alkyl optionally substituted with one to three phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to three R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to three $R_{8'}$.

Embodiment 12: The compound according to Embodiment 1, 2, or 8, wherein $R_{4'}$ is H.

Embodiment 13: The compound according to Embodiment 12, wherein n is 0 and m is 0.

Embodiment 14: The compound according to any one of Embodiments 12 or 13, wherein one of R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 is not H.

Embodiment 15: The compound according to any one of Embodiments 1-9, wherein $R_{4'}$ is H.

Embodiment 16: The compound according to Embodiments 15, wherein m is 0 or 1 and n is 1, 2, or 3.

Embodiment 17: The compound according to any one of Embodiments 12-16, wherein R_7 is (C_1-C_6)alkyl optionally substituted with one to three phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to three R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to three $R_{8'}$.

Embodiment 18: The compound according to Embodiment 15, wherein n is 0 and m is 1.

Embodiment 19: The compound according to Embodiment 18, wherein R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, and R_7 is (C_1-C_6)alkyl optionally substituted with one to three phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one to three R_8, the heteroaryl is optionally substituted with one to three R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one to three $R_{8'}$.

Embodiment 20: The compound according to any one of Embodiments 1-9, wherein n is 0.

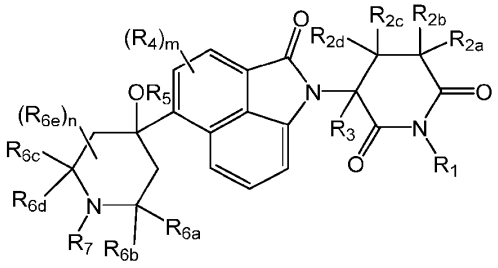
Embodiment 21: The compound according to any one of Embodiments 1-9, wherein n is 1.

Embodiment 22: The compound according to any one of Embodiments 1-9, wherein n is 2.

Embodiment 23: The compound according to any one of Embodiments 20-22, wherein m is 0.

Embodiment 24: The compound according to any one of Embodiments 20-22, wherein m is 1.

Embodiment 25: A compound of Formula (II):



(II),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

R_1 is H, D, -C(O)R_{11}, -CH_2OC(O)R_{11}, -CH_2OC(O)NHR_{12}, -CH_2OC(O)OR_{12}, -P(O)(OR_{12})$_2$, -CH_2OP(O)(OR_{12})$_2$, -CH_2OP(O)(OH)OR_{12}, -CH_2OP(O)(R_{12})$_2$, -CH_2OC(O)CH_2NHC(O)CH_2N_2, -CH_2OC(O)CH($R_{12'}$)N$HR_{12'}$, -CH_2OC(O)(CH_2)$_q$C(O)O$R_{12'}$, or -CH_2OC(O)-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S);

R_{2a}, R_{2b}, R_{2c}, and R_{2d} are each independently H or D;

R_3 is H, D, (C_1-C_3)alkyl, or (C_1-C_3)deuteroalkyl;

each R_4 is independently at each occurrence D;

R_5 is H, D, (C_1-C_6)alkyl, -C(O)R_{12}, -CH_2OC(O)R_{12}, -CH_2OC(O)N(R_{12})$_2$, -CH_2OC(O)$_2R_{12}$, -P(O)(OR_{12})$_2$, -CH_2OP(O)(OH)OR_{12}, or -CH_2OP(O)(R_{12})$_2$;

R_{6a}, R_{6b}, R_{6c}, and R_{6d} are each independently H, D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl;

each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10})aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one or more R_9, the aryl and heteroaryl are optionally substituted with one or more R_{16}, and the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{19}; or

two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one or more R_{14};

R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{15a}, -$NR_{15}R_{15'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$;

R_8 and $R_{8'}$ are each independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{28}R_{29}$, -SF_5, -SR_{22}, -CN, -C(O)$NR_{30}R_{31}$, -C(O)OR_{30}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{33}R_{34}$, -C(O)$NR_{35}R_{36}$, -C(O)R_{35}, -C(O)OR_{35}, -SF_5, -SR_{38}, and -CN; or

two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH,

and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R_{10};

two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{10}; or

two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, NH, N, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{10}; or

two $R_{8'}$ when on the same carbon atom form C=(O);

each R_9 is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{13}R_{13'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein carbocyclyl and heterocyclyl are optionally substituted with one or more R_{20} and the aryl and heteroaryl are optionally substituted with one or more R_{21};

R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{23}, or -CN;

R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN;

R_{12} is independently at each occurrence H, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN;

$R_{12'}$ is independently at each occurrence H or (C_1-C_6)alkyl;

R_{13} and $R_{13'}$ are each independently at each occurrence H or (C_1-C_6)alkyl;

each R_{14} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$;

R_{15} and $R_{15'}$ are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{15a} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

each R_{16} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy,

(C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{16}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

R_{17} is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{18} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{19} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{20} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, and R_{27} are each independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{28} and R_{29} are each independently at each occurrence H, (C_1-C_6)alkyl, or -C(O)R_{32};

R_{30}, R_{31}, and R_{32} are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{33} and R_{34} are each independently at each occurrence H, (C_1-C_6)alkyl, or -C(O)R_{37};

R_{35}, R_{36}, and R_{37} are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{38} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

m is 0, 1, or 2;

q is 1, 2, or 3; and

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

Embodiment 26: The compound according to Embodiment 25, wherein R_3 is H.

Embodiment 27: The compound according to any one of Embodiments 25 or 26, wherein R_5 is H.

Embodiment 28: The compound according to any one of Embodiments 25-27, wherein R_{2a} is H.

Embodiment 29: The compound according to any one of Embodiments 25-28, wherein R_{2b} is H.

Embodiment 30: The compound according to any one of Embodiments 25-29, wherein R_{2c} is H.

Embodiment 31: The compound according to any one of Embodiments 25-30, wherein R_{2d} is H.

Embodiment 32: The compound according to any one of Embodiments 25-31, R_7 is $(C_1$-$C_6)$alkyl, wherein the alkyl is optionally substituted with one to three phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to three R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to three $R_{8'}$.

Embodiment 33: The compound according to any one of Embodiments 25-32, R_7 is $(C_1$-$C_6)$alkyl, wherein the alkyl is substituted with one to three phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to three R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to three $R_{8'}$.

Embodiment 34: A compound selected from the group consisting of:
3-(5-(1-benzyl-4-hydroxypiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(4-fluoro-5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(4-fluoro-5-(4-hydroxy-1-(4-phenoxybenzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
4-((4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-4-hydroxypiperidin-1-yl)methyl)benzonitrile;
3-(4-fluoro-5-(4-hydroxy-1-(4-(4-(trifluoromethyl)phenoxy)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(4-fluoro-5-(4-hydroxy-1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
4-((4-(2-(2,6-dioxopiperidin-3-yl)-4-methyl-1-oxoisoindolin-5-yl)-4-hydroxypiperidin-1-yl)methyl)benzonitrile;
3-(5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-methyl-1-oxoisoindolin-2-yl)piperidine-2,6-dione;

3-(4-chloro-5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-methoxy-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-benzyl-4-hydroxypiperidin-4-yl)-4-methoxy-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-benzyl-4-hydroxypiperidin-4-yl)-4-chloro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(4-hydroxy-5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-benzyl-4-hydroxypiperidin-4-yl)-1-oxo-4-(trifluoromethyl)isoindolin-2-yl)piperidine-2,6-dione;
3-(5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxo-4-(trifluoromethyl)isoindolin-2-yl)piperidine-2,6-dione;
3-(5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-benzyl-4-hydroxy-3,3-dimethylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxo-4-(trifluoromethoxy)isoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-benzyl-4-hydroxypiperidin-4-yl)-1-oxo-4-(trifluoromethoxy)isoindolin-2-yl)piperidine-2,6-dione;
3-(4-amino-5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(3-fluoro-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(8-hydroxy-5-(4-(trifluoromethyl)benzyl)-5-azaspiro[2.5]octan-8-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(5-hydroxy-9,9-dimethyl-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(3-(cyclopropylmethyl)-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(3-ethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;

3-(4-fluoro-5-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(4-hydroxy-3-isobutyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(3-(cyclopropylmethyl)-4-hydroxy-3-methyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(3,3-diethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-((S)-2-ethyl-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(4-hydroxy-3-(methoxymethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(5-hydroxy-2-(3,3,3-trifluoro-2-hydroxypropyl)-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(2-((5-amino-1-phenyl-1H-pyrazol-4-yl)methyl)-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(2-(3-chloro-4-methoxybenzyl)-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
2-chloro-4-((5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-5-hydroxy-2-azaspiro[5.5]undecan-2-yl)methyl)benzonitrile;
3-(5-(2-((2-amino-6-(trifluoromethyl)pyridin-3-yl)methyl)-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(2-(2-amino-5-chlorobenzyl)-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(5-hydroxy-2-((1-methyl-1H-pyrrol-2-yl)methyl)-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(5-hydroxy-2-((5-methyl-1H-pyrrol-2-yl)methyl)-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
methyl 5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecane-9-carboxylate;
5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-5-hydroxy-N,N-dimethyl-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecane-9-carboxamide;
3-(5-(5-hydroxy-9-isobutyryl-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;

3-(5-(5-hydroxy-2-((3-methyl-1H-pyrrol-2-yl)methyl)-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(3,3-diethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(3,3-diethyl-4-hydroxy-1-methylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(4-fluoro-1-oxo-5-(1,3,3-triethyl-4-hydroxypiperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione;
3-(5-(3,3-diethyl-4-hydroxy-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-((4,4-difluorocyclohexyl)methyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
5-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)picolinonitrile;
3-(5-(3,3-diethyl-4-hydroxy-1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(3,3-diethyl-4-hydroxy-1-isobutylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-(4-(difluoromethyl)-3-methoxybenzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile;
3-(5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-9-oxa-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(9,9-difluoro-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(4-chloro-5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.6]dodecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-(4-chlorobenzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(4-fluoro-5-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(4-chloro-5-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(3,3-diethyl-4-hydroxy-1-((tetrahydro-2H-pyran-4-yl)methyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;

3-(5-(1-benzyl-3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-(4-(difluoromethyl)benzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-(4-(difluoromethoxy)benzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-(4-cyclopropylbenzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(4-fluoro-5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-9-oxa-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-(4-(2,2-difluoroethoxy)benzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(4-fluoro-5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-(4-cyclopropoxybenzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(3,3-diethyl-4-hydroxy-1-(3-methoxy-4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(3,3-diethyl-4-hydroxy-1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-benzyl-3,3-diethyl-4-hydroxypiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-(4-(difluoromethyl)benzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-(4-(difluoromethoxy)benzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-(4-cyclopropylbenzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-4-methyl-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-(4-(2,2-difluoroethoxy)benzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(4-fluoro-5-(9-hydroxy-6-(4-(trifluoromethyl)benzyl)-6-azaspiro[3.5]nonan-9-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;

3-(5-(1-(4-cyclopropoxybenzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(3,3-diethyl-4-hydroxy-1-(3-methoxy-4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-(4-(difluoromethyl)-3-methoxybenzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
4-((4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile;
3-(5-(3,3-diethyl-4-hydroxy-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(4-fluoro-5-(10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-(4-chlorobenzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
5-((4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)picolinonitrile;
3-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)-1H-indole-7-carbonitrile;
3-((4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)-1H-indole-7-carbonitrile;
3-(5-(1-((4,4-difluorocyclohexyl)methyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(3,3-diethyl-4-hydroxy-1-((tetrahydro-2H-pyran-4-yl)methyl)piperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(3,3-diethyl-4-hydroxy-1-isobutylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(3,3-diethyl-4-hydroxy-1-((1-methyl-1H-pyrazol-5-yl)methyl)piperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(4-fluoro-5-(4-hydroxy-3,3-dimethyl-1-(4-(pentafluoro-l6-sulfaneyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(4-fluoro-5-(4-hydroxy-3,3-dimethyl-1-(4-(thiazol-5-yl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;

3-(5-(1-(4-(3,3-difluorocyclobutyl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-(4-(2H-1,2,3-triazol-2-yl)benzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-((1H-pyrrol-2-yl)methyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-3-methyl-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(3,3-diethyl-4-hydroxy-1-(4-(thiazol-5-yl)benzyl)piperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-oxobenzo[cd]indol-1(2H)-yl)piperidine-2,6-dione;
3-(5-(1-(4-(1H-pyrazol-1-yl)benzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
4-(((S)-4-(2-((S)-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile;
4-(((S)-4-(2-((R)-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile;
4-(((R)-4-(2-((S)-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile;
4-(((R)-4-(2-((R)-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile;
3-(4-fluoro-5-(4-hydroxy-3,3-dimethyl-1-(3-methyl-4-(1,2,4-oxadiazol-3-yl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(5-(1-((6-(1,2,4-oxadiazol-3-yl)pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(4-fluoro-5-(4-hydroxy-1-(4-(isoxazol-3-yl)benzyl)-3,3-dimethylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(4-fluoro-5-(4-hydroxy-3,3-dimethyl-1-((6-(oxazol-4-yl)pyridin-3-yl)methyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
3-(4-fluoro-5-(4-hydroxy-1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione-3-d;

3-(4-fluoro-5-(4-hydroxy-1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)-3-methylpiperidine-2,6-dione;
3-(5-(1-(4-(1,3,4-oxadiazol-2-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
(S)-3-(5-((R)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
(R)-3-(5-((S)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
(R)-3-(5-((R)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
(S)-3-(5-((S)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
(S)-3-(5-((S)-10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
(R)-3-(5-((R)-10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
(R)-3-(5-((S)-10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
(S)-3-(5-((R)-10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;
4-(((4S)-4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)benzonitrile;
4-(((4R)-4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)benzonitrile;
(S)-3-(5-((R)-5-(4-chlorobenzyl)-8-hydroxy-5-azaspiro[2.5]octan-8-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione-3-d;
(R)-3-(5-((S)-5-(4-chlorobenzyl)-8-hydroxy-5-azaspiro[2.5]octan-8-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione-3-d;
(R)-3-(5-((R)-5-(4-chlorobenzyl)-8-hydroxy-5-azaspiro[2.5]octan-8-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione-3-d;
(S)-3-(5-((S)-5-(4-chlorobenzyl)-8-hydroxy-5-azaspiro[2.5]octan-8-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione-3-d;
3-(5-((R)-5-(4-chlorobenzyl)-8-hydroxy-5-azaspiro[2.5]octan-8-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione-3-d; and

3-(5-((S)-5-(4-chlorobenzyl)-8-hydroxy-5-azaspiro[2.5]octan-8-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione-3-d;

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 35: A pharmaceutical composition comprising a compound according to any one of Embodiments 1-34, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof; and a pharmaceutically acceptable carrier or excipient.

Embodiment 36: The pharmaceutical composition according to Embodiment 35, further comprising at least one additional pharmaceutical agent.

Embodiment 37: The pharmaceutical composition according to Embodiment 35 or 36 for use in the treatment of a disease or disorder that is affected by the reduction of HIF-1β levels.

Embodiment 38: A method of degrading HIF-1β, comprising administering to a patient in need thereof an effective amount of a compound according to any one of Embodiments 1-34, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 39: A method of modulating HIF-1β levels comprising administering to a patient in need thereof an effective amount of a compound according to any one of Embodiments 1-34, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 40: An *in vitro* method of reducing the proliferation of a cell, comprising contacting the cell with an effective amount of a compound according to any one of Embodiments 1-34, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 41: A method of treating a disease or disorder that is affected by the modulation of HIF-1β levels, comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of Embodiments 1-34, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 42: The method according to Embodiment 41, wherein the disease or disorder is selected from cancer, von Hippel-Lindau (VHL) disease. iron overload disorders, cardiovascular diseases, pulmonary arterial hypertension (PAH), autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, metabolic diseases, and allergic and genetic diseases.

Embodiment 43: The method according to Embodiments 41 and 42, wherein the disease or disorder is selected renal cell carcinoma (RCC), von Hippel-Lindau disease (VHL), pulmonary arterial hypertension (PAH), glioblastoma, colitis, Crohn's disease, ulcerative colitis, T cell leukemia or T cell lymphoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), melanoma,

triple-negative breast cancer (TNBC), nasopharyngeal cancer (NPC), microsatellite stable colorectal cancer (mssCRC), thymoma, carcinoid, gastrointestinal stromal tumor (GIST), myeloid leukemia, and coronary heart disease.

Embodiment 44: A method of treating cancer, comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of Embodiments 1-34, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 45: The method according to Embodiment 44, wherein the cancer is VHL-deficient cancer.

Embodiment 46: The method according to Embodiment 44, wherein the cancer is selected from renal cell carcinoma (RCC), glioblastoma, T cell leukemia or T cell lymphoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), melanoma, triple-negative breast cancer (TNBC), nasopharyngeal cancer (NPC), microsatellite stable colorectal cancer (mssCRC), thymoma, carcinoid, gastrointestinal stromal tumor (GIST), and myeloid leukemia.

Embodiment 47: A method for reducing HIF-1β levels, comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of Embodiments 1-34, or a pharmaceutically acceptable salt thereof.

Embodiment 48: A method of treating von Hippel-Lindau (VHL) disease, comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of Embodiments 1-34, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 49: A method of treating a neoplastic condition, comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of Embodiments 1-34, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 50: A method of treating renal cell carcinoma (RCC), comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of Embodiments 1-34, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 51: The method of Embodiment 50, wherein the renal cell carcinoma is clear cell renal cell carcinoma (ccRCC).

Embodiment 52: The method according to any one of Embodiments 38-51, wherein the administration is oral, parenteral, subcutaneous, by injection, or by infusion.

Embodiment 53: A compound according to any one of Embodiments 1-34, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in the treatment of a disease or disorder that is affected by the reduction of HIF-1β levels.

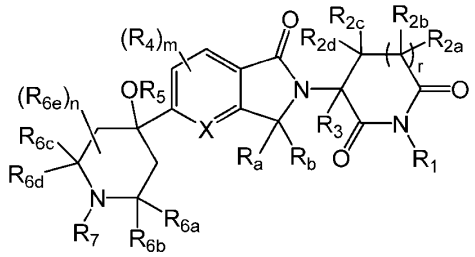
Embodiment 54: A compound according to any one of Embodiments 1-34, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in treating a disease or disorder associated with the reduction of HIF-1β levels.

Embodiment 55: Use of a compound according to any one of Embodiments 1-34, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for treating a disease or disorder that is affected by the reduction of HIF-1β levels.

Embodiment 56: Use of a compound according to any one of Embodiments 1-34, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the treatment of a disease or disorder associated with the reduction of HIF-1β levels.

Embodiment 57: The compound for use according to Embodiment 53 or 54 or the use according to Embodiment 55 or 56, wherein the disease or disorder is selected from cancer, von Hippel-Lindau (VHL) disease, iron overload disorders, cardiovascular diseases, pulmonary arterial hypertension (PAH), autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, metabolic diseases, and allergic and genetic diseases.

In another aspect, the present disclosure features a compound of Formula (III):



(III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein X is N or N(O); R_a and R_b are each independently H, D, or (C_1-C_6)alkyl; R_1 is H, D, -C(O)R_{11}, -$CH_2OC(O)R_{11}$, -$CH_2OC(O)NHR_{12}$, -$CH_2OC(O)OR_{12}$, -P(O)(OR_{12})$_2$, -$CH_2OP(O)(OR_{12})_2$, -$CH_2OP(O)(OH)OR_{12}$, -$CH_2OP(O)(R_{12})_2$, -$CH_2OC(O)CH_2NHC(O)CH_2NH_2$, -$CH_2OC(O)CH(R_{12'})NHR_{12'}$, -$CH_2OC(O)(CH_2)_qC(O)OR_{12'}$, or -$CH_2OC(O)$-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S); R_{2a}, R_{2b}, R_{2c}, and R_{2d} are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, halogen, or -OH, wherein two of R_{2a}, R_{2b}, R_{2c}, and R_{2d} may be taken together with the carbon atom to which they are

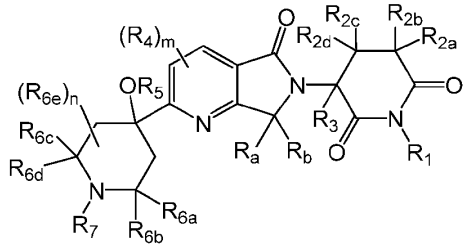
attached form a (C_3-C_7)carbocyclyl or (C_3-C_7)spirocarbocyclyl; R_3 is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, or halogen, wherein R_3 may be taken together with one of R_{2a}, R_{2b}, R_{2c}, and R_{2d} with the carbon atom to which they are attached to form a (C_3-C_7)carbocyclyl or (C_3-C_7)spirocarbocyclyl; each R_4 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, or halogen; R_5 is H, D, (C_2-C_6)alkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)aminoalkyl, (C_1-C_6)alkyl-O-(C_1-C_6)hydroxyalkyl, -C(O)R_{12}, -CH_2OC(O)R_{12}, -CH_2OC(O)N(R_{12})$_2$, -CH_2OC(O)$_2R_{12}$, -P(O)(OR_{12})$_2$, -CH_2OP(O)(OH)OR_{12}, or -CH_2OP(O)(R_{12})$_2$; R_{6a}, R_{6b}, R_{6c}, and R_{6d} are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy,, or (C_3-C_7)carbocyclyl; or two of R_{6a}, R_{6b}, R_{6c}, and R_{6d} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl, (C_3-C_7)spirocarbocyclyl, 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl, heterocyclyl, and spiroheterocyclyl are optionally substituted with one or more R_{10}; each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, -(C_1-C_6)alkylene-O-(C_1-C_6)alkyl, (C_6-C_{10})aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one or more R_{13}, the aryl and heteroaryl are optionally substituted with one or more R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{23}; or two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)carbocyclyl, (C_3-C_7)spirocarbocyclyl, a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl, heterocyclyl, and spiroheterocyclyl are optionally substituted with one or more R_{15}; or one R_{6e} is taken together with any one of R_{6a}, R_{6b}, R_{6c}, and R_{6d} and the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{15}; R_7 is (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_3-C_7)carbocyclyl, wherein alkyl, haloalkyl, hydroxyalkyl, halohydroxyalkyl, and carbocyclyl are optionally substituted with one or more substituents independently selected from R_{21}, D, (C_1-C_6)alkoxy, -SF_5, -SR_{14a}, -$NR_{14}R_{14'}$,-C(O)$NR_{29}R_{30}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one or more

$R_{8'}$; R_8 and $R_{8'}$ are each independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -C(O)$NR_{29}R_{30}$, -C(O)OR_{29}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more substituents selected from (C_1-C_6)alkyl, (C_3-C_7)carbocyclyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -C(O)$NR_{34}R_{35}$, -C(O)R_{34}, -C(O)OR_{34}, -SF_5, -SR_{37}, and -CN; or two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R_{10}; two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{10}; or two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{10}; or two $R_{8'}$ when on the same carbon atom form C=(O); R_9 is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, or -CN; R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN; R_{12} is independently at each occurrence H, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN; $R_{12'}$ is independently at each occurrence H or (C_1-C_6)alkyl; each R_{13} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -

$C(O)OR_{15'}$, $-C(O)R_{15}$, or $-C(O)NR_{15'}R_{15'}$; R_{14} and $R_{14'}$ are each independently at each occurrence H or (C_1-C_6)alkyl; R_{14a} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{15} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; $R_{15'}$ is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, $-NR_{17}R_{17'}$, -CN,(C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein carbocyclyl and heterocyclyl are optionally substituted with one or more R_{22} and the aryl and heteroaryl are optionally substituted with one or more R_{23}; R_{17} and $R_{17'}$ are each independently at each occurrence H or (C_1-C_6)alkyl; each R_{18} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{20}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{18}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{21}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{19} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; R_{20} and R_{21} are each independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; each R_{22} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{24}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{22} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; each R_{23} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{25}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; R_{24}, R_{25} and R_{26} are each independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{27} and R_{28} are each independently at each occurrence H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_3-C_7)carbocyclyl, $-C(O)R_{31}$, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl

or heteroaryl can be substituted with one or more R_{17}; R_{29}, R_{30}, and R_{31} are each independently at each occurrence H or (C_1-C_6)alkyl; R_{32} and R_{33} are each independently at each occurrence H, (C_1-C_6)alkyl, or -C(O)R_{36}; R_{34}, R_{35}, and R_{36} are each independently at each occurrence H or (C_1-C_6)alkyl; R_{37} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; q is 1, 2, or 3; m is 0, 1 or 2; n is 0, 1, 2, 3 or 4; r is 0 or 1.

In some embodiments, the compound of Formula (III) is a compound of Formula (III'):



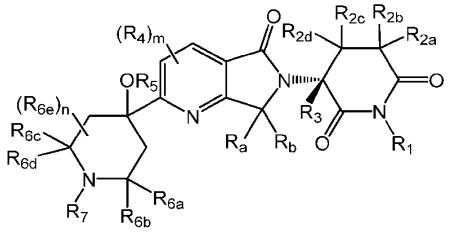
(III'), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R_a and R_b are each independently H or D; R_1 is H, D, -C(O)R_{11}, -$CH_2OC(O)R_{11}$, -$CH_2OC(O)NHR_{12}$, -$CH_2OC(O)OR_{12}$, -P(O)(OR_{12})$_2$, -$CH_2OP(O)(OR_{12})_2$, -$CH_2OP(O)(OH)OR_{12}$, -$CH_2OP(O)(R_{12})_2$, -$CH_2OC(O)CH_2NHC(O)CH_2NH_2$, -$CH_2OC(O)CH(R_{12'})NHR_{12'}$, -$CH_2OC(O)(CH_2)_qC(O)OR_{12'}$, or -$CH_2OC(O)$-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S); R_{2a}, R_{2b}, R_{2c}, and R_{2d} are each independently H or D; R_3 is H, D, (C_1-C_3)alkyl, or (C_1-C_3)deuteroalkyl; each R_4 is independently at each occurrence D or halogen; R_5 is H, D, -C(O)R_{11}, -$CH_2OC(O)R_{11}$, -$CH_2OC(O)NHR_{12}$, -$CH_2OC(O)OR_{12}$, -P(O)(OR_{12})$_2$, -$CH_2OP(O)(OH)OR_{12}$, or -$CH_2OP(O)(R_{12})_2$; R_{6a}, R_{6b}, R_{6c}, and R_{6d} are each independently H, D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl; each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10})aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one or more R_{16}, the aryl and heteroaryl are optionally substituted with one or more R_{18}, and the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{19}; or two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one or more R_{13}; R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{14a}, -$NR_{14}R_{14'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or

more R_8 and the carbocyclyl, and heterocyclyl are optionally substituted with one or more $R_{8'}$; R_8 and $R_{8'}$ are each independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -$C(O)NR_{29}R_{30}$, -$C(O)OR_{29}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -$C(O)NR_{34}R_{35}$, -$C(O)R_{34}$, -$C(O)OR_{34}$, -SF_5, -SR_{37}, and -CN; or two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R_{10}; two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{10}; or two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{10}; or two $R_{8'}$ when on the same carbon atom form C=(O); R_9 is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, or -CN; R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN; R_{12} is independently at each occurrence H, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN; $R_{12'}$ is independently at each occurrence H or (C_1-C_6)alkyl; each R_{13} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-

C_6)hydroxyalkyl, halogen, -C(O)$OR_{15'}$, -C(O)R_{15}, or -C(O)$NR_{15'}R_{15'}$; R_{14} and $R_{14'}$ are each independently at each occurrence H or (C_1-C_6)alkyl; R_{14a} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{15} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; $R_{15'}$ is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{17}R_{17'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein carbocyclyl and heterocyclyl are optionally substituted with one or more R_{22} and the aryl and heteroaryl are optionally substituted with one or more R_{23}; R_{17} and $R_{17'}$ are each independently at each occurrence H or (C_1-C_6)alkyl; each R_{18} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{20}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{18}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{21}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{19} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; R_{20} and R_{21} are each independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; each R_{22} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or two R_{22} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; each R_{23} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; R_{24}, R_{25} and R_{26} are each independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{27} and R_{28} are each independently at each occurrence H, (C_1-C_6)alkyl, or -C(O)R_{31}; R_{29}, R_{30}, and R_{31} are each independently at each occurrence H or (C_1-C_6)alkyl; R_{32} and R_{33} are each independently at each occurrence H, (C_1-C_6)alkyl, or -C(O)R_{36}; R_{34}, R_{35}, and R_{36} are each independently at each occurrence

H or (C_1-C_6)alkyl; R_{37} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; q is 1, 2, or 3; m is 0, 1 or 2; and n is 0, 1, 2, 3 or 4.

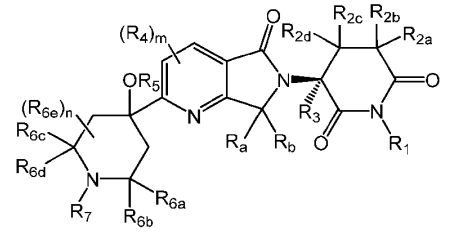
In one embodiment, the compounds of Formula (III) have the structure of Formula (IIIa):



(IIIa),

or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

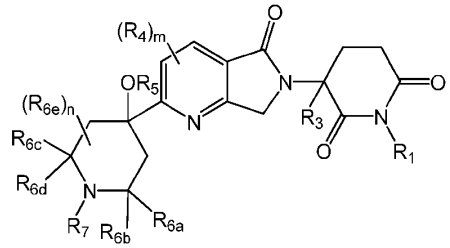
In another embodiment, the compounds of Formula (I) have the structure of Formula (IIIb):



(IIIb),

or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

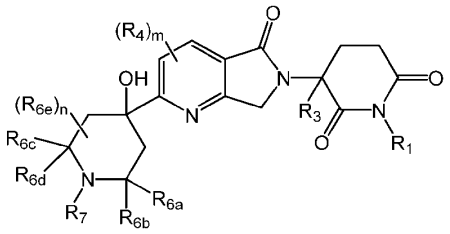
In another embodiment, the compounds of Formula (I) have the structure of Formula (IIIc):



(IIIc),

or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

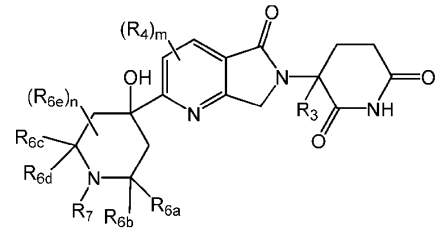
In another embodiment, the compounds of Formula (I) have the structure of Formula (IIId):



(IIId),

or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

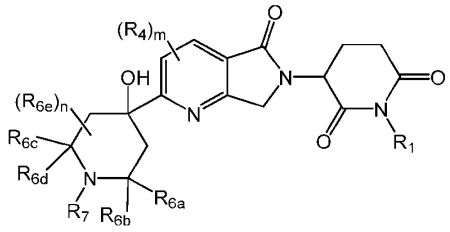
In another embodiment, the compounds of Formula (I) have the structure of Formula (IIIe):



(IIIe),

or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

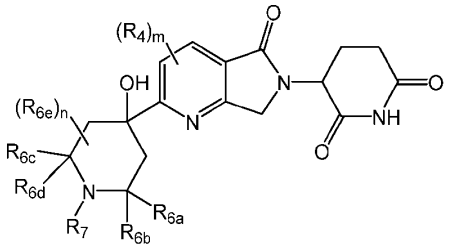
In another embodiment, the compounds of Formula (I) have the structure of Formula (IIIf):



(IIIf),

or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

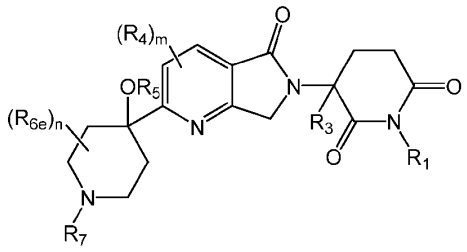
In another embodiment, the compounds of Formula (I) have the structure of Formula (IIIg):



(IIIg),

or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

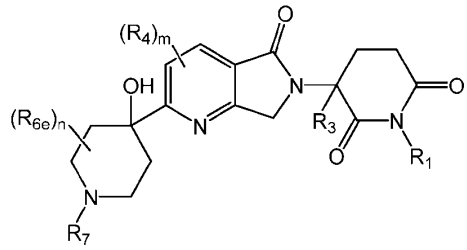
In another embodiment, the compounds of Formula (I) have the structure of Formula (IIIh):



(IIIh),

or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

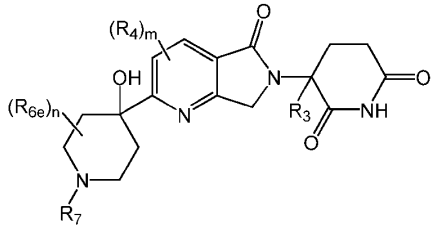
In another embodiment, the compounds of Formula (I) have the structure of Formula (IIIi):



(IIIi),

or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

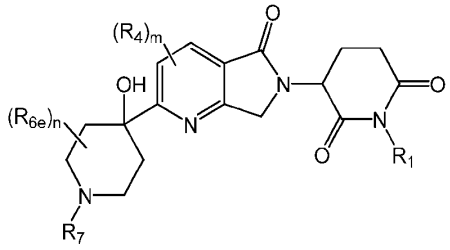
In another embodiment, the compounds of Formula (I) have the structure of Formula (IIIj):



(IIIj),

or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

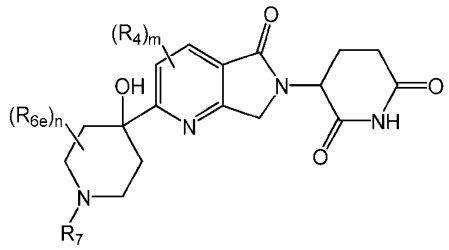
In another embodiment, the compounds of Formula (I) have the structure of Formula (IIIk):



(IIIk),

or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

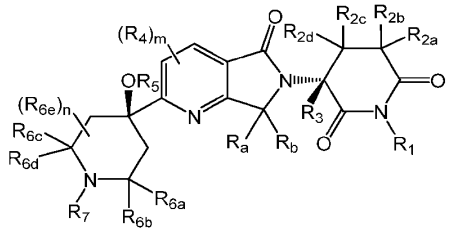
In another embodiment, the compounds of Formula (I) have the structure of Formula (IIII):



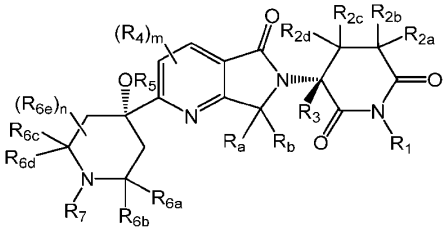
(IIII),

or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (IIIm):

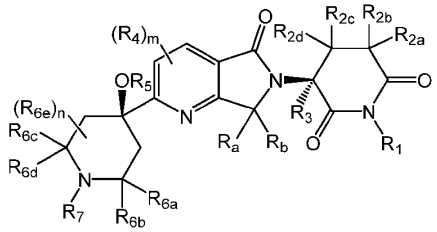


(IIIm), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (IIIo):



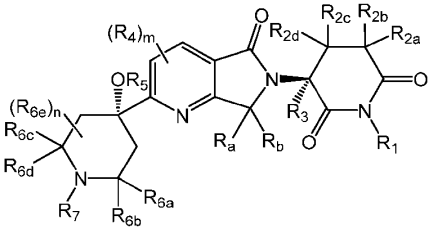
(IIIo), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (IIIp):



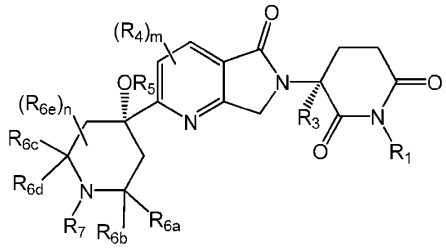
(IIIp), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have

the structure of Formula (IIIq):

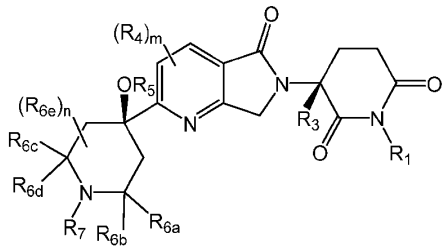


(IIIq), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (IIIr):

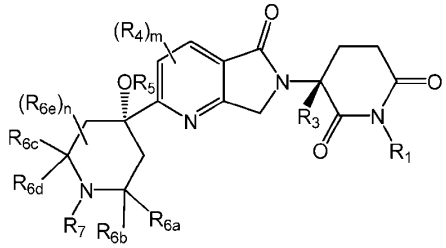


(IIIr), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (IIIu):



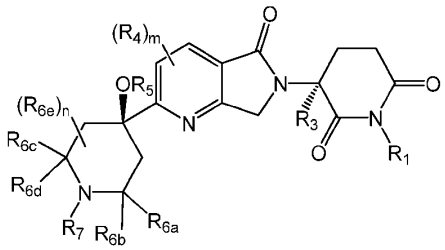
(IIIu), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (IIIv):



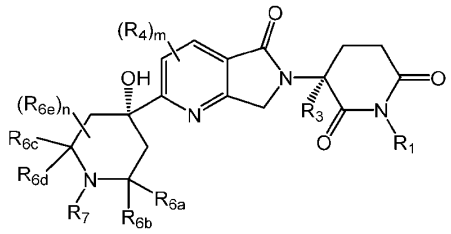
(IIIv), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have

the structure of Formula (IIIw):



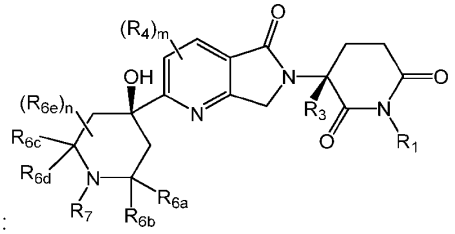
(IIIw), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (IIIx):



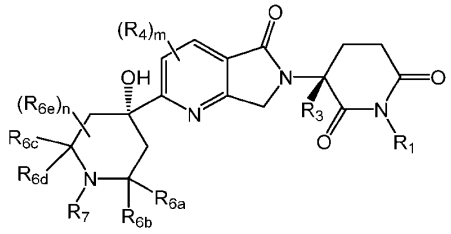
(IIIx), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have

the structure of Formula (IIIy):



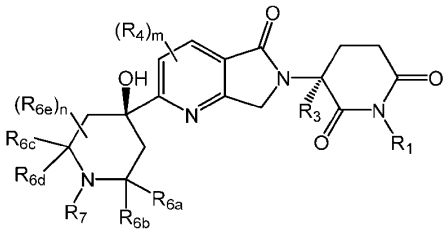
(IIIy), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (IIIz):



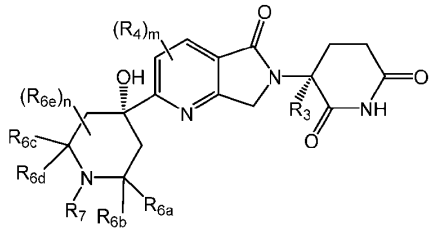
(IIIz), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have

the structure of Formula (IIIaa):

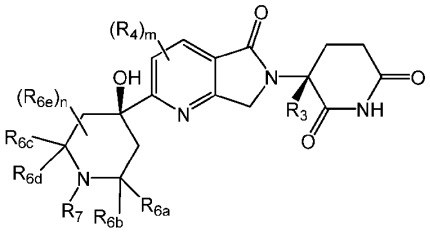


(IIIaa), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (Ibb):



(IIIbb), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (IIIcc):



In some embodiments of the formulae above (*e.g.*, Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), Formula (Iac), Formula (Iad), Formula (Iae), Formula (Iaf), Formula (Iag), Formula (Iah), Formula (Iai), Formula (Iaj), Formula (Iak), Formula (Ial), Formula (Iam), Formula (Iao), and/or Formula (Iap)), wherein:

R_a and R_b are each independently H or D;

R_1 is H, D, $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OR_{12})_2$,

$-CH_2OP(O)(OH)OR_{12}$, $-CH_2OP(O)(R_{12})_2$, $-CH_2OC(O)CH_2NHC(O)CH_2NH_2$, $-CH_2OC(O)CH(R_{12'})NHR_{12'}$, $-CH_2OC(O)(CH_2)_qC(O)OR_{12'}$, or $-CH_2OC(O)$-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S);

R_{2a}, R_{2b}, R_{2c}, and R_{2d} are each independently H or D;

R_3 is H, D, $(C_1$-$C_3)$alkyl, or $(C_1$-$C_3)$deuteroalkyl;

each R_4 is independently at each occurrence D or halogen;

R_5 is H, D, $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$;

R_{6a}, R_{6b}, R_{6c}, and R_{6d} are each independently H, D, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl;

each R_{6e} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, $(C_1$-$C_6)$hydroxyalkyl, -CN, -OH, -O-$(C_1$-$C_6)$hydroxyalkyl, $(C_6$-$C_{10})$aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to four R_{16}, the aryl and heteroaryl are optionally substituted with one to four R_{18}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}; or

two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a $(C_3$-$C_7)$spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one to four R_{13};

R_7 is $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$halohydroxyalkyl, or $(C_1$-$C_6)$alkyl optionally substituted with one to four substituents independently selected from D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{14a}$, $-NR_{14}R_{14'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$;

R_8 and $R_{8'}$ are each independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{27}R_{28}$, $-SF_5$, $-SR_9$, -CN, $-C(O)NR_{29}R_{30}$, $-C(O)OR_{29}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from

O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -$C(O)NR_{34}R_{35}$, -$C(O)R_{34}$, -$C(O)OR_{34}$, -SF_5, -SR_{37}, and -CN; or

two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four R_{10};

two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_{10}; or

two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{10}; or

two $R_{8'}$ when on the same carbon atom form C=(O);

R_9 is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, or -CN;

R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN;

R_{12} is independently at each occurrence H, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN;

$R_{12'}$ is independently at each occurrence H or (C_1-C_6)alkyl;

each R_{13} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -$C(O)OR_{15'}$, -$C(O)R_{15}$, or -$C(O)NR_{15'}R_{15'}$;

R_{14} and $R_{14'}$ are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{14a} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{15} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

$R_{15'}$ is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{17}R_{17'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22} and the aryl and heteroaryl are optionally substituted with one to four R_{23};

R_{17} and $R_{17'}$ are each independently at each occurrence H or (C_1-C_6)alkyl;

each R_{18} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{20}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{18}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{21}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{19} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

R_{20} and R_{21} are each independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

each R_{22} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{22} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{23} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

R_{24}, R_{25} and R_{26} are each independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{27} and R_{28} are each independently at each occurrence H, (C_1-C_6)alkyl, or -C(O)R_{31};

R_{29}, R_{30}, and R_{31} are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{32} and R_{33} are each independently at each occurrence H, (C_1-C_6)alkyl, or -C(O)R_{36};

R_{34}, R_{35}, and R_{36} are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{37} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

q is 1, 2, or 3;

m is 0, 1, or 2; and

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

In some embodiments of the formulae above, R_a is H or D. In another embodiment, R_a is D. In yet another embodiment, R_a is H.

In some embodiments of the formulae above, R_b is H or D. In another embodiment, R_b is D. In yet another embodiment, R_b is H.

In some embodiments of the formulae above, R_1 is H, D, -C(O)R_{11}, -CH_2OC(O)R_{11}, -CH_2OC(O)NHR_{12}, -CH_2OC(O)OR_{12}, -P(O)(OR_{12})$_2$, -CH_2OP(O)(OR_{12})$_2$, -CH_2OP(O)(OH)OR_{12}, -CH_2OP(O)(R_{12})$_2$, -CH_2OC(O)CH_2NHC(O)CH_2NH_2, -CH_2OC(O)CH($R_{12'}$)NH$R_{12'}$, -CH_2OC(O)(CH_2)$_q$C(O)O$R_{12'}$, or -CH_2OC(O)-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S). In another embodiment, R_1 is H, D, -C(O)R_{11}, -CH_2OC(O)R_{11}, -CH_2OC(O)NHR_{12}, -CH_2OC(O)OR_{12}, -P(O)(OR_{12})$_2$, -CH_2OP(O)(OR_{12})$_2$, -CH_2OP(O)(OH)OR_{12}, or -CH_2OP(O)(R_{12})$_2$. In yet another embodiment, R_1 is H, D, -CH_2OC(O)CH_2NHC(O)CH_2NH_2, -CH_2OC(O)CH($R_{12'}$)NH$R_{12'}$, -CH_2OC(O)(CH_2)$_q$C(O)O$R_{12'}$, or -CH_2OC(O)-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S).

In some embodiments of the formulae above, R_1 is -C(O)R_{11}, -CH_2OC(O)R_{11}, -CH_2OC(O)NHR_{12}, -CH_2OC(O)OR_{12}, -P(O)(OR_{12})$_2$, -CH_2OP(O)(OR_{12})$_2$, -CH_2OP(O)(OH)OR_{12}, -CH_2OP(O)(R_{12})$_2$, -CH_2OC(O)CH_2NHC(O)CH_2NH_2, -CH_2OC(O)CH($R_{12'}$)NH$R_{12'}$, -CH_2OC(O)(CH_2)$_q$C(O)O$R_{12'}$, or -CH_2OC(O)-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S). In yet another embodiment, R_1 is -C(O)R_{11}, -CH_2OC(O)R_{11}, -CH_2OC(O)NHR_{12}, -CH_2OC(O)OR_{12}, -P(O)(OR_{12})$_2$, -CH_2OP(O)(OR_{12})$_2$, -CH_2OP(O)(OH)OR_{12}, or -CH_2OP(O)(R_{12})$_2$, In another embodiment, R_1 is -CH_2OC(O)CH_2NHC(O)CH_2NH_2, -CH_2OC(O)CH($R_{12'}$)NH$R_{12'}$, -CH_2OC(O)(CH_2)$_q$C(O)O$R_{12'}$, or -CH_2OC(O)-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S). In another embodiment, R_1 is H or D. In yet another embodiment, R_1 is D. In another embodiment, R_1 is H.

In some embodiments of the formulae above, R_{2a} is H or D. In another embodiment, R_{2a} is D. In yet another embodiment, R_{2a} is H.

In some embodiments of the formulae above, R_{2b} is H or D. In another embodiment, R_{2b} is D. In yet another embodiment, R_{2b} is H.

In some embodiments of the formulae above, R_{2c} is H or D. In another embodiment, R_{2c} is D. In yet another embodiment, R_{2c} is H.

In some embodiments of the formulae above, R_{2d} is H or D. In another embodiment, R_{2d} is D. In yet another embodiment, R_{2d} is H.

In some embodiments of the formulae above, R_3 is H, D, $(C_1$-$C_3)$alkyl, or $(C_1$-$C_3)$deuteroalkyl. In another embodiment, R_3 is D, $(C_1$-$C_3)$alkyl, or $(C_1$-$C_3)$deuteroalkyl. In yet another embodiment, R_3 is H, $(C_1$-$C_3)$alkyl, or $(C_1$-$C_3)$deuteroalkyl. In another embodiment, R_3 is H, D, or $(C_1$-$C_3)$alkyl. In yet another embodiment, R_3 is H, D, or $(C_1$-$C_3)$deuteroalkyl. In another embodiment, R_3 is $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$deuteroalkyl. In another embodiment, R_3 is D or $(C_1$-$C_3)$deuteroalkyl. In another embodiment, R_3 is H or $(C_1$-$C_3)$deuteroalkyl. In another embodiment, R_3 is D or $(C_1$-$C_3)$alkyl. In another embodiment, R_3 is H or $(C_1$-$C_3)$alkyl. In another embodiment, R_3 is H or D. In yet another embodiment, R_3 is D. In another embodiment, R_3 is H.

In some embodiments of the formulae above, R_4 is halogen. In another embodiment, R_4 is D.

In some embodiments of the formulae above, R_5 is H, D, $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In another embodiment, R_5 is H, D, $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, or $-CH_2OP(O)(OH)OR_{12}$. In yet another embodiment, R_5 is H, D, $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, or $-CH_2OP(O)(R_{12})_2$. In another embodiment, R_5 is H, D, $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In yet another embodiment, R_5 is H, D, $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In another embodiment, R_5 is H, D, $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In yet another embodiment, R_5 is H, D, $-C(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In another embodiment, R_5 is H, D, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In yet another embodiment, R_5 is H, $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In another embodiment, R_5 is D, $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In yet another embodiment, R_5 is H, D, $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, or $-CH_2OC(O)OR_{12}$. In another embodiment, R_5 is H, D, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In yet another embodiment, R_5 is $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$. In another embodiment, R_5 is H or D. In yet another embodiment, R_5 is D. In another embodiment, R_5 is H.

In some embodiments of the formulae above, R_{6a} is H, D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{6a} is H, D, (C_1-C_2)alkyl, or (C_1-C_2)deuteroalkyl. In yet another embodiment, R_{6a} is H, D, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{6a} is H, D, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6a} is H, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{6a} is D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6a} is H, D, or (C_1-C_2)alkyl. In another embodiment, R_{6a} is H, D, or (C_1-C_2)deuteroalkyl. In yet another embodiment, R_{6a} is H, D, or (C_1-C_2)haloalkyl. In another embodiment, R_{6a} is H, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6a} is D, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6a} is (C_1-C_2)alkyl or (C_1-C_2)haloalkyl. In another embodiment, R_{6a} is H or D. In yet another embodiment, R_{6a} is D. In another embodiment, R_{6a} is H.

In some embodiments of the formulae above, R_{6b} is H, D, (C_1-C_2)alkyl, or (C_1-C_2)deuteroalkyl. In yet another embodiment, R_{6b} is H, D, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{6b} is H, D, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6b} is H, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{6b} is D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6b} is H, D, or (C_1-C_2)alkyl. In another embodiment, R_{6b} is H, D, or (C_1-C_2)deuteroalkyl. In yet another embodiment, R_{6b} is H, D, or (C_1-C_2)haloalkyl. In another embodiment, R_{6b} is H, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6b} is D, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6b} is (C_1-C_2)alkyl or (C_1-C_2)haloalkyl. In another embodiment, R_{6b} is H or D. In yet another embodiment, R_{6b} is D. In another embodiment, R_{6b} is H.

In some embodiments of the formulae above, R_{6c} is H, D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{6c} is H, D, (C_1-C_2)alkyl, or (C_1-C_2)deuteroalkyl. In yet another embodiment, R_{6c} is H, D, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{6c} is H, D, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6c} is H, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{6c} is D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6c} is H, D, or (C_1-C_2)alkyl. In another embodiment, R_{6c} is H, D, or (C_1-C_2)deuteroalkyl. In yet another embodiment, R_{6c} is H, D, or (C_1-C_2)haloalkyl. In another embodiment, R_{6c} is H, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6c} is D, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6c} is (C_1-C_2)alkyl or (C_1-C_2)haloalkyl. In another embodiment, R_{6c} is H or D. In yet another embodiment, R_{6c} is D. In another embodiment, R_{6c} is H.

In some embodiments of the formulae above, R_{6d} is H, D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{6d} is H, D, (C_1-C_2)alkyl, or (C_1-C_2)deuteroalkyl. In yet another embodiment, R_{6d} is H, D, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{6d} is H, D, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6d} is H, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{6d} is D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl,

or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6d} is H, D, or (C_1-C_2)alkyl. In another embodiment, R_{6d} is H, D, or (C_1-C_2)deuteroalkyl. In yet another embodiment, R_{6d} is H, D, or (C_1-C_2)haloalkyl. In another embodiment, R_{6d} is H, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6d} is D, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{6d} is (C_1-C_2)alkyl or (C_1-C_2)haloalkyl. In another embodiment, R_{6d} is H or D. In yet another embodiment, R_{6d} is D. In another embodiment, R_{6d} is H.

In some embodiments of the formulae above, each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_{16}, the aryl and heteroaryl are optionally substituted with one to six R_{18}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}. In another embodiment, each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or (C_3-C_7)carbocyclyl, wherein the alkyl is optionally substituted with one to six R_{16}, the aryl and heteroaryl are optionally substituted with one to six R_{18}, and the carbocyclyl is optionally substituted with one to four R_{19}.

In another embodiment, each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to four R_{16}, the aryl and heteroaryl are optionally substituted with one to six R_{18}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}. In another embodiment, each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_{16}, the aryl and heteroaryl are optionally substituted with one to six R_{18}, and the heterocyclyl is optionally substituted with one to four R_{19}.

In another embodiment, each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted

with one to four R_{16}, the aryl is optionally substituted with one to six R_{18}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}. In yet another embodiment, each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_{16}, the heteroaryl is optionally substituted with one to six R_{18}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}.

In another embodiment, each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_{16}, the aryl and heteroaryl are optionally substituted with one to six R_{18}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}. In yet another embodiment, each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_{16}, the aryl and heteroaryl are optionally substituted with one to six R_{18}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}.

In another embodiment, each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_{16}, the aryl and heteroaryl are optionally substituted with one to six R_{18}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}. In yet another embodiment, each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_{16}, the aryl and heteroaryl are optionally substituted with one to six R_{18}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}.

In another embodiment, each R_{6e} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, -CN, -OH, -O-$(C_1$-$C_6)$hydroxyalkyl, $(C_6$-$C_{10})$ aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_{16}, the aryl and heteroaryl are optionally substituted with one to six R_{18}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}. In yet another embodiment, each R_{6e} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, halogen, $(C_1$-$C_6)$hydroxyalkyl, -CN, -OH, -O-$(C_1$-$C_6)$hydroxyalkyl, $(C_6$-$C_{10})$ aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_{16}, the aryl and heteroaryl are optionally substituted with one to six R_{18}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}.

In another embodiment, each R_{6e} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$haloalkoxy, halogen, $(C_1$-$C_6)$hydroxyalkyl, -CN, -OH, -O-$(C_1$-$C_6)$hydroxyalkyl, $(C_6$-$C_{10})$ aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_{16}, the aryl and heteroaryl are optionally substituted with one to six R_{18}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}. In yet another embodiment, each R_{6e} is independently at each occurrence D, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, $(C_1$-$C_6)$hydroxyalkyl, -CN, -OH, -O-$(C_1$-$C_6)$hydroxyalkyl, $(C_6$-$C_{10})$ aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one six R_{16}, the aryl and heteroaryl are optionally substituted with one to six R_{18}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}. In another embodiment, each R_{6e} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, $(C_1$-$C_6)$hydroxyalkyl, -CN, -OH, -O-$(C_1$-$C_6)$hydroxyalkyl, $(C_6$-$C_{10})$ aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one six R_{16}, the aryl and heteroaryl are optionally substituted with one to six R_{18}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}.

In another embodiment, each R_{6e} is independently at each occurrence D, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, $(C_1$-$C_6)$hydroxyalkyl, -CN, -OH, -O-$(C_1$-

C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the aryl and heteroaryl are optionally substituted with one to four R_{18}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}. In yet another embodiment, each R_{6e} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one to six R_{16}, the aryl and heteroaryl are optionally substituted with one to six R_{18}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}.

In another embodiment, each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, wherein the alkyl is optionally substituted with one to six R_{16}. In another embodiment, each R_{6e} is independently at each occurrence (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the aryl and heteroaryl are optionally substituted with one to six R_{18}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{19}.

In another embodiment, each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, halogen, (C_1-C_6)hydroxyalkyl, -OH, (C_6-C_{10}) aryl, or (C_3-C_7)carbocyclyl, wherein the alkyl is optionally substituted with one to six R_{16}, the aryl is optionally substituted with one to six R_{18}, and the carbocyclyl is optionally substituted with one to four R_{19}. In yet another embodiment, each R_{6e} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, halogen, (C_1-C_6)hydroxyalkyl, -OH, (C_6-C_{10}) aryl, or (C_3-C_7)carbocyclyl, wherein the alkyl is optionally substituted with one to six R_{16}, the aryl is optionally substituted with one to six R_{18}, and the carbocyclyl is optionally substituted with one to four R_{19}.

In some embodiments of the formulae above, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one to four R_{13}. In another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are

substituted with one to four R_{13}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl is optionally substituted with one to four R_{13}. In another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spiroheterocyclyl is optionally substituted with one to four R_{13}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 6-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one to four R_{13}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 6-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are substituted with one to four R_{13}.

In another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- or 5-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one to four R_{13}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- or 5-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are substituted with one to four R_{13}.

In another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 5- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one to four R_{13}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 5- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are substituted with one to four R_{13}.

In another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 5- or 6-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and

spiroheterocyclyl are optionally substituted with one to four R_{13}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 5- or 6-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are substituted with one to four R_{13}.

In another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 6- or 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one to four R_{13}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 6- or 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are substituted with one to four R_{13}.

In another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl, wherein the spirocarbocyclyl is optionally substituted with one to four R_{13}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl, wherein the spirocarbocyclyl is substituted with one to four R_{13}. In another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl.

In another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a 5- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spiroheterocyclyl is optionally substituted with one to four R_{13}. In yet another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a 5- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spiroheterocyclyl is substituted with one to four R_{13}. In another embodiment, two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a 5- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of the formulae above, R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{14a}, -$NR_{14}R_{14'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{14a}, -$NR_{14}R_{14'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4

heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In another embodiment, R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{14a}, -$NR_{14}R_{14'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_7 is (C_1-C_6)haloalkyl, or (C_1-C_6)hydroxyalkyl. In another embodiment, R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{14a}, -$NR_{14}R_{14'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In another embodiment, R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{14a}, -$NR_{14}R_{14'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In yet another embodiment, R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, or (C_1-C_6)halohydroxyalkyl. In yet another embodiment, R_7 is (C_1-C_6)haloalkyl, or (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl.

In another embodiment, R_7 is (C_1-C_6)haloalkyl or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{14a}, -$NR_{14}R_{14'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_7 is (C_1-C_6)hydroxyalkyl or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{14a}, -$NR_{14}R_{14'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4

heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, R_7 is (C_1-C_6)halohydroxyalkyl or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{14a}, -$NR_{14}R_{14'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In another embodiment, R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, -SF_5, -SR_{14a}, -$NR_{14}R_{14'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkoxy, -SF_5, -SR_{14a}, -$NR_{14}R_{14'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SR_{14a}, -$NR_{14}R_{14'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In another embodiment, R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -$NR_{14}R_{14'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy,

-SF_5, -SR_{14a}, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In another embodiment, R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{14a}, -$NR_{14}R_{14'}$, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heteroaryl is optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{14a}, -$NR_{14}R_{14'}$, phenyl, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heteroaryl is optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In another embodiment, R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{14a}, -$NR_{14}R_{14'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the heterocyclyl is optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{14a}, -$NR_{14}R_{14'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, and (C_3-C_7)carbocyclyl, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl is optionally substituted with one to four $R_{8'}$.

In another embodiment, R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, or (C_1-C_6)alkyl substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-

C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In another embodiment, R_7 is (C_1-C_6)haloalkyl or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_7 is (C_1-C_6)hydroxyalkyl or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_7 is (C_1-C_6)halohydroxyalkyl or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In some embodiments of the formulae above, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -C(O)$NR_{29}R_{30}$, -C(O)OR_{29}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -C(O)$NR_{34}R_{35}$, -C(O)R_{34}, -C(O)OR_{34}, -SF_5, -SR_{37}, and -CN. In another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -C(O)$NR_{29}R_{30}$, -C(O)OR_{29}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl

comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{32}R_{33}$, $-C(O)NR_{34}R_{35}$, $-C(O)R_{34}$, $-C(O)OR_{34}$, $-SF_5$, $-SR_{37}$, and -CN.

In another embodiment, R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{27}R_{28}$, $-SF_5$, $-SR_9$, -CN, $-C(O)NR_{29}R_{30}$, $-C(O)OR_{29}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{32}R_{33}$, $-C(O)NR_{34}R_{35}$, $-C(O)R_{34}$, $-C(O)OR_{34}$, $-SF_5$, $-SR_{37}$, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{27}R_{28}$, $-SF_5$, $-SR_9$, -CN, $-C(O)NR_{29}R_{30}$, $-C(O)OR_{29}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{32}R_{33}$, $-C(O)NR_{34}R_{35}$, $-C(O)R_{34}$, $-C(O)OR_{34}$, $-SF_5$, $-SR_{37}$, and -CN.

In another embodiment, R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{27}R_{28}$, $-SF_5$, $-SR_9$, -CN, $-C(O)NR_{29}R_{30}$, $-C(O)OR_{29}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{32}R_{33}$, $-C(O)NR_{34}R_{35}$, $-C(O)R_{34}$, $-C(O)OR_{34}$, $-SF_5$, $-SR_{37}$, and -CN. In

yet another embodiment, R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{27}R_{28}$, $-SF_5$, $-SR_9$, -CN, $-C(O)NR_{29}R_{30}$, $-C(O)OR_{29}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{32}R_{33}$, $-C(O)NR_{34}R_{35}$, $-C(O)R_{34}$, $-C(O)OR_{34}$, $-SF_5$, $-SR_{37}$, and -CN.

In another embodiment, R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{27}R_{28}$, $-SF_5$, $-SR_9$, -CN, $-C(O)NR_{29}R_{30}$, $-C(O)OR_{29}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{32}R_{33}$, $-C(O)NR_{34}R_{35}$, $-C(O)R_{34}$, $-C(O)OR_{34}$, $-SF_5$, $-SR_{37}$, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{27}R_{28}$, $-SF_5$, $-SR_9$, -CN, $-C(O)NR_{29}R_{30}$, $-C(O)OR_{29}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{32}R_{33}$, $-C(O)NR_{34}R_{35}$, $-C(O)R_{34}$, $-C(O)OR_{34}$, $-SF_5$, $-SR_{37}$, and -CN.

In another embodiment, R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{27}R_{28}$, $-SF_5$, $-SR_9$, -CN, $-C(O)NR_{29}R_{30}$, $-C(O)OR_{29}$, $(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -

O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{32}R_{33}$, $-C(O)NR_{34}R_{35}$, $-C(O)R_{34}$, $-C(O)OR_{34}$, $-SF_5$, $-SR_{37}$, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{27}R_{28}$, $-SF_5$, $-SR_9$, -CN, $-C(O)NR_{29}R_{30}$, $-C(O)OR_{29}$, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{32}R_{33}$, $-C(O)NR_{34}R_{35}$, $-C(O)R_{34}$, $-C(O)OR_{34}$, $-SF_5$, $-SR_{37}$, and -CN.

In another embodiment, R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{27}R_{28}$, $-SF_5$, $-SR_9$, -CN, $-C(O)NR_{29}R_{30}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{32}R_{33}$, $-C(O)NR_{34}R_{35}$, $-C(O)R_{34}$, $-C(O)OR_{34}$, $-SF_5$, $-SR_{37}$, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{27}R_{28}$, $-SF_5$, $-SR_9$, -CN, $-C(O)OR_{29}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted

with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -$C(O)NR_{34}R_{35}$, -$C(O)R_{34}$, -$C(O)OR_{34}$, -SF_5, -SR_{37}, and -CN.

In another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -$C(O)NR_{29}R_{30}$, -$C(O)OR_{29}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -$C(O)NR_{34}R_{35}$, -$C(O)R_{34}$, -$C(O)OR_{34}$, -SF_5, -SR_{37}, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -CN, -$C(O)NR_{29}R_{30}$, -$C(O)OR_{29}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -$C(O)NR_{34}R_{35}$, -$C(O)R_{34}$, -$C(O)OR_{34}$, -SF_5, -SR_{37}, and -CN.

In another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SR_9, -CN, -$C(O)NR_{29}R_{30}$, -$C(O)OR_{29}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -$C(O)NR_{34}R_{35}$, -$C(O)R_{34}$, -$C(O)OR_{34}$, -SF_5,

-SR_{37}, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -SF_5, -SR_9, -CN, -C(O)$NR_{29}R_{30}$, -C(O)OR_{29}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -C(O)$NR_{34}R_{35}$, -C(O)R_{34}, -C(O)OR_{34}, -SF_5, -SR_{37}, and -CN.

In another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -C(O)$NR_{29}R_{30}$, -C(O)OR_{29}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -C(O)$NR_{34}R_{35}$, -C(O)R_{34}, -C(O)OR_{34}, -SF_5, -SR_{37}, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -C(O)$NR_{29}R_{30}$, -C(O)OR_{29}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -C(O)$NR_{34}R_{35}$, -C(O)R_{34}, -C(O)OR_{34}, -SF_5, -SR_{37}, and -CN.

In another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9,

-CN, -C(O)$NR_{29}R_{30}$, -C(O)OR_{29}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -C(O)$NR_{34}R_{35}$, -C(O)R_{34}, -C(O)OR_{34}, -SF_5, -SR_{37}, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -C(O)$NR_{29}R_{30}$, -C(O)OR_{29}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -C(O)$NR_{34}R_{35}$, -C(O)R_{34}, -C(O)OR_{34}, -SF_5, -SR_{37}, and -CN.

In another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -C(O)$NR_{29}R_{30}$, -C(O)OR_{29}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -C(O)$NR_{34}R_{35}$, -C(O)R_{34}, -C(O)OR_{34}, -SF_5, -SR_{37}, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -C(O)$NR_{29}R_{30}$, -C(O)OR_{29}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms

selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{32}R_{33}$, $-C(O)NR_{34}R_{35}$, $-C(O)R_{34}$, $-C(O)OR_{34}$, $-SF_5$, $-SR_{37}$, and -CN.

In another embodiment, R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{27}R_{28}$, $-SF_5$, $-SR_9$, -CN, $-C(O)NR_{29}R_{30}$, $-C(O)OR_{29}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{32}R_{33}$, $-C(O)NR_{34}R_{35}$, $-C(O)R_{34}$, $-C(O)OR_{34}$, $-SF_5$, $-SR_{37}$, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{27}R_{28}$, $-SF_5$, $-SR_9$, -CN, $-C(O)NR_{29}R_{30}$, $-C(O)OR_{29}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{32}R_{33}$, $-C(O)NR_{34}R_{35}$, $-C(O)R_{34}$, $-C(O)OR_{34}$, $-SF_5$, $-SR_{37}$, and -CN.

In another embodiment, R_8 is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{27}R_{28}$, $-SF_5$, $-SR_9$, -CN, $-C(O)NR_{29}R_{30}$, $-C(O)OR_{29}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted

with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -$C(O)NR_{34}R_{35}$, -$C(O)R_{34}$, -$C(O)OR_{34}$, -SF_5, -SR_{37}, and -CN. In yet another embodiment, R_8 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -$C(O)NR_{29}R_{30}$, or -$C(O)OR_{29}$.

In another embodiment, R_8 is independently at each occurrence $(C_3$-$C_7)$carbocyclyl, -$O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -$C(O)NR_{34}R_{35}$, -$C(O)R_{34}$, -$C(O)OR_{34}$, -SF_5, -SR_{37}, and -CN.

In yet another embodiment, R_8 is independently at each occurrence $(C_3$-$C_7)$carbocyclyl, -$O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -$C(O)NR_{34}R_{35}$, -$C(O)R_{34}$, -$C(O)OR_{34}$, -SF_5, -SR_{37}, and -CN.

In some embodiments of the formulae above, $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -$C(O)NR_{29}R_{30}$, -$C(O)OR_{29}$, $(C_3$-$C_7)$carbocyclyl, -$O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -$C(O)NR_{34}R_{35}$, -$C(O)R_{34}$, -$C(O)OR_{34}$, -SF_5, -SR_{37}, and -CN. In another embodiment, $R_{8'}$ is independently at each occurrence D, $(C_1$-

C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -C(O)$NR_{29}R_{30}$, -C(O)OR_{29}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -C(O)$NR_{34}R_{35}$, -C(O)R_{34}, -C(O)OR_{34}, -SF_5, -SR_{37}, and -CN.

In another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -C(O)$NR_{29}R_{30}$, -C(O)OR_{29}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -C(O)$NR_{34}R_{35}$, -C(O)R_{34}, -C(O)OR_{34}, -SF_5, -SR_{37}, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -C(O)$NR_{29}R_{30}$, -C(O)OR_{29}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -C(O)$NR_{34}R_{35}$, -C(O)R_{34}, -C(O)OR_{34}, -SF_5, -SR_{37}, and -CN.

In another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -C(O)$NR_{29}R_{30}$, -C(O)OR_{29}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N,

NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{32}R_{33}$, $-C(O)NR_{34}R_{35}$, $-C(O)R_{34}$, $-C(O)OR_{34}$, $-SF_5$, $-SR_{37}$, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{27}R_{28}$, $-SF_5$, $-SR_9$, -CN, $-C(O)NR_{29}R_{30}$, $-C(O)OR_{29}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{32}R_{33}$, $-C(O)NR_{34}R_{35}$, $-C(O)R_{34}$, $-C(O)OR_{34}$, $-SF_5$, $-SR_{37}$, and -CN.

In another embodiment, $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{27}R_{28}$, $-SF_5$, $-SR_9$, -CN, $-C(O)NR_{29}R_{30}$, $-C(O)OR_{29}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{32}R_{33}$, $-C(O)NR_{34}R_{35}$, $-C(O)R_{34}$, $-C(O)OR_{34}$, $-SF_5$, $-SR_{37}$, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{27}R_{28}$, $-SF_5$, $-SR_9$, -CN, $-C(O)NR_{29}R_{30}$, $-C(O)OR_{29}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{32}R_{33}$, $-C(O)NR_{34}R_{35}$, $-C(O)R_{34}$, $-C(O)OR_{34}$, $-SF_5$, $-SR_{37}$, and -CN.

In another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -C(O)$NR_{29}R_{30}$, -C(O)OR_{29}, (C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -C(O)$NR_{34}R_{35}$, -C(O)R_{34}, -C(O)OR_{34}, -SF_5, -SR_{37}, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -C(O)$NR_{29}R_{30}$, -C(O)OR_{29}, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -C(O)$NR_{34}R_{35}$, -C(O)R_{34}, -C(O)OR_{34}, -SF_5, -SR_{37}, and -CN.

In another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -C(O)$NR_{29}R_{30}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -C(O)$NR_{34}R_{35}$, -C(O)R_{34}, -C(O)OR_{34}, -SF_5, -SR_{37}, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -C(O)OR_{29}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N,

NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{32}R_{33}$, $-C(O)NR_{34}R_{35}$, $-C(O)R_{34}$, $-C(O)OR_{34}$, $-SF_5$, $-SR_{37}$, and -CN.

In another embodiment, $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{27}R_{28}$, $-SF_5$, $-SR_9$, $-C(O)NR_{29}R_{30}$, $-C(O)OR_{29}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{32}R_{33}$, $-C(O)NR_{34}R_{35}$, $-C(O)R_{34}$, $-C(O)OR_{34}$, $-SF_5$, $-SR_{37}$, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{27}R_{28}$, $-SF_5$, -CN, $-C(O)NR_{29}R_{30}$, $-C(O)OR_{29}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{32}R_{33}$, $-C(O)NR_{34}R_{35}$, $-C(O)R_{34}$, $-C(O)OR_{34}$, $-SF_5$, $-SR_{37}$, and -CN.

In another embodiment, $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{27}R_{28}$, $-SR_9$, -CN, $-C(O)NR_{29}R_{30}$, $-C(O)OR_{29}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected

from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -$C(O)NR_{34}R_{35}$, -$C(O)R_{34}$, -$C(O)OR_{34}$, -SF_5, -SR_{37}, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -SF_5, -SR_9, -CN, -$C(O)NR_{29}R_{30}$, -$C(O)OR_{29}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -$C(O)NR_{34}R_{35}$, -$C(O)R_{34}$, -$C(O)OR_{34}$, -SF_5, -SR_{37}, and -CN.

In another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -$C(O)NR_{29}R_{30}$, -$C(O)OR_{29}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -$C(O)NR_{34}R_{35}$, -$C(O)R_{34}$, -$C(O)OR_{34}$, -SF_5, -SR_{37}, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -$C(O)NR_{29}R_{30}$, -$C(O)OR_{29}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-

C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -C(O)$NR_{34}R_{35}$, -C(O)R_{34}, -C(O)OR_{34}, -SF_5, -SR_{37}, and -CN.

In another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -C(O)$NR_{29}R_{30}$, -C(O)OR_{29}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -C(O)$NR_{34}R_{35}$, -C(O)R_{34}, -C(O)OR_{34}, -SF_5, -SR_{37}, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -C(O)$NR_{29}R_{30}$, -C(O)OR_{29}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -C(O)$NR_{34}R_{35}$, -C(O)R_{34}, -C(O)OR_{34}, -SF_5, -SR_{37}, and -CN.

In another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -C(O)$NR_{29}R_{30}$, -C(O)OR_{29}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -C(O)$NR_{34}R_{35}$, -C(O)R_{34}, -C(O)OR_{34}, -SF_5, -SR_{37}, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-

C_6)deuteroalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -C(O)$NR_{29}R_{30}$, -C(O)OR_{29}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -C(O)$NR_{34}R_{35}$, -C(O)R_{34}, -C(O)OR_{34}, -SF_5, -SR_{37}, and -CN.

In another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -C(O)$NR_{29}R_{30}$, -C(O)OR_{29}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -C(O)$NR_{34}R_{35}$, -C(O)R_{34}, -C(O)OR_{34}, -SF_5, -SR_{37}, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -C(O)$NR_{29}R_{30}$, -C(O)OR_{29}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -C(O)$NR_{34}R_{35}$, -C(O)R_{34}, -C(O)OR_{34}, -SF_5, -SR_{37}, and -CN.

In another embodiment, $R_{8'}$ is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -C(O)$NR_{29}R_{30}$, -C(O)OR_{29}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N,

NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{32}R_{33}$, $-C(O)NR_{34}R_{35}$, $-C(O)R_{34}$, $-C(O)OR_{34}$, $-SF_5$, $-SR_{37}$, and -CN. In yet another embodiment, $R_{8'}$ is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{27}R_{28}$, $-SF_5$, $-SR_9$, -CN, $-C(O)NR_{29}R_{30}$, or $-C(O)OR_{29}$.

In another embodiment, $R_{8'}$ is independently at each occurrence $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{32}R_{33}$, $-C(O)NR_{34}R_{35}$, $-C(O)R_{34}$, $-C(O)OR_{34}$, $-SF_5$, $-SR_{37}$, and -CN.

In yet another embodiment, $R_{8'}$ is independently at each occurrence $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are substituted with one to four substituents selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{32}R_{33}$, $-C(O)NR_{34}R_{35}$, $-C(O)R_{34}$, $-C(O)OR_{34}$, $-SF_5$, $-SR_{37}$, and -CN.

In some embodiments of the formulae above, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four R_{10}. In another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl

comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are substituted with one to four R_{10}. In another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or (C_3-C_7)carbocyclyl, wherein the phenyl, heteroaryl, and carbocyclyl are optionally substituted with one to four R_{10}.

In another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, and heterocyclyl are optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, carbocyclyl, and heterocyclyl are optionally substituted with one to four R_{10}. In another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one to four R_{10}.

In another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{10}. In another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or (C_3-C_7)carbocyclyl, wherein the phenyl and carbocyclyl are optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heteroaryl and heterocyclyl are optionally substituted with one to four R_{10}.

In another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, wherein the phenyl is optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heteroaryl is optionally substituted with one to four R_{10}. In another embodiment, two R_8, when on adjacent

atoms, together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two R_8, when on adjacent atoms, together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{10}.

In some embodiments of the formulae above, two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is optionally substituted with one to four R_{10} and the heteroaryl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one to four R_{10} and the heteroaryl is optionally substituted with one to four R_{10}.

In another embodiment, two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, wherein the phenyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heteroaryl is optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, wherein the phenyl is substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heteroaryl is substituted with one to four R_{10}.

In some embodiments of the formulae above, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl

or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}.

In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- or 5-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 5- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 6- or 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- or 5-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 5- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 6- or 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}.

In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- or 5-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 5- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms

selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 6- or 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}.

In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- or 5-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 5- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 6- or 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}.

In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_5)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_4)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_4-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}.

In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_5-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_6-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_5-C_6)carbocyclyl or 4- to 7-membered heterocyclyl

comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{10}.

In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_5)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_4)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_4-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}.

In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_5-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_6-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_5-C_6)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is substituted with one to four R_{10} and the heterocyclyl is optionally substituted with one to four R_{10}.

In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_5)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_4)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4

heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_4-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}.

In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_5-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_6-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_5-C_6)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl is optionally substituted with one to four R_{10} and the heterocyclyl is substituted with one to four R_{10}.

In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}.

In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_5)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_5)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_4)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_4)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}.

In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_4-C_7)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_4-C_7)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_5-C_7)carbocyclyl, wherein the carbocyclyl is optionally substituted with

one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_5-C_7)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}.

In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_6-C_7)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_6-C_7)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_4-C_6)carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a (C_4-C_6)carbocyclyl, wherein the carbocyclyl is substituted with one to four R_{10}.

In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a 5- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a 5- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is substituted with one to four R_{10}.

In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a 6- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a 6- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a 4- to 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a 4- to 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is substituted with one to four R_{10}.

In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a 4- to 5-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a 4- to 5-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is substituted with one to four R_{10}. In another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{10}. In yet another embodiment, two $R_{8'}$ together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is substituted with one to four R_{10}.

In some embodiments of the formulae above, two $R_{8'}$ when on the same carbon atom form C=(O).

In some embodiments of the formulae above, R_9 is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_9 is independently at each occurrence H, (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_9 is independently at each occurrence H or (C_1-C_6)alkyl. In another embodiment, R_9 is independently at each occurrence H or (C_1-C_6)haloalkyl. In yet another embodiment, R_9 is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_9 is independently at each occurrence (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_9 is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, R_9 is independently at each occurrence (C_1-C_3)alkyl. In another embodiment, R_9 is independently at each occurrence (C_1-C_6)haloalkyl. In another embodiment, R_9 is independently at each occurrence (C_1-C_3)haloalkyl. In another embodiment, R_9 is independently at each occurrence H.

In some embodiments of the formulae above, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{26}$, or -CN. In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, or $-SR_{26}$. In yet another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, or -CN. In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SR_{26}$, or -CN. In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-SF_5$, $-SR_{26}$, or -CN. In yet another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, $-NH_2$, $-SF_5$, $-SR_{26}$, or -CN. In another embodiment, R_{10} is

independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl,-OH, -NH_2, -SF_5, -SR_{26}, or -CN. In yet another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -NH_2, -SF_5, -SR_{26}, or -CN.

In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, or -CN. In yet another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, or -CN. In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, or -CN. In yet another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, or -CN. In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, or -CN. In yet another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, or -CN.

In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, or halogen. In yet another embodiment, R_{10} is independently at each occurrence halogen, -OH, -NH_2, -SF_5, -SR_{26}, or -CN. In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, or -CN. In yet another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, or -CN. In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, or -CN. In yet another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, halogen, or -CN. In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, halogen, or -CN.

In another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, or halogen. In yet another embodiment, R_{10} is independently at each occurrence halogen, -OH, -NH_2, -SF_5, -SR_{26}, or -CN. In another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, or -CN. In yet another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, or -CN. In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, or -CN. In another embodiment, R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, halogen, or -CN.

In another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, or halogen. In yet another embodiment, R_{10} is independently at each occurrence halogen, -OH, -NH_2, -SF_5, -SR_{26}, or -CN. In another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, or -CN. In yet another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, or -CN. In another embodiment, R_{10} is independently

at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, or -CN. In yet another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, halogen, or -CN. In another embodiment, R_{10} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, halogen, or -CN.

In some embodiments of the formulae above, R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In another embodiment, R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, or (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In another embodiment, R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN.

In another embodiment, R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In yet another embodiment, R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN.

In another embodiment, R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In yet another embodiment, R_{11} is independently at each occurrence H, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from

(C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN.

In another embodiment, R_{11} is independently at each occurrence (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In yet another embodiment, R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN.

In some embodiments of the formulae above, R_{12} is independently at each occurrence H, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In yet another embodiment, R_{12} is independently at each occurrence H, (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_5-C_{10})aryl, (C_1-C_6)alkoxy, or (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In another embodiment, R_{12} is independently at each occurrence H, (C_1-C_6)alkyl substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN.

In another embodiment, R_{12} is independently at each occurrence H, or (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In yet another embodiment, R_{12} is independently at each occurrence H. In another embodiment, R_{12} is independently at each occurrence (C_1-C_6)alkyl optionally substituted with one to four substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN. In another embodiment, R_{12} is independently at each occurrence (C_6-C_{10})aryl optionally substituted with one to four substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN.

In another embodiment, R_{12} is independently at each occurrence $(C_1$-$C_6)$alkyl substituted with one to four substituents independently selected from $(C_6$-$C_{10})$aryl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$haloalkyl, halogen, -OH, $-NH_2$, and -CN. In yet another embodiment, R_{12} is independently at each occurrence $(C_6$-$C_{10})$aryl substituted with one to four substituents independently selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$haloalkyl, halogen, -OH, $-NH_2$, and -CN.

In some embodiments of the formulae above, $R_{12'}$ is independently at each occurrence H or $(C_1$-$C_6)$alkyl. In another embodiment, $R_{12'}$ is independently at each occurrence H or $(C_1$-$C_3)$alkyl. In another embodiment, $R_{12'}$ is independently at each occurrence $(C_1$-$C_6)$alkyl. In another embodiment, $R_{12'}$ is independently at each occurrence H.

In some embodiments of the formulae above, each R_{13} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, $-C(O)OR_{15'}$, $-C(O)R_{15}$, or $-C(O)NR_{15'}R_{15'}$. In another embodiment, each R_{13} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, $-C(O)OR_{15'}$, or $-C(O)R_{15}$. In yet another embodiment, each R_{13} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, $-C(O)OR_{15'}$, or $-C(O)NR_{15'}R_{15'}$. In another embodiment, each R_{13} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, $-C(O)R_{15}$, or $-C(O)NR_{15'}R_{15'}$.

In another embodiment, each R_{13} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, $-C(O)OR_{15'}$, $-C(O)R_{15}$, or $-C(O)NR_{15'}R_{15'}$. In yet another embodiment, each R_{13} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, $-C(O)OR_{15'}$, $-C(O)R_{15}$, or $-C(O)NR_{15'}R_{15'}$. In another embodiment, each R_{13} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, $-C(O)OR_{15'}$, $-C(O)R_{15}$, or $-C(O)NR_{15'}R_{15'}$. In yet another embodiment, each R_{13} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, $-C(O)OR_{15'}$, $-C(O)R_{15}$, or $-C(O)NR_{15'}R_{15'}$.

In another embodiment, each R_{13} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, $-C(O)OR_{15'}$, $-C(O)R_{15}$, or $-C(O)NR_{15'}R_{15'}$. In yet another embodiment, each R_{13} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, $-C(O)OR_{15'}$, $-C(O)R_{15}$, or $-C(O)NR_{15'}R_{15'}$. . In yet another embodiment, each R_{13} is independently at each occurrence D, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, $-C(O)OR_{15'}$, $-C(O)R_{15}$, or $-C(O)NR_{15'}R_{15'}$. In yet another embodiment, each R_{13} is independently at each

occurrence (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)$OR_{15'}$, -C(O)R_{15}, or -C(O)$NR_{15'}R_{15'}$. In another embodiment, each R_{13} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, or halogen. In another embodiment, each R_{13} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, or halogen.

In another embodiment, each R_{13} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, or halogen. In yet another embodiment, each R_{13} is independently at each occurrence halogen, -C(O)$OR_{15'}$, -C(O)R_{15}, or -C(O)$NR_{15'}R_{15'}$. In another embodiment, each R_{13} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, or halogen.

In some embodiments of the formulae above, R_{14} is independently at each occurrence H or (C_1-C_6)alkyl. In another embodiment, R_{14} is independently at each occurrence H or (C_1-C_3)alkyl. In yet another embodiment, R_{14} is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, R_{14} is independently at each occurrence (C_1-C_3)alkyl. In another embodiment, R_{14} is independently at each occurrence H.

In some embodiments of the formulae above, $R_{14'}$ is independently at each occurrence H or (C_1-C_6)alkyl. In another embodiment, $R_{14'}$ is independently at each occurrence H or (C_1-C_3)alkyl. In yet another embodiment, $R_{14'}$ is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, $R_{14'}$ is independently at each occurrence (C_1-C_3)alkyl. In another embodiment, $R_{14'}$ is independently at each occurrence H.

In some embodiments of the formulae above, R_{14a} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{14a} is H, (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{14a} is H or (C_1-C_6)alkyl. In another embodiment, R_{14a} is H or (C_1-C_6)haloalkyl. In yet another embodiment, R_{14a} is (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{14a} is (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{14a} is (C_1-C_6)alkyl. In another embodiment, R_{14a} is (C_1-C_3)alkyl. In another embodiment, R_{14a} is (C_1-C_6)haloalkyl. In another embodiment, R_{14a} is (C_1-C_3)haloalkyl. In another embodiment, R_{14a} is H.

In some embodiments of the formulae above, R_{15} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{15} is independently at each occurrence (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In another embodiment, R_{15} is independently at each occurrence (C_1-C_6)haloalkyl. In another embodiment, R_{15} is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, R_{15} is independently at each occurrence (C_1-C_3)haloalkyl. In another embodiment, R_{15} is independently at each occurrence (C_1-C_3)alkyl.

In some embodiments of the formulae above, $R_{15'}$ is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, $R_{15'}$ is independently at each occurrence H, (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, $R_{15'}$ is independently at each occurrence H or (C_1-C_6)alkyl. In another embodiment, $R_{15'}$ is independently at each occurrence H or (C_1-C_6)haloalkyl. In yet another embodiment, $R_{15'}$ is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, $R_{15'}$ is independently at each occurrence (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, $R_{15'}$ is independently at each occurrence (C_1-C_6)alkyl. In another embodiment, $R_{15'}$ is independently at each occurrence (C_1-C_3)alkyl. In another embodiment, $R_{15'}$ is independently at each occurrence (C_1-C_6)haloalkyl. In another embodiment, $R_{15'}$ is independently at each occurrence (C_1-C_3)haloalkyl. In another embodiment, $R_{15'}$ is independently at each occurrence H.

In some embodiments of the formulae above, each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{17}R_{17'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22} and the aryl and heteroaryl are optionally substituted with one to four R_{23}. In another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{17}R_{17'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are substituted with one to four R_{22} and the aryl and heteroaryl are optionally substituted with one to four R_{23}. In yet another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{17}R_{17'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22} and the aryl and heteroaryl are substituted with one to four R_{23}.

In another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{17}R_{17'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or (C_6-C_{10}) aryl, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22} and the aryl is optionally substituted with one to four R_{23}. In yet another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{17}R_{17'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4

heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22} and the heteroaryl is optionally substituted with one to four R_{23}.

In another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{17}R_{17'}$, -CN, (C_3-C_7)carbocyclyl, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein carbocyclyl is optionally substituted with one to four R_{22} and the aryl and heteroaryl are optionally substituted with one to four R_{23}. In yet another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{17}R_{17'}$, -CN, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{22} and the aryl and heteroaryl are optionally substituted with one to four R_{23}.

In another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22} and the aryl and heteroaryl are optionally substituted with one to four R_{23}. In another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{17}R_{17'}$, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22} and the aryl and heteroaryl are optionally substituted with one to four R_{23}. In yet another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, -$NR_{17}R_{17'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22} and the aryl and heteroaryl are optionally substituted with one to four R_{23}.

In another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)haloalkoxy, -$NR_{17}R_{17'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22} and the aryl and heteroaryl are optionally substituted with one to four R_{23}. In yet another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-

C_6)haloalkoxy, -$NR_{17}R_{17'}$, or -CN. In yet another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, or -$NR_{17}R_{17'}$.

In another embodiment, each R_{16} is independently at each occurrence (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22} and the aryl and heteroaryl are optionally substituted with one to four R_{23}. In yet another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{17}R_{17'}$, -CN, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}), wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22}.

In another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{17}R_{17'}$, -CN, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the aryl and heteroaryl are optionally substituted with one to four R_{23}. In yet another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{17}R_{17'}$, -CN, (C_3-C_7)carbocyclyl, or (C_6-C_{10}) aryl, wherein the carbocyclyl is optionally substituted with one to four R_{22} and the aryl is optionally substituted with one to four R_{23}. In another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{17}R_{17'}$, -CN, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{22} and the heteroaryl is optionally substituted with one to four R_{23}.

In another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, -$NR_{17}R_{17'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22} and the aryl and heteroaryl are optionally substituted with one to four R_{23}. In yet another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, -$NR_{17}R_{17'}$, -CN, (C_3-C_7)carbocyclyl, or (C_6-C_{10}) aryl, wherein the carbocyclyl is substituted with one to four R_{22} and the aryl is optionally substituted with one to four R_{23}.

In another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{17}R_{17'}$, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the aryl and heteroaryl are optionally substituted with one to four R_{23}. In yet another embodiment, each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{17}R_{17'}$, (C_3-C_7)carbocyclyl, or (C_6-C_{10}) aryl, wherein the carbocyclyl

is optionally substituted with one to four R_{22} and the aryl is optionally substituted with one to four R_{23}. In another embodiment, each R_{16} is independently at each occurrence $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, $-NR_{17}R_{17'}$, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the heterocyclyl is optionally substituted with one to four R_{22} and the heteroaryl is optionally substituted with one to four R_{23}.

In another embodiment, each R_{16} is independently at each occurrence $(C_1\text{-}C_6)$alkoxy, $-NR_{17}R_{17'}$, $(C_3\text{-}C_7)$carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_6\text{-}C_{10})$ aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22} and the aryl and heteroaryl are optionally substituted with one to four R_{23}. In yet another embodiment, each R_{16} is independently at each occurrence $(C_1\text{-}C_6)$alkoxy, $-NR_{17}R_{17'}$, $(C_3\text{-}C_7)$carbocyclyl, or $(C_6\text{-}C_{10})$ aryl, wherein the carbocyclyl is substituted with one to four R_{22} and the aryl is optionally substituted with one to four R_{23}.

In some embodiments of the formulae above, R_{17} is independently at each occurrence H or $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{17} is independently at each occurrence H or $(C_1\text{-}C_3)$alkyl. In yet another embodiment, R_{17} is independently at each occurrence $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{17} is independently at each occurrence $(C_1\text{-}C_3)$alkyl. In yet another embodiment, R_{17} is independently at each occurrence H.

In some embodiments of the formulae above, $R_{17'}$ is independently at each occurrence H or $(C_1\text{-}C_6)$alkyl. In another embodiment, $R_{17'}$ is independently at each occurrence H or $(C_1\text{-}C_3)$alkyl. In yet another embodiment, $R_{17'}$ is independently at each occurrence $(C_1\text{-}C_6)$alkyl. In another embodiment, $R_{17'}$ is independently at each occurrence $(C_1\text{-}C_3)$alkyl. In yet another embodiment, $R_{17'}$ is independently at each occurrence H.

In some embodiments of the formulae above, each R_{18} is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, $(C_1\text{-}C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{20}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3\text{-}C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{18} is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, $(C_1\text{-}C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{20}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or $(C_3\text{-}C_7)$carbocyclyl. In yet another embodiment, each R_{18} is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, $(C_1\text{-}C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{20}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N,

NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In another embodiment, each R_{18} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{20}, -CN, phenyl, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{18} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{20}, -CN, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{18} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{20}, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In another embodiment, each R_{18} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{18} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SR_{20}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{18} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -SF_5, -SR_{20}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In another embodiment, each R_{18} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -NH_2, -SF_5, -SR_{20}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{18} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, -OH, -NH_2, -SF_5, -SR_{20}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH,

and S. In another embodiment, each R_{18} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{20}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In another embodiment, each R_{18} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{20}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{18} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{20}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{18} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{20}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{18} is independently at each occurrence $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{20}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In another embodiment, each R_{18} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{20}$, or -CN. In yet another embodiment, each R_{18} is independently at each occurrence halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{20}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{18} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{20}$, -CN, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{18} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{20}$, -CN, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{18} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, -CN, phenyl, 5- or 6-

membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of the formulae above, two R_{18}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, two R_{18}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl. In yet another embodiment, two R_{18}, when on adjacent atoms, together with the atoms to which they are attached form a 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, two R_{18}, when on adjacent atoms, together with the atoms to which they are attached form a 5-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, two R_{18}, when on adjacent atoms, together with the atoms to which they are attached form a 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of the formulae above, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{21}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{21}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or (C_3-C_7)carbocyclyl. In yet another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{21}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{21}, -CN, phenyl, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{21}, -CN, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{21}, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-

C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SR_{21}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -SF_5, -SR_{21}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -NH_2, -SF_5, -SR_{21}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, -OH, -NH_2, -SF_5, -SR_{21}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -NH_2, -SF_5, -SR_{21}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{21}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{21}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another

embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{21}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{21}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{21}, or -CN. In yet another embodiment, each R_{19} is independently at each occurrence halogen, -OH, -NH_2, -SF_5, -SR_{21}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{21}, -CN, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{21}, -CN, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of the formulae above, two R_{19} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, two R_{19} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl. In another embodiment, two R_{19} together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl. In yet another embodiment, two R_{19} together with the atoms to which they are attached form a (C_3-C_5)carbocyclyl. In another embodiment, two R_{19} together with the atoms to which they are attached form a (C_3-C_4)carbocyclyl. In yet another embodiment, two R_{19} together with the atoms to which they are attached form a (C_4-C_7)carbocyclyl. In another embodiment, two R_{19} together with the atoms to which they are attached form a (C_5-C_7)carbocyclyl. In yet another embodiment, two R_{19} together with the atoms to which they are attached form a (C_6-C_7)carbocyclyl.

In another embodiment, two R_{19} together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, two R_{19} together with the atoms to which they are attached form a 4- to 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, two R_{19} together with the atoms to which they are attached form a 4- or 5-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, two R_{19} together with the atoms to which they are attached form a 5- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, two R_{19} together with the atoms to which they are attached form a 6- or 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of the formulae above, R_{20} is H, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{20} is H, $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$haloalkyl. In yet another embodiment, R_{20} is H or $(C_1$-$C_6)$alkyl. In another embodiment, R_{20} is H or $(C_1$-$C_6)$haloalkyl. In yet another embodiment, R_{20} is $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{20} is $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$haloalkyl. In yet another embodiment, R_{20} is $(C_1$-$C_6)$alkyl. In another embodiment, R_{20} is $(C_1$-$C_3)$alkyl. In another embodiment, R_{20} is $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{20} is $(C_1$-$C_3)$haloalkyl. In another embodiment, R_{20} is H.

In some embodiments of the formulae above, R_{21} is H, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{21} is H, $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$haloalkyl. In yet another embodiment, R_{21} is H or $(C_1$-$C_6)$alkyl. In another embodiment, R_{21} is H or $(C_1$-$C_6)$haloalkyl. In yet another embodiment, R_{21} is $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{21} is $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$haloalkyl. In yet another embodiment, R_{21} is $(C_1$-$C_6)$alkyl. In another embodiment, R_{21} is $(C_1$-$C_3)$alkyl. In another embodiment, R_{21} is $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{21} is $(C_1$-$C_3)$haloalkyl. In another embodiment, R_{21} is H.

In some embodiments of the formulae above, each R_{22} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{24}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{22} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{24}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or $(C_3$-$C_7)$carbocyclyl. In yet another embodiment, each R_{22} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{24}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In another embodiment, each R_{22} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{24}$, -CN, phenyl, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{22} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{24}$, -CN, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{22} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{24}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In another embodiment, each R_{22} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{24}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{22} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{22} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SR_{24}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In another embodiment, each R_{22} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-SF_5$, $-SR_{24}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{22} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, $-NH_2$, $-SF_5$, $-SR_{24}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{22} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-

C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In another embodiment, each R_{22} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{22} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{22} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In another embodiment, each R_{22} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{22} is independently at each occurrence D, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{22} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In another embodiment, each R_{22} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, or -CN. In yet another embodiment, each R_{22} is independently at each occurrence halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{22} is independently at each occurrence D, (C_1-C_6)alkyl,

(C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{22} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{22} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In another embodiment, each R_{22} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, or -CN. In yet another embodiment, each R_{22} is independently at each occurrence halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{22} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{22} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{22} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of the formulae above, two R_{22} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, two R_{22} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl. In another embodiment, two R_{22} together with the atoms to which they are attached form a (C_3-C_6)carbocyclyl. In yet another embodiment, two R_{22} together with the atoms to which they are attached form a (C_3-C_5)carbocyclyl. In another embodiment, two R_{22} together with the atoms to which they are attached form a (C_3-C_4)carbocyclyl. In yet another embodiment, two R_{22} together with the atoms to which they are attached form a (C_4-C_7)carbocyclyl. In another embodiment, two R_{22} together

with the atoms to which they are attached form a (C_5-C_7)carbocyclyl. In yet another embodiment, two R_{22} together with the atoms to which they are attached form a (C_6-C_7)carbocyclyl.

In another embodiment, two R_{22} together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, two R_{22} together with the atoms to which they are attached form a 4- to 6-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, two R_{22} together with the atoms to which they are attached form a 4- or 5-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, two R_{22} together with the atoms to which they are attached form a 5- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, two R_{22} together with the atoms to which they are attached form a 6- or 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of the formulae above, each R_{23} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{23} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or (C_3-C_7)carbocyclyl. In yet another embodiment, each R_{23} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In another embodiment, each R_{23} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{23} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{23} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-

C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In another embodiment, each R_{23} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{23} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{23} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In another embodiment, each R_{23} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{23} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl,-OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{23} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In another embodiment, each R_{23} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{23} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-

membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{23} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{25}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{23} is independently at each occurrence D, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{25}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{23} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{25}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In another embodiment, each R_{23} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{25}$, or -CN. In yet another embodiment, each R_{23} is independently at each occurrence halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{25}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{23} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{25}$, -CN, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{23} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{25}$, -CN, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{23} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl.

In another embodiment, each R_{23} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{25}$, or -CN. In yet another embodiment, each R_{23} is independently at each occurrence halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{25}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{23} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-

C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In yet another embodiment, each R_{23} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S. In another embodiment, each R_{23} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S.

In some embodiments of the formulae above, R_{24} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{24} is H, (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{24} is H or (C_1-C_6)alkyl. In another embodiment, R_{24} is H or (C_1-C_6)haloalkyl. In yet another embodiment, R_{24} is (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{24} is (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{24} is (C_1-C_6)alkyl. In another embodiment, R_{24} is (C_1-C_3)alkyl. In another embodiment, R_{24} is (C_1-C_6)haloalkyl. In another embodiment, R_{24} is (C_1-C_3)haloalkyl. In another embodiment, R_{24} is H.

In some embodiments of the formulae above, R_{25} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{25} is H, (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{25} is H or (C_1-C_6)alkyl. In another embodiment, R_{25} is H or (C_1-C_6)haloalkyl. In yet another embodiment, R_{25} is (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{25} is (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{25} is (C_1-C_6)alkyl. In another embodiment, R_{25} is (C_1-C_3)alkyl. In another embodiment, R_{25} is (C_1-C_6)haloalkyl. In another embodiment, R_{25} is (C_1-C_3)haloalkyl. In another embodiment, R_{25} is H.

In some embodiments of the formulae above, R_{26} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{26} is H, (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{26} is H or (C_1-C_6)alkyl. In another embodiment, R_{26} is H or (C_1-C_6)haloalkyl. In yet another embodiment, R_{26} is (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{26} is (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{26} is (C_1-C_6)alkyl. In another embodiment, R_{26} is (C_1-C_3)alkyl. In another embodiment, R_{26} is (C_1-C_6)haloalkyl. In another embodiment, R_{26} is (C_1-C_3)haloalkyl. In another embodiment, R_{26} is H.

In some embodiments of the formulae above, R_{27} is H, (C_1-C_6)alkyl, or -C(O)R_{31}. In another embodiment, R_{27} is H, (C_1-C_3)alkyl, or -C(O)R_{31}. In yet another embodiment, R_{27} is H or (C_1-C_6)alkyl. In another embodiment, R_{27} is H or -C(O)R_{31}. In yet another embodiment, R_{27} is (C_1-C_3)alkyl or -C(O)R_{31}. In another embodiment, R_{27} is (C_1-C_3)alkyl. In yet another embodiment, R_{27} is -C(O)R_{31}. In another embodiment, R_{27} is H.

In some embodiments of the formulae above, R_{28} is H, (C_1-C_6)alkyl, or -C(O)R_{31}. In another embodiment, R_{28} is H, (C_1-C_3)alkyl, or -C(O)R_{31}. In yet another embodiment, R_{28} is H or (C_1-C_6)alkyl. In

another embodiment, R_{28} is H or -C(O)R_{31}. In yet another embodiment, R_{28} is (C_1-C_3)alkyl or -C(O)R_{31}. In another embodiment, R_{28} is (C_1-C_3)alkyl. In yet another embodiment, R_{28} is -C(O)R_{31}. In another embodiment, R_{28} is H.

In some embodiments of the formulae above, R_{29} is H or (C_1-C_6)alkyl. In another embodiment, R_{29} is H or (C_1-C_3)alkyl. In yet another embodiment, R_{29} is (C_1-C_6)alkyl. In another embodiment, R_{29} is (C_1-C_3)alkyl. In yet another embodiment, R_{29} is H.

In some embodiments of the formulae above, R_{30} is H or (C_1-C_6)alkyl. In another embodiment, R_{30} is H or (C_1-C_3)alkyl. In yet another embodiment, R_{30} is (C_1-C_6)alkyl. In another embodiment, R_{30} is (C_1-C_3)alkyl. In yet another embodiment, R_{30} is H.

In some embodiments of the formulae above, R_{31} is H or (C_1-C_6)alkyl. In another embodiment, R_{31} is H or (C_1-C_3)alkyl. In yet another embodiment, R_{31} is (C_1-C_6)alkyl. In another embodiment, R_{31} is (C_1-C_3)alkyl. In yet another embodiment, R_{31} is H.

In some embodiments of the formulae above, R_{32} is H, (C_1-C_6)alkyl, or -C(O)R_{36}. In another embodiment, R_{32} is H, (C_1-C_3)alkyl, or -C(O)R_{36}. In yet another embodiment, R_{32} is H or (C_1-C_6)alkyl. In another embodiment, R_{32} is H or -C(O)R_{36}. In yet another embodiment, R_{32} is (C_1-C_3)alkyl or -C(O)R_{36}. In another embodiment, R_{32} is (C_1-C_3)alkyl. In yet another embodiment, R_{32} is -C(O)R_{36}. In another embodiment, R_{32} is H.

In some embodiments of the formulae above, R_{33} is H, (C_1-C_6)alkyl, or -C(O)R_{36}. In another embodiment, R_{33} is H, (C_1-C_3)alkyl, or -C(O)R_{36}. In yet another embodiment, R_{33} is H or (C_1-C_6)alkyl. In another embodiment, R_{33} is H or -C(O)R_{36}. In yet another embodiment, R_{33} is (C_1-C_3)alkyl or -C(O)R_{36}. In another embodiment, R_{33} is (C_1-C_3)alkyl. In yet another embodiment, R_{33} is -C(O)R_{36}. In another embodiment, R_{33} is H.

In some embodiments of the formulae above, R_{34} is H or (C_1-C_6)alkyl. In another embodiment, R_{34} is H or (C_1-C_3)alkyl. In yet another embodiment, R_{34} is (C_1-C_6)alkyl. In another embodiment, R_{34} is (C_1-C_3)alkyl. In yet another embodiment, R_{34} is H.

In some embodiments of the formulae above, R_{35} is H or (C_1-C_6)alkyl. In another embodiment, R_{35} is H or (C_1-C_3)alkyl. In yet another embodiment, R_{35} is (C_1-C_6)alkyl. In another embodiment, R_{35} is (C_1-C_3)alkyl. In yet another embodiment, R_{35} is H.

In some embodiments of the formulae above, R_{36} is H or (C_1-C_6)alkyl. In another embodiment, R_{36} is H or (C_1-C_3)alkyl. In yet another embodiment, R_{36} is (C_1-C_6)alkyl. In another embodiment, R_{36} is (C_1-C_3)alkyl. In yet another embodiment, R_{36} is H.

In some embodiments of the formulae above, R_{37} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{37} is H, (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{37} is H or (C_1-C_6)alkyl. In another embodiment, R_{37} is H or (C_1-C_6)haloalkyl. In yet another embodiment, R_{37} is (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{37} is (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, R_{37} is (C_1-C_6)alkyl. In another embodiment, R_{37} is (C_1-C_3)alkyl. In another embodiment, R_{37} is (C_1-C_6)haloalkyl. In another embodiment, R_{37} is (C_1-C_3)haloalkyl. In another embodiment, R_{37} is H.

In some embodiments of the formulae above, q is 1, 2, or 3. In another embodiment, q is 1 or 3. In yet another embodiment, q is 2 or 3. In another embodiment, q is 1 or 2. In yet another embodiment, q is 1. In another embodiment, q is 2. In yet another embodiment, q is 3.

In some embodiments of the formulae above, m is 0 or 1. In another embodiment, m is 1 or 2. In yet another embodiment, m is 0 or 2. In another embodiment, m is 0. In yet another embodiment, m is 1. In another embodiment, m is 2.

In some embodiments of the formulae above, n is 0, 1, 2, 3, or 4. In another embodiment, n is 0, 1, 2, or 3. In yet another embodiment, n is 0, 1, 2, or 4. In another embodiment, n is 0, 1, 3 or 4. In yet another embodiment, n is 0, 2, 3, or 4. In another embodiment, n is 1, 2, 3 or 4. In yet another embodiment, n is 0, 1, or 2. In another embodiment, n is 2, 3, or 4. In yet another embodiment, n is 1, 2, or 3. In another embodiment, n is 0 or 1. In yet another embodiment, n is 1 or 2. In another embodiment, n is 2 or 3. In yet another embodiment, n is 3 or 4. In another embodiment, n is 0 or 2. In yet another embodiment, n is 0 or 3. In another embodiment, n is 0 or 4. In yet another embodiment, n is 1 or 2. In another embodiment, n is 1 or 3. In yet another embodiment, n is 1 or 4. In another embodiment, n is 0 or 2. In yet another embodiment, n is 2 or 4. In another embodiment, n is 0. In yet another embodiment, n is 1. In another embodiment, n is 2. In yet another embodiment, n is 4.

In some embodiments of the formulae above, R_1 is H or D and R_{2a} is H. In another embodiment, R_1 is H or D, R_{2a} is H, and R_{2b} is H. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H and R_{2c} is H. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H and R_{2d} is H. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, and R_3 is H or D. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, and m is 0. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0 and R_{6a} is H. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, and R_{6b} is H. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, and R_{6c} is H. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, and R_{6d} is H.

In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H and R_5 is H. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H,

R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 0. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of the formulae above, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 1 or 2. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising

1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of the formulae above, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, and R_{6a} is H. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, and R_{6b} is H. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, and R_{6c} is H. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, and R_{6d} is H. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, and R_5 is H.

In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_5 is H, and n is 0. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl

and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of the formulae above, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 1 or 2. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-

C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of the formulae above, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, and R_3 is H. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, and m is 0. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H and R_5 is H. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 0. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of the formulae above, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 1 or 2. In another embodiment, R_1 is H

or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of the formulae above, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, and R_{6a} is H. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, and R_{6b} is H. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, and R_{6c} is H. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, and R_{6d} is H. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, and R_5 is H.

In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 0. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to

four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is $(C_1$-$C_6)$alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is $(C_1$-$C_6)$alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is $(C_1$-$C_6)$alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of the formulae above, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 1 or 2. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is $(C_1$-$C_6)$alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is $(C_1$-$C_6)$alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is $(C_1$-$C_6)$alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-

C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H or D, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of the formulae above, R_1 is H and R_{2a} is H. In another embodiment, R_1 is H, R_{2a} is H, and R_{2b} is H. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H and R_{2c} is H. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H and R_{2d} is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, and R_3 is H or D. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, and m is 0. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H and R_5 is H. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 0. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with

one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of the formulae above, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 1 or 2. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of the formulae above, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, and R_{6a} is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, and R_{6b} is H. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, and R_{6c} is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, and R_{6d} is H.

In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, and R_5 is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 0. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is $(C_1$-$C_6)$alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is $(C_1$-$C_6)$alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_5 is H, n is 0, and R_7 is $(C_1$-$C_6)$alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is $(C_1$-$C_6)$alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of the formulae above, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_5 is H, and n is 1 or 2. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is $(C_1$-$C_6)$alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is $(C_1$-$C_6)$alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered

heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H or D, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of the formulae above, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, and R_3 is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H and m is 0. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, and R_5 is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 0. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-

C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of the formulae above, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 1 or 2. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, m is 0, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

In some embodiments of the formulae above, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, and R_{6a} is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, and

R_{6b} is H. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, and R_{6c} is H. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, and R_{6d} is H. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, and R_5 is H.

In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 0. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 0, and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

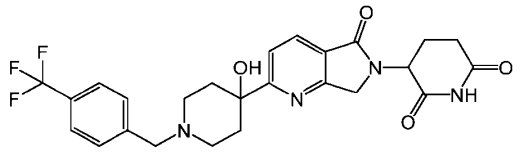
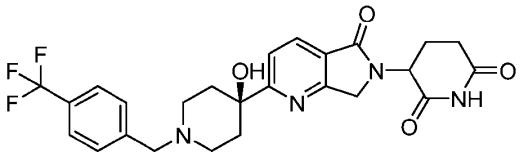
In some embodiments of the formulae above, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, and n is 1 or 2. In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are

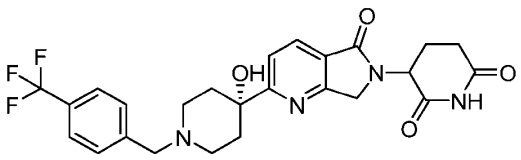
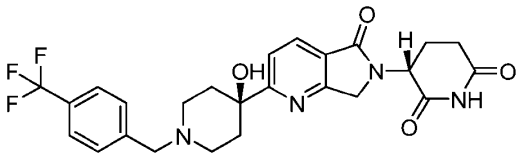
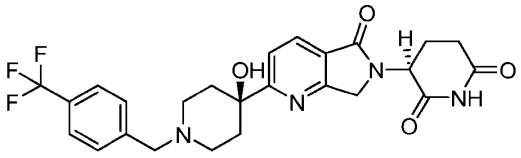
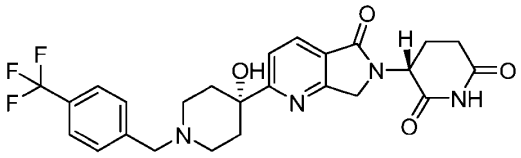
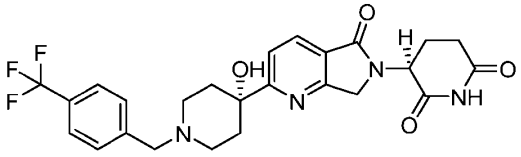
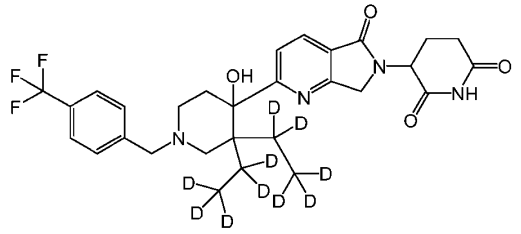
optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

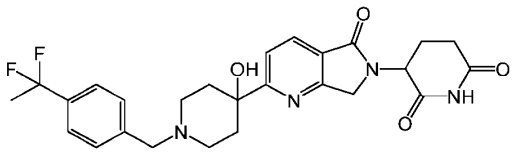
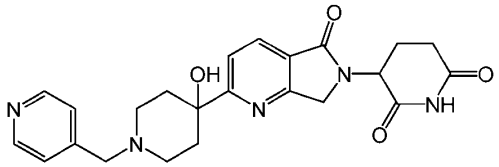
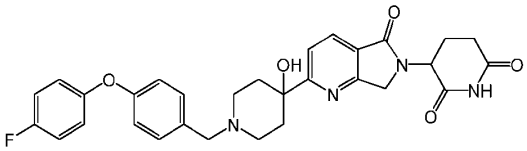
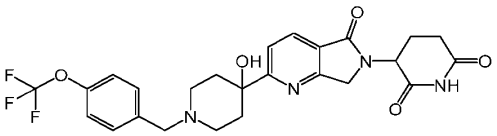
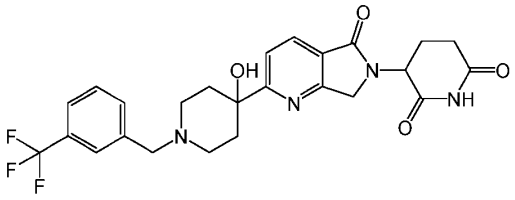
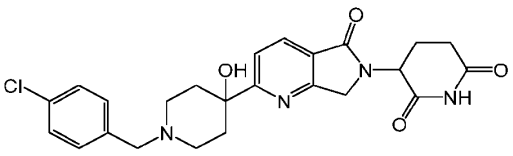
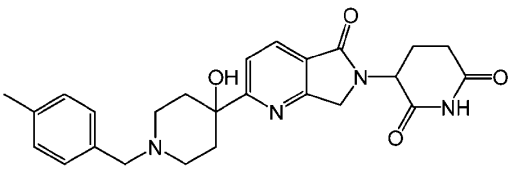
In another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl optionally substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$. In yet another embodiment, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_{6a} is H, R_{6b} is H, R_{6c} is H, R_{6d} is H, R_5 is H, n is 1 or 2, and R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to four phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are substituted with one to four R_8 and the carbocyclyl and heterocyclyl are substituted with one to four $R_{8'}$.

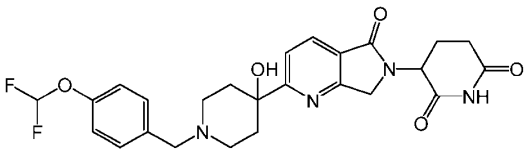
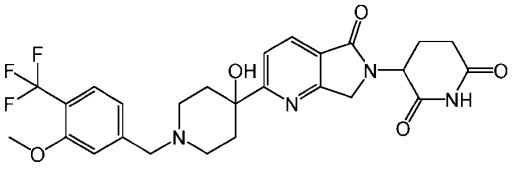
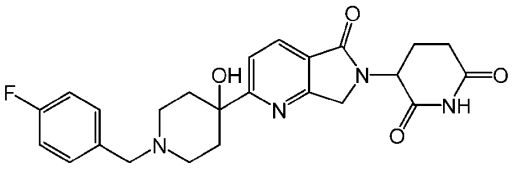
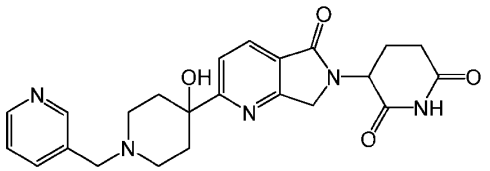
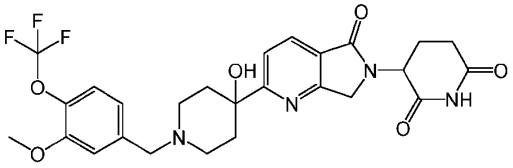
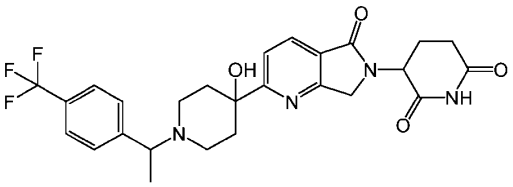
Non-limiting illustrative compounds of a compound of Formula (III) include the compounds in Table 2.

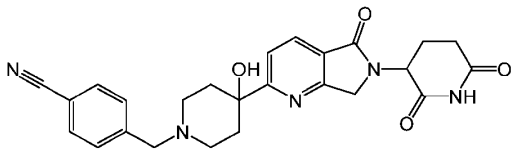
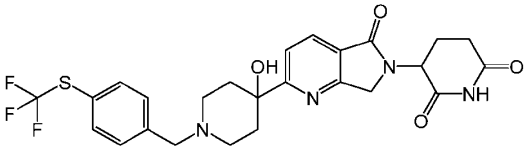
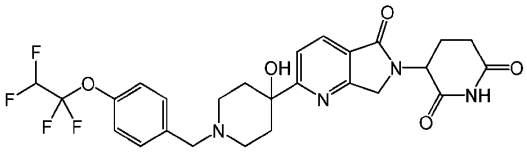
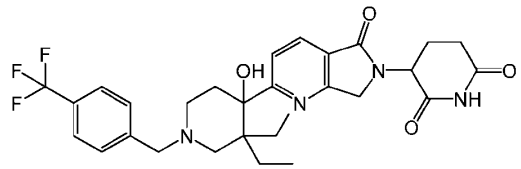
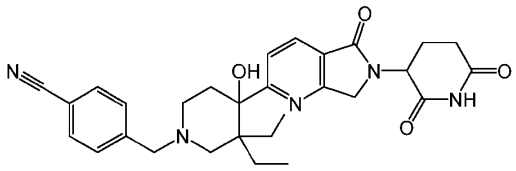
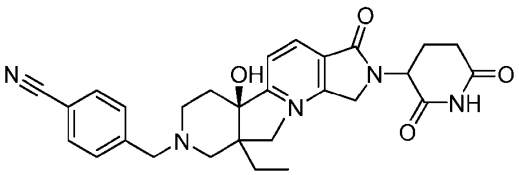
Table 2: Exemplary compounds of the disclosure

Cmpd No.	Compound Structure
I-400	
I-401	

Cmpd No.	Compound Structure
I-402	
I-403	
I-404	
I-405	
I-406	
I-407	

Cmpd No.	Compound Structure
I-408	
I-409	
I-410	
I-411	
I-412	
I-413	
I-414	

Cmpd No.	Compound Structure
I-415	
I-416	
I-417	
I-418	
I-419	
I-420	

Cmpd No.	Compound Structure
I-421	
I-422	
I-423	
I-424	
I-425	
I-426	

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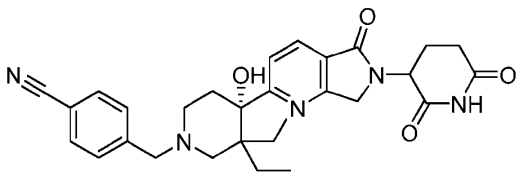
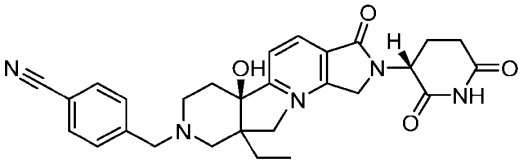
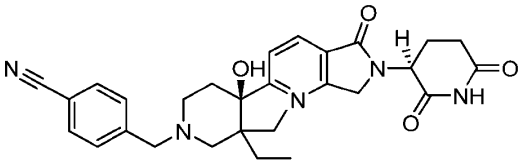
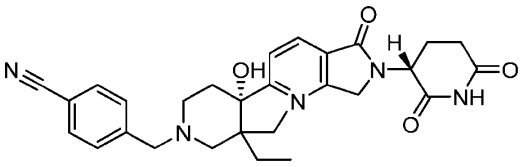
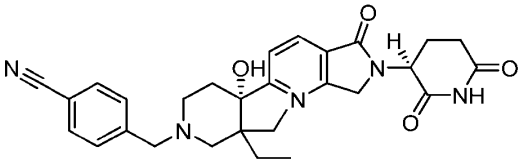
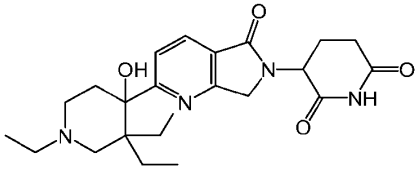
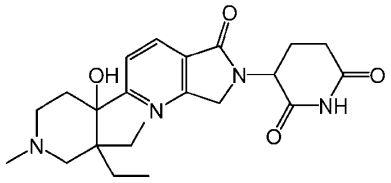
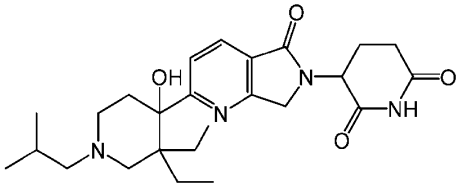
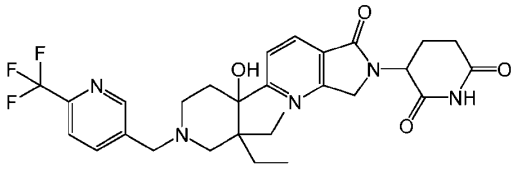
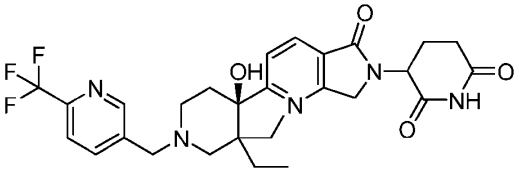
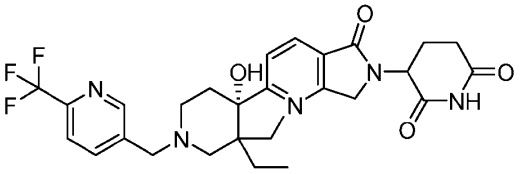
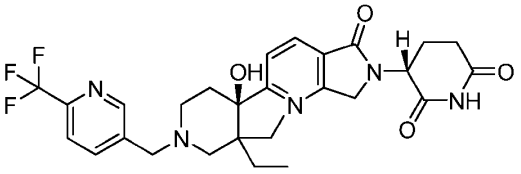
I-427	
I-428	
I-429	
I-430	
I-431	
I-432	

Cmpd No.	Compound Structure
I-433	
I-434	
I-435	
I-436	
I-437	
I-438	

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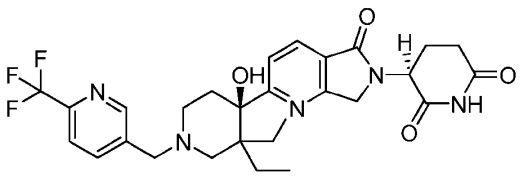
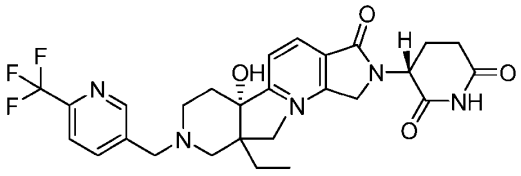
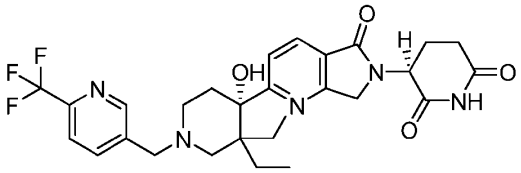
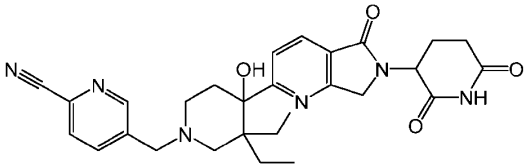
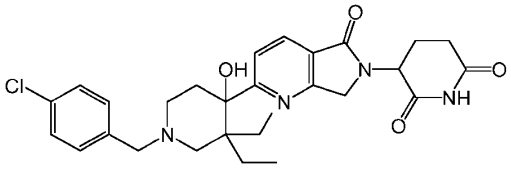
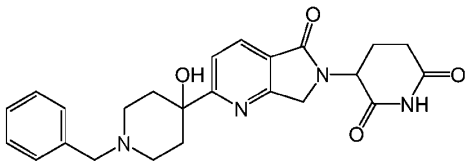
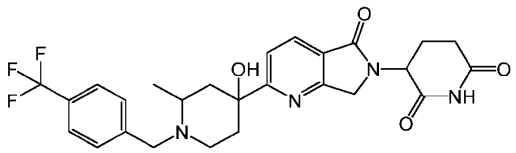
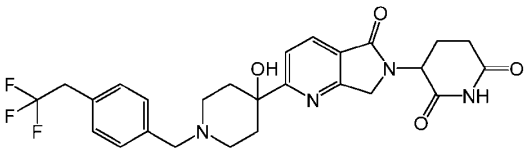
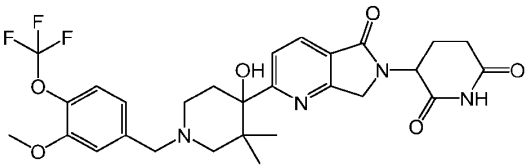
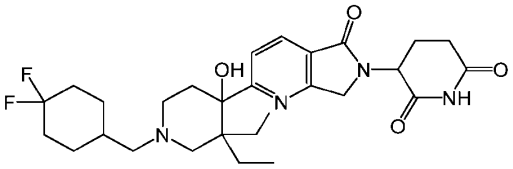
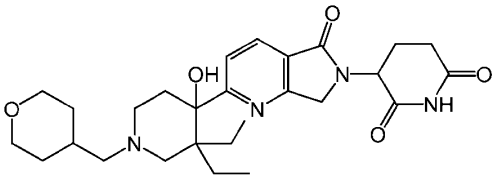
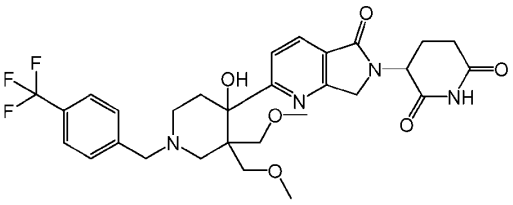
I-439	
I-440	
I-441	
I-442	
I-443	
I-444	

Cmpd No.	Compound Structure
I-445	
I-446	
I-447	
I-448	
I-449	
I-450	

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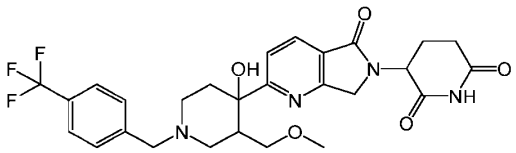
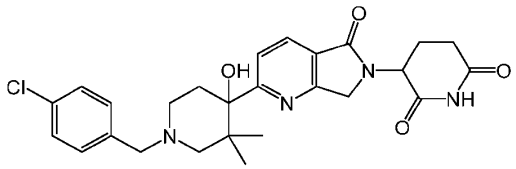
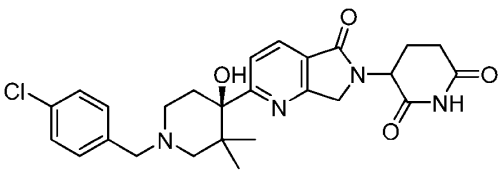
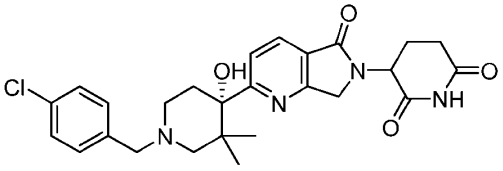
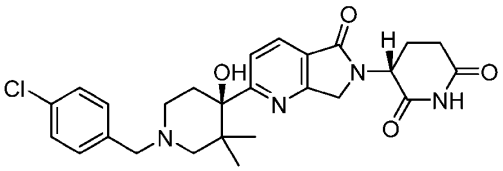
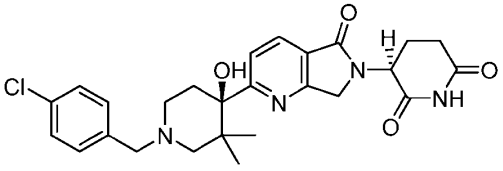
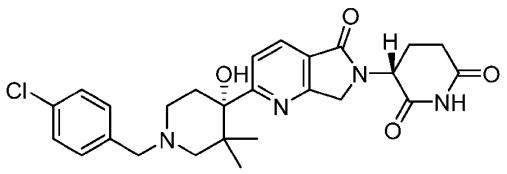
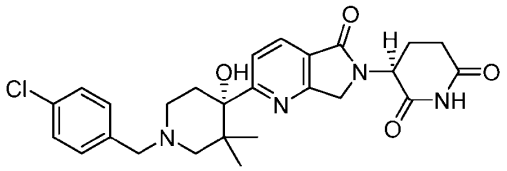
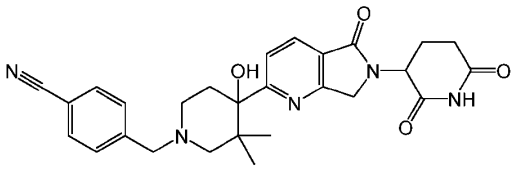
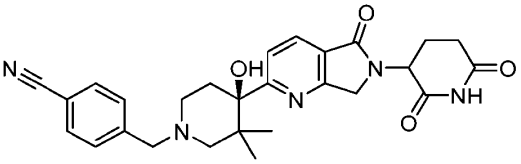
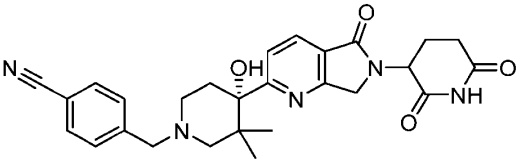
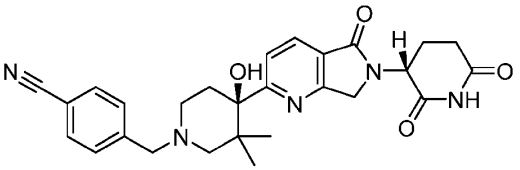
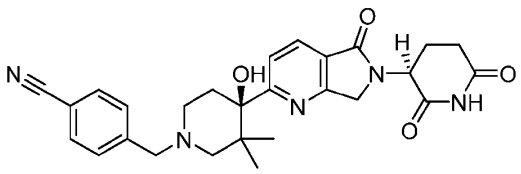
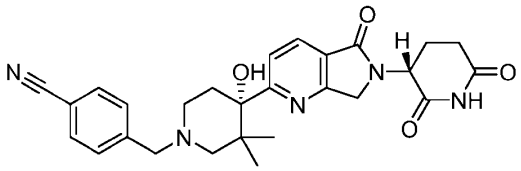
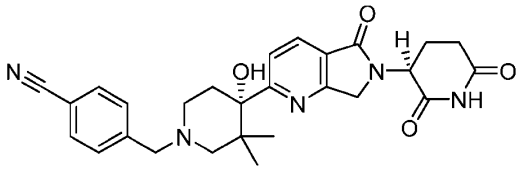
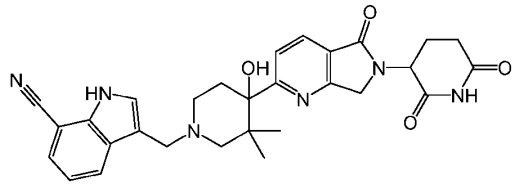
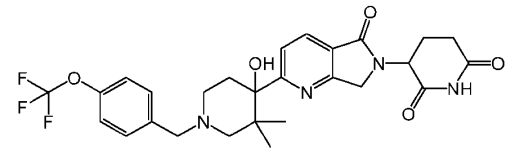
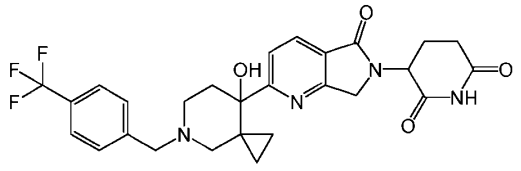
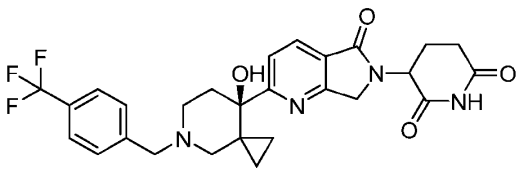
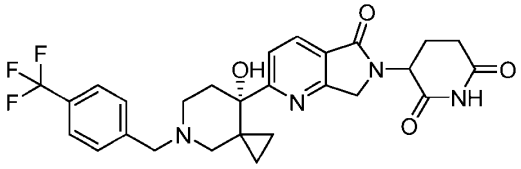
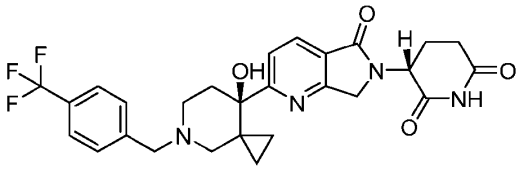
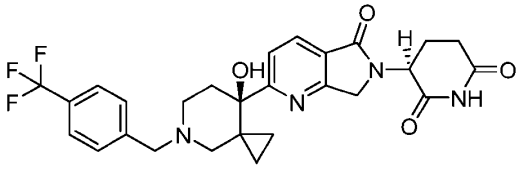
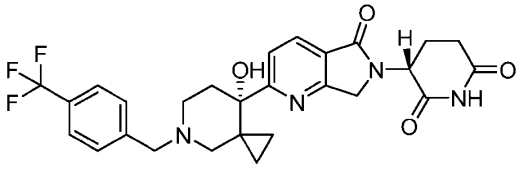
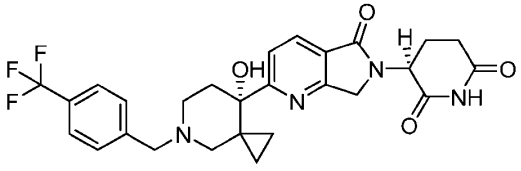
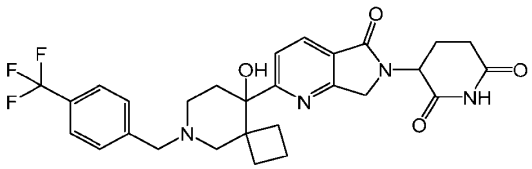
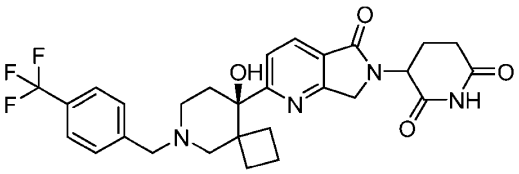
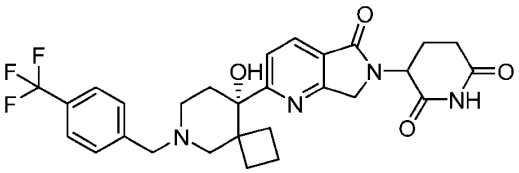
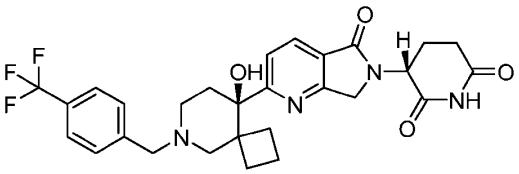
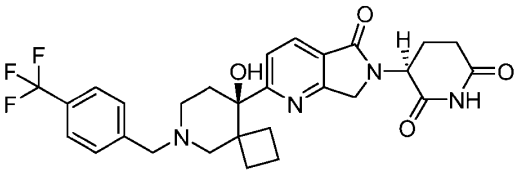
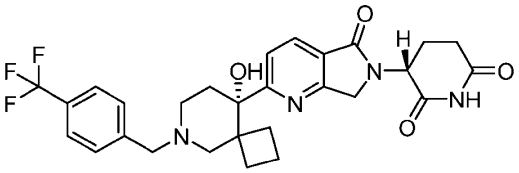
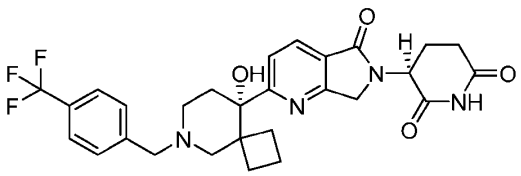
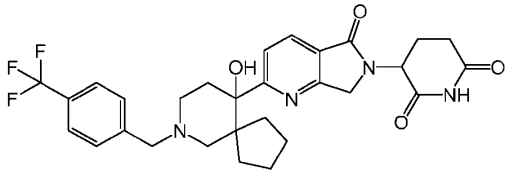
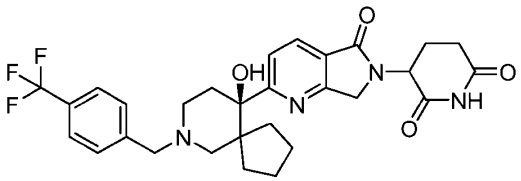
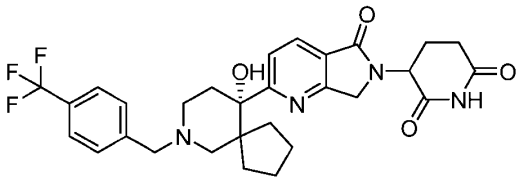
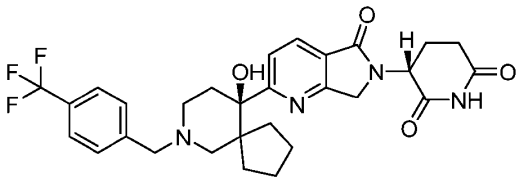
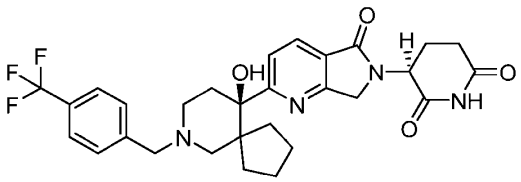
I-451	
I-452	
I-453	
I-454	
I-455	
I-456	

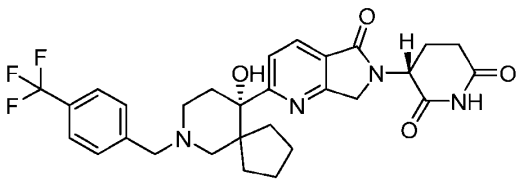
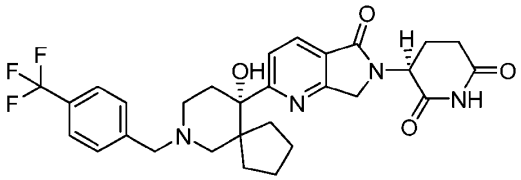
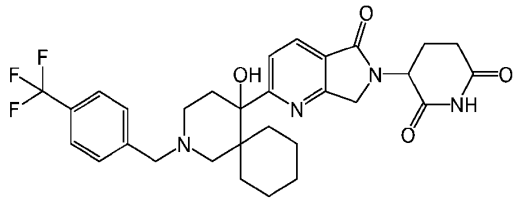
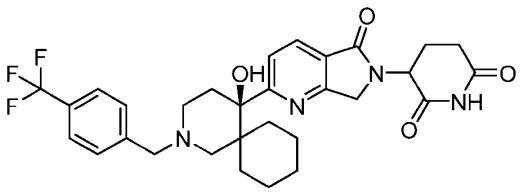
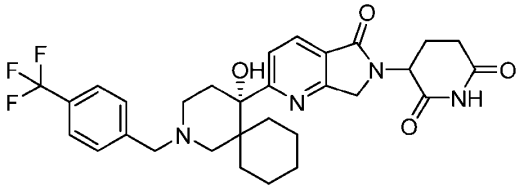
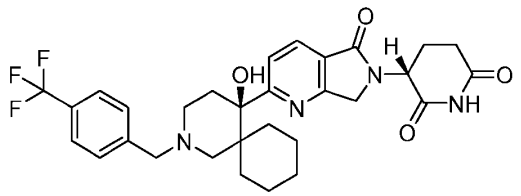
Cmpd No.	Compound Structure
I-457	
I-458	
I-459	
I-460	
I-461	
I-462	

Cmpd No.	Compound Structure
I-463	
I-464	
I-465	
I-466	
I-467	
I-468	

Cmpd No.	Compound Structure
I-469	
I-470	
I-471	
I-472	
I-473	
I-474	

Cmpd No.	Compound Structure
I-475	
I-476	
I-477	
I-478	
I-479	
I-480	

Cmpd No.	Compound Structure
I-481	
I-482	
I-483	
I-484	
I-485	
I-486	

Cmpd No.	Compound Structure
I-487	
I-488	
I-489	
I-490	
I-491	
I-492	

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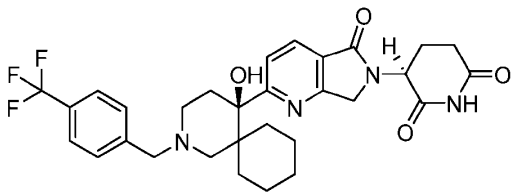
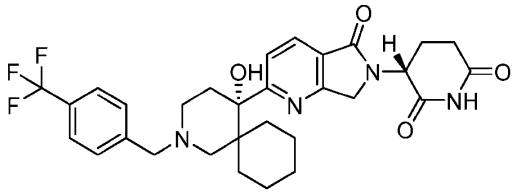
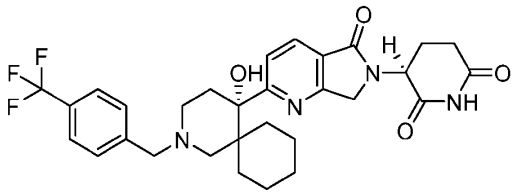
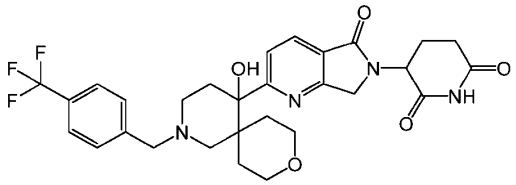
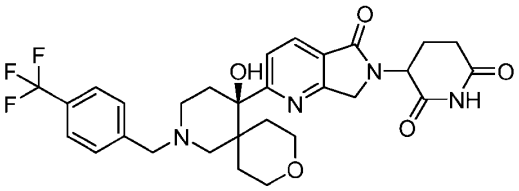
I-493	
I-494	
I-495	
I-496	
I-497	

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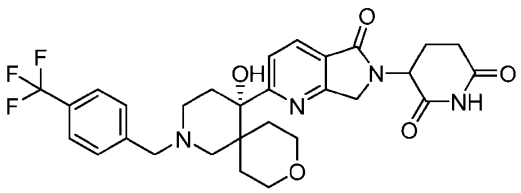
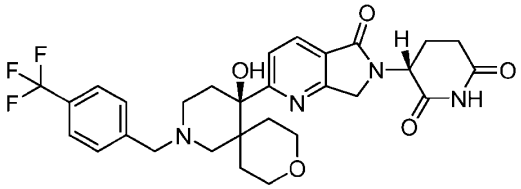
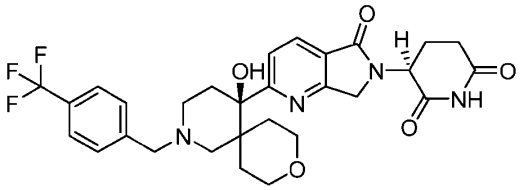
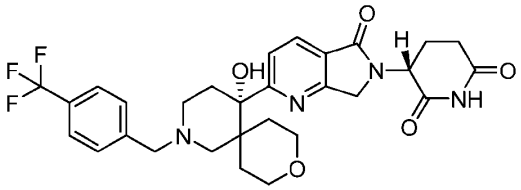
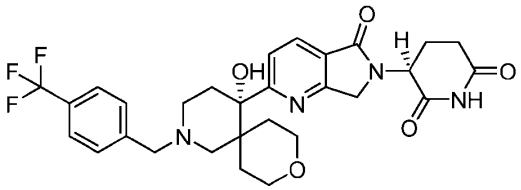
I-498	
I-499	
I-500	
I-501	
I-502	

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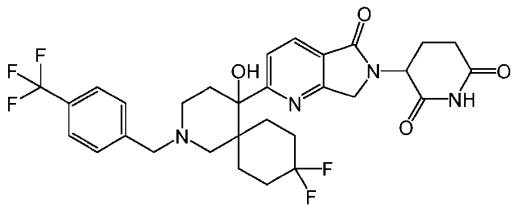
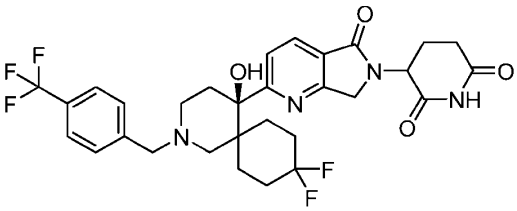
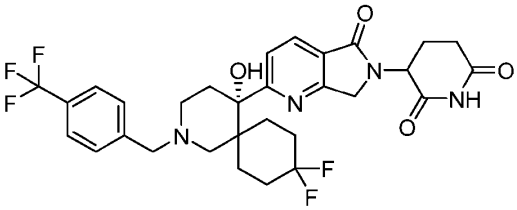
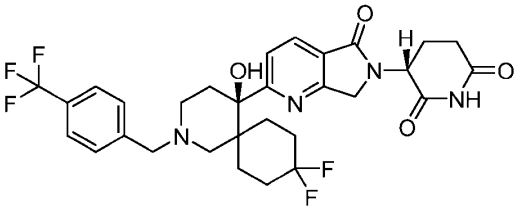
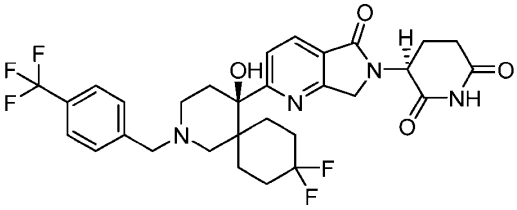
I-503	
I-504	
I-505	
I-506	
I-507	

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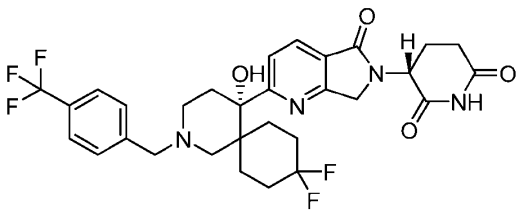
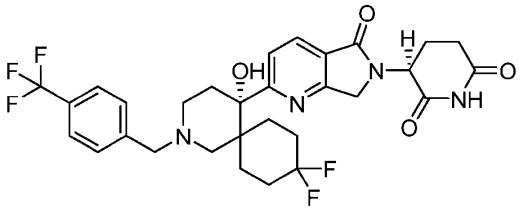
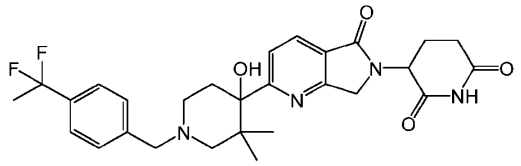
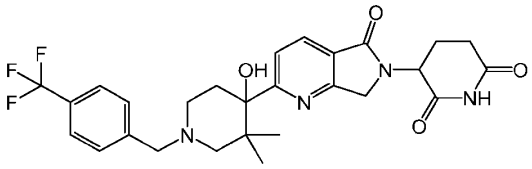
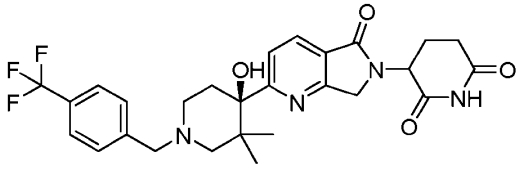
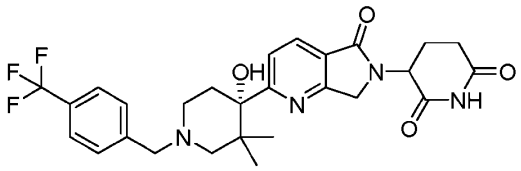
I-508	
I-509	
I-510	
I-511	
I-512	
I-513	

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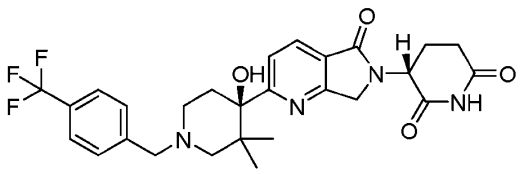
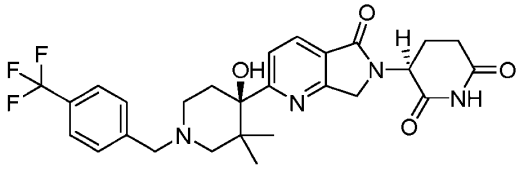
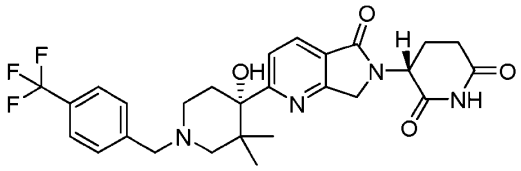
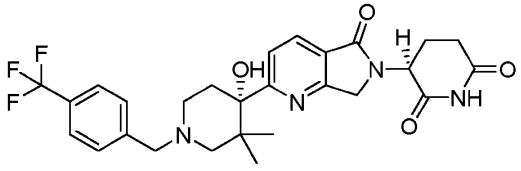
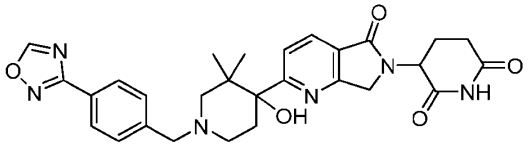
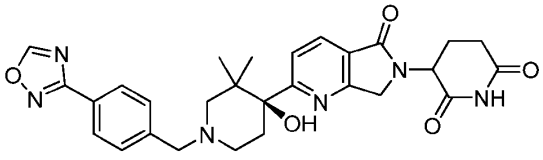
I-514	
I-515	
I-516	
I-517	
I-518	
I-519	

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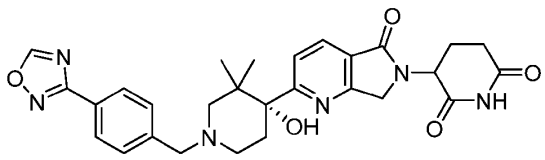
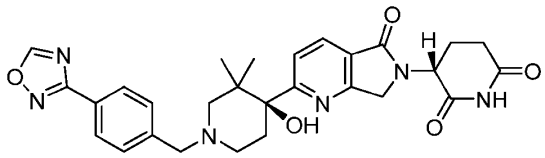
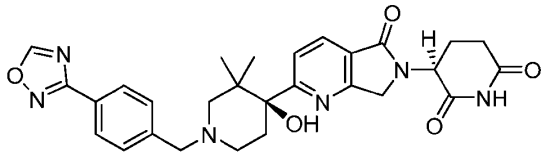
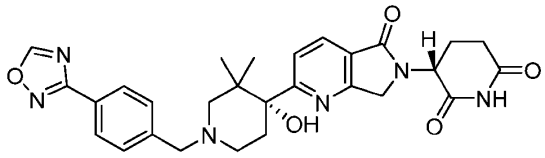
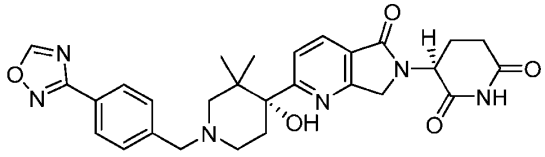
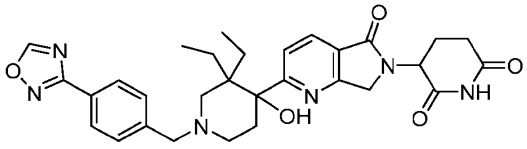
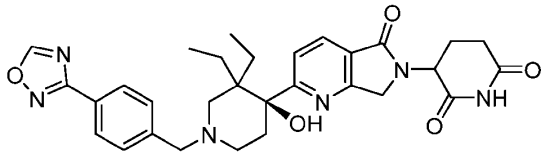
I-520	
I-521	
I-522	
I-523	
I-524	
I-525	
I-526	

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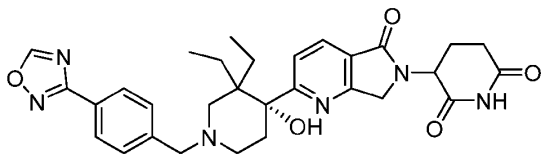
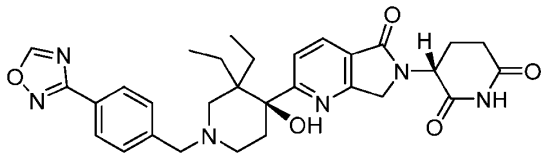
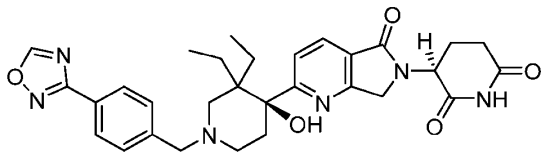
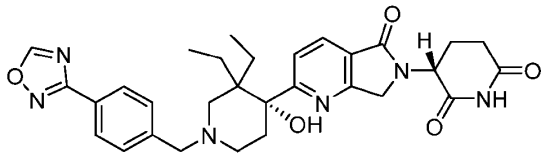
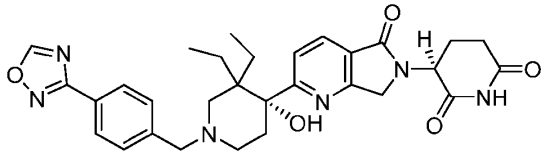
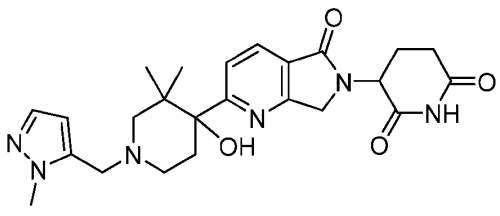
I-527	
I-528	
I-529	
I-530	
I-531	
I-532	

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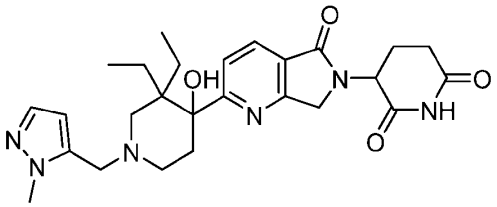
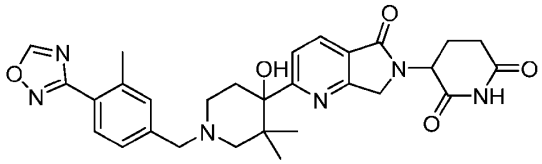
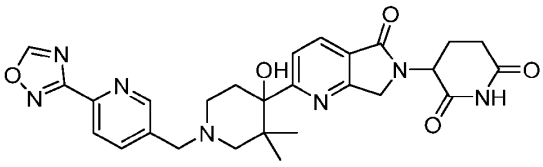
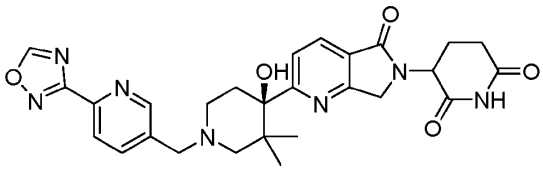
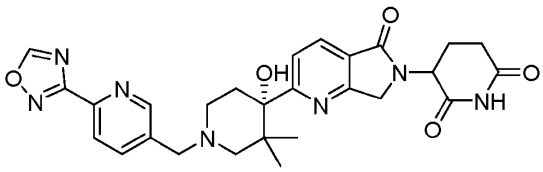
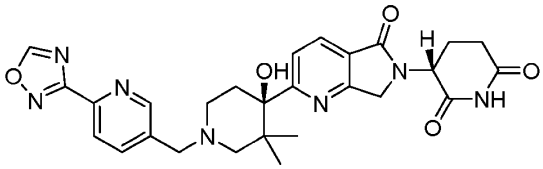
I-533	
I-534	
I-535	
I-536	
I-537	
I-538	

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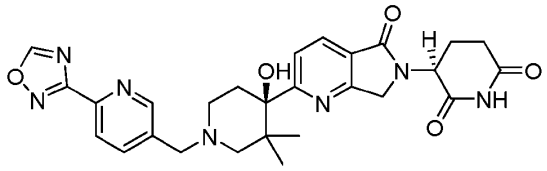
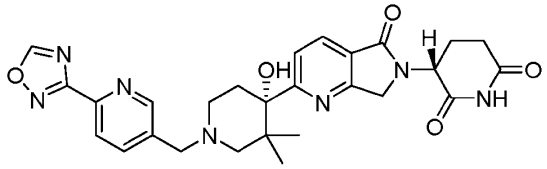
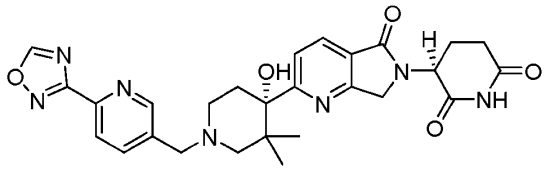
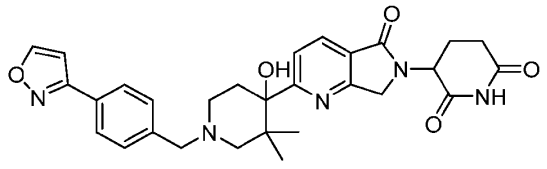
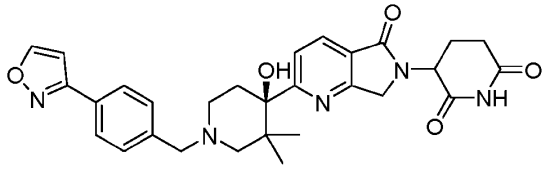
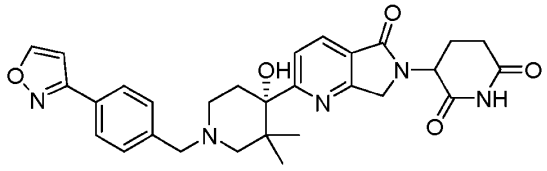
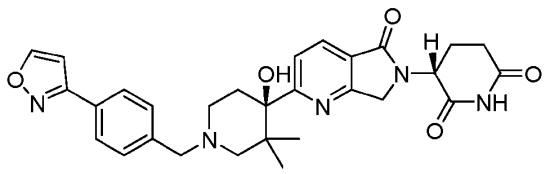
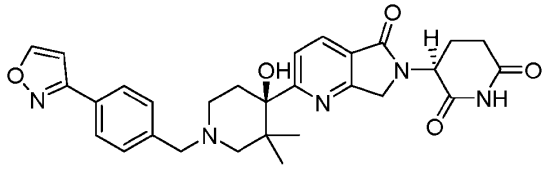
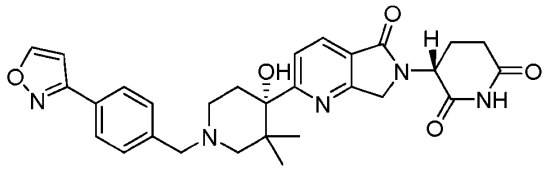
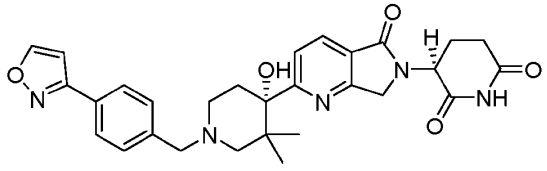
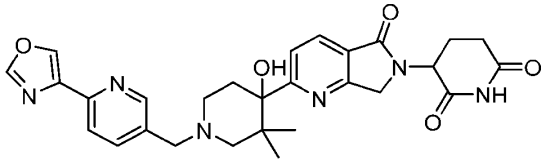
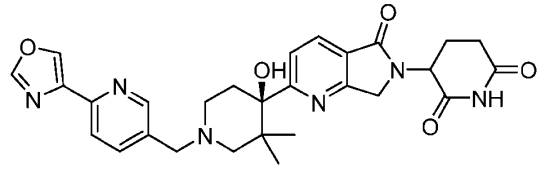
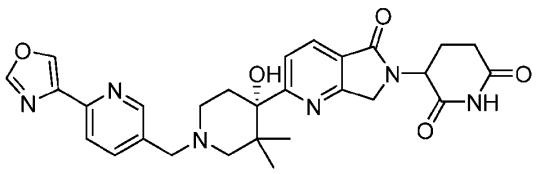
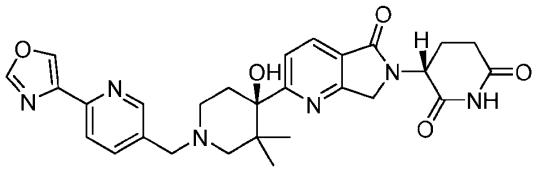
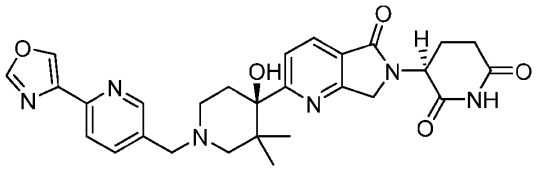
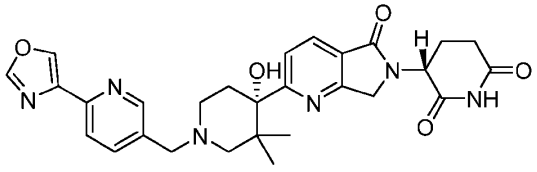
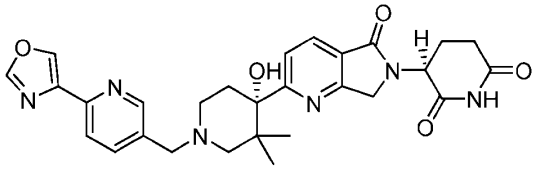
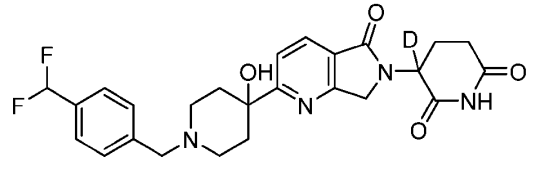
I-539	
I-540	
I-541	
I-542	
I-543	
I-544	

Cmpd No.	Compound Structure
I-545	
I-546	
I-547	
I-548	
I-549	
I-550	

Cmpd No.	Compound Structure
I-551	
I-552	
I-553	
I-554	
I-555	
I-556	

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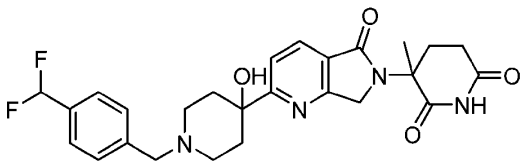
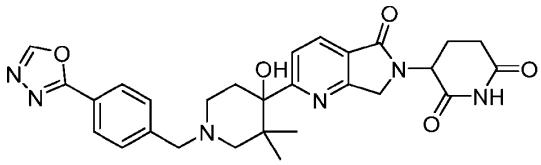
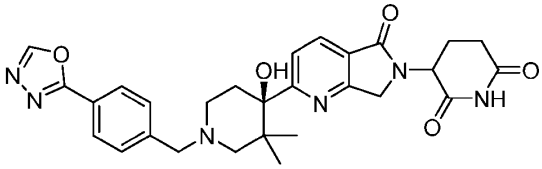
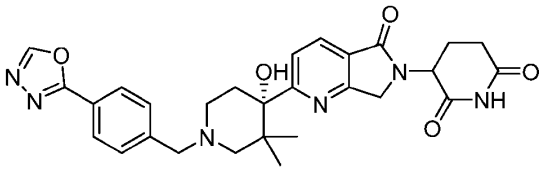
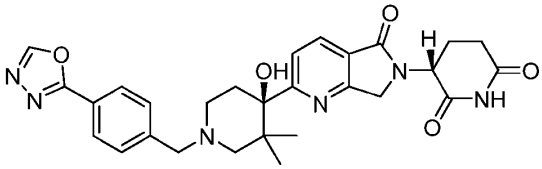
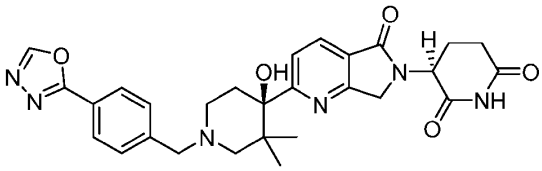
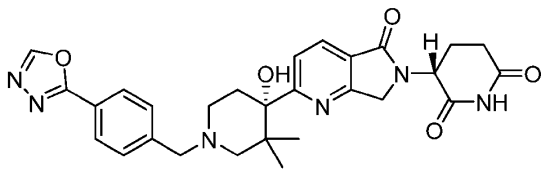
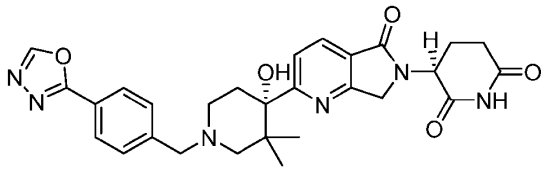
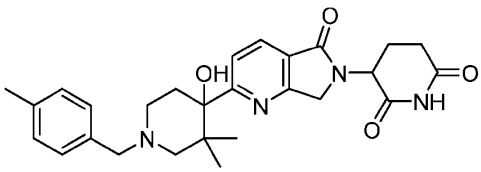
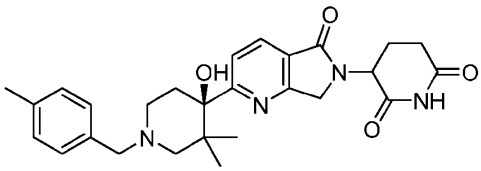
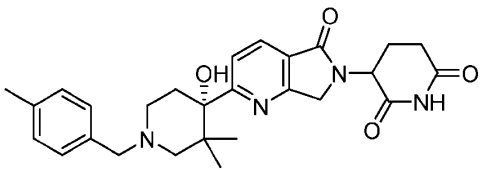
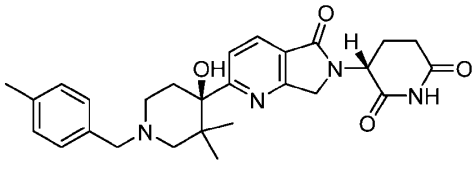
I-557	
I-558	
I-559	
I-560	
I-561	
I-562	

Cmpd No.	Compound Structure
I-563	
I-564	
I-565	
I-566	
I-567	
I-568	

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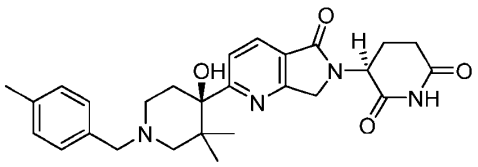
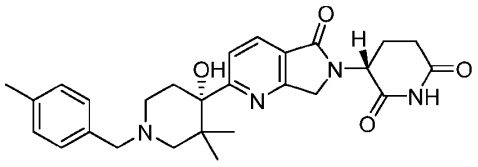
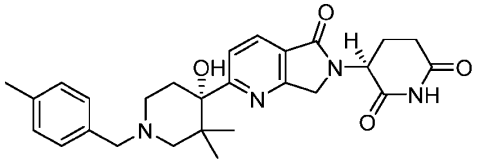
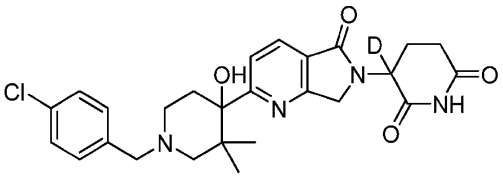
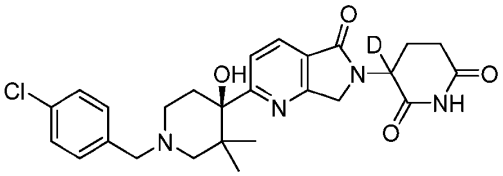
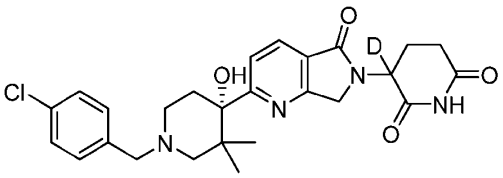
I-569	
I-570	
I-571	
I-572	
I-573	
I-574	

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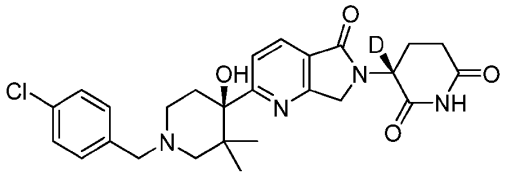
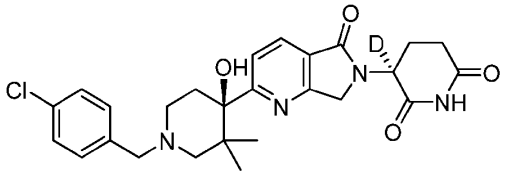
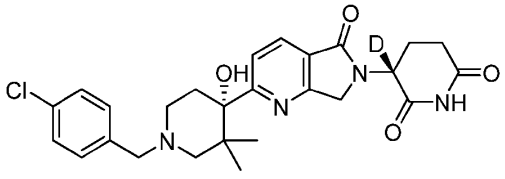
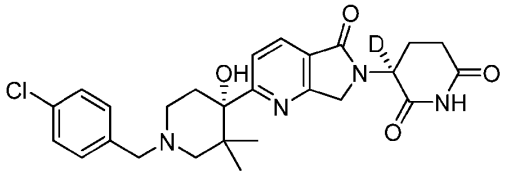
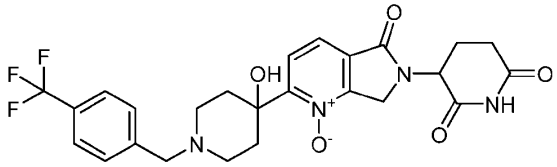
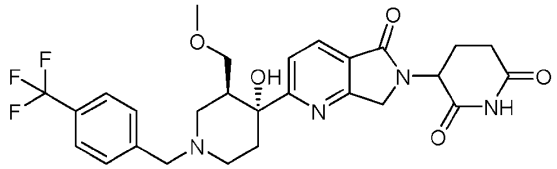
I-575	
I-576	
I-577	
I-578	
I-579	
I-580	

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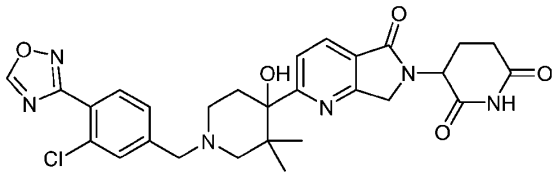
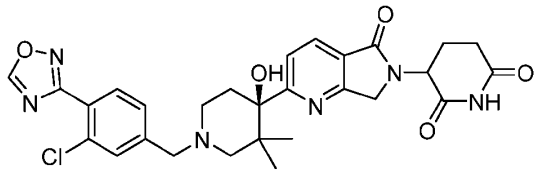
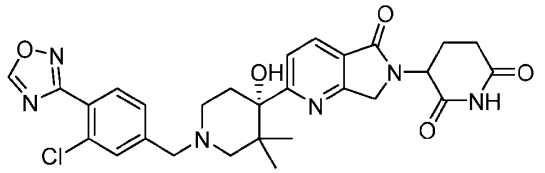
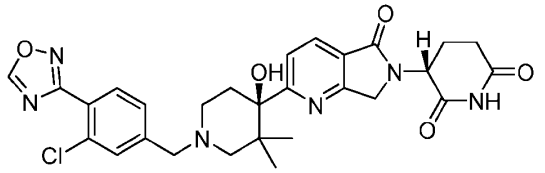
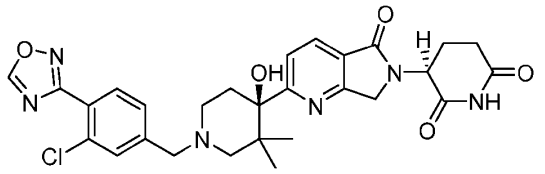
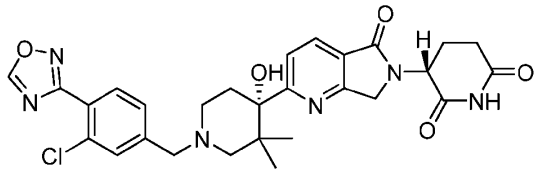
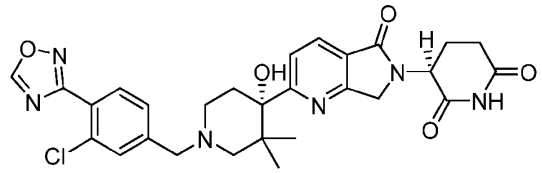
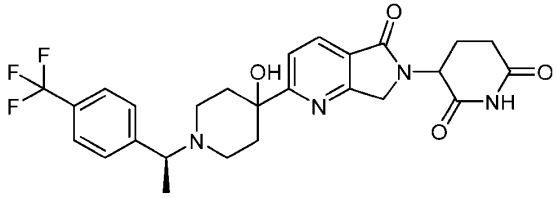
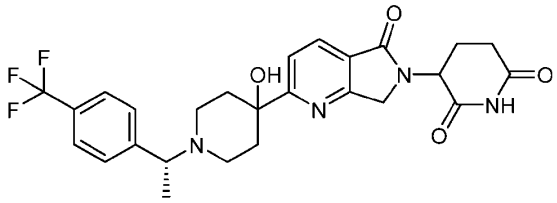
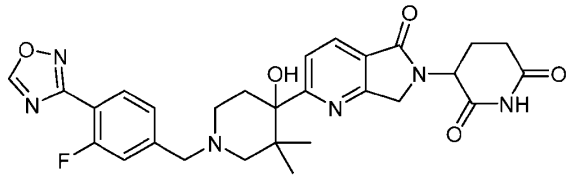
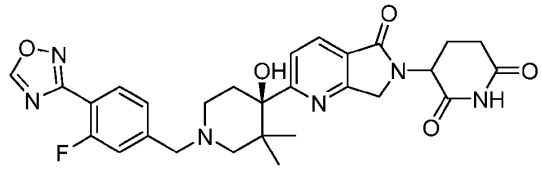
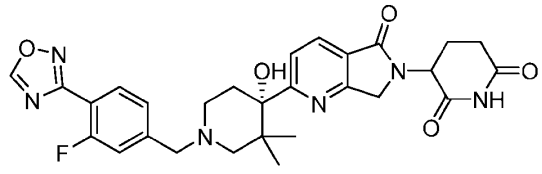
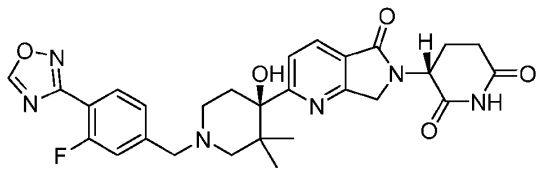
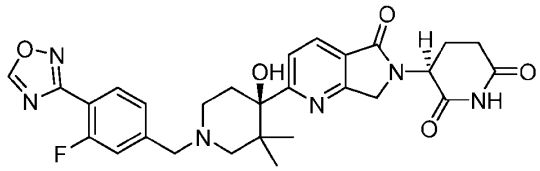
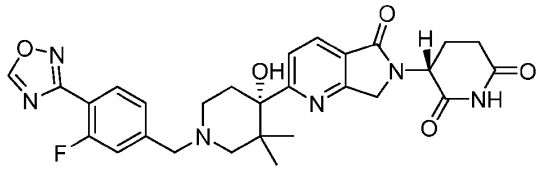
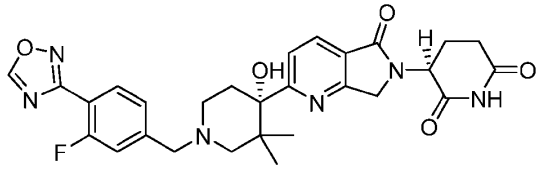
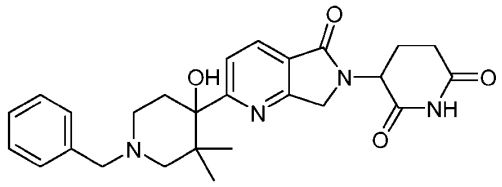
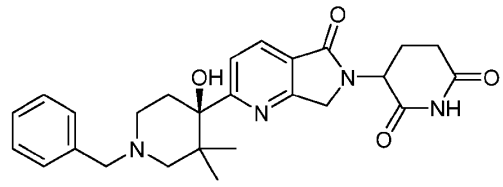
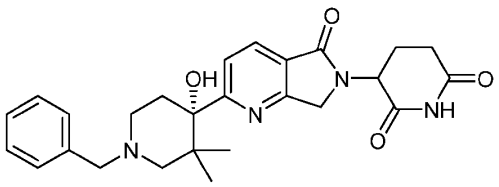
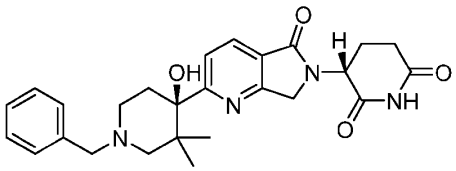
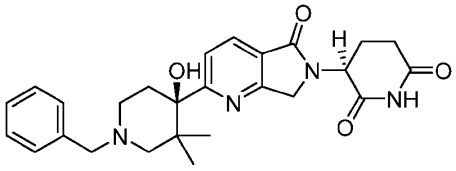
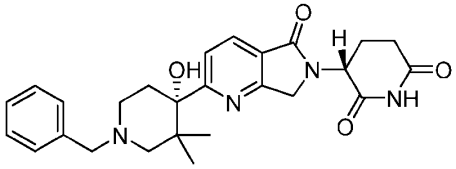
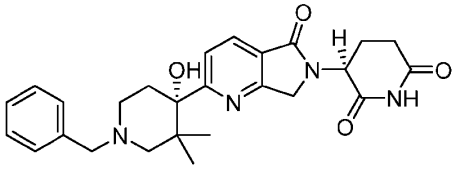
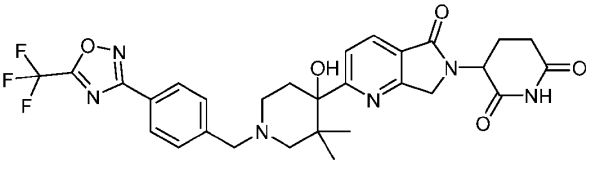
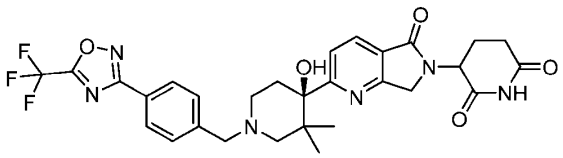
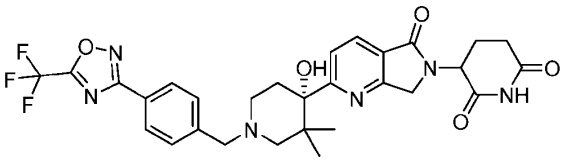
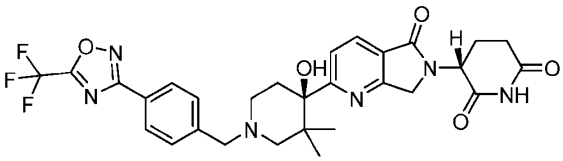
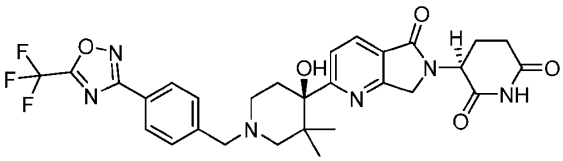
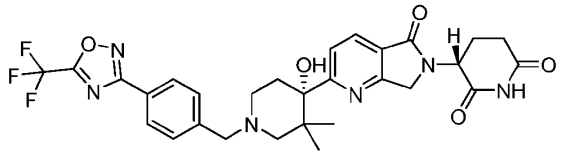
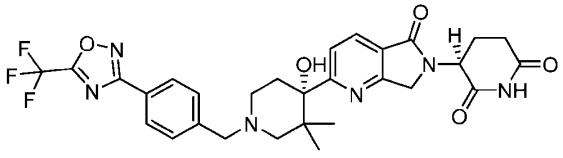
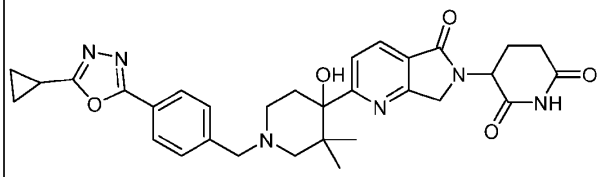
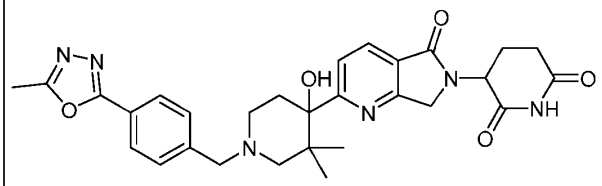
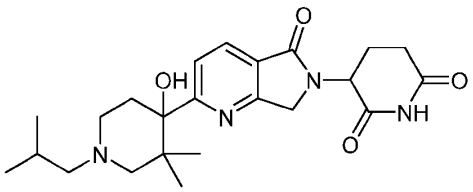
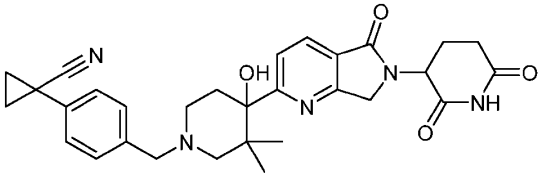
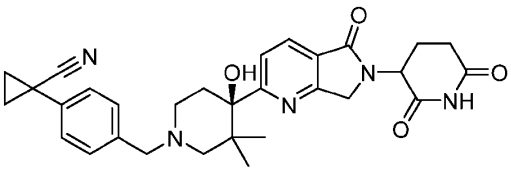
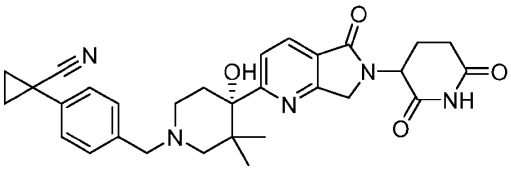
I-581	
I-582	
I-583	
I-584	
I-585	
I-586	

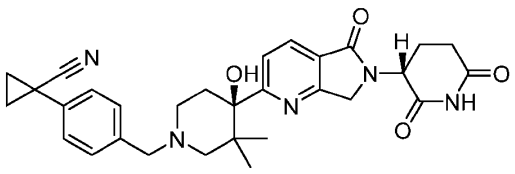
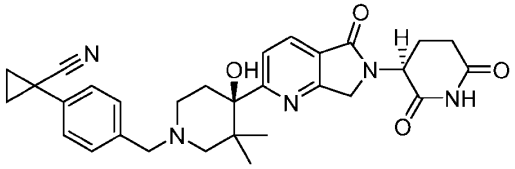
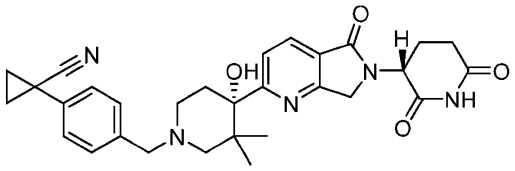
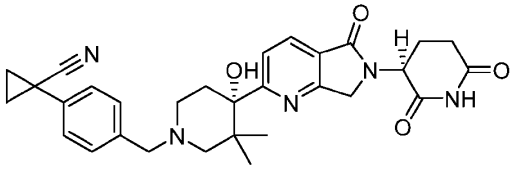
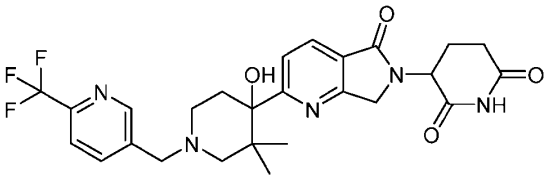
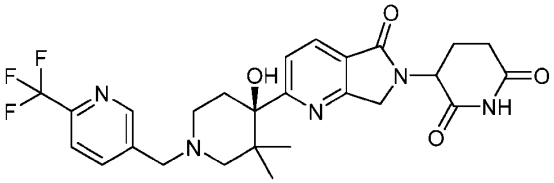
Cmpd No.	Compound Structure
I-587	
I-588	
I-589	
I-590	
I-591	
I-592	

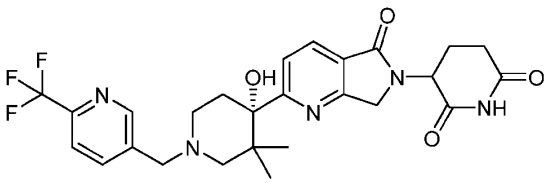
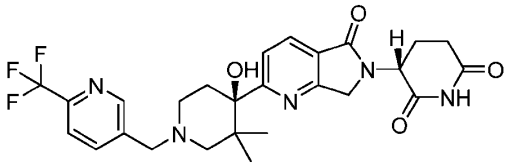
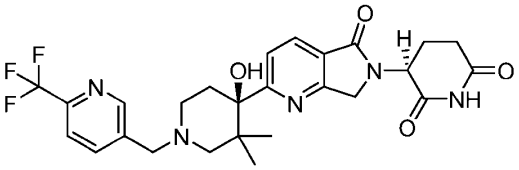
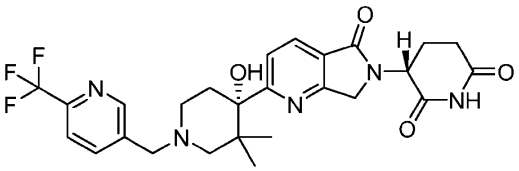
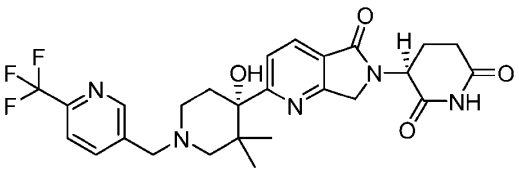
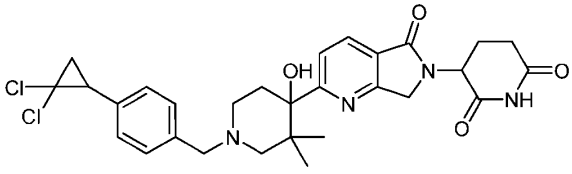
Cmpd No.	Compound Structure
I-593	
I-594	
I-595	
I-596	
I-597	
I-598	

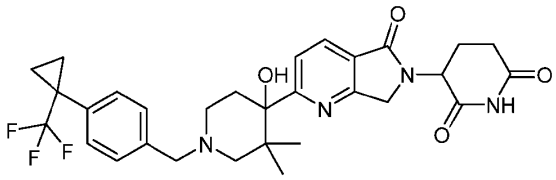
Cmpd No.	Compound Structure
I-599	
I-600	
I-601	
I-602	
I-603	
I-604	

Cmpd No.	Compound Structure
I-605	
I-606	
I-607	
I-608	
I-609	
I-610	

Cmpd No.	Compound Structure
I-611	
I-612	
I-613	
I-614	
I-615	
I-616	

Cmpd No.	Compound Structure
I-617	
I-618	
I-619	
I-620	
I-621	
I-622	

Cmpd No.	Compound Structure
I-623	
I-624	
I-625	
I-626	
I-627	
I-628	

Cmpd No.	Compound Structure
I-629	

* Absolute and relative stereochemistry was not assigned.

Embodiment 1: A Compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

R_a and R_b are each independently H or D;

R_1 is H, D, -C(O)R_{11}, -$CH_2OC(O)R_{11}$, -$CH_2OC(O)NHR_{12}$, -$CH_2OC(O)OR_{12}$, -P(O)$(OR_{12})_2$, -$CH_2OP(O)(OR_{12})_2$, -$CH_2OP(O)(OH)OR_{12}$, -$CH_2OP(O)(R_{12})_2$, -$CH_2OC(O)CH_2NHC(O)CH_2NH_2$, -$CH_2OC(O)CH(R_{12'})NHR_{12'}$, -$CH_2OC(O)(CH_2)_qC(O)OR_{12'}$, or -$CH_2OC(O)$-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S);

R_{2a}, R_{2b}, R_{2c}, and R_{2d} are each independently H or D;

R_3 is H, D, $(C_1$-$C_3)$alkyl, or $(C_1$-$C_3)$deuteroalkyl;

each R_4 is independently at each occurrence D or halogen;

R_5 is H, D, -C(O)R_{11}, -$CH_2OC(O)R_{11}$, -$CH_2OC(O)NHR_{12}$, -$CH_2OC(O)OR_{12}$, -P(O)$(OR_{12})_2$, -$CH_2OP(O)(OH)OR_{12}$, or -$CH_2OP(O)(R_{12})_2$;

R_{6a}, R_{6b}, R_{6c}, and R_{6d} are each independently H, D, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl;

each R_{6e} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, $(C_1$-$C_6)$hydroxyalkyl, -CN, -OH, -O-$(C_1$-$C_6)$hydroxyalkyl, $(C_6$-$C_{10})$aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one or more R_{16}, the aryl and heteroaryl are optionally substituted with one or more R_{18}, and the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{19}; or

two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a $(C_3$-$C_7)$spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms

selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one or more R_{13};

R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{14a}, -$NR_{14}R_{14'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_8 and the carbocyclyl, and heterocyclyl are optionally substituted with one or more $R_{8'}$;

R_8 and $R_{8'}$ are each independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -$C(O)NR_{29}R_{30}$, -$C(O)OR_{29}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more substituents selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -$C(O)NR_{34}R_{35}$, -$C(O)R_{34}$, -$C(O)OR_{34}$, -SF_5, -SR_{37}, and -CN; or

two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R_{10};

two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{10}; or

two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{10}; or

two $R_{8'}$ when on the same carbon atom form C=(O);

R_9 is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, or -CN;

R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN;

R_{12} is independently at each occurrence H, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN;

$R_{12'}$ is independently at each occurrence H or (C_1-C_6)alkyl;

each R_{13} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)O$R_{15'}$, -C(O)R_{15}, or -C(O)N$R_{15'}$$R_{15'}$;

R_{14} and $R_{14'}$ are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{14a} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{15} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

$R_{15'}$ is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -N$R_{17}$$R_{17'}$, -CN, ($C_3$-$C_7$)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein carbocyclyl and heterocyclyl are optionally substituted with one or more R_{22} and the aryl and heteroaryl are optionally substituted with one or more R_{23};

R_{17} and $R_{17'}$ are each independently at each occurrence H or (C_1-C_6)alkyl;

each R_{18} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{20}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{18}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{21}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{19} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

R_{20} and R_{21} are each independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

each R_{22} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{22} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{23} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

R_{24}, R_{25} and R_{26} are each independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{27} and R_{28} are each independently at each occurrence H, (C_1-C_6)alkyl, or -C(O)R_{31};

R_{29}, R_{30}, and R_{31} are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{32} and R_{33} are each independently at each occurrence H, (C_1-C_6)alkyl, or -C(O)R_{36};

R_{34}, R_{35}, and R_{36} are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{37} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

q is 1, 2, or 3;

m is 0, 1 or 2; and

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

Embodiment 2: The compound according to Embodiment 1, having a Formula (IIIa), Formula (IIIb), Formula (IIIc), Formula (IIId), Formula (IIIe), Formula (IIIf), or Formula (IIIg), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 3: The compound according to Embodiment 1 or 2, wherein R_5 is H.

Embodiment 4: The compound according to any one of Embodiments 1-3, wherein R_{6a} is H.

Embodiment 5: The compound according to any one of Embodiments 1-4, wherein R_{6b} is H.

Embodiment 6: The compound according to any one of Embodiments 1-5, wherein R_{6c} is H.

Embodiment 7: The compound according to any one of Embodiments 1-6, wherein R_{6d} is H.

Embodiment 8: The compound according to Embodiment 1, having a Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), or Formula (Il), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 9: The compound according to any one of Embodiments 1-8, wherein R_1 is H.

Embodiment 10: The compound according to any one of Embodiments 1-9, wherein R_3 is H.

Embodiment 11: The compound according to any one of Embodiments 1-10, wherein n is 0.

Embodiment 12: The compound according to any one of Embodiments 1-10, wherein n is 1.

Embodiment 13: The compound according to any one of Embodiments 1-10, wherein n is 2.

Embodiment 14: The compound according to any one of Embodiments 1-13, wherein m is 0.

Embodiment 15: The compound according to any one of Embodiments 1-13, wherein m is 1.

Embodiment 16: The compound according to any one of Embodiments 1-15, wherein R_7 is (C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one or two phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

Embodiment 17: The compound according to any one of Embodiments 1-16, wherein R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one or two phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

Embodiment 18: A compound selected from the group consisting of:

3-(2-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;

3-(2-(3,3-bis(ethyl-d_5)-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;

3-(2-(1-(4-(1,1-difluoroethyl)benzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;

3-(2-(4-hydroxy-1-(pyridin-4-ylmethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;

3-(2-(1-(4-(4-fluorophenoxy)benzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;

3-(2-(4-hydroxy-1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;

3-(2-(4-hydroxy-1-(3-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;

3-(2-(1-(4-chlorobenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(4-hydroxy-1-(4-methylbenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(1-(4-(difluoromethoxy)benzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(4-hydroxy-1-(3-methoxy-4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(1-(4-fluorobenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(4-hydroxy-1-(pyridin-3-ylmethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(4-hydroxy-1-(3-methoxy-4-(trifluoromethoxy)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(4-hydroxy-1-(1-(4-(trifluoromethyl)phenyl)ethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
4-((4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-4-hydroxypiperidin-1-yl)methyl)benzonitrile;
3-(2-(4-hydroxy-1-(4-((trifluoromethyl)thio)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(4-hydroxy-1-(4-(1,1,2,2-tetrafluoroethoxy)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(3,3-diethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
4-((4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile;
3-(5-oxo-2-(1,3,3-triethyl-4-hydroxypiperidin-4-yl)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(3,3-diethyl-4-hydroxy-1-methylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(3,3-diethyl-4-hydroxy-1-isobutylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(3,3-diethyl-4-hydroxy-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;

5-((4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)picolinonitrile;
3-(2-(1-(4-chlorobenzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(1-benzyl-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(4-hydroxy-2-methyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(4-hydroxy-1-(4-(2,2,2-trifluoroethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(4-hydroxy-1-(3-methoxy-4-(trifluoromethoxy)benzyl)-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(1-((4,4-difluorocyclohexyl)methyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(3,3-diethyl-4-hydroxy-1-((tetrahydro-2H-pyran-4-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(4-hydroxy-3,3-bis(methoxymethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(4-hydroxy-3-(methoxymethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
4-((4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)benzonitrile;
3-((4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)-1H-indole-7-carbonitrile;
3-(2-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(8-hydroxy-5-(4-(trifluoromethyl)benzyl)-5-azaspiro[2.5]octan-8-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(9-hydroxy-6-(4-(trifluoromethyl)benzyl)-6-azaspiro[3.5]nonan-9-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;

3-(2-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-9-oxa-2-azaspiro[5.5]undecan-5-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(9,9-difluoro-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(1-(4-(1,1-difluoroethyl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(4-hydroxy-3,3-dimethyl-1-((1-methyl-1H-pyrazol-5-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(3,3-diethyl-4-hydroxy-1-((1-methyl-1H-pyrazol-5-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
4-(((R)-4-(6-((S)-2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile;
4-(((R)-4-(6-((R)-2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile;
4-(((S)-4-(6-((S)-2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile;
4-(((S)-4-(6-((R)-2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile;
3-(2-(4-hydroxy-3,3-dimethyl-1-(3-methyl-4-(1,2,4-oxadiazol-3-yl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(1-((6-(1,2,4-oxadiazol-3-yl)pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(4-hydroxy-1-(4-(isoxazol-3-yl)benzyl)-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
3-(2-(4-hydroxy-3,3-dimethyl-1-((6-(oxazol-4-yl)pyridin-3-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;

3-(2-(1-(4-(difluoromethyl)benzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione-3-d;
3-(2-(1-(4-(difluoromethyl)benzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-3-methylpiperidine-2,6-dione;
3-(2-(1-(4-(1,3,4-oxadiazol-2-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
(S)-3-(2-((R)-4-hydroxy-3,3-dimethyl-1-(4-methylbenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
(R)-3-(2-((S)-4-hydroxy-3,3-dimethyl-1-(4-methylbenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
(R)-3-(2-((R)-4-hydroxy-3,3-dimethyl-1-(4-methylbenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
(S)-3-(2-((S)-4-hydroxy-3,3-dimethyl-1-(4-methylbenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
(S)-3-(2-((S)-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
(R)-3-(2-((R)-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
(R)-3-(2-((S)-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
(S)-3-(2-((R)-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione;
4-(((4R)-4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)benzonitrile;
4-(((4S)-4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)benzonitrile;
(R)-3-(2-((S)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione-3-d;
(S)-3-(2-((S)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione-3-d;
3-(2-((S)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione-3-d;
(R)-3-(2-((R)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione-3-d;

(S)-3-(2-((R)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione-3-d; and
3-(2-((R)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione-3-d;

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 19: A pharmaceutical composition comprising a compound according to any one of Embodiments 1-18, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof; and a pharmaceutically acceptable carrier or excipient.

Embodiment 20: The pharmaceutical composition according to Embodiment 19, further comprising at least one additional pharmaceutical agent.

Embodiment 21: The pharmaceutical composition according to Embodiment 19 or 20 for use in the treatment of a disease or disorder that is affected by the reduction of HIF-1b levels.

Embodiment 22: A method of degrading HIF-1b, comprising administering to a patient in need thereof an effective amount of a compound according to any one of Embodiments 1-18, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 23: A method of modulating HIF-1b levels comprising administering to a patient in need thereof an effective amount of a compound according to any one of Embodiments 1-18, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 24: An *in vitro* method of reducing the proliferation of a cell, comprising contacting the cell with an effective amount of a compound according to any one of Embodiments 1-18, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 25: A method of treating a disease or disorder that is affected by the modulation of HIF-1b levels, comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of Embodiments 1-18, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 26: The method according to Embodiment 25, wherein the disease or disorder is selected from cancer, von Hippel-Lindau (VHL) disease. iron overload disorders, cardiovascular diseases, pulmonary arterial hypertension (PAH), autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, metabolic diseases, and allergic and genetic diseases.

Embodiment 27: The method according to Embodiments 25 or 26, wherein the disease or disorder is selected renal cell carcinoma (RCC), von Hippel-Lindau disease (VHL), pulmonary arterial hypertension (PAH), glioblastoma, colitis, Crohn's disease, ulcerative colitis, T cell leukemia or T cell lymphoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), melanoma, triple-negative breast cancer (TNBC), nasopharyngeal cancer (NPC), microsatellite stable colorectal cancer

(mssCRC), thymoma, carcinoid, gastrointestinal stromal tumor (GIST), myeloid leukemia, and coronary heart disease.

Embodiment 28: A method of treating cancer, comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of Embodiments 1-18, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 29: The method according to Embodiment 28, wherein the cancer is VHL-deficient cancer.

Embodiment 30: The method according to Embodiment 28, wherein the cancer is selected from renal cell carcinoma (RCC), glioblastoma, T cell leukemia or T cell lymphoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), melanoma, triple-negative breast cancer (TNBC), nasopharyngeal cancer (NPC), microsatellite stable colorectal cancer (mssCRC), thymoma, carcinoid, gastrointestinal stromal tumor (GIST), and myeloid leukemia.

Embodiment 31: A method for reducing HIF-1β levels, comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of Embodiments 1-18, or a pharmaceutically acceptable salt thereof.

Embodiment 32: A method of treating von Hippel-Lindau (VHL) disease, comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of Embodiments 1-18, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 33: A method of treating a neoplastic condition, comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of Embodiments 1-18, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 34: A method of treating renal cell carcinoma (RCC), comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of Embodiments 1-18, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 35: The method of Embodiment 34, wherein the renal cell carcinoma is clear cell renal cell carcinoma (ccRCC).

Embodiment 36: The method according to any one of Embodiments 22-35, wherein the administration is oral, parenteral, subcutaneous, by injection, or by infusion.

Embodiment 37: A compound according to any one of Embodiments 1-18, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in the treatment of a disease or disorder that is affected by the reduction of HIF-1β levels.

Embodiment 38: A compound according to any one of Embodiments 1-18, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in treating a disease or disorder associated with the reduction of HIF-1β levels.

Embodiment 39: Use of a compound according to any one of Embodiments 1-18, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for treating a disease or disorder that is affected by the reduction of HIF-1β levels.

Embodiment 40: Use of a compound according to any one of Embodiments 1-18, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the treatment of a disease or disorder associated with the reduction of HIF-1β levels.

Embodiment 41: The compound for use according to Embodiment 37 or 38 or the use according to claim 39 or 40, wherein the disease or disorder is selected from cancer, von Hippel-Lindau (VHL) disease, iron overload disorders, cardiovascular diseases, pulmonary arterial hypertension (PAH), autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, metabolic diseases, and allergic and genetic diseases.

In another embodiment of the disclosure, the compounds of the present disclosure are enantiomers. In some embodiments the compounds are the (S)-enantiomer. In other embodiments the compounds are the (R)-enantiomer. In yet other embodiments, the compounds of the present disclosure may be (+) or (-) enantiomers.

It should be understood that all isomeric forms are included within the present disclosure, including mixtures thereof. If the compound contains a double bond, the substituent may be in the E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans configuration. All tautomeric forms are also intended to be included.

Compounds of the disclosure, and pharmaceutically acceptable salts, hydrates, solvates, stereoisomers, and prodrugs thereof may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present disclosure.

The compounds of the disclosure may contain asymmetric or chiral centers and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the disclosure as well as mixtures thereof, including racemic mixtures, form part of the present disclosure. In addition, the present disclosure embraces all geometric and positional isomers. For example, if a compound of the disclosure incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the disclosure. Each compound herein disclosed includes all the enantiomers that conform to the general structure of the compound. The compounds may be in a racemic

or enantiomerically pure form, or any other form in terms of stereochemistry. The assay results may reflect the data collected for the racemic form, the enantiomerically pure form, or any other form in terms of stereochemistry.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (*e.g.*, chiral auxiliary such as a chiral alcohol or Masher's acid chloride), separating the diastereomers and converting (*e.g.*, hydrolyzing) the individual diastereomers to the corresponding pure enantiomers or via chiral chromatography. Also, some of the compounds of the disclosure may be atropisomers (*e.g.*, substituted biaryls) and are considered as part of this disclosure. Enantiomers can also be separated by use of a chiral HPLC column.

It is also possible that the compounds of the disclosure may exist in different tautomeric forms, and all such forms are embraced within the scope of the disclosure and chemical structures and names. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the disclosure.

All stereoisomers (for example, geometric isomers, optical isomers, and the like) of the present compounds (including those of the salts, solvates, esters, and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this disclosure, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). (For example, if a Compound of Formula (I) of Formula (II) incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the disclosure. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the disclosure.) Individual stereoisomers of the compounds of the disclosure may, for example, be substantially free of other isomers, or is admixed, for example, as racemates or with all other, or other selected, stereoisomers.

The chiral centers of the compounds of the disclosure can have the S or R configuration as defined by the IUPAC 1974 Recommendations. In certain embodiments, each asymmetric atom has at least 50% enantiomeric excess, at least 60% enantiomeric excess, at least 70% enantiomeric excess, at least 80% enantiomeric excess, at least 90% enantiomeric excess, at least 95% enantiomeric excess, or at least 99% enantiomeric excess in the (R)- or (S)- configuration. Substituents at atoms with unsaturated double bonds may, if possible, be present in cis-(Z)- or trans-(E)- form.

The use of the terms "salt", "solvate", "ester," "prodrug", and the like, is intended to equally apply to the salt, solvate, ester, and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates, or prodrugs of the inventive compounds.

The compounds of the disclosure may form salts which are also within the scope of this disclosure. Reference to a compound of the Formula herein is generally understood to include reference to salts thereof, unless otherwise indicated.

The compounds and intermediates may be isolated and used as the compound per se. Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, and fluorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F, ^{31}P, ^{32}P, respectively.

The disclosure includes various isotopically labeled compounds as defined herein, for example those into which radioactive isotopes, such as ^{3}H, ^{13}C, and ^{14}C, are present. Such isotopically labelled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F, lie or labeled compound may be particularly desirable for PET or SPECT studies.

Further, substitution with heavier isotopes, particularly deuterium (i.e., ^{2}H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life, reduced dosage requirements, reduced CYP450 inhibition (competitive or time dependent) or an improvement in therapeutic index. For example, substitution with deuterium may modulate undesirable side effects of the undeuterated compound, such as competitive CYP450 inhibition, time dependent CYP450 inactivation, etc. It is understood that deuterium in this context is regarded as a substituent in compounds of the present disclosure. The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this disclosure is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation, at 6333.3 (95% deuterium incorporation), at

least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

Isotopically-labeled compounds of the present disclosure can generally be prepared by conventional techniques known to those skilled in the art or by carrying out the procedures disclosed in the schemes or in the examples and preparations described below using an appropriate isotopically-labeled reagent in place of the non-isotopically labeled reagent.

Pharmaceutically acceptable solvates in accordance with the disclosure include those wherein the solvent of crystallization may be isotopically substituted, *e.g.*, D_2O, d_6-acetone, d_6-DMSO.

The present disclosure relates to compounds which are modulators of HIF-1β protein levels. In one embodiment, the compounds of the present disclosure decrease HIF-1β protein levels. In yet one embodiment, the compounds of the present disclosure reduce HIF-1β protein levels. In another embodiment, the compounds of the present disclosure are degraders of HIF-1β.

As used herein, the term "IC_{50}" refers to half maximal inhibitory concentration. As used herein, the term "DC_{50}" refers to half maximal degradation concentration. As used herein, the term "EC_{50}" refers to half maximal effective concentration. As used herein, the term "AC_{50}" refers to half maximal activation. As used herein, Dmax is the maximum level of degradation achievable.

In some embodiments, the degradation of HIF-1β is measured by DC_{50}.

Potency of a compound of the present disclosure towards degradation of HIF-1β can be measured by its DC_{50} value. A compound with a lower DC_{50} value, as determined under substantially similar degradation conditions, is a more potent degrader relative to a compound with a higher DC_{50} value. In some embodiments, the substantially similar conditions comprise determining degradation of protein levels in cells expressing the specific protein, or a fragment of any thereof.

In some embodiments, a compound of the present disclosure exhibits selectivity for HIF-1b over another target, such as IKZF1, IKZF2, IKZF3, CK1a. SALL4, or GSPT1. Selectivity for modulating the degradation of one target protein (e.g., HIF-1b) over another protein may be measured using any number of methods known in the art. In some embodiments, a compound of Formula (I), (II), (III) or a pharmaceutically acceptable salt thereof exhibits selectivity for degradation of HIF-1b over another protein (e.g., IKZF1, IKZF2, IKZF3, CK1a. SALL4, or GSPT1) at a ratio of greater than 1.1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 75, or 100.

In some embodiments, a compound of the present disclosure exhibits improved cell membrane permeability upon administration to a cell or subject compared to another compound, e.g., in a standard assay for measuring cell permeability. In some embodiments, a compound of the present disclosure exhibits improved cell viability upon administration to a cell or subject compared with another compound, e.g., in a standard assay for measuring cell viability. In some embodiments, a compound of the present disclosure

exhibits improved metabolic stability upon administration to a cell or subject compared with another compound, e.g., in a standard assay for measuring metabolic stability. In some embodiments, a compound of the present disclosure exhibits reduced hERG inhibition upon administration to a cell or subject compared with another compound, e.g., in a standard assay for measuring hERG inhibition.

The disclosure is directed to compounds as described herein and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, or tautomers thereof, and pharmaceutical compositions comprising one or more compounds as described herein, or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, or tautomers thereof.

F. Methods of Synthesizing Compounds of Formula (I), (II), or (III)

The compounds of the present disclosure may be made by a variety of methods, including standard chemistry. Suitable synthetic routes are depicted in the Schemes given below.

The compounds of the present disclosure may be prepared by methods known in the art of organic synthesis as set forth in part by the following synthetic schemes. In the schemes described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles or chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection processes, as well as the reaction conditions and order of their execution, shall be consistent with the preparation of Compounds of Formula (I), (II), or (III).

Those skilled in the art will recognize if a stereocenter exists in the compounds of the present disclosure. Accordingly, the present disclosure includes all possible stereoisomers (unless specified in the synthesis) and includes not only racemic compounds but the individual enantiomers and/or diastereomers as well. When a compound is desired as a single enantiomer or diastereomer, it may be obtained by stereo specific synthesis or by resolution of the final product or any convenient intermediate. Resolution of the final product, an intermediate, or a starting material may be affected by any suitable method known in the art. See, for example, "Stereochemistry of Organic Compounds" by E.L. Eliel, S.H. Wilen, and L.N. Mander (Wiley-Interscience, 1994).

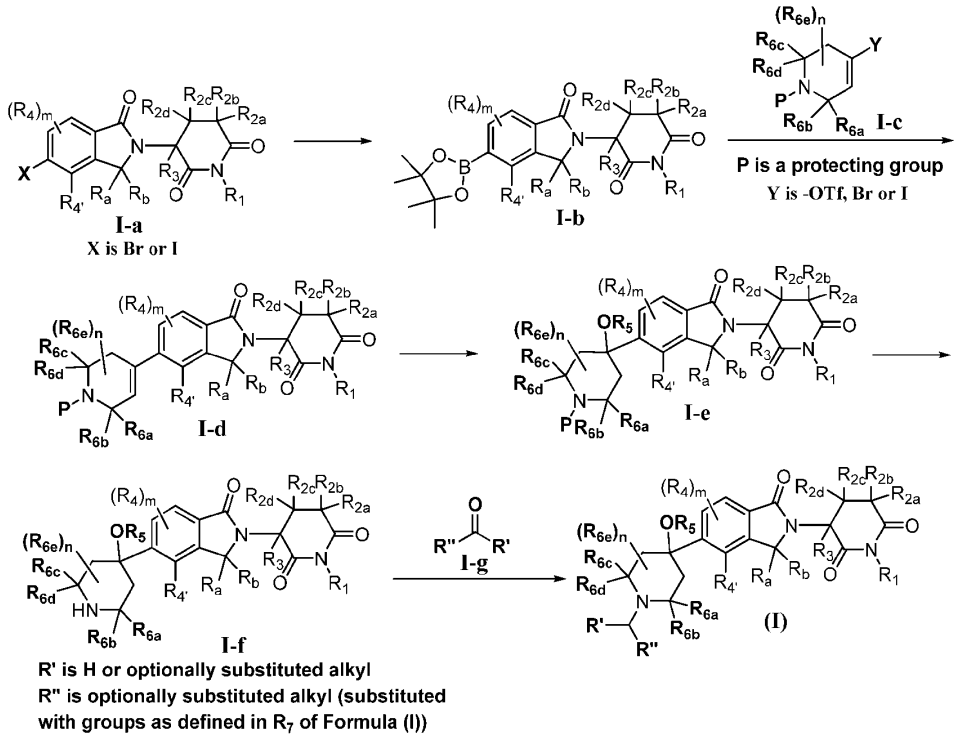
The compounds described herein may be made from commercially available starting materials or synthesized using known organic, inorganic, and/or enzymatic processes.

Preparation of Compounds

Compounds of the present disclosure can be synthesized by following the steps outlined in General Schemes I, II, III, IV, V, VI, VII, and VIII which comprise different sequences of assembling intermediates **I-a**, **I-b**, **I-c**, **I-d**, **I-e**, **I-f**, **I-g**, **II-a**, **II-b**, **III-a**, **IV-a**, **V-a**, **V-b**, **V-c**, **V-d**, **V-e**, **V-f**, **V-g**, **VI-a**, **VII-a**, and

VIII-a. Starting materials are either commercially available or made by known procedures in the reported literature or as illustrated in the Examples section herein below.

General Scheme I

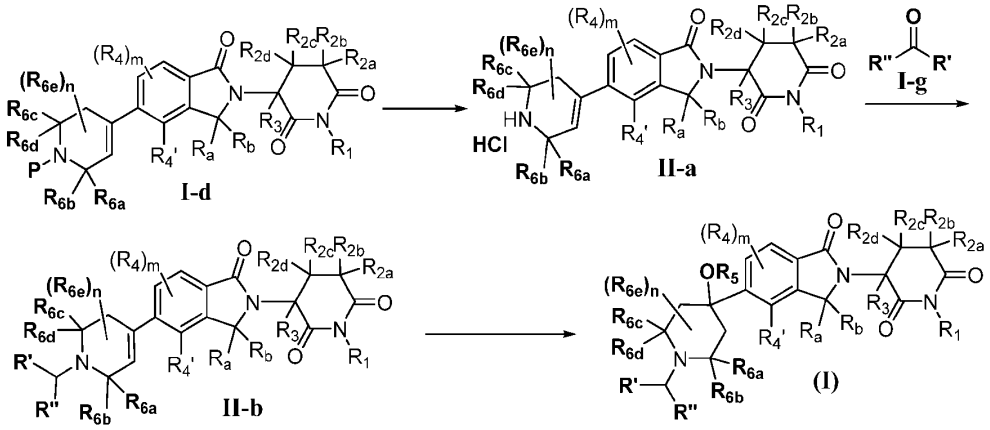


wherein R_a, R_b, R_1, R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, R_4, $R_{4'}$, R_5, R_{6a}, R_{6b}, R_{6c}, R_{6d}, R_{6e}, m and n are as defined in Formula (I).

The general way of preparing Compounds of Formula (I), wherein R_5 is H and R_7 is (C_1-C_6)alkyl substituted with optionally substituted phenyl, 5- or 6-membered heteroaryl, carbocyclyl, or heterocyclyl by using intermediates **I-a**, **I-b**, **I-c**, **I-d**, **I-e**, **I-f**, and **I-g** is outlined in General Scheme I. Borylation of **I-a** using a borylation reagent (*e.g.*, bis(pinacolato)diboron (B_2Pin_2), or bis(catecholato)diboron (B_2Cat_2), etc.) in the presence of a metal catalyst (e.g., Pd(dppf)Cl_2•DCM, Pd(tBu_3P)$_2$, etc.) and a base (*e.g.*, potassium carbonate (K_2CO_3), cesium carbonate (Cs_2CO_3), potassium acetate (KOAc), etc.) in a solvent (*e.g.* N,N-dimethylformamide (DMF), dioxane, water, etc.) and optionally at elevated temperature provides **I-b**. Coupling of boronic ester **I-b** with **I-c** using a metal catalyst (*e.g.*, Pd(dppf)Cl_2•DCM, Pd(tBu_3P)$_2$, etc.), and a base (*e.g.*, N,N-diisopropylethylamine (DIPEA), triethylamine (Et_3N), potassium acetate (KOAc), cesium carbonate (Cs_2CO_3), etc.), in a solvent (*e.g.*, DMF, 1,4-dioxane, water, etc.) optionally at elevated temperature (*e.g.*, heat, microwave) provides **I-d**. Hydration of **I-d** using oxygen, a metal catalyst (*e.g.*, tris(2,2,6,6-tetramethyl-3,5-heptanedionato)manganese(III) (Mn(dpm)$_3$), cobalt(II) acetylacetonate

$(Co(acac)_2)$, etc.) and an alkyl or aryl silane (*e.g.*, phenylsilane, triethylsilane, etc.) in a solvent (*e.g.*, dichloromethane (DCM), isopropanol (IPA), DMF, etc.) provides **I-e**. When P is an acid labile amine protecting group (*e.g.*, tert-butyloxycarbonyl (Boc), etc.) intermediate **I-e** is deprotected using a strong acid such as trifluoroacetic acid (TFA), hydrochloric acid (HCl), or methanesulfonic acid in a solvent (*e.g.*, tetrahydrofuran (THF), 1,2,-dichloroethane, dioxane or dichloromethane (DCM), acetonitrile (ACN), etc.) optionally at elevated temperature to provide **I-f**. Reductive animation of **I-f** with aldehyde or ketone **I-g** in the presence of a reducing agent (*e.g.*, sodium borohydride ($NaBH_4$), sodium triacetoxyborohydride (STAB), sodium cyanoborohydride ($NaBH_3CN$), MP-cyanoborohydride, etc.), optionally a base (*e.g.*, DIPEA, sodium acetate, etc.) or an acid (*e.g.*, acetic acid, etc.), and in a solvent (*e.g.*, DMF, methanol (MeOH), dichloroethane, (DCE), DCM, etc.) optionally at elevated temperature provides a Compound of Formula (I) where R_5 is H and R_7 is (C_1-C_6)alkyl substituted with optionally substituted phenyl, 5- or 6-membered heteroaryl, carbocyclyl, or heterocyclyl.

General Scheme II



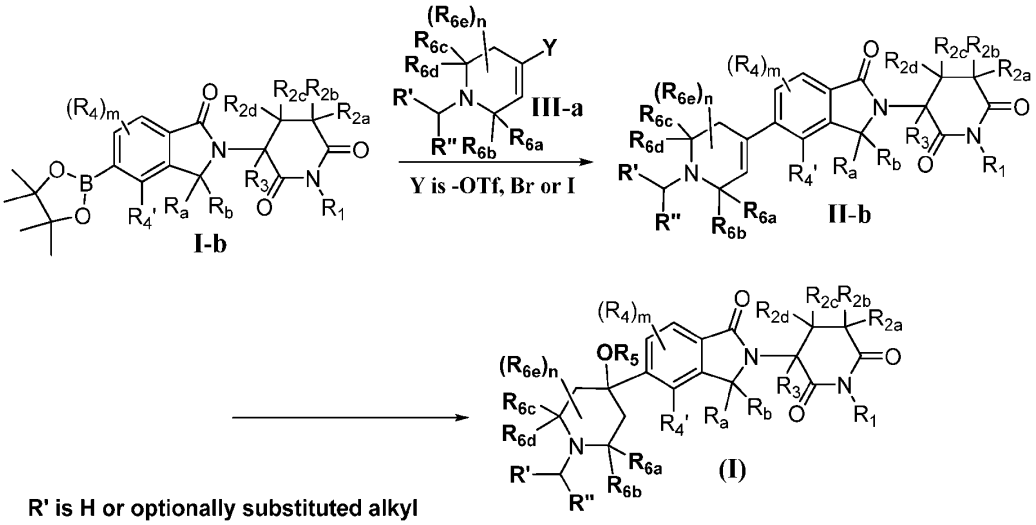
R' is H or optionally substituted alkyl
R" is optionally substituted alkyl (substituted with groups as defined in R_7 of Formula (I))

wherein R_a, R_b, R_1, R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, R_4, $R_{4'}$, R_5, R_{6a}, R_{6b}, R_{6c}, R_{6d}, R_{6e}, m and n are as defined in Formula (I).

Alternatively, the Compounds of Formula (I) wherein R_5 is H and R_7 is (C_1-C_6)alkyl substituted with optionally substituted phenyl, 5- or 6-membered heteroaryl, carbocyclyl, or heterocyclyl can be prepared by using intermediates **I-d**, **I-g**, **II-a**, and **II-b** as outlined in General Scheme II. When P is an acid labile amine protecting group (*e.g.*, Boc, etc.) intermediate **I-d** is deprotected using a strong acid such as trifluoroacetic acid (TFA), hydrochloric acid (HCl), or methanesulfonic acid in a solvent (*e.g.*, THF, 1,2-dichloroethane, dioxane or DCM) optionally at elevated temperature to provide **II-a**. Reductive animation

of **II-a** with aldehyde or ketone **I-g** in the presence of a reducing agent (*e.g.*, $NaBH_4$, STAB, $NaBH_3CN$, MP-cyanoborohydride, etc.), optionally a base (*e.g.*, DIPEA, sodium acetate, etc.) or an acid (*e.g.*, acetic acid, etc.), and in a solvent (*e.g.*, DMF, MeOH, DCM, etc.) optionally at elevated temperature provides **II-b**. Hydration of **II-b** using oxygen, a metal catalyst (*e.g.*, $Mn(dpm)_3$, $Co(acac)_2$, etc.) and an alkyl or aryl silane (*e.g.*, phenylsilane, triethylsilane, etc.) in a solvent (*e.g.*, DCM, IPA, DMF, etc.) provides a Compound of Formula (I) where R_5 is H and R_7 is (C_1-C_6)alkyl substituted with optionally substituted phenyl, 5- or 6-membered heteroaryl, carbocyclyl, or heterocyclyl.

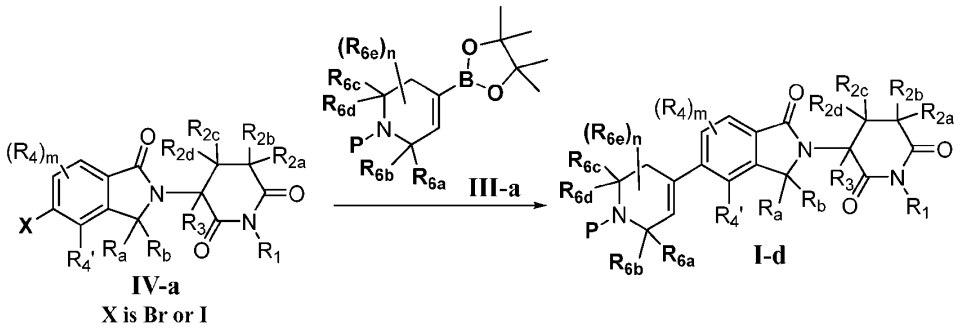
General Scheme III



wherein R_a, R_b, R_1, R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, R_4, $R_{4'}$, R_5, R_{6a}, R_{6b}, R_{6c}, R_{6d}, R_{6e}, m and n are as defined in Formula (I).

Compounds of Formula (I) wherein R_5 is H and R_7 is (C_1-C_6)alkyl substituted with optionally substituted phenyl, 5- or 6-membered heteroaryl, carbocyclyl, or heterocyclyl can also be prepared by using intermediates **I-b**, **II-b**, and **III-a** as outlined in General Scheme III. Coupling of boronic ester **I-b** with **III-a** using a metal catalyst (*e.g.*, $Pd(dppf)Cl_2$•DCM, $Pd(tBu_3P)_2$, etc.), and a base (*e.g.*, N,N-diisopropylethylamine (DIPEA), triethylamine (Et_3N), potassium acetate (KOAc), cesium carbonate (Cs_2CO_3), etc.), in a solvent (*e.g.*, DMF, 1,4-dioxane, water, etc.) optionally at elevated temperature (*e.g.*, heat, microwave) provides **II-b**. Hydration of **II-b** using oxygen, a metal catalyst (*e.g.*, $Mn(dpm)_3$, $Co(acac)_2$, etc.) and an alkyl or aryl silane (*e.g.*, phenylsilane, triethylsilane, etc.) in a solvent (*e.g.*, DCM, IPA, DMF, etc.) provides the Compound of Formula (I) where R_5 is H and R_7 is (C_1-C_6)alkyl substituted with optionally substituted phenyl, 5- or 6-membered heteroaryl, carbocyclyl, or heterocyclyl.

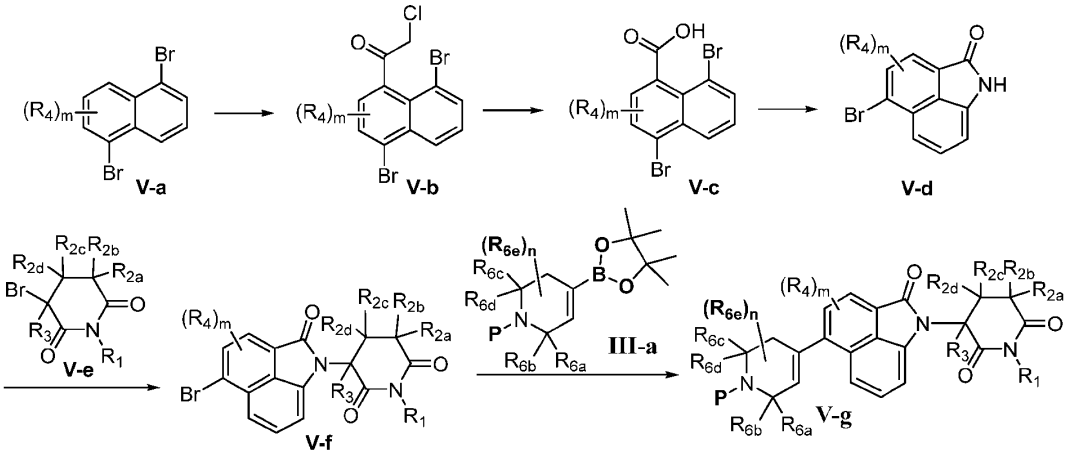
General Scheme IV



wherein R_a, R_b, R_1, R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, R_4, $R_{4'}$, R_{6a}, R_{6b}, R_{6c}, R_{6d}, R_{6e}, m and n are as defined in Formula (I).

Intermediate **I-d** can also be prepared by using intermediates **III-a** and **IV-a** as outlined in General Scheme IV. Coupling of boronic ester **III-a** with **IV-a** using a metal catalyst (*e.g.*, $Pd(dppf)Cl_2$•DCM, $Pd(tBu_3P)_2$, etc.), and a base (*e.g.*, N,N-diisopropylethylamine (DIPEA), triethylamine (Et_3N), potassium acetate (KOAc), cesium carbonate (Cs_2CO_3), etc.), in a solvent (*e.g.*, DMF, 1,4-dioxane, water, etc.) optionally at elevated temperature (*e.g.*, heat, microwave) provides intermediate **I-d**.

General Scheme V

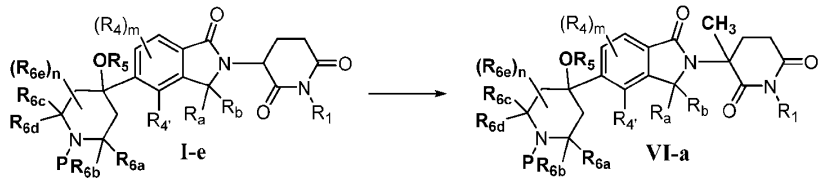


wherein R_1, R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, R_4, R_{6a}, R_{6b}, R_{6c}, R_{6d}, R_{6e}, m and n are as defined in Formula (II).

The general way of preparing intermediate **V-g** for the synthesis of Compounds of Formula (II), wherein R_5 is H and R_7 is (C_1-C_6)alkyl substituted with optionally substituted phenyl, 5- or 6-membered heteroaryl, carbocyclyl, or heterocyclyl by using intermediates **V-a**, **V-b**, **V-c**, **V-d**, **V-e**, **V-f**, and **V-g** is outlined in General Scheme V. Alkylation of **V-a** with chloroacetyl chloride in the presence of a Lewis acid (e.g., $AlCl_3$, $TiCl_4$, etc.) and in a solvent (*e.g.* DCE, DCM, etc.) and optionally at lower temperature provides

V-b. Treatment of V-b with a strong acid (e.g., sulfuric acid (H_2SO_4), HCl, etc.) and sodium nitrite in water provides carboxylic acid **V-c**. Cyclization of **V-c** using a metal catalyst (e.g., copper) and ammonium hydroxide optionally at elevated temperature provides **V-d**. Alkylation of **V-d** with **V-e** in the presence of a base (e.g., NaH, LiH, etc.) in a solvent (e.g., THF, DCM, etc.) provides **V-f**. Coupling of boronic ester **III-a** with **V-f** using a metal catalyst (*e.g.*, $Pd(dppf)Cl_2$•DCM, $Pd(tBu_3P)_2$, etc.), and a base (*e.g.*, N,N-diisopropylethylamine (DIPEA), triethylamine (Et_3N), potassium acetate (KOAc), cesium carbonate (Cs_2CO_3), etc.), in a solvent (*e.g.*, DMF, 1,4-dioxane, water, etc.) optionally at elevated temperature (*e.g.*, heat, microwave) provides intermediate **V-g**. The Compound of Formula (II) where R_5 is H and R_7 is (C_1-C_6)alkyl substituted with optionally substituted phenyl, 5- or 6-membered heteroaryl, carbocyclyl, or heterocyclyl can be then obtained from intermediate **V-g** using the same sequence as shown above in General Schemes 1 and 2 for the synthesis of the Compound of Formula (I) from intermediate **I-d**.

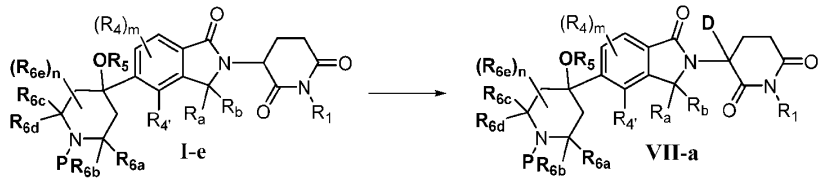
General Scheme VI



wherein R_a, R_b, R_1, R_4, $R_{4'}$, R_5, R_{6a}, R_{6b}, R_{6c}, R_{6d}, R_{6e}, m and n are as defined in Formula (I).

Intermediate **VI-a**, wherein R_{2a}, R_{2b}, R_{2c}, and R_{2d} are H and R_3 is methyl, can be prepared according to the procedures and examples as reported in PCT Application Publication No. WO2017/197046 by using Intermediate **I-e** as outlined in General Scheme VI. Deprotonation of **I-e** with a suitable base such as lithium bis(trimethylsilylamide) in a suitable solvent such as tetrahydrofuran, at a suitable temperature, for example, about -78 °C, followed by treatment with iodomethane provides **VI-a**. Intermediate **VI-a** can be deprotected and alkylated via reductive amination with an aldehyde or ketone as described in General Scheme I to provide a Compound of Formula (I) where R_5 is H and R_7 is (C_1-C_6)alkyl substituted with optionally substituted phenyl, 5- or 6-membered heteroaryl, carbocyclyl, or heterocyclyl.

General Scheme VII:

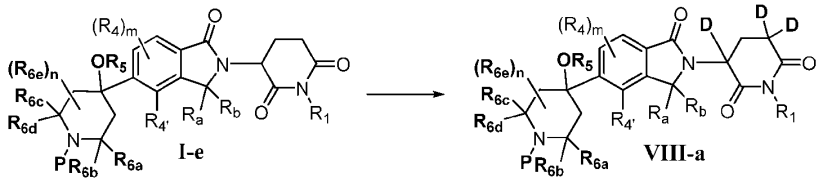


wherein R_a, R_b, R_1, R_4, $R_{4'}$, R_5, R_{6a}, R_{6b}, R_{6c}, R_{6d}, R_{6e}, m and n are as defined in Formula (I).

Intermediate **VII-a**, wherein R_{2a}, R_{2b}, R_{2c}, and R_{2d} are H and R_3 is deuterium, can be prepared according to the procedures and examples as reported in PCT Application Publication No. WO2017/197046

by using Intermediate **I-e** as outlined in General Scheme VII. Deprotonation of **I-e** with a suitable a base such as lithium bis(trimethylsilyl)amide in a suitable solvent such as tetrahydrofuran, at a suitable temperature, for example, about -78 °C, followed by treatment with acetic acid-*d* provides Intermediate **VII-a.** Intermediate **VII-a** can be deprotected and alkylated via reductive amination with an aldehyde or ketone as described in General Scheme I to provide a Compound of Formula (I) where R_5 is H and R_7 is (C_1-C_6)alkyl substituted with optionally substituted phenyl, 5- or 6-membered heteroaryl, carbocyclyl, or heterocyclyl.

General Scheme VIII:



wherein R_a, R_b, R_1, R_4, $R_{4'}$, R_5, R_{6a}, R_{6b}, R_{6c}, R_{6d}, R_{6e}, m and n are as defined in Formula (I).

Intermediate **VIII-a**, wherein R_{2c} and R_{2d} are H, R_3 is deuterium, and R_{2a} and R_{2b} are deuterium, can be prepared as reported in PCT Application Publication No. WO2022/012622 by using Intermediate **I-e** as outlined in General Scheme VIII. Treatment of **I-e** with chlorotrimethylsilane and triethylamine in a suitable solvent, such as acetonitrile, at a suitable temperature, for example, between 23 °C and 80 °C, followed by treatment with D_2O at low temperature, for example at 0 °C, provides **VIII-a.** Intermediate **VIII-a** can be deprotected and alkylated via reductive amination with an aldehyde or ketone as described in General Scheme I to provide a Compound of Formula (I) where R_5 is H and R_7 is (C_1-C_6)alkyl substituted with optionally substituted phenyl, 5- or 6-membered heteroaryl, carbocyclyl, or heterocyclyl.

A mixture of enantiomers, diastereomers, and cis/trans isomers resulting from the process described above can be separated into their single components by chiral salt technique, chromatography using normal phase, reverse phase or chiral column, depending on the nature of the separation.

Any resulting racemates of compounds of the present disclosure or of intermediates can be resolved into the optical antipodes by known methods, *e.g.*, by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic moiety may thus be employed to resolve the compounds of the present disclosure into their optical antipodes, *e.g.*, by fractional crystallization of a salt formed with an optically active acid, *e.g.*, tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-O,O'-p-toluoyl tartaric acid, mandelic acid, malic acid, or camphor-10-sulfonic acid. Racemic compounds of the present disclosure or racemic intermediates can also be resolved by chiral chromatography, *e.g.*, high pressure liquid chromatography (HPLC) using a chiral adsorbent.

Any resulting mixtures of stereoisomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

It should be understood that in the description and formula shown above, the various groups R_a, R_b, R_1, R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, R_4, $R_{4'}$, R_5, R_{6a}, R_{6b}, R_{6c}, R_{6d}, R_{6e}, m and n and other variables are of Formula (I) or (II) are as defined above, except where otherwise indicated. Furthermore, for synthetic purposes, the compounds of General Schemes I, II, III, IV, V, VI, VII, and VIII are merely representative with elected radicals to illustrate the general synthetic methodology of the Compounds of Formula (I), (II), or (III) as defined herein.

G. Methods of Using Compounds of Formula (I), (II), or (III)

In one aspect of the disclosure relates to a method of treating, preventing, inhibiting, or eliminating a disease or disorder in a patient associated with or affected by modulation of HIF-1β protein levels. The method comprises administering to a patient in need of a treatment for diseases or disorders associated with modulation of HIF-1β protein levels an effective amount of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. Examples of diseases or conditions associated with or affected by modulation of HIF-1β protein levels include, but not limited to, cell proliferative diseases and disorders (*e.g.*, cancer or benign neoplasms), von Hippel-Lindau (VHL) disease, iron overload disorders, immune-related disorders, cardiovascular diseases, pulmonary arterial hypertension (PAH), inflammatory diseases and conditions, autoimmune diseases, neurodegenerative diseases, viral diseases, bacterial infections, fungal infections, parasitic infections, chronic and acute kidney diseases or injuries, metabolic diseases, and allergic and genetic diseases. In another embodiment, the disease or disorder is selected from renal cell carcinoma, von Hippel-Lindau disease, pulmonary arterial hypertension, glioblastoma, colitis, Crohn's disease, ulcerative colitis, T cell leukemia or T cell lymphoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), melanoma, triple-negative breast cancer (TNBC), nasopharyngeal cancer (NPC), microsatellite stable colorectal cancer (mssCRC), thymoma, carcinoid, gastrointestinal stromal tumor (GIST), myeloid leukemia, and coronary heart disease. In one embodiment, the disease or condition is selected from renal cell carcinoma, von Hippel-Lindau disease, pulmonary arterial hypertension, glioblastoma, and colitis. In another embodiment, compounds of the present invention may be used to treat T cell leukemia or T cell lymphoma. In yet another embodiment, the disease or disorder is Hodgkin's lymphoma or non-Hodgkin's lymphoma. In another embodiment, the disease or disorder is non-small cell lung cancer (NSCLC). In yet another embodiment, the disease or

disorder is renal cell carcinoma (RCC). In one embodiment, the renal cell carcinoma is clear cell renal cell carcinoma (ccRCC). In another embodiment, the disease or disorder is melanoma. In yet another embodiment, the disease or disorder is triple-negative breast cancer (TNBC). In another embodiment, the disease or disorder is nasopharyngeal cancer (NPC). In yet another embodiment, the disease or disorder is microsatellite stable colorectal cancer (mssCRC). In another embodiment, the disease or disorder is thymoma. In yet another embodiment, the disease or disorder is carcinoid. In another embodiment, the disease or disorder is gastrointestinal stromal tumor (GIST). In yet another embodiment, the disease or disorder is myeloid leukemia. In another embodiment, the disease or disorder is coronary heart disease. In yet another embodiment, the disease or disorder is pulmonary arterial hypertension (PAH).

In another aspect, the disclosure relates to a method of treating, preventing, inhibiting, or eliminating a disease or disorder that is affected by the reduction of or decrease in HIF-1β protein levels. The method comprises administering to a patient in need of a treatment for diseases or disorders affected by the reduction of HIF-1β protein levels an effective amount of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. In one embodiment, the disease or disorder is selected from cancer, von Hippel-Lindau (VHL) disease, iron overload disorders, cardiovascular diseases, pulmonary arterial hypertension (PAH), autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, metabolic diseases, and allergic and genetic diseases. In another embodiment, the disease or disorder is selected from renal cell carcinoma, von Hippel-Lindau disease, pulmonary arterial hypertension, glioblastoma, colitis, Crohn's disease, ulcerative colitis, T cell leukemia or T cell lymphoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), melanoma, triple-negative breast cancer (TNBC), nasopharyngeal cancer (NPC), microsatellite stable colorectal cancer (mssCRC), thymoma, carcinoid, gastrointestinal stromal tumor (GIST), myeloid leukemia, and coronary heart disease. In one embodiment, the disease or condition is selected from renal cell carcinoma, von Hippel-Lindau disease, pulmonary arterial hypertension, glioblastoma, and colitis. In another embodiment, compounds of the present invention may be used to treat T cell leukemia or T cell lymphoma. In yet another embodiment, the disease or disorder is Hodgkin's lymphoma or non-Hodgkin's lymphoma. In another embodiment, the disease or disorder is non-small cell lung cancer (NSCLC). In yet another embodiment, the disease or disorder is renal cell carcinoma (RCC). In one embodiment, the renal cell carcinoma is clear cell renal cell carcinoma (ccRCC). In another embodiment, the disease or disorder is melanoma. In yet another embodiment, the disease or disorder is triple-negative breast cancer (TNBC). In another embodiment, the disease or disorder is nasopharyngeal cancer (NPC). In yet another embodiment, the disease or disorder is microsatellite stable colorectal cancer (mssCRC). In another

embodiment, the disease or disorder is thymoma. In yet another embodiment, the disease or disorder is carcinoid. In another embodiment, the disease or disorder is gastrointestinal stromal tumor (GIST). In yet another embodiment, the disease or disorder is myeloid leukemia. In another embodiment, the disease or disorder is coronary heart disease. In yet another embodiment, the disease or disorder is pulmonary arterial hypertension (PAH).

Another aspect of the disclosure relates to the use of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for the treatment, prevention, inhibition or elimination of a disease or disorder that is associated with or affected by the modulation of HIF-1β protein levels. In one embodiment, the disease or disorder is selected from cancer, von Hippel-Lindau (VHL) disease, iron overload disorders, cardiovascular diseases, pulmonary arterial hypertension (PAH), autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, metabolic diseases, and allergic and genetic diseases. In another embodiment, the disease or disorder is selected from renal cell carcinoma, von Hippel-Lindau disease, pulmonary arterial hypertension, glioblastoma, colitis, Crohn's disease, ulcerative colitis, T cell leukemia or T cell lymphoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), melanoma, triple-negative breast cancer (TNBC), nasopharyngeal cancer (NPC), microsatellite stable colorectal cancer (mssCRC), thymoma, carcinoid, gastrointestinal stromal tumor (GIST), myeloid leukemia, and coronary heart disease. In one embodiment, the disease or condition is selected from renal cell carcinoma, von Hippel-Lindau disease, pulmonary arterial hypertension, glioblastoma, and colitis. In another embodiment, compounds of the present invention may be used to treat T cell leukemia or T cell lymphoma. In yet another embodiment, the disease or disorder is Hodgkin's lymphoma or non-Hodgkin's lymphoma. In another embodiment, the disease or disorder is non-small cell lung cancer (NSCLC). In yet another embodiment, the disease or disorder is renal cell carcinoma (RCC). In one embodiment, the renal cell carcinoma is clear cell renal cell carcinoma (ccRCC). In another embodiment, the disease or disorder is melanoma. In yet another embodiment, the disease or disorder is triple-negative breast cancer (TNBC). In another embodiment, the disease or disorder is nasopharyngeal cancer (NPC). In yet another embodiment, the disease or disorder is microsatellite stable colorectal cancer (mssCRC). In another embodiment, the disease or disorder is thymoma. In yet another embodiment, the disease or disorder is carcinoid. In another embodiment, the disease or disorder is gastrointestinal stromal tumor (GIST). In yet another embodiment, the disease or disorder is myeloid leukemia. In another embodiment, the disease or disorder is coronary heart disease. In yet another embodiment, the disease or disorder is pulmonary arterial hypertension (PAH).

In another aspect, the disclosure relates to the use of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for the treatment, prevention, inhibition or elimination of a disease or disorder that is affected by the reduction of or a decrease in HIF-1β protein levels. In one embodiment, the disease or disorder is selected from cancer, von Hippel-Lindau (VHL) disease, iron overload disorders, cardiovascular diseases, pulmonary arterial hypertension (PAH), autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, metabolic diseases, and allergic and genetic diseases. In another embodiment, the disease or disorder is selected from renal cell carcinoma, von Hippel-Lindau disease, pulmonary arterial hypertension, glioblastoma, colitis, Crohn's disease, ulcerative colitis, T cell leukemia or T cell lymphoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), melanoma, triple-negative breast cancer (TNBC), nasopharyngeal cancer (NPC), microsatellite stable colorectal cancer (mssCRC), thymoma, carcinoid, gastrointestinal stromal tumor (GIST), myeloid leukemia, and coronary heart disease. In one embodiment, the disease or condition is selected from renal cell carcinoma, von Hippel-Lindau disease, pulmonary arterial hypertension, glioblastoma, and colitis. In another embodiment, compounds of the present invention may be used to treat T cell leukemia or T cell lymphoma. In yet another embodiment, the disease or disorder is Hodgkin's lymphoma or non-Hodgkin's lymphoma. In another embodiment, the disease or disorder is non-small cell lung cancer (NSCLC). In yet another embodiment, the disease or disorder is renal cell carcinoma (RCC). In one embodiment, the renal cell carcinoma is clear cell renal cell carcinoma (ccRCC). In another embodiment, the disease or disorder is melanoma. In yet another embodiment, the disease or disorder is triple-negative breast cancer (TNBC). In another embodiment, the disease or disorder is nasopharyngeal cancer (NPC). In yet another embodiment, the disease or disorder is microsatellite stable colorectal cancer (mssCRC). In another embodiment, the disease or disorder is thymoma. In yet another embodiment, the disease or disorder is carcinoid. In another embodiment, the disease or disorder is gastrointestinal stromal tumor (GIST). In yet another embodiment, the disease or disorder is myeloid leukemia. In another embodiment, the disease or disorder is coronary heart disease. In yet another embodiment, the disease or disorder is pulmonary arterial hypertension (PAH).

Another aspect of the disclosure relates to a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in the manufacture of a medicament for treating, preventing, inhibiting, or eliminating a disease or disorder that is associated with or affected by the modulation of HIF-1β protein levels. In one embodiment, the disease or disorder is selected from

cancer, von Hippel-Lindau (VHL) disease, iron overload disorders, cardiovascular diseases, pulmonary arterial hypertension (PAH), autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, metabolic diseases, and allergic and genetic diseases. In another embodiment, the disease or disorder is selected from renal cell carcinoma, von Hippel-Lindau disease, pulmonary arterial hypertension, glioblastoma, colitis, Crohn's disease, ulcerative colitis, T cell leukemia or T cell lymphoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), melanoma, triple-negative breast cancer (TNBC), nasopharyngeal cancer (NPC), microsatellite stable colorectal cancer (mssCRC), thymoma, carcinoid, gastrointestinal stromal tumor (GIST), myeloid leukemia, and coronary heart disease. In one embodiment, the disease or condition is selected from renal cell carcinoma, von Hippel-Lindau disease, pulmonary arterial hypertension, glioblastoma, and colitis. In another embodiment, compounds of the present invention may be used to treat T cell leukemia or T cell lymphoma. In yet another embodiment, the disease or disorder is Hodgkin's lymphoma or non-Hodgkin's lymphoma. In another embodiment, the disease or disorder is non-small cell lung cancer (NSCLC). In yet another embodiment, the disease or disorder is renal cell carcinoma (RCC). In one embodiment, the renal cell carcinoma is clear cell renal cell carcinoma (ccRCC). In another embodiment, the disease or disorder is melanoma. In yet another embodiment, the disease or disorder is triple-negative breast cancer (TNBC). In another embodiment, the disease or disorder is nasopharyngeal cancer (NPC). In yet another embodiment, the disease or disorder is microsatellite stable colorectal cancer (mssCRC). In another embodiment, the disease or disorder is thymoma. In yet another embodiment, the disease or disorder is carcinoid. In another embodiment, the disease or disorder is gastrointestinal stromal tumor (GIST). In yet another embodiment, the disease or disorder is myeloid leukemia. In another embodiment, the disease or disorder is coronary heart disease. In yet another embodiment, the disease or disorder is pulmonary arterial hypertension (PAH).

Another aspect of the disclosure relates to a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in the manufacture of a medicament for treating, preventing, inhibiting, or eliminating a disease or disorder that is associated with or affected by the reduction of, or a decrease in HIF-1β protein levels. In one embodiment, the disease or disorder is selected from cancer, von Hippel-Lindau (VHL) disease, iron overload disorders, cardiovascular diseases, pulmonary arterial hypertension (PAH), autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, metabolic diseases, and allergic and genetic diseases. In another embodiment, the disease or disorder is selected from renal cell carcinoma, von Hippel-Lindau disease, pulmonary arterial hypertension, glioblastoma, colitis, Crohn's disease, ulcerative colitis, T cell leukemia

or T cell lymphoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), melanoma, triple-negative breast cancer (TNBC), nasopharyngeal cancer (NPC), microsatellite stable colorectal cancer (mssCRC), thymoma, carcinoid, gastrointestinal stromal tumor (GIST), myeloid leukemia, and coronary heart disease. In one embodiment, the disease or condition is selected from renal cell carcinoma, von Hippel-Lindau disease, pulmonary arterial hypertension, glioblastoma, and colitis. In another embodiment, compounds of the present invention may be used to treat T cell leukemia or T cell lymphoma. In yet another embodiment, the disease or disorder is Hodgkin's lymphoma or non-Hodgkin's lymphoma. In another embodiment, the disease or disorder is non-small cell lung cancer (NSCLC). In yet another embodiment, the disease or disorder is renal cell carcinoma (RCC). In one embodiment, the renal cell carcinoma is clear cell renal cell carcinoma (ccRCC). In another embodiment, the disease or disorder is melanoma. In yet another embodiment, the disease or disorder is triple-negative breast cancer (TNBC). In another embodiment, the disease or disorder is nasopharyngeal cancer (NPC). In yet another embodiment, the disease or disorder is microsatellite stable colorectal cancer (mssCRC). In another embodiment, the disease or disorder is thymoma. In yet another embodiment, the disease or disorder is carcinoid. In another embodiment, the disease or disorder is gastrointestinal stromal tumor (GIST). In yet another embodiment, the disease or disorder is myeloid leukemia. In another embodiment, the disease or disorder is coronary heart disease. In yet another embodiment, the disease or disorder is pulmonary arterial hypertension (PAH).

In another aspect, the present disclosure is directed to a method of modulating, reducing, or decreasing HIF-1β protein levels. The method involves administering to a patient in need thereof an effective amount of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. In some embodiments, HIF-1β protein levels are modulated, reduced, or decreased through degradation of the HIF-1β protein. In other embodiments, HIF-1β protein levels are modulated, reduced, or decreased through degradation of the HIF-1β protein mediated by an E3 ligase.

Another aspect of the disclosure relates to the use of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for the treatment, prevention, inhibition or elimination of a disease or disorder that is associated with or affected by the modulation, reduction, decrease of HIF-1β protein levels. In some embodiments, HIF-1β protein levels are modulated, reduced, or decreased through degradation of the HIF-1β protein. In other

embodiments, HIF-1β protein levels are modulated, reduced, or decreased through degradation of the HIF-1β protein mediated by an E3 ligase.

In another aspect, the present disclosure relates to a method of treating, preventing, inhibiting, or eliminating an HIF-1β-dependent disease or disorder in a patient in need thereof by modulating HIF-1β protein levels through the degradation of HIF-1β. In some embodiments, HIF-1β protein degradation is mediated by an E3 ligase.

Another aspect of the disclosure relates to the use of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereo isomer, or tautomer thereof, for treating, preventing, inhibiting, or eliminating an HIF-1β-dependent disease or disorder in a patient in need thereof by modulating HIF-1β protein levels through the degradation of HIF-1β. In some embodiments, I HIF-1β protein degradation is mediated by an E3 ligase.

In another aspect, the present disclosure relates to a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in the treatment, prevention, inhibition or elimination of an HIF-1β-dependent disease or disorder in a patient in need thereof by modulating HIF-1β protein levels through the degradation of HIF-1β. In some embodiments, I HIF-1β protein degradation is mediated by an E3 ligase.

Another aspect of the disclosure relates to a method of reducing the proliferation of a cell, the method comprising contacting the cell with a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereo isomer, or tautomer thereof, or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, that reduces HIF-1β protein levels. In some embodiments, HIF-1β protein levels are reduced through degradation of the HIF-1β protein. In some embodiments, HIF-1β protein levels are reduced through degradation of the HIF-1β protein is mediated by an E3 ligase.

Another aspect of the disclosure relates to a method of degrading HIF-1β. The method comprises administering to a patient in need thereof an effective amount of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. In some embodiments, HIF-1β protein degradation is mediated by an E3 ligase.

In another aspect, the present disclosure relates to a method for treating a HIF-1β-dependent disease or disorder. The method comprises the step of administering to a subject in need thereof a therapeutically effective amount of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. In one embodiment, the disease or disorder is selected from cancer, von Hippel-Lindau (VHL) disease, iron overload disorders, cardiovascular diseases, pulmonary arterial hypertension (PAH), autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, metabolic diseases, and allergic and genetic diseases. In another embodiment, the disease or disorder is selected from renal cell carcinoma, von Hippel-Lindau disease, pulmonary arterial hypertension, glioblastoma, colitis, Crohn's disease, ulcerative colitis, T cell leukemia or T cell lymphoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), melanoma, triple-negative breast cancer (TNBC), nasopharyngeal cancer (NPC), microsatellite stable colorectal cancer (mssCRC), thymoma, carcinoid, gastrointestinal stromal tumor (GIST), myeloid leukemia, and coronary heart disease. In one embodiment, the disease or condition is selected from renal cell carcinoma, von Hippel-Lindau disease, pulmonary arterial hypertension, glioblastoma, and colitis. In another embodiment, compounds of the present invention may be used to treat T cell leukemia or T cell lymphoma. In yet another embodiment, the disease or disorder is Hodgkin's lymphoma or non-Hodgkin's lymphoma. In another embodiment, the disease or disorder is non-small cell lung cancer (NSCLC). In yet another embodiment, the disease or disorder is renal cell carcinoma (RCC). In one embodiment, the renal cell carcinoma is clear cell renal cell carcinoma (ccRCC). In another embodiment, the disease or disorder is melanoma. In yet another embodiment, the disease or disorder is triple-negative breast cancer (TNBC). In another embodiment, the disease or disorder is nasopharyngeal cancer (NPC). In yet another embodiment, the disease or disorder is microsatellite stable colorectal cancer (mssCRC). In another embodiment, the disease or disorder is thymoma. In yet another embodiment, the disease or disorder is carcinoid. In another embodiment, the disease or disorder is gastrointestinal stromal tumor (GIST). In yet another embodiment, the disease or disorder is myeloid leukemia. In another embodiment, the disease or disorder is coronary heart disease. In yet another embodiment, the disease or disorder is pulmonary arterial hypertension (PAH).

Another aspect of the disclosure relates to a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in the treatment of a HIF-1β-dependent disease or disorder. In one embodiment, the disease or disorder is selected from cancer, von Hippel-Lindau (VHL) disease, iron overload disorders, cardiovascular diseases, pulmonary arterial hypertension (PAH),

autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, metabolic diseases, and allergic and genetic diseases. In another embodiment, the disease or disorder is selected from renal cell carcinoma, von Hippel-Lindau disease, pulmonary arterial hypertension, glioblastoma, colitis, Crohn's disease, ulcerative colitis, T cell leukemia or T cell lymphoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), melanoma, triple-negative breast cancer (TNBC), nasopharyngeal cancer (NPC), microsatellite stable colorectal cancer (mssCRC), thymoma, carcinoid, gastrointestinal stromal tumor (GIST), myeloid leukemia, and coronary heart disease. In one embodiment, the disease or condition is selected from renal cell carcinoma, von Hippel-Lindau disease, pulmonary arterial hypertension, glioblastoma, and colitis. In another embodiment, compounds of the present invention may be used to treat T cell leukemia or T cell lymphoma. In yet another embodiment, the disease or disorder is Hodgkin's lymphoma or non-Hodgkin's lymphoma. In another embodiment, the disease or disorder is non-small cell lung cancer (NSCLC). In yet another embodiment, the disease or disorder is renal cell carcinoma (RCC). In one embodiment, the renal cell carcinoma is clear cell renal cell carcinoma (ccRCC). In another embodiment, the disease or disorder is melanoma. In yet another embodiment, the disease or disorder is triple-negative breast cancer (TNBC). In another embodiment, the disease or disorder is nasopharyngeal cancer (NPC). In yet another embodiment, the disease or disorder is microsatellite stable colorectal cancer (mssCRC). In another embodiment, the disease or disorder is thymoma. In yet another embodiment, the disease or disorder is carcinoid. In another embodiment, the disease or disorder is gastrointestinal stromal tumor (GIST). In yet another embodiment, the disease or disorder is myeloid leukemia. In another embodiment, the disease or disorder is coronary heart disease. In yet another embodiment, the disease or disorder is pulmonary arterial hypertension (PAH).

In another aspect, the present disclosure relates to the use of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for treating a HIF-1β-dependent disease or disorder. In one embodiment, the disease or disorder is selected from cancer, von Hippel-Lindau (VHL) disease, iron overload disorders, cardiovascular diseases, pulmonary arterial hypertension (PAH), autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, metabolic diseases, and allergic and genetic diseases. In another embodiment, the disease or disorder is selected from renal cell carcinoma, von Hippel-Lindau disease, pulmonary arterial hypertension, glioblastoma, colitis, Crohn's disease, ulcerative colitis, T cell leukemia or T cell lymphoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), melanoma, triple-negative breast cancer (TNBC), nasopharyngeal cancer (NPC), microsatellite stable colorectal cancer (mssCRC), thymoma, carcinoid, gastrointestinal stromal tumor (GIST), myeloid leukemia, and coronary heart disease. In one embodiment, the disease or condition is selected from renal cell carcinoma, von Hippel-Lindau disease, pulmonary arterial hypertension,

glioblastoma, and colitis. In another embodiment, compounds of the present invention may be used to treat T cell leukemia or T cell lymphoma. In yet another embodiment, the disease or disorder is Hodgkin's lymphoma or non-Hodgkin's lymphoma. In another embodiment, the disease or disorder is non-small cell lung cancer (NSCLC). In yet another embodiment, the disease or disorder is renal cell carcinoma (RCC). In one embodiment, renal cell carcinoma is clear cell renal cell carcinoma (ccRCC). In another embodiment, the disease or disorder is melanoma. In yet another embodiment the disease or disorder is triple-negative breast cancer (TNBC). In another embodiment, the disease or disorder is nasopharyngeal cancer (NPC). In yet another embodiment, the disease or disorder is microsatellite stable colorectal cancer (mssCRC). In another embodiment, the disease or disorder is thymoma. In yet another embodiment, the disease or disorder is carcinoid. In another embodiment, the disease or disorder is gastrointestinal stromal tumor (GIST). In yet another embodiment, the disease or disorder is myeloid leukemia. In another embodiment, compounds of the present invention may be used to treat coronary heart disease. In yet another embodiment, the disease or disorder is pulmonary arterial hypertension (PAH).

Another aspect of the disclosure relates to a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in the manufacture of a medicament for treating a HIF-1β-dependent disease or disorder. In one embodiment, the disease or disorder is selected from cancer, von Hippel-Lindau (VHL) disease, iron overload disorders, cardiovascular diseases, pulmonary arterial hypertension (PAH), autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, metabolic diseases, and allergic and genetic diseases. In another embodiment, the disease or disorder is selected from renal cell carcinoma, von Hippel-Lindau disease, pulmonary arterial hypertension, glioblastoma, colitis, Crohn's disease, ulcerative colitis, T cell leukemia or T cell lymphoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), melanoma, triple-negative breast cancer (TNBC), nasopharyngeal cancer (NPC), microsatellite stable colorectal cancer (mssCRC), thymoma, carcinoid, gastrointestinal stromal tumor (GIST), myeloid leukemia, and coronary heart disease. In one embodiment, the disease or condition is selected from renal cell carcinoma, von Hippel-Lindau disease, pulmonary arterial hypertension, glioblastoma, and colitis. In another embodiment, compounds of the present invention may be used to treat T cell leukemia or T cell lymphoma. In yet another embodiment, the disease or disorder is Hodgkin's lymphoma or non-Hodgkin's lymphoma. In another embodiment, the disease or disorder is non-small cell lung cancer (NSCLC). In yet another embodiment, the disease or disorder is renal cell carcinoma (RCC). In one embodiment, renal cell carcinoma is clear cell renal cell carcinoma (ccRCC). In another embodiment, the disease or disorder is melanoma. In yet another embodiment the disease or disorder is triple-negative breast cancer (TNBC). In

another embodiment, the disease or disorder is nasopharyngeal cancer (NPC). In yet another embodiment, the disease or disorder is microsatellite stable colorectal cancer (mssCRC). In another embodiment, the disease or disorder is thymoma. In yet another embodiment, the disease or disorder is carcinoid. In another embodiment, the disease or disorder is gastrointestinal stromal tumor (GIST). In yet another embodiment, the disease or disorder is myeloid leukemia. In another embodiment, compounds of the present invention may be used to treat coronary heart disease. In yet another embodiment, the disease or disorder is pulmonary arterial hypertension (PAH).

In another aspect, the present disclosure relates to a method of reducing HIF-1β protein levels. The method comprises administering to the patient in need thereof a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

In another aspect, the present disclosure relates to a method of reducing HIF-1β protein levels, wherein reduction of HIF-1β protein levels treats or ameliorates the disease or disorder. The method comprises administering to the patient in need thereof a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

In another aspect, the disclosure relates to a method of treating, preventing, inhibiting, or eliminating von Hippel-Lindau (VHL) disease. The method comprises administering to a patient in need of a treatment for VHL disease an effective amount of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Another aspect of the disclosure relates to the use of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for the treatment, prevention, inhibition or elimination of von Hippel-Lindau (VHL) disease.

In another aspect, the disclosure relates to a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in the manufacture of a medicament for treating, preventing, inhibiting, or eliminating von Hippel-Lindau (VHL) disease.

In one embodiment, the patient suffering from VHL disease also suffers from hemangioblastoma, a pheochromocytoma, a pancreatic neuroendocrine tumor or renal cell carcinoma.

In another embodiment, the patient suffering from VHL disease also suffers from renal cell carcinoma.

In another aspect, the disclosure relates to a method of treating, preventing, inhibiting, or eliminating renal cell carcinoma (RCC). The method comprises administering to a patient in need of a treatment for renal cell carcinoma an effective amount of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Another aspect of the disclosure relates to the use of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for the treatment, prevention, inhibition or elimination of renal cell carcinoma.

In another aspect, the disclosure relates to a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in the manufacture of a medicament for treating, preventing, inhibiting, or eliminating renal cell carcinoma. In one embodiment, the renal cell carcinoma is clear cell renal cell carcinoma (ccRCC).

In another aspect, the disclosure relates to a method of reducing inflammation of the digestive system in a patient in need thereof. The method comprises administering to a patient in need of reduction in inflammation an effective amount of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. In one embodiment, the patient suffers from inflammatory bowel disease. In another embodiment, the patient suffers from Crohn's disease or colitis. In another embodiment, the patient suffers from ulcerative colitis. In one embodiment, the administration of a compound of the present disclosure induces remission of the inflammation. In another embodiment, the administration of a compound of the present disclosure reduces intestinal inflammation. In yet another embodiment, the administration of a compound of the present disclosure inhibits recruitment of inflammatory cells.

Another aspect of the disclosure relates to the use of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a

composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for reducing inflammation of the digestive system in a patient in need thereof. In one embodiment, the patient suffers from inflammatory bowel disease. In another embodiment, the patient suffers from Crohn's disease or colitis. In another embodiment, the patient suffers from ulcerative colitis. In one embodiment, the administration of a compound of the present disclosure induces remission of the inflammation. In another embodiment, the administration of a compound of the present disclosure reduces intestinal inflammation. In yet another embodiment, the administration of a compound of the present disclosure inhibits recruitment of inflammatory cells.

In another aspect, the disclosure relates to a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in the manufacture of a medicament for reducing inflammation of the digestive system in a patient in need thereof. In one embodiment, the patient suffers from inflammatory bowel disease. In another embodiment, the patient suffers from Crohn's disease or colitis. In another embodiment, the patient suffers from ulcerative colitis. In one embodiment, the administration of a compound of the present disclosure induces remission of the inflammation. In another embodiment, the administration of a compound of the present disclosure reduces intestinal inflammation. In yet another embodiment, the administration of a compound of the present disclosure inhibits recruitment of inflammatory cells.

Another aspect of the disclosure relates to a method of reducing inflammation of the digestive system. The method comprises administering to a patient in need of a treatment in need of reduction in inflammation of the digestive system an effective amount of a HIF-1β modulator Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. In one embodiment, the patient suffers from inflammatory bowel disease. In another embodiment, the patient suffers from Crohn's disease or colitis. In another embodiment, the patient suffers from ulcerative colitis. In one embodiment, the administration of a compound of the present disclosure induces remission of the inflammation. In another embodiment, the administration of a compound of the present disclosure reduces intestinal inflammation. In yet another embodiment, the administration of a compound of the present disclosure inhibits recruitment of inflammatory cells.

Another aspect of the disclosure relates to the use of a HIF-1β modulator Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer

thereof, or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for reducing inflammation of the digestive system in a patient in need thereof. In one embodiment, the patient suffers from inflammatory bowel disease. In another embodiment, the patient suffers from Crohn's disease or colitis. In another embodiment, the patient suffers from ulcerative colitis. In one embodiment, the administration of a compound of the present disclosure induces remission of the inflammation. In another embodiment, the administration of a compound of the present disclosure reduces intestinal inflammation. In yet another embodiment, the administration of a compound of the present disclosure inhibits recruitment of inflammatory cells.

In another aspect, the disclosure relates to a HIF-1β modulator Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in the manufacture of a medicament for reducing inflammation of the digestive system in a patient in need thereof. In one embodiment, the patient suffers from inflammatory bowel disease. In another embodiment, the patient suffers from Crohn's disease or colitis. In another embodiment, the patient suffers from ulcerative colitis. In one embodiment, the administration of a compound of the present disclosure induces remission of the inflammation. In another embodiment, the administration of a compound of the present disclosure reduces intestinal inflammation. In yet another embodiment, the administration of a compound of the present disclosure inhibits recruitment of inflammatory cells.

Examples of cell proliferative diseases and disorders (e.g., cancers) that can be treated with compounds of the present disclosure include, but are not limited to, acanthoma, acinic cell carcinoma, acoustic neuroma, acral lentiginous melanoma, acrospiroma, acute eosinophilic leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute myeloblastic leukemia with maturation, acute myeloid dendritic cell leukemia, acute myeloid leukemia, acute promyelocytic leukemia, adamantinoma, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adrenocortical carcinoma, adult T-cell leukemia, aggressive NK-cell leukemia, agnogenic myeloid metaplasia, AIDS-related cancers, AIDS-related lymphoma, ALK+ anaplastic large cell lymphoma, alveolar soft part sarcoma, ameloblastic fibroma, anal cancer, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, appendix cancer, astrocytoma, atypical teratoid rhabdoid tumor, basal cell carcinoma, basal-like carcinoma, B-cell leukemia, B-cell lymphoma, B-cell non-Hodgkin's lymphoma, bellini duct carcinoma, benign monoclonal gammopathy, biliary cancer, biliary tract cancer, bladder cancer, blastoma, bone cancer, bone tumor, brain stem glioma, brain cancer, brain tumor, breast cancer, brenner tumor,

bronchial tumor, bronchial adenomas/carcinoids, bronchioloalveolar carcinoma, brown tumor, Burkitt's lymphoma/leukemia, carcinoid tumor, carcinoma, carcinosarcoma, Castleman's disease, central nervous system embryonal tumor, cerebellar astrocytoma, cerebral astrocytoma, cervical cancer, cholangiocarcinoma, chondroma, chondrosarcoma, chordoma, choriocarcinoma, choroid plexus papilloma, chronic lymphocytic leukemia, chronic monocytic leukemia, chronic myelocytic leukemia, chronic myelogenous leukemia, chronic myeloproliferative disorder, chronic neutrophilic leukemia, clear cell renal cell carcinoma, clear-cell tumor, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, dermatofibrosarcoma protuberans, dermoid cyst, desmoplastic small round cell tumor, diffuse large B cell lymphoma (DLBCL) (*e.g.*, germinal center B-cell-like diffuse large B-cell lymphoma or activated B-cell-like diffuse large B-cell lymphoma), dysembryoplastic neuroepithelial tumor, embryonal carcinoma, endodermal sinus tumor, endometrial cancer, endometrial uterine cancer, endometrioid tumor, enteropathy-associated T-cell lymphoma, ependymoblastoma, ependymoma, epithelioid sarcoma, erythroleukemia, esophageal cancer, essential thrombocythemia, esthesioneuroblastoma, Ewing's sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, extrahepatic cholangiocarcinoma extramammary Paget's disease, fallopian tube cancer, fibroma, fibrosarcoma, follicular lymphoma (FL), follicular thyroid cancer, gallbladder cancer, ganglioglioma, ganglioneuroma, gastric cancer, gastric lymphoma, gastrointestinal cancer, gastrointestinal/stomach (GIST) cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), germ cell tumor, germinoma, gestational choriocarcinoma, gestational trophoblastic tumor, gestational trophoblastic tumor glioma, giant cell tumor of bone, glioblastoma, glioblastoma multiforme (GBM), glioma, gliomatosis cerebri, glomus tumor, glucagonoma, gonadoblastoma, granulosa cell tumor, hairy cell leukemia, head and neck cancer, heart cancer, hemangioblastoma, hemangioendothelioma, hemangiopericytoma, hemangiosarcoma, hematological malignancy, hepatocellular carcinoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, hypopharyngeal cancer, hypothalamic glioma, inflammatory breast cancer, intrahepatic bile duct cancer, intraocular (eye) melanoma, intrahepatic cholangiocarcinoma, islet cell tumors (endocrine, pancreas), islet cell carcinoma, islet cell pancreatic cancer, myxosarcoma, myxosarcoma enile, myelomonocytic leukemia, Kaposi's sarcoma, kidney cancer, klatskin tumor, krukenberg tumor, laryngeal cancer, leiomyosarcoma, lentigo maligna melanoma, leukemia, lip and oral cavity cancer, liposarcoma, liver cancer, lung cancer, luteoma, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoid leukemia, lymphoid neoplasm, lymphoma, lymphomatoid papulosis, lymphoplasmacytic lymphoma, macroglobulinemia, malignant fibrous histiocytoma, malignant glioma, malignant mesothelioma, malignant peripheral nerve sheath tumor, malignant rhabdoid tumor, malignant triton tumor, malt lymphoma, mantle cell lymphoma (MCL), mast cell leukemia, mast cell neoplasms, mediastinal germ cell tumor, mediastinal tumor, mediastinal (thymic) large B-cell lymphoma, medullary thyroid cancer,

medulloblastoma, medulloepithelioma, melanoma, meningioma, merkel cell carcinoma, mesenchymous or mixed mesodermal tumor, mesothelioma, mesothelial sarcoma, metastatic pancreatic adenocarcinoma, metastatic squamous neck cancer with occult primary, metastatic urothelial carcinoma, mixed mullerian tumor, monocytic leukemia, mouth cancer, mucinous tumor, multiple endocrine neoplasia (MEN), multiple endocrine neoplasia syndrome, multiple myeloma, mycosis fungoides, myelodysplasia, myelodysplastic disease/syndromes, myeloid leukemia, myeloid neoplasms, myeloid sarcoma, myeloproliferative disease, myxoma, nasal cavity cancer, nasopharyngeal cancer, neoplasm, nervous system cancer (*e.g.*, central nervous system cancer, central nervous system lymphoma), neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, non-Hodgkin's lymphoma, nonmelanoma skin cancer, non-small cell lung cancer, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, oral cancer, oropharyngeal cancer, osteogenic sarcoma, osteosarcoma, ovarian cancer, ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor, pancoast tumor, pancreatic cancer, pancreatic neuroendocrine tumor, papillary thyroid cancer, papillomatosis, paraganglioma, paranasal sinus cancer, parathyroid cancer, penile cancer, perivascular epithelioid cell tumor, pharyngeal cancer, pheochromocytoma, pineal parenchymal tumor of intermediate differentiation, pineoblastoma, pituicytoma, pituitary adenoma, pituitary tumor, plasma cell neoplasm, pleuropulmonary blastoma, polycythemia vera, polyembryoma, precursor T-lymphoblastic lymphoma, primitive neuroectodermal tumor, prostate cancer (*e.g.*, metastatic castration resistant prostate cancer), pseudomyxoma peritonei, rectal cancer, refractory B-cell non-Hodgkin's lymphoma, relapsed B-cell non-Hodgkin's lymphoma, renal cancer, renal cell carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, sacrococcygeal teratoma, salivary gland cancer, sarcoma, schwannomatosis, sebaceous gland carcinoma, secondary neoplasm, seminoma, serous tumor, Sertoli-Leydig cell tumor, sex cord-stromal tumor, sezary syndrome, signet ring cell carcinoma, skin cancer (non-melanoma), small blue round cell tumor, small cell carcinoma, small cell lung cancer, small cell lymphoma, small intestine cancer, small lymphocytic leukemia, small lymphocytic lymphoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, stomach cancer, superficial spreading melanoma, supratentorial primitive neuroectodermal tumor, surface epithelial-stromal tumor, synovial sarcoma, T-cell acute lymphoblastic leukemia, T-cell large granular lymphocyte leukemia, T-cell leukemia, T-cell lymphoma, T-cell prolymphocytic leukemia, teratoma, terminal lymphatic cancer, testicular cancer, thecoma, throat cancer, thymic carcinoma, thymoma, thyroid cancer (medullary and papillary thyroid carcinoma), tongue cancer, transitional cell cancer of renal pelvis and ureter, transitional cell carcinoma, transitional cell cancer of the renal pelvis and ureter and other urinary organs, urachal cancer, urethral cancer, urinary bladder cancer, urogenital neoplasm, uterine cancer, uterine sarcoma, uveal melanoma, vaginal cancer, verner morrison syndrome, verrucous carcinoma, visual pathway glioma, vulvar cancer,

labial carcinoma, larynx carcinoma, hypopharynx carcinoma, tongue carcinoma, salivary gland carcinoma, gastric carcinoma, renal carcinoma, kidney parenchyma carcinoma, cervix carcinoma, cervix cancer, uterine corpus carcinoma, uterine corpus cancer, endometrium carcinoma, chorion carcinoma, testis carcinoma, urinary carcinoma, brain tumors such as glioblastoma, medulloblastoma and peripheral neuroectodermal tumors, gall bladder carcinoma, bronchial carcinoma, basalioma, choroidea melanoma, craniopharyngeoma, myosarcoma, fibrosarcoma, colon carcinoma, familiary adenomatous polyposis carcinoma, and hereditary non-polyposis colorectal cancer, melanoma, plasmocytoma, Waldenstrom's macroglobulinemia, Warthin's tumor, visual pathway and hypothalamic glioma, and Wilms' tumor, or any combination thereof.

Examples of other diseases or disorders that can be treated with compounds of the present disclosure include, but are not limited to, von Hippel-Lindau (VHL) disease, iron overload disorders, cardiovascular diseases, autoimmune and inflammatory-related diseases and conditions, pulmonary arterial hypertension (PAH), neurodegenerative diseases, viral diseases, chronic and acute kidney diseases or injuries, metabolic diseases, allergic and genetic diseases, etc.) that can be treated with compounds of the present disclosure include, but are not limited to, pulmonary arterial hypertension (*e.g.*, primary or secondary iron overload disorders including, but not limited to, hemochromatosis (*e.g.*, iron hemochromatosis, HFE mutation hemochromatosis, ferroportin mutation hemochromatosis, transferrin receptor 2 mutation hemochromatosis, hemojuvelin mutation hemochromatosis, hepcidin mutation hemochromatosis, juvenile hemochromatosis, neonatal hemochromatosis), polycythemia (*e.g.*, polycythemia vera), Pacak-Zhuang Syndrome, erythrocytosis, porphyria cutanea tarda, hereditary spherocytosis, hyprochromic anemia, hysererythropoietic anemia (CDAI), faciogenital dysplasia (FGDY), Aarskog syndrome, atransferrinemia, sideroblastic anemia (SA), aplastic anemia, pure red cell anemia, pyridoxine-responsive sidero-blastic anemia, and hemoglobinopathies such as thalassemia and sickle cell disease, cardiac ischemia, and pulmonary arterial hypertension; idiopathic PAH, heritable PAH (*e.g.*, BMPR2, ALK 1, endoglin), drug-induced PAH, toxin-induced PAH, and PAH associated with another condition (*e.g.*, connective tissue diseases, HIV infection, HIV-1, HIV-2, human T-cell leukemia virus-I (HTLV-I), HTLV-II, HTLV-III, simian immunodeficiency virus (SIV), lymphadenopathy associated virus (LAV-2), simian T-lymphotrophic virus-I (STLV-I), STLV-II, STLV-III, simian B-lymphotrophic (SBL) virus, Gibbon ape leukemia virus (GALV), bovine leukemia virus (BLV), equine infectious anemia virus (EIAV), feline leukemia virus (FELV), murine leukemia virus (MuLV), avian leukosis virus (ALV), other virus infections such as hepadnaviridae (Hepatitis B), herpesviridae (Herpes simplex I, Herpes simplex II, Varicella-Zoster, Herpes Zoster, Epstein-Barr virus and cytomegalovirus), parvoviridae (human parvovirus B-19), papovaviridae (human papilloma virus types I to 60, JC and BK viruses), pox viruses (variola major, variola minor, vaccinia, monkey pox, cowpox, paravaccinia or milker's node virus, parapox or ORF virus,

molluscum contagiosum, AIDS, influenza virus cytomegalovirus, portal hypertension, congenital heart diseases, schistosomiasis, or chronic hemolytic anemia), arthritis (*e.g.*, rheumatoid arthritis), kidney failure, lupus, asthma, psoriasis, pancreatitis, hyaline membrane disease, allergies, fibrosis, surgical complications (*e.g.*, where inflammatory cytokines prevent healing), anemia, fibromyalgia, Alzheimer's disease, chronic heart failure, congestive heart failure, stroke, aortic valve stenosis, arteriosclerosis, acute coronary syndrome, osteoporosis, Parkinson's disease, infections, inflammatory bowel disease (*e.g.*, Crohn's disease and colitis such as ulcerative colitis), chronic obstructive pulmonary disease (COPD), atherosclerosis, glomerular disease, allergic contact dermatitis and other eczemas, atopic dermatitis, dermatitis herpetiformis, erythema multiforma, systemic sclerosis, transplantation multiple sclerosis, type II diabetes, multiple sclerosis, chronic gastritis, irritable bowel syndrome, cachexia, Graves' disease, Bechteref's disease, myasthenia gravis, autoimmune hepatitis, autoimmune multiglandular endocrine insufficiency Disease (APECED), endocrine opthalmopathy, Churg-Strauss syndrome, glomerulonephritis (with and without nephrotic syndrome, e g. including idiopathic nephrotic syndrome or minal change nephropathy), nephritis, celiac disease, periodontitis, eosinophilic enteropathy, appendicitis, Guillain-Barre syndrome, Hashimoto's disease, sclerosis of lichen, systemic lupus erythematosus, pediatric autoimmune streptococcal-related neuropsychiatric disorder (PANDAS), Rheumatic fever, sarcoidosis, Sjogren's syndrome, systemic stiffness syndrome, scleroderma, Wegener's granulomatosis, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, autoimmune enteropathy, Goodpasture syndrome, autoimmune allergic disease, allergic rhinitis, ocular allergy, allergic conjunctivitis, chronic granulomatous disease, asthma and organ transplantation, systemic lupus erythematosus, alopecia areata, anklosing spondylitis, antiphospholipid syndrome, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune inner ear disease, autoimmune lymphoproliferative syndrome (alps), autoimmune thrombocytopenic purpura (ATP), Behcet's disease, vasculitis, diverticulitis, interstitial cystitis, bullous pemphigoid, cardiomyopathy, celiac sprue-dermatitis, chronic fatigue syndrome immune deficiency, syndrome (CFIDS), chronic inflammatory demyelinating polyneuropathy, cicatricial pemphigoid, cold agglutinin disease, Crest syndrome, Crohn's disease, Dego's disease, dermatomyositis-juvenile, discoid lupus, essential mixed cryoglobulinemia, fibromyalgia-fibromyositis, guillain-barre, hashimoto's thyroiditis, idiopathic sprue, idiopathic pulmonary fibrosis, idiopathic thrombocytopenia purpura (ITP), IgA nephropathy, juvenile arthritis, systemic juvenile idiopathic arthritis, Meniere's disease, mixed connective tissue disease, pernicious anemia, polyarteritis nodosa, polychondritis, polyglancular syndromes, acute lung injury, acute respiratory distress syndrome, polymyalgia rheumatica, cryopyrin-associated periodic syndrome, polymyositis and dermatomyositis, primary agammaglobulinemia, primary biliary cirrhosis, cirrhosis, Raynaud's phenomenon, Reiter's syndrome, rheumatic fever, sarcoidosis,

alveolitis, stiff-man syndrome, Takayasu arteritis, temporal arteritis/giant cell arteritis, uveitis (anterior and posterior), vasculitis, Hashimoto's thyroiditis, autoimmune hemolytic anemia, glaucoma, retinal disease, autoimmune atrophic gastritis of pernicious anemia, autoimmune encephalomyelitis, autoimmune orchitis, sepsis, septic shock, dacryoadenitis, cryopyrin associated periodic syndrome (CAPS), endotoxic shock, endometritis, gram-negative sepsis, CD14 mediated sepsis, Steven-Johnson syndrome, non-CD14 mediated sepsis, keratoconjunctivitis sicca, vernal keratoconjunctivitis, vernal conjunctivitis, toxic shock syndrome, asthma, adult respiratory distress syndrome, pulmonary disease, chronic pulmonary inflammation, chronic graft rejection, hidradenitis suppurativa, Goodpasture's disease, autoimmune thrombocytopenia, sympathetic ophthalmia, juvenile-onset diabetes, Addison's disease, lichen planus, bullous pemphigus, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, immunoglobulin A nephropathy, Wegener granulomatosis, granulomatous orchitis, autoimmune oophoritis, psoriatic arthritis, acute and chronic renal disease, leptospiriosis renal disease, pancreatic fibrosis, hepatic fibrosis, sarcoidosis, rheumatic carditis, pyresis, restenosis, cervicitis, stroke and ischemic injury, neural trauma, acute and chronic pain, chronic aggressive and active hepatitis, membranous glomerulopathy, malaria, leprosy, leishmaniasis, Lyme disease, acute synovitis, muscle degeneration, bursitis, tendonitis, tenosynovitis, herniated, ruptured, or prolapsed intervertebral disk syndrome, osteopetrosis, rhinosinusitis, thrombosis, silicosis, pulmonary sarcosis, 22ql 1.2 deletion syndrome, Angelman syndrome, Canavan disease, Charcot-Marie-Tooth disease, color blindness, Cri du chat, Down syndrome, cystic fibrosis, Duchenne muscular dystrophy, haemophilia, Klinefleter's syndrome, neurofibromatosis, phenylketonuria, Prader-Willi syndrome, Tay-Sachs disease, Turner syndrome, urea cycle disorders, otitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, chronic hypersensitivity pneumonitis, interstitial lung fibrosis, amyotrophic lateral sclerosis, asociality, varicosis, vaginitis, depression, Sudden Infant Death Syndrome, gout, asbestosis, alcoholic liver disease, nonalcoholic steatohepatitis, diabetic nephropathy, diabetic retinopathy, diabetic cardiomyopathy, macular degeneration, proliferative retinopathy, macular edema, retinopathy of prematurity, ascites, pleural effusion, cerebral oedema, pulmonary oedema, ischemic heart disease, cerebrovascular disorders, endometriosis, insulin resistance, and obesity, or any combination thereof.

In one embodiment of the methods herein above, the disease or condition is selected from renal cell carcinoma, von Hippel-Lindau disease, pulmonary arterial hypertension, glioblastoma, and colitis.

In some embodiments, the compounds of the present invention may be used to treat T cell leukemia or T cell lymphoma.

In some embodiments, the compounds of the present invention may be used to treat Hodgkin's lymphoma or non-Hodgkin's lymphoma.

In some embodiments, the compounds of the present invention may be used to treat on-small cell lung cancer (NSCLC).

In some embodiments, the compounds of the present invention may be used to renal cell carcinoma (RCC). In one embodiment, the renal cell carcinoma is clear cell renal cell carcinoma (ccRCC).

In some embodiments, the compounds of the present invention may be used to treat melanoma.

In some embodiments, the compounds of the present invention may be used to treat triple-negative breast cancer (TNBC).

In some embodiments, the compounds of the present invention may be used to treat nasopharyngeal cancer (NPC).

In some embodiments, the compounds of the present invention may be used to treat microsatellite stable colorectal cancer (mssCRC).

In some embodiments, the compounds of the present invention may be used to treat thymoma.

In some embodiments, the compounds of the present invention may be used to treat carcinoid.

In some embodiments, the compounds of the present invention may be used to treat gastrointestinal stromal tumor (GIST).

In some embodiments, the compounds of the present invention may be used to treat myeloid leukemia.

In some embodiments, the compounds of the present invention may be used to treat coronary heart disease.

In some embodiments, the compounds of the present invention may be used to pulmonary arterial hypertension (PAH).

In one embodiment, the present disclosure provides a method of treating, preventing, inhibiting, or eliminating a proliferative disorder in a patient in need thereof. The method comprises administering to a patient in need of a treatment for said proliferative disorder an effective amount of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. In some embodiments, the proliferative disorder is a HIF-1β-dependent or HIF-1β-associated proliferative disorder. In one embodiment, the proliferative disorder is a cancer. Representative cancers that compounds of Formula (I), (II), or (III), are useful for treating, preventing, inhibiting, or eliminating include, but are not limited to, cancer of the head, neck, eye, mouth, throat, esophagus, bronchus, larynx, pharynx, chest, bone, lung, colon, rectum, stomach, prostate, urinary bladder, uterine, cervix, breast, ovaries, testicles or other reproductive organs, skin, thyroid, blood, lymph nodes, kidney, liver, pancreas, brain, central nervous system, solid tumors and blood-borne tumors.

In some embodiments, the cancer is a cancer selected from the group consisting of lung cancer, head and neck squamous cell carcinoma, pancreatic cancer, breast cancer, ovarian cancer, renal cell carcinoma, prostate cancer, neuroendocrine cancer, gastric cancer, bladder cancer, uterus cancer, testes cancer, kidney cancer, skin cancer, gastrointestinal tract cancer (*e.g.*, esophagus, oropharynx, stomach, small or large intestines, colon, or rectum), cervix cancer, and colon cancer. In some further embodiments, said cancer condition is a cancer selected from the group consisting of lung cancer, head and neck squamous cell carcinoma, pancreatic cancer, breast cancer, ovarian cancer, renal cell carcinoma, prostate cancer, neuroendocrine cancer, gastric cancer, bladder cancer and colon cancer. In some further embodiments, the cancer condition is selected from the group consisting of non-small-cell lung carcinoma, melanoma, renal cell carcinoma, colorectal cancer, castration-resistant prostate cancer, hepatocellular carcinoma, squamous cell carcinoma of the head and neck, carcinomas of the esophagus, ovary, gastrointestinal tract and breast, and a hematologic malignancy. In another embodiment, the cancer is selected from the group consisting of bladder cancer, breast cancer, non-small cell lung cancer (NSCLC), colorectal cancer (CRC), renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), and melanoma. In another embodiment, the cancer condition is renal cell carcinoma (RCC).

In a further embodiment, the present disclosure provides a method of treating a cancer condition, wherein the HIF-2a inhibitor is effective in one or more of inhibiting proliferation of cancer cells, inhibiting metastasis of cancer cells, killing cancer cells and reducing severity or incidence of symptoms associated with the presence of cancer cells. In some other embodiments, said method comprises administering to the cancer cells a therapeutically effective amount of a HIF-2a inhibitor. In some embodiments, the administration takes place *in vitro*. In other embodiments, the administration takes place *in vivo*.

In certain embodiments, the cancer is metastatic. In some embodiments, the cancer is relapsed. In other embodiments, the cancer is refractory. In yet other embodiments, the cancer is relapsed and refractory. In yet still another embodiment, the cancer is VHL-deficient RCC.

In another embodiment, the cancer is bladder cancer. In yet another embodiment, the cancer is breast cancer. In another embodiment, the cancer is NSCLC. In still another embodiment, the cancer is CRC. In another embodiment, the cancer is RCC. In yet another embodiment, the cancer is HCC. In another embodiment, the cancer is melanoma.

In one embodiment, the cancer is advanced RCC. In another embodiment, the RCC is advanced RCC with clear cell component (ccRCC). In yet another embodiment, the cancer is metastatic RCC. In yet another embodiment, the cancer is relapsed RCC. In another embodiment, the cancer is refractory RCC. In yet still another embodiment, the cancer is relapsed and refractory RCC. In another embodiment, the cancer is VHL-deficient RCC.

The disclosed compounds of the disclosure can be administered in effective amounts to treat or prevent a disorder and/or prevent the development thereof in subjects.

H. Administration, Pharmaceutical Compositions, and Dosing of Compounds of the Disclosure

Administration of the disclosed compounds can be accomplished via any mode of administration for therapeutic agents. These modes include systemic or local administration such as oral, nasal, parenteral, transdermal, subcutaneous, vaginal, buccal, rectal or topical administration modes.

Depending on the intended mode of administration, the disclosed compositions can be in solid, semi-solid or liquid dosage form, such as, for example, injectables, tablets, suppositories, pills, time-release capsules, elixirs, tinctures, emulsions, syrups, powders, liquids, suspensions, or the like, sometimes in unit dosages and consistent with conventional pharmaceutical practices. Likewise, they can also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous, or intramuscular form, and all using forms well known to those skilled in the pharmaceutical arts.

Another aspect of the disclosure is directed to pharmaceutical compositions comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier. The pharmaceutical acceptable carrier may further include an excipient, diluent, or surfactant. In a further embodiment, the composition comprises at least two pharmaceutically acceptable carriers, such as those described herein. The pharmaceutical composition can be formulated for particular routes of administration such as oral administration, parenteral administration (*e.g.*, by injection, infusion, transdermal or topical administration), and rectal administration. Topical administration may also pertain to inhalation or intranasal application. The pharmaceutical compositions of the present disclosure can be made up in a solid form (including, without limitation, capsules, tablets, pills, granules, powders or suppositories), or in a liquid form (including, without limitation, solutions, suspensions or emulsions). Tablets may be either film coated or enteric coated according to methods known in the art. Typically, the pharmaceutical compositions are tablets or gelatin capsules comprising the active ingredient together with one or more of:

a) diluents, *e.g.*, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, *e.g.*, silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethylene glycol; for tablets also

c) binders, *e.g.*, magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired

d) disintegrants, *e.g.*, starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and

e) absorbents, colorants, flavors and sweeteners.

Liquid, particularly injectable, compositions can, for example, be prepared by dissolution, dispersion, etc. For example, the disclosed compound is dissolved in or mixed with a pharmaceutically acceptable solvent such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form an injectable isotonic solution or suspension. Proteins such as albumin, chylomicron particles, or serum proteins can be used to solubilize the disclosed compounds.

The disclosed compounds can be also formulated as a suppository that can be prepared from fatty emulsions or suspensions; using polyalkylene glycols such as propylene glycol, as the carrier.

Parental injectable administration is generally used for subcutaneous, intramuscular or intravenous injections and infusions. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions or solid forms suitable for dissolving in liquid prior to injection.

Compositions can be prepared according to conventional mixing, granulating or coating methods, respectively, and the present pharmaceutical compositions can contain from about 0.1 % to about 99%, from about 5% to about 90%, or from about 1 % to about 20% of the disclosed compound by weight or volume.

The dosage regimen utilizing the disclosed compound is selected in accordance with a variety of factors including type, species, age, weight, sex, and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal or hepatic function of the patient; and the particular disclosed compound employed. A physician or veterinarian of ordinary skill in the art can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Effective dosage amounts of the disclosed compounds, when used for the indicated effects, range from about 0.5 mg to about 5000 mg of the disclosed compound as needed to treat the condition. Compositions for *in vivo* or *in vitro* use can contain about 0.5, 5, 20, 50, 75, 100, 150, 250, 500, 750, 1000, 1250, 2500, 3500, or 5000 mg of the disclosed compound, or, in a range of from one amount to another amount in the list of doses. In one embodiment, the compositions are in the form of a tablet that can be scored. The therapeutically effective dosage of a compound, the pharmaceutical composition, or the combinations thereof, is dependent on the species of the subject, the body weight, age and individual condition, the disorder or disease or the severity thereof being treated. A physician, clinician or veterinarian of ordinary skill can readily determine the effective amount of each of the active ingredients necessary to prevent, treat or inhibit the progress of the disorder or disease.

The above-cited dosage properties are demonstrable *in vitro* and *in vivo* tests using advantageously mammals, *e.g.*, mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. The compounds of the present disclosure can be applied *in vitro* in the form of solutions, *e.g.*, aqueous solutions, and *in vivo* either enterally, parenterally, advantageously intravenously, *e.g.*, as a suspension or in aqueous

solution. The dosage *in vitro* may range between about 10-30 molar and 10-90 molar concentrations. A therapeutically effective amount *in vivo* may range depending on the route of administration, between about 0.1-500 mg/kg, or between about 1-100 mg/kg.

I. Combination Therapy

The compounds of the disclosure can be administered in therapeutically effective amounts in a combinational therapy with one or more therapeutic agents (pharmaceutical combinations) or modalities, *e.g.*, non-drug therapies. For example, synergistic effects can occur with other cancer agents. Where the compounds of the application are administered in conjunction with other therapies, dosages of the co-administered compounds will of course vary depending on the type of co-drug employed, on the specific drug employed, on the condition being treated and so forth.

The compounds can be administered simultaneously (as a single preparation or separate preparation), sequentially, separately, or over a period of time to the other drug therapy or treatment modality. In general, a combination therapy envisions administration of two or more drugs during a single cycle or course of therapy. A therapeutic agent is, for example, a chemical compound, peptide, antibody, antibody fragment or nucleic acid, which is therapeutically active or enhances the therapeutic activity when administered to a patient in combination with a compound of the present disclosure.

In another aspect, the disclosure includes a Compound of Formula (I), Formula (II), Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), Formula (Iac), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), a compound according to any one of embodiment No. 1 to No. 57, or any embodiment Formula (I), Formula (II), Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), Formula (Iac), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf) described herein, or a pharmaceutically acceptable salt thereof, for use

in a combination therapy. A compound, composition, medicament and compounds for use of Formula (I), Formula (II), Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), Formula (Iac), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf), a compound according to any one of embodiment No. 1 to No. 57, or any embodiment of Formula (I), Formula (II), Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), Formula (Icc), Formula (Idd), Formula (Iee), Formula (Iff), Formula (Igg), Formula (Ihh), Formula (Iii), Formula (Ijj), Formula (Ikk), Formula (Imm), Formula (Ioo), Formula (Ipp), Formula (Iqq), Formula (Irr), Formula (Iss), Formula (Itt), Formula (Iuu), Formula (Ivv), Formula (Iww), Formula (Ixx), Formula (Iyy), Formula (Izz), Formula (Iab), Formula (Iac), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), and/or Formula (IIf) described herein, or a pharmaceutically acceptable salt thereof, may also be used to advantage in combination with one or more other therapeutic agents.

Another aspect of the disclosure is directed to pharmaceutical compositions comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, a pharmaceutically acceptable carrier, and one or more therapeutic agents. The pharmaceutical acceptable carrier may further include an excipient, diluent, or surfactant.

Combination therapy includes the administration of the subject compounds in further combination with other biologically active ingredients (such as, but not limited to, a second agent such as, but not limited to, a second agent that targets HIF-1β (e.g., a second HIF-1β inhibitor or degrader), a second agent that targets one or more of the HIF transcription factors, non-drug therapies (such as, but not limited to, surgery or radiation treatment), anti-cancer agents, immune-modulators, therapeutic antibodies, anti-Von Hippel-Lindau disease agents, antibiotics, anti-inflammatory, immunosuppressive, vasoactive antiseptic agents (e.g., anti-bacterial agents, anti-fungicides, anti-viral agents, anti-parasitic agents, etc.), immunomodulatory agents, immuno-oncology agents, RNA interference-based therapies to silence gene expression, anti-nausea agents (or anti-emetics), pain relievers, cytoprotective agents, cardiovascular agents, hypertension agents, and combinations thereof.

"Combination therapy" is intended to embrace administration of these therapeutic agents in a sequential manner, wherein each therapeutic agent is administered at a different time and in any order, or in alternation and in any order, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner.

Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single capsule having a fixed ratio of each therapeutic agent or in multiple, single capsules for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be affected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other therapeutic agents of the combination may be administered orally. Alternatively, for example, all therapeutic agents may be administered orally, or all therapeutic agents may be administered by intravenous injection. The sequence in which the therapeutic agents are administered is not narrowly critical.

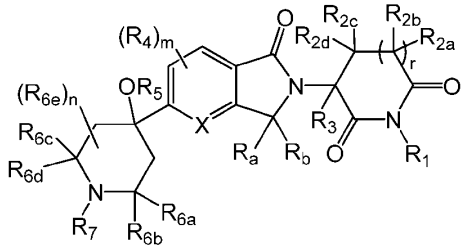
In accordance with the foregoing, the present disclosure also provides a therapeutic combination, *e.g.*, a kit, kit of parts, *e.g.*, for use in any method as defined herein, comprising a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof, to be used concomitantly or in sequence with at least one pharmaceutical composition comprising at least one or more other therapeutic agents, or a pharmaceutically acceptable salt thereof. The kit may comprise instructions for its administration. The combination can be a fixed combination (*e.g.*, in the same pharmaceutical composition) or a free combination (*e.g.*, in separate pharmaceutical compositions).

Similarly, the present disclosure provides a kit of parts comprising: (i) a pharmaceutical composition of the disclosure; and (ii) a pharmaceutical composition comprising one or more other therapeutic agents, or a pharmaceutically acceptable salt thereof, in the form of two separate units of the components (i) to (ii).

Likewise, the present disclosure provides a method as defined above comprising co- administration, *e.g.*, concomitantly or in sequence, of a therapeutically effective amount of a Compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof, and one or more other therapeutic agents.

ENUMERATED EMBODIMENTS

1. A compound of Formula (I):



(I),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

R_a and R_b are each independently H, D, or (C_1-C_6)alkyl;

R_1 is H, D, -C(O)R_{11}, -CH_2OC(O)R_{11}, -CH_2OC(O)NHR_{12}, -CH_2OC(O)OR_{12}, -P(O)(OR_{12})$_2$, -CH_2OP(O)(OR_{12})$_2$, -CH_2OP(O)(OH)OR_{12}, -CH_2OP(O)(R_{12})$_2$, -CH_2OC(O)CH_2NHC(O)CH_2NH_2, -CH_2OC(O)CH($R_{12'}$)N$HR_{12'}$, -CH_2OC(O)(CH_2)$_q$C(O)O$R_{12'}$, or -CH_2OC(O)-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S);

R_{2a}, R_{2b}, R_{2c}, and R_{2d} are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, halogen, or -OH, wherein two of R_{2a}, R_{2b}, R_{2c}, and R_{2d} may be taken together with the carbon atom to which they are attached form a (C_3-C_7)carbocyclyl or (C_3-C_7)spirocarbocyclyl;

R_3 is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, or halogen, wherein R_3 may be taken together with one of R_{2a}, R_{2b}, R_{2c}, and R_{2d} with the carbon atom to which they are attached to form a (C_3-C_7)carbocyclyl or (C_3-C_7)spirocarbocyclyl;

each R_4 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)halohalkyl, or halogen;

each $R_{4'}$ is independently at each occurrence H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)deuteroalkoxy, (C_1-C_6)haloalkoxy, (C_3-C_7)carbocyclyl, O(C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -S(O)$_p$$R_{19}$;

R_5 is H, D, (C_2-C_6)alkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)aminoalkyl, (C_1-C_6)alkyl-O-(C_1-C_6)hydroxyalkyl, -C(O)R_{12}, -CH_2OC(O)R_{12}, -CH_2OC(O)N(R_{12})$_2$, -CH_2OC(O)$_2$$R_{12}$, -P(O)($OR_{12}$)$_2$, -$CH_2$OP(O)(OH)O$R_{12}$, or -$CH_2$OP(O)($R_{12}$)$_2$;

R_{6a}, R_{6b}, R_{6c}, and R_{6d} are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy,, or (C_3-C_7)carbocyclyl; or

two of R_{6a}, R_{6b}, R_{6c}, and R_{6d} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl, (C_3-C_7)spirocarbocyclyl, 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl, heterocyclyl, and spiroheterocyclyl are optionally substituted with one or more R_{10};

each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl,

(C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, -(C_1-C_6)alkylene-O-(C_1-C_6)alkyl, (C_6-C_{10})aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one or more R_{13}, the aryl and heteroaryl are optionally substituted with one or more R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{23}; or

two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)carbocyclyl, (C_3-C_7)spirocarbocyclyl, a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl, heterocyclyl, and spiroheterocyclyl are optionally substituted with one or more R_{15}; or

one R_{6e} is taken together with any one of R_{6a}, R_{6b}, R_{6c}, and R_{6d} and the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{15};

R_7 is (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_3-C_7)carbocyclyl, wherein alkyl, haloalkyl, hydroxyalkyl, halohydroxyalkyl, and carbocyclyl are optionally substituted with one or more substituents independently selected from R_{21}, D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$,-C(O)$NR_{32}R_{33}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$;

when $R_{4'}$ is H, m is 1, n is 0 and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are all simultaneously H, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)alkyl, or (C_3-C_7)carbocyclyl optionally substituted with one or more substituents independently selected from R_{41}, D, (C_1-C_6)alkoxy, -OR_{16a}, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one or more R_8, the heteroaryl is optionally substituted with one or more R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$

when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)alkyl, or (C_3-C_7)carbocyclyl optionally substituted with one or more substituents independently selected from R_{41}, D, (C_1-C_6)alkoxy, -OR_{16a}, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5-

or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$;

when $R_{4'}$ is (C_1)alkyl, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one or more R_8, the heteroaryl is optionally substituted with one or more R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$;

when $R_{4'}$ is D, (C_2-C_4)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)alkyl, or (C_3-C_7)carbocyclyl optionally substituted with one or more substituents independently selected from R_{41}, D, (C_1-C_6)alkoxy, -OR_{16a}, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$;

R_8 and $R_{8'}$ are each independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -$C(O)NR_{32}R_{33}$, -$C(O)OR_{32}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the alkyl, deuteroalkyl, haloalkyl, alkoxy, haloalkoxy, hydroalkyl, phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more substituents selected from (C_1-C_6)alkyl, (C_3-C_7)carbocyclyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -$C(O)NR_{37}R_{38}$, -$C(O)R_{37}$, -$C(O)OR_{37}$, -SF_5, -SR_{40}, and -CN, and R_{13}; or

two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S,

(C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R_{10};

two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{10}; or

two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{10}; or

two $R_{8'}$ when on the same carbon atom form C=(O);

each R_9 and $R_{9'}$ are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, C(O)OR_9, -C(O)R_9, and -C(O)$NR_9R_{9'}$;

R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN;

R_{12} is independently at each occurrence H, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN;

$R_{12'}$ is independently at each occurrence H or (C_1-C_6)alkyl;

each R_{13} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{14}R_{14'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein carbocyclyl and heterocyclyl are optionally substituted with one or more R_{20} and the aryl and heteroaryl are optionally substituted with one or more R_{21}; or

two R_{13} when on the same carbon atom may be taken together to form C=(O);

R_{14} and $R_{14'}$ are each independently at each occurrence H or (C_1-C_6)alkyl;

each R_{15} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl,

(C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$ optionally substituted with one or more R_{20};

R_{16} and $R_{16'}$ are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{16a} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{17} is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{18} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{19} is (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{20} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{22} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{28}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{22}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{23} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{29}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{23} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{30} and R_{31} are each independently at each occurrence H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_3-C_7)carbocyclyl, -C(O)R_{34}, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl or heteroaryl can be substituted with one or more R_{17};

R_{32}, R_{33}, and R_{34} are each independently at each occurrence H or $(C_1$-$C_6)$alkyl;

R_{35} and R_{36} are each independently at each occurrence H, $(C_1$-$C_6)$alkyl, or -C(O)R_{39};

R_{37}, R_{38}, and R_{39} are each independently at each occurrence H or $(C_1$-$C_6)$alkyl;

R_{40} is H, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl;

two R_{41}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{10}; or

two R_{41} together with the atoms to which they are attached form a $(C_3$-$C_7)$carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{10}; or

m and p are each independently 0, 1, or 2;

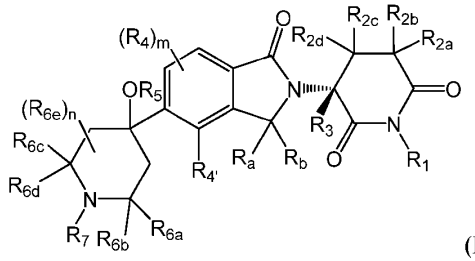
q is 1, 2, or 3;

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

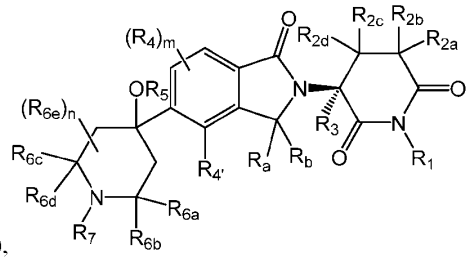
r is 0 or 1.

.

2. The compound according to embodiment 1, having a Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (Ie), or Formula (If):



(Ia),



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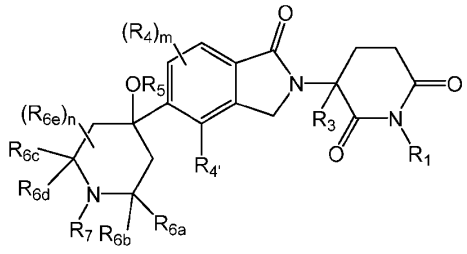

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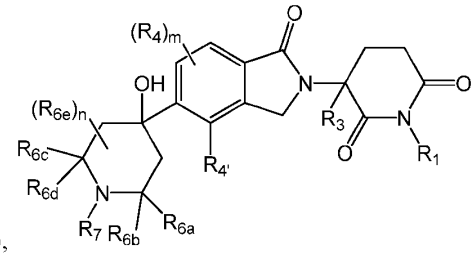
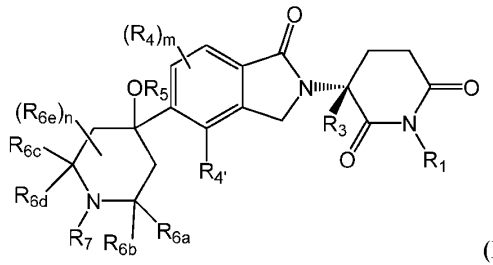
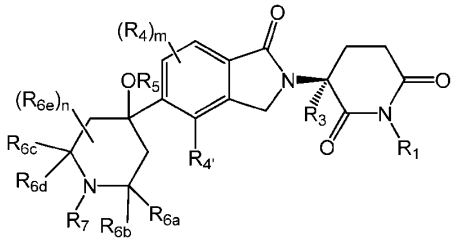


(Id),



(Ie), or



(If),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

3. The compound according to embodiment 1 or 2, wherein R_5 is H.

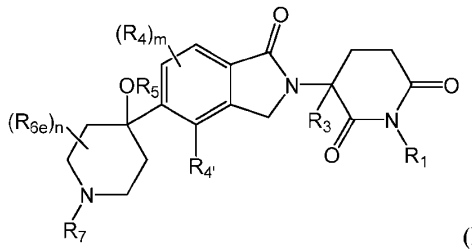
4. The compound according to any one of embodiments 1-3, wherein R_{6a} is H.

5. The compound according to any one of embodiments 1-4, wherein R_{6b} is H.

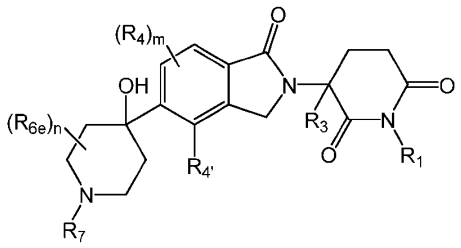
6. The compound according to any one of embodiments 1-5, wherein R_{6c} is H.

7. The compound according to any one of embodiments 1-6, wherein R_{6d} is H.

8. The compound according to embodiment 1-7, having a Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), or Formula (Im):



(Ig),



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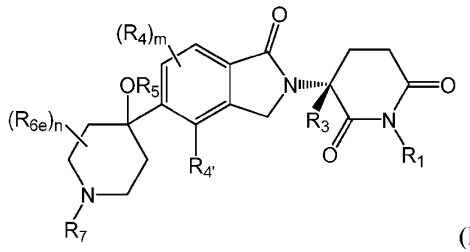
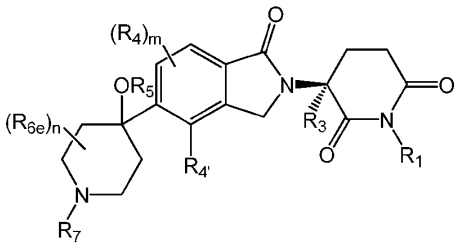
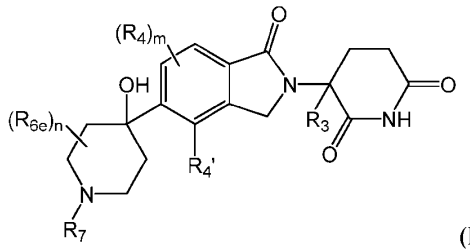


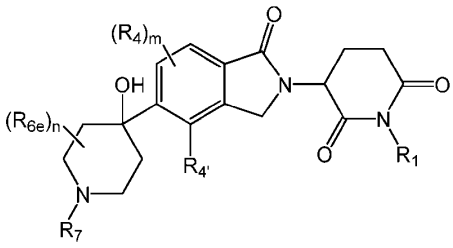
(Ii),



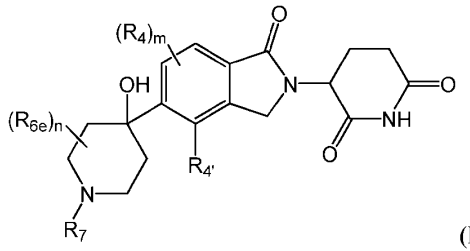
(Ij),



(Ik),



(Il), or



(Im).

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

9. The compound according to any one of embodiments 1-8, wherein R_3 is H.

10. The compound according to any one of embodiments 1-9, wherein $R_{4'}$ is (C_1)alkyl and R_7 is $(C_1$-$C_6)$alkyl optionally substituted with one to three phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to three R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to three $R_{8'}$.

11. The compound according to any one of embodiments 1-9, wherein $R_{4'}$ is $(C_2$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$ and R_7 is $(C_1$-$C_6)$alkyl optionally substituted with one to three phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to three R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to three $R_{8'}$.

12. The compound according to any one of embodiments 1, 2, or 8, wherein $R_{4'}$ is H.

13. The compound according to embodiment 12, wherein n is 0 and m is 0.

14. The compound according to any one of embodiments 12 or 13, wherein one of R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 is not H.

15. The compound according to any one of embodiments 1-14, wherein $R_{4'}$ is H.

16. The compound according to embodiment 15, wherein m is 0 or 1 and n is 1, 2, or 3.

17. The compound according to any one of embodiments 12-16, wherein R_7 is (C_1-C_6)alkyl optionally substituted with one to three phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to three R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to three $R_{8'}$.

18. The compound according to embodiment 17, wherein n is 0 and m is 1.

19. The compound according to embodiment 18, wherein R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, and R_7 is (C_1-C_6)alkyl optionally substituted with one to three phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one to three R_8, the heteroaryl is optionally substituted with one to three R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one to three $R_{8'}$.

20. The compound according to any one of embodiments 1-19, wherein n is 0.

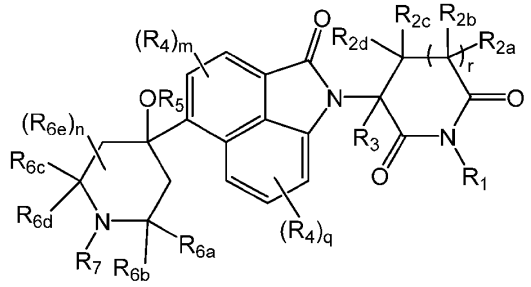
21. The compound according to any one of embodiments 1-19, wherein n is 1.

22. The compound according to any one of embodiments 1-19, wherein n is 2.

23. The compound according to any one of embodiments 1-22, wherein m is 0.

24. The compound according to any one of embodiments 1-22, wherein m is 1.

25. A compound of Formula (II):



(II),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

R_1 is H, D, -C(O)R_{11}, -CH_2OC(O)R_{11}, -CH_2OC(O)NHR_{12}, -CH_2OC(O)OR_{12}, -P(O)(OR_{12})$_2$, -CH_2OP(O)(OR_{12})$_2$, -CH_2OP(O)(OH)OR_{12}, -CH_2OP(O)(R_{12})$_2$, -CH_2OC(O)CH_2NHC(O)CH_2NH_2, -CH_2OC(O)CH($R_{12'}$)N$HR_{12'}$, -CH_2OC(O)(CH_2)$_q$C(O)O$R_{12'}$, or -CH_2OC(O)-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S);

R_{2a}, R_{2b}, R_{2c}, and R_{2d} are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, halogen, or -OH, wherein two of R_{2a}, R_{2b}, R_{2c}, and R_{2d} may be taken together with the carbon atom to which they are attached form a (C_3-C_7)carbocyclyl or (C_3-C_7)spirocarbocyclyl;

R_3 is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, or halogen, wherein R_3 may be taken together with one of R_{2a}, R_{2b}, R_{2c}, and R_{2d} with the carbon atom to which they are attached to form a (C_3-C_7)carbocyclyl or (C_3-C_7)spirocarbocyclyl;

each R_4 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)halohalkyl, or halogen;

R_5 is H, D, (C_2-C_6)alkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)aminoalkyl, (C_1-C_6)alkyl-O-(C_1-C_6)hydroxyalkyl, $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, $-CH_2OC(O)_2R_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$;

R_{6a}, R_{6b}, R_{6c}, and R_{6d} are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy,, or (C_3-C_7)carbocyclyl; or

two of R_{6a}, R_{6b}, R_{6c}, and R_{6d} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl, (C_3-C_7)spirocarbocyclyl, 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl, heterocyclyl, and spiroheterocyclyl are optionally substituted with one or more R_{10};

each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, -(C_1-C_6)alkylene-O-(C_1-C_6)alkyl, (C_6-C_{10})aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one or more R_{13}, the aryl and heteroaryl are optionally substituted with one or more R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{23}; or

two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)carbocyclyl, (C_3-C_7)spirocarbocyclyl, a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl, heterocyclyl, and spiroheterocyclyl are optionally substituted with one or more R_{15}; or

one R_{6e} is taken together with any one of R_{6a}, R_{6b}, R_{6c}, and R_{6d} and the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{15};

R_7 is $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$halohydroxyalkyl, or $(C_3$-$C_7)$carbocyclyl, wherein alkyl, haloalkyl, hydroxyalkyl, halohydroxyalkyl, and carbocyclyl are optionally substituted with one or more substituents independently selected from R_{21}, D, $(C_1$-$C_6)$alkoxy, $-SF_5$, $-SR_{16a}$, $-NR_{16}R_{16'}$,$-C(O)NR_{32}R_{33}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$;

R_8 and $R_{8'}$ are each independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{24}$, -CN, $-C(O)NR_{32}R_{33}$, $-C(O)OR_{32}$, $(C_3$-$C_7)$carbocyclyl, $-O(C_3$-$C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the alkyl, deuteroalkyl, haloalkyl, alkoxy, haloalkoxy, hydroalkyl, phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more substituents selected from $(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$carbocyclyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{40}$, and -CN, and R_{13}; or

two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R_{10};

two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{10}; or

two $R_{8'}$ together with the atoms to which they are attached form a $(C_3$-$C_7)$carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, NH, N, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{10}; or

two $R_{8'}$ when on the same carbon atom form C=(O);

each R_9 and $R_{9'}$ are each independently is independently at each occurrence $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $-NR_{13}R_{13'}$, -CN,

(C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein carbocyclyl and heterocyclyl are optionally substituted with one or more R_{20} and the aryl and heteroaryl are optionally substituted with one or more R_{21};

R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, - OH, $-NH_2$, $-SF_5$, $-SR_{25}$, -CN, $C(O)OR_9$, $-C(O)R_9$, and $-C(O)NR_9R_9$;

R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, $-NH_2$, $-N(H)(C_1$-$C_6)$alkyl, $-N((C_1$-$C_6)alkyl)_2$, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, $-NH_2$, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, $-NH_2$, and -CN;

R_{12} is independently at each occurrence H, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, $-NH_2$, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, $-NH_2$, and -CN;

$R_{12'}$ is independently at each occurrence H or (C_1-C_6)alkyl;

R_{13} and $R_{13'}$ are each independently at each occurrence H or (C_1-C_6)alkyl;

each R_{14} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, $-C(O)OR_{17}$, $-C(O)R_{18}$, or $-C(O)NR_{17}R_{17}$;

R_{15} and $R_{15'}$ are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{15a} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

each R_{16} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{24}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{16}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S

R_{17} is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{18} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy,

(C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{19} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{20} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, and R_{27} are each independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{30} and R_{31} are each independently at each occurrence H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_3-C_7)carbocyclyl, -C(O)R_{32}, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl or heteroaryl can be substituted with one or more R_{17};

R_{30}, R_{31}, and R_{32} are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{33} and R_{34} are each independently at each occurrence H, (C_1-C_6)alkyl, or -C(O)R_{37};

R_{35}, R_{36}, and R_{37} are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{38} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

m is 0, 1, or 2;

q is 1, 2, or 3;

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

r is 0 or 1.

26. The compound according to embodiment 25, wherein R_3 is H.

27. The compound according to any one of embodiments 25 or 26, wherein R_5 is H.

28. The compound according to any one of embodiments 25-27, wherein R_{2a} is H.

29. The compound according to any one of embodiments 25-28, wherein R_{2b} is H.

30. The compound according to any one of embodiments 25-29, wherein R_{2c} is H.

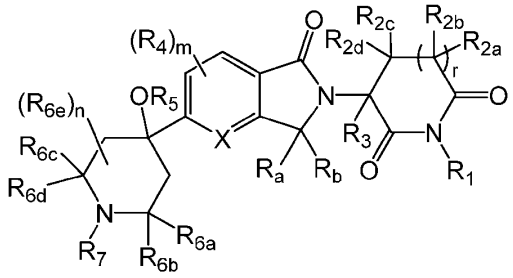
31. The compound according to any one of embodiments 25-30, wherein R_{2d} is H.

32. The compound according to any one of embodiments 25-31, R_7 is (C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one to three phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to three R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to three $R_{8'}$.

33. The compound according to any one of embodiments 25-32, R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to three phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to three R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to three $R_{8'}$.

34. The compound of any one of the preceding embodiments, wherein the compound of Formula (I) or (II) is a compound provided in Table 1.

35. A compound of Formula (III):



(III),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

X is N or N(O);

R_a and R_b are each independently H, D, or (C_1-C_6)alkyl;

R_1 is H, D, -C(O)R_{11}, -CH_2OC(O)R_{11}, -CH_2OC(O)NHR_{12}, -CH_2OC(O)OR_{12}, -P(O)(OR_{12})$_2$, -CH_2OP(O)(OR_{12})$_2$, -CH_2OP(O)(OH)OR_{12}, -CH_2OP(O)(R_{12})$_2$, -CH_2OC(O)CH_2NHC(O)CH_2NH_2, -CH_2OC(O)CH($R_{12'}$)N$HR_{12'}$, -CH_2OC(O)(CH_2)$_q$C(O)O$R_{12'}$, or -CH_2OC(O)-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S);

R_{2a}, R_{2b}, R_{2c}, and R_{2d} are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, halogen, or -OH, wherein two of R_{2a}, R_{2b}, R_{2c}, and R_{2d} may be taken together with the carbon atom to which they are attached form a (C_3-C_7)carbocyclyl or (C_3-C_7)spirocarbocyclyl;

R_3 is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, or halogen, wherein R_3 may be taken together with one of R_{2a}, R_{2b}, R_{2c}, and R_{2d} with the carbon atom to which they are attached to form a (C_3-C_7)carbocyclyl or (C_3-C_7)spirocarbocyclyl;

each R_4 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, or halogen;

R_5 is H, D, (C_2-C_6)alkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)aminoalkyl, (C_1-C_6)alkyl-O-(C_1-C_6)hydroxyalkyl, -C(O)R_{12}, -$CH_2OC(O)R_{12}$, -$CH_2OC(O)N(R_{12})_2$, -$CH_2OC(O)_2R_{12}$, -$P(O)(OR_{12})_2$, -$CH_2OP(O)(OH)OR_{12}$, or -$CH_2OP(O)(R_{12})_2$;

R_{6a}, R_{6b}, R_{6c}, and R_{6d} are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy,, or (C_3-C_7)carbocyclyl; or

two of R_{6a}, R_{6b}, R_{6c}, and R_{6d} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl, (C_3-C_7)spirocarbocyclyl, 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl, heterocyclyl, and spiroheterocyclyl are optionally substituted with one or more R_{10};

each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, -(C_1-C_6)alkylene-O-(C_1-C_6)alkyl, (C_6-C_{10})aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one or more R_{13}, the aryl and heteroaryl are optionally substituted with one or more R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{23}; or

two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)carbocyclyl, (C_3-C_7)spirocarbocyclyl, a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl, heterocyclyl, and spiroheterocyclyl are optionally substituted with one or more R_{15}; or

one R_{6e} is taken together with any one of R_{6a}, R_{6b}, R_{6c}, and R_{6d} and the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{15};

R_7 is (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_3-C_7)carbocyclyl, wherein alkyl, haloalkyl, hydroxyalkyl, halohydroxyalkyl, and carbocyclyl are optionally substituted with one or more substituents independently selected from R_{21}, D, (C_1-C_6)alkoxy, -SF_5, -SR_{14a},

$-NR_{14}R_{14'}$,$-C(O)NR_{29}R_{30}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$;

R_8 and $R_{8'}$ are each independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NR_{27}R_{28}$, $-SF_5$, $-SR_9$, -CN, $-C(O)NR_{29}R_{30}$, $-C(O)OR_{29}$, (C_3-C_7)carbocyclyl, $-O(C_3-C_7)$carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more substituents selected from (C_1-C_6)alkyl, (C_3-C_7)carbocyclyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy,
(C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, $-NR_{32}R_{33}$, $-C(O)NR_{34}R_{35}$, $-C(O)R_{34}$, $-C(O)OR_{34}$, $-SF_5$, $-SR_{37}$, and -CN; or

two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R_{10};

two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{10}; or

two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{10}; or

two $R_{8'}$ when on the same carbon atom form C=(O);

R_9 is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{26}$, or -CN;

R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, $-NH_2$, $-N(H)(C_1-C_6)$alkyl,

-N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN;

R_{12} is independently at each occurrence H, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN;

$R_{12'}$ is independently at each occurrence H or (C_1-C_6)alkyl;

each R_{13} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)$OR_{15'}$, -C(O)R_{15}, or -C(O)$NR_{15'}R_{15'}$;

R_{14} and $R_{14'}$ are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{14a} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{15} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

$R_{15'}$ is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{17}R_{17'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein carbocyclyl and heterocyclyl are optionally substituted with one or more R_{22} and the aryl and heteroaryl are optionally substituted with one or more R_{23};

R_{17} and $R_{17'}$ are each independently at each occurrence H or (C_1-C_6)alkyl;

each R_{18} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{20}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{18}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy,

(C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{21}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{19} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

R_{20} and R_{21} are each independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

each R_{22} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{22} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{23} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

R_{24}, R_{25} and R_{26} are each independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{27} and R_{28} are each independently at each occurrence H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_3-C_7)carbocyclyl, -C(O)R_{31}, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl or heteroaryl can be substituted with one or more R_{17};

R_{29}, R_{30}, and R_{31} are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{32} and R_{33} are each independently at each occurrence H, (C_1-C_6)alkyl, or -C(O)R_{36};

R_{34}, R_{35}, and R_{36} are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{37} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

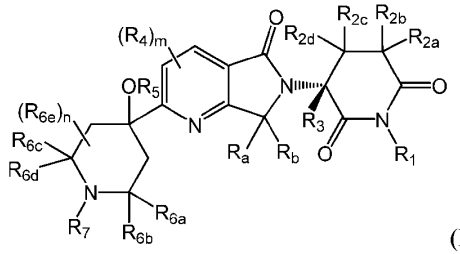
q is 1, 2, or 3;

m is 0, 1 or 2;

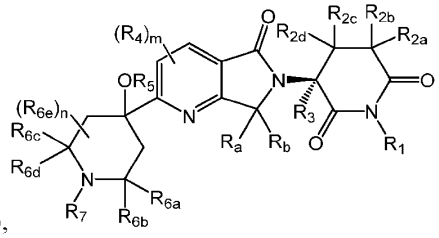
n is 0, 1, 2, 3 or 4;

r is 0 or 1.

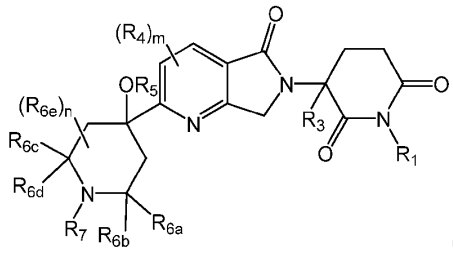
36. The compound according to embodiments 35, having a Formula (IIIa), Formula (IIIb), Formula (IIIc), Formula (IIId), Formula (IIIe), Formula (IIIf), or Formula (IIIg):



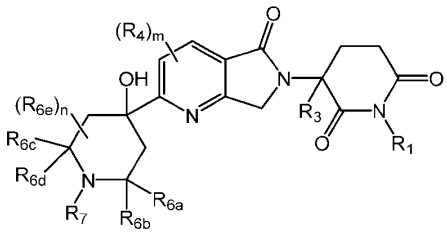
(IIIa),



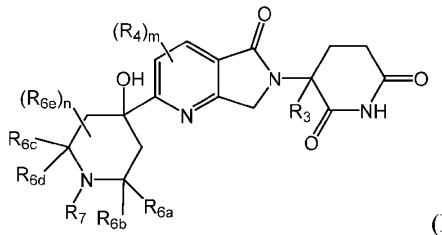
(IIIb),



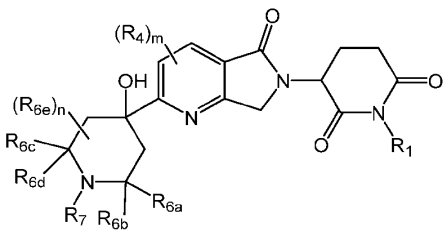
(IIIc),



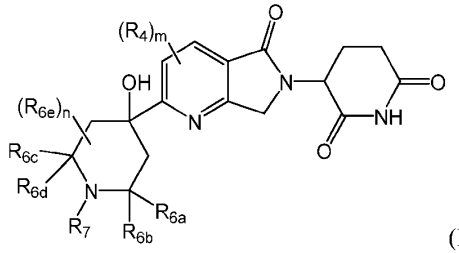
(IIId),



(IIIe),



(IIIf), or



(IIIg),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

37. The compound according to embodiment 36 or 37, wherein R_5 is H.

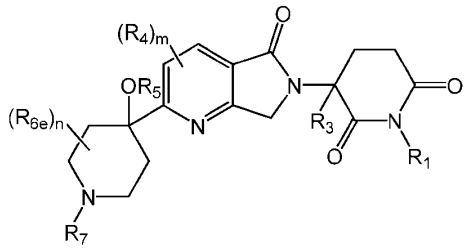
38. The compound according to any one of embodiments 35-37, wherein R_{6a} is H.

39. The compound according to any one of embodiments 35-38, wherein R_{6b} is H.

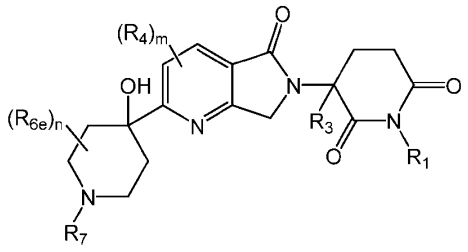
40. The compound according to any one of embodiments 35-39, wherein R_{6c} is H.

41. The compound according to any one of embodiments 35-40, wherein R_{6d} is H.

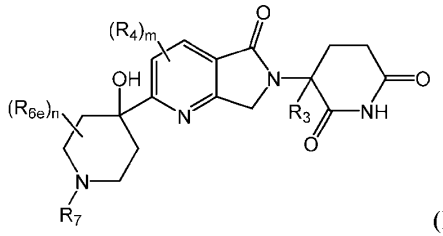
42. The compound according to embodiments 35-41, having a Formula (IIIh), Formula (IIIi), Formula (IIIj), Formula (IIIk), or Formula (IIIl):



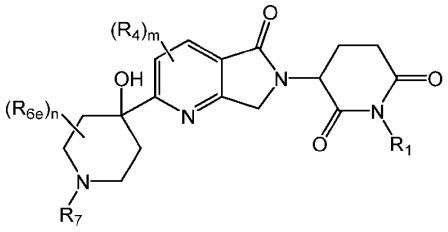
(IIIh),



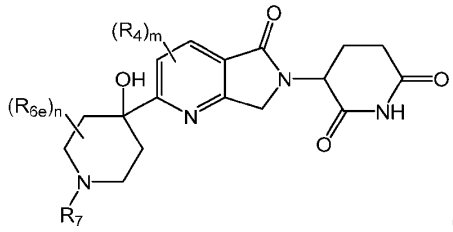
(IIIi),



(IIIj),



(IIIk), or



(IIIl),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

43. The compound according to one of embodiments 35-42, wherein R_1 is H.

44. The compound according to one of embodiments 35-43, wherein R_{2a}, R_{2b}, R_{2c}, and R_{2d} are each H.

45. The compound according to any one of embodiments 35-44, wherein R_3 is H, D, or methyl.

46. The compound according to any one of embodiments 35-45, wherein R_a and R_b are both H.7. The compound according to any one of the above claims, wherein m is 0.

47. The compound according to any one of embodiments 35-46, wherein R_{6a}, R_{6b}, R_{6c}, and R_{6d} are each independently H or (C_1-C_6)alkyl.

48. The compound according to any one of embodiments 35-47, wherein each R_{6e} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl,

-(C_1-C_6)alkylene-O-(C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one or more R_{13}, the aryl is optionally substituted with one or more R_{22}; or

two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one or more R_{15}.

49. The compound according to any one of embodiments 35-48, wherein n is 0.

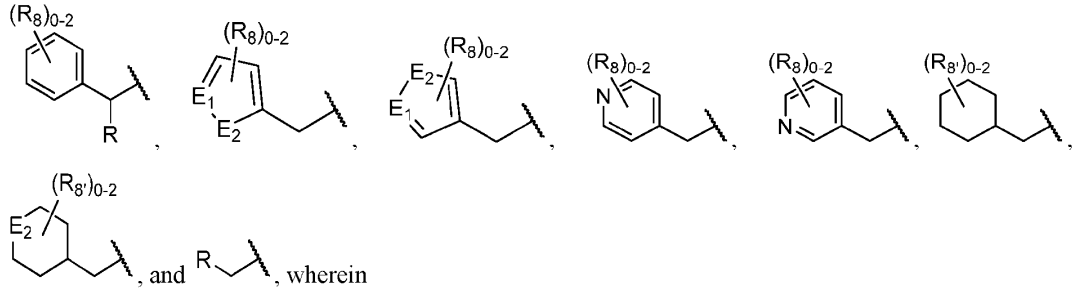
50. The compound according to any one of embodiments 35-49, wherein n is 1.

51. The compound according to any one of embodiments 35-49, wherein n is 2.

52. The compound according to any one of embodiments 35-51, wherein R_7 is (C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one or two phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

53. The compound according to any one of embodiments 35-52, wherein R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one or two phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl, and heterocyclyl are optionally substituted with one to four $R_{8'}$.

54. The compound according to any one of embodiments 35-53, wherein R_7 is selected from



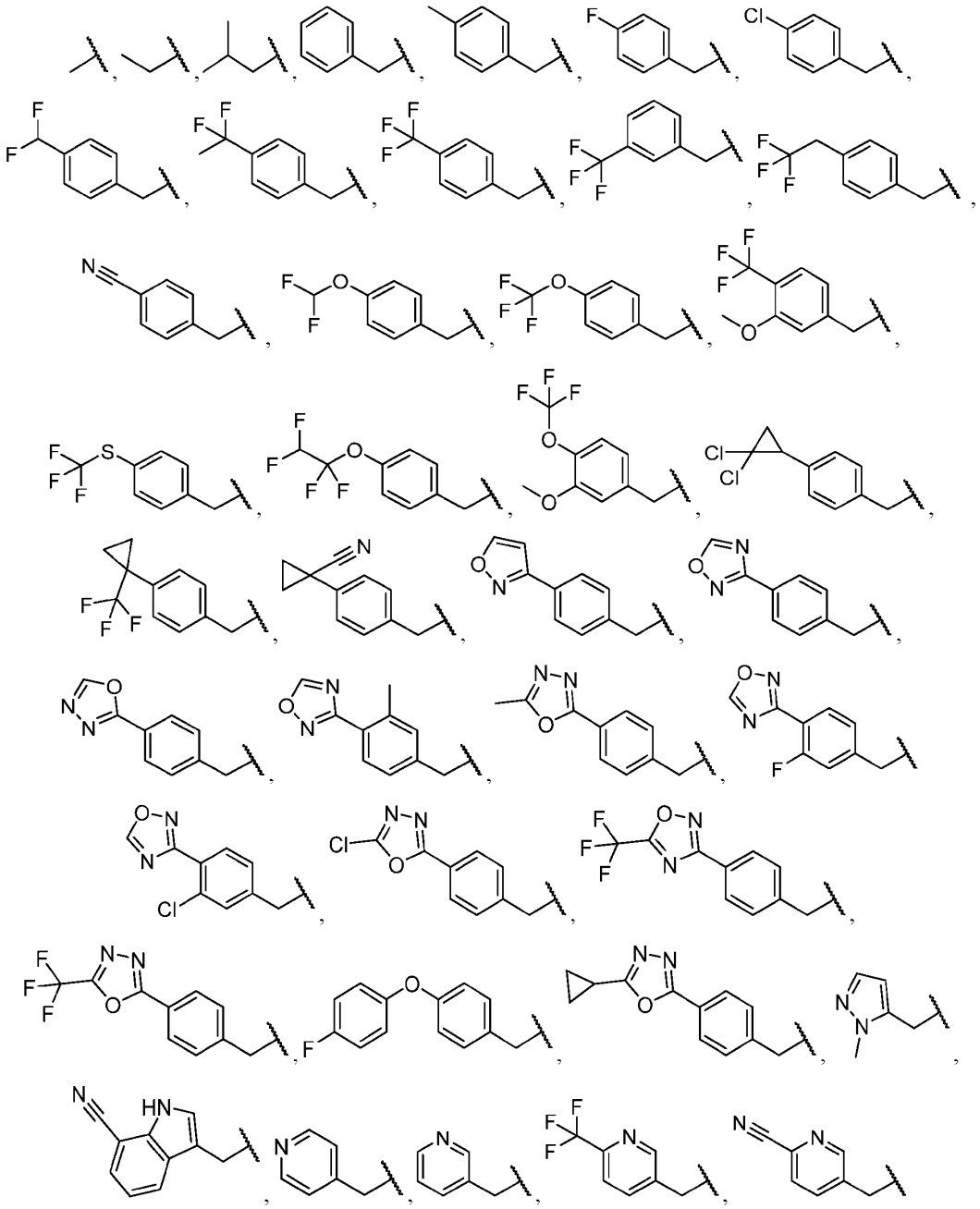
, and

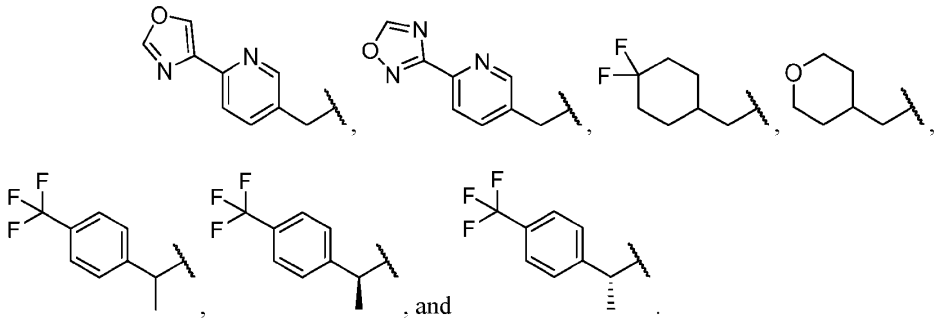
, wherein

R is selected from H and (C_1-C_3)alkyl; E_1 is selected from CH and N; E_2 is selected from O, NH, NR_8, and S; and

R_8 and $R_{8'}$ are defined according to the above embodiment 35.

55. The compound according to any one of embodiments 35-54, wherein R_7 is selected from





56. The compound of any one of embodiments 35-55, wherein the compound is provided in Table 2.

57. A pharmaceutical composition according to any one of embodiments 1-56, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

58. The pharmaceutical composition according to embodiment 57, further comprising a pharmaceutically acceptable additive or excipient.

59. The pharmaceutical composition according to embodiments 57-58 for use in the treatment of a disease or disorder that is affected by the reduction of HIF-1β levels.

60. A method of degrading HIF-1β, comprising administering to a patient in need thereof an effective amount of a compound according to any one of embodiments 1-56, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

61. A method of modulating HIF-1β levels comprising administering to a patient in need thereof an effective amount of a compound according to any one of embodiments 1-56, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

62. An *in vitro* method of reducing the proliferation of a cell, comprising contacting the cell with an effective amount of a compound according to any one of embodiments 1-56, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

63. A method of treating a disease or disorder that is affected by the modulation of HIF-1β levels, comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of embodiments 1-56, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

64. The method according to embodiment 63, wherein the disease or disorder is selected from cancer, von Hippel-Lindau (VHL) disease, iron overload disorders, cardiovascular diseases, pulmonary diseases, autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, metabolic diseases, neovascular diseases, retinal vascular diseases, fibrosis, endometriosis, preeclampsia, and allergic and genetic diseases.

65. The method according to embodiments 63-64 wherein the disease or disorder is selected from renal cell carcinoma (RCC), von Hippel-Lindau disease (VHL), advanced pheochromocytoma/paraganglioma (PPGL), pancreatic neuroendocrine tumor (pNET), pulmonary arterial hypertension (PAH), glioblastoma, colitis, Crohn's disease, ulcerative colitis, T cell leukemia or T cell lymphoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), melanoma, triple-negative breast cancer (TNBC), nasopharyngeal cancer (NPC), microsatellite stable colorectal cancer (mssCRC), thymoma, carcinoid, gastrointestinal stromal tumor (GIST), myeloid leukemia, and coronary heart disease.

66. A method of treating cancer, comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of embodiments 1-56, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

67. The method according to embodiment 66, wherein the cancer is VHL-deficient cancer.

68. The method according to embodiment 66, wherein the cancer is selected from renal cell carcinoma (RCC), glioblastoma, T cell leukemia or T cell lymphoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), melanoma, triple-negative breast cancer (TNBC), nasopharyngeal cancer (NPC), microsatellite stable colorectal cancer (mssCRC), thymoma, carcinoid, gastrointestinal stromal tumor (GIST), and myeloid leukemia.

69. A method for reducing HIF-1β levels, comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of embodiments 1-56, or a pharmaceutically acceptable salt thereof.

70. A method of treating von Hippel-Lindau (VHL) disease, comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of embodiments 1-56, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

71. A method of treating a neoplastic condition, comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of embodiments 1-56, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

72. A method of treating renal cell carcinoma (RCC), comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of embodiments 1-56, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

73. The method of embodiment 72, wherein the renal cell carcinoma is clear cell renal cell carcinoma (ccRCC).

74. The method according to any one of embodiments 63-73, wherein the administration is oral, parenteral, subcutaneous, by injection, or by infusion.

75. A compound according to any one of embodiments 1-56, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in the treatment of a disease or disorder that is affected by the reduction of HIF-1β levels.

74. A compound according to any one of embodiments 1-56, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in treating a disease or disorder associated with the reduction of HIF-1β levels.

75. Use of a compound according to any one of embodiments 1-56, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for treating a disease or disorder that is affected by the reduction of HIF-1β levels.

76. Use of a compound according to any one of embodiments 1-56, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the treatment of a disease or disorder associated with the reduction of HIF-1β levels.

77. The compound for use according to embodiments 75-76 or the use according to embodiments 65-74, wherein the disease or disorder is selected from cancer, von Hippel-Lindau (VHL) disease, iron overload disorders, cardiovascular diseases, pulmonary arterial hypertension (PAH), autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, metabolic diseases, and allergic and genetic diseases.

EXAMPLES

The disclosure is further illustrated by the following examples and synthesis schemes, which are not to be construed as limiting this disclosure in scope or spirit to the specific procedures herein described. It is to be understood that the examples are provided to illustrate certain embodiments and that no limitation to the scope of the disclosure is intended thereby. It is

to be further understood that resort may be had to various other embodiments, modifications, and equivalents thereof which may suggest themselves to those skilled in the art without departing from the spirit of the present disclosure and/or scope of the appended claims.

Compounds of the present disclosure may be prepared by methods known in the art of organic synthesis. In all of the methods it is understood that protecting groups for sensitive or reactive groups may be employed where necessary in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T.W. Green and P.G.M. Wuts (1999) Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art.

Analytical Methods, Materials, and Instrumentation

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Proton nuclear magnetic resonance (NMR) spectra were obtained on either 500 MHz Bruker Avance II, AV-500 spectrometer, 400 MHz Bruker spectrometer, or Varian Oxford 400 MHz spectrometer unless otherwise noted. Spectra are given in ppm (d) and coupling constants, J, are reported in Hertz. Tetramethylsilane (TMS) was used where indicated as an internal standard. Chemical shifts are reported in ppm using dimethyl sulfoxide (d 2.50), methanol (d 3.31), chloroform (d 7.26) or other solvent residual protons as an internal reference, as indicated in NMR spectral data. A small amount of the dry sample (2-5 mg) is dissolved in an appropriate deuterated solvent (1 mL). The chemical names were generated using ChemBioDraw Ultra v21 from CambridgeSoft.

Mass spectra (HESI-MS) were collected using a Thermo Scientific UHPLC-MS Vanquish with a LTQ quadrupole or mass spectra (ESI-MS) were collected using a Waters System (Acquity UPLC and a Micromass ZQ mass spectrometer) or Agilent-1260 Infinity (6120 Quadrupole); all masses reported are the m/z of the protonated parent ions unless recorded otherwise. The sample was dissolved in a suitable solvent such as MeCN, DMSO, or MeOH and was injected directly into the column using an automated sample handler. The analysis is performed on one of the following:

Waters Acquity UPLC system. Column: Waters Acquity UPLC BEH C18 1.7μm, 2.1 × 30 mm; Flow rate: 1 mL/min; Column temperature: 55°C; Solvent A: 0.05% formic acid in water, Solvent B: 0.04% formic acid in MeOH; gradient 95% Solvent A from 0 to 0.10 min; 95%

Solvent A to 20% Solvent A from 0.10 to 0.50 min; 20% Solvent A to 5% Solvent A from 0.50 to 0.60 min; hold 25 at 5% Solvent A from 0.6 min to 0.8 min; 5% Solvent A to 95% Solvent A from 0.80 to 0.90 min; and hold 95% Solvent A from 0.90 to 1.15 min.

Thermo Vanquish UHPLC-MS system. Column: Waters Acquity UPLC BEH C18 1.7μm, 2.1 × 50 mm; Flow rate: 0.3 mL/min; Column temperature: 25°C; Solvent A: 0.1% formic acid in water, Solvent B: 0.1% formic acid in acetonitrile; gradient: 95% Solvent A from 0 to 0.50 min; 95% Solvent A to 0% Solvent A from 0.5 to 2.5 min; hold 0% Solvent A from 2.50 to 3.50 min; Flow rate increased to 0.6 mL/min and Solvent A to 95% 3.5 mins to 3.7 mins; hold 95% Solvent A at 0.6 mL/min 3.7 mins to 4.4 mins; drop flow rate to 0.3 mL/min and hold at 95% Solvent A from 4.4 min to 4.5 min.

Agilent 1290 Infinity II UHPLC-MS system. Column: Waters Acquity UPLC BEH C18 1.7μm, 2.1 × 30 mm; Flow rate: 1.6 mL/min; Column temperature: 60°C; Solvent A: 0.1% formic acid in water, Solvent B: 0.5% formic acid in acetonitrile. Gradient: 99% Solvent A from 0 to 0.15 min; 99% Solvent A to 1% Solvent A from 0.15 to 1.65 min; hold 1% Solvent A from 1.65 to 1.90 min; 1% Solvent A to 99% Solvent A from 1.90 to 1.91 min; hold 99% Solvent A from 1.91 to 2.0 min.

Purification of final compounds, salt forms, and stereochemistry

Final compounds of the invention were in many cases purified by reverse-phase chromatography in the presence of additives such as formic acid, hydrochloric acid, acetic acid or ammonium acetate, followed by lyophilization. In some cases, the salt form of a final compound was changed by re-lyophilization in the presence of the desired salt, for example, by taking up a formic acid salt in a mixture of acetonitrile and dilute hydrochloric acid and lyophilizing to provide the hydrochloric acid salt. Depending on the characteristics of the final compound and the lyophilization conditions, the free base form can be generated following lyophilization, even when the chromatography mobile phase contained salt-forming additives. The stated salt forms of final compounds of the invention are based on NMR evidence and consideration of the purification conditions and the characteristics of the compound. Further, in cases where stereoisomers were purified from a mixture of stereoisomers, the stereochemistry assigned is relative and arbitrary.

Abbreviations used in the following examples and elsewhere herein are:

ACN	Acetonitrile
AcOH	acetic acid
AIBN	azobisisobutyronitrile

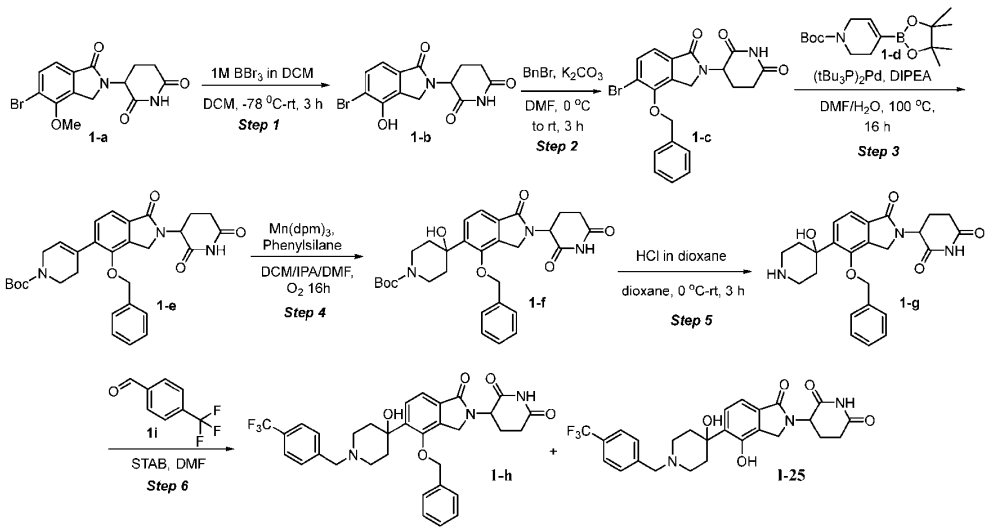
APCI	atmospheric pressure chemical ionization
aq.	aqueous
BBr_3	boron tribromide
B_2pin_2	bis(pinacolato)diboron
Boc_2O or Boc anhydride	di-tert-butyl dicarbonate
Bn	benzyl
BnBr	benzyl bromide
Bu	butyl
br	broad
CO	carbon monoxide
Comins' reagent	2-(N,N-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine
Cs_2CO_3	cesium carbonate
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
ddq	doublet of doublet of quartets
ddt	doublet of doublet of triplets
dq	doublet of quartets
dt	doublet of triplets
dtd	doublet of triplet of doublets
DC_{50}	half maximal degradation concentration
DCE	1,2-dichloroethane
DCM	dichloromethane
DIEA	diisopropylethylamine or N,N-diisopropylethylamine
DIPEA	diisopropylethylamine or N,N-diisopropylethylamine
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
D_{max}	maximum level of degradation
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide

EC_{50}	half maximal effective concentration
ES	electrospray
EtOH	ethanol
Et_2O	diethyl ether
Et_3N	triethylamine
EtOAc	ethyl acetate
FA	formic acid
Grubbs® 2nd gen. catalyst	(1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)-dichloro(phenylmethylene)(tricyclohexylphosphine) ruthenium
HCl	hydrogen chloride
hept	heptet
HPLC	high performance liquid chromatography
h or hr	hour
HRMS	high resolution mass spectrometry
g	gram
IC_{50}	half maximal inhibitory concentration
IPA	isopropyl alcohol
K_2CO_3	potassium carbonate
KI	potassium iodide
KOAc	potassium acetate
K_2CO_3	potassium carbonate
K_3PO_4	tripotassium phosphate
KOtBu	potassium tert-butoxide
LAH	lithium aluminum hydride
LCMS	liquid chromatography mass spectrometry
LDA	lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
m	multiplet
M	molar
MeI	methyl iodide

MTBE	methyl tertiary-butyl ether
MeCN	acetonitrile
MeOH	methanol
mg	milligram
MHz	megahertz
min	minute(s)
mL	milliliter
mmol	millimole
$Mn(dpm)_3$	tris(2,2,6,6-tetramethyl-3,5-heptanedionato)manganese(III)
MP-cyanoborohydride	macroporous polymer supported cyanoborohydride
MS	mass spectrometer
MW	microwave
$NaHCO_3$	sodium bicarbonate
$NaBH(OAc)_3$	sodium triacetoxyborohydride
$NaCNBH_3$ or $NaBH_3CN$	sodium cyanoborohydride
NaOtBu	sodium tert-butoxide
Na_2SO_4	sodium sulfate
NBS	*N*-bromosuccinimide
NIS	*N*-Iodosuccinimide
n-BuLi	n-butyllithium
NMR	nuclear magnetic resonance
$POBr_3$	phosphoryl bromide or phosphorus(V) oxybromide
$PdCl_2(dppf)$• DCM	[1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II), complex with dichloromethane
$PhSO_3H$	benzene sulfonic acid
q	quartet
qd	quartet of doublets
quint	quintet
quintd	quintet of doublets
rt	room temperature
Rt	retention time

s	singlet
SFC	supercritical fluid chromatography
$SOCl_3$	thionyl chloride
STAB	sodium triacetoxyborohydride
t	triplet
td	triplet of doublets
tdd	triplet of doublet of doublets
$(tBu_3P)_2Pd$	bis(tri-tert-butylphosphine)palladium(0)
TEA (NEt_3)	triethylamine
TFA	trifluoroacetic acid
TfOH	triflic acid
Tf_2NPh	N-phenyl-bis(trifluoromethanesulfonimide) or N-phenylbis(trifluoromethanesulfonyl)amine
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMP	2,2,6,6-tetramethylpiperidine
TMPMgCl·LiCl	2,2,6,6-Tetramethylpiperidinylmagnesium chloride lithium chloride complex
Ts	tosyl or *p*-toluenesulfonyl
tt	triplet of triplets
ttd	triplet of triplet of doublets
TTFA	thallium(III) trifluoroacetate
UPLC	ultra-Performance Liquid Chromatography

Example 1: Synthesis of 3-(4-hydroxy-5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-25)



Step 1: **Synthesis of 3-(5-bromo-4-hydroxy-1-oxoisoindolin-2-yl)piperidine-2,6-dione (1-b)**

To a stirred solution of 3-(5-bromo-4-methoxy-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**1-a**, 15 g, 42.50 mmol) in DCM (150 mL) at -78 °C and under an atmosphere of nitrogen was added BBr_3 in DCM (149 mL, 149 mmol) and the resulting mixture was stirred at 25 °C for 3 h. The reaction mixture was then quenched with MeOH at 0 ^{0}C. The solvent was removed under reduced pressure and the crude product triturated with ACN. The obtained solid was filtered to provide 3-(5-bromo-4-hydroxy-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**1-b**). LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2H]^+$ = 338.8, 340.9. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 10.46 (s, 1H), 7.66 (d, J = 7.80 Hz, 1H), 7.15 (d, J = 7.80 Hz, 1H), 5.10 (dd, J = 5.20, 13.40 Hz, 1H), 4.41 (d, J = 17.60 Hz, 1H), 4.28 (d, J = 17.60 Hz, 1H), 2.95-2.87 (m, 1H), 2.61 (d, J = 16.80 Hz, 1H), 2.41-2.31 (m, 1H), 2.07-2.02 (m, 1H).

Step 2: **Synthesis of 3-(4-(benzyloxy)-5-bromo-1-oxoisoindolin-2-yl)piperidine-2,6-dione (1-c)**

To a stirred solution of 3-(5-bromo-4-hydroxy-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**1-b**, 0.5 g, 1.47 mmol) in DMF (5 mL) was added K_2CO_3 (0.306 g, 2.21 mmol) and the resulting mixture was stirred at room temperature for 30 mins. After 30 mins, the reaction mixture was cooled to 0 °C and benzyl bromide (0.303 g, 1.77 mmol) was then added and stirring was continued at room temperature for 3 h. The reaction mixture was then quenched with ice and a precipitate was observed. This solid was filtered and dried to provide 3-(4-(benzyloxy)-5-bromo-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**1c**). LCMS: m/z MM-ES+APCI, Positive $[M+, M+2]^+$ = 428.9, 430.7. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H), 7.81 (d, J = 8.00 Hz, 1H), 7.56-7.52 (m, 2H), 7.45-7.37 (m, 4H), 5.25 (s, 2H), 5.12 (dd, J = 5.20, 13.40 Hz, 1H), 4.64 (d, J = 17.60 Hz, 1H), 4.50 (d, J = 17.60 Hz, 1H), 2.96-2.89 (m, 1H), 2.60 (d, J = 2.00 Hz, 1H), 2.48-2.41 (m, 1H), 2.02-1.98 (m, 1H).

Step 3: **Synthesis of tert-butyl 4-(4-(benzyloxy)-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1-e)**

To a stirred solution of 3-(4-(benzyloxy)-5-bromo-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**1-c**, 0.7 g, 1.63 mmol) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**1-d**, 0.5 g, 0.70 mmol) in DMF (10 mL) at room temperature and under an atmosphere of nitrogen was added N-ethyl-N-isopropylpropan-2-amine (1.139 mL, 6.52 mmol) followed by bis(tri-tert-butylphosphine)palladium(0) (0.167 g, 0.33 mmol) and the resulting mixture was stirred at 100 °C for 16 h. The reaction mixture was then quenched with ice and a solid precipitate was observed. The solid was filtered and then purified via silica gel flash column chromatography (Biotage® Isolera,100 g silica gel cartridge) eluting with 100% ethyl acetate. The pure fractions were concentrated under reduced pressure to provide tert-butyl 4-(4-(benzyloxy)-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**1-e**). LCMS: m/z MM-ES+APCI, Positive $[M\text{-}Boc]^+$ = 432.1. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 7.51-7.36 (m, 7H), 5.88 (s, 1H), 5.26-5.09 (m, 1H), 5.03 (s, 2H), 4.56 (d, J = 17.20 Hz, 1H), 4.44-4.40 (m, 1H), 4.03 (s, 2H), 3.48 (t, J = 5.60 Hz, 2H), 3.35-3.32 (m, 1H), 2.95-2.91 (m, 1H), 2.52-2.41 (m, 3H), 2.01-1.97 (m, 1H), 1.44 (s, 9H).

Step 4: **Synthesis of tert-butyl 4-(4-(benzyloxy)-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate (1-f)**

A solution of tert-butyl 4-(4-(benzyloxy)-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**1-e**, 0.45 g, 0.85 mmol) in DMF (1 mL), 2-propanol (5 mL) and DCM (5 mL) was stirred at 0 °C for 5 min. $Mn(dpm)_3$ (0.154 g, 0.25 mmol) was then added followed by phenylsilane (0.313 mL, 2.54 mmol) at 0 °C and under an atmosphere of oxygen. The reaction mixture was purged with O_2 gas and stirred at room temperature under O_2 for 16 h. The reaction mixture was then filtered through Celite® and the filtrate was concentrated under reduced pressure. The crude product was purified via silica gel flash column chromatography (Biotage® Isolera, 100 g silica gel cartridge) eluting with 100% EtOAc. The pure fractions were concentrated under reduced pressure to provide tert-butyl 4-(4-(benzyloxy)-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate (**1-f**) a solid. LCMS: m/z MM-ES+APCI, Negative $[M\text{-}H]^-$ = 547.8. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 7.52-7.35 (m, 7H), 5.57 (s, 1H), 5.26-5.22 (m, 3H), 4.80-4.55 (m, 2H), 3.86-3.75 (m, 1H), 3.29-3.36 (m, 4H), 3.20-3.10 (m, 1H), 2.52-2.41 (m, 4H), 2.03-1.98 (m, 2H), 1.36 (s, 9H).

Step 5: **Synthesis of 3-(4-(benzyloxy)-5-(4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride (1-g)**

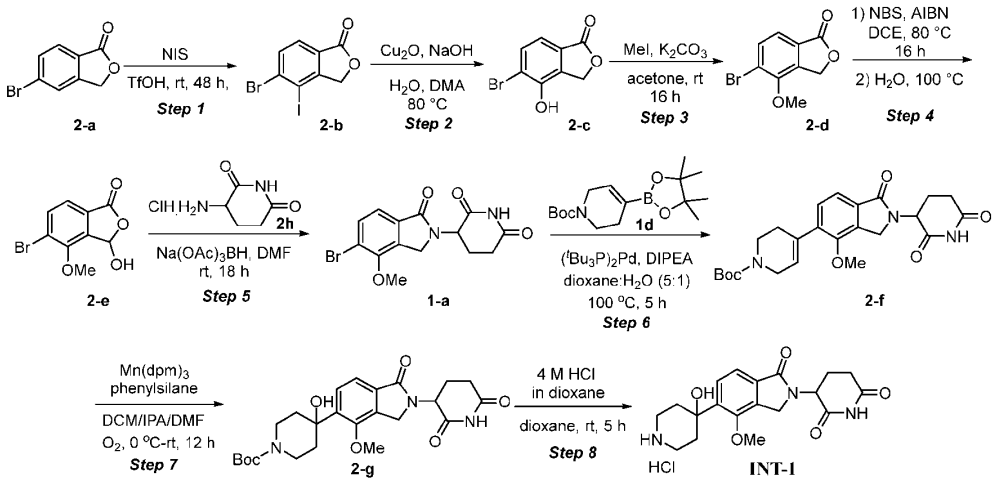
To a stirred solution of tert-butyl 4-(4-(benzyloxy)-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate (**1-f**, 100 mg, 0.18 mmol) in DCM (2 mL) at 0 °C was added HCl (4M in dioxane) (0.364 mL, 1.46 mmol) and the resulting mixture was stirred at room temperature

for 3 h. The reaction mixture was then concentrated under reduced pressure and the resulting residue was washed with MTBE. The crude compound was purified by reverse phase column chromatography on a C^{18} column eluting with 0.1% FA in H_2O: 100% ACN (Flow rate: 15 mL/min) and followed by lyophilization to give 3-(4-(benzyloxy)-5-(4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**1-g**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 450.2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.03 (br s, 1H), 8.35 (br s, 2H), 7.76-7.71 (m, 7H), 5.62 (s, 1H), 5.24-5.06 (m, 3H), 4.60-4.23 (m, 3H), 3.28-3.21 (m, 4H), 2.95-2.87 (m, 1H), 2.63-2.43 (m, 3H), 2.03-1.97 (m, 2H).

Step 6: **Synthesis of 3-(4-hydroxy-5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-25)**

A solution of 3-(4-(benzyloxy)-5-(4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride (**1-g**, 30 mg, 0.06 mmol) and 4-(trifluoromethyl)-benzaldehyde (**1-i**, 10.75 mg, 0.062 mmol) in DMF (1 mL) was stirred at room temperature for 30 mins. To this resulting solution was added sodium triacetoxyborohydride (32.7 mg, 0.15 mmol) at room temperature. The resulting mixture was stirred at rt for 4 h and then concentrated under reduced pressure. The crude product was purified by reverse phase preparative HPLC [Method info: Shim-pack column 19 × 250 mm, 5um; eluting with 0.05% HCl in H_2O: 100% ACN, Flow rate: 15 mL/min, RT: 9.0 and 8.8 min]. Two peaks were observed and separated. The fractions containing each of the two peaks were collected and concentrated via lyophilization to give 3-(4-(benzyloxy)-5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**1-h**) (***Peak-1***) LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 608.2 and **3-(4-hydroxy-5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione** (**I-25** (***Peak-2***). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 518.0. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 10.27 (s, 1H), 9.87 (s, 1H), 7.86-7.90 (m, 5H), 7.55 (d, J = 8.00 Hz, 1H), 7.25-7.27 (m, 1H), 6.23 (s, 1H), 5.08-5.13 (m, 1H), 4.50 (d, J = 4.80 Hz, 2H), 4.36-4.40 (m, 1H), 4.23-4.27 (m, 1H), 3.32-3.39 (m, 3H), 2.83-2.90 (m, 2H), 2.63-2.68 (m, 2H), 2.50-2.51 (m, 1H), 2.32-2.39 (m, 1H), 2.01-2.08 (m, 2H).

Example 2: Synthesis of 3-(5-(4-hydroxypiperidin-4-yl)-4-methoxy-1-oxoisoindolin-2-yl) piperidine-2,6-dione hydrochloride (INT-1)



Step 1: **Synthesis of 5-bromo-4-iodoisobenzofuran-1(3H)-one (2-b)**

To a solution of 5-bromoisobenzofuran-1(3H)-one (**2-a**, 50 g, 235 mmol) in triflic acid (313 mL, 3521 mmol), was added N-iodosuccinimide (55.4 g, 246 mmol) at 0 °C in portions. This mixture was allowed to warm to rt and stirred for 16 h. The progress of the reaction was monitored by UPLC. The reaction mixture was poured into ice-water (2 L) and a solid precipitate was formed. The mixture was filtered, and the filtered cake was washed with water. The filtered cake was dissolved in EtOAc (1000 mL) and the resulting organic solution was dried over sodium sulfate. The mixture was filtered, and the filtrate was concentrated to afford a solid. The residue was triturated with EtOAc (100 mL), filtered, and washed with EtOAc (50 mL × 2) to get 5-bromo-4-iodoisobenzofuran-1(3H)-one. LCMS: m/z Positive $[M+H, M+2H]^+$ = 339, 341. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 5.33 (s, 2H).

Step 2: **Synthesis of 5-bromo-4-hydroxyisobenzofuran-1(3H)-one (2-c)**

To a stirred solution of 5-bromo-4-iodoisobenzofuran-1(3H)-one (**2-b**, 20 g, 59.0 mmol) in water (200 mL) and DMA (100 mL), was added copper (I) oxide (1.689 g, 11.80 mmol) and sodium hydroxide (11.80 g, 295 mmol) at 25 °C. The reaction mixture was stirred at 80 °C for 16 h. Upon completion, the reaction mixture was poured into 1 N hydrochloric acid solution (200 mL) and extracted with ethyl acetate (300 mL × 2). The combined organic layers were concentrated and dissolved in ethyl acetate (300 mL) and washed with saturated aqueous sodium bicarbonate (150 mL), brine (150 mL) and then dried over sodium sulfate. The mixture was filtered, and the filtrate was concentrated under reduced pressure to get crude compound. The crude material was adsorbed on silica gel and purified by silica gel flash column chromatography using ethyl acetate-hexane as eluents. The pure fractions were combined together and evaporated under reduced pressure to get 5-bromo-4-hydroxyisobenzofuran-1(3H)-one (**2-c**).

LCMS: m/z Positive $[M+H, M+2H]^+$ = 229, 231. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.91 (s, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 5.35 (s, 2H).

Step 3: **Synthesis of 5-bromo-4-methoxyisobenzofuran-1(3H)-one (2-d)**

To a stirred solution of 5-bromo-4-hydroxyisobenzofuran-1(3H)-one (**2-c**, 18 g, 79 mmol) in acetone (200 mL) was added potassium carbonate (32.6 g, 236 mmol) and iodomethane (49.1 mL, 786 mmol) under an atmosphere of nitrogen at 20 °C. The reaction mixture was stirred at 20 °C for 15 h. The progress of the reaction was monitored by TLC and UPLC. The reaction mixture was quenched with water (400 mL) and extracted with ethyl acetate (400 mL × 2). The combined organic layers were washed with saturated brine solution (150 mL) and then dried over sodium sulfate, and filtered, and the filtrate concentrated under reduced pressure. The crude residue was adsorbed on silica gel and purified by silica gel flash column chromatography using ethyl acetate-hexane as eluents. The pure fractions were combined and evaporated under reduced pressure to get the 5-bromo-4-methoxyisobenzofuran-1(3H)-one (**2-d**). LCMS: m/z Positive $[M+H, M+2H]^+$ = 242.9, 244.9. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.82 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 5.75 (s, 2H), 4.03 (s, 3H).

Step 4: **Synthesis of 5-bromo-3-hydroxy-4-methoxyisobenzofuran-1(3H)-one (2-e)**

To a stirred solution of 5-bromo-4-methoxyisobenzofuran-1(3H)-one (**2-d**, 6 g, 24.69 mmol) in DCE (60 mL) was added AIBN (0.162 g, 0.99 mmol) and NBS (5.71 g, 32.1 mmol) at 25 °C and the resulting mixture was heated at 80 °C for 5 h. The progress of the reaction was monitored by TLC. The solvent was removed under vacuum. The crude residue was dissolved in ethyl acetate (250 mL) and the resulting solution was washed with brine (140 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum to afford crude 3,5-dibromo-4-methoxyisobenzofuran-1(3H)-one. The crude compound, 3,5-dibromo-4-methoxyisobenzofuran-1(3H)-one, (8 g, 24.84 mmol) was dissolved in water (60 mL) and heated at 100 °C for 3 h. The reaction mixture was allowed to stir at 25 °C for 5 h and was then extracted with ethyl acetate (2 × 150 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude residue was purified by silica gel flash column chromatography (silica gel, 100-200 mesh) eluting with EtOAc in hexanes (25-30%). Pure fractions were concentrated to afford 5-bromo-3-hydroxy-4-methoxyisobenzofuran-1(3H)-one (**2-e**). LCMS: m/z Negative $[M-2, M-]^-$ = 257, 259. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.34 (d, J = 8.8 Hz, 1H), 7.90 (d, J = 7.9 Hz, 1H), 7.42 (d, J = 7.9 Hz, 1H), 6.95 (d, J = 8.8 Hz, 1H), 4.09 (s, 3H).

Step 5: **Synthesis of 3-(5-bromo-4-methoxy-1-oxoisoindolin-2-yl) piperidine-2,6-dione (1-a)**

To a stirred solution of 5-bromo-3-hydroxy-4-methoxyisobenzofuran-1(3H)-one (**2-e**, 7 g, 27.0 mmol) in DMF (70 mL), 3-aminopiperidine-2,6-dione hydrochloride (**2-h**, 6.67 g, 40.5 mmol) and sodium cyanoborohydride (1.698 g, 27.0 mmol) were added at 25 °C under an atmosphere of nitrogen. The reaction mixture was stirred at 70 °C for 16 h. The reaction mixture then poured into ice cold water

(700 mL) and the resulting precipitate was collected by vacuum. The crude product was triturated with MTBE (2 x 15 mL) and dried under vacuum to afford 3-(5-bromo-4-methoxy-1-oxoisoindolin-2-yl) piperidine-2,6-dione (**1-a**). LCMS: m/z Positive $[M+H, M+2H]^+$ = 353, 355. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 5.12 (q, J = 6.1 Hz, 1H), 4.74 (d, J = 17.4 Hz, 1H), 4.56 (d, J = 17.4 Hz, 1H), 4.00 (s, 3H), 2.92 (m, J = 5.2 Hz, 1H), 2.61 (q, J = 5.8 Hz, 1H), 2.45 (t, J = 6.5 Hz, 1H), 2.02 (m, J = 2.5 Hz, 1H).

Step 6: **Synthesis of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-methoxy-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (2-f)**

In a microwave vial, to a mixture of 3-(5-bromo-4-methoxy-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**1-a**, 1.5 g, 4.25 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**1-d**, 1.97 g, 6.37 mmol), 1,4-dioxane (10 mL), and water (2 mL) was added DIPEA (2.225 mL, 12.74 mmol) and bis(tri-tert-butylphosphine)palladium(0) (0.217 g, 0.43 mmol) under continuous N_2 bubbling. The reaction mixture was stirred at 90 °C under microwave irradiation for 2 h. The reaction mixture was then filtered and washed with THF, and the filtrate was concentrated. The crude residue was purified by silica gel flash column chromatography (Biotage® Isolera, silica gel cartridge, 300 g) using ethyl acetate in petroleum ether followed by MeOH and DCM (0-10%) as eluents. Pure fractions were concentrated to provide tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-methoxy-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**2-f**). LCMS: m/z Positive $[M+H]^+$ = 456. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 7.41 (d, J = 7.7 Hz, 1H), 7.32 (d, J = 7.7 Hz, 1H), 5.87 (s, 1H), 5.11 (q, J = 6.1 Hz, 1H), 4.63 (d, J = 17.1 Hz, 1H), 4.45 (d, J = 17.1 Hz, 1H), 4.00 (s, 1H), 3.85 (s, 3H), 3.53 (t, J = 5.5 Hz, 2H), 2.93 (m, J = 5.2 Hz, 2H), 2.61 (q, J = 5.9 Hz, 1H), 2.44 (d, J = 4.0 Hz, 3H), 2.01 (m, J = 2.9 Hz, 1H), 1.44 (s, 9H).

Step 7: **Synthesis of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-methoxy-1-oxoisoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate (2-g)**

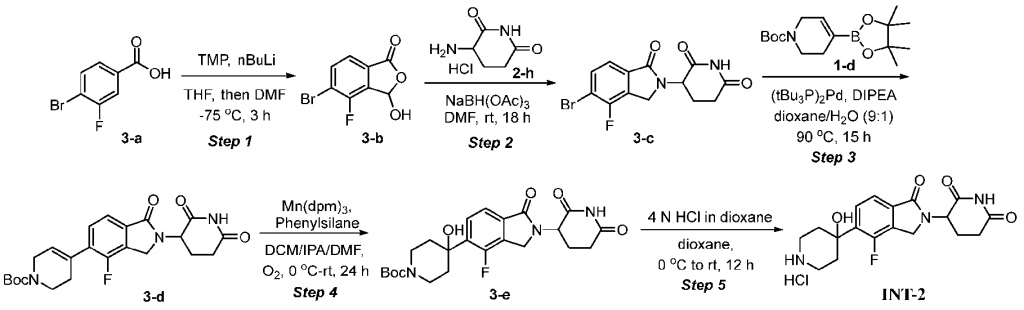
A solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-methoxy-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**2-f**, 730 mg, 1.60 mmol) in DMF (0.70 mL), 2-propanol (7.00 mL) and DCM (7 mL) was stirred at 0 °C for 5 min. To this reaction mixture $Mn(dpm)_3$ (291 mg, 0.481 mmol) and phenylsilane (0.605 mL, 4.81 mmol) were added at 0 °C under an atmosphere of nitrogen. The reaction mixture was purged with O_2 gas and stirred at rt under O_2 for 24 h. The reaction mixture was filtered and washed with THF, and the filtrate was concentrated to give crude compound. The compound was purified by reverse phase column chromatography using a 340 g C^{18} column, eluting with 0.05% formic acid in H_2O:100% ACN, flow rate: 15.0 mL/min collected and followed by lyophilization for 24 h to afford tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-methoxy-1-oxoisoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate (**2-g**, 580 mg, 0.98 mmol). LCMS: m/z Positive $[M+Na]^+$ = 496. ^{1}H-NMR (400 MHz,

DMSO-d_6) δ 11.00 (s, 1H), 7.41 (d, J = 7.7 Hz, 1H), 7.32 (d, J = 7.7 Hz, 1H), 5.87 (s, 1H), 5.11 (q, J = 6.1 Hz, 1H), 4.63 (d, J = 17.1 Hz, 1H), 4.45 (d, J = 17.1 Hz, 1H), 4.00 (s, 3H), 3.85 (bs, 2H), 3.53 (t, J = 5.5 Hz, 2H), 2.93 (m, J = 5.2 Hz, 2H), 2.61 (q, J = 5.9 Hz, 1H), 2.44 (d, J = 4.0 Hz, 3H), 2.01 (m, J = 2.9 Hz, 1H), 1.44 (s, 10H).

Step 8: **Synthesis of 3-(5-(4-hydroxypiperidin-4-yl)-4-methoxy-1-oxoisoindolin-2-yl) piperidine-2,6-dione hydrochloride (INT-1)**

To a stirred solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-methoxy-1-oxoisoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate (**2-g**, 500 mg, 1.06 mmol) in DCM (10 mL) was added HCl (4.0 M in dioxane) (0.032 mL, 1.06 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred for 3 h. The reaction mixture was concentrated, and the residue was washed with MTBE to provide 3-(5-(4-hydroxypiperidin-4-yl)-4-methoxy-1-oxoisoindolin-2-yl) piperidine-2,6-dione hydrochloride (**INT-1**). LCMS: m/z Positive $[M+H]^+$ = 374. ^{1}H-NMR (400 MHz, MSO-d_6) δ 11.04 (s, 1H), 8.61 (bs, 2H), 7.81 (d, J = 7.8 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 5.61 (bs, 1H), 5.12 (m, 1H), 4.68 (d, J = 16.8 Hz, 1H), 4.45 (d, J = 16.8 Hz, 1H), 3.92 (bs, 2H), 3.67 (m, 1H), 3.62 (m, 2H), 3.19 (m, 2H), 2.92 (m, 1H), 2.64 (m, 3H), 2.33 (m, 1H), 2.02 (m, 1H), 1.63 (m, 2H).

Example 3: Synthesis of 3-(4-fluoro-5-(4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride (INT-2)



Step 1: **Synthesis of 5-bromo-4-fluoro-3-hydroxyisobenzofuran-1(3H)-one (3-b)**

To a stirred solution of 2,2,6,6-tetramethylpiperidine (48.4 g, 342 mmol) in THF (150 mL) at-75 °C was added dropwise n-BuLi (2 M in cyclohexane) (137 mL, 274 mmol) and the resulting mixture was stirred at 0 °C for 20 min. The reaction mixture was then cooled to-75 °C and a solution 4-bromo-3-fluorobenzoic acid (**3-a**, 15 g, 68.50 mmol) in THF (30.00 mL) was added dropwise and stirring was continued for 40 min. DMF (10.01 g, 137 mmol) in THF (15.00 mL) was then added dropwise at-75 °C and the resulting mixture was stirred for additional 2 h. The reaction mixture was quenched with 5M HCl (10 mL), diluted with brine (50 mL), and extracted with DCM (2 × 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude compound was purified by Biotage® Isolera using a silica gel (100-200 mesh) cartridge (100 g) and

eluting with ethyl acetate in hexanes (60-80%). The pure product containing fractions were concentrated to afford 5-bromo-4-fluoro-3-hydroxyisobenzofuran-1(3H)-one (**3-b**). LCMS: m/z MM-ES+APCI, Negative $[M-H]^-$ = 244.8.

Step 2: **Synthesis of 3-(5-bromo-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (3-c)**

3-(5-Bromo-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**3-c**) was prepared according to the procedures and examples as reported in PCT Application Publication Nos. WO2022/081976 and WO2020/012337.

To a stirred solution of 5-bromo-4-fluoro-3-hydroxyisobenzofuran-1(3H)-one (**3-b**, 2 g, 8.10 mmol) in DMF (20 mL) at 25 °C and under an atmosphere of nitrogen was added 3-aminopiperidine-2,6-dione hydrochloride (**2-h**, 1.999 g, 12.14 mmol) and the resulting mixture was stirred for 30 min. Sodium triacetoxyborohydride (5.15 g, 24.29 mmol) was then added and stirring was continued for 18 h at room temperature. The reaction mixture was then quenched with brine (15 mL) and extracted with EtOAc (2 × 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was dissolved in ACN (5 mL)/MTBE (5 mL) and stirred for 10 min. The precipitated solid was collected and washed with excess MTBE. The obtained solid was then dried under vacuum to afford 3-(5-bromo-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**3-c**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 340.9. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 11.20-10.76 (m, 1H), 7.88 (dd, J = 6.1, 7.9 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 5.13 (dd, J = 5.1, 13.4 Hz, 1H), 4.67-4.59 (m, 1H), 4.50-4.43 (m, 1H), 2.98-2.86 (m, 1H), 2.66-2.56 (m, 1H), 2.44 (dd, J = 4.4, 12.9 Hz, 1H), 2.01 (dtd, J = 2.3, 5.2, 12.7 Hz, 1H).

Step 3: **Synthesis of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (3-d)**

To a stirred solution of 3-(5-bromo-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**3c**, 1.32 g, 3.87 mmol) in dioxane (20 mL)/Water (2.22 mL), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**1-d**, 2.393 g, 7.74 mmol) at room temperature and under continuous bubbling of nitrogen was added DIPEA (1.00 g, 7.74 mmol) and $Pd(tBu_3P)_2$ (0.198 g, 0.39 mmol) over 20 min. The resulting mixture was stirred at 90°C for 15 h. The excess solvent was then removed under reduced pressure to afford the crude compound, which was dissolved in ACN (5 mL)/MTBE (5 mL) and stirred for 10 min. The precipitated solid was collected via filtration and washed with excess MTBE. The obtained solid was dried under vacuum to afford tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**3-d**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 444.2. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 11.01 (s, 1H), 7.80-7.35 (m, 2H), 6.11 (br s, 1H), 5.12 (dd, J = 5.1, 13.3 Hz, 1H), 4.62-4.49 (m, 1H), 4.46-4.25

(m, 1H), 4.03 (br s, 2H), 3.56 (t, J = 5.5 Hz, 2H), 2.98-2.81 (m, 1H), 2.73-2.56 (m, 1H), 2.49-2.41 (m, 2H), 2.45-2.35 (m, 1H), 2.08-1.89 (m, 1H), 1.44 (s, 9H).

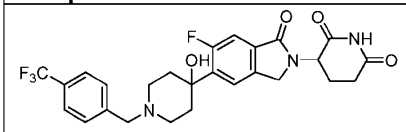
Step 4: **Synthesis of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate (3-e)**

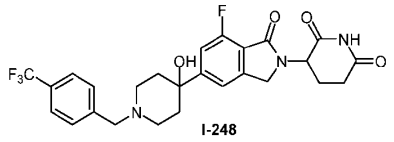
To a stirred solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**3-d**, 900 mg, 2.03 mmol) in DCM (6 mL), 2-propanol (6 mL) and DMF (0.5 mL) at 0 °C and under bubbling of oxygen was added $Mn(dpm)_3$ (368 mg, 0.61 mmol) followed by phenylsilane (439 mg, 4.06 mmol) over 15 minutes. The resulting mixture was then stirred under an atmosphere of oxygen using an O_2 balloon at room temperature for 24 h. The solvents were then evaporated to dryness. The crude product was purified by reverse phase chromatography [(Column: X select (150 mm × 19) 5 µm, eluting with mobile phase A: 0.05% FA in H_2O, mobile phase B: ACN, flow rate: 15 mL/min)]. The product containing fractions were concentrated via lyophilization to afford tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate (**3-e**). LCMS: m/z MM-ES+APCI, Negative $[M-H]^-$ = 459.9. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 11.00 (s, 1H), 7.88-7.80 (m, 1H), 7.60 (d, J = 8 Hz, 1H), 5.59 (s, 1H), 5.15-5.05 (m, 1H), 4.55 (d, J = 17.2 Hz, 1H), 4.45 (d, J = 17.2 Hz, 1H), 3.93-3.76 (m, 2H), 3.30-3.00 (m, 2H), 2.99-2.84 (m, 1H), 2.65-2.55 (m, 1H), 2.45-2.37 (m, 1H), 2.18-1.95 (m, 3H), 1.65-1.55 (m, 2H), 1.42 (s, 9H).

Step 5: **Synthesis of 3-(4-fluoro-5-(4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride (INT-2)**

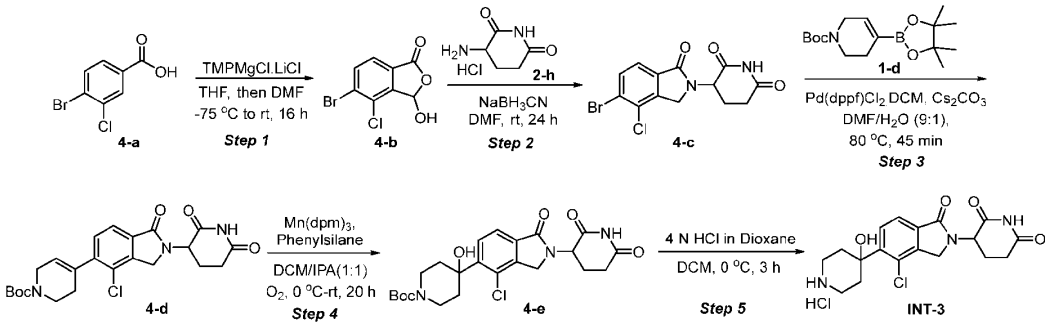
To a stirred solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate (**3-e**, 500 mg, 1.08 mmol) in DCM (6 mL) at 0 °C was added HCl (4M in 1,4-dioxane) (1.354 mL, 5.42 mmol) and the resulting mixture was stirred for 12 h. The solvents were then removed under reduced pressure. The crude solid was washed with DCM/hexanes and dried to afford 3-(4-fluoro-5-(4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride (**INT-2**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 362.0. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 11.01 (s, 1H), 8.96 (d, J = 9.2 Hz, 1H), 8.76 (br s, 1H), 7.83 (t, J = 7.2 Hz, 1H), 7.63 (d, J = 8 Hz, 1H), 5.15-5.10 (m, 1H), 4.56 (d, J = 17.6 Hz, 1H), 4.39 (d, J = 17.6 Hz, 1H), 3.57 (s, 2H), 3.23 (s, 3H), 2.94-2.88 (m, 1H), 2.63-2.59 (m, 1H), 2.45-2.42 (m, 1H), 2.02-1.99 (m, 1H), 1.85-1.75 (m, 2H).

The following compounds were synthesized in a similar fashion to **INT-2** and **I-2.**

Compound	Characterization
 **I-247**	LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 520.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 10.24 (s, 1H), 7.91-7.86 (m, 5H), 7.52 (d, J = 10.80 Hz, 1H), 5.99 (s, 1H), 5.12 (q, J = 4.80 Hz, 1H), 4.53-4.44 (m, 3H), 4.35-4.31 (m, 1H), 3.33 (m, 3H), 2.93-2.87 (m, 1H), 2.63-2.50 (m, 2H), 2.50-2.40 (m, 2H), 2.10-1.90 (m, 1H), 1.90-1.75 (m, 2H).

3-(6-fluoro-5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-247**)	
 **I-248** 3-(7-fluoro-5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-248**)	LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 520.0; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 10.40 (s, 1H), 7.91-7.86 (m, 4H), 7.47 (s, 1H), 7.32 (d, J = 10.80 Hz, 1H), 5.84 (s, 1H), 5.09 (q, J = 5.20 Hz, 1H), 4.53-4.48 (m, 4H), 4.38-4.34 (m, 1H), 2.92-2.89 (m, 1H), 2.70-2.60 (m, 2H), 2.63-2.51 (m, 1H), 2.43-2.34 (m, 3H), 2.02-2.00 (m, 1H), 1.89-1.85 (m, 2H).

Example 4: Synthesis of 3-(4-chloro-5-(4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride (INT-3)



Step 1: **Synthesis of 5-bromo-4-chloro-3-hydroxyisobenzofuran-1(3H)-one (4-b)**

To a stirred solution of 4-bromo-3-chlorobenzoic acid (10 g, 42.5 mmol) in THF (200 mL) at 0 °C was added TMPMgCl.LiCl (1 M in THF) (170 mL, 170 mmol) dropwise and the resulting mixture was stirred for 90 min at room temperature. DMF (24.83 g, 340 mmol) was then added dropwise at 0 °C and stirring was continued at room temperature for 16 h. The reaction mixture was then quenched with 0.5 N HCl (600 mL) and extracted by using ethyl acetate (3 × 250 mL). The combined organic phases were washed with brine solution, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by silica gel column chromatography (100-200 mesh) using 2% MTBE/hexane as eluents. The product containing fractions were collected and concentrated to afford 5-bromo-4-chloro-3-hydroxyisobenzofuran-1(3H)-one (**4-b**). LCMS: m/z MM-ES+APCI, Negative $[M-, M-2]^-$ = 260.9, 262.9. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 8.376 (s, 1H), 8.07 (d, J = 8 Hz, 1H), 7.73 (d, J = 8 H z, 1H), 6.715 (s, 1H).

Step 2: **Synthesis of 3-(5-bromo-4-chloro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (4-c)**

3-(5-Bromo-4-chloro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**4-c**) was prepared according to the procedures and examples as reported in PCT Application Publication No. WO2020/165834.

To a stirred solution of 5-bromo-4-chloro-3-hydroxyisobenzofuran-1(3H)-one (**4-b**, 1.7 g, 6.45 mmol) in DMF (15 mL) at 0 °C was added 3-aminopiperidine-2,6-dione (**2-h**, 1.24 g, 9.68 mmol) followed by sodium cyanoborohydride (0.405 g, 6.45 mmol) and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was then poured into cold water and a solid precipitated. The solid was washed with a minimal amount of cold water and MTBE, and then dried under reduced pressure to afford 3-(5-bromo-4-chloro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**4-c**). LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2H]^+$ = 356.9, 358.9. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 11.01 (s, 1H), 7.96 (d, J = 8.00 Hz, 1H), 7.66 (d, J = 8.00 Hz, 1H), 5.16-5.12 (m, 1H), 4.54 (d, J = 18.0 Hz, 1H), 4.38 (d, J = 18.00 Hz, 1H), 2.95-2.87 (m, 1H), 2.68-2.58 (m, 1H), 2.52-2.51 (m, 1H), 2.05-2.02 (m, 1H).

Step 3: **Synthesis of tert-butyl 4-(4-chloro-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (4-d)**

A 10 mL microwave vial was charged with 3-(5-bromo-4-chloro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**4-c**, 50 mg, 0.14 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**1-d**, 64.9 mg, 0.21 mmol) and DMF (5 mL). Cs_2CO_3 dissolved in water (0.14 mL, 0.28 mmol) was then added and the resulting mixture was purged with nitrogen for 10 min. $PdCl_2$(dppf)-DCM adduct (7.99 mg, 9.79 μmol) was added, and the sealed reaction vial was subjected to microwave irradiation at 80 °C for 45 min. The reaction mixture was filtered and concentrated under reduced pressure to provide the crude compound, which was purified by reverse phase chromatography using a C^{18} 120 g column, eluting with 50% ACN in Water (0.1 N formic acid). The collected pure fractions were concentrated via lyophilization to provide tert-butyl 4-(4-chloro-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**4-d**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 460.3. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 11.01 (s, 1H), 7.70 (d, J = 7.60, Hz, 1H), 7.47 (d, J = 7.60 Hz, 1H), 5.83 (s, 1H), 5.16-5.12 (m, 1H), 4.49 (d, J = 18.00 Hz, 1H), 4.32 (d, J = 17.60 Hz, 1H), 4.01 (s, 2H), 3.57 (s, 2H), 2.94 (t, J = 8.80 Hz, 1H), 2.68-2.67 (m, 1H), 2.46-2.45 (m, 3H), 2.03-2.01 (m, 1H), 1.44 (s, 9H).

Step 4: **Synthesis of tert-butyl 4-(4-chloro-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate (4-e)**

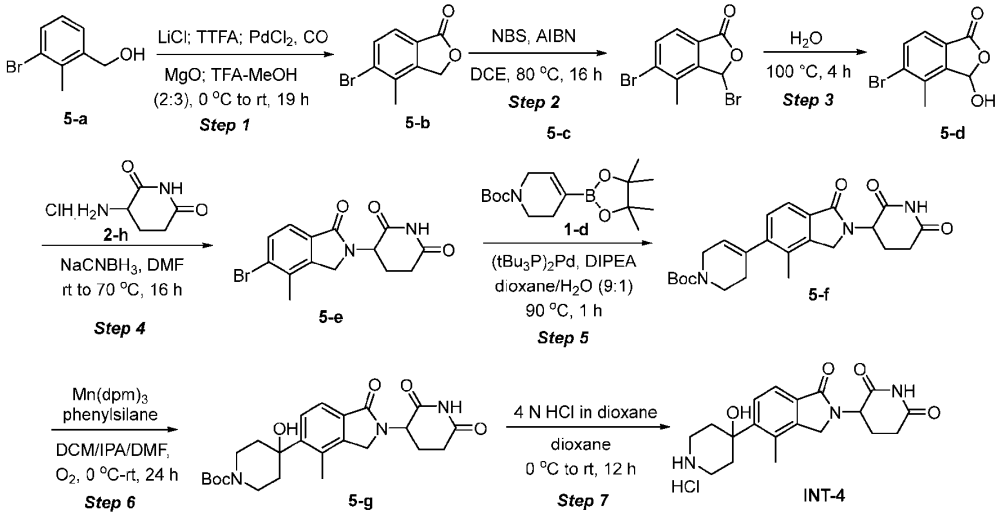
To a stirred solution of tert-butyl 4-(4-chloro-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**4-d**, 50 mg, 0.109 mmol) in DCM (2 mL) and 2-propanol (2 mL) at 0 °C was added tris(2,2,6,6-tetramethyl-3,5-heptanedionato)manganese(III) (19.72 mg, 0.033 mmol) followed by phenylsilane (0.027 mL, 0.217 mmol). The resulting mixture was purged with oxygen for 10 minutes and then stirred at 0 °C under an atmosphere of oxygen for 20 h. The reaction mixture was

diluted with water (7 mL) and extracted with ethyl acetate (15 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide crude compound (65 mg) as gum. The crude compound was purified by reverse phase column chromatography using a C^{18} column, (Mobile phase A: 0.1% formic acid in H_2O, Mobile phase B: ACN, flow rate: 15 mL/min). The product containing fractions were concentrated via lyophilization to afford tert-butyl 4-(4-chloro-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate (**4-e**). LCMS: m/z MM-ES+APCI, Negative $[M-H]^-$ = 476.0. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 11.01 (s, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 5.60 (s, 1H), 5.13 (dd, J = 8.0, 16 Hz, 1H), 4.38 (dd, J = 16, 68 Hz, 2H), 3.90-3.86 (m, 2H), 3.20-3.19 (m, 2H), 2.98-2.86 (m, 1H), 2.60-2.40 (m, 4H), 2.06-1.98 (m, 1H), 1.59-1.50 (m, 2H), 1.43 (s, 9H).

Step 5: **Synthesis of 3-(4-chloro-5-(4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride (INT-3)**

To a stirred solution of tert-butyl 4-(4-chloro-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate (**4-e**, 30 mg, 0.063 mmol) in DCM (2 mL) at 0 °C and under an atmosphere of nitrogen was added HCl (4M in 1,4-dioxane) (0.2 mL, 0.063 mmol) and the resulting mixture was stirred at 0 °C for 3 h. The reaction mixture was then concentrated under vacuum. The crude residue was purified by reverse phase preparative HPLC [(Column: SUNFIRE C^{18} 150 × 21.0, 5 µm; eluting with Mobile phase A: 0.05% HCl in H_2O, Mobile phase B: ACN, flow rate: 15 mL/min)]. The product containing fractions were collected and concentrated via lyophilization to afford 3-(4-chloro-5-(4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride (**INT-3**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 378.2. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 11.02 (s, 1H), 8.68 (br s, 1H), 8.54 (br s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 5.93 (s, 1H), 5.17-5.12 (dd, J = 12, 4 Hz, 1H), 4.48 (d, J = 18 Hz, 1H), 4.34 (d, J = 18 Hz, 1H), 3.92-3.33 (m, 4H), 2.92-2.89 (m, 1H), 2.77-2.63 (m, 1H), 2.78-2.61 (m, 2H), 2.49-2.44 (m, 1H), 2.08-1.98 (m, 1H), 1.43-1.28 (m, 2H).

Example 5: Synthesis of 3-(5-(4-hydroxypiperidin-4-yl)-4-methyl-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride (INT-4)



Step 1: **Synthesis of 5-bromo-4-methylisobenzofuran-1(3H)-one (5-b)**

To a stirred solution of (3-bromo-2-methylphenyl)methanol (**5-a**, 10 g, 49.7 mmol) in trifluoroacetic acid (100 mL) at 0 °C was added thallium (III) trifluoroacetate (27.0 g, 49.7 mmol) and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was then concentrated under reduced pressure and the resulting residue was dissolved in methanol (150 mL). Lithium chloride (4.22 g, 99 mmol), magnesium oxide (4.01 g, 99 mmol) and palladium (II) chloride (0.882 g, 4.97 mmol) were added and the resulting mixture was flushed with CO twice and stirred at room temperature and under an atmosphere of CO (5 atm) for 3h. The reaction mixture was filtered through a Celite® pad, and the pad was washed with methanol. The filtrate was concentrated under reduced pressure to provide the crude compound, which was purified by column chromatography using Biotage® Isolera (cartridge size 350 g) eluting with 0% to 19% of ethyl acetate /hexane. The pure fractions were collected and concentrated to afford 5-bromo-4-methylisobenzofuran-1(3H)-one (**5-b**). LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2H]^+$ = 227, 229. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.73 (d, J = 8 Hz, 1H), 7.60 (d, J = 8 Hz, 1H), 5.27 (s, 2H), 2.39 (s, 3H).

Step 2: **Synthesis of 3,5-dibromo-4-methylisobenzofuran-1(3H)-one (5-c)**

To a stirred solution of 5-bromo-4-methylisobenzofuran-1(3H)-one (**5-b**, 4 g, 17.62 mmol) in DCE (40 mL) at room temperature was added NBS (4.08 g, 22.90 mmol) followed by AIBN (0.116 g, 0.71 mmol) and the resulting mixture was heated at 80 °C for 16 h. The reaction mixture was cooled to room temperature and the excess solvent was concentrated under vacuum. The crude residue was dissolved in ethyl acetate (150 mL) and the organic phase was washed with brine (50 mL), dried with Na_2SO_4, filtered, and concentrated under vacuum to afford 3,5-dibromo-4-methylisobenzofuran-1(3H)-one (**5-c**). The product was taken onto the next step without further purification. LCMS: m/z MM-

ES+APCI, Positive $[M+H, M+2H]^+$ = Not ionized. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 7.89 (d, J = 8.00 Hz, 1H), 7.58 (d, J = 8.00 Hz, 1H), 6.73 (s, 1H), 2.42 (s, 3H).

Step 3: **Synthesis of 5-bromo-3-hydroxy-4-methylisobenzofuran-1(3H)-one (5-d)**

A suspension of 3,5-dibromo-4-methylisobenzofuran-1(3H)-one (**5-c**, 18 g, 58.8 mmol) in water (180 mL, 58.8 mmol) was heated at 100 °C for 4 h. The resulting mixture was then cooled to room temperature and stirred for 16 h. The reaction mixture was poured into ice cold water (100 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by column chromatography using Biotage® Isolera using a silica-gel cartridge size (100 g) and eluting with 5-10% ethyl acetate/hexanes. The pure product containing fractions were concentrated under reduced pressure to afford 5-bromo-3-hydroxy-4-methylisobenzofuran-1(3H)-one (**5-d**). LCMS: m/z MM-ES+APCI, Negative $[M-, M-2]^-$ = 241.1, 243.0. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) = 8.1 (d, J = 8.6 Hz, 1H). 7.8 (d, J = 8 Hz, 1H), 7.5 (d, J =8 Hz, 1H), 6.7 (d, J = 8.6 Hz, 1H), 2.41 (s, 3H).

Step 4: **Synthesis of 3-(5-bromo-4-methyl-1-oxoisoindolin-2-yl)piperidine-2,6-dione (5-e)**

To a stirred solution of 5-bromo-3-hydroxy-4-methylisobenzofuran-1(3H)-one (**5-d**, 2.3g, 9.46 mmol) in DMF (40 mL) at room temperature was added 3-aminopiperidine-2,6-dione hydrochloride (**2-h**, 2.336 g, 14.19 mmol) followed by sodium cyanoborohydride (0.595 g, 9.46 mmol) and the resulting mixture was stirred at 70 °C for 16 h. The reaction mixture was then poured into ice chilled water (160 mL) and a solid precipitated. The solid was isolated by filtration to afford 3-(5-bromo-4-methyl-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**5-e**). LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2H]^+$ = 337.1, 339.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 5.14 (q, J = 6.1 Hz, 1H), 4.50 (d, J = 17.5 Hz, 1H), 4.33 (d, J = 17.5 Hz, 1H), 2.95-2.92 (m, 1H), 2.63-2.59 (m, 1H), 2.50-2.42 (m, 1H), 2.36 (s, 3H), 2.05-1.90 (m, 1H).

Step 5: **Synthesis of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-methyl-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (5-f)**

A 10 mL microwave vial was charged with 3-(5-bromo-4-methyl-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**5-e**, 500 mg, 1.48 mmol) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**1-d**, 550 mg, 1.78 mmol) in 1,4-dioxane (19 mL) and water (1 mL). DIPEA (384 mg, 2.97 mmol) was added, and the resulting mixture was purged with argon gas for 15 minutes. Bis(tri-tert-butylphosphine)palladium(0) (75.8 mg, 0.15 mmol) was then added and the resulting mixture was stirred at 90 °C for 1 h. The reaction mixture was filtered through a pad of Celite® and the pad was washed with ethyl acetate (50 mL). The filtrate was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude product. The crude product was purified by Biotage® Isolera using 100-200 mesh silica gel and eluting with 10% IPA/DCM. The pure

fractions were combined and evaporated under reduced pressure to afford tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-methyl-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**5-f**. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 440.1. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 7.8 Hz, 1H), 5.64 (s, 1H), 5.14 (q, J = 6.1 Hz, 1H), 4.43 (d, J = 17.0 Hz, 1H), 4.26 (d, J = 17.1 Hz, 1H), 3.99 (s, 2H), 3.63-3.52 (m, 2H), 3.20-3.15 (m, 1H), 3.00-2.92 (m, 1H), 2.73-2.56 (m, 1H), 2.50-2.36 (m, 2H), 2.23 (s, 3H), 2.01-1.90 (m, 1H), 1.45 (s, 9H).

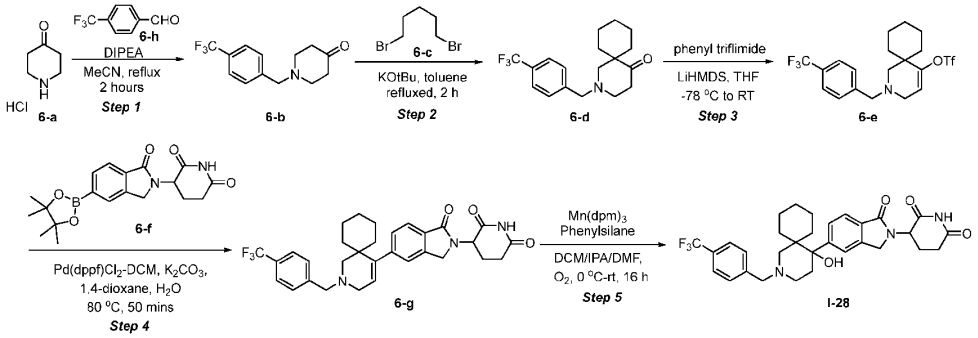
Step 6: **Synthesis of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-methyl-1-oxoisoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate (5-g)**

To a stirred solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-methyl-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**5-f**, 100 mg, 0.23 mmol) in DCM (5 mL)/DMF (2 mL)/2-propanol (5 mL) at 0 °C was added $Mn(dpm)_3$ (41.3 mg, 0.07 mmol) and phenylsilane (0.062 mL, 0.46 mmol) and the resulting mixture was stirred at 0 °C under an atmosphere of oxygen for 16 h. The reaction mixture was then filtered through a pad of Celite® and the pad was washed with ethyl acetate. The filtrate was then concentrated under reduced pressure to provide the crude product. The crude product was purified by reverse phase preparative HPLC [(Column: X select (150 mm × 19) 5 µm, eluting with Mobile phase A: 0.1% FA in H_2O, Mobile phase B: ACN, flow rate:15 mL/min)]. The product containing fractions were concentrated via lyophilization to afford tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-methyl-1-oxoisoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate (**5-g**). LCMS: m/z MM-ES+APCI, Positive $[M+Na]^+$ = 480.1. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 7.61 (d, J = 8.1 Hz, 1H), 7.51 (d, J = 8.1 Hz, 1H), 5.19 (s, 1H), 5.15-5.10 (m, 1H), 4.40 (d, J = 16.8 Hz, 1H), 4.23 (d, J = 17.2 Hz, 1H), 3.86 (d, J = 11.4 Hz, 1H), 3.61 (t, J = 6.2 Hz, 2H), 2.92-2.68 (m, J = 6.2 Hz, 2H), 2.67-2.64 (m, 1H), 2.33 (d, J = 2.8 Hz, 1H), 2.02-1.83 (m, J = 6.0 Hz, 8H), 1.43 (s, 9H).

Step 7: **Synthesis of 3-(5-(4-hydroxypiperidin-4-yl)-4-methyl-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride (INT-4)**

To a stirred solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-methyl-1-oxoisoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate (**5-g**, 40 mg, 0.09 mmol) at 0 °C was added HCl (4M in dioxane) (0.2 mL, 0.80 mmol) and the resulting mixture was stirred at 25 °C for 6 h. The reaction mixture was then concentrated under reduced pressure. The crude product was triturated with MTBE (5 mL), filtered, and dried to afford 3-(5-(4-hydroxypiperidin-4-yl)-4-methyl-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride (**INT-4**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 358.2. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 8.75-8.51 (m, 2H), 7.61-7.56 (m, 2H), 5.58 (s, 1H), 5.14 (q, J = 6.1 Hz, 1H), 4.43 (d, J = 17.1 Hz, 1H), 4.25 (d, J = 17.1 Hz, 1H), 3.74 (m, J = 4.0 Hz, 1H), 3.22 (d, J = 40.7 Hz, 1H), 2.94-2.85 (m, J = 6.1 Hz, 2H), 2.70-2.50 (m, 4H), 2.35-2.24 (m, 1H), 2.01-1.93 (d, J = 15.0 Hz, 2H), 1.90-1.85 (m, 2H), 1.60-1.52 (m, 2H).

Example 6: Synthesis of 3-(5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-28)



Step 1: **Synthesis of 1-(4-(trifluoromethyl)benzyl)piperidin-4-one (6-b)**

To a stirred solution of piperidin-4-one hydrochloride (**6-a**, 5.17 g, 38.1 mmol) and 1-(bromomethyl)-4-(trifluoromethyl)benzene (**6-h**, 10.0 g, 41.90 mmol) in acetonitrile (95.3 mL) was added DIPEA (13.3 mL, 76.30 mmol) and the resulting mixture was stirred at reflux for 2 h. The progress of the reaction was monitored through TLC and LCMS. The reaction mixture was then concentrated under reduced pressure. The crude compound was purified via silica gel chromatography eluting with heptanes and EtOAc. The desired fractions were collected, combined and concentrated *in vacuo* to yield 1-(4-(trifluoromethyl)benzyl)piperidin-4-one (**6-b**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+ = 258$.

Step 2: **Synthesis of 2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-one (6-d)**

To a stirred solution of 1-(4-(trifluoromethyl)benzyl)piperidin-4-one (**6-b**, 4g, 15.55 mmol) in toluene (31.10 mL) was added KOtBu (3.856 g, 34.36 mmol) and the resulting mixture was stirred for 1 hour at room temperature. 1,5-Dibromopentane (**6-c**, 2.118 mL, 15.55 mmol) was then added dropwise and the reaction mixture was refluxed for 2 h. The reaction mixture was cooled to room temperature and quenched with saturated NH_4Cl solution. The aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified via silica gel column chromatography eluting with heptanes and EtOAc. The desired fractions were collected, combined, and concentrated *in vacuo* to yield 2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-one (**6-d**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+ = 326$.

Step 3: **Synthesis of 2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl trifluoromethanesulfonate (6-e)**

To a stirred solution of 2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-one (**6-d**, 1g, 3.07 mmol) in tetrahydrofuran (6.147 mL) at -78 °C was added lithium bis(trimethylsilyl)amide solution (3.381 mL, 3.38 mmol) and the resulting mixture was stirred for 30 mins at -78 °C. Phenyl triflimide

(1.098 g, 3.07 mmol) in tetrahydrofuran (6.147 mL) was then added at -78 °C, the -78 °C bath was removed and the resulting mixture allowed to warm up to room temperature. The reaction mixture was then stirred for 2 h at room temperature and then quenched with a saturated solution of NH_4Cl and extracted with DCM. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to provide 2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl trifluoromethanesulfonate (**6e**). The product was carried onto the next step without further purification. Quantitative yield is assumed for this reaction. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+ = 458$.

Step 4: **Synthesis of 3-(1-oxo-5-(2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)isoindolin-2-yl)piperidine-2,6-dione (6-g)**

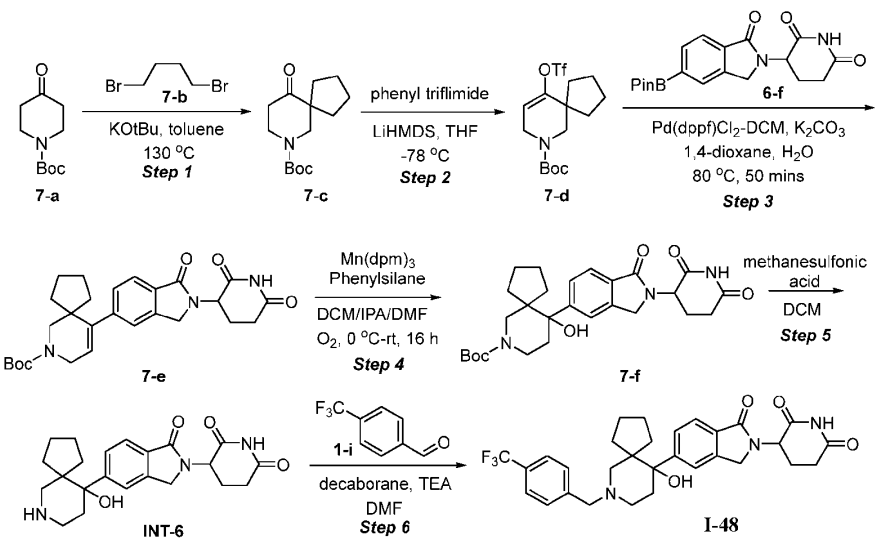
To a stirred solution of 2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl trifluoromethanesulfonate (**6-e**, 1.1 g, 2.405 mmol), 3-(1-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-2-yl)piperidine-2,6-dione (**6-f**, 801.2 mg, 2.16 mmol; **6-f** was prepared according to the procedures and examples as reported in PCT Application Publication No. WO2019/038717), and $PdCl_2$(dppf)-CH_2Cl_2adduct (294.6 mg, 0.15 eq, 360.7 μmol) in 1,4-dioxane (12 mL), was added potassium carbonate (332.2 mg, 2.41 mmol) in H_2O (1 g, 1 mL). The resulting mixture was degassed with argon for 5 mins and then heated to 80 °C for 50 mins. The reaction mixture was then concentrated *in vacuo* and dry loaded onto a silica column for purification eluting with heptanes and EtOAc. The desired fractions were collected, combined, and concentrated via lyophilization to yield 3-(1-oxo-5-(2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)isoindolin-2-yl)piperidine-2,6-dione (**6-g**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+ = 552$.

Step 5: **Synthesis of 3-(5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-28)**

A stirred solution of 3-(1-oxo-5-(2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)isoindolin-2-yl)piperidine-2,6-dione (**6-g**, 0.89 g, 1.61 mmol) in DCM (8.07 mL), IPA (8.07 mL), and DMF (2.34 mL), was sparged with argon for 5 mins, and then sparged with oxygen for 3 mins. $Mn(dpm)_3$ (488 mg, 807 μmol) and phenylsilane (400 μL, 3.23 mmol) were then added at 0 °C and oxygen was bubbled through the reaction mixture for 3 h. The reaction mixture was then concentrated *in vacuo* and loaded onto a silica column for purification eluting with heptanes and EtOAc/20% IPA. The desired fractions were collected, combined, and concentrated *in vacuo* to yield 3-(5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-28**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+ = 570$. ^{1}H-NMR (499 MHz, DMSO-d_6) δ ppm 11.03-10.97 (m, 1H), 7.73-7.57 (m, 7H), 5.15-5.09 (m, 1H), 4.78-4.74 (m, 1H), 4.50-4.42 (m, 1H), 4.36-4.27 (m, 1H), 3.68-3.62 (m, 1H), 3.59-3.53 (m, 1H), 2.89 (s, 2H), 2.73 (s, 4H), 2.43-2.34 (m, 1H), 2.31-2.22 (m, 2H),

2.06-1.96 (m, 1H), 1.71-1.64 (m, 1H), 1.47-1.40 (m, 1H), 1.36-1.23 (m, 3H), 1.14-0.97 (m, 3H), 0.91-0.78 (m, 1H), 0.72-0.56 (m, 2H).

Example 7: Synthesis of 3-(5-(10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-48)



Step 1: **Synthesis of tert-butyl 10-oxo-7-azaspiro[4.5]decane-7-carboxylate (7-c)**

To a 3-necked 100 mL round bottomed flask with a stir bar, condenser and two septa was added tert-butyl 4-oxopiperidine-1-carboxylate (**7-a,** 2.00 g, 10.0 mmol) and anhydrous toluene (20.0 mL, 0.50 M) under an inert atmosphere. Potassium tert-butoxide (2.49 g, 22.20 mmol) was then added in one portion and the resulting solution was stirred for 1 h at room temperature. After 1 h, 1,4-dibromobutane (**7-b**, 1.37 mL, 11.50 mmol) was added dropwise and the resulting mixture was brought to reflux (~140 °C) for 2 h. The solution was cooled, diluted with 1:1 sat. NH_4Cl: H_2O (20 mL) and extracted with EtOAc (3 × 25 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and filtered before being concentrating onto silica gel. The crude product was purified via silica gel flash chromatography using 80 g of silica gel and eluting with a gradient of 0 to 30% ethyl acetate in heptanes. The product containing fractions were confirmed by TLC, collected and concentrated *in vacuo* to yield tert-butyl 10-oxo-7-azaspiro[4.5]decane-7-carboxylate (**7-c**). ^{1}H-NMR (499 MHz, $CDCl_3$-*d*) δ ppm 3.71 (br s, 2H), 3.45 (br s, 2H), 2.48 (t, J = 6.30 Hz, 2H), 1.89-1.96 (m, 2H), 1.67 (br s, 4H), 1.49 (s, 11H).

Step 2: **Synthesis of tert-butyl 10-(((trifluoromethyl)sulfonyl)oxy)-7-azaspiro[4.5]dec-9-ene-7-carboxylate (7-d)**

To a 100 mL round bottomed flask with stir bar was added tert-butyl 10-oxo-7-azaspiro[4.5]decane-7-carboxylate (**7c**, 567 mg, 2.24 mmol) and bis(trifluoromethanesulfonyl)aniline

(951 mg, 2.66 mmol). The flask was purged with argon and sealed with a septum before adding anhydrous THF (13.5 mL, 0.16 M). The resulting mixture was cooled to -78 °C in an acetone dry ice bath and LiHMDS 1M in THF (2.69 mL, 2.69 mmol) was added. The reaction mixture was allowed to warm to RT with stirring. After 2 h, TLC (3:2 heptanes:EtOAc) indicated that the starting material was consumed (visualized with CAM stain) and the solvent was removed *in vacuo*. The crude residue was resuspended in EtOAc (25 mL) and washed with 1M HCl (2 × 50 mL). The combined acidic washes were back extracted with EtOAc (50 mL) and then the combined phases were washed with brine (100 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to yield tert-butyl 10-(((trifluoromethyl)sulfonyl)oxy)-7-azaspiro[4.5]dec-9-ene-7-carboxylate (**7-d**). The product was carried on to the next step without further purification. LCMS: m/z ESI Positive, no ionization observed.

Step 3: **Synthesis of tert-butyl 10-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-7-azaspiro[4.5]dec-9-ene-7-carboxylate (7-e)**

To a 20 mL microwave reaction vial with stir bar was added 3-(1-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-2-yl)piperidine-2,6-dione (**6-f**, 638 mg, 1.72 mmol) and $PdCl_2$(dppf)-DCM adduct (211 mg, 0.26 mmol). The crude tert-butyl 10-(((trifluoromethyl)sulfonyl)oxy)-7-azaspiro[4.5]dec-9-ene-7-carboxylate (**7-d**, 863 mg, 2.24 mmol) dissolved in anhydrous dioxane (6.89 mL, 0.25 M) was then added followed by potassium carbonate 2 M in H_2O (1.38 mL, 2.76 mmol). The resulting solution was degassed before heating via microwave irradiation at 85 °C for 1 h. After 1 h, the desired mass was observed by LCMS. The crude reaction mixture was concentrated onto silica gel and purified via normal phase silica gel flash chromatography using a 20 g column and eluting with a gradient of 20% to 100% EtOAc in heptanes. The desired fractions were combined and concentrated *in vacuo* to yield tert-butyl 10-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-7-azaspiro[4.5]dec-9-ene-7-carboxylate (**7-e**). LCMS: m/z ESI Positive $[M+H]^+ = 480.41$.

Step 4: **Synthesis of tert-butyl 10-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-10-hydroxy-7-azaspiro[4.5]decane-7-carboxylate (7-f)**

To a 40 mL vial containing tert-butyl 10-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-7-azaspiro[4.5]dec-9-ene-7-carboxylate (**7-e**, 593 mg, 1.24 mmol) was added dichloromethane (6.87 mL) propan-2-ol (6.87 mL) and N,N-dimethylformamide (2.10 mL) (15.84 mL total, 0.08 M) and the resulting solution was cooled to 0 °C via ice bath. Oxygen was then bubbled into the reaction for 5 mins. $Mn(dpm)_3$ (374 mg, 0.62 mmol) and phenylsilane (305 µL, 2.48 mmol) were then added. Oxygen was bubbled into the reaction for 2 h and the resulting mixture was allowed to stir overnight under an atmosphere of oxygen. After 12 h, LCMS showed formation of the desired product. The reaction mixture was concentrated *in vacuo* and purified on a 40 g C^{18} column eluting with MeCN (+ 0.1% formic acid) and H_2O (+ 0.1% formic acid). The desired fractions were collected, combined, and concentrated via

lyophilization to yield tert-butyl 10-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-10-hydroxy-7-azaspiro[4.5]decane-7-carboxylate (**7-f**). LCMS: m/z ESI Positive $[M+H\text{-}Boc]^+$ = 398.32.

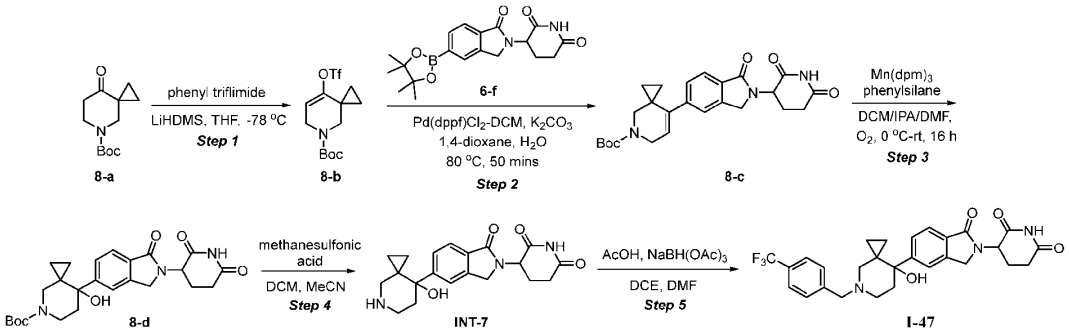
Step 5: **Synthesis of 3-(5-(10-hydroxy-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (INT-6)**

To a stirred solution of tert-butyl 10-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-10-hydroxy-7-azaspiro[4.5]decane-7-carboxylate (**7-f**, 75 mg, 0.15 mmol) in DCM (5.00 mL, 0.03 M) was added methanesulfonic acid (130 µL, 2.00 mmol) and the resulting mixture was allowed to stir for 3 h. The reaction mixture was then concentrated under reduced pressure and carried onto the next step without further purification. Quantitative yield is assumed for this reaction. LCMS: m/z ESI Positive $[M+H]^+$ = 398.31.

Step 6: **Synthesis of 3-(5-(10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-48)**

To a 20 mL vial containing crude 3-(5-(10-hydroxy-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**INT-6**, 60 mg, 0.15 mmol) was added a stir bar, DMF (1.9 mL, 0.08 M), TEA (0.31 mL, 2.2 mmol) and 4-(trifluoromethyl)benzaldehyde (**1-i**, 23 µL, 0.17 mmol). After 5 min of stirring, decaborane (7.4 mg, 0.06 mmol) was added and the resulting mixture was stirred at 80 °C. The reaction mixture was then concentrated *in vacuo*. The crude residue was dissolved in EtOAc (25 mL) and was washed with saturated sodium bicarbonate (2 × 20 mL) and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was then dissolved in a minimal amount of DMSO, filtered through a PTFE syringe filter and purified by preparatory HPLC on a C^{18} column eluting with MeCN (+ 0.1% formic acid) and H_2O (+ 0.1% formic acid). The desired product containing fractions were collected, combined, and concentrated via lyophilization with HCl to yield 3-(5-(10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-48**) as a hydrochloride salt. LCMS: m/z ESI Positive $[M+H]^-$ = 556.35. ^{1}H NMR (499 MHz, DMSO-d_6) δ ppm 11.00 (s, 1H), 10.15-10.29 (br s, 1H), 7.96 (br d, J = 8.21 Hz, 2H), 7.88 (d, J = 8.21 Hz, 2H), 7.72 (br d, J = 8.21 Hz, 2H), 7.61-7.69 (m, 1H), 5.60 (d, J = 6.02 Hz, 1H), 5.12 (dd, J = 13.14, 4.93 Hz, 1H), 4.42-4.56 (m, 3H), 4.29-4.41 (m, 1H), 3.49 (br s, 1H), 3.26-3.29 (m, 1H), 2.81-3.01 (m, 3H), 2.54-2.63 (m, 2H), 2.33-2.45 (m, 1H), 1.95-2.13 (m, 2H), 1.78-1.87 (m, 2H), 1.33-1.44 (m, 1H), 1.19-1.32 (m, 2H), 1.04-1.15 (m, 1H), 0.92-1.03 (m, 1H), 0.84 (dt, J = 8.90, 4.59 Hz, 1H).

Example 8: Synthesis of 3-(5-(8-hydroxy-5-(4-(trifluoromethyl)benzyl)-5-azaspiro[2.5]octan-8-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-47)



Step 1: **tert-butyl 8-(((trifluoromethyl)sulfonyl)oxy)-5-azaspiro[2.5]oct-7-ene-5-carboxylate (8-b)**

To a 40 mL round bottomed flask with a stir bar was added tert-butyl 8-oxo-5-azaspiro[2.5]octane-5-carboxylate (**8-a**, 200 mg, 0.88 mmol) and bis(trifluoromethanesulfonyl)-aniline (411 mg, 1.15 mmol) and the resulting mixture was sealed with a septum and purged with argon. Anhydrous THF (5.35 mL, 0.166 M) was then added and the flask was cooled to -78 °C in an acetone dry ice bath. LiHMDS 1M in THF (1.07 mL, 1.07 mmol) was added and the resulting mixture was allowed to warm to rt with stirring. After 2 h, TLC (3:2 heptanes;EtOAc) indicated that the starting material was completely consumed (visualized with CAM stain). The reaction mixture was then concentrated *in vacuo*. The crude residue was resuspended in EtOAc (25 mL) and washed with 1M HCl (2 × 50 mL). The combined acidic washes were back extracted with EtOAc (50 mL) and the combined organic phases were washed with brine (100 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to yield tert-butyl 8-(((trifluoromethyl)sulfonyl)oxy)-5-azaspiro[2.5]oct-7-ene-5-carboxylate (**8-b**). The product was carried onto the next step without further purification. LCMS: m/z ESI Positive No ionization observed.

Step 2: **Synthesis of tert-butyl 8-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-5-azaspiro[2.5]oct-7-ene-5-carboxylate (8-c)**

To a 5 mL microwave reaction vial with stir bar was added 3-(1-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-2-yl)piperidine-2,6-dione (**6-f**, 330 mg, 0.89 mmol) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with dichloromethane (109 mg, 0.13 mmol). The crude tert-butyl 8-(((trifluoromethyl)sulfonyl)oxy)-5-azaspiro[2.5]oct-7-ene-5-carboxylate (**8-b**, 317 mg, 0.88 mmol) dissolved in anhydrous dioxane (3.57 mL, 0.25 M) was then added followed by potassium carbonate 2 M in H_2O (713 µL, 1.43 mmol). The resulting mixture was degassed before heating via microwave irradiation at 85 °C for 1 h. After 1 h, the desired mass was observed by LCMS. The reaction mixture was concentrated onto silica gel and purified via normal phase silica gel flash chromatography on a 20 g column eluting with a gradient of 65% to 100% EtOAc in heptanes. The desired product coeluted with dppf impurities and was then further purified via reverse phase flash chromatography on a 40 g C^{18} column eluting with a gradient of 5 to 100% acetonitrile in water. The

desired product containing fractions were collected, combined, and concentrated via lyophilization to yield tert-butyl 8-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-5-azaspiro[2.5]oct-7-ene-5-carboxylate (**8-c**). LCMS: m/z ESI Positive $[M+H]^+$ = expected 452.22; observed 452.37.

Step 3: **Synthesis of tert-butyl 8-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-8-hydroxy-5-azaspiro[2.5]octane-5-carboxylate (8-d)**

A stirred solution of tert-butyl 8-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-5-azaspiro[2.5]oct-7-ene-5-carboxylate (**8-c**, 60 mg, 0.13 mmol) in dichloromethane (0.74 mL), propan-2-ol (0.74 mL), and N,N-dimethylformamide (0.23 mL) was cooled to 0 °C. Oxygen was bubbled into the resulting mixture for 5 mins and $Mn(dpm)_3$ (40 mg, 66 μmol) and phenylsilane (29 mg, 33 μL, 0.27 mmol) were then added. Oxygen was again bubbled into the reaction mixture for 2 h and stirring was continued overnight under an atmosphere of oxygen. The reaction mixture was then concentrated *in vacuo* and purified with a C^{18} column eluting with MeCN (+0.1% formic acid) and H_2O (+0.1% formic acid). The desired fractions were collected, combined, and concentrated *in vacuo* to yield tert-butyl 8-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-8-hydroxy-5-azaspiro[2.5]octane-5-carboxylate (**8-d**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 470.

Step 4: **Synthesis of 3-(5-(8-hydroxy-5-azaspiro[2.5]octan-8-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (INT-7)**

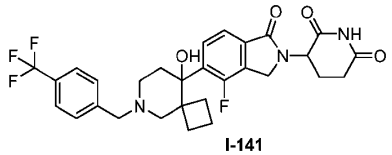
To a stirred solution of tert-butyl 8-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-8-hydroxy-5-azaspiro[2.5]octane-5-carboxylate (**8-d**, 0.023 g, 49 μmol) in DCM (0.7 mL) and MeCN (0.7 mL) was added methanesulfonic acid (19 mg, 13 μL, 0.20 mmol) and the resulting mixture was allowed to stir for 30 mins. The reaction mixture was then cooled to 0 °C, quenched with triethylamine (27 μL, 0.20 mmol), and concentrated under reduced pressure to provide 3-(5-(8-hydroxy-5-azaspiro[2.5]octan-8-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**INT-7**). The crude product was carried onto the next step without further purification. Quantitative yield is assumed for this reaction. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 370.

Step 5: **Synthesis of 3-(5-(8-hydroxy-5-(4-(trifluoromethyl)benzyl)-5-azaspiro[2.5]octan-8-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-47)**

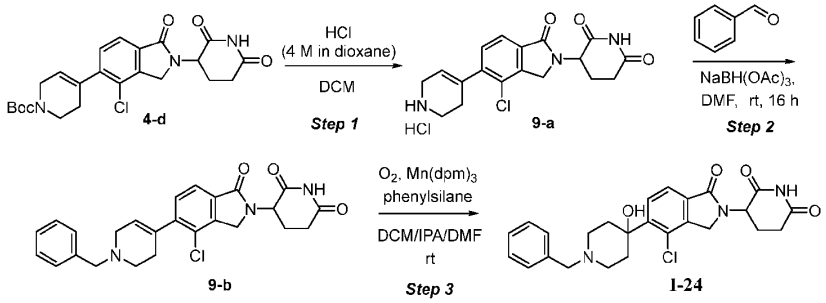
To a stirred solution of 3-(5-(8-hydroxy-5-azaspiro[2.5]octan-8-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**INT-7**, 0.023 g, 62 μmol) and 4-(trifluoromethyl)benzaldehyde (**1-i**, 0.11 g, 85 μL, 0.62 mmol) in DCE (1 mL) and N,N-dimethylformamide (0.3 mL) was added acetic acid (3.7 mg, 0.2 mL, 62 μmol) and sodium triacetoxyborohydride (26 mg, 0.12 mmol) and the resulting mixture was allowed to stir overnight. The reaction mixture was then purified on a C18 column eluting with MeCN (+0.1%formic acid) and H_2O (+0.1% formic acid). The desired fractions were collected, combined and concentrated *in vacuo* to yield 3-(5-(8-hydroxy-5-(4-(trifluoromethyl)benzyl)-5-azaspiro[2.5]octan-8-yl)-

1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-47**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 528. ^{1}H-NMR (499 MHz, DMSO-d_6) δ ppm 11.01-10.97 (m, 1H), 7.74-7.64 (m, 5H), 7.58-7.53 (m, 2H), 5.14-5.03 (m, 2H), 4.47-4.41 (m, 1H), 4.35-4.28 (m, 1H), 3.62-3.51 (m, 3H), 2.95-2.87 (m, 1H), 2.75-2.67 (m, 2H), 2.65-2.57 (m, 2H), 2.43-2.34 (m, 2H), 2.03-1.92 (m, 2H), 0.32-0.18 (m, 3H), 0.09-0.00 (m, 1H).

The following compounds were synthesized in a similar fashion to **Example 8 (I-47)**.

Compound	Characterization
 **I-141** 3-(4-fluoro-5-(9-hydroxy-6-(4-(trifluoromethyl)benzyl)-6-azaspiro[3.5]nonan-9-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-141**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 560.1; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.03 (s, 1H), 9.86-9.64 (m, 1H), 8.00-7.85 (m, 5H), 7.69 (d, J = 7.9 Hz, 1H), 5.90-5.81 (m, 1H), 5.14 (dd, J = 5.2, 13.2 Hz, 1H), 4.67-4.34 (m, 4H), 3.70-3.59 (m, 1H), 3.39 (m, 1H), 3.24 (br s, 1H), 3.06-2.81 (m, 2H), 2.61 (d, J = 18.6 Hz, 2H), 2.47-2.35 (m, 1H), 2.23-2.10 (m, 1H), 2.06-1.77 (m, 4H), 1.70-1.39 (m, 2H), 1.13-0.90 (m, 1H).

Example 9: Synthesis of 3-(5-(1-benzyl-4-hydroxypiperidin-4-yl)-4-chloro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-24)



Step 1: **Synthesis of 3-(4-chloro-1-oxo-5-(1,2,3,6-tetrahydropyridin-4-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride (9-a)**

To a stirred solution of tert-butyl 4-(4-chloro-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**4-d**, 500 mg, 1.09 mmol) in DCM (5 mL) at 0 °C was added HCl (4M in dioxane) (3 mL, 12.00 mmol) and the resulting mixture was stirred at 25 °C for 3 h. The reaction mixture was then concentrated under reduced pressure. The resulting residue was triturated with MTBE (10 mL), filtered, and dried under reduced pressure to provide 3-(4-chloro-1-oxo-5-(1,2,3,6-tetrahydropyridin-4-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride (**9-a**). The crude product was taken onto the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2H]^+$ = 360.2, 362.2. 1H-NMR (400 MHz, DMSO-d_6): δ 11.022 (s, 1H), 9.100 (br s, 2H), 7.749-7.769

(d, J = 8.0 Hz, 2H), 7.444-7.464 (d, J = 8.0, 2H), 5.865 (s, 1H), 5.125-5.865 (m, 1H), 4.317-4.526 (m, 2H), 3.573-3.783 (m, 2H), 2.896-2.927 (m, 2H), 2.628-2.676- (m, 4H), 2.038-2.080 (m, 1H).

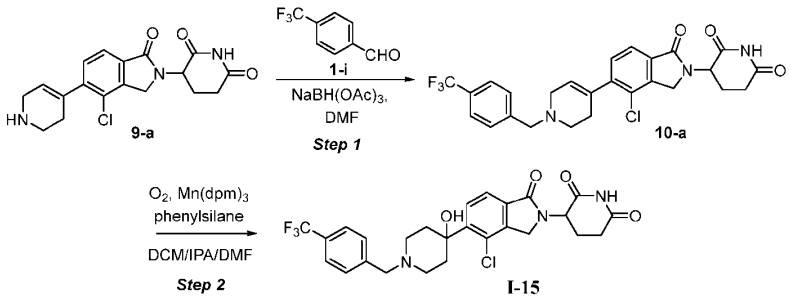
Step 2: **Synthesis of 3-(5-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-4-chloro-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride (9-b)**

A solution of 3-(4-chloro-1-oxo-5-(1,2,3,6-tetrahydropyridin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (**9-a**, 455 mg, 1.265 mmol) and benzaldehyde (161 mg, 1.517 mmol) in DMF (7 mL) was stirred at 25 °C for 30 min. Sodium triacetoxyborohydride (536 mg, 2.53 mmol) was then added in portions and stirring was continued at room temperature for 16 h. The reaction mixture was then concentrated under reduced pressure to afford the crude compound which was purified by reverse phase preparative HPLC [(Column: C^{18}, eluting with Mobile phase A: 0.1% HCl in H_2O, Mobile phase B: ACN, flow rate: 15 mL/min]. The pure fractions were combined and concentrated via lyophilization to afford 3-(5-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-4-chloro-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride (**9-b**). LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2H]^+$ = 450, 452. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 10.43 (br s, 1H), 7.77-7.70 (m, 1H), 7.62-7.55 (m, 2H), 7.52-7.47 (m, 4H), 5.86 (s, 1H), 5.14 (dd, J = 16.2, 4.8 Hz, 1H), 4.53-4.43 (m, 3H), 4.36-4.27 (m, 1H), 3.83-3.78 (m, 2H), 3.67-3.61 (m, 1H), 2.96-2.84 (m, 2H), 2.72-2.59 (m, 3H), 2.03-2.01 (m, 1H).

Step 3: **Synthesis of 3-(5-(1-benzyl-4-hydroxypiperidin-4-yl)-4-chloro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-24)**

To a stirred solution of 3-(5-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-4-chloro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**9b**, 30 mg, 0.07 mmol) in DCM (0.5 mL), 2-propanol (0.5 mL) and DMF (0.5 mL) at 0 °C were added $Mn(dpm)_3$ (40.3 mg, 0.07 mmol) and phenylsilane (7.21 mg, 0.07 mmol). The resulting mixture was stirred at 0 °C under an atmosphere of oxygen for 18 h. The progress of the reaction was monitored by UPLC. The reaction mixture was then quenched with sodium thiosulfate solution (15 mL) and stirred for 1 h. The aqueous mixture was extracted with ethyl acetate (2 × 20 mL) and the combined organic phases were dried over sodium sulfate, filtered and concentrated under vacuum to afford. The crude compound was purified by reverse phase preparative HPLC [Column: C18, eluting with Mobile phase A: 0.1% HCl in H_2O, Mobile phase B: ACN, flow rate: 15 mL/min]. The pure fractions were combined and concentrated via lyophilization to afford 3-(5-(1-benzyl-4-hydroxypiperidin-4-yl)-4-chloro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-24**). LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2H]^+$ = 468, 470. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 9.67 (s, 1H), 7.97 (d, J = 8.00 Hz, 1H), 7.78 (d, J = 8.00 Hz, 1H), 7.60 (t, J = 1.60 Hz, 2H), 7.51 (t, J = 2.00 Hz, 3H), 5.96 (s, 1H), 5.14 (dd, J = 4.80, 13.40 Hz, 1H), 4.50-4.28 (m, 4H), 3.33 (br s, 4H), 2.92-2.88 (m, 1H), 2.79 (m, 2H), 2.30 (br s, 2H), 2.03-2.00 (m, 1H), 1.90 (d, J = 12.40 Hz, 2H).

Example 10: Synthesis of 3-(4-chloro-5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-15)



Step 1: **Synthesis of 3-(4-chloro-1-oxo-5-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (10-a)**

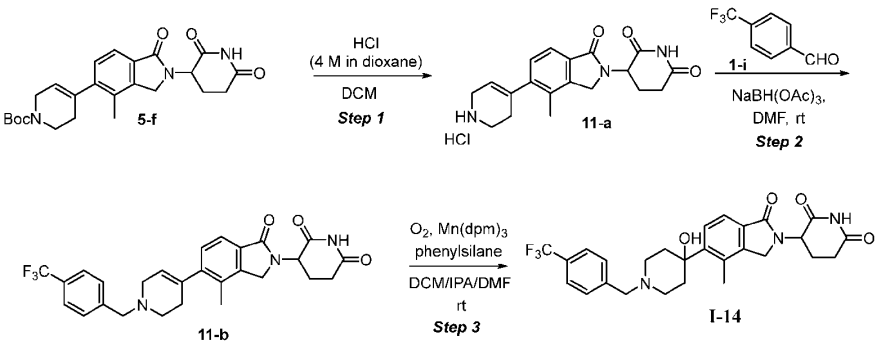
To a stirred solution of 3-(4-chloro-1-oxo-5-(1,2,3,6-tetrahydropyridin-4-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride (**9-a**, 200 mg, 0.51 mmol) in DMF (2 mL) at 25 °C was added 4-(trifluoromethyl)benzaldehyde (**1-i**, 0.083 mL, 0.61 mmol) and the resulting mixture was stirred at 25 °C for 30 min. Sodium triacetoxyborohydride (267 mg, 1.26 mmol) was then added in portions and stirring was continued at room temperature for 16 h. The reaction mixture was then concentrated under reduced pressure. The crude product was dissolved in water and ACN and a solid precipitated out of the solution. The solid was filtered, washed with water (20 mL) and MTBE (20 mL) and dried under vacuum. The crude material was purified via normal phase column chromatography on a 24 g SNAP silica gel column and eluting with a gradient of 100% EtOAc to afford 3-(4-chloro-1-oxo-5-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (**10-a**). LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2H]^+$ = 518, 520. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 7.73-7.68 (m, 4H), 7.61 (d, J = 8.00 Hz, 1H), 7.46 (d, J = 7.60 Hz, 1H), 5.79 (s, 1H), 5.16-5.13 (m, 1H), 4.50-4.29 (m, 2H), 3.73 (s, 2H), 3.13 (s, 2H), 2.91 (m, 1H), 2.70-2.58 (m, 4H), 2.53-2.34 (m, 2H), 2.02 (m, 1H).

Step 2: **Synthesis of 3-(4-chloro-5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-15)**

To a solution of 3-(4-chloro-1-oxo-5-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (**10-a**, 0.2 g, 0.39 mmol) in DMF (0.5 mL), 2-propanol (1 mL) and DCM (1 mL) at 0 °C and under an atmosphere of nitrogen was added $Mn(dpm)_3$ (0.07 g, 0.12 mmol) and phenylsilane (0.096 mL, 0.77 mmol). The resulting mixture was purged with oxygen and stirred at room temperature under an atmosphere of oxygen for 2 days. The reaction mixture was then concentrated under reduced pressure. The crude product was purified by reverse phase column chromatography on a C^{18} column [eluting with Mobile phase A: 0.1% FA in H_2O, Mobile phase B: ACN, flow rate: 10 mL/min]. The desired fractions were collected, combined and concentrated via lyophilization to afford 3-

(4-chloro-5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-15**). LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2H]^+$ = 536.2, 538.2. 1H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 0.17 (s, 1H), 7.97 (d, J = 8.40 Hz, 1H), 7.92-7.87 (m, 4H), 7.78 (d, J = 8.00 Hz, 1H), 5.98 (s, 1H), 5.16-5.12 (m, 1H), 4.53-4.45 (m, 3H), 3.34 (m, 2H), 2.52-2.50 (m, 3H), 2.44-2.33 (m, 4H), 2.03-2.02 (m, 1H), 2.02-2.00 (m, 2H).

Example 11: Synthesis of 3-(5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-methyl-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-14)



Step 1: **Synthesis of 3-(4-methyl-1-oxo-5-(1,2,3,6-tetrahydropyridin-4-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride (11-a)**

To a stirred solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-methyl-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**5-f**, 450 mg, 1.024 mmol) in DCM (2 mL) at 0 °C was added HCl (4M in Dioxane) (2 mL, 8.00 mmol) and the resulting mixture was stirred at 25 °C for 16 h. The reaction mixture was concentrated under reduced pressure. The crude product was triturated with MTBE (10 mL) to afford 3-(4-methyl-1-oxo-5-(1,2,3,6-tetrahydropyridin-4-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride (**11-a**), which was carried onto the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 340.0.

Step 2: **Synthesis of 3-(4-methyl-1-oxo-5-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (11-b)**

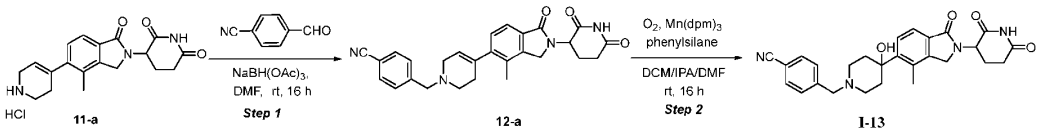
To a stirred solution of 3-(4-methyl-1-oxo-5-(1,2,3,6-tetrahydropyridin-4-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride (**11-a**, 200 mg, 0.53 mmol) in DMF (10 mL) at room temperature was added 4-(trifluoromethyl)benzaldehyde (**1-i**, 0.077 mL, 0.53 mmol) and the resulting mixture was stirred at room temperature for 1 h. Sodium triacetoxyborohydride (226 mg, 1.06 mmol) was then added at room temperature and stirring was continued for 16 h. The reaction mixture was filtered through a pad of Celite® and the pad was washed with EtOAc (50 mL). The filtrate was evaporated under reduced pressure to give the crude product, which was purified by reverse phase chromatography on a C^{18} column [eluting with Mobile phase A: 0.1% FA in H_2O, Mobile phase B: ACN, flow rate: 10 mL/min]. The

product containing fractions were collected and concentrated via lyophilization to afford 3-(4-methyl-1-oxo-5-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (**11-b**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 498.1.

Step 2: **Synthesis of 3-(5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-methyl-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-14)**

To a stirred solution of 3-(4-methyl-1-oxo-5-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (**11-b**, 120 mg, 0.24 mmol) in DCM (6 mL), DMF (3 mL), and 2-propanol (6 mL) at 0 °C was added $Mn(dpm)_3$ (43.8 mg, 0.07 mmol) and phenylsilane (0.065 mL, 0.48 mmol), and the resulting mixture was stirred at 0 °C under an atmosphere of oxygen for 16 h. The reaction mixture was filtered through a pad of Celite® and the pad was washed with EtOAc (50 mL). The filtrate was evaporated under reduced pressure to give the crude product, which was purified by reverse phase chromatography on a C^{18} column eluting with Mobile phase A: 0.1% NH_4OAc in H_2O, Mobile phase B: ACN, flow rate: 10 mL/min. The product containing fractions were collected and concentrated via lyophilization to afford 3-(5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-methyl-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-14**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 516.3. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 7.70 (d, J = 8.00 Hz, 2H), 7.64-7.50 (m, 4H), 5.15-5.10 (m, 1H), 4.94 (s, 1H), 4.42-4.21 (m, 2H), 3.62 (s, 2H), 2.96-2.88 (m, 1H), 2.63-2.50 (m, 3H), 2.07-2.00 (m, 3H), 1.89 (d, J = 12.80 Hz, 3H), 1.29 (dd, J = 12.00, Hz, 2H), 1.11 (dd, J = 26.40, Hz, 3H).

Example 12: **Synthesis of 4-((4-(2-(2,6-dioxopiperidin-3-yl)-4-methyl-1-oxoisoindolin-5-yl)-4-hydroxypiperidin-1-yl)methyl)benzonitrile acetate (I-13)**



Step 1: **Synthesis of 4-((4-(2-(2,6-dioxopiperidin-3-yl)-4-methyl-1-oxoisoindolin-5-yl)-3,6-dihydropyridin-1(2H)-yl)methyl)benzonitrile (12-a)**

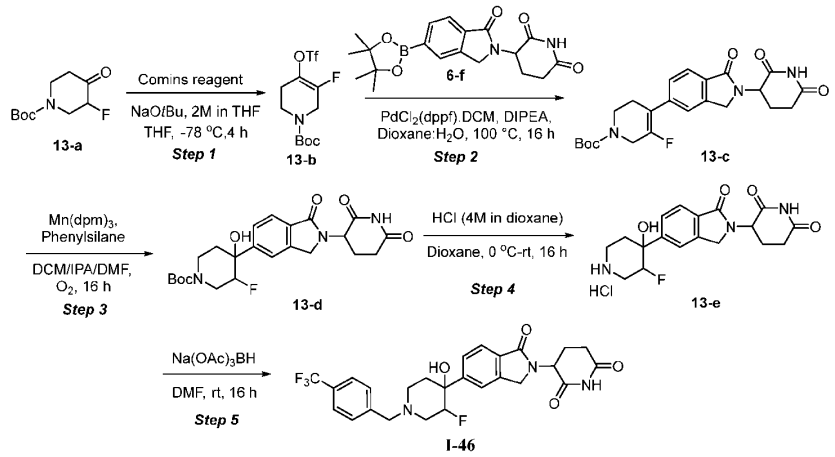
To a stirred solution of 3-(4-methyl-1-oxo-5-(1,2,3,6-tetrahydropyridin-4-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride (**11-a**, 150 mg, 0.40 mmol) in DMF (10 mL), was added 4-formylbenzonitrile (87 mg, 0.66 mmol) at room temperature and the resulting mixture was stirred for 1 h. Sodium triacetoxyborohydride (206 mg, 0.97 mmol) was added and the resulting reaction mixture was stirred at room temperature for 16 h. The reaction mixture was then concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography (Biotage® Isolera, silica 100-200 mesh gel) eluting with 10% 2-propanol in dichloromethane. The product fractions were concentrated

under reduced pressure to afford 4-((4-(2-(2,6-dioxopiperidin-3-yl)-4-methyl-1-oxoisoindolin-5-yl)-3,6-dihydropyridin-1(2H)-yl)methyl)benzonitrile (**12-a**). LCMS: Positive $[M+1]^+ = 455.3$.

Step 2: **Synthesis of 4-((4-(2-(2,6-dioxopiperidin-3-yl)-4-methyl-1-oxoisoindolin-5-yl)-4-hydroxypiperidin-1-yl)methyl)benzonitrile acetate (I-13)**:

To a stirred solution of 4-((4-(2-(2,6-dioxopiperidin-3-yl)-4-methyl-1-oxoisoindolin-5-yl)-3,6-dihydropyridin-1(2H)-yl)methyl)benzonitrile (**12-a**, 90 mg, 0.20 mmol) in dichloromethane (3 mL)/*n.n*-dimethylformamide (1.5 mL)/2-propanol (3 mL) at 0 °C, $Mn(dpm)_3$ (35.9 mg, 0.06 mmol) and phenylsilane (0.054 mL, 0.40 mmol) were added. The resulting reaction mixture was purged with oxygen and stirred under an oxygen atmosphere for 16 h. The reaction mixture was then filtered through a pad of celite and washed with EtOAc (10 mL). The combined organic filtrate was concentrated under reduced pressure to afford crude compound. The crude residue was purified by reverse phase chromatography using a C-18 column [Mobile phase A: 0.1% NH_4OAc in H_2O, Mobile phase B: ACN, flow rate: 10 mL/min)]. The product fractions were lyophilized to afford 4-((4-(2-(2,6-dioxopiperidin-3-yl)-4-methyl-1-oxoisoindolin-5-yl)-4-hydroxypiperidin-1-yl)methyl)benzonitrile acetate (**I-13**). LCMS: Positive $[M+H]^+ = 473.1$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.90 (br s, 1H), 7.82 (d, J = 2.00 Hz, 2H), 7.80-7.50 (m, 4H), 5.15-5.10 (m, 1H), 4.94 (s, 1H), 4.42-4.21 (m, 2H), 3.66-3.62 (m, 2H), 2.95-2.80 (m, 1H), 2.80-2.70 (m, 1H), 2.75-2.50 (m, 3H), 2.48-2.30 (m, 3H), 2.09-2.00 (m, 4H), 1.89-1.82 (m, 3H).

Example 13: Synthesis of 3-(5-(3-fluoro-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-46)



Step 1: **Synthesis of tert-butyl 5-fluoro-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (13-b):**

To a stirred solution of tert-butyl 3-fluoro-4-oxopiperidine-1-carboxylate (**13-a**, 8 g, 36.80 mmol) in THF (60 mL) was added sodium tert-butoxide solution (1M in THF) (73.7 mL, 73.70 mmol) dropwise

at -78°C and the reaction mixture was stirred for -78 °C for 1h. N-(5-chloropyridin-2-yl)-1,1,1-trifluoro-N-((trifluoromethyl)sulfonyl)methanesulfonamide (14.46 g, 36.8 mmol) in THF (20 mL) was then added to the resulting mixture at -78 °C which was then allowed warm to room temperature and stirred for 3 h. Aqueous ammonium chloride solution (10 mL) was added and the resulting mixture was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography (Isco Combi-flash) eluting with 6% EtOAc/Hexane to afford tert-butyl 5-fluoro-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (**13-b**). LCMS: Positive $[M+H-tBu]^+ = 492.2$.

Step 2: **Synthesis of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-5-fluoro-3,6-dihydropyridine-1(2H)-carboxylate (13-c):**

To a stirred solution of tert-butyl 5-fluoro-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (**13-b**, 250 mg, 0.72 mmol) in 1,4-dioxane (5 mL) and H_2O (1 mL) was added DIPEA (0.346 mL, 2.15 mmol) and 3-(1-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-2-yl)piperidine-2,6-dione (397 mg, 1.07 mmol). The reaction mixture was purged with N_2 gas for 10 min and then $PdCl_2$(dppf) DCM adduct (58.4 mg, 0.07 mmol) was added at room temperature, and the resulting mixture was further purged with N_2 for 5 min. The reaction mixture was heated at 100°C and stirred for 16 h. The reaction mixture was filtered through a pad of Celite®, and the obtained filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (100-200 mesh silica) eluting with 85% ethyl acetate/hexane to afford tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-5-fluoro-3,6-dihydropyridine-1(2H)-carboxylate (**13-c**). LCMS: m/z 442.5 $[M-H]^-$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 7.74 (d, J = 8.00 Hz, 1H), 7.66 (s, 1H), 7.57 (d, J = 8.00 Hz, 1H), 5.15-5.10 (m, 1H), 4.48 (d, J = 17.20 Hz, 1H), 4.34 (d, J = 17.20 Hz, 1H), 4.11 (s, 2H), 2.96-2.88 (m, 2H), 2.68-2.51 (m, 5H), 2.11-2.01 (m, 1H), 1.50 (s, 9H).

Step 3: **Synthesis of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3-fluoro-4-hydroxypiperidine-1-carboxylate (13-d):**

A solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-5-fluoro-3,6-dihydropyridine-1(2H)-carboxylate (**13-c**, 200 mg, 0.45 mmol) in DCM (3 mL), 2-propanol (3 mL) and DMF (1 mL) was stirred at 0 °C for 5 min. To this reaction mixture $Mn(dpm)_3$ (82 mg, 0.14 mmol) and phenylsilane (0.112 mL, 0.90 mmol) were added at 0 °C under N_2 atmosphere. The resulting reaction mixture was purged with O_2 gas and stirred at room temperature for 16 h. The reaction mixture was then concentrated under reduced pressure. The crude residue was purified by reverse phase chromatography, (C^{18} column, Mobile Phase A: 0.01% FA in Water, Mobile Phase B: ACN, flow rate: 15 mL/min), RT: 8], ACN/H_2O mixture. The collected product fractions were evaporated under lyophilization to afford tert-

butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3-fluoro-4-hydroxypiperidine-1-carboxylate (**13-d**). LCMS: m/z 460.5 $[M-H]^-$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 7.74-7.67 (m, 3H), 5.91 (br s, 1H), 5.13-5.10 (m, 1H), 4.48-4.39 (m, 2H), 4.35-4.12 (m, 2H), 3.80-3.14 (m, 4H), 2.95-2.88 (m, 2H), 2.58-2.33 (m, 2H), 1.99-1.70 (m, 1H), 1.71 (d, J = 12.80 Hz, 9H).

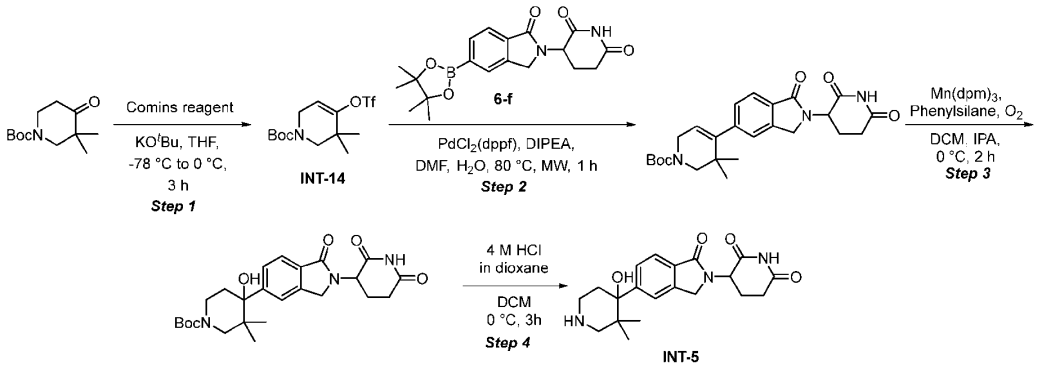
Step 4: **Synthesis of 3-(5-(3-fluoro-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride (13-e)**:

To a stirred solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3-fluoro-4-hydroxypiperidine-1-carboxylate (**13-d**, 75 mg, 0.16 mmol) in 1,4-dioxane (5 mL) was added 4M HCl in dioxane (0.122 mL, 0.49 mmol) drop wise at 0°C under nitrogen and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was then concentrated under reduced pressure. The crude compound was triturated with MTBE to afford 3-(5-(3-fluoro-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride (**13-e**). LCMS: LCMS: m/z 362.2 $[M+H]^+$. 1H-NMR (400 MHz, DMSO-d6): δ ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 9.12 (br s, 1H), 8.84 (br s, 1H), 7.78-7.73 (m, 3H), 6.23 (s, 1H), 5.15-5.11 (m, 1H), 4.51-4.34 (m, 2H), 3.70-3.14 (m, 4H), 2.99-2.88 (m, 2H), 2.58-2.33 (m, 3H), 1.99-1.70 (m, 2H).

Step 5: **Synthesis of 3-(5-(3-fluoro-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-46)**:

To a stirred solution of 3-(5-(3-fluoro-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride (**13-e**, 70 mg, 0.19 mmol) in DMF (3 mL) was added 4-(trifluoromethyl)benzaldehyde (33.7 mg, 0.19 mmol) at room temperature and the resulting mixture stirred for 1h. To this resulting mixture was added sodium triacetoxyborohydride (144 mg, 0.68 mmol) and stirring was continued at 25 °C for 16 h. The progress of the reaction was monitored by UPLC and TLC. The reaction mixture was then concentrated under reduced pressure. The crude residue was purified by reverse phase preparative HPLC [X-select C18, 150 mm X 19 (Mobile Phase A: 0.01% FA in Water, Mobile Phase B: ACN, flow rate: 15 mL/min)], ACN/H_2O mixture. Pure product fraction was lyophilized to afford 3-(5-(3-fluoro-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione. The product was treated with aqueous HCl solution (0.1 mL, 10.00 µmol) and water (0.5 mL), and the resulting mixture was lyophilized to provide 3-(5-(3-fluoro-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-46**). LCMS: 520.4 m/z $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 10.30 (br s, 1H), 7.90-7.78 (m, 3H), 7.76-7.65 (m, 4H), 6.37 (br s, 1H), 5.15-5.11 (m, 1H), 4.58-4.33 (m, 2H), 3.56-3.34 (m, 4H), 2.92-2.88 (m, 1H), 2.67-2.51 (m, 6H), 2.07-2.00 (m, 2H).

Example 14: Synthesis of 3-(5-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (INT-5)



Step 1: **Synthesis of tert-butyl 3,3-dimethyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (INT-14)**

To a stirred solution of tert-butyl 3,3-dimethyl-4-oxopiperidine-1-carboxylate (3.0 g, 13.20 mmol) in THF (50 mL) was added potassium tert-butoxide (1 M in THF, 15.84 mL, 15.84 mmol) at -78 °C under N_2 atmosphere and stirred for 1 h. To this resulting mixture was added Comins' reagent (6.22 g, 15.84 mmol) dissolved in THF (20 mL) dropwise and the reaction mixture was allowed to stir at room temperature for 3 h under N_2 atmosphere. The reaction mixture was quenched with sat. NH_4Cl at 0 °C and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get the crude compound. The crude compound was purified by Biotage isolera (silica gel 100-200 mesh) and a linear gradient of 0-5% ethyl acetate in hexane as eluent to afford tert-butyl 3,3-dimethyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (**INT-14**). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.67 (d, J = 12.00 Hz, 1H), 4.10 (br s, 2H), 3.40 (s, 2H), 1.50 (s, 9H), 1.17 (s, 6H).

Step 2: **Synthesis of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate**

In a microwave vial, a solution of tert-butyl 3,3-dimethyl-4-(((trifluoromethyl)-sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (500 mg, 1.39 mmol), DIPEA (360 mg, 2.78 mmol) and 3-(1-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-2-yl)piperidine-2,6-dione (618 mg, 1.67 mmol) in DMF (18 mL) and water (2 mL) was purged with N_2 at room temperature over 10 minutes. To this resulting mixture was added $PdCl_2$(dppf) (102 mg, 0.14 mmol) in one lot and the reaction mixture was again purged with N_2 for 10 min. This resulting reaction mixture was subjected to react under microwave irradiation at 80 °C for 1 hr. The reaction mixture was filtered through a pad of celite and washed with ethyl acetate (10 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography using Biotage isolera (silica gel 100-200 mesh) and a linear gradient of 0-10% IPA in DCM as eluents to afford tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-dimethyl-

3,6-dihydropyridine-1(2H)-carboxylate. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 454.4 ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 7.68 (d, J = 7.80 Hz, 1H), 7.41 (s, 1H), 7.32 (dd, J = J = 1.20, 7.80 Hz, 1H), 5.54 (br s, 1H), 5.12 (dd, J = 5.20, 13.20 Hz, 1H), 4.46 (d, J = 17.20 Hz, 1H), 4.33 (d, J = 17.20 Hz, 1H), 4.00 (s, 2H), 3.30 (s, 2H), 2.93-2.88 (m, 1H), 2.63-2.56 (m, 1H), 2.50-2.38 (m, 1H), 2.05-1.98 (m, 1H), 1.45 (s, 9H), 1.02 (s, 6H).

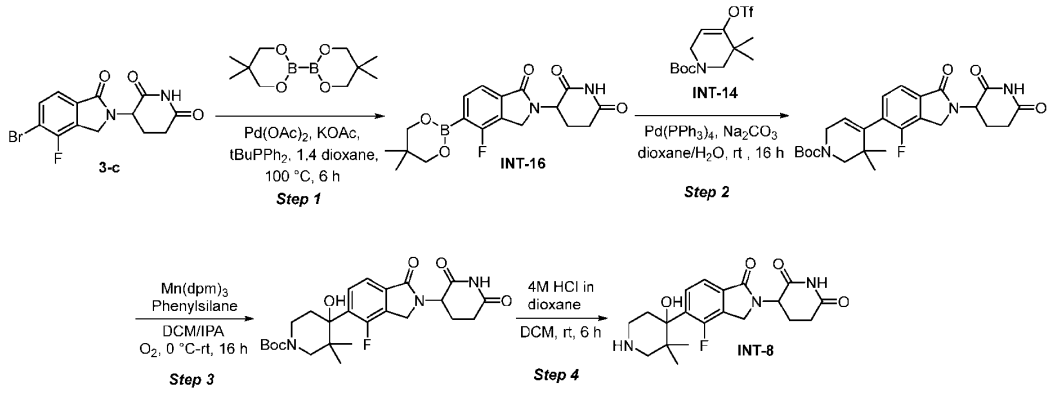
Step 3: **Synthesis of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate**

To a stirred solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (300 mg, 0.66 mmol) in DCM (16 mL) and 2-propanol (4 mL) were added phenyl silane (143 mg, 1.32 mmol) and $Mn(dpm)_3$ (120 mg, 0.19 mmol). The reaction mixture was stirred with O_2 purging at 0 °C for 2 h. The reaction mixture was filtered through a pad of celite and washed with EtOAc (100 mL) and the filtrate was concentrated under reduced pressure. The crude compound was purified by flash column chromatography using Biotage isolera (silica gel 100-200 mesh) and a linear gradient of 0-10% IPA in DCM as eluents to afford tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 472.0, ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 7.71-7.62 (m, 3H), 5.14-5.09 (m, 2H), 4.48-4.28 (m, 2H), 4.00 (br s, 1H), 3.51-3.41 (m, 2H), 3.28-3.06 (m, 2H), 3.00-2.87 (m, 1H), 2.63-2.56 (m, 2H), 2.50-2.38 (m, 1H), 2.05-1.98 (m, 1H), 1.42 (s, 9H), 0.73 (s, 3H), 0.70 (s, 3H).

Step 4: **Synthesis of 3-(5-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (INT-5)**

To a stirred solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (200 mg, 0.424 mmol) in DCM (10 mL) was added 4M HCl in 1,4-dioxane (1 mL, 4.00 mmol) at 0 °C and the reaction mixture was stirred for 3 h. The reaction mixture was concentrated under reduced pressure, triturated with MTBE (2 × 10 mL), and dried under vacuum to afford 3-(5-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione **(INT-5)**. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 372.1, ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 8.98 (br s, 1H), 8.33 (br s, 1H), 7.73-7.61 (m, 3H), 5.56 (s, 1H), 5.13 (dd, J = 4.80, 13.40 Hz, 1H), 4.51-4.33 (m, 2H), 3.27-3.15 (m, 3H), 2.92-2.80 (m, 2H), 2.72-2.56 (m, 2H), 2.48-2.42 (m, 1H), 2.03-2.00 (m, 1H), 1.70 (d, J = 5.20 Hz, 1H), 0.94 (s, 3H), 0.76 (s, 3H).

Example 15: Synthesis of 3-(4-fluoro-5-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (INT-8)



Step 1: **Synthesis of 3-(5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (INT-16)**

To a stirred solution of 3-(5-bromo-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (10 g, 29.3 mmol, 1 equiv.) and 5,5,5',5'-tetramethyl-2,2'-bi(1,3,2-dioxaborinane) (13.24 g, 58.6 mmol, 2 equiv.) in dioxane (100 mL) were added potassium acetate (8.63 g, 88 mmol, 3 equiv.), tert-butyldiphenylphosphine (1.421 g, 5.86 mmol, 0.2 equiv.). The mixture was degassed with N_2 for 10 min. Palladium(II) acetate (0.658 g, 2.93 mmol, 0.1 equiv.) was then added at room temperature. The reaction mixture was stirred at 100 °C for 6 h. Upon completion, the reaction mixture was poured into ice-cold water (100 mL). The resulting solid was filtered, washed with water, and dried to afford 3-(5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**INT-16**) without further purification. LCMS: m/z: MM-ES+APCI, positive $[M-H]^+$ 305.0 (corresponding boronic acid); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.16-10.69 (m, 1H), 7.83-7.72 (m, 1H), 7.56-7.42 (m, 1H), 5.11 (dd, J = 5.0, 13.1 Hz, 1H), 4.61-4.18 (m, 2H), 3.70 (s, 4H), 3.01-2.78 (m, 1H), 2.60 (td, J = 2.1, 15.2 Hz, 1H), 2.48-2.38 (m, 1H), 2.07-1.95 (m, 1H), 0.95 (s, 6H)

Step 2: **Synthesis of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate**

To a stirred solution of 3-(5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**INT-16**, 5 g, 13.36 mmol, 1 equiv.) and tert-butyl 3,3-dimethyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (**INT-14**, 5.76 g, 16.04 mmol, 1.2 equiv.) in dioxane (60 mL) and water (6.0 mL) at room temperature, was added sodium carbonate (1.56 g, 14.70 mmol, 1.1 equiv.) and the mixture was degassed with nitrogen for 10 min. Tetrakis(triphenylphosphine)palladium(0) (1.54 g, 1.34 mmol, 0.1 equiv.) was then added, and the reaction mixture was stirred at room temperature for 16 h. The progress of the reaction was monitored by TLC and LC-MS. Upon completion, the reaction mixture was filtered through a celite pad, washed with EtOAc, and concentrated under reduced pressure. The crude compound was washed with hexane and

dried under vacuum to yield a solid. The obtained solid was dissolved in 10% MeOH in DCM (60 mL) and treated with SiliaMetS DMT (3 g). The mixture was stirred for 1 h. The solution was then filtered, and the filtrate was concentrated under reduced pressure to afford tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate. LCMS: m/z: MM-ES+APCI, positive $[M-H]^+$ 470.1; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.12-10.86 (m, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.32 (t, J = 6.9 Hz, 1H), 5.62-5.50 (m, 1H), 5.19-5.07 (m, 1H), 4.63-4.50 (m, 1H), 4.44-4.35 (m, 1H), 4.00 (s, 2H), 3.39-3.35 (m, 2H), 3.00-2.85 (m, 1H), 2.65-2.56 (m, 1H), 2.47-2.37 (m, 1H), 2.08-1.95 (m, 1H), 1.45 (s, 9H), 0.97 (s, 6H).

Step 3: **Synthesis of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate**

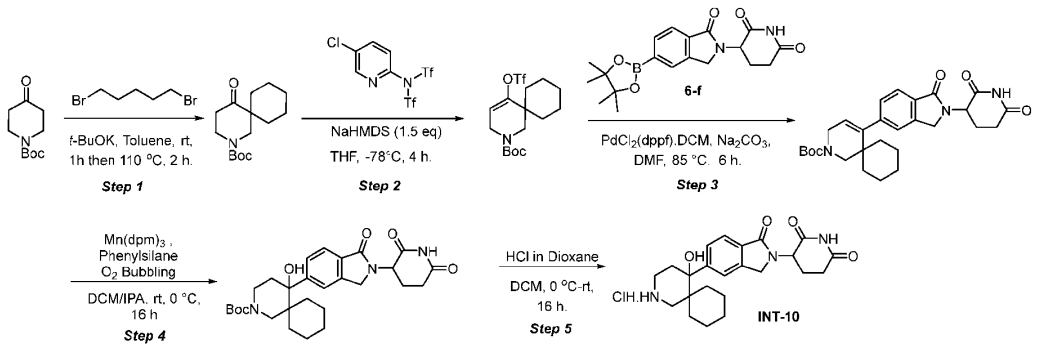
To a stirred solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (3g, 6.36 mmol, 1 equiv.) in DCM (50 mL) and 2-propanol (15 mL) at 0 °C, phenyl silane (1.57 mL, 12.72 mmol, 2.00 equiv.) was added, followed by $Mn(dpm)_3$ (0.58 g, 0.95 mmol, 0.15 equiv.) under continuous bubbling of oxygen. The reaction mixture was stirred at room temperature for 16 h. Upon completion, the solvent was concentrated under reduced pressure to afford the crude compound and purified by flash chromatography on Biotage Isolera C18 (120 g) using 0.1% formic acid in water and acetonitrile. The pure fractions concentrated and redissolved in 10% MeOH in DCM (10 mL), and SiliaMetS DMT (1 g) was added. The mixture was stirred for 1 h. The solution was then filtered, and the filtrate was concentrated under reduced pressure to afford tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate.LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 490.4; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.80-12.60 (m, 1H), 11.01 (s, 1H), 7.94-7.84 (m, 1H), 7.59 (d, J = 8.1 Hz, 1H), 5.41 (d, J = 6.5 Hz, 1H), 5.18-5.07 (m, 1H), 4.54 (d, J = 17.5 Hz, 1H), 4.41-4.31 (m, 1H), 4.13-4.07 (m, 1H), 3.54-3.37 (m, 1H), 3.27-3.20 (m, 1H), 3.15-3.01 (m, 1H), 2.98-2.91 (m, 1H), 2.88-2.78 (m, 1H), 2.67-2.54 (m, 1H), 2.48-2.38 (m, 1H), 2.04-2.00 (m, 1H), 1.70-1.50 (m, 1H), 1.42 (s, 9H), 0.82 (s, 3H), 0.70 (d, J = 7.3 Hz, 3H).

Step 4: **Synthesis of 3-(4-fluoro-5-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (INT-8)**

To a stirred solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (2.5 g, 5.11 mmol, 1 equiv.) in dichloromethane (30 mL) at 10 °C under a nitrogen atmosphere was added 4 M HCl in dioxane (6.38 mL, 25.5 mmol, 5.0 equiv.). The resulting reaction mixture was stirred at room temperature for 6 h. The reaction was concentrated under reduced pressure to afford the crude compound. The crude compound was washed with hexane to afford 3-(4-fluoro-5-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**INT-8**). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 390.4; ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ

(ppm): ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 9.28 (d, J = 11.4 Hz, 1H), 8.62-8.41 (m, 1H), 7.89 (t, J = 6.8 Hz, 1H), 7.62 (d, J = 7.9 Hz, 1H), 5.83 (br. s, 1H), 5.13 (ddd, J = 2.5, 5.0, 13.2 Hz, 1H), 4.60-4.51 (m, 1H), 4.44-4.34 (m, 1H), 3.58 (s, 2H), 3.28-3.01 (m, 2H), 2.95-2.86 (m, 2H), 2.66-2.56 (m, 1H), 2.48-2.37 (m, 1H), 2.07-1.97 (m, 1H), 1.90-1.79 (m, 1H), 1.04 (s, 3H), 0.76 (d, J = 7.3 Hz, 3H).

Example 16: Synthesis of (3-(5-(5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride) (INT-10):



Step 1: **Synthesis of tert-butyl 5-oxo-2-azaspiro[5.5]undecane-2-carboxylate**

To a stirred solution of tert-butyl 4-oxopiperidine-1-carboxylate (30 g, 151 mmol, 1.0 equiv.) in toluene (150 mL) was added 1,5-dibromopentane (20.51 mL, 151 mmol, 1.0 equiv.) and potassium tert-butoxide (37.2 g, 331 mmol, 2.19 equiv.) in portions under a nitrogen atmosphere at 25 °C. The reaction mixture was stirred for 1 h at 25 °C and then heated to 110 °C and stirred for 2 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was cooled to room temperature and quenched with ice-cold saturated ammonium chloride solution (100 mL). The mixture was then extracted with ethyl acetate (2 × 200 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to obtain the crude product. The crude compound was purified by silica gel column chromatography (230-400 mesh) using a gradient of 5 to 10% ethyl acetate in hexane as the eluent to afford tert-butyl 5-oxo-2-azaspiro[5.5]undecane-2-carboxylate.^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 2H), 3.55 (s, 2H), 2.49 (t, J = 6.4 Hz, 2H), 1.81-1.67 (m, 2H), 1.59-1.39 (m, 17H).

Step 2: **Synthesis of tert-butyl 5-(((trifluoromethyl)sulfonyl)oxy)-2-azaspiro[5.5]undec-4-ene-2-carboxylate**

To a stirred solution of tert-butyl 5-oxo-2-azaspiro[5.5]undecane-2-carboxylate (9 g, 33.7 mmol, 1.0 equiv.) in tetrahydrofuran (100 mL) was added NaHMDS (50.5 mL of a 1.0 M solution in THF, 50.5 mmol, 1.49 equiv.) at -78 °C. The mixture was stirred for 1 h at -78 °C. Comins' reagent (17.18 g, 43.8 mmol, 1.29 equiv.) was added, and the reaction mixture was stirred for 4 h. Upon completion, the reaction mixture was quenched with saturated ammonium chloride solution (150 mL) and extracted with ethyl

acetate (2 × 200 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to obtain the crude product. The crude compound was purified by Biotage Isolera chromatography using silica gel and a gradient of 1 to 5% ethyl acetate in hexane as the eluent. The pure fractions were concentrated under reduced pressure to afford tert-butyl 5-(((trifluoromethyl)sulfonyl)oxy)-2-azaspiro[5.5]undec-4-ene-2-carboxylate. LCMS: m/z: MM-ES+APCI, positive $[M-56]^+$ 344.0; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 5.97-5.76 (m, 1H), 4.02 (d, J = 3.3 Hz, 2H), 3.58 (s, 2H), 1.75-1.55 (m, 3H), 1.53-1.32 (m, 16H).

Step 3: **Synthesis of tert-butyl 5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate**

To a stirred solution of 3-(1-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-2-yl)piperidine-2,6-dione (6 g, 16.21 mmol, 1.0 equiv.) and tert-butyl 5-(((trifluoromethyl)sulfonyl)oxy)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (8.74 g, 21.88 mmol, 1.34 equiv.) in dimethylformamide (100 mL), potassium carbonate (6.72 g, 48.6 mmol, 2.99 equiv.) was added at room temperature. The reaction mixture was degassed with argon for 15 min. $PdCl_2$(dppf)-CH_2Cl_2 adduct (1.32 g, 1.621 mmol, 0.1 equiv.) was added, and the mixture was stirred at 85 °C for 6 h. Upon completion, the reaction mixture was cooled to room temperature and filtered through a celite bed. The filtrate was concentrated under reduced pressure to obtain the crude product which was triturated with a mixture of 10% DCM in hexane, filtered, and dried to afford tert-butyl 5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 494.4; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.05 (br s, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.23 (d, J = 12.6 Hz, 1H), 5.55-5.36 (m, 1H), 5.26 (dd, J = 5.0, 13.3 Hz, 1H), 4.59-4.27 (m, 2H), 4.15-3.87 (m, 2H), 3.63 (d, J = 6.8 Hz, 2H), 3.12-2.77 (m, 3H), 2.55-2.06 (m, 2H), 1.78-1.27 (m, 19H).

Step 4: **Synthesis of tert-butyl 5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-5-hydroxy-2-azaspiro[5.5]undecane-2-carboxylate**

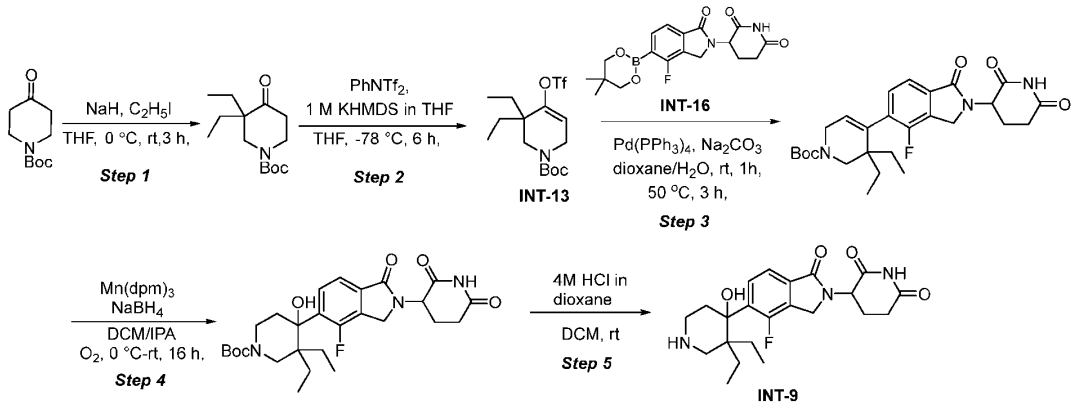
To a stirred solution of tert-butyl 5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (3.0 g, 6.08 mmol) in dichloromethane (30 mL) and 2-propanol (30 mL) was added $Mn(dpm)_3$ (1.10 g, 1.82 mmol, 0.30 equiv.) and phenyl silane (1.97 g, 18.23 mmol, 3.0 equiv.) at 0 °C. Oxygen was bubbled continuously through the reaction mixture for 16h at RT. Upon completion, the reaction mixture was cooled to room temperature, filtered through a celite bed, and the filtrate was concentrated to the crude compound which was purified by reversed-phase chromatography using a Combi Flash C18 column (330 g) with a gradient of 0.1% formic acid in water and acetonitrile at a flow rate of 30 mL/min. The pure fractions were concentrated under reduced pressure to afford tert-butyl 5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-5-hydroxy-2-azaspiro[5.5]undecane-2-carboxylate. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 512.4; ^{1}H-NMR (400 MHz, DMSO-d_6) δ

10.99 (s, 1H), 7.82-7.50 (m, 3H), 5.28-4.93 (m, 2H), 4.60-4.22 (m, 2H), 4.21-3.82 (m, 2H), 3.16-2.85 (m, 3H), 2.66-2.55 (m, 2H), 2.46-2.37 (m, 1H), 2.06-1.98 (m, 1H), 1.79-1.52 (m, 3H), 1.51-1.22 (m, 14H), 0.97-0.52 (m, 3H).

Step 5: **Synthesis of 3-(5-(5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (INT-10)**

To a stirred solution of tert-butyl 5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-5-hydroxy-2-azaspiro[5.5]undecane-2-carboxylate (3.1 g, 6.06 mmol) in DCM (30 mL) at 0 °C, was added 4 M HCl in dioxane (15.15 mL, 60.6 mmol, 10 equiv.) and stirred the reaction mixture at room temperature for 16 h. The progress of the reaction was monitored by TLC and LC-MS. Upon completion, the reaction mixture is concentrated under reduced pressure to get a crude compound. The crude compound was triturated with ethyl acetate and then lyophilized compound to afford 3-(5-(5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride **(INT-10)**. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 412.2; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 9.47 (d, J = 10.5 Hz, 1H), 8.70 (d, J = 9.8 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.67 (d, J = 6.8 Hz, 1H), 7.63-7.56 (m, 1H), 5.64-5.39 (m, 1H), 5.13 (dd, J = 5.0, 13.3 Hz, 1H), 4.64-4.19 (m, 2H), 3.45 (d, J = 12.8 Hz, 1H), 3.28-2.71 (m, 5H), 2.62 (d, J = 16.8 Hz, 1H), 2.47-2.33 (m, 1H), 2.24-1.96 (m, 2H), 1.85-1.62 (m, 2H), 1.55-1.10 (m, 5H), 1.02-0.61 (m, 3H).

Example 17: Synthesis of 3-(5-(3,3-diethyl-4-hydroxypiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (INT-9)



Step 1: **Synthesis of tert-butyl 3,3-diethyl-4-oxopiperidine-1-carboxylate**

To a stirred solution of tert-butyl 4-oxopiperidine-1-carboxylate (25 g, 125 mmol, 1 equiv.) in THF (500 mL) 60% NaH in mineral oil (11.04 g, 276 mmol, 2.2 equiv.) was added at 5 °C. The reaction mixture was stirred at the same temperature for 30 min, followed by the addition of iodoethane (25.3 mL, 314 mmol, 2.5 equiv.) at 5 °C. The mixture was allowed to reach ambient temperature and stirred for 5 h.

Upon completion, the reaction mixture was quenched with water (1000 mL) and extracted with ethyl acetate (3 × 500 mL). The combined organic layers were washed with water (250 mL) and brine solution (250 mL), then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using 3-4% ethyl acetate in hexane, resulting in pure tert-butyl 3,3-diethyl-4-oxopiperidine-1-carboxylate. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.71 (t, J = 6.1 Hz, 2H), 3.51 (s, 2H), 2.45 (t, J = 6.4 Hz, 2H), 1.66 (d, J = 5.1 Hz, 1H), 1.59-1.45 (m, 12H), 0.81 (t, J = 7.6 Hz, 6H).

Step 2: **Synthesis of tert-butyl 3,3-diethyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (INT-13)**

To a stirred solution of tert-butyl 3,3-diethyl-4-oxopiperidine-1-carboxylate (25 g, 98 mmol, 1 equiv.) in THF (250 mL) 1 M potassium hexamethyldisilazide (147 mL, 147 mmol, 1.5 equiv.) was added at -78 °C and stirred at the same temperature for 30 min. Subsequently, N-(5-chloropyridin-2-yl)-1,1,1-trifluoro-N-((trifluoromethyl)sulfonyl)methanesulfonamide (50.0 g, 127 mmol) in THF (125 mL) was added and stirred at -78 °C for 2 h. The progress of the reaction was monitored by TLC and LCMS. Upon completion, the reaction mixture was quenched with saturated NH_4Cl solution (30 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude product. The crude product was purified by flash column chromatography using 2% ethyl acetate in hexane. The pure fractions obtained were concentrated and dried under reduced pressure to afford tert-butyl 3,3-diethyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 5.96 (t, J = 3.3 Hz, 1H), 4.01 (s, 2H), 3.43 (s, 2H), 1.53-1.31 (m, 13H), 0.85 (t, J = 7.4 Hz, 6H).

Step 3: **Synthesis of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-3,3-diethyl-3,6-dihydropyridine-1(2H)-carboxylate**

To a stirred solution of 3-(5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**INT-16**, 5.0 g, 10.69 mmol, 1 equiv.) and tert-butyl 3,3-diethyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (**INT-13**, 4.35 g, 11.22 mmol, 1.05 equiv.) in 1,4-dioxane (25 mL) and water (2.5 mL) were added sodium carbonate (1.246 g, 11.76 mmol, 1.1 equiv.) and tetrakis(triphenylphosphine)palladium(0) (1.235 g, 1.069 mmol, 0.1 equiv.) at room temperature. The mixture was degassed with N_2 for 10 min and stirred at RT for 16h. The reaction mixture was filtered through a Celite pad, washed with ethyl acetate (100 mL), and concentrated under vacuum to afford the crude compound. The crude product (8.5 g) was purified by reversed-phase C18 chromatography (330 g) using mobile phase A: 0.1% FA in H_2O and mobile phase B: ACN, with a flow rate of 30 mL/min. Pure fractions were concentrated under reduced pressure to obtain the desired product, tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-3,3-diethyl-3,6-dihydropyridine-

1(2H)-carboxylate. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 500.4. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.20-10.72 (m, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.39-7.28 (m, 1H), 5.73 (s, 1H), 5.13 (dd, J = 5.1, 13.2 Hz, 1H), 4.58 (d, J = 17.5 Hz, 1H), 4.44-4.32 (m, 1H), 3.96 (d, J = 6.8 Hz, 2H), 3.43 (s, 2H), 2.99-2.84 (m, 1H), 2.61 (d, J = 16.7 Hz, 1H), 2.49-2.36 (m, 1H), 2.08-1.96 (m, 1H), 1.56-1.32 (m, 12H), 1.50 (s, 1H), 0.79 s, 6H).

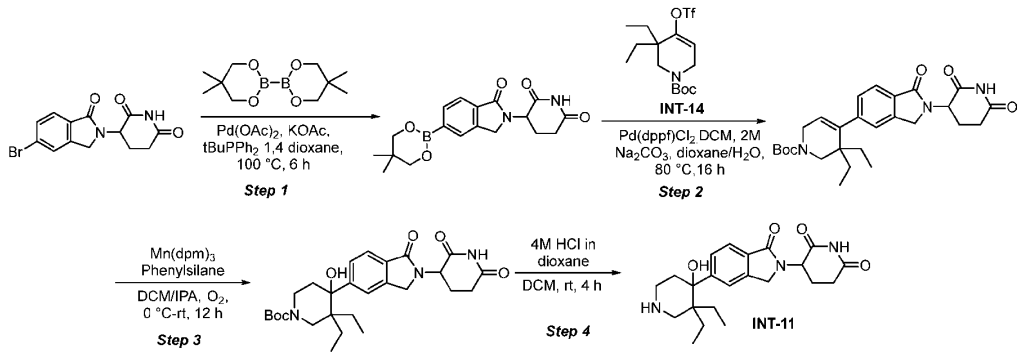
Step 4: **Synthesis of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidine-1-carboxylate**

To a stirred solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-3,3-diethyl-3,6-dihydropyridine-1(2H)-carboxylate (2.0 g, 3.72 mmol, 1 equiv.) in 2-propanol (6.00 mL) and DCM (14.0 mL), $Mn(dpm)_3$ (0.45 g, 0.745 mmol, 0.2 equiv.) and phenyl silane (1.007 g, 9.31 mmol, 2.5 equiv.) were added. The reaction was stirred under continuous bubbling of oxygen for 2 h and then allowed to stir at 25 °C for 16 h in the presence of oxygen. The reaction mixture was filtered through celite, and the celite bed was washed with ethyl acetate (100 mL). The mixture was then concentrated under reduced pressure and purified by reverse phase chromatography using a C18 330 g SNAP cartridge using mobile phase A: 0.1% FA in H_2O and mobile phase B: ACN, with a flow rate of 30 mL/min. Pure fractions were concentrated under reduced pressure to obtain the desired product, tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidine-1-carboxylate (). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 518.4. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.08-10.91 (m, 1H), 8.07-7.90 (m, 1H), 7.57 (d, J = 8.1 Hz, 1H), 5.43 (d, J = 8.7 Hz, 1H), 5.11 (td, J = 2.1, 13.3 Hz, 1H), 4.65-4.26 (m, 2H), 4.02-3.78 (m, 1H), 3.74-3.54 (m, 1H), 2.99-2.82 (m, 2H), 2.71-2.57 (m, 2H), 2.44 (d, J = 12.1 Hz, 1H), 2.07-1.96 (m, 1H), 1.62-1.50 (m, 4H), 1.43 (s, 9H), 1.34-1.22 (m, 2H), 1.10-1.02 (m, 3H), 0.87 (t, J = 7.4 Hz, 3H).

Step 5: **Synthesis of 3-(5-(3,3-diethyl-4-hydroxypiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (INT-9)**

To a stirred solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidine-1-carboxylate (1.2 g, 2.318 mmol, 1 equiv.) in DCM (40 mL), was added 4.0 M HCl in dioxane (2.90 mL, 11.59 mmol, 5.0 equiv.). The reaction mixture was then stirred at 25 °C for 2 h. The progress of the reaction was monitored by LCMS, After completion of the reaction as confirmed by LCMS, the solvent was then evaporated to afford 3-(5-(3,3-diethyl-4-hydroxypiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione **(INT-9)**. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 418.3. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 9.04 (d, J = 9.7 Hz, 1H), 8.44-8.24 (m, 1H), 8.07-7.91 (m, 1H), 7.62 (d, J = 8.1 Hz, 1H), 5.88 (d, J = 6.4 Hz, 1H), 5.13 (ddd, J = 3.3, 4.9, 13.3 Hz, 1H), 4.62-4.32 (m, 2H), 3.27-2.75 (m, 6H), 2.61 (d, J = 17.2 Hz, 1H), 2.47-2.39 (m, 1H), 2.09-1.92 (m, 2H), 1.34-1.26 (m, 2H), 1.16-1.06 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H), 0.79-0.69 (m, 3H).

Example 18: Synthesis of 3-(5-(3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl) piperidine-2,6-dione (INT-11)



Step 1: **Synthesis of 3-(5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-oxoisoindolin-2-yl) piperidine-2,6-dione**

To a stirred solution of 3-(5-bromo-1-oxoisoindolin-2-yl)piperidine-2,6-dione (10 g, 30.9 mmol, 1 equiv.) and 5,5,5',5'-tetramethyl-2,2'-bi(1,3,2-dioxaborinane) (13.98 g, 61.9 mmol, 2 equiv.) in dioxane (100 mL) was added potassium acetate (9.11 g, 93 mmol, 3 equiv.) and the mixture was degassed with nitrogen for 5 min. $Pd(OAc)_2$ (0.69 g, 3.09 mmol, 0.1 equiv.) and $tBuPPh_2$ (1.49 g, 6.19 mmol, 0.2 equiv.) were added at room temperature. The reaction mixture was stirred for 6 h at 100 °C. Upon completion of the reaction, the reaction mixture was concentrated under reduced pressure, quenched with ice-cold water (100 mL), and stirred for 10 min. The resulting solid was filtered and dried to yield the crude product, which was then triturated with MTBE (100 mL), filtered, and dried to afford 3-(5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 289.0 (Corresponding boronic acid mass observed); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.04-10.91 (m, 1H), 7.91 (s, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.74-7.65 (m, 1H), 5.17-5.08 (m, 1H), 4.50-4.42 (m, 1H), 4.38-4.28 (m, 1H), 3.80 (s, 4H), 2.98-2.83 (m, 1H), 2.61 (d, J = 16.8 Hz, 1H), 2.40 (dd, J = 4.5, 13.1 Hz, 1H), 2.06-1.96 (m, 1H), 0.98 (s, 6H), 0.75 (s, 1H).

Step 2: **Synthesis of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-3,6-dihydropyridine-1(2H)-carboxylate**

To a stirred solution of 3-(5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (5 g, 14.04 mmol, 1 equiv.) and tert-butyl 3,3-diethyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (**INT-14,** 6.53 g, 16.85 mmol, 1.2 equiv.) in dioxane (50 mL) was added 2 M sodium carbonate (7.72 mL, 15.44 mmol, 1.1 equiv.) at room temperature. The mixture was degassed with nitrogen for 5 min. [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1.146 g, 1.404

mmol, 0.1 equiv.) was then added, and the reaction mixture was stirred at 80 °C for 16 h. Upon completion of the reaction, the reaction mixture was concentrated under reduced pressure to obtain the crude product. The crude compound was triturated with ice-cold water (100 mL), and the resulting solid was filtered, washed with MTBE (100 mL), and dried to afford tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-3,6-dihydropyridine-1(2H)-carboxylate. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 482.5; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.07-10.84 (m, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.50-7.31 (m, 2H), 5.84-5.72 (m, 1H), 5.12 (dd, J = 5.2, 13.3 Hz, 1H), 4.52-4.41 (m, 1H), 4.38-4.28 (m, 1H), 3.97 (br. s, 2H), 3.41 (br. s, 2H), 2.99-2.86 (m, 1H), 2.61 (dd, J = 1.9, 15.4 Hz, 1H), 2.46-2.36 (m, 1H), 2.07-1.95 (m, 1H), 1.61-1.41 (m, 13H), 0.78 (t, J = 7.3 Hz, 6H)

Step 3: **Synthesis of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidine-1-carboxylate**

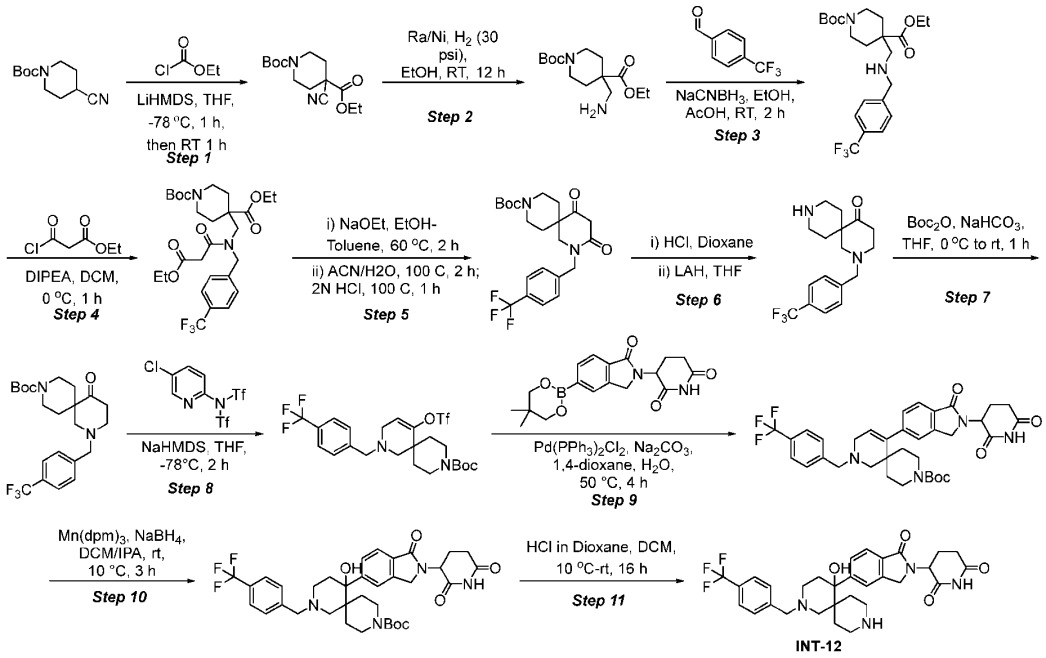
To a stirred solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-3,6-dihydropyridine-1(2H)-carboxylate (3.00 g, 4.98 mmol, 1 equiv.) in 2-propanol (30 mL) and dichloromethane (70 mL) was added $Mn(dpm)_3$ (0.452 g, 0.748 mmol, 0.15 equiv.) followed by phenyl silane (1.228 mL, 9.97 mmol, 2 equiv.) under an oxygen atmosphere at 0 °C. The reaction mixture was stirred at room temperature for 12 h. Upon completion, the reaction mixture was concentrated under reduced pressure. The crude compound was purified by column chromatography using a Biotage Isolera C18 column (350 g) with a gradient of 0.1% formic acid in water and acetonitrile, at a flow rate of 35 mL/min. Pure fractions were combined and concentrated under reduced pressure to afford tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidine-1-carboxylate . LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 500.4; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 7.76-7.67 (m, 2H), 7.67-7.62 (m, 1H), 5.16-5.06 (m, 2H), 4.48-4.39 (m, 1H), 4.35-4.27 (m, 1H), 4.04 (q, J = 7.1 Hz, 1H), 2.98-2.86 (m, 1H), 2.66-2.57 (m, 2H), 2.44-2.37 (m, 1H), 2.06-2.00 (m, 1H), 1.69-1.55 (m, 1H), 1.53-1.47 (m, 1H), 1.47-1.34 (m, 1H), 1.46-1.34 (m, 14H), 0.82-0.63 (m, 3H), 0.52-0.43(m, 3H).

Step 4: **Synthesis of 3-(5-(3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl) piperidine-2,6-dione (INT-11)**

To a stirred solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidine-1-carboxylate (1.9 g, 3.80 mmol, 1 equiv.) in DCM (20 mL) was added 4M HCl in dioxane (4.75 mL, 19.01 mmol, 5 equiv.) at 0 °C under nitrogen atmosphere and the stirred for 3 h at room temperature. Upon completion of the reaction, the reaction mixture was concentrated under reduced pressure and triturated with hexane (100 mL). The resulting solid was filtered and dried to afford 3-(5-(3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**INT-11**). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 400.3; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 9.21 (dd, J = 1.7, 9.5 Hz, 1H), 8.57-8.31 (m, 1H), 7.75-7.63 (m, 3H), 5.66-5.49 (m, 1H), 5.12 (dd, J = 5.0, 13.3 Hz,

1H), 4.53-4.27 (m, 2H), 3.26-3.03 (m, 2H), 3.01-2.74 (m, 2H), 2.62 (d, J = 16.5 Hz, 1H), 2.44-2.36 (m, 1H), 2.07-1.97 (m, 1H), 1.93-1.82 (m, 1H), 1.72-1.42 (m, 2H), 1.33-1.14 (m, 2H), 0.91-0.73 (m, 2H), 0.68 (t, J = 7.3 Hz, 3H), 0.48 (dt, J = 2.9, 7.5 Hz, 3H).

Example 19: Synthesis of 3-(5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (INT-12)



Step 1: **Synthesis of 1-(tert-butyl) 4- ethyl 4-cyanopiperidine-1,4-dicarboxylate**

To the stirred solution of tert-butyl 4-cyanopiperidine-1-carboxylate (25 g, 119 mmol) in THF (350 mL) was added LiHMDS (190 mL, 190 mmol) at -78 °C and the reaction was stirred at -78 °C for 1 h. To this was added ethyl chloroformate (18.11 mL, 190 mmol) dropwise at -78 °C over 10 mins and the reaction mixture was allowed to stir at 25 °C for 1 h. The reaction mixture was cooled to 0 °C, reaction mixture was quenched with saturated $NaHCO_3$ and extracted with ethyl acetate (2 × 200 mL). The combined organic extract was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure (bath temperature: 40 °C) to afford crude. The crude product was purified by flash column chromatography (silica-gel, 100-200 mesh) using ethyl acetate in hexane (5-7%) as an eluent to obtain desired product 1-(tert-butyl) 4-ethyl 4-cyanopiperidine-1,4-dicarboxylate. LCMS: m/z M-ES+APCI, Positive $[M+H]^+$ 283.2. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 4.31 (q, J = 7.20 Hz, 2H), 4.16-4.10 (m, 2H), 3.14 (s, 2H), 2.09-2.06 (m, 2H), 2.01-1.94 (m, 2H), 1.48 (s, 9H), 1.35 (t, J = 6.80 Hz, 3H).

Step 2: **Synthesis of 1-(tert-butyl) 4-ethyl 4-(aminomethyl)piperidine-1,4-dicarboxylate**

To a solution of 1-(tert-butyl) 4-ethyl 4-cyanopiperidine-1,4-dicarboxylate (5 g, 17.71 mmol) in ethanol (50 mL) at 25 °C was added Raney nickel (4.66 g, 53.1 mmol). The reaction mixture was bubbled with nitrogen for 5 min and then was stirred under hydrogen pressure (30 psi) at 25 °C for 12 h. The reaction mixture was filtered through celite, washed with methanol (50 mL). The filtrate was removed under vacuum and then purified via reverse phase chromatography using a 330 g C18 flash cartridge and gradient method of 50 to 60% acetonitrile/0.1% formic acid in water/0.1% formic acid. The desired fractions were concentrated under vacuum and dried under vacuum to afford 1-(tert-butyl) 4-ethyl 4-(aminomethyl)piperidine-1,4-dicarboxylate. LCMS: m/z M-ES+APCI, Positive $[M+H]^+$ 287.4.

Step 3: **Synthesis of 1-(tert-butyl) 4-ethyl 4-(((4-(trifluoromethyl)benzyl)-amino)methyl)piperidine-1,4-dicarboxylate**

To the solution of 1-(tert-butyl) 4-ethyl 4-(aminomethyl)piperidine-1,4-dicarboxylate (18 g, 62.9 mmol) and 4-(trifluoromethyl)benzaldehyde (12.04 g, 69.1 mmol) in ethanol (5 mL) was added $NaCNBH_4$ (7.90 g, 126 mmol) followed by acetic acid (1.8 mL, 31.4 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The excess solvent was evaporated under vacuum, and the resulting residue was quenched with sat. $NaHCO_3$ solution (250 mL). The product was extracted with DCM (2 × 200 mL). The combined organic extract was washed with brine (200 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to get crude product. The crude product was purified by flash chromatography using Biotage Isolera (Silica gel 100-200 mesh) and a linear gradient of 0-20% ethyl acetate in hexane as eluent to afford 1-(tert-butyl) 4-ethyl 4-(((4-(trifluoromethyl)benzyl)amino)methyl)piperidine-1,4-dicarboxylate. LCMS: m/z M-ES+APCI, Positive $[M+H]^+$ 445.5. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.70-7.65 (m, 2H), 7.53-7.50 (m, 2H), 4.60 (d, J = 6.00 Hz, 1H), 4.09 (q, J = 6.80 Hz, 2H), 3.74-3.63 (m, 4H), 2.87 (s, 1H), 2.57 (s, 1H), 1.93 (d, J = 13.60 Hz, 2H), 1.35-1.17 (m, 2H), 1.35-1.17 (m, 11H), 1.14 (t, J = 1.60 Hz, 3H).

Step 4: **Synthesis of 4-((3-ethoxy-3-oxo-N-(4-(trifluoromethyl)benzyl)propanamido)methyl)-piperidine-1,4-dicarboxylate**

To the stirred solution of ethyl 3-chloro-3-oxopropanoate (13.55 g, 90 mmol) in DCM (300 mL) was added DIPEA (5.52 g, 42.7 mmol) at 0 °C followed by 1-(tert-butyl) 4-ethyl 4-(((4-(trifluoromethyl)benzyl)amino)methyl)piperidine-1,4-dicarboxylate (225 mL, 45.0 mmol) at 0 °C. The reaction mixture was stirred for 1 h. The reaction mixture was diluted with DCM before quenching with 1 M HCl (100 mL). The organic layers were separated, and aqueous layer was further extracted with DCM twice. The combined organic layers were then washed with brine and dried over anhydrous Na2SO4. The crude material was purified by flash column chromatography (silica-gel, 100-200 mesh) using ethyl acetate in hexane (20-25%) as an eluent to obtain 1-(tert-butyl) 4-ethyl 4-((3-ethoxy-3-oxo-N-(4-

(trifluoromethyl)benzyl)propanamido)-methyl)piperidine-1,4-dicarboxylate. LCMS: m/z M-ES+APCI, Positive $[M+H]^+$ 559.4. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.67-7.60 (m, 2H), 7.26-7.24 (m, 1H), 4.60 (s, 1H), 4.21-4.17 (m, 4H), 3.98 (d, J = 13.60 Hz, 2H), 3.63-3.58 (m, 2H), 3.41-3.38 (m, 2H), 2.88-2.82 (m, 2H), 2.17-2.07 (m, 2H), 1.49-1.46 (m, 11H), 1.33-1.29 (m, 7H).

Step 5: **Synthesis of 9-(tert-butyl) 4-ethyl tert-butyl 3,5-dioxo-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecane-9-carboxylate**

To a stirred solution of 1-(tert-butyl) 4-ethyl 4-((3-ethoxy-3-oxo-N-(4-(trifluoromethyl)-benzyl)propanamido)methyl)piperidine-1,4-dicarboxylate (24 g, 43.0 mmol) in toluene (120 mL) was added sodium ethoxide (4.39 g, 64.4 mmol) dissolved in EtOH (120 mL) at room temperature. The reaction mixture was stirred at 60 °C for 2 h. The reaction mixture was cooled, and the solvent was evaporated under vacuum. To the crude residue was added acetonitrile (56 mL) and water (6 mL) at room temperature and then heated at 100 °C for 1 h. To this resulting mixture was added HCl (21.48 mL, 43.0 mmol) at room temperature and reaction mixture was heated at 100 °C for 5 h. The reaction mixture solvent was concentrated under vacuum, and the resulting residue was dissolved in DCM (150 mL) and filtered. The filtrate was concentrated under vacuum to get tert-butyl 3,5-dioxo-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecane-9-carboxylate. LCMS: m/z M-ES+APCI, Negative $[M-H]^-$ 439.2.

Step 6: **Synthesis of 2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecan-5-one**

To a stirred solution of tert-butyl 3,5-dioxo-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecane-9-carboxylate (10 g, 22.70 mmol) in DCM (100 mL) was added 4 M HCl in dioxane (56.8 mL, 227 mmol) and the reaction mixture was stirred at room temperature for 1 h. After completion of the reaction, solvent was removed by vacuum. The crude material was dissolved in THF (45 mL) and to this was added LAH (45.4 mL, 45.4 mmol) at 0 °C. After complete addition, and once vigorous hydrogen evolution was ceased, the solution was heated to 60 °C for 1 h. The reaction was cooled to 0 °C and diluted with MTBE, and to this was added 1 mL of water, followed by 1 mL of 15% NaOH, followed by 4 mL of water. The solution was stirred for 15 minutes and $NaSO_4$ was added. The inorganic salts were removed by filtration and the filtrate was concentrated to afford 2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecan-5-one. LCMS: m/z M-ES+APCI, Positive $[M+H]^+$ 327.7.

Step 7: **Synthesis of tert-butyl 5-oxo-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecane-9-carboxylate**

To a stirred solution of 2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecan-5-one (7.5 g, 22.98 mmol) in THF (70 mL) was added sodium bicarbonate (3.86 g, 46.0 mmol) at 0 °C and stirred for 30 minutes. To this reaction mixture was added Boc_2O (5.87 mL, 25.3 mmol) in water (20 mL) reaction

mixture was allowed to stir at room temperature for 1 h. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by flash chromatography using Biotage Isolera (Silica gel 100-200 mesh) and a linear gradient of 0-20% ethyl acetate in hexane as eluent to afford tert-butyl 5-oxo-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecane-9-carboxylate. LCMS: m/z M-ES+APCI, Positive $[M+H]^+$ 427.9. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.73 (d, J = 8.00 Hz, 2H), 7.61 (d, J = 8.00 Hz, 2H), 3.68 (s, 2H), 3.32-3.28 (m, 4H), 2.71-2.52 (m, 2H), 2.51-2.47 (m, 2H), 1.87-1.81 (m, 2H), 1.44-1.20 (m, 13H).

Step 8: **Synthesis of tert-butyl 2-(4-(trifluoromethyl)benzyl)-5-(((trifluoromethyl)sulfonyl)oxy)-2,9-diazaspiro[5.5]undec-4-ene-9-carboxylate**

To a stirred solution of tert-butyl 5-oxo-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecane-9-carboxylate (0.5 g, 1.172 mmol) in THF (5 mL) was added NaHMDS (1.76 mL, 1.76 mmol) at -78 °C. The reaction mixture was stirred at the same temperature for 30 min. To the reaction mixture was added N-(5-chloropyridin-2-yl)-1,1,1-trifluoro-N-((trifluoromethyl)sulfonyl)methanesulfonamide (0.598 g, 1.524 mmol) dissolved in THF (5 mL) at -78 °C and stirred for 2 h. The reaction mixture was quenched with saturated NH_4Cl solution (10 mL). The product was extracted with ethyl acetate (200 mL). The separated organic extract was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude was purified by flash chromatography using Biotage Isolera (Neutral Alumina) and a linear gradient of 0-5% ethyl acetate in hexane as eluent to afford tert-butyl 2-(4-(trifluoromethyl)benzyl)-5-(((trifluoromethyl)sulfonyl)oxy)-2,9-diazaspiro[5.5]undec-4-ene-9-carboxylate. LCMS: m/z M-ES+APCI, Positive $[M+H]^+$ 559.6. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.89-7.78 (m, 4H), 5.87-5.75 (m, 1H), 4.63-4.60 (m, 2H), 4.21-4.18 (m, 4H), 3.93 (s, 2H), 3.45-3.33 (m, 4H), 2.34-2.33 (m, 2H), 1.40-1.37 (m, 9H).

Step 9: **Synthesis of tert-butyl 5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undec-4-ene-9-carboxylate**

To a solution of 3-(5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (0.6 g, 1.69 mmol) and tert-butyl 2-(4-(trifluoromethyl)benzyl)-5-(((trifluoromethyl)sulfonyl)oxy)-2,9-diazaspiro[5.5]undec-4-ene-9-carboxylate (1.04 g, 1.85 mmol) in 1,4-dioxane (10 mL) and water (2 mL) was added sodium carbonate (0.19 g, 1.85 mmol) at room temperature. The reaction mixture was degassed with argon for 10 min. To this reaction mixture was added bis(triphenylphosphine)palladium(II) dichloride (0.118 g, 0.168 mmol) at room temperature and the reaction mixture was heated at 50 °C for 4 h. The reaction mixture was filtered through celite bed, washed with ethyl acetate and the filtrate was concentrated under vacuum. The crude product was purified by Biotage-Isolera using 100-200 silica gel mesh and eluting with 70-75% ethyl acetate in n-Hexane. The pure fractions were concentrated under

reduced pressure to afford tert-butyl 5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undec-4-ene-9-carboxylate. LCMS: m/z M-ES+APCI, Positive $[M+H]^+$ 653.3 ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.73 (d, J = 8.00 Hz, 2H), 7.64-7.56 (m, 4H), 7.33 (s, 1H), 7.22 (d, J = 8.00 Hz, 1H), 5.52 (t, J = 2.80 Hz, 1H), 5.14-5.09 (m, 1H), 4.44-4.03 (m, 2H), 3.75 (s, 2H), 3.63 (d, J = 8.00 Hz, 2H), 3.08 (s, 2H), 2.80-2.67 (m, 1H), 2.62-2.50 (m, 5H), 2.41-2.37 (m, 1H), 1.99 (s, 1H), 1.66 (d, J = 12.00 Hz, 2H), 1.47-1.36 (m, 2H), 1.28 (s, 9H).

Step 10: **Synthesis of tert-butyl 5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecane-9-carboxylate**

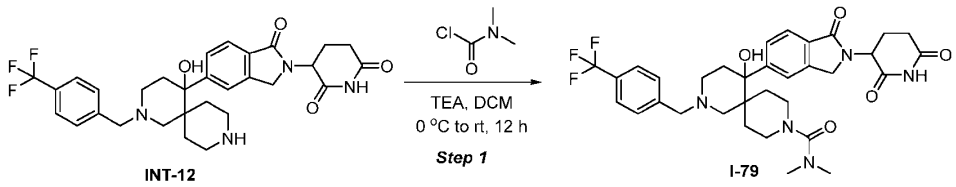
To a stirred solution of tert-butyl 5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undec-4-ene-9-carboxylate (0.6 g, 0.92 mmol) in 2-propanol (5 mL) and DCM (5 mL) were added $Mn(dpm)_3$ (0.11 g, 0.184 mmol), followed by $NaBH_4$ (0.07 g, 1.84 mmol) at 10 °C. The reaction mixture was purged with O_2 by using an oxygen bladder for 3 h at 10 °C. The reaction was filtered through a Celite bed, washed with ethyl acetate, and the filtrate was concentrated under vacuum. The crude product was purified by reverse-phase chromatography using CombiFlash 120 g SNAP C18 column and eluting with 60-65% ACN in 0.1% NH_4OAc in water. The pure fractions were concentrated under vacuum to afford tert-butyl 5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecane-9-carboxylate. LCMS: m/z M-ES+APCI, Positive $[M+H]^+$ 671.3. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.01 (br s, 1H), 7.72-7.58 (m, 7H), 5.14-5.09 (m, 1H), 5.14-5.09 (m, 1H), 4.97-4.95 (m, 1H), 4.45-4.43 (m, 1H), 4.35-4.34 (m, 1H), 3.64 (s, 2H), 3.30-3.17 (m, 2H), 2.95-2.93 (m, 1H), 2.68-2.53 (m, 5H), 2.39-2.37 (m, 2H), 2.23-2.20 (m, 1H), 2.02-1.98 (m, 1H), 1.53-1.46 (m, 2H), 1.28 (m, 9H), 1.26-1.21 (m, 1H), 0.93-0.84 (m, 1H).

Step 11: **Synthesis of 3-(5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (INT-12)**

To a stirred solution of tert-butyl 5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecane-9-carboxylate (1 g, 1.49 mmol) in 1,4-dioxane (10 mL) was added 4M HCl in 1,4-dioxane (1.864 mL, 7.45 mmol) at 10 °C. The reaction mixture was allowed to stir at room temperature for 16 h. The reaction mixture solvent was concentrated under vacuum to get crude product. The crude product was triturated with MTBE (5 mL), filtered, dried and lyophilized to afford 3-(5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**INT-12**). LCMS: m/z M-ES+APCI, Positive $[M+H]^+$ 571.3. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.26 (s, 1H), 11.01 (s, 1H), 8.95 (s, 1H), 8.05 (d, J = 8.00 Hz, 2H), 7.89 (d, J = 8.00 Hz, 2H), 7.79-7.76 (m, 1H), 7.68-7.56 (m, 2H), 5.79 (d, J = 2.40 Hz, 1H), 5.13 (t, J = 4.80 Hz,

1H), 4.57-4.32 (m, 4H), 3.97 (d, J = 16.00 Hz, 1H), 3.27-2.89 (m, 10H), 2.61 (d, J = 16.00 Hz, 1H), 2.42-2.39 (m, 1H), 2.00-1.99 (m, 1H), 1.78-1.60 (m, 2H), 1.35-1.22 (m, 2H).

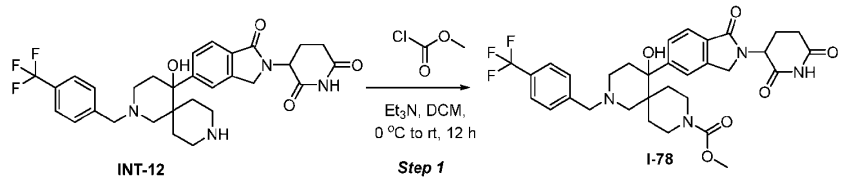
Example 20: Synthesis of 5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-5-hydroxy-N,N-dimethyl-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecane-9-carboxamide (I-79):



Step 1: **5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-5-hydroxy-N,N-dimethyl-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecane-9-carboxamide (I-79)**

To a stirred solution of 3-(5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**INT-12**, 20 mg, 0.035 mmol) and dimethylcarbamic chloride (4.52 mg, 0.042 mmol) in DCM (2 mL), was added TEA (9.77 µl, 0.07 mmol) at 0 °C and the resulting reaction mixture was stirred at room temperature for 12 h. The resulting reaction mixture was dried under reduced pressure and purified by preparative-HPLC [Column: GEMINI NX C18 250X 21} in 10% acetonitrile in water. The ACN/water mixture was removed by Genevac to afford 5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-5-hydroxy-N,N-dimethyl-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecane-9-carboxamide (**I-79**). LCMS: m/z M-ES+APCI, Positive $[M+H]^+$ 642.6. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.72-7.58 (m, 7H), 5.14-5.09 (m, 1H), 4.94 (d, J=5.6 Hz, 1H), 4.50-4.43 (m, 1H), 4.35-4.29 (m, 1H), 3.65 (s, 2H), 3.32-3.13 (m, 3H), 2.98-2.92 (m, 2H), 2.72-2.60 (m, 2H), 2.70-2.56(m, 7H), 2.45-2.40 (m, 3H), 2.40-2.37 (m, 1H), 2.06-2.01 (m, 1H), 1.55-1.52 (m, 2H), 1.48-1.45 (m, 1H), 1.14-0.97 (m, 1H).

Example 21: Synthesis of methyl 5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecane-9-carboxylate (I-78):

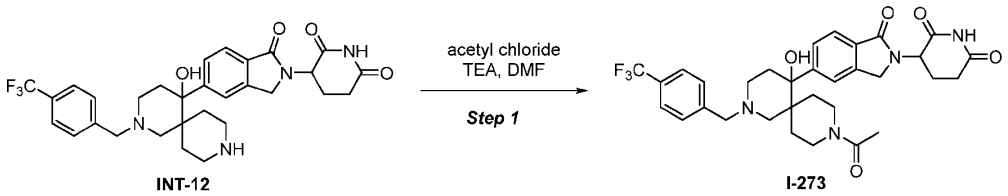


Step 1: **Synthesis of methyl 5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecane-9-carboxylate (I-78)**

To a stirred solution of 3-(5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**INT-12**, 20 mg, 0.035 mmol) and methyl carbonochloridate (3.97 mg, 0.042 mmol) in DCM (2 mL), was added TEA (4.89 µl, 0.035

mmol) and the reaction mixture was stirred at room temperature for 12 h. The resulting reaction mixture was dried under reduced pressure and was purified by preparative HPLC [Method info: column: GEMINI NX C18 250X 21} in 10 mM ammonium acetate in H_2O/ACN. The ACN/water mixture was removed by Genevac to afford methyl 5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecane-9-carboxylate (**I-78**). LCMS: m/z M-ES+APCI, Positive $[M+H]^+$ 629.5. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 7.58-7.73 (m, 7H), 5.12 (dd, J =-5.20,-13.20 Hz, 1H), 4.99 (d, J =-6.00 Hz, 1H), 4.44-4.51 (m, 1H), 4.29-4.36 (m, 1H), 3.65 (s, 3H), 3.41 (s, 3H), 2.94 (d, J =-11.20 Hz, 2H), 2.55-2.73 (m, 7H), 2.39 (d, J =-12.40 Hz, 1H), 2.33 (d, J =-2.00 Hz, 1H), 2.01-2.26 (m, 1H), 1.55 (dd, J =-13.20, Hz, 2H), 0.90-1.10 (m, 2H).

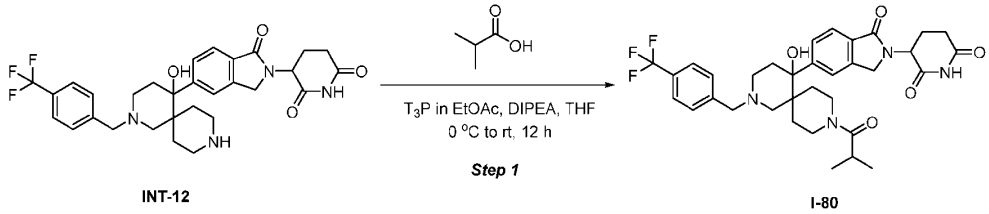
Example 22: Synthesis of 3-(5-(9-acetyl-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-273)



Step 1: **Synthesis of 3-(5-(9-acetyl-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-273)**

To a 1 dram vial containing 3-(5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (51 mg, 0.089 mmol, 1 equiv) and a stir bar was added TEA (56 µL, 0.40 mmol, 4.5 equiv) and DMF (0.89 mL, 0.1 M). The solution was cooled to 0 °C with an ice bath and acetyl chloride (6.4 µL, 0.089 mmol, 1 equiv) was added and stirred for 10 min. The solution was diluted with DMSO and purified via Waters Prep-HPLC [Method info: Phenomenex Luna C18 column 50 × 21.2 mm; 5 µm; eluting with 0.1% formic acid in H_2O: 0.1% formic acid in MeCN. Flow rate: 50 mL/min for 15 min]. The desired fractions were collected, combined and concentrated via lyophilization to afford 3-(5-(9-acetyl-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-273**, 39 mg, 0.064 µmol, 71%). LCMS: m/z HESI, positive $[M+H]^+$ = 613. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99 (br s, 1H), 10.93-10.67 (m, 1H), 8.02 (br t, J = 7.7 Hz, 2H), 7.92-7.85 (m, 2H), 7.72 (d, J = 8.2 Hz, 1H), 7.67-7.48 (m, 2H), 5.68 (br s, 1H), 5.12 (br dd, J = 4.7, 13.4 Hz, 1H), 4.57-4.41 (m, 3H), 4.39-4.29 (m, 1H), 3.92 (br dd, J = 2.7, 10.4 Hz, 1H), 3.85-3.69 (m, 1H), 3.55-3.34 (m, 2H), 3.30-3.15 (m, 2H), 3.09 (br t, J = 14.0 Hz, 1H), 2.98-2.89 (m, 2H), 2.71-2.56 (m, 2H), 2.47-2.31 (m, 1H), 2.04-1.95 (m, 1H), 1.84-1.73 (m, 3H), 1.67 (br d, J = 12.0 Hz, 1H), 1.27-1.13 (m, 1H), 1.11-1.03 (m, 1H), 1.03-0.95 (m, 1H), 0.93-0.81 (m, 1H).

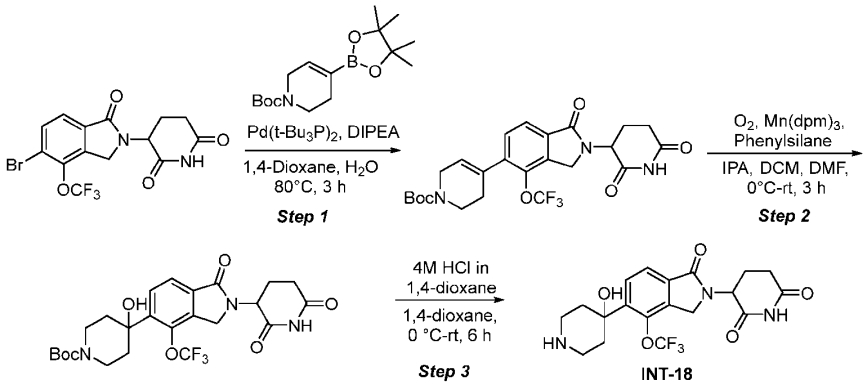
Example 23: Synthesis of 3-(5-(5-hydroxy-9-isobutyryl-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-80)



Step 1: **3-(5-(5-hydroxy-9-isobutyryl-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-80)**

To a stirred solution of 3-(5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (20 mg, 0.035 mmol) and isobutyric acid (3.71 mg, 0.042 mmol) in THF (2 mL) was added DIPEA (0.018 mL, 0.11 mmol) and T_3P in EtOAc (0.033 mL, 0.053 mmol) under nitrogen at 0 °C. The resulting reaction mixture was stirred at room temperature for 12 h before being concentrated and purified by preparative-HPLC [Method info: column: GEMINI NX C18 250X 21} in 10 mM ammonium acetate in H_2O/ACN]. Fractions were concentrated to afford 3-(5-(5-hydroxy-9-isobutyryl-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione **(I-80)**. LCMS: m/z M-ES+APCI, Positive $[M+H]^+$ 641.6.

Example 24: Synthesis of 3-(5-(4-hydroxypiperidin-4-yl)-1-oxo-4-(trifluoromethoxy)-isoindolin-2-yl)piperidine-2,6-dione (INT-18)



Step 1: **tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxo-4-(trifluoromethoxy)isoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate**

The stirred solution of 3-(5-bromo-1-oxo-4-(trifluoromethoxy)isoindolin-2-yl)piperidine-2,6-dione (600 mg, 1.47 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-

dihydropyridine-1(2H)-carboxylate (456 mg, 1.47 mmol) and DIPEA (0.77 mL, 4.42 mmol) in 1,4-dioxane (2 mL) and water (0.1 mL) was purged with nitrogen for 5 min. To this resulting mixture was added $Pd(t\text{-}Bu_3P)_2$ (75 mg, 0.15 mmol) at room temperature and the reaction mixture was stirred at 80 °C for 3 h. The reaction was filtered through a pad of celite, and the filtrate was concentrated under reduced pressure to afford crude product. The crude was purified by flash chromatography (Biotage Isolera; silica gel 100-200 mesh) with a gradient of 0-70% ethyl acetate in hexane as eluent to afford tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxo-4-(trifluoromethoxy)isoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate. LCMS: m/z MM-ES+APCI, Positive $[M+H]^-$ 510.3.; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 7.79 (d, J = 8.00 Hz, 1H), 7.59 (d, J = 8.00 Hz, 1H), 5.96 (s, 1H), 5.14 (dd, J = 4.80, 13.40 Hz, 1H), 4.57 (d, J = 17.60 Hz, 1H), 4.43 (d, J = 17.60 Hz, 1H), 4.01 (s, 2H), 3.55-3.53 (m, 2H), 2.87-2.96 (m, 1H), 2.43-2.62 (m, 4H), 2.00-2.03 (m, 1H), 1.44 (s, 9H).

Step 2: **tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxo-4-(trifluoromethoxy)isoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate**

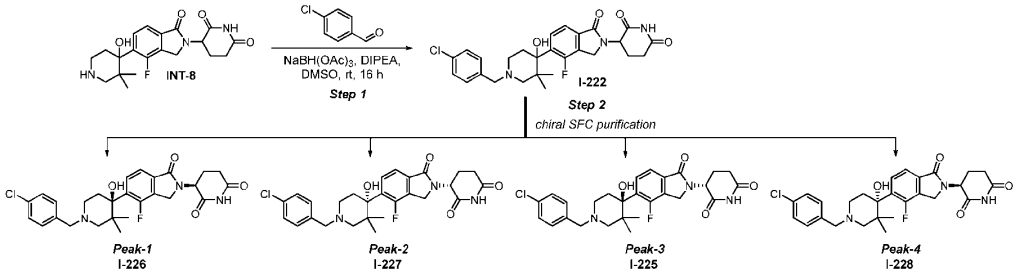
A solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxo-4-(trifluoromethoxy)-isoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (550 mg, 1.08 mmol) in DMF (3 mL), 2-propanol (10 mL) and DCM (10 mL) was stirred at 0 °C for 5 min. To this reaction mixture were added $Mn(dpm)_3$ (196 mg, 0.32 mmol) and phenylsilane (0.269 mL, 2.16 mmol) at 0 °C. The reaction mixture was purged with O_2 gas and stirred at room temperature under O_2 for 3 h. The reaction mixture was concentrated under reduced pressure to afford crude product. The crude was purified by flash chromatography using Biotage Isolera (Silica gel 100-200 mesh) and a linear gradient of 0-80% EtOAc in hexane as eluent to afford give tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxo-4-(trifluoromethoxy)isoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate. LCMS: m/z MM-ES+APCI, Positive $[M-H]^+$ 526.5, ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.00 (s, 1H), 7.96 (d, J = 8.00 Hz, 1H), 7.78 (dd, J = 4.40, 8.00 Hz, 1H), 5.56 (s, 1H), 5.13 (dd, J = 5.20, 13.20 Hz, 1H), 4.53 (d, J = 17.20 Hz, 1H), 4.41 (d, J = 17.60 Hz, 1H), 3.90-3.87 (m, 2H), 3.17-3.23 (m, 2H), 2.85-2.93 (m, 2H), 2.46-2.61 (m, 2H), 1.97-2.34 (m, 2H), 1.70 (t, J = 12.00 Hz, 2H), 1.41 (s, 9H).

Step 3: **3-(5-(4-hydroxypiperidin-4-yl)-1-oxo-4-(trifluoromethoxy)isoindolin-2-yl)piperidine-2,6-dione (INT-18)**

To a stirred solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxo-4-(trifluoromethoxy)isoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate (300 mg, 0.57 mmol) in 1,4-dioxane (10 mL) was added 4 M HCl in 1,4-dioxane (1.14 mL, 4.55 mmol) at 0 °C and stirred for 6 h at room temperature. The reaction mixture was concentrated under reduced pressure to afford 3-(5-(4-hydroxypiperidin-4-yl)-1-oxo-4-(trifluoromethoxy)isoindolin-2-yl)piperidine-2,6-dione (**INT-18**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 428.2. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 8.60 (s, 1H), 8.60 (s, 1H), 7.815 (s, 2H), 5.81 (s, 1H), 5.14 (dd, J = 4.80, 13.40 Hz, 1H), 4.55 (d, J = 17.60

Hz, 1H), 4.44 (d, *J* = 17.60 Hz, 1H), 3.26-3.33 (m, 3H), 2.90-2.90 (m, 1H), 2.48-2.53 (m, 3H), 2.06-2.22 (m, 4H).

Example 25: Synthesis of 3-(5-(1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-222), (S)-3-(5-((R)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-226), (R)-3-(5-((S)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-227), (R)-3-(5-((R)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-225), (S)-3-(5-((S)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-228)



Step 1: **Synthesis of 3-(5-(1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-222)**

To a stirred solution of 3-(4-fluoro-5-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**INT-8**, 1.5 g, 3.52 mmol, 1 equiv.) and 4-chlorobenzaldehyde (0.52 g, 3.70 mmol, 1.05 equiv.) in DMSO (15 mL), was added DIPEA (0.68 mL, 3.87 mmol, 1.09 equiv.) under nitrogen atmosphere at 10 °C. The resulting reaction mixture was stirred at ambient temperature for 1 h. Subsequently, sodium triacetoxyborohydride (2.24 g, 10.57 mmol, 3 equiv.) was added and stirred at ambient temperature for 16 h. Upon completion of the reaction, the reaction mixture was diluted with water (60 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude compound was purified by Biotage isolera C18 (120 g) using 0.1% formic acid in water and acetonitrile to afford 3-(5-(1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-222**) LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 514.3. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 8.14 (s, 1H), 7.95-7.84 (m, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.45-7.31 (m, 4H), 5.12 (dd, *J* = 4.8, 11.3 Hz, 2H), 4.61-4.47 (m, 1H), 4.36 (dd, *J* = 4.8, 17.4 Hz, 1H), 3.65-3.42 (m, 3H), 3.07-2.86 (m, 2H), 2.61 (d, *J* = 18.6 Hz, 2H), 2.47-2.37 (m, 2H), 2.18 (d, *J* = 9.1 Hz, 1H), 2.06-1.94 (m, 1H), 1.72-1.58 (m, 1H), 0.98 (br. s, 3H), 0.64 (d, *J* = 6.8 Hz, 3H).

Step 2: **Synthesis of (S)-3-(5-((R)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-226), (R)-3-(5-((S)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-227), (R)-3-(5-((R)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-225), (S)-3-(5-((S)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-228)**

3-(5-(1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-222**, 1.44 g) was purified by SFC purification using the following method: Instrument: PIC 175*[22-027]; Column: I Cellulose Z-(250 × 30 mm), 5 μm; Mobile Phase: CO_2: 2-propanol_Acetonitrile; Gradient [CO_2:Co-solvent]: [60:40]; Total Flow: 100 mL/min; Back pressure: 100 bar; Wavelength: 254 nm; Cycle time: 11.0 min.

The pure fractions were concentrated under reduced pressure to afford:

Peak 3: (R)-3-(5-((R)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-225**, 120 mg); LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 514.3; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 10.01 (br. s, 1H), 7.87 (t, J = 7.4 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.64-7.55 (m, 3H), 5.86 (s, 1H), 5.12 (dd, J = 5.1, 13.4 Hz, 1H), 4.59-4.52 (m, 1H), 4.45-4.33 (m, 3H), 3.26-3.18 (m, 4H), 2.98-2.81 (m, 2H), 2.61 (d, J = 17.2 Hz, 1H), 2.48-2.38 (m, 1H), 2.06-1.87 (m, 2H), 1.06 (d, J = 3.0 Hz, 3H), 0.74 (s, 3H)

Peak 4: (S)-3-(5-((S)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-228**, 180 mg); LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 514.3; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 10.11-9.92 (m, 1H), 7.87 (t, J = 7.4 Hz, 1H), 7.73 (d, J = 7.5 Hz, 2H), 7.65-7.53 (m, 3H), 5.87 (s, 1H), 5.13 (dd, J = 5.1, 13.4 Hz, 1H), 4.56 (d, J = 17.3 Hz, 1H), 4.48-4.28 (m, 3H), 3.21 (t, J = 11.6 Hz, 4H), 2.98-2.79 (m, 2H), 2.61 (d, J = 17.3 Hz, 1H), 2.47-2.39 (m, 1H), 2.06-1.88 (m, 2H), 1.05 (d, J = 2.7 Hz, 3H), 0.72 (s, 3H).

The mixture of peak 1 and peak 2 (380 mg) was subjected to further SFC purification using the following method: Instrument: PIC 175* [22-027]; Column: I Cellulose B- (250 × 30 mm), 5 μm; Mobile Phase: CO_2: 0.2% FA in 2-Propanol: Acetonitrile; Gradient [CO_2:Co-solvent]: [65:35]; Total Flow: 100 mL/min; Back pressure: 100 bar; Wavelength: 254 nm; Cycle time: 13 min.

The pure fractions were concentrated under reduced pressure and lyophilized to afford:

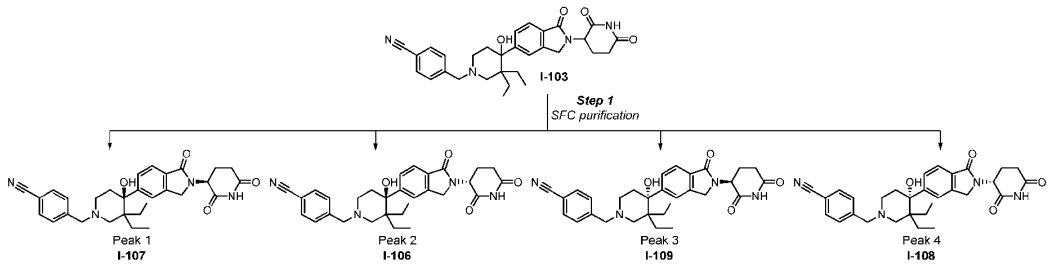
Peak 1: (S)-3-(5-((R)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-226**, 120 mg); LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 514.4; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 9.85 (br. s, 1H), 7.87 (t, J = 7.5 Hz, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.65-7.52 (m, 3H), 5.87 (s, 1H), 5.12 (dd, J = 5.1, 13.4 Hz, 1H), 4.55 (d, J = 17.5 Hz,

1H), 4.47-4.29 (m, 3H), 3.32-3.16 (m, 4H), 2.98-2.82 (m, 2H), 2.65-2.56 (m, 1H), 2.46-2.36 (m, 1H), 2.04-1.90 (m, 2H), 1.04 (d, J = 3.3 Hz, 3H), 0.72 (s, 3H)

Peak 2: (R)-3-(5-((S)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-227**, 55 mg); LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 514.4; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 9.97-9.50 (m, 1H), 7.87 (t, J = 7.4 Hz, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.65-7.53 (m, 3H), 5.86 (s, 1H), 5.12 (dd, J = 5.0, 13.3 Hz, 1H), 4.61-4.50 (m, 1H), 4.47-4.31 (m, 3H), 3.31-3.16 (m, 4H), 2.99-2.85 (m, 2H), 2.61 (d, J = 17.3 Hz, 1H), 2.47-2.40 (m, 1H), 2.06-1.88 (m, 2H), 1.05 (d, J = 2.7 Hz, 3H), 0.75 (s, 3H).

NOTE: the stereochemistry for all 4 diastereomers (peaks 1-4) has been arbitrarily assigned.

Example 26: Synthesis of 4-(((S)-4-(2-((S)-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile (I-107), 4-(((S)-4-(2-((R)-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile (I-106), 4-(((R)-4-(2-((S)-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile (I-109), 4-(((R)-4-(2-((R)-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile (I-108)



Step 1: **Synthesis of 4-(((S)-4-(2-((S)-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile (I-107), 4-(((S)-4-(2-((R)-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile (I-106), 4-(((R)-4-(2-((S)-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile (I-109), 4-(((R)-4-(2-((R)-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile (I-108)**

4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile (**I-103**, 1.4 g) was purified by SFC purification using the following method: Instrument: PIC 175* [22-027]; Column: I Cellulose Z- (250 × 30 mm), 5 µm; Mobile Phase: CO_2: 2-propanol_Acetonitrile; Gradient [CO_2: Co-solvent]: [50:50]; Total Flow: 120 mL/min; Back pressure: 100 bar; Wavelength: 254 nm; Cycle time: 13.0 min. The pure fractions were concentrated under reduced pressure to afford:

Peak 3: 4-(((R)-4-(2-((S)-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile (**I-109,** 85 mg); LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 515.3; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 10.21-9.80 (m, 1H), 8.04-7.94 (m, 4H), 7.74-7.57 (m, 3H), 5.65 (s, 1H), 5.12 (dd, J = 5.1, 13.2 Hz, 1H), 4.61-4.27 (m, 4H), 3.44-3.37 (m, 1H), 3.32-3.26 (m, 1H), 3.27-3.14 (m, 1H), 3.07-2.86 (m, 2H), 2.75 (d, J = 12.6 Hz, 1H), 2.66-2.56 (m, 1H), 2.45-2.35 (m, 1H), 2.07-1.95 (m, 2H), 1.78-1.65 (m, 1H), 1.58-1.45 (m, 1H), 1.20-1.03 (m, 2H), 0.45 (q, J = 7.6 Hz, 6H).

Peak 4: (4-(((R)-4-(2-((R)-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile (**I-108,** 100 mg); LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 515.2; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.12-10.82 (m, 1H), 10.29-9.66 (m, 1H), 8.05-7.91 (m, 4H), 7.76-7.62 (m, 3H), 5.67 (s, 1H), 5.12 (dd, J = 5.0, 13.3 Hz, 1H), 4.61-4.28 (m, 4H), 3.38 (br. s, 2H), 3.27-3.12 (m, 1H), 3.09-2.97 (m, 1H), 2.97-2.85 (m, 1H), 2.81-2.71 (m, 1H), 2.61 (d, J = 17.2 Hz, 1H), 2.45-2.35 (m, 1H), 2.06-1.95 (m, 2H), 1.79-1.69 (m, 1H), 1.59-1.45 (m, 1H), 1.21-1.04 (m, 2H), 0.52-0.38 (m, 6H).

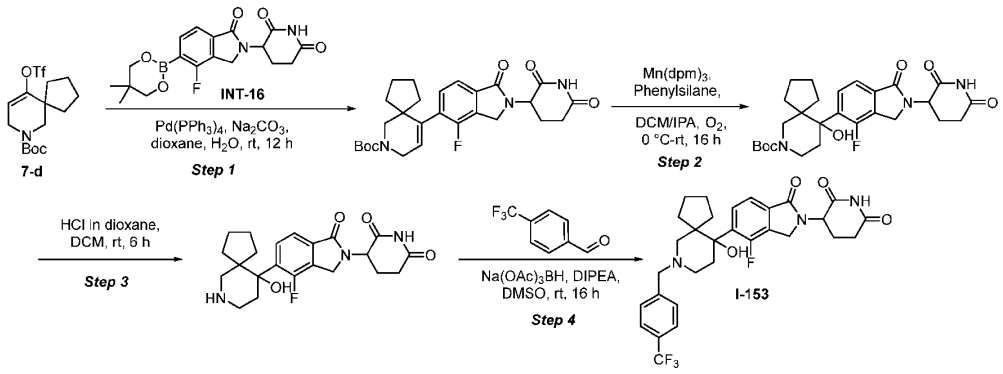
The mixture of peak 1 and peak 2 (380 mg) was further purified by SFC purification using the following method: Instrument: PIC 175* [22-027]; Column: I Cellulose Z- (250 × 30 mm), 5 μm; Mobile Phase: CO_2: 2-propanol_Acetonitrile; Gradient [CO_2:Co-solvent]: [50:50]; Total Flow: 120 mL/min; Back pressure: 100 bar; Wavelength: 254 nm; Cycle time: 13.0 min. The pure fractions were concentrated under reduced pressure and lyophilized to afford:

Peak 1: 4-(((S)-4-(2-((S)-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile (**I-107,** 100 mg); LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 515.2; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 9.98-9.84 (m, 1H), 8.04-7.92 (m, 4H), 7.75-7.60 (m, 3H), 5.66 (s, 1H), 5.12 (dd, J = 5.1, 13.2 Hz, 1H), 4.61-4.41 (m, 3H), 4.38-4.30 (m, 1H), 3.45-3.36 (m, 2H), 3.26-3.16 (m, 1H), 3.05-2.85 (m, 2H), 2.76 (d, J = 12.1 Hz, 1H), 2.61 (d, J = 17.2 Hz, 1H), 2.38 (dd, J = 4.3, 13.4 Hz, 1H), 2.06-1.93 (m, 2H), 1.78-1.69 (m, 1H), 1.52 (qd, J = 7.7, 14.8 Hz, 1H), 1.18-1.03 (m, 2H), 0.51-0.37 (m, 6H)

Peak 2: 4-(((S)-4-(2-((R)-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile (**I-106,** 80 mg); LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 515.2; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 10.05 (br. s, 1H), 8.05-7.90 (m, 4H), 7.76-7.54 (m, 3H), 5.65 (s, 1H), 5.12 (dd, J = 5.1, 13.4 Hz, 1H), 4.65-4.27 (m, 4H), 3.45-3.37 (m, 1H), 3.26-3.12 (m, 1H), 3.07-2.84 (m, 2H), 2.81-2.56 (m, 3H), 2.46-2.27 (m, 1H), 2.12-1.93 (m, 2H), 1.78-1.63 (m, 1H), 1.52 (qd, J = 7.3, 14.8 Hz, 1H), 1.27-0.99 (m, 2H), 0.45 (q, J = 7.5 Hz, 6H).

Note: the stereochemistry for all 4 diastereomers (peaks 1-4) has been arbitrarily assigned.

Example 27: Synthesis of 3-(4-fluoro-5-(10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-153)



Step 1: **Synthesis of tert-butyl 10-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-7-azaspiro[4.5] dec-9-ene-7-carboxylate**

To a stirred solution of 3-(5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**INT-16**, 2.45 g, 3.92 mmol, 1.0 equiv) in 1,4-dioxane (15 mL) was added tert-butyl 10-(((trifluoromethyl)sulfonyl)oxy)-7-azaspiro[4.5]dec-9-ene-7-carboxylate (**7-d**, 1.5 g, 3.27 mmol, 1.2 equiv.), Na_2CO_3 (0.38 g, 3.60 mmol, 1.1 equiv), and the reaction mixture was degassed with argon for 10 min. Tetrakis(triphenylphosphine)palladium(0) (0.378 g, 0.327 mmol, 0.1 equiv) was then added at 25 °C, and the reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was cooled to room temperature, filtered through a Celite bed, washed with ethyl acetate, and concentrated under reduced pressure. The crude product was purified by reverse phase column chromatography using a C18 cartridge (330 g) and eluted with 40% acetonitrile in 0.1% formic acid in water. Pure fractions were collected and concentrated under reduced pressure to afford tert-butyl 10-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-7-azaspiro[4.5]dec-9-ene-7-carboxylate. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 498.5; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.36-10.73 (m, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.32 (t, J = 6.8 Hz, 1H), 5.62 (s, 1H), 5.13 (dd, J = 5.0, 13.3 Hz, 1H), 4.58 (d, J = 17.5 Hz, 1H), 4.45-4.30 (m, 1H), 4.00 (s, 2H), 3.36 (s, 2H), 3.04-2.82 (m, 1H), 2.61 (td, J = 2.0, 15.3 Hz, 1H), 2.47-2.37 (m, 1H), 2.06-1.96 (m, 1H), 1.61 (m, 2H), 1.57-1.29 (m, 15H).

Step 2: **Synthesis of tert-butyl 10-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-10-hydroxy-7-azaspiro[4.5]decane-7-carboxylate**

To a stirred solution of tert-butyl 10-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-7-azaspiro[4.5]dec-9-ene-7-carboxylate (0.71 g, 1.25 mmol, 1.0 equiv.) in dichloromethane (25 mL) and isopropanol (10.71 mL) were added $Mn(dpm)_3$ (0.11 g, 0.19 mmol, 0.15 equiv) and phenyl silane (0.39 mL, 3.12 mmol, 2.5 equiv) at 0 °C under an oxygen atmosphere. The reaction mixture was bubbled with

O_2 and stirred at 25 °C for 4 h. An additional charge of $Mn(dpm)_3$ (0.076 g, 0.125 mmol, 0.1 equiv) was then added to the reaction mixture, and it was stirred at 25 °C for 16 h under an oxygen atmosphere. The reaction mixture was concentrated under reduced pressure. The crude product was subsequently purified by reverse-phase column chromatography using a C18 cartridge (120 g), with a gradient of 10 to 50% acetonitrile in 0.1% ammonium acetate in water. Pure fractions were collected and concentrated under reduced pressure to yield tert-butyl 10-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-10-hydroxy-7-azaspiro[4.5]decane-7-carboxylate. The obtained product was dissolved in 10% methanol in DCM (20 mL) and SiliametS DMT (0.2 g) was added at room temperature. The reaction mixture was stirred at room temperature for 1 h. After 1 h, the reaction mixture was filtered through a Celite bed and washed with 10% methanol in DCM. The filtrate was concentrated and dried under vacuum to afford tert-butyl 10-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-10-hydroxy-7-azaspiro[4.5]decane-7-carboxylate. LCMS: m/z: MM-ES+APCI, negative $[M-H]^-$ 514.3; Rt 2.04 and 2.08 min (two diastereomers). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.51-10.01 (m, 1H), 7.95 (t, J = 6.3 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 5.42 (d, J = 5.1 Hz, 1H), 5.20-4.99 (m, 1H), 4.61-4.47 (m, 1H), 4.36 (dd, J = 11.3, 17.3 Hz, 1H), 4.15-3.53 (m, 4H), 3.17 (s, 3H), 2.97-2.84 (m, 1H), 2.60 (d, J = 18.3 Hz, 2H), 2.47-2.37 (m, 1H), 2.07-1.95 (m, 2H), 1.72-1.63 (m, 2H), 1.62-1.47 (m, 4H), 1.42 (s, 9H).

Note: ^{1}H NMR Integration given for one diastereomer.

Step 3: **Synthesis of 3-(4-Fluoro-5-(10-hydroxy-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione**

To a stirred solution of tert-butyl 10-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-10-hydroxy-7-azaspiro[4.5] decane-7-carboxylate (0.125 g, 0.22 mmol, 1.0 equiv) in dichloromethane (5 mL) was added 4M HCl in dioxane (0.27 mL, 1.12 mmol, 5.0 equiv) at 0 °C. The reaction mixture was then stirred at 25 °C for 3 h. The reaction mixture was concentrated under reduced pressure, washed with hexane (2 × 10 mL), and dried under vacuum to afford 3-(4-fluoro-5-(10-hydroxy-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 416.3; Rt 1.24 and 1.28 min (two diastereomers). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 9.03 (d, J = 10.5 Hz, 1H), 8.29 (d, J = 9.7 Hz, 1H), 7.96 (t, J = 6.4 Hz, 1H), 7.63 (d, J = 8.1 Hz, 1H), 5.84 (d, J = 5.7 Hz, 1H), 5.25-5.02 (m, 1H), 4.56 (dd, J = 9.3, 17.4 Hz, 1H), 4.44-4.32 (m, 1H), 3.22-3.08 (m, 3H), 3.05-2.84 (m, 3H), 2.65-2.57 (m, 1H), 2.47-2.38 (m, 2H), 2.06-1.85 (m, 3H), 1.75-1.65 (m, 1H), 1.54-1.45 (m, 1H), 1.34-1.15 (m, 4H).

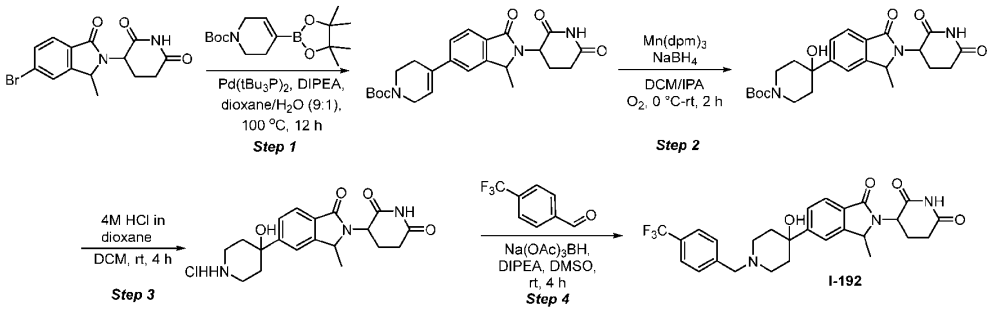
Note: ^{1}H NMR Integration given for one diastereomer.

Step 4: **Synthesis of 3-(4-fluoro-5-(10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-153)**

To a stirred solution of 3-(4-fluoro-5-(10-hydroxy-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (0.12 g, 0.21 mmol, 1.0 equiv) in dimethyl sulfoxide (1 mL) was added N,N-diisopropylethylamine (0.037 mL, 0.21 mmol, 1.0 equiv) and 4-(trifluoromethyl)benzaldehyde (0.029 mL, 0.21 mmol, 1.0 equiv) at 10 °C. The reaction mixture was stirred at 25 °C for 1 h. Sodium triacetoxyborohydride (0.14 g, 0.64 mmol, 3.0 equiv) was then added to the reaction mixture at 10 °C, and the mixture was allowed to stir at 25 °C for 16 h. The reaction mixture was concentrated and purified by reverse-phase column chromatography using a C18 cartridge (40 g) and eluted with 70% ACN in 0.1% formic acid in water. Pure fractions were collected and concentrated under reduced pressure and subjected to a second purification by reverse-phase column chromatography using a C18 cartridge (40 g) with ACN and 0.05% HCl in water as the mobile phase. The collected pure fractions were lyophilized to obtain 3-(4-fluoro-5-(10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione **(I-153)**. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 574.4; Rt 2.68 and 2.74 min (two diastereomers). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 10.14-9.76 (m, 1H), 7.98-7.85 (m, 5H), 7.63 (d, J = 8.1 Hz, 1H), 5.87 (d, J = 5.6 Hz, 1H), 5.16-5.07 (m, 1H), 4.61-4.48 (m, 3H), 4.39 (dd, J = 13.2, 17.5 Hz, 1H), 3.29-3.20 (m, 2H), 3.19-3.01 (m, 2H), 2.98-2.86 (m, 1H), 2.65-2.57 (m, 1H), 2.47-2.35 (m, 2H), 2.23-2.14 (m, 1H), 2.06-1.92 (m, 2H), 1.79-1.68 (m, 1H), 1.42-1.10 (m, 5H), 0.98-0.81 (m, 1H).

Note: ^{1}H NMR Integration given for one diastereomer.

Example 28: Synthesis of 3-(5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-3-methyl-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-192)



Step 1: **Synthesis of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-3-methyl-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate**

To a stirred solution of 3-(5-bromo-3-methyl-1-oxoisoindolin-2-yl)piperidine-2,6-dione (1.5 g, 4.45 mmol, 1 equiv.) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.79 g, 5.78 mmol, 1.3 equiv.) in dioxane (18 mL) and water (2 mL) was added DIPEA (1.17 mL, 6.67 mmol, 1.5 equiv.) at room temperature, and the resulting mixture was degassed with nitrogen for 15 min. Bis(tri-t-butyl phosphine)palladium(0) (0.23 g, 0.45 mmol, 0.1 equiv.) was

added to the reaction mixture at room temperature, which was then heated to 100 °C and stirred for 12 h. The mixture was cooled to room temperature and filtered through a celite bed. The filtrate was concentrated under reduced pressure to obtain the crude product. The crude product was diluted with ice-cold water (25 mL) and then extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography using 60-120 silica gel and 50% EtOAc in hexane as eluent, affording tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-3-methyl-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 440.3; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99-10.81 (m, 1H), 7.70 (d, J = 3.2 Hz, 1H), 7.67-7.60 (m, 1H), 7.60-7.53 (m, 1H), 6.32 (s, 1H), 4.82-4.62 (m, 2H), 4.12-4.02 (m, 2H), 3.64-3.47 (m, 2H), 2.86-2.53 (m, 6H), 1.52-1.34 (m, 12H).

Step 2: **Synthesis of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-3-methyl-1-oxoisoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate**

To a stirred solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-3-methyl-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.26 g, 2.87 mmol, 1 equiv.) in dichloromethane (21 mL) and 2-propanol (9 mL) was added $Mn(dpm)_3$ (0.26 g, 0.43 mmol, 0.15 equiv.) followed by $NaBH_4$ (0.22 g, 5.73 mmol, 1.8 equiv.) under an oxygen atmosphere at 0 °C. The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was then cooled to room temperature and filtered through a celite bed. The filtrate was concentrated under reduced pressure to obtain the crude product. The crude product was diluted with ice-cold water (25 mL) and extracted with DCM (2 × 25 mL). The combined organic layers were dried over sodium sulfate (Na_2SO_4), concentrated under reduced pressure, and purified using Biotage Isolera C18 (120 g) with 0.1% formic acid in water and acetonitrile, affording tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-3-methyl-1-oxoisoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 458.2; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.92 (d, J = 13.2 Hz, 1H), 7.74 (s, 1H), 7.68-7.57 (m, 2H), 5.30 (s, 1H), 4.81-4.58 (m, 2H), 3.89 (d, J = 8.4 Hz, 2H), 3.25-2.94 (m, 2H), 2.92-2.57 (m, 3H), 2.06-1.93 (m, 1H), 1.88 (d, J = 3.7 Hz, 2H), 1.61 (d, J = 13.0 Hz, 2H), 1.54-1.30 (m, 12H).

Step 3: **Synthesis of 3-(5-(4-hydroxypiperidin-4-yl)-3-methyl-1-oxoisoindolin-2-yl)piperidine-2,6-dione**

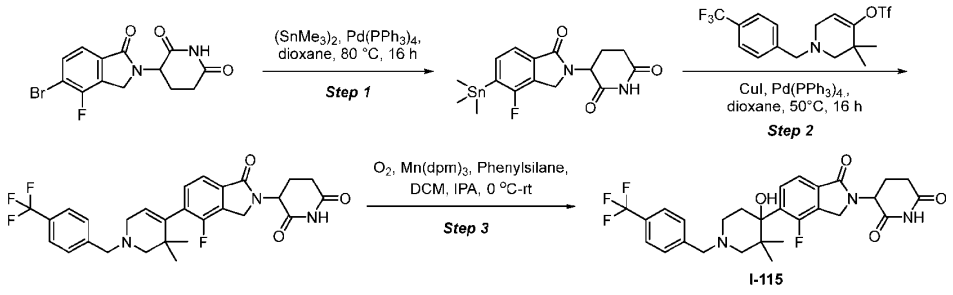
To a stirred solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-3-methyl-1-oxoisoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate (1 g, 2.19 mmol, 1 equiv.) in dichloromethane (20 mL) at 0 °C under a nitrogen atmosphere was added 4 M HCl in dioxane (2.73 mL, 10.93 mmol, 5 equiv.). The reaction mixture was stirred for 3 h at room temperature and then concentrated under reduced pressure to yield the crude product. The crude compound was triturated with hexane (2 × 50 mL) and then dried to afford 3-(5-(4-hydroxypiperidin-4-yl)-3-methyl-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride. LCMS:

m/z: MM-ES+APCI, positive $[M+H]^+$ 358.4; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.94 (d, J = 13.4 Hz, 1H), 8.84 (br. s, 2H), 7.74-7.65 (m, 2H), 7.62-7.55 (m, 1H), 4.84-4.66 (m, 2H), 3.43-3.34 (m, 1H), 3.29-3.17 (m, 4H), 2.93-2.55 (m, 3H), 2.38-2.16 (m, 3H), 2.07-1.95 (m, 1H), 1.87-1.74 (m, 2H), 1.45 (dd, J = 6.8, 9.6 Hz, 3H).

Step 4: **Synthesis of 3-(5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-3-methyl-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-192)**

To a stirred solution of 3-(5-(4-hydroxypiperidin-4-yl)-3-methyl-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride (0.25 g, 0.69 mmol, 1 equiv.) in DMSO (10 mL) at room temperature, was added 4-(trifluoromethyl)benzaldehyde (0.121 g, 0.69 mmol, 1 equiv.) and DIPEA (0.183 mL, 1.049 mmol, 1.5 equiv.). Sodium triacetoxyborohydride (0.45 g, 2.09 mmol, 3 equiv.) was then added at 15 °C. The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was quenched with ice-cold water and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield the crude product. The crude compound was purified using a Biotage Isolera C18 column (40 g) with a gradient of 0.1% formic acid in water and acetonitrile. The pure fractions were collected and concentrated, and subjected to HCl salt formation using a Biotage Isolera C18 column (40 g) with 0.05% HCl in water and acetonitrile. The pure fractions were lyophilized to afford 3-(5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-3-methyl-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-192**). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 516.2; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.96-10.85 (m, 2H), 7.97-7.83 (m, 4H), 7.74-7.64 (m, 2H), 7.59 (t, J = 6.6 Hz, 1H), 5.71 (s, 1H), 4.84-4.64 (m, 2H), 4.52 (d, J = 5.1 Hz, 2H), 3.33-3.28 (m, 4H), 2.87-2.69 (m, 1H), 2.53 (m, 3H), 2.48-2.42 (m, 1H), 2.05-1.94 (m, 1H), 1.91-1.78 (m, 2H), 1.44 (dd, J = 6.8, 10.1 Hz, 3H).

Example 29: Synthesis of 3-(4-fluoro-5-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-115):



Step 1: **Synthesis of 3-(4-fluoro-1-oxo-5-(trimethylstannyl)isoindolin-2-yl)piperidine-2,6-dione**

To a stirred solution of 3-(5-bromo-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (1 g, 2.65 mmol) in 1,4-dioxane (10 mL) under N_2 was added hexamethylditin (1.04 g, 3.18 mmol) at 25 °C. The

reaction mixture was purged with N_2 for 10 min. To this resulting mixture was added tetrakis(triphenylphosphine)palladium(0) (0.61 g, 0.53 mmol) at room temperature and again purged with N_2 for 10 min. This reaction mixture heated at 80 °C for 16 h. The reaction mixture was cooled to room temperature, quenched with water (50 mL), extracted with ethyl acetate (2 X 100 mL), and the combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was triturated with MTBE (10 mL × 2) and dried under reduced pressure to afford 3-(4-fluoro-1-oxo-5-(trimethylstannyl)isoindolin-2-yl)piperidine-2,6-dione. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 425.2 and 427.2, ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 7.61 (s, 3H), 5.12 (t, J = 5.20 Hz, 1H), 4.56-4.52 (m, 1H), 4.34-4.39 (m, 1H), 2.96-2.92 (m, 1H), 2.87-2.62 (m, 1H), 2.58 (m, 1H), 2.50 (d, J = 1.60 Hz, 1H), 0.32 (s, 9H).

Step 2: **Synthesis of 3-(5-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione**

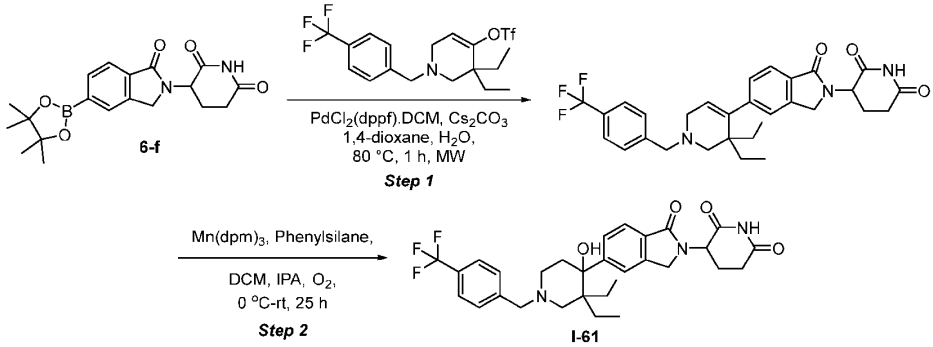
To a stirred solution of 3-(4-fluoro-1-oxo-5-(trimethylstannyl)isoindolin-2-yl)piperidine-2,6-dione (150 mg, 0.35 mmol) in 1,4-dioxane (10 mL) was added 3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (147 mg, 0.35 mmol)) under nitrogen at room temperature. The reaction mixture was purged with N_2 for 5 min and then copper(I) iodide (67.2 mg, 0.353 mmol) and $Pd(PPh_3)_4$ (408 mg, 0.353 mmol) were added. The mixture was purged with N_2 for 5 min and then heated to 50 °C for 16 h. The reaction mixture was cooled to room temperature and partitioned between water (20 mL) and ethyl acetate (30 mL × 2). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get crude. The crude compound was purified by Biotage Isolera (silica gel 100-200 mesh) and a linear gradient of 50-100% ethyl acetate in hexane to afford 3-(5-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 530.3.

Step 3: **Synthesis of 3-(4-fluoro-5-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-115)**

To a stirred solution of 3-(5-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (150 mg, 0.28 mmol) in dichloromethane (10 mL) and 2-propanol (2 mL) was added $Mn(dpm)_3$ (171 mg, 0.28 mmol) and phenyl silane (153 mg, 1.42 mmol) under O_2 at 0 °C. The reaction stirred at RT for 16 h and then concentrated under reduced pressure. The crude residue was washed with n-pentane (2 × 10 mL, dried, and purified by preparative-HPLC [(Column: X select (C18 150 mm × 19) 5 µm, Mobile phase A: 0.05% HCl in H_2O, Mobile phase B: ACN, flow rate: 15 mL/min)]. The fractions containing the product were combined to afford 3-(4-fluoro-5-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-

oxoisoindolin-2-yl)piperidine-2,6-dione (**I-115**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 548.6, ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.03 (s, 1H), 9.81 (s, 1H), 7.89 (t, J = 7.60 Hz, 5H), 7.62 (dd, J = 8.00, Hz, 1H), 5.89 (dd, J = 6.40, Hz, 1H), 5.15-5.11 (m, 1H), 4.54 (dd, J = 6.80, Hz, 2H), 4.41-4.35 (m, 1H), 3.34 (s, 3H), 2.92 (t, J = 9.20 Hz, 2H), 2.68-2.51 (m, 2H), 2.42 (s, 2H), 2.02-2.01 (m, 2H), 1.05 (t, J = Hz, 3H), 0.74 (dd, J = 8.40, Hz, 3H).

Example 30: Synthesis of 3-(5-(3,3-diethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-61):



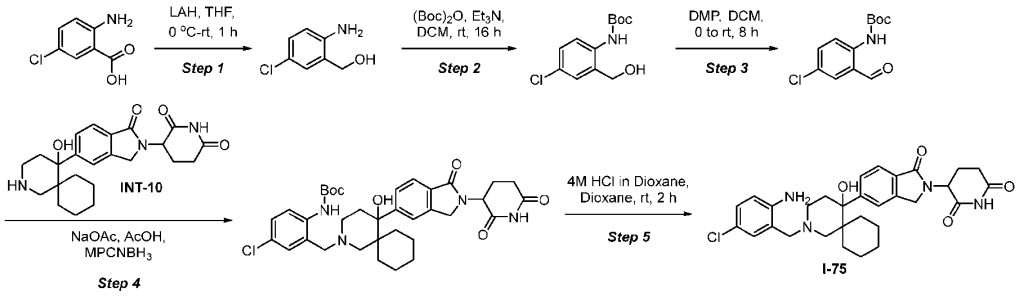
Step 1: **Synthesis of 3-(5-(3,3-diethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione**

To a stirred solution of 3,3-diethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (350 mg, 0.786 mmol) in 1,4-dioxane (6 mL) and water (0.6 mL) was added 3-(1-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-2-yl)piperidine-2,6-dione (**6-f**, 291 mg, 0.79 mmol) and cesium carbonate (512 mg, 1.57 mmol). The reaction mixture was degassed with nitrogen for 10 minutes. Then, $PdCl_2$(dppf)-DCM adduct (64.2 mg, 0.079 mmol) was added and again degassed with nitrogen for 10 minutes. The resulting reaction mixture was irradiated under microwave at 80 °C for 1 h. The reaction mixture was filtered through a pad of celite, washed with EtOAc (100 mL), and the filtrate was concentrated under reduced pressure. The crude compound was purified by Biotage Isolera (silica gel 100-200 mesh) and a linear gradient of 0-85% EtOAc in hexane as eluent to afford 3-(5-(3,3-diethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 540.8. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 7.74-7.72 (m, 2H), 7.68-7.61 (m, 1H), 7.59-7.58 (m, 2H), 7.44 (s, 1H), 7.36-7.34 (m, 2H), 5.75 (s, 1H), 5.14-5.09 (m, 1H), 4.48-4.43 (m, 1H), 4.34-4.30 (m, 1H), 3.93 (s, 1H), 3.65 (s, 2H), 3.03-3.01 (m, 2H), 2.73-2.63 (m, 1H), 2.52-2.51 (m, 2H), 2.41-2.40 (m, 1H), 2.00-1.98 (m, 1H), 1.58-1.54 (m, 2H), 1.52-1.48 (m, 2H), 0.81-0.77 (m, 6H).

Step 2: **Synthesis of 3-(5-(3,3-diethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-61)**

To a stirred solution of 3-(5-(3,3-diethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (400 mg, 0.74 mmol) in DCM (10 mL) and 2-propanol (10 mL) was added $Mn(dpm)_3$ (134 mg, 0.22 mmol) and phenylsilane (0.23 mL, 1.85 mmol) at 0 °C. The resulting mixture was stirred at 25 °C for 20 h. The reaction mixture was concentrated under reduced pressure and purified by preparative-HPLC [X SELECT C18 (19 × 150)}, Mobile phase A: 10 mm Ammonium Acetate in water, Mobile phase B: ACN, flow rate: 15 mL/min)], RT: 10.5 min. The fractions containing the product were combined and lyophilized to afford 3-(5-(3,3-diethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione **(I-61)**. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 558.2; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 7.77-7.70 (m, 4H), 7.64-7.58 (m, 3H), 5.14-5.09 (m, 1H), 4.83 (d, J = 5.20 Hz, 1H), 4.43-4.42 (m, 1H), 4.33-4.32 (m, 1H), 3.56 (s, 2H), 2.63-2.61 (m, 1H), 2.53-2.50 (m, 3H), 2.36-2.33 (m, 3H), 2.00-1.99 (m, 3H), 1.43-1.40 (m, 2H), 1.21-0.99 (m, 3H), 0.55-0.44 (m, 6H).

Example 31: Synthesis of 3-(5-(2-(2-amino-5-chlorobenzyl)-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-75)



Step 1: **Synthesis of (2-amino-5-chlorophenyl)methanol**

To a stirred solution of 2-amino-5-chlorobenzoic acid (1 g, 5.83 mmol) in THF (7 mL) was added LAH (8.74 mL, 8.74 mmol) at 0 °C. The reaction was stirred at room temperature for 5 h. The reaction was filtered, concentrated, and purified by flash chromatography using Biotage Isolera (Silica gel 100-200 mesh) and a linear gradient of 0-4% EtOAc in hexane as eluent to afford 2-amino-5-chlorophenyl)methanol. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 158.2. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.09 (d, J = 2.40 Hz, 1H), 6.96 (dd, J = 2.40, 8.40 Hz, 1H), 6.61 (dd, J = 8.40 Hz, 1H), 5.12 (t, J = 5.60 Hz, 1H), 5.03 (s, 2H), 4.35 (d, J = 5.60 Hz, 2H).

Step 2: **Synthesis of tert-butyl (4-chloro-2-(hydroxymethyl)phenyl)carbamate**

To a stirred solution of (2-amino-5-chlorophenyl)methanol (500 mg, 3.17 mmol) in DCM (5 mL) was added Boc anhydride (0.88 mL, 3.81 mmol) and Et_3N (0.663 mL, 4.76 mmol). The reaction mixture was stirred at room temperature for 16h. The reaction mixture was concentrated and purified by flash chromatography using Biotage Isolera (Silica gel 100-200 mesh) with a linear gradient of 0-4% ethyl

acetate in hexane as eluent to afford tert-butyl (4-chloro-2-(hydroxymethyl)phenyl)carbamate. LCMS: m/z MM-ES+APCI, Negative $[M-H]^-$ =256.3. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 7.55 (dd, J = 8.40, 2.00 Hz, 1H), 7.38 (d, J = 2.00 Hz, 1H), 7.26 (dd, J = 2.00, 8.60 Hz, 1H), 5.50 (t, J = 5.60 Hz, 1H), 4.50 (d, J = 5.60 Hz, 2H), 1.47 (s, 12H).

Step 3: **Synthesis of tert-butyl (4-chloro-2-formylphenyl)carbamate**

To a stirred solution of tert-butyl (4-chloro-2-(hydroxymethyl)phenyl)carbamate (20 mg, 0.078 mmol) in DCM (1 mL) was added DMP (39 mg, 0.093 mmol) and the reaction was stirred at room temperature for 8h. The reaction was concentrated to afford tert-butyl (4-chloro-2-formylphenyl)carbamate. LCMS: m/z MM-ES+APCI, Positive $[M-56+H]^+$ 200. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.31 (s, 1H), 9.95 (s, 1H), 8.14 (dd, J = 8.80, 2.00 Hz, 1H), 7.98-7.87 (m, 1H), 7.74-7.64 (m, 2H), 1.50 (s, 9H).

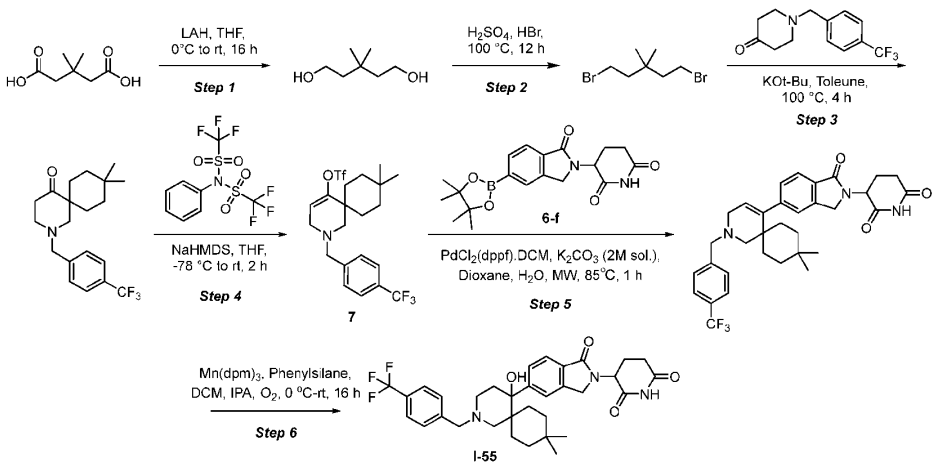
Step 4: **Synthesis of tert-butyl (4-chloro-2-((5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-5-hydroxy-2-azaspiro[5.5]undecan-2-yl)methyl)phenyl)carbamate**

To a stirred solution of tert-butyl (4-chloro-2-formylphenyl)carbamate (31 mg, 0.12 mmol) in DMF (2 mL) was added 3-(5-(5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (50 mg, 0.12 mmol), sodium acetate (59.8 mg, 0.73 mmol) and acetic acid (36.5 mg, 0.61 mmol). The reaction mixture was stirred at room temperature for 5 min and heated to 80 °C for 1 h. MP-Cyanoborohydride (50 mg, 0.12 mmol) was added, and the reaction was stirred for 16 h. The reaction mixture was filtered and concentrated to afford tert-butyl (4-chloro-2-((5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-5-hydroxy-2-azaspiro[5.5]undecan-2-yl)methyl)phenyl)carbamate.

Step 5: **Synthesis of 3-(5-(2-(2-amino-5-chlorobenzyl)-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-75)**

To a stirred solution of tert-butyl (4-chloro-2-((5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-5-hydroxy-2-azaspiro[5.5]undecan-2-yl)methyl)phenyl)carbamate (0.08 g, 0.12 mmol) in 1,4-dioxane (2 mL) was added 4M HCl in 1,4-dioxane (0.092 mL, 0.369 mmol) at 0°C. The reaction stirred at 25 °C for 2 h. The reaction was concentrated and then purified by prep HPLC using (Column: X select (150 mm × 19) 5 µm, Mobile phase A: 0.1% FA in H_2O, Mobile phase B: ACN, flow rate: 10 mL/min)]. The fractions containing the product were combined and lyophilized to afford 3-(5-(2-(2-amino-5-chlorobenzyl)-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-75**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 551.29. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99 (m, 1H), 7.69-7.62 (m, 3H), 7.05-7.00 (m, 2H), 6.65 (d, J = 8.40 Hz, 1H), 5.49 (s, 2H), 5.12 (dd, J = 4.80, 12.80 Hz, 1H), 4.81 (d, J = 4.00 Hz, 1H), 4.46 (dd, J = 12.40, 17.20 Hz, 1H), 4.32 (dd, J = 8.40, 17.20 Hz, 1H), 2.91-2.86 (m, 2H), 2.63-2.50 (m, 4H), 2.42-2.18 (m, 6H), 2.11-1.91 (m, 3H), 1.70 (d, J = 12.40 Hz, 1H), 1.47-1.24 (m, 6H), 1.14-0.96 (m, 2H), 0.86-0.59 (m, 4H).

Example 32: Synthesis of 3-(5-(5-hydroxy-9,9-dimethyl-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-55):



Step 1: **Synthesis of 3,3-dimethylpentane-1,5-diol**

To a solution of 3,3-dimethylpentanedioic acid (5.0 g, 31.2 mmol) in THF (50 mL) was added LAH (31.2 mL, 62.4 mmol) drop wise at 0 °C. The reaction mixture was slowly warmed to room temperature and was allowed to stir for 16 h. The reaction mixture was quenched with 1.0 M NaOH (aq.) at 0 °C and extracted with EtOAc (3 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get 3,3-dimethylpentane-1,5-diol. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.24 (t, J = 4.80 Hz, 2H), 3.45-3.43 (m, 4H), 1.39-1.35 (m, 4H), 0.86 (s, 6H).

Step 2: **Synthesis of 1,5-dibromo-3,3-dimethylpentane**

To a solution of 3,3-dimethylpentane-1,5-diol (500 mg, 3.78 mmol) in HBr (4 mL, 73.7 mmol), was added H_2SO_4 (0.202 mL, 3.78 mmol) dropwise at 0 °C. The reaction mixture was slowly heated to 100 °C and was allowed to stir for 12 h. The reaction mixture was quenched with $NaHCO_3$ solution (50 mL) and extracted with EtOAc (2 × 100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude compound. The crude compound was purified by Biotage Isolera (silica gel 100-200 mesh) and a linear gradient of 0-100% EtOAc in hexane as eluent to afford 1,5-dibromo-3,3-dimethylpentane. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.40-3.36 (m, 4H), 1.90-1.86 (m, 4H), 0.96 (s, 6H).

Step 3: **Synthesis of 9,9-dimethyl-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-one**

To a stirred solution of 1-(4-(trifluoromethyl)benzyl)piperidin-4-one (2.0 g, 7.77 mmol) in anhydrous toluene (20 mL) was added potassium tert-butoxide (1.75 g, 15.55 mmol) in one portion and the mixture was stirred at room temperature for 1 h. After 1 h, to this resulting mixture was added 1,5-dibromo-3,3-dimethylpentane (2.00 g, 7.77 mmol) dropwise. The reaction mixture was stirred at 100 °C for 4 h. The reaction mixture was allowed to cool, and then quenched with sat. ammonium chloride (100

mL), the aqueous layer was extracted with ethyl acetate (2 × 250 mL). The combined organics dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude product. The crude was purified by flash chromatography (Biotage Isolera; silica gel 100-200 mesh) and a linear gradient of 0-30% ethyl acetate in hexane as eluent to afford 9,9-dimethyl-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-one. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.72 (d, J = 8.00 Hz, 2H), 7.61 (d, J = 8.00 Hz, 2H), 3.66 (s, 2H), 2.67 (t, J = 6.40 Hz, 2H), 2.50-2.42 (m, 4H), 1.77-1.71 (m, 2H), 1.47-1.41 (m, 2H), 1.19-1.15 (m, 2H), 1.14-1.06 (m, 2H), 0.80 (s, 3H), 0.75 (s, 3H).

Step 4: **Synthesis of 9,9-dimethyl-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl trifluoromethanesulfonate**

To a stirred solution of 9,9-dimethyl-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-one (500 mg, 1.42 mmol) in THF (5 mL) was added NaHMDS (2.12 mL, 2.12 mmol) at -78 °C under N_2 atmosphere and the resulting reaction mixture stirred for 30 min at -78 °C. Then 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (606 mg, 1.69 mmol) was added to the reaction mixture at -78 °C. The reaction mixture stirred for 2h at -78 °C. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine and concentrated under reduced pressure. The crude residue was purified by flash chromatography (Biotage Isolera; silica gel 100-200 mesh) and a linear gradient of 0-20% EtOAc in hexane as eluents to afford 9,9-dimethyl-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl trifluoromethanesulfonate. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.87 (d, J = 8.00 Hz, 1H), 7.79 (d, J = 8.00 Hz, 1H), 7.73-7.71 (m, 1H), 7.59-7.57 (m, 1H), 5.83-5.68 (m, 1H), 4.62 (s, 1H), 4.22-4.15 (m, 2H), 3.72 (s, 1H), 3.10 (s, 2H), 2.17 (s, 1H), 1.91 (s, 1H), 1.63 (t, J = 10.00 Hz, 1H), 1.47-1.40 (m, 3H), 1.15-1.00 (m, 2H), 0.93 (s, 3H), 0.89 (s, 3H).

Step 5: **3-(5-(9,9-dimethyl-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione**

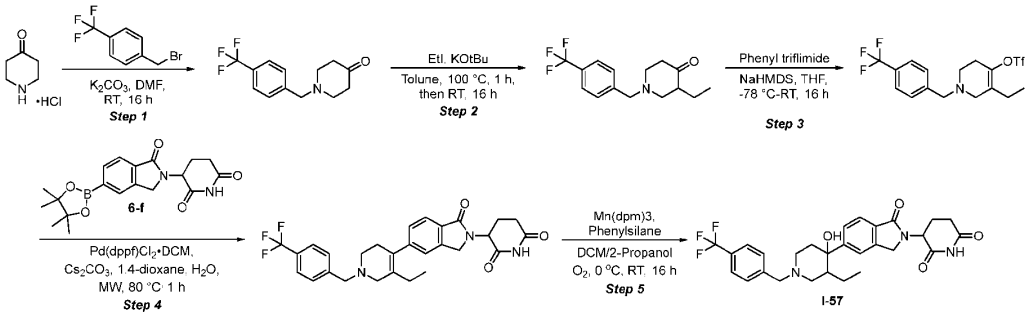
To the stirred solution of 3-(1-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-2-yl)piperidine-2,6-dione (170 mg, 0.459 mmol) in 1,4-dioxane (10 mL) in a microwave vial under nitrogen atmosphere were added 9,9-dimethyl-2-(4-(trifluoromethyl)-benzyl)-2-azaspiro[5.5]undec-4-en-5-yl trifluoromethanesulfonate (223 mg, 0.46 mmol) and K_2CO_3 (2M in water) (0.34 mL, 0.69 mmol) at room temperature. The resulting reaction mixture was purged with nitrogen for 10 min, then $PdCl_2$(dppf)-DCM adduct (38 mg, 0.046 mmol) was added, and the resulting reaction mixture was irradiated under microwave at 85 °C for 1 h. The reaction was filtered through a pad of celite, and the filtrate obtained was concentrated under reduced pressure. The crude residue was purified by flash chromatography (Biotage Isolera; silica gel 100-200 mesh) and a linear gradient of 50-100% ethyl acetate in hexane as eluent to

afford 3-(5-(9,9-dimethyl-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 580.5.

Step 6: **Synthesis of 3-(5-(5-hydroxy-9,9-dimethyl-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-55)**

To a stirred solution of 3-(5-(9,9-dimethyl-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (100 mg, 0.173 mmol) in dichloromethane (4 mL) and 2-propanol (2 mL) at 0 °C were added phenylsilane (37 mg, 0.35 mmol) and $Mn(dpm)_3$ (31.6 mg, 0.052 mmol). The resulting reaction mixture was stirred under oxygen bladder at 0 °C for 16 h. The solvents were distilled under reduced pressure and the crude product was purified by reverse phase chromatography using a C18 column, [Mobile phase A: HCl 0.1% in H_2O, Mobile phase B: ACN, flow rate: 10 mL/min)]. The fractions containing the product were combined and lyophilized to afford 3-(5-(5-hydroxy-9,9-dimethyl-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione **(I-55)**. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 598.3. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 9.82 (s, 1H), 7.98 (d, J = 8.00 Hz, 2H), 7.92 (d, J = 8.40 Hz, 2H), 7.73 (d, J = 8.40 Hz, 1H), 7.67 (d, J = 10.80 Hz, 1H), 7.59 (t, J = 9.20 Hz, 1H), 5.57 (s, 1H), 5.13 (dd, J = 5.20, 13.20 Hz, 1H), 4.58-4.46 (m, 3H), 4.39-4.33 (m, 1H), 3.37-3.10 (m, 1H), 3.10 (t, J = Hz, 1H), 2.91 (t, J = 5.20 Hz, 1H), 2.68-2.59 (m, 1H), 2.50-2.40 (m, 1H), 2.04 (t, J = 5.20 Hz, 2H), 1.76 (d, J = 13.20 Hz, 2H), 1.53 (d, J = 12.80 Hz, 2H), 0.99-0.90 (m, 6H), 0.67 (s, 3H), 0.31 (s, 3H).

Example 33: Synthesis of 3-(5-(3-ethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-57)



Step 1: **Synthesis of 1-(4-(trifluoromethyl)benzyl)piperidin-4-one**

To a stirred solution of piperidin-4-one (10 g, 73.8 mmol) in DMF (100 mL) was added K_2CO_3 (20.39 g, 148 mmol) at room temperature and stirred for 10 minutes. 1-(bromomethyl)-4-(trifluoromethyl)benzene (17.6 g, 73.8 mmol) was added at room temperature and the resulting reaction mixture was stirred for 16 h. The reaction mixture was poured in 50 mL ice cold water and extracted with ethyl acetate (2 × 50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The

crude residue was purified by flash chromatography (Biotage Isolera; silica gel 100-200 mesh) and a linear gradient of 0-100% EtOAc in hexane as eluents to afford 1-(4-(trifluoromethyl)benzyl)piperidin-4-one. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 258.0, ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.71 (d, J = 8.00 Hz, 2H), 7.60 (d, J = 8.00 Hz, 2H), 3.72 (s, 2H), 2.70 (d, J = 6.00 Hz, 2H), 2.36 (d, J = 6.00 Hz, 2H).

Step 2: **Synthesis of 3-ethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-one**

To a stirred solution of 1-(4-(trifluoromethyl)benzyl)piperidin-4-one (1 g, 3.89 mmol) in toluene (10 mL) was added KOtBu (0.57 g, 5.05 mmol) at 25 °C. The resulting reaction mixture was stirred at 100 °C, for 1 h. After 1 hour ethyl iodide (0.38 mL, 4.66 mmol) was added and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with water (100 mL) and extracted with ethyl acetate (2 × 200 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by Biotage Isolera (silica gel cartridge 50 g) using 0-100% ethyl acetate in hexane as an eluent. Pure fractions were concentrated to afford 3-ethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-one. LCMS: m/z MM-ES+APCI, Positive $[M-56]^+$ 286.6, ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.72 (d, J = 8.00 Hz, 2H), 7.60 (d, J = 8.00 Hz, 2H), 3.78-3.74 (m, 1H), 3.69-3.66 (m, 1H), 3.02-2.90 (m, 2H), 2.54-2.40 (m, 3H), 2.27-2.20 (m, 2H), 1.70-1.65 (m, 1H), 1.24-1.18 (m, 1H), 0.81 (t, J = 7.60 Hz, 3H).

Step 3: **Synthesis of 3-ethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate**

To a stirred solution of 3-ethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-one (0.6 g, 2.103 mmol) in THF (5 mL) was added NaHMDS (2.52 mL, 2.52 mmol) at -78 °C under N_2 atmosphere. The resulting reaction mixture stirred for 0.5 h at -78 °C and then N-phenyl-bis(trifluoromethanesulfonimide) (0.83 g, 2.31 mmol) was added at -78 °C. The reaction mixture was stirred for 16 h at 25 °C. The reaction was quenched with saturated ammonium chloride solution (50 mL) and extracted with the ethyl acetate (2 × 150 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude residue. The crude compound was purified by Biotage Isolera (silica gel cartridge 150 g) using 2% ethyl acetate in hexane as an eluent. The pure fractions were concentrated under reduced pressure to afford 3-ethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate. LCMS: m/z MM-ES+ APCI, Positive $[M+H]^+$ 418.7. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.72 (d, J = 8.00 Hz, 2H), 7.60 (d, J = 8.00 Hz, 2H), 3.79-3.68 (m, 2H), 3.33-3.19 (m, 2H), 3.15-3.02 (m, 2H), 2.51-2.50 (m, 2H), 1.66-1.45 (m, 2H), 0.83 (t, J = 7.60 Hz, 3H).

Step 3: **Synthesis of 3-(5-(3-ethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione**

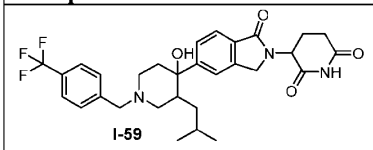
To a stirred solution of 3-(1-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-2-yl)piperidine-2,6-dione (**6-f**, 0.4 g, 1.08 mmol) in 1,4-dioxane (9 mL) and water (1 mL) was added 3-

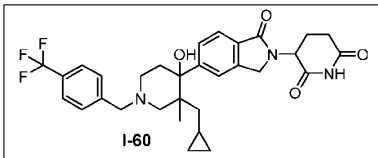
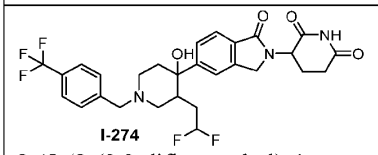
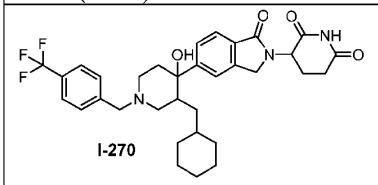
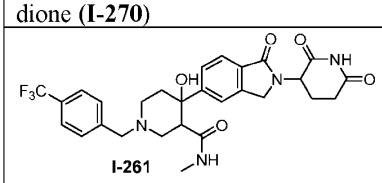
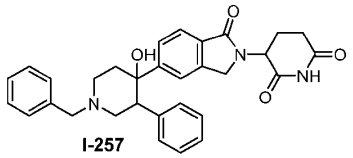
ethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (0.54 g, 1.29 mmol) and Cs_2CO_3 (0.70 g, 2.16 mmol). The reaction mixture was degassed with nitrogen for 10 minutes. Then, $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.088 g, 0.11 mmol) was added and again degassed with nitrogen for 10 minutes. The resulting mixture was stirred at 80 °C for 1 h under microwave. The reaction mixture was concentrated under reduced pressure and purified by Biotage Isolera (silica gel cartridge 150 g) using 80% ethyl acetate in hexane as an eluent. The pure fractions were concentrated under reduced pressure to afford 3-(5-(3-ethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione. LCMS: m/z MM-ES+ APCI, Positive $[M+H]^+$ 512.9. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 7.89-7.50 (m, 7H), 6.08 (s, 1H), 5.11 (t, J = 5.20 Hz, 1H), 4.45 (d, J = 4.80 Hz, 1H), 4.32 (d, J = 3.60 Hz, 1H), 3.32 (m, 1H), 2.96-2.50 (m, 9H), 2.42-2.33 (m, 2H), 2.02-1.99 (m, 1H), 1.99-1.33 (m, 2H), 0.72 (t, J = 7.20 Hz, 3H).

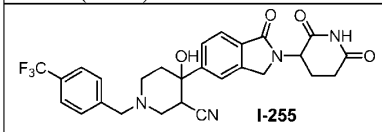
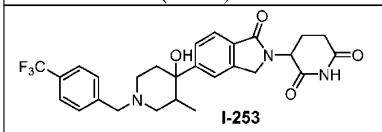
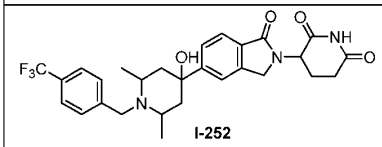
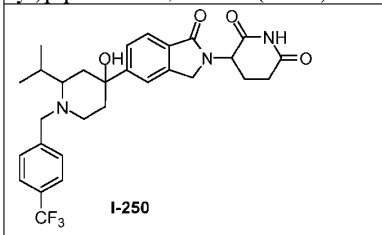
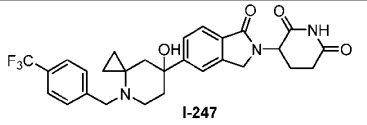
Step 5: **Synthesis of 3-(5-(3-ethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-57)**

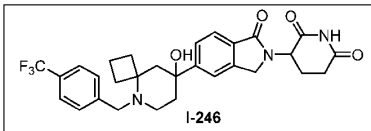
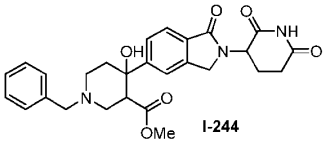
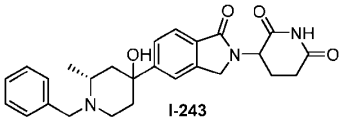
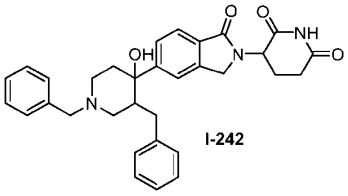
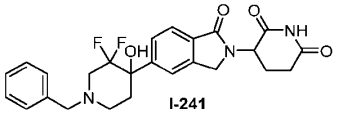
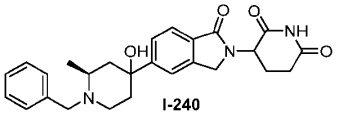
To a stirred solution of 3-(5-(3-ethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (0.4 g, 0.78 mmol) in IPA (10 mL) and DCM (10 mL) was added phenyl silane (0.24 mL, 1.95 mmol) and $Mn(dpm)_3$ (0.14 g, 0.23 mmol) under O_2 atmosphere, at 0 °C. The reaction mixture was stirred at the RT for 16 h. The reaction mixture was concentrated under reduced pressure and purified by preparative-HPLC [X Select C18(250 × 19 mm), Mobile phase A: 0.05% HCl in H_2O, Mobile phase B: ACN, flow rate: 15 mL/min, RT:12.5]. The pure fractions were collected and lyophilized to afford 3-(5-(3-ethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-57**). LCMS: m/z MM-ES+ APCI, Positive $[M+H]^+$ 530.2, ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 9.70 (s, 1H), 7.95-7.91 (m, 4H), 7.85 (d, J = 58.40 Hz, 1H), 7.68 (d, J = 34.00 Hz, 1H), 7.57-7.56 (m, 1H), 5.70 (s, 1H), 5.12 (t, J = 5.20 Hz, 1H), 4.54-4.44 (m, 3H), 4.36-4.36 (m, 1H), 3.48-3.33 (m, 2H), 3.19-2.92 (m, 1H), 2.92-2.63 (m, 1H), 2.58-2.51 (m, 2H), 2.41-2.38 (m, 2H), 2.02-1.99 (m, 3H), 1.95-1.86 (m, 1H), 0.57-0.53 (m, 3H).

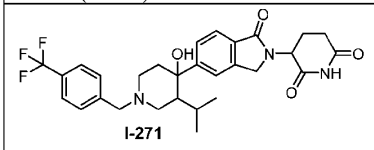
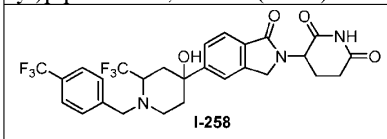
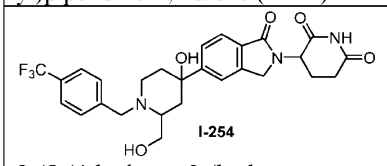
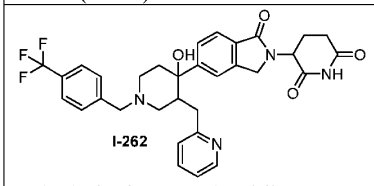
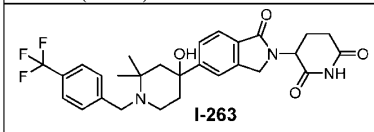
The following compounds were synthesized in a similar fashion to Example 33 (**I-57**).

Compound	Characterization
 I-59 3-(5-(4-hydroxy-3-isobutyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-59**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z M-ES+APCI, Positive $[M+H]^+$ 558.3. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 7.69-7.63 (m, 3H), 7.59-7.52 (m, 4H), 5.14-5.09-(m, 3H), 4.99 (s, 1H), 4.44-4.32 (s, 2H), 3.69-3.33 (m, 2H), 2.88-2.92 (m, 1H), 2.68-2.50 (m, 3H), 2.46-2.37 (m, 3H), 2.13-2.03 (m, 1H), 1.76-1.63 (m, 2H), 1.13-1.03(m, 1H), 0.65 (d, J =6.8Hz, 3H), 0.46-0.44 (m, 3H), 0.29-0.27 (m, 1H).

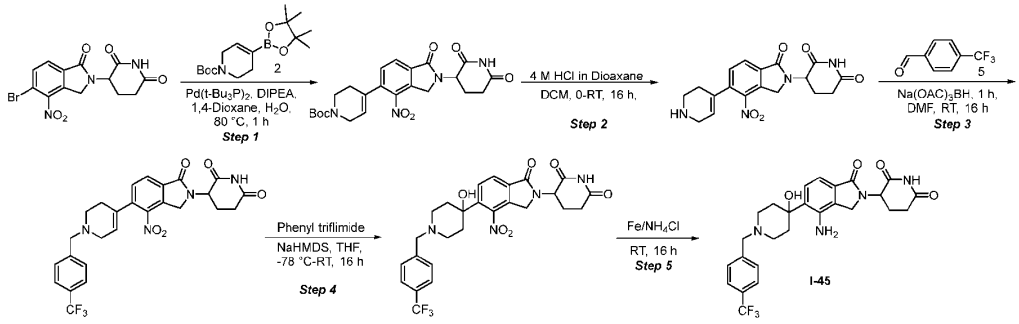
 I-60 3-(5-(3-(cyclopropylmethyl)-4-hydroxy-3-methyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-60**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z M-ES+APCI, Positive $[M+H]^+$ 570.4. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.03-10.94 (m, 1H), 8.45-8.39 (m, 1H), 7.74-7.69 (m, 2H), 7.68-7.53 (m, 5H), 5.15-5.06 (m, 1H), 4.87-4.76 (m, 1H), 4.48-4.39 (m, 1H), 4.34-4.25 (m, 1H), 3.64-3.58 (m, 1H), 3.54-3.48 (m, 2H), 2.96-2.86 (m, 1H), 2.63-2.57 (m, 2H), 2.44-2.33 (m, 2H), 2.05-1.94 (m, 2H), 1.90-1.83 (m, 1H), 1.49-1.41 (m, 1H), 1.27-1.21 (m, 1H), 1.06-1.03 (m, 1H), 0.87-0.79 (m, 1H), 0.78-0.75 (m, 2H), 0.56-0.49 (m, 1H), 0.38-0.31 (m, 1H), 0.24-0.16 (m, 2H),-0.01--0.08 (m, 1H),-0.19--0.26 (m, 1H).
 I-274 3-(5-(3-(2,2-difluoroethyl)-4-hydroxy-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-274**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 566.2, ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.71 (s, 1H), 7.69 (d, J = 8.00 Hz, 4H), 7.62 (d, J = 8.00 Hz, 3H), 5.22-5.13 (m, 1H), 5.11 (s, 1H), 5.09 (d, J = 3.20 Hz, 1H), 4.45 (d, J = 8.00 Hz, 1H), 4.34 (d, J = 8.00 Hz, 1H), 3.63 (s, 2H), 3.40-3.31 (m, 3H), 2.89-2.87 (m, 1H), 2.51-2.33 (m, 3H), 2.01-1.97 (m, 6H), 1.89 (s, 3H).
 I-270 3-(5-(3-(cyclohexylmethyl)-4-hydroxy-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-270**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 598.2. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 9.55 (br s,1H), 7.91 (d, J = 4.00 Hz, 3H), 7.74-7.56 (m, 4H), 5.69 (s, 1H), 5.13-4.50 (m, 4H), 3.18-2.97 (m, 1H), 2.68-2.68 (m, 2H), 2.34-2.34 (m, 2H), 2.09-2.02 (m, 4H), 1.52-1.42 (m, 8H), 0.95-0.85 (m, 6H), 0.37-0.32 (m, 2H).
 I-261 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-4-hydroxy-N-methyl-1-(4-(trifluoromethyl)-benzyl)piperidine-3-carboxamide (**I-261**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 559.3. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 9.22 (s, 1H), 8.12-7.64 (m, 7H), 6.07 (s, 1H), 5.14-5.09 (m, 1H), 4.45-4.31 (m, 3H), 3.73-3.66 (m, 1H), 3.54-3.50 (m, 1H), 3.32 (m, 3H), 2.98-2.89 (m, 2H), 2.69-2.68 (m, 1H), 2.62-2.51 (m, 2H), 2.42-2.41 (m, 2H), 2.39 (d, J = 4.00 Hz, 1H), 2.02-2.01 (m, 1H), 1.99-1.74 (m, 2H).
 I-257 3-(5-(1-benzyl-4-hydroxy-3-phenylpiperidin-4-yl)-1-	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 510.2; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 7.41-7.39 (m, 8H), 7.25-7.21 (m, 2H), 7.01 (s, 3H), 5.27 (s, 1H), 5.06 (dd, J = 4.80, 13.20 Hz, 1H), 4.20-4.10 (m, 2H), 3.62 (d, J = 13.20 Hz, 1H), 3.52 (d, J = 12.80 Hz, 1H), 2.98-2.89 (m, 4H), 2.69-2.68 (m, 2H), 2.67-2.64 (m, 2H), 2.50-2.50 (m, 1H), 1.81 (m, 1H), 1.76 (m, 1H).

oxoisoindolin-2-yl)piperidine-2,6-dione (**I-257**)	
 **I-255** 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidine-3-carbonitrile (**I-255**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 527.2. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 7.76-7.66 (m, 6H), 7.46-7.42 (m, 1H), 5.14 (s, 1H), 4.34 (m, 1H), 4.33-4.32 (m, 1H), 3.84-3.69 (m, 3H), 3.27-3.26 (m, 1H), 3.06-3.01 (m, 1H), 2.92-2.89 (m, 2H), 2.68-2.67 (m, 2H), 2.33-2.33 (m, 1H), 2.24-2.16 (m, 2H), 2.02-2.01 (m, 1H), 1.76 (m, 1H).
 **I-253** 3-(5-(4-hydroxy-3-methyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-253**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 516.2; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 9.80 (s, 1H), 7.93-7.88 (m, 4H), 7.74 (d, J = 8.00 Hz, 1H), 7.65 (s, 1H), 7.57-7.55 (m, 1H), 5.70 (s, 1H), 5.12 (dd, J = 5.20, 13.20 Hz, 1H), 4.53-4.49 (m, 3H), 4.46-4.35 (m, 1H), 3.55-3.54 (m, 1H), 3.41-3.36 (m, 2H), 3.08-3.05 (m, 1H), 2.92 (m, 1H), 2.68-2.67 (m, 1H), 2.63-2.51 (m, 1H), 2.50-2.50 (m, 1H), 2.25-2.15 (m, 1H), 2.10-1.90 (m, 2H), 0.73 (d, J = 7.60 Hz, 3H).
 **I-252** 3-(5-(4-hydroxy-2,6-dimethyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-252**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 530. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 10.76 (s, 1H), 8.04 (d, J = 8.00 Hz, 1H), 7.67-7.89 (m, 6H), 5.73-5.66 (m, 1H), 5.14-5.10 (m, 1H), 4.64-4.49 (m, 3H), 4.46-4.27 (m, 2H), 4.05-3.89 (m, 1H), 3.56-3.34 (m, 1H), 2.93-2.89 (m, 1H), 2.63-2.52 (m, 1H), 2.50-0.39 (m, 1H), 2.02-1.78 (m, 3H), 1.62-1.34 (m, 6H).
 **I-250** 3-(5-(4-hydroxy-2-isopropyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-250**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 544.1. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 7.73-7.60 (m, 7H), 5.14-5.05 (m, 2H), 4.46-4.44 (m, 1H), 4.34-4.30 (m, 1H), 4.20-4.16 (m, 1H), 2.93-2.88 (m, 1H), 2.67-2.55 (m, 3H), 2.40-2.35 (m, 1H), 2.30-2.20 (m, 1H), 1.99-1.96 (m, 2H), 1.87 (s, 2H), 1.76-1.62 (m, 2H), 1.50-1.44 (m, 1H), 0.88 (d, *J* = 6.80 Hz, 6H).
 **I-247** 3-(5-(7-hydroxy-4-(4-(trifluoromethyl)benzyl)-4-azaspiro[2.5]octan-7-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-247**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 528.3; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 10.00 (s, 1H), 7.97 (d, J = 8.40 Hz, 3H), 7.89 (t, *J* = 7.60 Hz, 3H), 7.78 (d, *J* = 8.00 Hz, 1H), 5.62 (s, 1H), 5.14 (q, *J* = 5.20 Hz, 1H), 5.07-4.97 (m, 1H), 4.80-4.74 (m, 1H), 4.52-4.47 (m, 1H), 4.39-4.35 (m, 1H), 3.72-3.62 (m, 1H), 3.02-2.94 (m, 3H), 2.65-2.51 (m, 1H), 2.45-2.42 (m, 1H), 2.04-2.02 (m, 1H), 1.83 (d, J = 13.60 Hz, 1H), 1.52-1.65 (m, 1H), 1.31 (d, J = 15.20 Hz, 1H), 1.21-1.10 (m, 1H), 1.05-0.90 (m, 1H), 0.80-0.72 (m, 1H).

 I-246 3-(5-(8-hydroxy-5-(4-(trifluoromethyl)benzyl)-5-azaspiro[3.5]nonan-8-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-246**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 542.1; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 7.76 (s, 1H), 7.71-7.65 (m, 6H), 5.12 (dd, J = 4.80, 13.40 Hz, 1H), 4.96 (s, 1H), 4.33 (d, J = 17.20 Hz, 1H), 4.18 (d, J = 17.20 Hz, 1H), 4.18 (d, J = 14.80 Hz, 1H), 3.51 (d, J = 15.20 Hz, 1H), 2.92-2.86 (m, 2H), 2.68-2.59 (m, 1H), 2.44-2.25 (m, 4H), 2.08-2.03 (m, 3H), 1.90-1.86 (m, 2H), 1.76-1.67 (m, 3H), 1.42 (d, J = 12.00 Hz, 1H).
 I-244 methyl 1-benzyl-4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-4-hydroxy-piperidine-3-carboxylate (**I-244**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 492.4. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 7.58-7.51 (m, 3H), 7.33-7.26 (m, 5H), 5.57 (s, 1H), 5.12-5.08 (m, 1H), 4.44-4.30 (m, 2H), 3.73-3.69 (m, 1H), 3.52 (s, 3H), 3.37-3.32 (m, 1H), 3.09-3.04 (m, 2H), 2.92-2.79 (m, 2H), 2.74-2.68 (m, 1H), 2.69-2.67 (m, 1H), 2.50-2.38 (m, 1H), 2.33 (t, J =2.0 Hz, 1H), 2.0-1.99 (m, 2H), 1.82-1.76 (m, 1H).
 I-243 3-(5-((2R)-1-benzyl-4-hydroxy-2-methylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-243**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 448.2. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 10.2 (s, 1H), 7.70-7.63 (m, 5H), 7.51-7.47 (m, 3H), 5.60 (s, 1H), 5.14-5.09 (m, 1H), 4.74-4.70 (m, 1H), 4.49-4.35 (m, 3H), 3.67 (s, 1H), 3.19-3.09 (m, 1H), 2.95-2.88 (m, 1H), 2.63-2.51 (m, 2H), 2.47-2.39 (m, 2H), 2.32 (d, J = 14.40 Hz, 1H), 2.02-1.88 (m, 2H), 1.81-1.76 (m, 1H), 1.58 (d, J = 9.60, Hz, 3H).
 I-242 3-(5-(1,3-dibenzyl-4-hydroxy-piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-242**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive [M+H]+ 524.2. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99 (m, 1H), 10.15 (s, 1H), 7.79-7.73 (m, 5H), 7.43-7.41 (m, 3H), 7.01 (t, J = 3.60 Hz, 3H), 6.85 (t, J = 2.80 Hz, 2H), 5.83 (s, 1H), 5.16-5.11 (m, 1H), 4.54-4.50 (m, 3H), 4.25 (m, 1H), 3.61 (s, 1H), 3.57 (s, 1H), 2.95 (t, J = 11.20 Hz, 3H), 2.67-2.53 (m, 2H), 2.51-2.46 (m, 2H), 2.18-2.03 (m, 3H), 1.88 (d, J = 11.20 Hz, 1H).
 I-241 3-(5-(1-benzyl-3,3-difluoro-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-241**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 470.10; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 2H), 7.78-7.48 (m, 8H), 6.90 (bs, 1H), 5.15-5.10 (m, 1H), 4.52-4.33 (m, 4H), 3.41-2.63 (m, 4H), 2.42-2.38 (m, 2H), 2.37-2.33 (m, 2H), 2.03-2.00 (m, 2H).
 I-240 3-(5-((2S)-1-benzyl-4-hydroxy-2-methylpiperidin-4-yl)-1-	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 446.0; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 10.6-10.5 (br, 1H), 7.76-7.60 (m, 5H), 7.49-7.44 (m, 3H), 5.76 (bs, 1H), 5.13-5.10 (m, 1H), 4.80-4.66 (m, 2H), 4.48-4.31 (m, 2H), 3.47-3.35 (m, 1H),

oxoisoindolin-2-yl)piperidine-2,6-dione (**I-240**)	2.68-2.58 (m, 3H), 2.46-2.35 (m, 2H), 2.01-1.99 (m, 2H), 1.60-1.54 (m, 3H), 1.48 (d, *J* = 4.0 Hz, 3H).
 **I-271** 3-(5-(4-hydroxy-3-isopropyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-271**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, $[M+H]^+$ 544.7. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 9.42 (bs, 1H), 7.94-7.85 (m, 4H), 7.71-7.65 (m, 3H), 5.73 (s, 1H), 5.15-5.10 (m, 1H), 4.48-4.37 (m, 4H), 3.44-3.34 (m, 3H), 3.10 (d, *J* = 12.40 Hz, 1H), 2.68-2.63 (m, 2H), 2.51-2.42 (m, 1H), 2.03-2.02 (m, 2H), 1.75 (m, 1H), 0.90 (d, *J* = 6.80 Hz, 1H), 0.62 (d, *J* = 6.40 Hz, 3H), 0.19 (t, *J* = 6.40 Hz, 1H), 0.01 (d, *J* = 0.40 Hz, 3H).
 **I-258** 3-(5-(4-hydroxy-2-(trifluoromethyl)-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-258**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 570.0; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 7.78-7.73 (m, 5H), 7.64 (d, *J* = 7.60 Hz, 2H), 5.12 (dd, *J* = 4.80, 13.40 Hz, 1H), 4.48 (d, *J* = 2.00 Hz, 1H), 4.44 (d, *J* = 1.60 Hz, 1H), 4.35 (d, *J* = Hz, 1H), 3.69 (m, 2H), 2.95-2.91 (m, 2H), 2.63-2.52 (m, 2H), 2.51-2.50 (m, 2H), 2.13-2.08 (m, 3H), 1.96 (d, *J* = 26.80 Hz, 1H), 1.62 (d, *J* = Hz, 1H).
 **I-254** 3-(5-(4-hydroxy-2-(hydroxy-methyl)-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-254**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 532.0; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 7.74-7.60 (m, 7H), 5.13-5.06 (m, 2H), 4.56 (m, 1H), 4.44-4.29 (m, 3H), 3.61-3.49 (m, 3H), 2.95-2.80 (m, 2H), 2.78-2.51 (m, 1H), 2.02-1.99 (m, 4H), 1.80-1.77 (m, 2H), 1.54-1.51 (m, 2H).
 **I-262** 3-(5-(4-hydroxy-3-(pyridin-2-ylmethyl)-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-262**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 593.3; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 8.35 (s, 1H), 7.95 (d, J = 8.00 Hz, 2H), 7.73-7.61 (m, 7H), 7.30 (s, 1H), 5.90 (s, 1H), 5.15-5.10 (m, 1H), 4.60-4.48 (m, 4H), 3.54-3.40 (m, 6H), 3.05-2.92 (m, 2H), 2.67-2.64 (m, 1H), 2.50-2.43 (m, 2H), 2.11-2.02 (m, 2H).
 **I-263** 3-(5-(4-hydroxy-2,2-dimethyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-263**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 530.5; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 7.94-7.88 (m, 4H), 7.73 (d, J = 8.00 Hz, 1H), 7.69 (s, 1H), 7.64 (d, J = 8.00 Hz, 1H), 5.65 (s, 1H), 5.14-5.09 (m, 1H), 4.81 (d, J = 12.80 Hz, 1H), 4.48-4.43 (m, 2H), 4.14 (d, J = 8.80 Hz, 1H), 3.59-3.50 (m, 1H), 3.08 (d, J = 12.40 Hz, 1H), 2.95-2.91 (m, 1H), 2.62-2.58 (m, 1H), 2.51-2.50 (m, 3H), 2.01-1.99 (m, 1H), 1.98-1.92 (m, 1H), 1.88-1.78 (m, 1H), 1.67 (s, 3H), 1.65 (s, 3H).

Example 34: Synthesis of 3-(4-amino-5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-45)



Step 1: **Synthesis of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-nitro-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate**

To the solution of 3-(5-bromo-4-nitro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (500 mg, 1.36 mmol) in 1,4-dioxane (8 mL) and water (2 mL) in a microwave vial was added tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (630 mg, 2.04 mmol) and DIPEA (439 mg, 3.40 mmol) at 25 °C. The mixture was purged with N_2 for 15 min. To this resulting mixture was added bis(tri-tert-butylphosphine) palladium(0) (69.4 mg, 0.14 mmol) and the reaction mixture was irradiated under microwave at 80 °C for 1 h. The excess solvent was evaporated and the crude residue was purified by flash chromatography using Biotage Isolera (Silica gel 100-200 mesh) and a linear gradient of 0-100% ethyl acetate in hexane as eluents to afford tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-nitro-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate. LCMS: m/z MM-ES+APCI, Positive $[M-56]^+$ 415.3. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.89 (s, 1H), 8.05 (d, J = 7.60 Hz, 1H), 7.64 (d, J = 8.00 Hz, 1H), 5.75 (s, 1H), 5.16 (t, J = 8.40 Hz, 1H), 4.77 (m, 1H), 4.65 (m, 1H), 3.97 (m, 2H), 3.57-3.55 (m, 2H), 2.91-2.88 (m, 1H), 2.63-2.58 (m, 1H), 2.58-2.52 (m, 1H), 2.51-2.51 (m, 2H), 2.03-1.99 (m, 1H), 1.45 (s, 9H).

Step 2: **Synthesis of 3-(4-nitro-1-oxo-5-(1,2,3,6-tetrahydropyridin-4-yl)isoindolin-2-yl)piperidine-2,6-dione**

To a stirred solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-nitro-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (200 mg, 0.43 mmol) in DCM (8 mL) at 0 °C was added 4 M HCl in 1,4-dioxane (0.53 mL, 2.13 mmol) and stirred at room temperature for 16 h The reaction was concentrated and the crude compound was washed with n-pentane to afford 3-(4-nitro-1-oxo-5-(1,2,3,6-tetrahydropyridin-4-yl)isoindolin-2-yl)piperidine-2,6-dione. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 371.3, ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.04 (s, 1H), 9.16 (s, 2H), 8.12 (d, J = 7.60 Hz, 1H), 7.59 (d, J

= 7.60 Hz, 1H), 5.77 (s, 1H), 5.17 (t, J = 5.20 Hz, 1H), 4.80-4.68 (m, 2H), 3.39-3.33 (m, 2H), 3.94-3.33 (m, 1H), 2.92-2.89 (m, 1H), 2.68-2.63 (m, 3H), 2.10-1.92 (m, 1H).

Step 3: **Synthesis of 3-(4-nitro-1-oxo-5-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)isoindolin-2-yl)piperidine-2,6-dione**

To a stirred solution of 3-(4-nitro-1-oxo-5-(1,2,3,6-tetrahydropyridin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (430 mg, 1.16 mmol) in DMF (8 mL) was added 4-(trifluoromethyl)-benzaldehyde (243 mg, 1.39 mmol) and stirred for 1 h at room temperature. Sodium triacetoxyborohydride (615 mg, 2.90 mmol) was then added and stirred at room temperature for 16 h. The excess solvent was evaporated and the crude residue was purified by flash chromatography using Biotage Isolera (Silica gel 100-200 mesh) and a linear gradient of 5% IPA in DCM as eluent to afford 3-(4-nitro-1-oxo-5-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)isoindolin-2-yl)piperidine-2,6-dione. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 530.0. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 8.02 (d, J = 8.00 Hz, 1H), 7.70 (d, J = 25.20 Hz, 2H), 7.62 (dd, J = 8.00, 15.80 Hz, 3H), 5.72 (s, 1H), 5.14 (t, J = 5.20 Hz, 1H), 4.75 (d, J = 18.40 Hz, 1H), 4.62 (d, J = 18.80 Hz, 1H), 3.73 (s, 2H), 3.33-3.07 (m, 2H), 2.91-2.70 (m, 1H), 2.61-2.53 (m, 2H), 2.52-2.51 (m, 1H), 2.51-2.50 (m, 1H), 2.50-2.34 (m, 2H), 2.02-1.91 (m, 1H).

Step 4: **Synthesis of 3-(5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-nitro-1-oxoisoindolin-2-yl)piperidine-2,6-dione:**

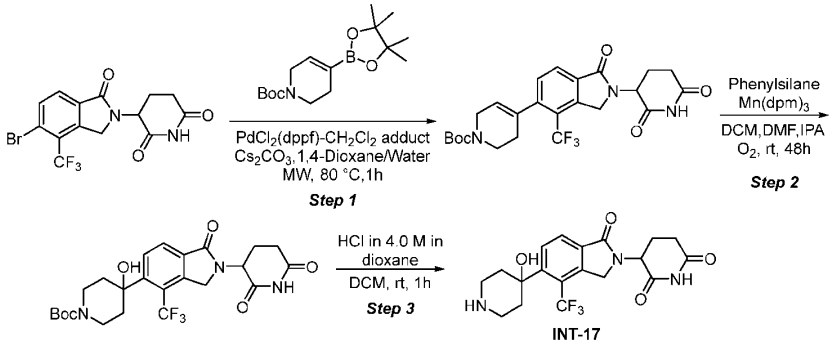
To a stirred solution of 3-(4-nitro-1-oxo-5-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (200 mg, 0.38 mmol) in DCM (5 mL) and 2-propanol (5 mL) were added phenylsilane (82 mg, 0.76 mmol) and $Mn(dpm)_3$ (69.3 mg, 0.11 mmol). The mixture stirred under O_2 bladder at 0 °C for 16 h. The excess solvents were evaporated to afford crude residue which was purified by reverse phase [Column: X select (150 mm × 19) 5 µm, Mobile phase A: 0.05% formic acid in H_2O, Mobile phase B: ACN, flow rate: 15 mL/min)]. The fractions containing the product were combined and lyophilized to afford 3-(5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-nitro-1-oxoisoindolin-2-yl)piperidine-2,6-dione. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 545.1. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 7.89 (d, J = 8.00 Hz, 1H), 7.83 (d, J = 8.40 Hz, 1H), 7.70 (d, J = 8.00 Hz, 2H), 7.58 (d, J = 8.00 Hz, 2H), 5.51 (s, 1H), 5.12 (t, J = 8.40 Hz, 1H), 4.46 (d, J = 18.00 Hz, 1H), 4.30 (d, J = 17.60 Hz, 1H), 3.61 (s, 2H), 2.91-2.85 (m, 2H), 2.63-2.60 (m, 2H), 2.51-2.50 (m, 2H), 2.05-2.01 (m, 1H), 1.99-1.87 (m, 3H), 1.38-1.11 (m, 2H).

Step 5: **Synthesis of 3-(4-amino-5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-45)**

To a stirred solution of 3-(5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-nitro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (50 mg, 0.091 mmol) in ethanol (5 mL) and water (5 mL) were

added NH_4Cl (49 mg, 0.92 mmol) and Fe (25.5 mg, 0.46 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 h., filtered through a pad of celite and concentrated. The crude residue was purified by preparative-HPLC [(Column: X select (150 mm × 19) 5 µm, Mobile phase A: 0.05% HCl in H_2O, Mobile phase B: ACN, flow rate: 15 mL/min)]. The pure fractions were collected and lyophilized to afford 3-(4-amino-5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-45**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 517.4. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 10.33 (s, 1H), 7.90-7.86 (m, 4H), 7.22 (d, J = 7.60 Hz, 1H), 6.97 (d, J = 8.00 Hz, 1H), 5.94 (s, 1H), 5.13 (s, 1H), 5.10 (t, J = 4.80 Hz, 1H), 4.50 (d, J = 5.20 Hz, 2H), 4.24 (d, J = 16.80 Hz, 1H), 4.12 (d, J = 17.20 Hz, 1H), 3.36-3.29 (m, 2H), 2.94-2.89 (m, 1H), 2.65-2.60 (m, 1H), 2.51-2.50 (m, 3H), 2.29-2.22 (m, 4H), 2.05-2.01 (m, 1H).

Example 35: Synthesis of 3-(5-(4-hydroxypiperidin-4-yl)-1-oxo-4-(trifluoromethyl)-isoindolin-2-yl)piperidine-2,6-dione (INT-17)



Step 1: **Synthesis of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxo-4-(trifluoromethyl)-isoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate**

The stirring solution of 3-(5-bromo-1-oxo-4-(trifluoromethyl)isoindolin-2-yl)piperidine-2,6-dione (0.5 g, 1.28 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (0.39 g, 1.28 mmol) and Cs_2CO_3 (0.833 g, 2.56 mmol) in 1,4-dioxane (10 mL) and water (1 mL) was purged with N_2 at room temperature over 10 minutes. To this resulting mixture was added $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.10 g, 0.12 mmol) in one lot and the reaction mixture was again purged with N_2 for 10 min. This resulting reaction mixture was subjected to react under microwave irradiation at 80 °C for 1 h. The reaction mixture was filtered through a pad of celite and washed with ethyl acetate (10 mL). The filtrate was concentrated under reduced pressure and the crude compound was purified by reverse phase [C18 column, 40 g, (Mobile phase A: 0.1% FA in H_2O, Mobile phase B: ACN, flow rate: 15 mL/min), RT: 10.5]. Pure fractions were lyophilized to afford tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxo-4-(trifluoromethyl)isoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate. LCMS: m/z MM-ES+APCI, Negative $[M-H]^-$ 492.2. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 7.99 (d, J = 7.20 Hz,

1H), 7.54 (d, J = 7.20 Hz, 1H), 5.64 (s, 1H), 5.17-5.14 (m, 1H), 4.70-4.50 (m, 2H), 3.97-3.96 (m, 2H), 3.55-3.54 (m, 2H), 3.33-3.32 (m, 1H), 2.92-2.88 (m, 1H), 2.62-2.51 (m, 1H), 2.33-2.32 (m, 2H), 2.06-2.01 (m, 1H), 1.43 (s, 9H).

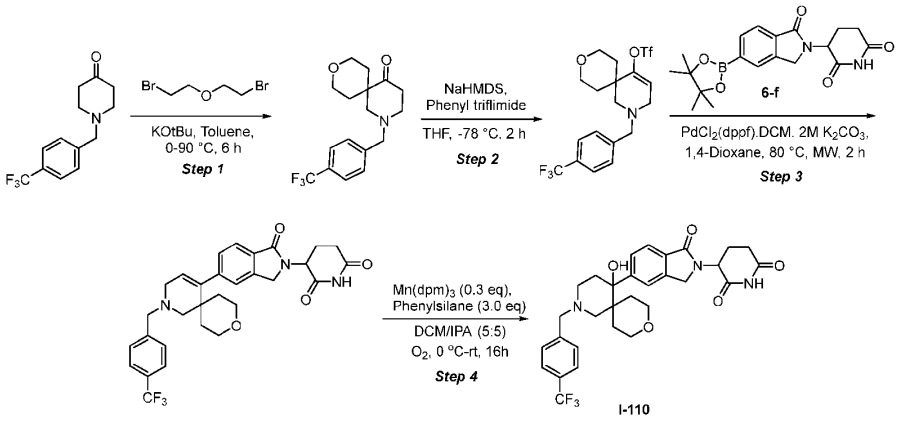
Step 2: **Synthesis of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxo-4-(trifluoromethyl)-isoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate**

A stirred solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxo-4-(trifluoromethyl)-isoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (0.3 g, 0.61 mmol) in 2-propanol (10 mL), DMF (5 mL), and DCM (10 mL) was purged with O_2 at room temperature over 10 minutes at 0 °C. To this resulting mixture was added $Mn(dpm)_3$ (0.44 g, 0.72 mmol) and phenyl silane (0.26 g, 2.42 mmol) under O_2 at 0 °C. The reaction mixture was again purged with O_2 for 10 min. This resulting reaction mixture was stirred at room temperature for 32 h. The reaction mixture was concentrated under reduced pressure to get crude compound. The crude compound was triturated with pentane (10 mL × 2) and the collected solid was dried to under reduced pressure. The crude compound was purified by reverse phase chromatography [C18, 40 g, (Mobile phase A: 0.1% FA in H_2O, Mobile phase B: ACN, flow rate: 15 mL/min), RT: 10.5]. Pure fractions were lyophilized to afford tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxo-4-(trifluoromethyl)isoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate. LCMS: m/z MM-ES+APCI, Negative $[M-H]^-$ 510.2; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 7.63 (d, J = 7.60 Hz, 1H), 7.37 (d, J = 7.60 Hz, 1H), 5.17-5.14 (m, 1H), 5.36 (s, 1H), 5.16-5.12 (m, 1H), 4.69-4.55 (m, 2H), 3.89-3.86 (m, 2H), 2.92-2.88 (m, 2H), 2.68-2.57 (m, 2H), 2.02-1.98 (m, 3H), 1.82-1.78 (m, 2H), 1.43 (s, 9H).

Step 3: **Synthesis of 3-(5-(4-hydroxypiperidin-4-yl)-1-oxo-4-(trifluoromethyl)isoindolin-2-yl)piperidine-2,6-dione (INT-17)**

To a stirred solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxo-4-(trifluoromethyl)isoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate (0.1 g, 0.19 mmol) in DCM (2 mL) was added 4 M HCl in 1,4-dioxane (0.036 g, 0.98 mmol) at 0 °C and stirred for 2h. The reaction mixture was directly concentrated under reduced pressure to get crude compound. The crude compound was triturated with MTBE (2 × 5 mL), and dried under vacuum to afford 3-(5-(4-hydroxypiperidin-4-yl)-1-oxo-4-(trifluoromethyl)isoindolin-2-yl)piperidine-2,6-dione (**INT-17**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 411.7; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 8.57-8.44 (m, 1H), 8.05 (d, J = 8.00 Hz, 1H), 7.80 (d, J = 8.00 Hz, 1H), 5.69 (s, 1H), 5.15 (dd, J = 5.20, 13.20 Hz, 1H), 4.75 (d, J = 31.20 Hz, 1H), 4.54 (d, J = 16.40 Hz, 1H), 3.51-3.34 (m, 2H), 2.96-2.88 (m, 1H), 2.68-2.51 (m, 6H), 2.34-2.26 (m, 1H), 2.04-2.01 (m, 2H).

Example 36: Synthesis of 3-(5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-9-oxa-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-110)



Step 1: **Synthesis of 2-(4-(trifluoromethyl)benzyl)-9-oxa-2-azaspiro[5.5]undecan-5-one**

To a stirred solution of 1-(4-(trifluoromethyl)benzyl)piperidin-4-one (5 g, 19.44 mmol) in toluene (30.0 mL) under nitrogen atmosphere at 0° C was added potassium tert-butoxide (1M THF, 38.9 mL, 38.9 mmol). After 40 min, 1-bromo-2-(2-bromoethoxy)ethane (4.51 g, 19.44 mmol) was added to the reaction mixture and then heated to 90°C for 6 h. The reaction was quenched with sat NH_4Cl (20 mL) and diluted with ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried over sodium sulfate, concentrated under reduced pressure, and purified by flash column chromatography using Biotage isolera (silica gel 100-200 mesh) and a linear gradient of 0-10% EtOAc in hexane as eluent to afford 2-(4-(trifluoromethyl) benzyl)-9-oxa-2-azaspiro [5.5]undecan-5-one. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 328; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.72 (d, J = 4.00 Hz, 2H), 7.60 (d, J = 8.00 Hz, 2H), 3.71 (t, J = 3.30 Hz, 2H), 3.66 (t, J = 7.20 Hz, 2H), 3.57 (s, 2H), 2.69 (t, J = 2.00 Hz, 1H), 2.55-2.53 (m, 2H), 2.49 (s, 2H), 2.37 (t, J = 6.00 Hz, 1H), 1.93 (d, J = 5.60 Hz, 2H), 1.48 (t, J = 2.40 Hz, 2H).

Step 2: **Synthesis of 2-(4-(trifluoromethyl) benzyl)-9-oxa-2-azaspiro [5.5]undec-4-en-5-yl trifluoromethanesulfonate**

To a stirred solution of 2-(4-(trifluoromethyl) benzyl)-9-oxa-2-azaspiro [5.5]undecan-5-one (1 g, 3.05 mmol) in THF (10 mL) was added NaHMDS (6.11 mL, 6.11 mmol) at -78 °C under N_2 atmosphere and stirred for 1 h. The reaction mixture was again cooled to -78 °C and added 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (1.64 g, 4.58 mmol) in THF (10 mL). The reaction mixture was stirred at -78 °C for 2 h under N_2 atmosphere. The reaction mixture was quenched with sat. NH_4Cl at 0 °C and extracted with EtOAc (2 × 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to get crude compound. The crude compound was purified by flash column chromatography using Biotage isolera (silica gel 100-200 mesh) and a linear gradient of 0-5% EtOAc in hexane as eluent to afford 2-(4-(trifluoromethyl)benzyl)-9-oxa-2-

azaspiro[5.5]undec-4-en-5-yl trifluoromethanesulfonate. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 460; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.72 (d, J = 8.40 Hz, 2H), 7.57 (d, J = 8.00 Hz, 2H), 5.89 (t, J = 3.60 Hz, 1H), 3.77 (s, 2H), 3.65 (t, J = 4.40 Hz, 2H), 3.23-3.20 (m, 2H), 3.12 (s, 2H), 2.77 (s, 2H), 1.75-1.70 (m, 2H), 1.54 (m, 2H).

Step 3: **Synthesis of 3-(1-oxo-5-(2-(4-(trifluoromethyl)benzyl)-9-oxa-2-azaspiro[5.5]undec-4-en-5-yl)isoindolin-2-yl)piperidine-2,6-dione**

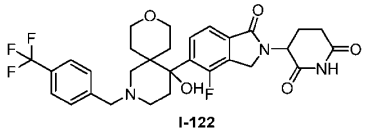
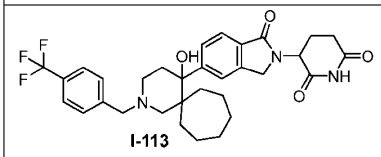
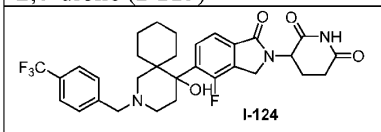
A stirred solution of 2-(4-(trifluoromethyl)benzyl)-9-oxa-2-azaspiro[5.5]undec-4-en-5-yl trifluoromethanesulfonate (400 mg, 0.87 mmol), 3-(1-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-2-yl)piperidine-2,6-dione (**6-f**, 322 mg, 0.87 mmol), and K_2CO_3 (2M in water) (0.65 mL, 1.31 mmol) in 1,4-dioxane (5 mL) was purged with N_2 at room temperature over 10 minutes. To this resulting mixture was added $PdCl_2$(dppf)-CH_2Cl_2 adduct (213 mg, 0.26 mmol) and the reaction mixture was again purged with N_2 for 10 min. The reaction was irradiated by microwave at 80 °C for 1 h. The reaction mixture was filtered through a pad of celite and washed with EtOAc (20 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography using Biotage isolera (silica gel 230-400 mesh) and a linear gradient of 50-100% EtOAc in hexane as eluent to afford 3-(1-oxo-5-(2-(4-(trifluoromethyl)benzyl)-9-oxa-2-azaspiro [5.5] undec-4-en-5-yl) isoindolin-2-yl) piperidine-2,6-dione. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 554; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 7.74-7.70 (m, 3H), 7.64 (t, J = 8.00 Hz, 2H), 7.35 (s, 1H), 7.25 (d, J = 7.60 Hz, 2H), 5.52 (t, J = 3.20 Hz, 1H), 5.12 (d, J = 4.80 Hz, 1H), 4.41 (d, J = 37.60 Hz, 1H), 4.34 (d, J = 17.20 Hz, 1H), 3.76 (s, 2H), 3.52 (t, J = 6.80 Hz, 2H), 3.22 (t, J = 12.00 Hz, 2H), 3.22 (t, J = 12.00 Hz, 1H), 2.95-2.92 (m, 2H), 2.79-2.72 (m, 1H), 2.63 (s, 1H), 2.51-2.50 (m, 1H), 2.51-2.50 (m, 1H), 1.98 (t, J = 12.80 Hz, 1H), 1.66-1.53 (m, 3H).

Step 4: **Synthesis of 3-(5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-9-oxa-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-110)**

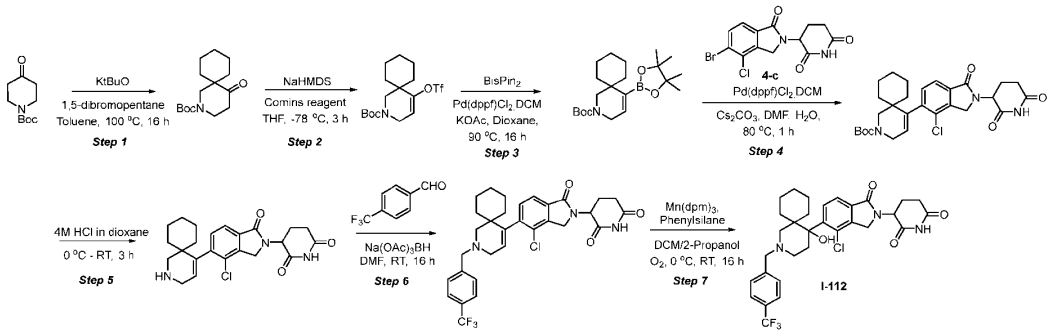
A stirred solution of 3-(1-oxo-5-(2-(4-(trifluoromethyl) benzyl)-9-oxa-2-azaspiro[5.5]-undec-4-en-5-yl)isoindolin-2-yl)piperidine-2,6-dione (500 mg, 0.903 mmol) in DCM:2-Propanol (9:1) (100 mL) was purged with O_2 at room temperature over 10 minutes at 0 °C. To this resulting mixture was added $Mn(dpm)_3$ (1.09 g, 1.81 mmol) and phenyl silane (0.33 mL, 2.71 mmol) were added under O_2 at 0 °C and the reaction mixture was again purged with O_2 for 10 min. The reaction was stirred at room temperature for 48 h and then concentrated under reduced pressure to get crude compound. The crude residue was triturated with pentane (10 mL × 2) and the collected solid was dried to under reduced pressure. The crude compound was purified by flash column chromatography using Biotage isolera (silica gel 230-400 mesh) and a linear gradient of 20-100% EtOAc in hexane as eluent, following by preparative HPLC purification [(Column: X select (C18 150 mm × 19) 5 µm, Mobile phase A: 0.05% HCl in H_2O, Mobile

phase B: ACN, flow rate: 15 mL/min)]. Pure fractions were lyophilized to afford 3-(5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-9-oxa-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-110**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 572.6; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 10.19 (s, 1H), 7.98 (d, J = 7.60 Hz, 2H), 7.91 (d, J = 8.00 Hz, 2H), 7.67 (s, 1H), 7.61-7.55 (m, 2H), 5.67 (d, J = 6.00 Hz, 1H), 5.13 (t, J = 4.80 Hz, 1H), 4.58 (s, 2H), 4.52 (d, J = 5.60 Hz, 1H), 4.34 (t, J = 5.20 Hz, 1H), 3.86 (d, J = 12.40 Hz, 1H), 3.53 (t, J = 14.80 Hz, 2H), 3.41 (m, 2H), 3.27-3.20 (m, 2H), 2.93-2.88 (m, 2H), 2.61 (d, J = 17.20 Hz, 1H), 2.41 (m, 2H), 2.34 (d, J = 30.40 Hz, 1H), 2.01 (t, J = 5.20 Hz, 1H), 1.77 (d, J = 13.20 Hz, 1H), 1.51 (m, 1H), 1.47 (m, 1H).

The following compounds were synthesized in a similar fashion to Example 36 (**I-110**).

Compound	Characterization
 I-122 3-(4-fluoro-5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-9-oxa-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-122**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 590.2; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 10.10 (s, 1H), 7.95 (t, J = 4.40 Hz, 1H), 7.86 (t, J = 6.80 Hz, 1H), 7.65 (d, J = 3.20 Hz, 2H), 7.63 (d, J = 3.20 Hz, 2H), 5.94 (s, 1H), 5.13 (t, J = 4.80 Hz, 1H), 4.61 (s, 2H), 4.58-4.35 (m, 3H), 3.91 (s, 2H), 3.88 (m, 1H), 3.60-3.21 (m, 4H), 3.17 (d, J = Hz, 1H), 2.92-2.91 (m, 1H), 2.67-2.51 (m, 2H), 2.09-2.00 (m, 1H), 1.91 (s, 1H), 1.90 (s, 1H), 1.49-1.16 (m, 3H).
 I-113 3-(5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.6]dodecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-113**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 584.6, 585.5; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 7.76-7.67 (m, 5H), 7.65-7.57 (m, 2H), 5.14-5.10 (m, 1H), 4.82 (s, 1H), 4.47-4.42 (m, 1H), 4.34-4.30 (m, 1H), 3.68-3.64 (m, 1H), 3.55-3.52 (m, 1H), 2.92-2.63 (m, 3H), 2.58-2.50 (m, 3H), 2.42-2.37 (m, 2H), 2.31-2.30 (m, 1H), 2.06-2.02 (m, 1H), 1.90-1.85 (m, 1H), 1.45-1.42 (m, 1H), 1.38-1.24 (m, 3H), 1.06-1.00 (m, 7H).
 I-124 3-(4-fluoro-5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-124**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z HESI, positive $[M+H]^+$ = 588. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 10.14 (br s, 1H), 7.98 (d, J = 8.2 Hz, 2H), 7.91 (d, J = 8.2 Hz, 2H), 7.87-7.80 (m, 1H), 7.62 (d, J = 8.2 Hz, 1H), 6.53 (br s, 1H), 5.89-5.74 (m, 1H), 5.19-5.05 (m, 1H), 4.62-4.48 (m, 3H), 4.47-4.32 (m, 1H), 3.58-3.49 (m, 1H), 3.29-3.20 (m, 2H), 3.19-3.05 (m, 1H), 2.96-2.84 (m, 1H), 2.66-2.56 (m, 1H), 2.48-2.35 (m, 2H), 2.08-1.93 (m, 1H), 1.92-1.80 (m, 1H), 1.75 (br d, J = 12.0 Hz, 1H), 1.50-1.29 (m, 2H), 1.28-1.16 (m, 2H), 1.10-0.97 (m, 1H), 0.95-0.84 (m, 1H), 0.84-0.71 (m, 2H).

Example 37: Synthesis of 3-(4-chloro-5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-112)



Step 1: **Synthesis of *tert*-butyl 5-oxo-2-azaspiro[5.5]undecane-2-carboxylate**

To a stirred solution of *tert*-butyl 4-oxopiperidine-1-carboxylate (10 g, 50.2 mmol) in toluene (100 mL), was added potassium *tert*-butoxide (11.26 g, 100 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 1 h. To this resulting mixture was added 1,5-dibromopentane (11.49 g, 50.2 mmol) and the reaction mixture was stirred at 100 °C for 16 h. The reaction mixture was cooled at 0 °C and quenched with sat. NH_4Cl and diluted with EtOAc. Both layers were separated, and aqueous portion was extracted with EtOAc (2 × 100 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 250-400 mesh, gradient EtOAc/hexane) and the compound was eluted at 10% EtOAc/hexane. The pure fractions were concentrated under reduced pressure to afford *tert*-butyl 5-oxo-2-azaspiro[5.5]undecane-2-carboxylate. LCMS: m/z MM-ES+APCI, Positive $[M-100]^+$ 168; ^1H NMR (400 MHz, $CDCl_3$) δ 3.75-3.71 (m, 2H), 3.58-3.54 (m, 2H), 1.77-1.73 (m, 2H), 1.54-1.50 (m, 10H), 1.48 (s, 9H).

Step 2: **Synthesis of *tert*-butyl 5-(((trifluoromethyl)sulfonyl)oxy)-2-azaspiro[5.5]undec-4-ene-2-carboxylate**

To a stirred solution of *tert*-butyl 5-oxo-2-azaspiro[5.5]undecane-2-carboxylate (8 g, 29.9 mmol) in THF (80 mL), was added NaHMDS (44.9 mL, 44.9 mmol) at -78 °C under nitrogen. The resulting reaction mixture was stirred at room temperature for 30 min. at -78 °C, and Comins' reagent (12.83 g, 35.9 mmol) was added. The reaction mixture stirred for 3h at -78 °C. The reaction mixture was quenched with sat. NH_4Cl and diluted with EtOAc. Both layers were separated and aqueous portion was extracted with EtOAc (2 × 100 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 250-400 mesh, gradient EtOAc /hexane). The pure fractions were concentrated under reduced pressure to obtain tert-butyl 5-(((trifluoromethyl)sulfonyl)oxy)-2-azaspiro[5.5]undec-4-ene-2-carboxylate. LCMS:

MM-ES+APCI, Positive $[M+H]^+$ 399; ^1H NMR (400 MHz, $CDCl_3$) δ 5.72-5.32 (m, 1H), 4.08-4.05 (m, 2H), 3.64-3.60 (m, 2H), 1.74-1.58 (m, 5H), 1.50 (s, 9H), 1.30-1.19 (m, 5H).

Step 3: **Synthesis of *tert*-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate**

To a stirred solution of *tert*-butyl 5-(((trifluoromethyl)sulfonyl)oxy)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (2 g, 5.01 mmol) in 1,4-dioxane (20 mL) was added bis(pinacolato)diboron (1.52 g, 6.01 mmol), and potassium acetate (0.737 g, 7.51 mmol). The reaction mixture was purged with N_2 for 10 min. To this reaction mixture was added $Pd(dppf)Cl_2$.DCM (0.49 g, 0.50 mmol) and further purged with N_2 for 5 min. Then reaction mixture was stirred at 90 °C for 16 h. The reaction was filtered through a pad of celite, and the obtained filtrate was concentrated under reduced pressure. The crude compound was purified by combi-flash chromatography (SiO_2, 100-200 silica gel) with 45% EtOAc in hexane as eluent. The pure fractions were concentrated under reduced pressure to afford *tert*-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate. LCMS: m/z MM-ES+APCI, Positive $[M-56]^+$ 322; ^1H NMR (400 MHz, $CDCl_3$) δ 6.44-6.40 (m, 1H), 3.94-3.91 (m, 2H), 3.57-3.42 (m, 2H), 1.79-1.68 (m, 4H), 1.57-1.51 (m, 6H), 1.49 (s, 9H), 1.29 (s, 6H), 1.26 (s, 6H).

Step 4: **Synthesis of *tert*-butyl 5-(4-chloro-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate**

To a stirred solution of 3-(5-bromo-4-chloro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**4-c,** 200 mg, 0.559 mmol) and *tert*-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (274 mg, 0.727 mmol) in DMF (4 mL) and water (0.4 mL) was added Cs_2CO_3 (547 mg, 1.67 mmol). The reaction mixture was purged with N_2 gas for 5 min. Then added $PdCl_2(dppf)$-CH_2Cl_2 adduct (45.7 mg, 0.056 mmol) was added at room temperature, and further purged with N_2 for 5 min. The resulting reaction mixture was stirred at 80 °C for 1h. The reaction was filtered through a pad of celite, and the obtained filtrate was concentrated under reduced pressure. The crude compound was purified by Combi-flash chromatography using (SiO_2, 100-200 silica gel) and eluting with 17% EtOAc in hexane to afford *tert*-butyl 5-(4-chloro-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate. LCMS: m/z MM-ES+APCI, Positive [M, M+2]$^+$ 528.4, 530.3.

Step 5: **Synthesis of 3-(4-chloro-1-oxo-5-(2-azaspiro[5.5]undec-4-en-5-yl)isoindolin-2-yl)piperidine-2,6-dione**

To a stirred solution of *tert*-butyl 5-(4-chloro-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (120 mg, 0.23 mmol) in DCM (3 mL) was added 4M HCl in 1,4-dioxane (0.5 mL, 2.00 mmol) at 0 °C, under N_2 atmosphere. The reaction mixture was stirred at room temperature for 3h. The mixture was concentrated under reduced pressure and the crude compound was purified by trituration using MTBE and *n*-pentane to afford 3-(4-chloro-1-oxo-5-(2-azaspiro[5.5]undec-4-

en-5-yl)isoindolin-2-yl)piperidine-2,6-dione. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 428.3; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.01 (bs 1H), 9.28-9.10 (m, 2H), 7.73 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 5.75-5.54 (m, 1H), 5.14-5.12 (m, 1H), 4.50-4.34 (m, 2H), 3.71-3.57 (m, 2H), 3.51-3.39 (m, 1H), 2.93-2.88 (m, 1H), 2.73-2.68 (m, 1H), 2.67-2.59 (m, 1H), 2.46-2.33 (m, 1H), 2.09-1.88 (m, 2H), 1.57-1.43 (m, 6H), 1.24-1.22 (m, 1H), 1.13-1.07 (m, 1H).

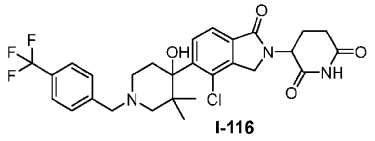
Step 6: **Synthesis of 3-(4-chloro-1-oxo-5-(2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)isoindolin-2-yl)piperidine-2,6-dione**

To a stirred solution of 3-(4-chloro-1-oxo-5-(2-azaspiro[5.5]undec-4-en-5-yl)isoindolin-2-yl)piperidine-2,6-dione (100 mg, 0.23 mmol) in DMF (1 mL) was added 4-(trifluoromethyl)benzaldehyde (81 mg, 0.47 mmol) under N_2. The reaction mixture was stirred for 1 h at room temperature. Then sodium acetoxyborohydride (149 mg, 0.70 mmol) was added and stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (silica gel 100-200 mesh, gradient EtOAc /hexane) to afford 3-(4-chloro-1-oxo-5-(2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)isoindolin-2-yl)piperidine-2,6-dione. LCMS: m/z M-ES+APCI, Positive $[M, M+2]^-$ 586.4, 588.1; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.00 (bs 1H), 7.96 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 1H), 7.68-7.62 (m, 2H), 7.35 (d, J = 8.0 Hz, 1H), 5.70-5.64 (m, 1H), 5.46-5.11 (m, 1H), 4.55-4.40 (m, 1H), 3.78-3.74 (m, 1H), 3.17-3.06 (m, 1H), 2.95-2.89 (m, 1H), 2.73-2.62 (m, 1H), 2.58-2.56 (m, 1H), 2.44-2.42 (m, 1H), 2.04-2.02 (m, 1H), 1.94-1.91 (1H), 1.89-1.86 (m, 1H), 1.42-1.24 (m, 4H), 1.10-1.07 (m, 4H), 1.05-1.03 (m, 4H).

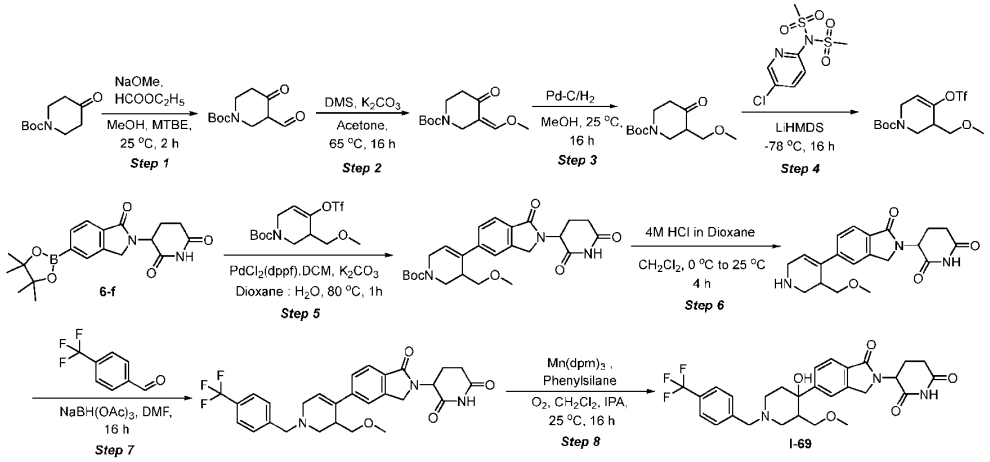
Step 6: **Synthesis of 3-(4-chloro-5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-112)**

To a stirred solution of 3-(4-chloro-1-oxo-5-(2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)isoindolin-2-yl)piperidine-2,6-dione (130 mg, 0.22 mmol) in 2-propanol (2 mL) and DCM (5 mL) was added phenyl silane (48 mg, 0.44 mmol), and $Mn(dpm)_3$ (67.7 mg, 0.111 mmol) at 0 °C, under oxygen purging. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture concentrated and purified by Prep-HPLC [Method info: column: X select C18 (150 mm × 19) 5um, 0.05% HCl, mobile phase B, ACN flow rate: 15 mL/min) RT 9:3, ACN/H_2O mixture] to afford 3-(4-chloro-5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-112**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 604.3; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.03 (bs 1H), 9.80 (s, 1H), 8.20-8.16 (m, 1H), 7.92-7.88 (m, 4H), 7.78-7.74 (m, 1H), 6.00-5.98 (m, 1H), 5.16-5.12 (m, 1H), 4.57-4.32 (m, 4H), 3.62-3.14 (m, 2H), 2.93-2.88 (m, 1H), 2.87-2.62 (m, 1H), 2.58-2.54 (m, 1H), 2.53-2.51 (m, 1H), 2.44-2.41 (m, 1H), 2.34-2.33 (m, 1H), 2.03-2.01 (m, 2H), 1.45-0.86 (m, 9H).

The following compound was synthesized in a similar fashion to Example 37 (**I-112**).

Compound	Characterization
 I-116 3-(4-chloro-5-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-116**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 564.1. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 9.60 (s, 1H), 8.00-7.74 (m, 6H), 5.92 (d, J = 9.60 Hz, 1H), 5.14 (q, J = 5.20 Hz, 1H), 4.53-4.28 (m, 4H), 3.33 (m, 1H), 2.96-2.89 (m, 2H), 2.68-2.63 (m, 3H), 2.34 (t, J = 1.60 Hz, 1H), 2.33-2.01 (m, 2H), 1.08 (s, 3H), 0.82 (s, 3H).

Example 38: Synthesis of 3-(5-(4-hydroxy-3-(methoxymethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-69)



Step 1: **Synthesis of *tert*-butyl 3-formyl-4-oxopiperidine-1-carboxylate**

To a stirred solution of sodium methoxide (5.60 mL, 25.09 mmol) in MeOH (5 mL) was added ethyl formate (3.04 mL, 37.6 mmol) dropwise at 0 °C and stirred for 5 min. Then, *tert*-butyl 4-oxopiperidine-1-carboxylate (5 g, 25.09 mmo)) was added and the reaction mixture was stirred at 25 °C for 16 h. The mixture was concentrated under reduced pressure to afford a crude *tert*-butyl 3-formyl-4-oxopiperidine-1-carboxylate which was directly used for the next step without further purification. m/z MM-ES+APCI, Positive $[M-56]^+$: 172

Step 2: **Synthesis of *tert*-butyl (*Z*)-3-(methoxymethylene)-4-oxopiperidine-1-carboxylate**

To a stirred solution of *tert*-butyl 3-formyl-4-oxopiperidine-1-carboxylate (2.5 g, 11.00 mmol) in acetone (10 mL) was added K_2CO_3 (3.04 g, 22.00 mmol) at 25 °C and stirred for 5 min. The dimethyl sulfate (1.067 mL, 11.00 mmol)) was added, and the reaction mixture was stirred at 65 °C for 16 h. The reaction mixture was directly concentrated under reduced pressure and the resulting material was partitioned between water (100 mL) and EtOAc (100 mL × 2). The organic layer was dried over

anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography (SiO_2/100-200 mesh; 50-60% EtOAc in hexanes) to afford *tert*-butyl (*Z*)-3-(methoxymethylene)-4-oxopiperidine-1-carboxylate. LCMS: m/z MM-ES+APCI, Positive $[M-56]^+$ 186.0. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 4.55 (s, 1H), 3.91 (s, 3H), 3.62-3.54 (m, 4H), 2.34 (t, J = 8.0 Hz, 2H), 1.49 (s, 9H).

Step 3: **Synthesis of *tert*-butyl 3-(methoxymethyl)-4-oxopiperidine-1-carboxylate**

To a stirred solution of *tert*-butyl (*Z*)-3-(methoxymethylene)-4-oxopiperidine-1-carboxylate (1.7 g, 7.05 mmol) in MeOH (20 mL) was added 10% Pd/C (2 g, 1.88 mmol) at 25 °C under H_2 bladder and stirred for 16 h. The reaction mixture was filtered through a celite pad and the pad was washed with methanol (50 mL). The filtrate was concentrated under reduced pressure to afford crude *tert*-butyl 3-(methoxymethyl)-4-oxopiperidine-1-carboxylate. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 244.0. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 4.12-3.81 (m, 1H), 3.60 (t, J = 8.0 Hz, 1H), 2.58-2.52 (m, 1H), 3.42-3.39 (m, 2H), 3.23 (s, 3H), 2.79-2.70 (m, 1H), 2.38-2.19 (m, 3H), 1.43 (s, 9H).

Step 4: **Synthesis of *tert*-butyl 3-(methoxymethyl)-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate**

To a stirred solution of *tert*-butyl 3-(methoxymethyl)-4-oxopiperidine-1-carboxylate (1.4 g, 5.75 mmol) in THF (50 mL) was added lithium bis(trimethylsilyl)amide (6.90 mL, 6.90 mmol) at 75°C and stirred for 1 h. *N*-(5-Chloropyridin-2-yl)-N-(methanesulfonyl)methanesulfonamide (3.38 g, 8.63 mmol) was then added and the reaction continued at 75 °C for 2 h, followed by 2 h at 25 °C. The reaction was quenched with 1N HCl solution (20 mL), extracted with EtOAc (150 mL × 2) and washed with water. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated to obtained as crude compound. The crude was purified by flash chromatography (SiO_2/100-200 mesh; 7-8% EtOAc in hexanes) to afford tert-butyl 3-(methoxymethyl)-4-(((trifluoromethyl) sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 6.05 (t, J = 8.4 Hz, 1H), 3.98 (s, 3H), 3.96-3.70 (m, 1H), 3.55 (t, J = 8.0 Hz, 1H), 3.46-3.31 (m, 2H), 3.29-3.16 (m, 1H), 2.78-2.72 (m, 1H), 2.39 (d, J = 46.8 Hz, 1H), 1.43 (s, 9H).

Step 5: **Synthesis of 3 *tert*-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3-(methoxymethyl)-3,6-dihydropyridine-1(*2H*)-carboxylate**

A microwave vial was charged with 3-(1-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-2-yl)piperidine-2,6-dione (**6-f**, 200 mg, 0.54 mmol) in 1,4-dioxane (3 mL) and water (3 mL) followed by *tert*-butyl 3-(methoxymethyl)-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (203 mg, 0.54 mmol) and K_2CO_3 (149 mg, 1.08 mmol). The reaction mixture was purged with N_2 for 10 min. Then $PdCl_2$(dppf)-CH_2Cl_2adduct (22.06 mg, 0.027 mmol) was added and the reaction was purged with N_2 for 10 min. The resulting reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was filtered through a pad of celite and washed with EtOAc (100 mL). The organic layer was

concentrated under reduced pressure and purified by flash column chromatography (silica gel 100-200 mesh) eluted with (5-10%) 2-propanol in DCM to afford tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3-(methoxymethyl)-3,6-dihydropyridine-1(2H)-carboxylate). LCMS: m/z MM-ES+APCI, Negative $[M-H]^-$ 468.3.

Step 6: **Synthesis of 3-(5-(3-(methoxymethyl)-1,2,3,6-tetrahydropyridin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione**

To a stirred solution of *tert*-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3-(methoxymethyl)-3,6-dihydropyridine-1(2H)-carboxylate (400 mg, 0.85 mmol) in DCM (10 mL) was added 4M HCl in 1,4-dioxane (2.13 mL, 8.52 mmol) dropwise at 0 °C. The reaction mixture stirred for 3 h. The reaction mixture was concentrated under reduced pressure and the crude solid was triturated with MTBE (15 mL) and dried under vacuum to afford 3-(5-(3-(methoxymethyl)-1,2,3,6-tetrahydropyridin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dioneLCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 370.4; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 9.30-9.00 (m, 2H), 7.77 (m, 1H), 7.65-7.61 (m, 2H), 6.40-6.15 (m, 1H), 5.14-5.12 (m, 1H), 4.52-4.30 (m, 2H), 3.80 (s, 2H), 3.48-3.32 (m, 2H), 3.28-3.21 (m, 1H), 3.14 (m, 3H), 2.98-2.85 (m, 2H), 2.59-2.57 (m, 1H), 2.40-2.35 (m, 1H), 2.07-1.97 (m, 1H).

Step 7: **Synthesis of 3-(5-(3-(methoxymethyl)-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydro pyridine-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione**

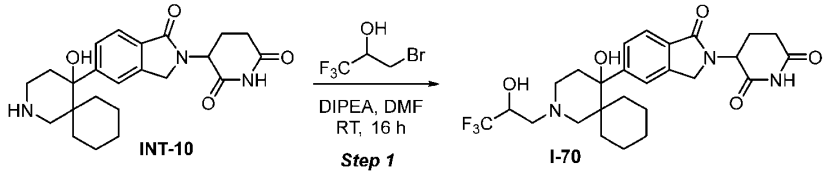
To a stirred solution of 3-(5-(3-(methoxymethyl)-1,2,3,6-tetrahydropyridin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (300 mg, 0.74 mmol) in DMF (10 mL) was added 4-(trifluoromethyl)benzaldehyde (129 mg, 0.74 mmol) and the reaction mixture was stirred for 1 h at 25 °C. To this resulting mixture was added sodium triacetoxyborohydride (313 mg, 1.48 mol) at room temperature and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (silica gel 100-200 mesh) eluted with (5-10%) 2-propanol in DCM to afford 3-(5-(3-(methoxymethyl)-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 528.5. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 7.77-7.67 (m, 3H), 6.65-7.54 (m, 4H), 6.21 (t, J = 2.0 Hz, 1H), 5.19-5.05 (m, 1H), 4.46-4.32 (m 2H), 3.50-3.45 (m, 2H), 3.06 (s, 3H), 2.99- 2.90 (m, 4H), 2.67-2.56 (m, 3H), 2.45-2.35 (m, 3H), 2.03-1.99 (m, 1H).

Step 8: **3-(5-(4-hydroxy-3-(methoxymethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-69)**

To a stirred solution of 3-(5-(3-(methoxymethyl)-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (190 mg, 0.36 mmol) in DCM (5 mL) and 2-propanol (5 mL) were added phenylsilane (78 mg, 0.72 mmol) and Mn $(dpm)_3$ (152 mg, 0.25

mmol) at 0 °C and stirred under O_2 atmosphere for 4 h. The reaction mixture was concentrated under reduced pressure, triturated with *n*-hexane (50 mL), and dried under vacuum. The crude compound was purified by Prep HPLC using (Column: X select (150 mm × 19)5 μm, Mobile phase A: 0.1% HCl in H_2O, Mobile phase B: ACN, flow rate: 10 mL/min)]. Product fractions were lyophilized to afford 3-(5-(4-hydroxy-3-(methoxymethyl)-1-(4-(trifluoromethyl) benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione **(I-69)**. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 546.3; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 7.75-7.69 (m, 3H), 7.65-7.53 (m, 4H), 6.21 (broad, 1H), 5.08 (dd, J = 5.20, 13.20 Hz, 1H), 4.51-4.37 (m, 4H), 3.49-3.36 (m, 2H), 3.65-3.44 (m, 2H), 3.11-3.05 (m, 2H), 3.00 (s, 3H), 2.65-2.55 (m, 3H), 2.05-1.95 (m, 3H).

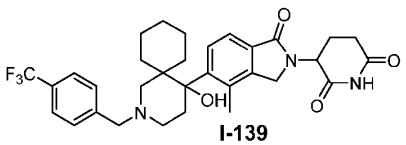
Example 39: Synthesis of 3-(5-(5-hydroxy-2-(3,3,3-trifluoro-2-hydroxypropyl)-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-70)



Step 1: **Synthesis of 3-(5-(5-hydroxy-2-(3,3,3-trifluoro-2-hydroxypropyl)-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-70)**

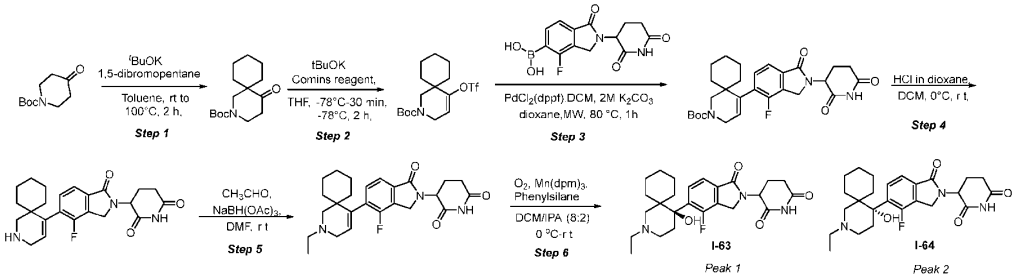
To a stirred solution of 3-(1-oxo-5-(2-azaspiro[5.5]undec-4-en-5-yl)isoindolin-2-yl)piperidine-2,6-dione (**INT-10**, 50 mg, 0.12 mmol) in DMF (2 mL) were added 3-bromo-1,1,1-trifluoropropan-2-ol (23 mg, 0.12 mmol) and DIPEA (47 mg, 0.37 mmol). The reaction stirred for 16 h at room temperature. The reaction was concentrated and the crude residue was purified by Prep-HPLC [Method info: column: X select C18 (150 mm × 19) 5um, 0.1% formic acid in H_2O:ACN, flow rate: 15 mL/min) RT 9:3, ACN/H_2O mixture, lyophilization for 16 h to afford 3-(5-(5-hydroxy-2-(3,3,3-trifluoro-2-hydroxypropyl)-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione **(I-70)**. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 524.9; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 7.60-7.60 (m, 3H), 6.01 (s, 1H), 5.14-5.09 (m, 1H), 4.77-4.75 (m, 1H), 4.46-4.14 (m, 1H), 2.95-2.72 (m, 2H), 2.68-2.61 (m, 7H), 2.59-2.56 (m, 1H), 2.41-2.33 (m, 1H), 2.18-2.15 (m, 1H), 2.04-2.01 (m, 1H), 1.71-1.67 (m, 1H), 1.43-1.30 (m, 8H), 0.65-0.62 (m, 2H).

Example 40: Synthesis of 3-(5-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-4-methyl-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-139)



The title compound was synthesized in a similar fashion to **Example 6 (I-28)** and was isolated as a mixture of diastereomers. LCMS: MM-ES+APCI, Positive $[M+H]^+$ 584.7; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.00 (bs 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 5.14 (d, J = 8.0 Hz, 1H), 5.10 (s, 1H), 4.78-4.75 (m, 1H), 4.46-4.43 (m, 1H), 3.67-3.54 (m, 2H), 2.89-2.81 (m, 3H), 2.69-2.55 (m, 6H), 2.43-2.30 (m, 2H), 1.93-1.89 (m, 1H), 1.88-1.75 (m, 3H), 1.45-1.39 (m, 1H), 1.35-1.30 (m, 2H), 1.07-1.03 (m, 3H), 0.95-0.80 (m, 2H).

Example 41: Synthesis of 3-(5-((S)-2-ethyl-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-63) and 3-(5-((R)-2-ethyl-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-64)



Step 1: **Synthesis of tert-butyl 5-oxo-2-azaspiro[5.5]undecane-2-carboxylate**

To a stirred solution of *tert*-butyl 4-oxopiperidine-1-carboxylate (20 g, 100 mmol) in toluene (200 mL) was added potassium tert-butoxide (22.53 g, 201 mmol) at 25 °C under N_2 atmosphere and stirred for 1 h. Then 1,5-dibromopentane (20.52 mL, 151 mmol) were added at 25 °C. The reaction mixture was stirred at 100 °C for 12 h. The reaction mixture was quenched with ice-cold water and diluted with EtOAc. The organic layer was separated and the aqueous portion was extracted with EtOAc (3 × 150 mL). The combined organic layers were dried over sodium sulfate, filtered, and evaporated under reduced pressure. The residue was purified by Biotage isolera (silica gel 100-200 mesh) and a linear gradient of 0-4% EtOAc in hexane as eluent to afford *tert*-butyl 5-oxo-2-azaspiro[5.5]undecane-2-carboxylate. LCMS: m/z MM-ES+APCI, Positive ($[M-Boc]^+$ 211), ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.71-3.55 (m, 4H), 2.49 (t, J= 6.80 Hz, 2H), 1.77-1.52 (m, 2H), 1.48-1.38 (m, 17H).

Step 2: **Synthesis of tert-butyl 5-(((trifluoromethyl)sulfonyl)oxy)-2-azaspiro[5.5]undec-4-ene-2-carboxylate**

To the stirred solution of *tert*-butyl 5-oxo-2-azaspiro[5.5]undecane-2-carboxylate (12 g, 44.9 mmol) in THF (100 mL), was added NaHMDS (67.3 mL, 67.3 mmol) at -78 °C and stirred at same temperature for 30 min. Comins' reagent (22.91 g, 58.3 mmol) in THF (20.0 mL) was then added and the reaction stirred at -78 °C for 2 h. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc. Organic layers were washed with brine, dried over Na_2SO_4, filtered, and

evaporated under vacuum to obtain crude residue which was purified by column chromatography (silica gel, 100-200 mesh, gradient EtOAc/Hexane) compound was eluted at 0 to 10% EtOAc in hexane to get *tert*-butyl 5-(((trifluoromethyl)sulfonyl)oxy)-2-azaspiro[5.5]undec-4-ene-2-carboxylate. LCMS: m/z MM-ES+APCI, Positive ($[M-H]^+$ 344, ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.73-5.66 (m, 1H), 4.07 (d, J = 16.00 Hz, 2H), 3.61 (d, J = 10.40 Hz, 2H), 1.75-1.50 (m, 18H), 1.46-1.19 (m, 1H).

Step 3: **Synthesis of tert-butyl 5-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate**

To a solution of (2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)boronic acid (200 mg, 0.653 mmol) in 1,4-dioxane (10 mL) was added tert-butyl 5-(((trifluoromethyl)sulfonyl)oxy)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (287 mg, 0.719 mmol) and K_2CO_3 (2.0 M solution) (90 mg, 0.65 mmol) under nitrogen at 25 °C. The reaction mixture was purged with N_2 for 10 min. To this resulting mixture was added $PdCl_2$(dppf)-CH_2Cl_2adduct (26.7 mg, 0.033 mmol) at 25 °C and again purged with N_2 for 10 min. The resulting reaction mixture was irradiated at 80 °C for 1 h. The reaction mixture was filtered through a pad of celite and washed with EtOAC (100 mL), the filtrate was concentrated under reduced pressure and purified by flash column chromatography using Biotage isolera (silica gel 100-200 mesh) and a linear gradient of 0-100% EtOAc in hexane as eluent to afford tert-butyl 5-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-2-azaspiro [5.5] undec-4-ene-2-carboxylate. LCMS: m/z MM-ES+APCI, Negative $[M-H]^-$ 510.1, ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 7.62-7.50 (m, 1H), 7.30-7.26 (m, 1H), 5.59 (m, 1H), 5.15-5.10 (m, 1H), 4.58 (dd, J = 16.80, Hz, 1H), 4.43-4.38 (m, 1H), 3.98 (s, 1H), 3.59-3.54 (m, 1H), 2.92-2.89 (m, 1H), 2.63-2.59 (m, 1H), 2.47-2.43 (m, 1H), 2.03 (m, 1H), 1.51-1.46 (m, 10H), 1.24 (m, 2H), 0.75 s, 9H).

Step 4: **Synthesis of 3-(4-fluoro-1-oxo-5-(2-azaspiro[5.5]undec-4-en-5-yl)isoindolin-2-yl)piperidine-2,6-dione**

To a stirred solution of tert-butyl 5-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (330 mg, 0.645 mmol) in DCM (10 mL) under nitrogen atmosphere was added 4 M HCl in 1,4 dioxane (0.65 mL, 2.58 mmol) was added at 0 °C and stirred for 4 h. The reaction mixture was concentrated under reduced pressure. The crude compound triturated with MTBE (2 X 10 mL), dried under vacuum to get 3-(4-fluoro-1-oxo-5-(2-azaspiro [5.5] undec-4-en-5-yl) isoindolin-2-yl) piperidine-2,6-dione. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 412.3, ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.03 (s, 1H), 7.62-7.60 (m, 1H), 7.29-7.26 (m, 1H), 5.63-5.61 (m, 1H), 5.16-5.12 (m, 1H), 4.59 (dd, J = 2.80, 17.40 Hz, 1H), 4.42 (dd, J = 17.20, Hz, 1H), 3.69 (br s, 2H), 3.57 (br s, 2H), 3.40 (br s, 2H), 2.96-2.88 (m, 1H), 2.68-2.59 (m, 1H), 2.47-2.42 (m, 1H), 2.04-2.00 (m, 1H), 1.82-1.79 (m, 2H), 1.57-1.41 (m, 6H).

Step 5: **Synthesis of 3-(5-(2-ethyl-2-azaspiro[5.5]undec-4-en-5-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione**

To a stirred solution of 3-(4-fluoro-1-oxo-5-(2-azaspiro[5.5]undec-4-en-5-yl)isoindolin-2-yl)piperidine-2,6-dione (210 mg, 0.47 mmol) in DMF (5 mL) was added acetaldehyde (21 mg, 0.47 mmol) at room temperature and stirred for 1 h. To this resulting mixture was added sodium triacetoxyborohydride (199 mg, 0.94 mmol)) at room temperature and stirred for 16 h. The reaction mixture was concentrated under reduced pressure and purified by Biotage isolera using 100-200 mesh silica gel and 20% IPA in DCM as eluent. The pure fractions were collected and concentrated under reduced pressure to afford 3-(5-(2-ethyl-2-azaspiro [5.5] undec-4-en-5-yl)-4-fluoro-1-oxoisoindolin-2-yl) piperidine-2,6-dione. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 440.4, ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 7.56-7.54 (m, 1H), 7.26-7.23 (m, 1H), 5.49-5.49 (m, 1H), 5.15-5.10 (m, 1H), 4.57 (dd, J = 17.20, Hz, 1H), 4.39 (dd, J = 17.60, Hz, 1H), 3.51 (br s, 1H), 3.01-2.88 (m, 3H), 2.68-2.55 (m, 2H), 2.46-2.34 (m, 2H), 2.03-2.00 (m, 1H), 1.74-1.69 (m, 2H), 1.58-1.53 (m, 1H), 1.40 (br s, 4H), 1.24-1.18 (m, 2H).

Step 6: **Synthesis of 3-(5-((S)-2-ethyl-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-63) and 3-(5-((R)-2-ethyl-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-64)**

To a stirred solution of 3-(5-(2-ethyl-2-azaspiro[5.5]undec-4-en-5-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (100 mg, 0.23 mmol) in DCM (5 mL) and 2-propanol (5 mL) was added phenyl silane (49.2 mg, 0.46 mmol) and $Mn(dpm)_3$ (96 mg, 0.16 mmol) at 0 °C and stirred under O_2 atmosphere for 16 h. The reaction mixture was concentrated under reduced pressure and was triturated with n-hexane and dried under a vacuum. The crude compound 3-(5-(2-ethyl-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (350 mg, 0.765 mmol) was purified by reverse phase using biotage isolera 30 g C-18 column Mobile phase A: 0.1% FA in H_2O, Mobile phase B: ACN, flow rate: 10 mL/min)]. The product obtained from above was further purified by preparative HPLC using (Column: X select (150 mm × 19)5 µm, Mobile phase A: 0.1% AA in H_2O, Mobile phase B: ACN, flow rate: 10 mL/min)]. Two peaks were observed and collected separately.

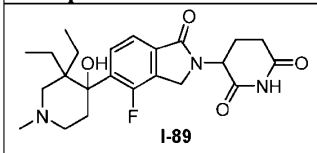
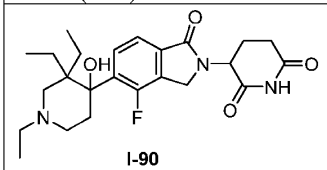
Peak 1: **3-(5-((S)-2-ethyl-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-63)** LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 458.5, ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.75 (s, 1H), 7.89-7.85 (m, 1H), 7.57-7.55 (m, 1H), 5.14-5.09 (m, 1H), 4.95 (m, 1H), 4.54 (dd, J = 17.60, Hz, 1H), 4.39 (dd, J = 17.20, Hz, 1H), 3.52 (br s, 1H), 2.99-2.68 (m, 3H), 2.68-2.51 (m, 2H), 2.46-2.41 (m, 3H), 2.40-2.36 (m, 1H), 2.11-2.09 (m, 1H), 1.90 (br s, 5H), 1.76 (m, 1H), 1.57-1.53 (m, 2H), 1.36-1.24 (m, 3H), 1.06-1.02 (m, 3H).

Peak 2: **3-(5-((R)-2-ethyl-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-64)**. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 458.5. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.65 (bs, 1H), 7.89 (t, J = 7.20 Hz, 1H), 7.63 (d, J= 8.00 Hz,1H), 5.16-5.11 (m, 1H), 4.95 (m, 1H), 4.59 (dd, J = 17.20, Hz, 1H), 4.38 (dd, J = 17.20, Hz, 1H), 3.66 (d, J = 8.80 Hz, 1H), 3.39-3.11 (m, 5H), 2.97-2.88 (m, 1H), 2.68-2.51 (m, 1H), 2.46-2.41 (m, 1H), 2.26-2.18 (m, 1H), 2.05-1.94 (m, 1H), 1.93-1.90 (m, 4H), 1.82-1.76 (m, 1H), 1.51-1.46 (m, 4H), 1.38-1.31 (m, 3H), 0.96-0.72 (m, 2H).

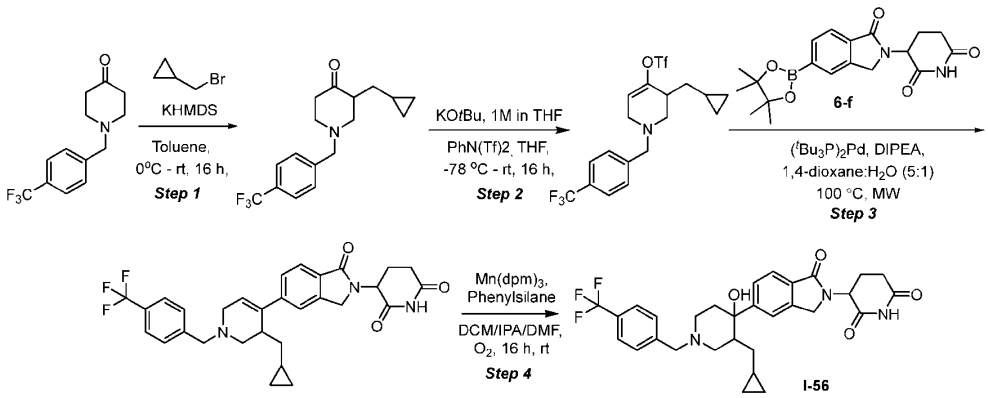
Note: ^{1}H NMR was recorded with a drop of TFA.

Note: absolute stereochemistry of the diastereomeric mixtures was arbitrarily assigned

The following compounds were synthesized in a similar fashion to **Example 41 (I-63)**.

Compound	Characterization
 **I-89** 3-(5-(3,3-diethyl-4-hydroxy-1-methylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-89**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 432. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 7.98 (s, 1H), 7.55 (d, J = 7.20 Hz, 1H), 5.05-5.12 (m, 2H), 4.54 (t, J = 17.20 Hz, 1H), 4.35 (t, J = 17.60 Hz, 1H), 2.92-3.33 (m, 3H), 2.22-2.51 (m, 6H), 2.03-2.17 (m, 2H), 1.50-1.52 (m, 2H), 1.01-1.19 (m, 2H), 0.60-0.68 (m, 3H), 0.52-0.50 (m, 3H).
 **I-90** 3-(4-fluoro-1-oxo-5-(1,3,3-triethyl-4-hydroxypiperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (**I-90**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 446.5. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 8.01 (s, 1H), 7.55 (d, J = 8.40 Hz, 1H), 5.04-5.06 (m, 2H), 4.54-4.50 (m, 1H), 4.39-4.35 (m, 1H), 3.01-2.91 (m, 1H), 2.68-2.62 (m, 2H), 2.58-2.51 (m, 3H), 2.41-2.39 (m, 1H), 2.37-2.36 (m, 1H), 2.34-2.33 (m, 2H), 1.87-1.86 (m, 2H), 1.53-1.52 (m, 2H), 1.05-1.03 (m, 1H), 1.03-1.01 (m, 4H), 0.71-0.69 (m, 3H), 0.54-0.48 (m, 3H).

Example 42: Synthesis of 3-(5-(3-(cyclopropylmethyl)-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-56)



Step 1: **Synthesis of 3-(cyclopropyl methyl)-1-(4-(trifluoromethyl) benzyl)piperidin-4-one**

To the solution of 1-(4-(trifluoromethyl)benzyl)piperidin-4-one (1.0 g, 3.89 mmol) in toluene (5 mL) under nitrogen atmosphere was added KHMDS (8.55 mL, 4.28 mmol) dropwise at 0 °C and the reaction mixture was stirred at room temperature for 1 h. This reaction mixture was cooled to 0 °C and (bromomethyl)cyclopropane (0.45 mL, 4.66 mmol) was added dropwise. The reaction mixture was allowed to stir at room temperature for 12 h. The reaction mixture was quenched with ice cold water, and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get the crude compound. The crude compound was purified by Biotage isolera (silica gel 100-200 mesh) and a linear gradient of 0-25% EtOAc in hexane as eluent to afford 3-(cyclopropylmethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-one. LCMS: m/z MM-ES+APCI, Positive [M+H] 312.1, ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.72 (d, J = 8.00 Hz, 2H), 7.60 (d, J = 8.00 Hz, 2H), 3.77 (d, J = 13.60 Hz, 1H), 3.67 (d, J = 13.60 Hz, 1H), 3.14-3.09 (m, 1H), 2.94-2.89 (m, 1H), 2.61-2.51 (m, 2H), 2.49-2.45 (m, 1H), 2.32-2.22 (m, 2H), 1.59-1.55 (m, 1H), 1.10-1.06 (m, 1H), 0.65-0.59 (m, 1H), 0.36-0.31 (m, 2H),-0.02--0.04(m, 2H).

Step 2: **Synthesis of 3-(cyclopropylmethyl)-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate**

To the solution of 3-(cyclopropylmethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-one (200 mg, 0.64 mmol) in THF (5 mL) under nitrogen atmosphere was added potassium tert-butoxide solution (1 M in THF, 1.28 mL, 1.28 mmol) dropwise at -78 °C and was stirred at for 1 h. To this resulting solution was added 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)-methanesulfonamide (344 mg, 0.96 mmol) dissolved in THF (2 mL) dropwise at -78 °C and the reaction mixture was allowed to stir at room temperature for 2 h. The reaction mixture was quenched with saturated ammonium chloride solution, and extracted with EtOAc (2 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get the crude compound. The crude compound was purified by Biotage isolera (silica gel 100-200 mesh) and a linear gradient of 0-5% EtOAc in hexane as eluent to afford 3-(cyclopropylmethyl)-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.72 (d, J = 8.00 Hz, 2H), 7.57 (d, J = 8.00 Hz, 2H), 5.93 (m, 1H), 3.80-3.62 (m, 2H), 3.21-2.98 (m, 2H), 2.72 (s, 2H), 2.54-2.50 (m, 2H), 1.52-1.44 (m, 1H), 1.27-1.15 (m, 1H), 0.39-0.34 (m, 2H),-0.05 (s, 2H).

Step 3: **Synthesis of 3-(5-(3-(cyclopropylmethyl)-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione**

The stirred solution of 3-(1-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-2-yl)piperidine-2,6-dione (0.25 g, 0.675 mmol) and 3-(cyclopropylmethyl)-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (0.359 g, 0.81 mmol) in 1,4-dioxane (10 mL)

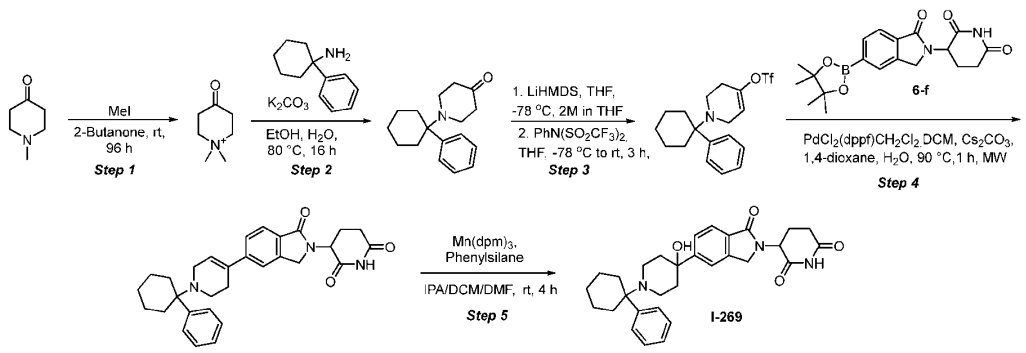
and water (1.5 mL) was purged with nitrogen for 10 min at room temperature. To this resulting mixture was added $Pd(tBu_3P)_2$ (0.035 g, 0.068 mmol) and the resulting reaction mixture was stirred at 80 °C for 16 h. The reaction was filtered through a pad of celite, washed with ethyl acetate and the filtrate was concentrated under reduced pressure to afford crude product. The crude material was purified by reverse phase column chromatography [(Column: 35 g, Mobile phase A: 0.1 formic acid in H_2O: ACN, Mobile phase B: ACN, flow rate: 15 mL/min)]. Fractions were concentrated under reduced pressure to obtain 3-(5-(3-(cyclopropylmethyl)-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 538.6, ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 7.88-7.49 (m, 7H), 6.06-6.02 (m, 1H), 5.20-5.08 (m, 1H), 4.46-4.33 (m, 2H), 3.73-3.63 (m, 1H), 3.29-3.23 (m, 2H), 2.97-2.88 (m, 3H), 2.72-2.38 (m, 3H), 2.04-1.98 (m, 1H), 1.49-1.24 (m, 2H), 1.07-0.84 (m, 2H), 0.57-0.44 (m, 1H), 0.25-0.12 (m, 2H),-0.17--0.23 (m, Hz, 1H).

Note: Splitting in 1H-NMR was observed due to the presence of a diastereomeric mixture.

Step 4: **Synthesis of 3-(5-(3-(cyclopropylmethyl)-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-56)**

To a stirred solution of 3-(5-(3-(cyclopropylmethyl)-1-(4-(trifluoromethyl) benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (0.2 g, 0.37 mmol) in 2-propanol (20 mL) and DCM (5 mL) at 0 °C was added phenyl silane (0.092 mL, 0.74 mmol) and $Mn(dpm)_3$ (0.11 g, 0.19 mmol). The resulting reaction mixture was stirred under oxygen bladder at 0 °C for 16 h. The reaction mixture was quenched with saturated sodium hypochlorite solution (20 mL) and stirred for 1 h at room temperature. This resulting mixture was extracted with DCM (2 × 50 mL). The combined organic layer was washed with water (20 mL) followed by brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude compound was purified by preparative-HPLC [(Column: X-SELECT CSH C18(150 × 19 × 5µm), Mobile phase A: 0.1% FA in water, Mobile phase B: ACN, flow rate: 15 mL/min, Room temperature:7.6 min)]. The fractions were lyophilized to afford 3-(5-(3-(cyclopropylmethyl)-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione as a mixture of diastereomers (**I-56**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 556.2, ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 9.90 (br s, 1H), 7.98 (d, J = 8.20 Hz, 2H), 7.98 (d, J = 8.20 Hz, 2H), 7.73 (d, J = 8.20 Hz, 1H), 7.62 (d, J = 6.40 Hz, 1H), 7.58-7.53 (m, 1H), 5.73 (s, 1H), 5.15-5.09 (m, 1H), 4.58-4.30 (m, 4H), 3.59-3.32 (m, 2H), 3.30-3.26 (m, 2H), 2.95-2.89 (m, 1H), 2.68-2.32 (m, 3H), 2.14-1.96 (m, 3H), 1.41-1.31 (m, 1H), 0.63-0.58 (m, 1H), 0.22-0.08 (m, 2H),-0.11--0.17 (m, 2H),-0.38--0.44 (m, 1H).

Example 43: Synthesis of 3-(5-(4-hydroxy-1-(1-phenylcyclohexyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-269)



Step 1: **Synthesis of 1,1-dimethyl-4-oxopiperidin-1-ium, iodide**

To a stirred solution of 1-methylpiperidin-4-one (10 g, 88 mmol) in 2-butanone (5 mL), was added methyl iodide (6.05 mL, 97 mmol) under a nitrogen atmosphere and the reaction mixture was stirred at room temperature for 96 h. The resulting solid was filtered and dried under vacuum to obtain the solid, which was dissolved in EtOAc (60 mL) and triturated with hexane (200 mL). The resulting solid was filtered and dried under vacuum to afford 1,1-dimethyl-4-oxopiperidin-1-ium iodide. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.76 (t, J = 6.80 Hz, 4H), 3.31 (d, J = 14.40 Hz, 6H), 2.72 (t, J = 6.40 Hz, 4H).

Step 2: **Synthesis of 1-(1-phenylcyclohexyl)piperidin-4-one**

To a stirred solution of 1,1-dimethyl-4-oxopiperidin-1-ium iodide (300 mg, 1.18 mmol) in ethanol (2 mL) was added potassium carbonate (K_2CO_3, 157 mg, 1.13 mmol) and 1,1-dimethyl-4-oxopiperidin-1-ium iodide (300 mg, 1.176 mmol) in water (1 mL) at room temperature. The reaction mixture was stirred at 80 °C for 16 h. The reaction was then diluted with water and extracted with ethyl acetate (EtOAc, 2 × 50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain 1-(1-phenylcyclohexyl)piperidin-4-one. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 258.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35-7.34 (m, 4H), 7.23-7.21 (m, 1H), 2.51-2.47 (m, 4H), 2.26 (t, J = 6.00 Hz, 4H), 2.22-2.14 (m, 2H), 2.03-1.92 (m, 2H), 1.76-1.69 (m, 2H), 1.52-1.311 (m, 4H).

Step 3: **Synthesis of 1-(1-phenylcyclohexyl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate**

To a stirred solution of 1-(1-phenylcyclohexyl)piperidin-4-one (80 mg, 0.31 mmol) in tetrahydrofuran (THF, 10 mL) was added LiHMDS (1 M in THF) (0.46 mL, 0.46 mmol) at -78 °C under a nitrogen atmosphere and stirred for 1 h. Then, 1,1,1-trifluoro-N-(pyridin-2-yl)-N-((trifluoromethyl)sulfonyl)methanesulfonamide (122 mg, 0.34 mmol) was added, and the reaction mixture was stirred for 3 h. The reaction was quenched with saturated ammonium chloride (50 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by flash chromatography using a Biotage Isolera

system with silica gel (100-200 mesh) and a linear gradient of 0-100% ethyl acetate in hexane as the eluent to afford 1-(1-phenylcyclohexyl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 390.0. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.39-7.37 (m, 5H), 5.67 (t, J = 3.60 Hz, 1H), 3.10 (s, 2H), 2.56 (t, J = 5.20 Hz, 2H), 2.37 (s, 2H), 2.20-2.16 (m, 2H), 2.07-2.04 (m, 2H), 1.70-1.61 (m, 2H), 1.48-1.45 (m, 2H), 1.37-1.35 (m, 2H).

Step 4: **Synthesis of 3-(1-oxo-5-(1-(1-phenylcyclohexyl)-1,2,3,6-tetrahydropyridin-4-yl)isoindolin-2-yl)piperidine-2,6-dione**

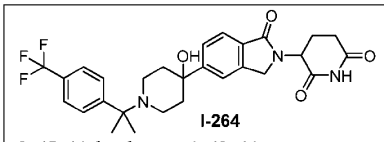
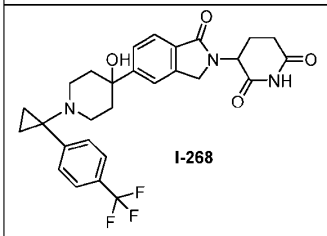
To a stirred solution of 3-(1-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-2-yl)piperidine-2,6-dione (**6-f**, 38.0 mg, 0.10 mmol) and 1-(1-phenylcyclohexyl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (40 mg, 0.10 mmol) in 1,4-dioxane (2 mL) was added cesium carbonate (2M in H_2O, 0.103 mL, 0.205 mmol) under a N_2 atmosphere. Then, $PdCl_2$(dppf)-CH_2Cl_2 adduct (4.19 mg, 5.14 μmol) was added, and the reaction mixture was stirred under microwave irradiation at 90 °C for 1 h. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography using a Biotage Isolera system with silica gel (100-200 mesh) and a linear gradient of 0-10% 2-propanol in DCM as eluent to afford 3-(1-oxo-5-(1-(1-phenylcyclohexyl)-1,2,3,6-tetrahydropyridin-4-yl)isoindolin-2-yl)piperidine-2,6-dione. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 484.2. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 7.65-7.53 (m, 8H), 6.25 (s, 1H), 5.12-5.08 (m, 1H), 4.40-4.27 (m, 2H), 3.08 (s, 1H), 2.91-2.88 (m, 2H), 2.68-2.61 (m, 2H), 2.46-2.34 (m, 2H), 2.10-2.01 (m, 4H), 1.68 (m, 2H), 1.42 (m, 2H), 1.24-1.17 (m, 2H), 1.04 (s, 3H).

Step 5: **Synthesis of 3-(5-(4-hydroxy-1-(1-phenylcyclohexyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-269)**

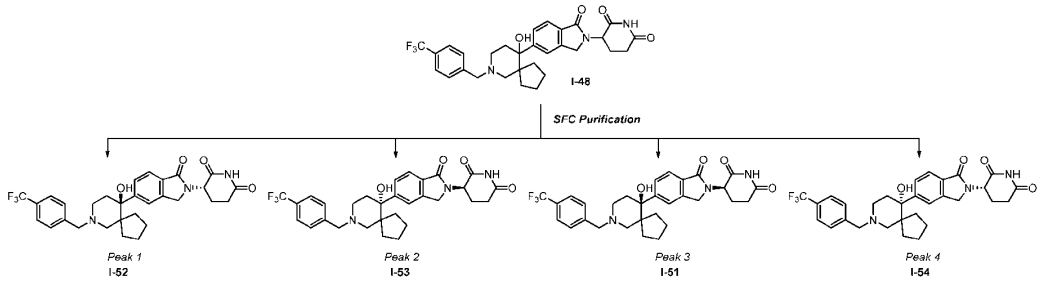
To a stirred solution of 3-(1-oxo-5-(1-(1-phenylcyclohexyl)-1,2,3,6-tetrahydropyridin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (50 mg, 0.10 mmol) in 2-propanol (2 mL), DCM (2 mL), and DMF (0.40 mL) was added $Mn(dpm)_3$ (18 mg, 0.031 mmol) and phenylsilane (0.031 mL, 0.26 mmol) under O_2 purging at 0 °C. The reaction was then stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and purified by prep-HPLC (Column: 150 g HP C18 Aq) eluted with 60% acetonitrile in water (0.05M HCl). Fractions were combined and lyophilized to afford 3-(5-(4-hydroxy-1-(1-phenylcyclohexyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 502.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 10.14 (br s, 1H), 7.72 (d, J = 8.00 Hz, 3H), 7.60-7.55 (m, 5H), 5.38 (s, 1H), 5.14-5.09 (m, 1H), 4.48-4.29 (m, 2H), 3.70 (s, 2H), 3.14-3.11 (m, 2H), 2.91 (t, J = 8.40 Hz, 2H), 2.68-2.62 (m, 5H), 2.40-2.38 (m, 1H), 2.08-2.06 (m, 3H), 1.78-1.75 (m, 4H), 1.54 (d, J = 11.60 Hz, 1H), 1.30-1.04 (m, 2H).

The following compounds were synthesized in a similar fashion to **Example 43 (I-269)**.

Compound	Characterization

 I-264 3-(5-(4-hydroxy-1-(2-(4-(trifluoromethyl)phenyl)propan-2-yl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-264**)	LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 530.5. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 10.53 (s, 1H), 8.12 (d, J = 8.40 Hz, 2H), 7.90 (d, J = 8.80 Hz, 2H), 7.74 (s, 1H), 7.71 (d, J = 9.60 Hz, 1H), 7.64 (d, J = 8.40 Hz, 1H), 5.61 (s, 1H), 5.13-5.09 (m, 1H), 4.47 (d, J = 17.20 Hz, 1H), 4.33 (d, J = 17.20 Hz, 1H), 3.37-3.32 (m, 2H), 3.14 (d, J = 10.40 Hz, 2H), 2.92-2.89 (m, 1H), 2.68-2.62 (m, 3H), 2.42 (d, J = 4.80 Hz, 1H), 2.09 (m, 1H), 2.00 (s, 6H), 1.81-1.77 (m, 2H).
 I-268 3-(5-(4-hydroxy-1-(1-(4-(trifluoro-methyl)phenyl)-cyclopropyl)-piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-268**)	LCMS: m/z MM-ES+APCI, $[M+H]^+$ 528.9. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 7.93 (s, 1H), 7.73 (d, J = 7.60 Hz, 2H), 7.64 (d, J = 5.20 Hz, 2H), 7.56 (t, J = 7.60 Hz, 2H), 5.14-5.08 (m, 1H), 4.80 (s, 1H), 4.45-4.31 (m, 2H), 3.71 (s, 1H), 2.91-2.87 (m, 3H), 2.62-2.44 (m, 4H), 1.99-1.58 (m, 5H), 1.24 (s, 1H), 0.91 (d, J = 40.40 Hz, 2H).

Example 44: Synthesis of (S)-3-(5-((S)-10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-52), (R)-3-(5-((R)-10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-53), (R)-3-(5-((S)-10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-51), (S)-3-(5-((R)-10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-54)



SFC purification method:

3-(5-(10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-48,** 1.1 g) was purified using the Instrument: PIC 175* [22-027]; Column: I Cellulose B- (250 × 21 mm), 5 µm; Mobile Phase: CO_2: 0.2% FA in 2-Propanol: Acetonitrile; Gradient [CO_2:Co-solvent]: [55:45]; Total Flow: 50 mL/min; Back pressure: 120 bar; Wavelength: 220 nm; Cycle time: 18 min. The pure fractions were concentrated under reduced pressure and lyophilized to afford:

Peak 3: **(R)-3-(5-((S)-10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-51**, 200 mg). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 556.1; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 9.42 (s, 1H), 7.97-7.87 (m, 4H), 7.78-7.58 (m, 3H), 5.60 (s, 1H), 5.12 (dd, J = 5.1, 13.4 Hz, 1H), 4.56-4.44 (m, 3H), 4.39-4.27 (m, 1H), 3.39-3.36 (m, 1H), 3.28 (br s, 2H), 3.09-3.00 (m, 1H), 2.99-2.86 (m, 1H), 2.85-2.73 (m, 1H), 2.65-2.56 (m, 1H), 2.46-2.36 (m, 1H), 2.08-1.79 (m, 4H), 1.47-1.20 (m, 3H), 1.18-1.06 (m, 1H), 1.01-0.91 (m, 1H), 0.90-0.79 (m, 1H).

Peak 4: **(S)-3-(5-((R)-10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-54**, 200 mg). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 556.3; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 9.81-9.44 (m, 1H), 7.98-7.84 (m, 4H), 7.76-7.60 (m, 3H), 5.62 (s, 1H), 5.12 (dd, J = 5.2, 13.4 Hz, 1H), 4.57-4.27 (m, 4H), 3.09-2.71 (m, 3H), 2.65-2.57 (m, 1H), 2.45-2.36 (m, 2H), 2.06-1.73 (m, 5H), 1.52-0.75 (m, 7H).

The remaining Peak 1 and Peak 2 mixture was subjected to a second SFC purification according to following method:

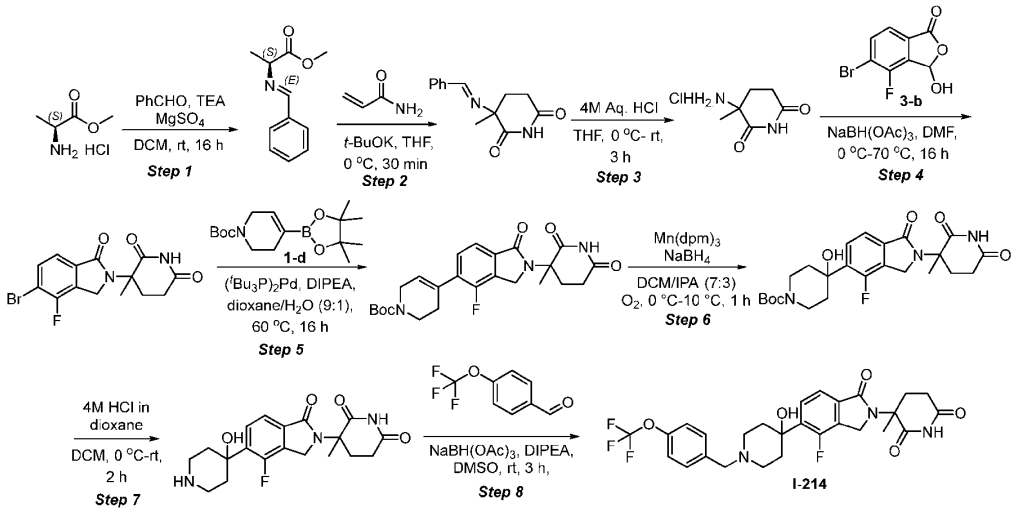
SFC Purification Method:

Instrument: PIC 175* [22-027]; Column: I Cellulose B- (250 × 21 mm), 5 μm; Mobile Phase: CO_2: 0.2% FA in 2-Propanol: Acetonitrile; Gradient [CO_2:Co-solvent]: [55:45]; Total Flow: 50 mL/min; Back pressure: 120 bar; Wavelength: 237 nm; Cycle time: 8 min. The pure fractions were concentrated under reduced pressure and lyophilized to afford:

Peak 1: **(S)-3-(5-((S)-10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-52**, 120 mg). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 556.3; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.20-10.59 (m, 1H), 9.79-9.21 (m, 1H), 7.91 (s, 4H), 7.78-7.60 (m, 3H), 5.62 (s, 1H), 5.12 (dd, J = 5.1, 13.4 Hz, 1H), 4.59-4.30 (m, 4H), 3.07 (d, J = 11.4 Hz, 1H), 2.98-2.85 (m, 1H), 2.84-2.70 (m, 1H), 2.61 (d, J = 19.4 Hz, 1H), 2.46-2.36 (m, 2H), 2.07-1.77 (m, 5H), 1.50-1.20 (m, 4H), 1.18-1.06 (m, 1H), 1.02-0.78 (m, 2H).

Peak 2: **(R)-3-(5-((R)-10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-53**, 20 mg). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 556.4; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.14-10.82 (m, 1H), 9.77 (d, J = 3.8 Hz, 1H), 8.00-7.82 (m, 4H), 7.78-7.57 (m, 3H), 5.60 (s, 1H), 5.12 (dd, J = 5.0, 13.3 Hz, 1H), 4.59-4.26 (m, 4H), 3.32-3.23 (m, 2H), 3.04 (d, J = 11.6 Hz, 1H), 2.98-2.86 (m, 1H), 2.85-2.72 (m, 1H), 2.65-2.56 (m, 1H), 2.40 (dt, J = 4.4, 13.2 Hz, 2H), 2.07-1.79 (m, 4H), 1.47-1.20 (m, 3H), 1.12 (td, J = 6.3, 12.9 Hz, 1H), 1.03-0.77 (m, 2H).

Example 45: Synthesis of 3-(4-fluoro-5-(4-hydroxy-1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)-3-methylpiperidine-2,6-dione (I-214)



Step 1: **Synthesis of methyl (*S,E*)-2-(benzylideneamino)propanoate**

A stirred solution of methyl L-alaninate hydrochloride (100 g, 716 mmol, 1 equiv.) in dichloromethane (1000 mL) was cooled to 0 °C. To this solution, magnesium sulfate (60.4 g, 502 mmol, 0.7 equiv.) and triethylamine (TEA, 120 mL, 860 mmol, 1.2 equiv.) were added sequentially. Benzaldehyde (65.4 mL, 645 mmol, 0.9 equiv.) was then added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 16 h. The progress of the reaction was monitored by TLC and LCMS. Upon completion, the reaction mixture was filtered through a celite bed and washed with DCM (200 mL). The combined filtrate was washed with saturated sodium chloride solution (2 × 200 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield methyl (*S.E*)-2-(benzylideneamino)propanoate. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.42 (s, 1H), 7.85-7.67 (m, 2H), 7.55-7.33 (m, 3H), 4.31-4.04 (m, 1H), 3.66 (s, 3H), 1.40 (d, J = 6.8 Hz, 3H).

Step 2: **Synthesis of (E)-3-(benzylideneamino)-3-methylpiperidine-2,6-dione**

To a stirred solution of methyl (*S,E*)-2-(benzylideneamino)propanoate (25 g, 131 mmol, 1 equiv.) and acrylamide (13.9 g, 196 mmol, 1.49 equiv.) in tetrahydrofuran (250 mL) was cooled to 0 °C. To this solution, potassium tert-butoxide (16.14 g, 144 mmol. 1.09 equiv.) was added portion wise. The reaction mixture was stirred at 0 °C for 30 min. The progress of the reaction was monitored by TLC and LCMS. Upon consumption of the starting material, the reaction mixture was quenched with solid ammonium chloride (7.69 g, 144 mmol, 1.09 equiv.) and stirred for 10 min. Ice-cold water (250 mL) was added, and THF was evaporated under reduced pressure, resulting in the formation of a solid. The solid was filtered and dried under reduced pressure to afford (*E*)-3-(benzylideneamino)-3-methylpiperidine-2,6-dione. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 231.3; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.83 (br s, 1H),

8.38 (s, 1H), 7.80 (dd, J = 1.5, 7.7 Hz, 2H), 7.59-7.31 (m, 3H), 2.76-2.62 (m, 1H), 2.47 (t, J = 4.1 Hz, 1H), 2.22-2.02 (m, 2H), 1.43 (s, 3H).

Step 3: **Synthesis of 3-amino-3-methylpiperidine-2,6-dione hydrochloride**

A stirred solution of (*E*)-3-(benzylideneamino)-3-methylpiperidine-2,6-dione (18 g, 78 mmol, 1 equiv.) in tetrahydrofuran (180 mL) was cooled to 0 °C. To this solution, aqueous 4M hydrochloric acid (35.2 mL, 141 mmol, 1.8 equiv.) was added, and the reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was filtered and dried to afford 3-amino-3-methylpiperidine-2,6-dione hydrochloride). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.24 (s, 1H), 8.92 (br s, 3H), 2.90-2.71 (m, 1H), 2.67-2.58 (m, 1H), 2.29 (dt, J = 5.4, 13.2 Hz, 1H), 2.19-2.06 (m, 1H), 1.54 (s, 3H).

Step 4: **Synthesis of 3-(5-bromo-4-fluoro-1-oxoisoindolin-2-yl)-3-methylpiperidine-2,6-dione**

To a stirred solution of 5-bromo-4-fluoro-3-hydroxyisobenzofuran-1(3H)-one (9.5 g, 38.5 mmol, 1 equiv.) in DMF (100 mL) was cooled to 0 °C under a nitrogen atmosphere. To this solution, 3-amino-3-methylpiperidine-2,6-dione hydrochloride (10.30 g, 57.7 mmol, 1.5 equiv.) was added, and the reaction mixture was stirred at 0 °C for 30 min. Sodium triacetoxyborohydride (24.45 g, 115 mmol, 3 equiv.) was then added at 0 °C, and the reaction mixture was stirred at 70 °C for 16 h. The progress of the reaction was monitored by TLC and LCMS. Upon completion, the reaction mixture was quenched with ice-cold water, and the precipitated solid was filtered and dried under vacuum to afford 3-(5-bromo-4-fluoro-1-oxoisoindolin-2-yl)-3-methylpiperidine-2,6-dione. LCMS: m/z: MM-ES+APCI, positive $[M]^+$ 355, [M+2] 357; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.91 (s, 1H), 7.85 (dd, J = 6.2, 7.8 Hz, 1H), 7.46 (d, J = 7.9 Hz, 1H), 4.94-4.72 (m, 2H), 2.83-2.68 (m, 1H), 2.67-2.54 (m, 2H), 1.96-1.84 (m, 1H), 1.70 (s, 3H).

Step 5: **Synthesis of tert-butyl 4-(4-fluoro-2-(3-methyl-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate**

To a stirred solution of 3-(5-bromo-4-fluoro-1-oxoisoindolin-2-yl)-3-methylpiperidine-2,6-dione (2.5 g, 7.04 mmol, 1 equiv.) in 1,4-dioxane (25 mL) and water (2.78 mL) was added tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (2.83 g, 9.15 mmol, 1.3 equiv.) and N,N-diisopropylethylamine (1.48 mL, 8.45 mmol, 1.2 equiv.) at 25 °C. The reaction mixture was degassed with argon for 10 min, followed by the addition of bis(tri-tert-butylphosphine)palladium(0) (0.18 g, 0.352 mmol, 0.05 equiv.). The reaction mixture was stirred at 60 °C for 16 h. The reaction mixture was filtered through a celite bed and washed with 10% methanol in DCM. The filtrate was concentrated under reduced pressure and purified by reverse-phase column chromatography using a C18 cartridge (330 g) with acetonitrile with 0.1% formic acid in water. Pure fractions were collected and concentrated under reduced pressure to obtain tert-butyl 4-(4-fluoro-2-(3-methyl-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate. LCMS: m/z: MM-ES+APCI, Positive $[M+1]^+$ 458.3; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.89 (s, 1H), 7.70-7.04 (m, 2H), 6.10 (br s, 1H), 4.94-

4.59 (m, 2H), 4.04 (br s, 2H), 3.56 (t, J = 5.5 Hz, 2H), 2.83-2.54 (m, 3H), 2.48 (s, 2H), 1.95-1.84 (m, 1H), 1.70 (s, 3H), 1.44 (s, 9H).

Step 6: **Synthesis of tert-butyl 4-(4-fluoro-2-(3-methyl-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate**

To a stirred solution of tert-butyl 4-(4-fluoro-2-(3-methyl-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.25 g, 2.73 mmol, 1 equiv.) in DCM (28 mL) and 2-propanol (12.0 mL), manganese(III) tris(2,2,6,6-tetramethyl-3,5-heptanedionate) (0.248 g, 0.41 mmol, 0.15 equiv.) and sodium borohydride (0.207 g, 5.46 mmol, 2 equiv.) were added at 0 °C under an oxygen atmosphere. The reaction mixture was bubbled with oxygen and stirred at 10 °C for 1 h. The reaction mixture was concentrated under reduced pressure and purified using reverse-phase column chromatography (C18 cartridge, 330 g) eluting with a gradient of 10 to 50% acetonitrile in 0.1% formic acid in water. Pure fractions were collected and concentrated under reduced pressure to yield tert-butyl 4-(4-fluoro-2-(3-methyl-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate (1.5 g). The obtained product (1.5 g) was dissolved in 10% methanol in DCM (100 mL), and SiliaMets DMT (0.6 g) was added at room temperature. The reaction mixture was stirred at room temperature for 12 h. After 12 h, the reaction mixture was filtered through a celite bed and washed with 10% MeOH in DCM. The filtrate was concentrated and dried under vacuum to afford tert-butyl 4-(4-fluoro-2-(3-methyl-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate. LCMS: m/z: MM-ES+APCI, negative $[M-H]^-$ 474.1; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.87 (s, 1H), 7.82 (t, J = 7.5 Hz, 1H), 7.51 (d, J = 7.9 Hz, 1H), 5.58 (s, 1H), 4.84-4.66 (m, 2H), 3.95-3.78 (m, 2H), 3.28-3.03 (m, 2H), 2.80-2.53 (m, 3H), 2.18-1.99 (m, 2H), 1.89 (td, J = 4.4, 12.6 Hz, 1H), 1.69 (s, 3H), 1.64-1.52 (m, 2H), 1.43 (s, 9H).

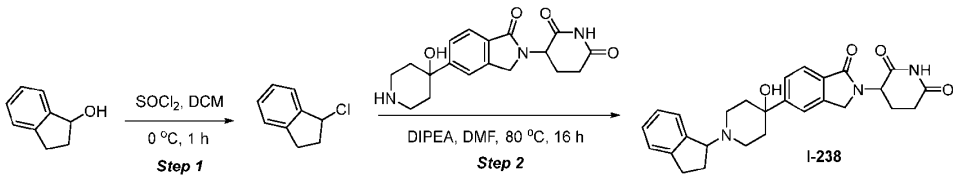
Step 7: **Synthesis of 3-(4-fluoro-5-(4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)-3-methylpiperidine-2,6-dione**

To a stirred solution of tert-butyl 4-(4-fluoro-2-(3-methyl-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-4-hydroxypiperidine-1-carboxylate (1.5 g, 3.15 mmol, 1 equiv.) in DCM (20 mL) was added 4 M hydrochloric acid in 1,4-dioxane (0.47 mL, 15.77 mmol, 5 equiv) at 0 °C. The reaction mixture was then stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure, washed with methyl tert-butyl ether (MTBE, 2 × 70 mL), and dried under vacuum to afford 3-(4-fluoro-5-(4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)-3-methylpiperidine-2,6-dione hydrochloride. LCMS: m/z: MM-ES+APCI, positive $[M+1]^+$ 376.1; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.89 (s, 1H), 9.15-8.64 (m, 2H), 7.81 (t, J = 7.5 Hz, 1H), 7.54 (d, J = 7.9 Hz, 1H), 5.96 (s, 1H), 4.89-4.47 (m, 2H), 3.23 (br s, 4H), 2.83-2.53 (m, 3H), 2.48-2.35 (m, 2H), 1.90 (td, J = 4.7, 12.4 Hz, 1H), 1.81 (dd, J = 2.2, 14.3 Hz, 2H), 1.70 (s, 3H).

Step 8: **Synthesis of 3-(4-fluoro-5-(4-hydroxy-1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)-3-methylpiperidine-2,6-dione (I-214)**

To a stirred solution of 3-(4-fluoro-5-(4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)-3-methylpiperidine-2,6-dione hydrochloride (0.25 g, 0.61 mmol, 1 equiv.) in DMSO (2 mL) was added DIPEA (0.106 mL, 0.61 mmol, 1 equiv.) and 4-(trifluoromethoxy) benzaldehyde (0.115 g, 0.61 mmol, 1 equiv.) at 10 °C. The reaction mixture was stirred at 25 °C for 1 h. Sodium triacetoxyborohydride (0.386 g, 1.82 mmol, 3 equiv.) was then added at 10 °C, and the reaction mixture was allowed to stir at 25 °C for 3 h. The reaction was concentrated under reduced pressure and purified using reverse-phase column chromatography (C18 cartridge, 120 g), eluting with 50% ACN in 0.1% formic acid in water. Pure fractions were collected and concentrated obtain 3-(4-fluoro-5-(4-hydroxy-1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)-3-methylpiperidine-2,6-dione **(I-214)**. LCMS: m/z: MM-ES+APCI, positive $[M+1]^+$ 550.5; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.05-10.77 (m, 1H), 10.33-10.06 (m, 1H), 7.85-7.72 (m, 3H), 7.53 (t, J = 8.7 Hz, 3H), 5.99 (s, 1H), 4.85-4.68 (m, 2H), 4.44 (d, J = 4.6 Hz, 2H), 3.48-3.34 (m, 3H), 2.82-2.54 (m, 4H), 2.49-2.44 (m, 2H), 1.95-1.81 (m, 3H), 1.70 (s, 3H).

Example 46: Synthesis of 3-(5-(1-(2,3-dihydro-1H-inden-1-yl)-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-238):



Step 1: **Synthesis of 1-chloro-2,3-dihydro-1*H*-indene**

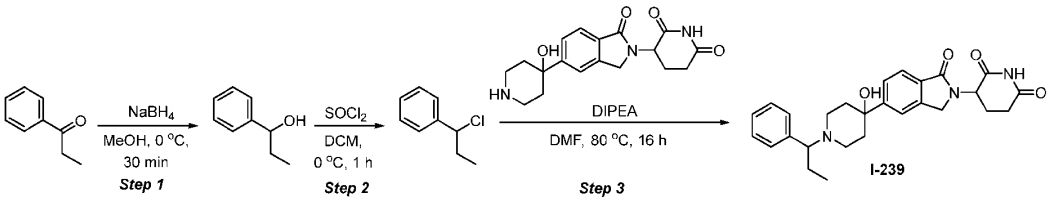
To a stirred solution of 2,3-dihydro-1H-inden-1-ol (0.3 g, 2.24 mmol) in DCM (5 mL) was added thionyl chloride (0.332 mL, 4.47 mmol) at 0 °C and the reaction mixture was stirred for 1 h. The reaction mixture was concentrated under reduced pressure and used in the next step without further purification. LCMS: m/z MM-ES+APCI, Negative $[M-H]^-$ 151.0; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.42 (d, J = 8.0 Hz, 1H), 7.31-7.25 (m, 3H), 5.76-5.62 (m, 1H), 3.11-3.06 (m, 1H), 2.91-2.89 (m, 1H), 2.61-2.55 (m, 1H), 2.28-2.23 (m, 1H).

Step 2: **Synthesis of 3-(5-(1-(2,3-dihydro-1*H*-inden-1-yl)-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione**

To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-(4-hydroxypiperidin-4-yl)isoindoline-1,3-dione (100 mg, 0.25 mmol) in DMF (2 mL) was added 1-chloro-2,3-dihydro-1*H*-indene (78 mg, 0.51 mmol) and DIPEA (0.141 mL, 0.762 mmol) at 0 °C. The reaction mixture was heated to 80 °C for 16 h. The reaction mixture was concentrated under reduced pressure and purified by Prep-HPLC [Method info:

column: X select (150 mm × 19) 5um, mobile phase A: 0.1% HCl in H_2O, mobile phase B:ACN, Flow rate: 15 mL/min] and lyophilized to obtain 3-(5-(1-(2,3-dihydro-1H-inden-1-yl)-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-238**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 460.2; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 10.90 (bs, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.0 Hz, 3H), 7.69-7.36 (m, 3H), 5.76 (bs, 1H), 5.14-5.01 (m, 2H), 4.49-4.31 (m, 2H), 3.23-3.19 (m, 4H), 2.97-2.92 (m, 4H), 2.68-2.59 (m, 4H), 2.47-2.33 (m, 2H), 1.83-1.80 (m, 2H).

Example 47: Synthesis of 3-(5-(4-hydroxy-1-(1-phenylpropyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-239)



Step 1: **Synthesis of 1-phenylpropan-1-ol**

To a stirred solution of propiophenone (1 g, 7.45 mmol) in methanol (10 mL) was added sodium borohydride (0.141 g, 3.73 mmol) at 0 °C. The reaction was stirred for 30 min. After completion of the reaction, the reaction mixture was concentrated and diluted with water (10 mL). The reaction was quenched with 1N HCl at 0 °C. The aqueous layer was extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated to obtain 1-phenylpropan-1-ol. LCMS: m/z MM-ES+APCI, POSITIVE$[M-17]^+$ 119.1; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.35 (m, 4H), 7.31 (d, J = 8.0 Hz, 1H), 4.62 (t, J = 8.0 Hz, 1H), 1.89-1.74 (m, 3H), 0.94 (t, J = 8.0 Hz, 3H).

Step 2: **Synthesis of (1-chloropropyl)benzene**

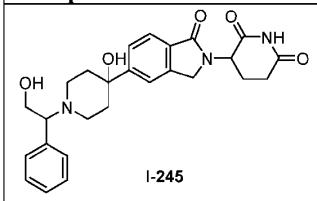
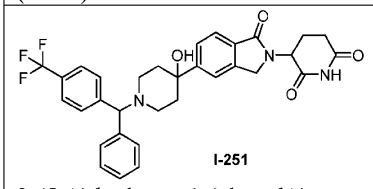
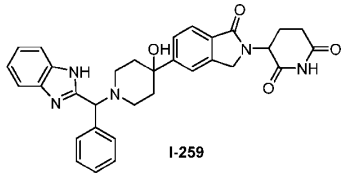
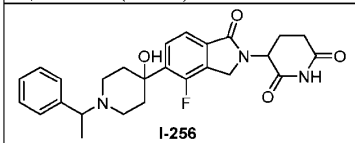
To a stirred solution of 1-phenylpropan-1-ol (950 mg, 6.98 mmol) in DCM (20 mL) was added thionyl chloride (1.018 mL, 13.95 mmol) at 0 °C and the reaction was stirred for 1 h. The reaction mixture was concentrated under reduced pressure twice by addition of DCM to afford (1-chloropropyl)benzene. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.31 (m, 5H), 4.83-4.79 (m, 1H), 2.21-2.06 (m, 2H), 1.04 (t, J = 8.0 Hz, 3H).

Step 3: **Synthesis of 3-(5-(4-hydroxy-1-(1-phenylpropyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione**

To a stirred solution of 3-(5-(4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (0.1 g, 0.29 mmol) in DMF (5 mL) was added (1-chloropropyl)benzene (0.113 g, 0.73 mmol) and DIPEA (0.152 mL, 0.87 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 16 h. The reaction concentrated under reduced pressure and purified by ZORBAX C18 150 × 19 5um, Mobile phase

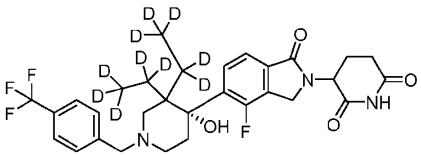
A: 0.1% formic acid IN H_2O; B: ACN, flow rate: 14 mL/min)]. Pure fractions were combined to afford 3-(5-(4-hydroxy-1-(1-phenylpropyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-239**, 10 mg, 0.021 mmol). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 462.0; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.98 (s, 1H), 8.23 (s, 1H), 7.68-7.60 (m, 3H), 7.36-7.24 (m, 5H), 5.12-5.08 (m, 1H), 4.83 (s, 1H), 4.44-4.27 (m, 2H), 2.91-2.88 (m, 2H), 2.75.2.66 (m, 4H), 2.26-2.22 (m, 2H), 2.00-1.89 (m, 4H), 1.76-1.53 (m, 3H), 0.75 (t, J = 7.60 Hz, 3H).

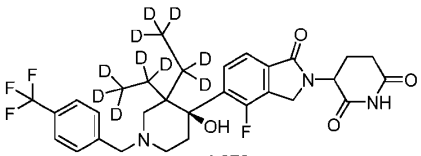
The following compounds were synthesized in a similar fashion to Example 47 (**I-239**).

Compound	Characterization
 I-245 3-(5-(4-hydroxy-1-(2-hydroxy-1-phenylethyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-245**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 464.2. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 10.01 (s, 1H), 7.67-7.62 (m, 5H), 7.52-7.50 (m, 3H), 5.57 (s, 1H), 5.14-5.10 (m, 1H), 4.56-4.55 (m, 1H), 4.47 (d, J = 17.20 Hz, 1H), 4.40 (d, J = 37.60 Hz, 1H), 4.22-4.19 (m, 1H), 4.02-4.01 (m, 1H), 3.73-3.70 (m, 1H), 3.22-3.13 (m, 3H), 2.93-2.91 (m, 1H), 2.68-2.63 (m, 3H), 2.44-2.41 (m, 2H), 2.02-2.00 (m, 1H), 1.80 (t, J = 14.00 Hz, 2H).
 I-251 3-(5-(4-hydroxy-1-(phenyl(4-(trifluoromethyl)phenyl)methyl)-piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-251**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 578.3. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.55 (s, 1H), 10.99 (s, 1H), 8.14 (d, J = 8.00 Hz, 2H), 7.99-7.83 (m, 4H), 7.79-7.62 (m, 3H), 7.50 (t, J = 7.60 Hz, 2H), 7.42 (d, J = 7.60 Hz, 1H), 5.95 (d, J = 9.60 Hz, 1H), 5.74 (s, 1H), 5.14-5.10 (m, 1H), 4.50-4.46 (m, 1H), 4.35-4.32 (m, 1H), 3.23-3.16 (m, 2H), 3.01-2.86 (m, 1H), 2.68-2.63 (m, 4H), 2.50-2.43 (m, 1H), 2.35-2.31 (m, 1H), 1.85-1.82 (m, 2H).
 I-259 3-(5-(1-((1H-benzo[d]imidazol-2-yl)(phenyl)methyl)-4-hydroxy-piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-259**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 550. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 7.72-7.66 (m, 7H), 7.55-7.52 (m, 3H), 7.32 (d, J = 4.00 Hz, 2H), 6.12 (s, 1H), 5.15-5.10 (m, 1H), 4.49 (dd, J = 3.20, 17.60 Hz, 2H), 3.54-3.48 (m, 5H), 3.48 (m, 2H), 3.16-3.13 (m, 1H), 2.93-2.90 (m, 1H), 2.68-2.67 (m, 1H), 2.40-2.39 (m, 1H), 2.03-2.02 (m, 1H), 1.88-184 (m, 2H).
 I-256 3-(4-fluoro-5-(4-hydroxy-1-(1-phenylethyl)piperidin-4-yl)-1-	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 466; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 10.42 (s, 1H), 7.77 (t, J = 7.20 Hz, 1H), 7.67-7.63 (m, 3H), 7.53-7.48 (m, 3H), 5.85 (s, 1H), 5.12 (dd, J = 5.20, 13.20 Hz, 1H), 4.62-4.61 (m, 2H), 4.60-4.54 (m, 1H), 3.66-3.63 (m, 1H), 3.16-3.07 (m, 3H), 2.92-2.89 (m, 1H), 2.68-

oxoisoindolin-2-yl)piperidine-2,6-dione **(I-256)**	2.68 (m, 2H), 2.45-2.41 (m, 1H), 2.01-2.00 (m, 1H), 1.75 (d, J = 7.20 Hz, 5H).

Example 48: Synthesis of 3-(5-((R)-3,3-bis(ethyl-d5)-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-277) and 3-(5-((S)-3,3-bis(ethyl-d5)-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-278)


I-277

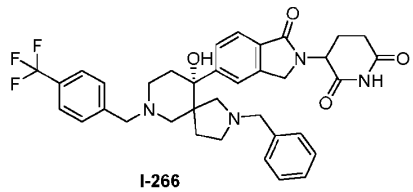

I-278

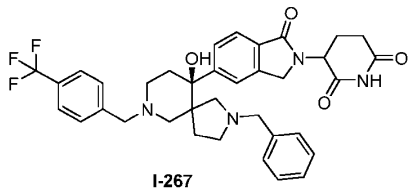
The title compounds were synthesized in a similar fashion to **Example 80 (I-82).** Two peaks were collected separately during final prep HPLC purification and stereochemistry was arbitrarily assigned.

Peak 1: 3-(5-((R)-3,3-bis(ethyl-d5)-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione **(I-277).** LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 586.5; ^{1}H NMR (499 MHz, DMSO-d_6) δ 10.91-11.07 (m, 1H), 7.90-8.03 (m, 1H), 7.70 (d, *J*=7.94 Hz, 2H), 7.49-7.58 (m, 2H), 6.94-7.02 (m, 2H), 5.04-5.14 (m, 2H), 4.51 (br d, *J*=17.25 Hz, 1H), 4.39 (s, 1H), 3.51-3.60 (m, 2H), 3.00-3.04 (m, 1H), 2.86-2.91 (m, 1H), 2.56-2.66 (m, 2H), 2.31-2.43 (m, 3H), 1.96-2.04 (m, 2H), 1.49-1.56 (m, 1H).

Peak 2: 3-(5-((S)-3,3-bis(ethyl-d5)-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione **(I-278).** LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 586.5; ^{1}H NMR (499 MHz, DMSO-d_6) δ 10.81-11.14 (m, 1H), 7.93-8.08 (m, 1H), 7.70 (d, *J*=8.21 Hz, 1H), 7.50-7.65 (m, 2H), 6.89-6.98 (m, 2H), 5.12 (m, 2H), 4.49-4.60 (m, 1H), 4.29-4.39 (m, 1H), 3.49-3.62 (m, 2H), 3.01-3.09 (m, 1H), 2.86-2.98 (m, 1H), 2.57-2.66 (m, 2H), 2.33 (m, 3H), 1.97-2.04 (m, 1H), 1.53-1.59 (m, 1H).

Example 49: Synthesis of 3-(5-((10R)-2-benzyl-10-hydroxy-7-(4-(trifluoromethyl)benzyl)-2,7-diazaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-266) and 3-(5-((10S)-2-benzyl-10-hydroxy-7-(4-(trifluoromethyl)benzyl)-2,7-diazaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-267)


I-266

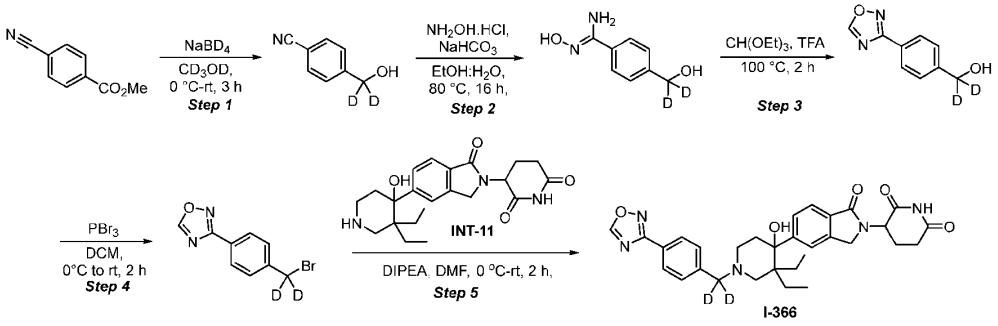

I-267

The title compounds were synthesized in a similar fashion to **Example 8 (I-47).** Two peaks were collected separately during final prep HPLC purification and stereochemistry was arbitrarily assigned.

Peak 1: 3-(5-((10R)-2-benzyl-10-hydroxy-7-(4-(trifluoromethyl)benzyl)-2,7-diazaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione **(I-266).** LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 647.2; ^{1}H NMR (499 MHz, DMSO-d_6) δ 11.01 (br d, *J*=6.57 Hz, 1H), 8.31-8.42 (m, 1H), 7.66-7.77 (m, 5H), 7.54-7.63 (m, 2H), 7.14-7.25 (m, 3H), 6.95-7.02 (m, 2H), 5.10-5.19 (m, 1H), 4.93-5.00 (m, 1H), 4.29-4.49 (m, 3H), 3.58-3.68 (m, 3H), 3.03-3.13 (m, 2H), 2.88-2.96 (m, 1H), 2.67-2.76 (m, 1H), 2.59-2.67 (m, 2H), 2.34-2.44 (m, 2H), 2.15-2.23 (m, 1H), 1.90-2.03 (m, 2H), 1.69-1.86 (m, 3H), 1.50-1.59 (m, 1H).

Peak 2: 3-(5-((10S)-2-benzyl-10-hydroxy-7-(4-(trifluoromethyl)benzyl)-2,7-diazaspiro[4.5]decan-10-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione **(I-267).** LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 647.2; ^{1}H NMR (499 MHz, DMSO-d_6) δ 11.01 (s, 1H), 8.40 (s, 1H), 7.77 (s, 1H), 7.68 (t, *J*=3.83 Hz, 3H), 7.53 (d, *J*=7.94 Hz, 2H), 7.15-7.25 (m, 3H), 6.95-7.01 (m, 2H), 5.11-5.17 (m, 1H), 4.92-5.01 (m, 1H), 4.31-4.51 (m, 2H), 3.65-3.70 (m, 1H), 3.52-3.57 (m, 1H), 3.17-3.26 (m, 4H), 2.89-2.97 (m, 1H), 2.85 (dd, *J*=9.31, 4.11 Hz, 1H), 2.55-2.67 (m, 3H), 2.38-2.47 (m, 2H), 2.20-2.29 (m, 2H), 2.01 (br d, *J*=6.84 Hz, 2H), 1.52-1.62 (m, 2H), 0.98-1.08 (m, 1H).

Example 50: Synthesis of 3-(5-(1-((4-(1,2,4-oxadiazol-3-yl)phenyl)methyl-d2)-3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-366)



Step 1: **Synthesis of 4-(hydroxymethyl-d_2)benzonitrile**

To a stirred solution of methyl 4-cyanobenzoate (1.2 g, 7.45 mmol) in methanol-d_4 (10 mL) and DMSO-d_6 (1 mL) was added deuterated sodium borohydride (0.779 g, 18.62 mmol) at room temperature and stirred for 3 h. The reaction mixture was poured into cooled deuterium oxide (D_2O, 10 mL). The compound was extracted with ethyl acetate (2 × 100 mL), and the organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to get the crude compound. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.80 (d, J = 8.40 Hz, 2H), 7.52 (d, J = 8.00 Hz, 2H), 5.41 (s, 1H).

Step 2: **Synthesis of (*Z*)-*N*'-hydroxy-4-(hydroxymethyl-d_2)benzimidamide**

To a stirred solution of 4-(hydroxymethyl-d_2)benzonitrile (1.2 g, 8.88 mmol) in ethanol (20 mL) and water (4 mL) was added hydroxylamine hydrochloride (1.554 g, 17.76 mmol) and sodium bicarbonate (2.237 g, 26.6 mmol) at room temperature. The reaction then stirred at 80 °C for 16 h. The reaction was filtered and concentrated to yield the crude compound (*Z*)-*N*'-hydroxy-4-(hydroxymethyl-d_2)benzimidamide. LCMS: m/z MM-ES+APCI, $[M+H]^+$ 169.2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.57 (s, 1H), 7.63 (d, J = 4.40 Hz, 2H), 7.31 (d, J = 4.80 Hz, 2H), 5.77 (s, 2H), 5.18 (s, 1H).

Step 3: **Synthesis of (4-(1,2,4-oxadiazol-3-yl)phenyl)methan-d_2-ol**

To a stirred solution of (*Z*)-*N*'-hydroxy-4-(hydroxymethyl-d_2)benzimidamide (300 mg, 1.78 mmol) in triethyl orthoformate (594 µL, 3.57 mmol) was added trifluoroacetic acid (137 µL, 1.78 mmol) at 25 °C. The reaction was stirred at 100 °C for 2 h and then poured into cooled water (100 mL). The compound was extracted with ethyl acetate (100 mL × 2) and the organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure to get a crude residue. The crude material was purified by flash chromatography using Biotage Isolera (Silica gel 100-200 mesh) and a linear gradient of 0-15% EtOAc in hexane as eluent to afford (4-(1,2,4-oxadiazol-3-yl)phenyl)methan-d_2-ol.^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.69 (s, 1H), 8.01 (d, J = 8.00 Hz, 2H), 7.52 (d, J = 8.00 Hz, 2H), 5.33 (s, 1H).

Step 4: **Synthesis of 3-(4-(bromomethyl-d_2)phenyl)-1,2,4-oxadiazole**

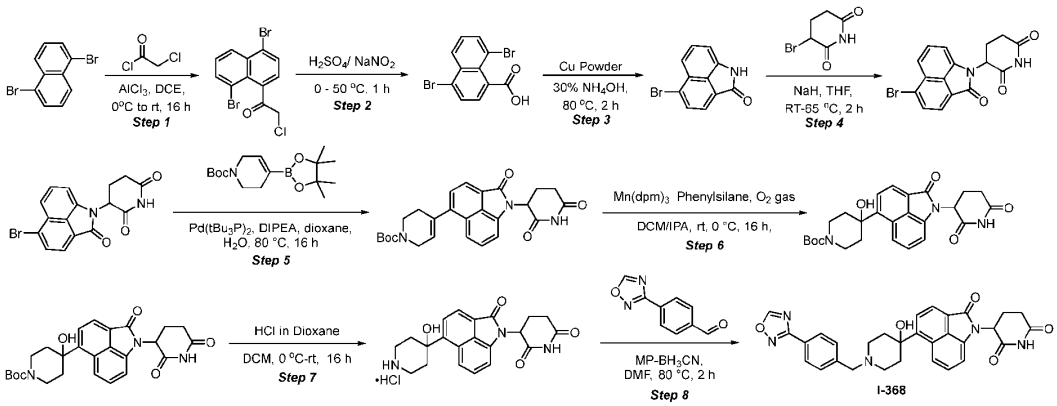
A solution of (4-(1,2,4-oxadiazol-3-yl)phenyl)methan-d_2-ol (80 mg, 0.44 mmol) in DCM (5 mL) was cooled to 0 °C and then phosphorus tribromide (0.051 mL, 0.539 mmol) was added at 0 °C. The resulting reaction mixture was allowed to stir at 25 °C for 2 h. The reaction mixture was poured into ice cold water (25 mL) and extracted with DCM (100 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain 3-(4-(bromomethyl-d_2)phenyl)-1,2,4-oxadiazole. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.79 (s, 1H), 8.12 (d, J = 2.00 Hz, 2H), 7.57 (d, J = 2.00 Hz, 2H).

Step 5: **Synthesis of 3-(5-(1-((4-(1,2,4-oxadiazol-3-yl)phenyl)methyl-d_2)-3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (I-366)**

To a solution of 3-(5-(3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**INT-11**, 70 mg, 0.175 mmol) in DMF (5 mL) was added DIPEA (0.061 mL, 0.35 mmol) and 3-(4-(bromomethyl-d_2)phenyl)-1,2,4-oxadiazole (42 mg, 0.17 mmol) at 0 °C and the resulting reaction mixture was allowed to stir at 25 °C for 2 h. The reaction was concentrated and the crude residue was triturated with DCM and dried under reduced pressure. The crude material was purified by Prep-HPLC using a Synergy Fusion RP column (21.2 × 250 mm, 4 µm), with a mobile phase of 0.1% formic acid in water and acetonitrile at a flow rate of 15 mL/min and a retention time of 12 minutes. The acetonitrile/water mixture was removed by lyophilization to afford 3-(5-(1-((4-(1,2,4-oxadiazol-3-yl)phenyl)methyl-d_2)-3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-366**). LCMS: m/z MM-

ES+APCI, $[M+H]^+$ 560.1. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 9.71 (s, 1H), 7.75-7.69 (m, 2H), 7.63 (m, 3H), 7.58-7.56 (m, 2H), 5.13 (d, J = 4.80 Hz, 1H), 4.83 (d, J = 5.20 Hz, 1H), 4.42 (d, J = 2.40 Hz, 1H), 3.83 (m, 1H), 2.95-2.85 (m, 1H), 2.83-2.75 (m, 1H), 2.69-2.63 (m, 3H), 2.48-2.33 (m, 3H), 2.03-1.99 (m, 2H), 1.43-1.40 (m, 2H), 2.98-2.18 (m, 1H), 1.23-0.89 (m, 1H), 0.53 (m, 3H), 0.46 (m, 3H).

Example 51: Synthesis of 3-(5-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxypiperidin-4-yl)-2-oxobenzo[cd]indol-1(2H)-yl)piperidine-2,6-dione (I-368)



Step 1: **Synthesis of 2-chloro-1-(4,8-dibromonaphthalen-1-yl)ethan-1-one**

To a stirred solution of 1,5-dibromonaphthalene (20 g, 69.9 mmol) in 1,2-dichloroethane (200 mL) was added aluminum chloride (23.31 g, 175 mmol) followed by the dropwise addition of 2-chloroacetyl chloride (12.24 mL, 154 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with DCM (100 mL) and poured into ice-cold water. The mixture was extracted twice with DCM (2 × 500 mL). The organic layer was washed with brine solution (500 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure afford the crude product. The crude was purified by flash chromatography using Biotage Isolera (Silica gel 100-200 mesh) and a linear gradient of 0-5% EtOAc in hexane as eluents to afford 2-chloro-1-(4,8-dibromonaphthalen-1-yl)ethan-1-one. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (dd, J = 1.20, 8.80 Hz, 1H), 7.96 (d, J = 1.20 Hz, 1H), 7.89 (d, J = 7.60 Hz, 1H), 7.53 (t, J = 7.60 Hz, 1H), 7.30 (t, J = 6.80 Hz, 1H), 4.76 (s, 2H).

Step 2: **Synthesis of 4,8-dibromo-1-naphthoic acid**

To a stirred solution of 2-chloro-1-(4,8-dibromonaphthalen-1-yl)ethan-1-one (4.3 g, 11.86 mmol) in H_2SO_4 (50 mL) was added sodium nitrite (0.859 g, 12.46 mmol) at 0 °C and the reaction mixture was allowed to stir at 50 °C for 1 h. The reaction mixture was poured into 10% sodium carbonate solution (500 mL) and stirred at room temperature for 30 min. The sodium carbonate solution was filtered and the filtrate was acidified with conc. HCl until solid precipitated. The solid was filtered, washed with water

and dried under vacuum to afford 4,8-dibromo-1-naphthoic acid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.49 (s, 1H), 8.33 (d, J = 0.80 Hz, 1H), 8.12 (d, J = 9.20 Hz, 1H), 8.10 (s, 1H), 7.66 (t, J = 8.00 Hz, 1H), 7.60 (t, J = 8.00 Hz, 1H).

Step 3: **Synthesis of 5-bromobenzo[cd]indol-2(1*H*)-one**

To a stirred solution of 4,8-dibromo-1-naphthoic acid (5.8 g, 14.06 mmol) in ammonium hydroxide (1.014 mL, 14.06 mmol) was added copper powder (0.447 g, 7.03 mmol) at 0 °C. The reaction mixture was stirred at 80 °C for 2 h. The reaction mixture was poured into ice-cold water and acidified with concentrated HCl until solid precipitation occurred. The solid precipitate was filtered, washed with water (2 × 50 mL), and dried under vacuum to get 5-bromobenzo[*cd*]indol-2(1*H*)-one. LCMS: m/z MM-ES+APCI, $[M+H]^+$ 248.0/250.1; bromine isotopes. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.88 (s, 1H), 8.07 (d, J = 7.20 Hz, 1H), 7.90 (d, J = 7.60 Hz, 1H), 7.63-7.56 (m, 2H), 7.06 (d, J = 6.80 Hz, 1H).

Step 4: **Synthesis of 3-(5-bromo-2-oxobenzo[cd]indol-1(2*H*)-yl)piperidine-2,6-dione**

To a stirred solution of 5-bromobenzo[*cd*]indol-2(1*H*)-one (1.5 g, 6.05 mmol) in THF (100 mL) was added NaH (2.41 g, 60.5 mmol) in portions at 0 °C. The reaction mixture was stirred at room temperature for 15 minutes. 3-bromopiperidine-2,6-dione (5.80 g, 30.2 mmol) was then added at 0 °C and the reaction mixture was stirred at 65 °C for 2 h. The reaction mixture was quenched with ice-cold water (100 mL) and extracted with ethyl acetate (400 mL × 2). The organic layer was dried over sodium sulfate and concentrated under vacuum to afford the crude compound. The crude product was purified by reverse-phase HPLC column chromatography using mobile phase A: 0.1% formic acid in H_2O and mobile phase B: ACN, with a flow rate of 15 mL/min. The fractions containing the product were combined and lyophilized to afford 3-(5-bromo-2-oxobenzo[*cd*]indol-1(2*H*)-yl)piperidine-2,6-dione. LCMS: m/z MM-ES+APCI, $[M+H]^+$ 359.0/361.3. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.15 (s, 1H), 8.13 (d, J = 7.60 Hz, 1H), 8.01 (d, J = 2.40 Hz, 1H), 7.67-7.63 (m, 2H), 7.27 (d, J = 6.80 Hz, 1H), 5.50-5.45 (m, 1H), 3.33-2.95 (m, 2H), 2.78-2.77 (m, 2H).

Step 5: **Synthesis of tert-butyl 4-(1-(2,6-dioxopiperidin-3-yl)-2-oxo-1,2-dihydrobenzo[*cd*]indol-5-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate**

The stirring solution of 3-(5-bromo-2-oxobenzo[*cd*]indol-1(2*H*)-yl)piperidine-2,6-dione (0.78 g, 2.17 mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (1.007 g, 3.26 mmol), and DIPEA (1.135 mL, 6.51 mmol) in 1,4-dioxane (13 mL) and water (1.44 mL) was degassed with N_2 for 10 minutes. To this mixture, bis (tri-*tert*-butyl phosphine) palladium (0) (0.111 g, 0.22 mmol) was added at room temperature, and the resulting reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (50 mL) then stirred for 10 minutes. The reaction mixture was filtered through celite pad and washed with ethyl acetate (50 mL). The collected filtrate was concentrated under reduced pressure to obtain the crude

residue which was purified by flash column chromatography (100-200 silica gel mesh) using ethyl acetate in hexanes (0-100%) as the eluent to obtain *tert*-butyl 4-(1-(2,6-dioxopiperidin-3-yl)-2-oxo-1,2-dihydrobenzo[*cd*]indol-5-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate. LCMS: m/z MM-ES+APCI, $[M+H]^+$ 462.5. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.13 (s, 1H), 8.07 (d, J = 7.20 Hz, 1H), 7.71 (t, J = 6.00 Hz, 2H), 7.54 (t, J = 8.40 Hz, 1H), 7.18 (d, J = 7.20 Hz, 1H), 5.99 (s, 1H), 5.49-5.45 (m, 1H), 4.12 (s, 2H), 3.66 (t, J = 5.20 Hz, 2H), 2.97-2.92 (m, 1H), 2.80-2.77 (m, 1H), 2.77-2.68 (m, 3H), 2.10 (t, J = 5.20 Hz, 1H), 1.47 (s, 9H).

Step 6: **Synthesis of *tert*-butyl 4-(1-(2,6-dioxopiperidin-3-yl)-2-oxo-1,2-dihydrobenzo[cd]indol-5-yl)-4-hydroxypiperidine-1-carboxylate**

To a stirred solution of *tert*-butyl 4-(1-(2,6-dioxopiperidin-3-yl)-2-oxo-1,2-dihydrobenzo-[*cd*]indol-5-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (700 mg, 1.52 mmol) in DCM (30 mL) and 2-propanol (30 mL) at 0 °C were added $Mn(dpm)_3$ (275 mg, 0.46 mmol) and phenylsilane (0.472 mL, 3.79 mmol). The reaction mixture was stirred under an oxygen balloon for 16 h. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by reverse-phase HPLC column chromatography using mobile phase A: 0.1% formic acid in H_2O and mobile phase B: ACN, with a flow rate of 15 mL/min. The pure fractions were collected and lyophilized to afford *tert*-butyl 4-(1-(2,6-dioxopiperidin-3-yl)-2-oxo-1,2-dihydrobenzo[*cd*]indol-5-yl)-4-hydroxypiperidine-1-carboxylate. LCMS: m/z MM-ES+APCI, Negative $[M-H]^-$. 478.4; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.12 (s, 1H), 8.19 (d, J = 8.80 Hz, 1H), 8.06 (d, J = 6.00 Hz, 1H), 7.92 (d, J = 7.60 Hz, 1H), 7.48 (t, J = 8.80 Hz, 1H), 7.06 (d, J = 7.60 Hz, 1H), 5.76 (s, 1H), 5.46-5.42 (m, 1H), 3.93 (m, 2H), 2.95-2.75 (m, 3H), 2.51-2.34 (m, 2H), 2.16-2.13 (m, 3H), 1.97-1.95 (m, 2H), 1.45 (s, 9H).

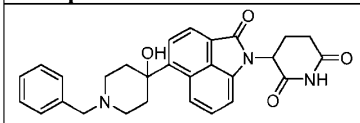
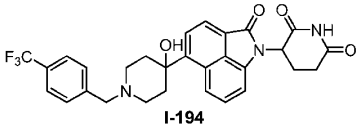
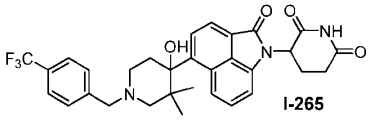
Step 7: **Synthesis of 3-(5-(4-hydroxypiperidin-4-yl)-2-oxobenzo[*cd*]indol-1(2*H*)-yl)piperidine-2,6-dione**

To a stirred solution of *tert*-butyl 4-(1-(2,6-dioxopiperidin-3-yl)-2-oxo-1,2-dihydrobenzo[*cd*]indol-5-yl)-4-hydroxypiperidine-1-carboxylate (360 mg, 0.75 mmol) in DCM (10 mL) was added 4 M HCl in 1,4-dioxane (0.188 mL, 0.75 mmol) at 0 °C. The reaction mixture was stirred at 25 °C under a N_2 atmosphere for 16 h. The reaction was concentrated under reduced pressure to obtain the 3-(5-(4-hydroxypiperidin-4-yl)-2-oxobenzo[*cd*]indol-1(2*H*)-yl)piperidine-2,6-dione. LCMS: m/z MM-ES+APCI, $[M+H]^+$ 380.4; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.12 (s, 1H), 8.63 (s, 1H), 8.33 (d, J = 9.20 Hz, 1H), 8.11 (d, J = 7.20 Hz, 1H), 7.98 (d, J = 7.60 Hz, 1H), 7.53 (t, J = 8.80 Hz, 1H), 7.16 (d, J = 7.20 Hz, 1H), 6.01 (s, 1H), 5.49-5.45 (m, 1H), 3.67-3.66 (m, 2H), 3.18-3.14 (m, 1H), 2.61-2.99 (m, 4H), 2.09-2.06 (m, 6H).

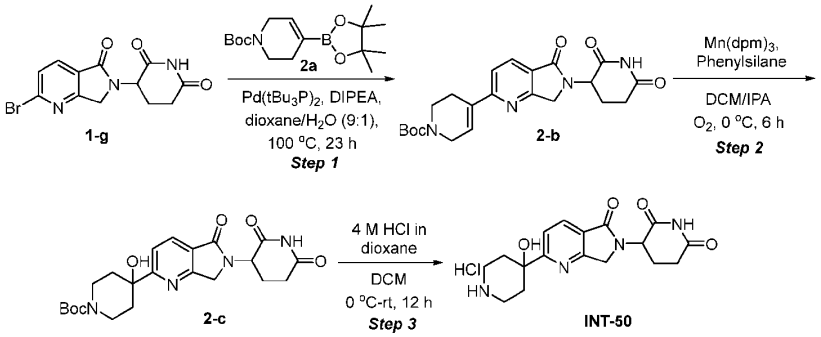
Step 8: **Synthesis of 3-(5-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxypiperidin-4-yl)-2-oxobenzo[cd]indol-1(2*H*)-yl)piperidine-2,6-dione (I-368)**

3-(5-(4-hydroxypiperidin-4-yl)-2-oxobenzo[cd]indol-1(2*H*)-yl)piperidine-2,6-dione (60 mg, 0.16 mmol) and 4-(1,2,4-oxadiazol-3-yl)benzaldehyde (41.3 mg, 0.24 mmol) were stirred in DMF (2 mL) at 80 °C for 1 h. MP-cyanoborohydride (60 mg, 0.16 mmol) was then added and the reaction mixture was stirred at 80 °C for an additional 2 h. The reaction mixture was filtered and concentrated under residue pressure. The crude residue was triturated with a minimal amount of DCM and hexane. The solid was concentrated under vacuum to obtain the crude compound which was purified by preparative HPLC [X-Select C18 (19 × 250 mm) 5 µm, Mobile phase A: 0.1% formic acid in water, Mobile phase B: ACN, flow rate: 15 mL/min, RT: 11.5 min]. The pure fractions were collected and lyophilized to afford 3-(5-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxypiperidin-4-yl)-2-oxobenzo[*cd*]indol-1(2*H*)-yl)piperidine-2,6-dione (**I-368**). LCMS: m/z MM-ES+APCI, $[M+H]^+$ 538.3; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.12 (s, 1H), 9.70 (s, 1H), 8.30 (d, J = 8.80 Hz, 1H), 8.03 (d, J = 2.00 Hz, 3H), 7.94 (t, J = 7.20 Hz, 1H), 7.60 (d, J = 8.00 Hz, 2H), 7.50 (t, J = 7.20 Hz, 1H), 7.12 (d, J = 7.20 Hz, 1H), 5.47-5.42 (m, 2H), 3.69 (s, 2H), 3.00-2.98 (m, 1H), 2.82-2.62 (m, 6H), 2.34-2.33 (m, 2H), 2.10-2.09 (m, 1H), 1.98-1.96 (m, 2H).

The following compounds were synthesized in a similar fashion to **Example 51 (I-368)**.

Compound	Characterization
 **I-367** 3-(5-(1-benzyl-4-hydroxypiperidin-4-yl)-2-oxobenzo[cd]indol-1(2*H*)-yl)piperidine-2,6-dione (**I-367**)	LCMS: m/z MM-ES+APCI, $[M+H]^+$ 470.3 ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.12 (s, 1H), 8.29 (d, J = 8.80 Hz, 1H), 8.04 (d, J = 7.20 Hz, 1H), 7.94 (d, J = 7.60 Hz, 1H), 7.51 (t, J = 1.20 Hz, 1H), 7.49-7.34 (m, 5H), 7.12 (d, J = 7.20 Hz, 1H), 5.47-5.42 (m, 2H), 3.60 (s, 2H), 3.00-2.95 (m, 1H), 2.79-2.72 (m, 3H), 2.68-2.61 (m, 3H), 2.34-2.29 (m, 2H), 2.19 (m, 1H), 1.96-1.94 (m, Hz, 2H).
 **I-194** 3-(5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-2-oxobenzo[cd]indol-1(2H)-yl)piperidine-2,6-dione (**I-194**)	LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 538.4; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.13 (s, 1H), 10.58 (s, 1H), 8.39 (d, J = 8.80 Hz, 1H), 8.10 (d, J = 7.60 Hz, 1H), 7.98-7.90 (m, 5H), 7.53-7.49 (m, 1H), 7.16 (d, J = 7.20 Hz, 1H), 6.08 (s, 1H), 5.48-5.43 (m, 1H), 4.57-4.56 (m, 2H), 3.59-3.45 (m, 4H), 3.00-0.95 (m, 1H), 2.92-2.91 (m, 1H), 2.78-2.68 (m, 2H), 2.14 (m, 3H).
 **I-265** 3-(5-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-2-oxobenzo[cd]-indol-1(2H)-yl)piperidine-2,6-dione (**I-265**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 467.1. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.11 (s, 1H), 8.72 (d, J = 8.80 Hz, 1H), 8.01 (d, J = 7.60 Hz, 1H), 7.80 (d, J = 7.20 Hz, 1H), 7.72 (d, J = 8.40 Hz, 2H), 7.61 (s, 2H), 7.41 (t, J = 7.60 Hz, 1H), 7.09-7.07 (m, 1H), 5.45 (s, 1H), 5.41 (s, 1H), 3.71-3.57 (m, 2H), 3.01-2.95 (m, 2H), 2.78-0.71 (m, 2H), 2.67-2.60 (m, 3H), 2.33-2.21 (m, 1H), 2.09-2.07 (m, 1H), 1.70 (d, J = 13.20 Hz, 1H), 0.95 (s, 3H), 0.76 (s, 3H).

Example 52: Synthesis of 3-(2-(4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione hydrochloride (INT-50)



Step 1: **Synthesis of *tert*-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (2-b)**:

To a stirred solution of 3-(2-bromo-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**1-g**, 550 mg, 1.697 mmol; **1-g** was prepared according to the procedures and examples as reported in PCT Application Publication No. WO2018/102725) and tert-butyl 4-(4,4,5-trimethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**2-a**, 751 mg, 2.55 mmol) in dioxane (4 mL) and water (1 mL) was added DIPEA (1.182 mL, 6.79 mmol) at room temperature. The resulting mixture was sparged with nitrogen for 10 min and bis(tri-t-butylphosphine)palladium(0) (87 mg, 0.17 mmol) was then added at room temperature. The reaction mixture was again sparged with nitrogen for 10 min and then stirred at 100°C for 23 h. The reaction mixture was concentrated and the resulting crude product was purified via flash silica gel chromatography on a Biotage® Isolera (100-200 mesh silica gel) eluting with 5% IPA/DCM to afford tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**2-b**). LCMS: m/z MM-ES+APCI, Negative $[M-H]^-$ = 425.1. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 6.89 (s, 1H), 5.18 (q, J = 6.1 Hz, 1H), 4.53-4.31 (m, 2H), 4.10 (s, 2H), 3.78-3.70 (m, 2H), 2.95-2.87 (m, 1H), 2.65-2.61 (m, 3H), 2.45-2.41 (m, 1H), 2.06-1.98 (m, 1H), 1.44 (s, 9H).

Step 2: **Synthesis of tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-4-hydroxypiperidine-1-carboxylate (2-c)**:

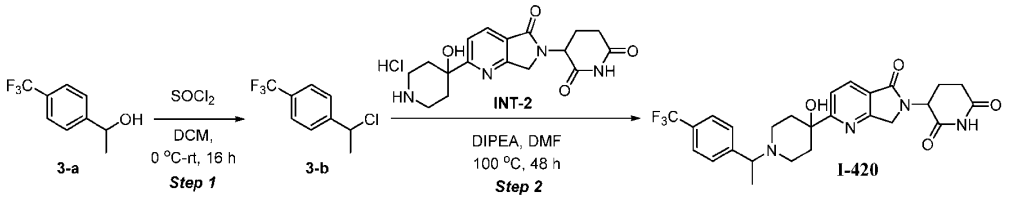
To a stirred solution of tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**2-b**, 0.7 g, 1.64 mmol) in DCM (10 mL)/IPA (10 mL) at 0°C under an atmosphere of oxygen was added $Mn(dpm)_3$ (0.298 g, 0.49 mmol) and phenyl silane (0.506 mL, 4.10 mmol). The resulting mixture was stirred at the same temperature for 6 h. The reaction mixture was concentrated. The residue with taken up in 10% IPA in DCM, filtered through Celite® pad, and the filtrate was concentrated to provide the crude product. The crude product was

washed with DCM/hexane to obtain tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-4-hydroxypiperidine-1-carboxylate (**2-c**). LCMS: m/z MM-ES+APCI, Negative $[M-H]^-$ = 443. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.85 (d, J =8.0 Hz, 1H), 5.56 (s, 1H), 5.20-5.15 (m, 1H), 4.62-4.31 (m, 2H), 3.92-3.86 (m, 2H), 3.17-3.09 (m, 2H), 2.97-2.88 (m, 1H), 2.64-2.58 (m, 1H), 2.44-2.41 (m, 1H), 2.11-1.98 (m, 3H), 1.56 (d, J = 13.3 Hz, 2H), 1.43 (s, 9H).

Step 3: **Synthesis of 3-(2-(4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione hydrochloride (INT-50)**:

To a stirred solution of tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-4-hydroxypiperidine-1-carboxylate (**2-c**, 650 mg, 1.462 mmol) in DCM (2 mL) was added HCl (4M in dioxane) (5.48 mL, 21.94 mmol) at 0°C. The resulting mixture was then stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the resulting crude residue was washed with MTBE. The resulting solid was collected via filtration to afford 3-(2-(4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione hydrochloride (**INT-50**), which was used in the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 345. ^{1}H-NMR (DMSO-d_6, 400 MHz) 11.02 (s, 1H), 8.96 (br s, 1H), 8.61 (br s, 1H), 8.20 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 5.19 (dd, J = 13.2, 4.8 Hz, 1H), 4.52 (d, J = 17.6 Hz, 1H), 4.52 (d, J = 17.6 Hz, 1H), 3.24-3.18 (m, 3H), 2.93-2.89 (m, 1H), 2,67-2.59 (m, 1H), 2.45-2.33 (m, 3H), 2.03 (m, 1H), 1.77-1.74 (m, 3H).

Example 53: Synthesis of 3-(2-(4-hydroxy-1-(1-(4-(trifluoromethyl)phenyl)ethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-420)



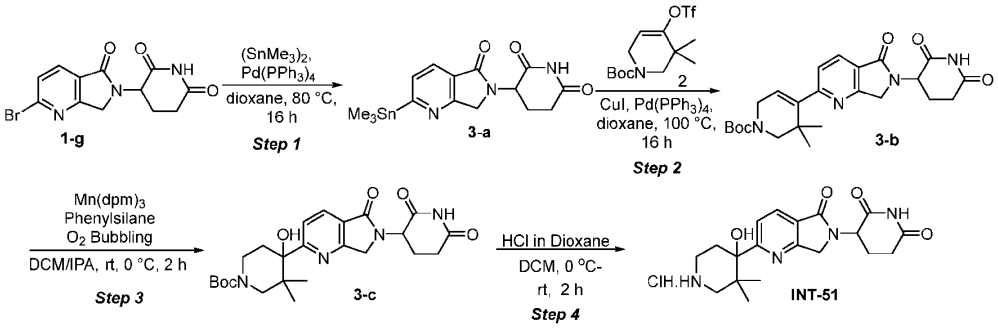
Step 1: **Synthesis of 1-(1-chloroethyl)-4-(trifluoromethyl) benzene (3-b):**

To a stirred solution of 1-(4-(trifluoromethyl) phenyl) ethan-1-ol (**3-a**, 500 mg, 2.63 mmol) in DCM (5 mL) at 0°C was added thionyl chloride (0.384 mL, 5.26 mmol) and the resulting mixture was stirred at room temperature for 16 h. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with DCM (2 × 10 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the 1-(1-chloroethyl)-4-(trifluoromethyl) benzene (**3-b**). **3-b** was used in the next step without further purification ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.72-7.70 (m, 4H), 5.45 (q, J = 9.20, 1H), 1.80 (d, J = 6.8 Hz, 3H).

Step 2: **Synthesis of 3-(2-(4-hydroxy-1-(1-(4-(trifluoromethyl)phenyl)ethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-420):**

To a stirred solution of 3-(2-(4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione hydrochloride (**INT-50**, 100 mg, 0.263 mmol) in DMF and at room temperature was added DIPEA (1.31 mmol, 5 equiv) and 1-(1-chloroethyl)-4-(trifluoromethyl) benzene (**3-b**, 219 mg, 1.05 mmol, 4 equiv) and the resulting mixture was heated at 100°C for 48 h. The reaction mixture was allowed to cool to room temperature, water (5 mL) was added, and the mixture was extracted with EtOAc (2 × 5 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford the crude product, which was purified via Prep-HPLC [X-Bridge C8, 150 mm × 19, (eluting with Mobile phase A: 10 mM HCl in water, Mobile phase B: ACN, flow rate: 15 mL/min), RT: 10]. The pure fractions were combined and concentrated via lyophilization. The isolated product was dissolved in ACN:water (1:1) and 0.5 M aq. HCl (0.2 mL) and the resulting mixture was concentrated via lyophilization to afford 3-(2-(4-hydroxy-1-(1-(4-(trifluoromethyl)phenyl)ethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-420**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 517.4. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H), 10.43 (br s, 1H), 8.20 (d, J = 8.00 Hz, 1H), 7.92-7.88 (m, 4H), 7.83 (d, J = 8.00 Hz, 1H), 5.8 (br s, 1H), 5.19 (dd, J = 5.20, 8.00 Hz, 1H), 4.75 (t, J = 6.40 Hz, 1H), 4.54 (d, J = 2.00 Hz, 1H), 4.50 (d, J = 1.60 Hz, 1H), 3.74-3.19 (m, 1H), 3.19-3.12 (m, 3H), 2.94-2.91 (m, 1H), 2.68-2.60 (m, 2H), 2.51-2.41 (m, 2H), 2.34-2.33 (m, 1H), 2.05-1.87 (m, 2H), 1.75 (d, J = 6.80 Hz, 3H).

Example 54: (3-(2-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione hydrochloride) (INT-51)



Step 1: **Synthesis of 3-(5-oxo-2-(trimethylstannyl)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (3-a)**:

To a stirred solution of 3-(2-bromo-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**1-g**, 10 g, 30.9 mmol, 1.0 equiv.) in dioxane (200 mL) was added hexamethylditin (13.1 g, 40.1 mmol, 1.29 equiv.) at 25 °C. The reaction mixture was degassed with argon for 10 min.

Subsequently, Tetrakis(triphenylphosphine)palladium(0) (3.57 g, 3.09 mmol, 0.1 equiv.) was added at room temperature. The resulting mixture was stirred at 80 °C for 16 h. The progress of the reaction was monitored by TLC and LC-MS. Upon completion, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was triturated with methyl tert-butyl ether (2 × 350 mL), filtered, and dried to afford 3-(5-oxo-2-(trimethylstannyl)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**3-a**). LCMS: m/z: MM-ES+APCI, positive [M+H]+ 410.3; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 7.97 (d, J = 7.5 Hz, 1H), 7.72 (d, J = 7.5 Hz, 1H), 5.18 (dd, J = 5.0, 13.3 Hz, 1H), 4.60-4.51 (m, 1H), 4.42-4.28 (m, 1H), 3.02-2.84 (m, 1H), 2.65-2.58 (m, 1H), 2.46-2.36 (m, 1H), 2.10-1.95 (m, 1H), 0.45-0.20 (m, 9H).

Step 2: **Synthesis of tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (3-b)**:

To a stirred solution of 3-(5-oxo-2-(trimethylstannyl)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**3-a**, 12 g, 29.4 mmol, 1.0 equiv.) and tert-butyl 3,3-dimethyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (10.57 g, 29.4 mmol, 1.0 equiv.) in dioxane (220 mL), copper(I) iodide (1.12 g, 5.88 mmol, 0.2 equiv.) was added at 25 °C. The reaction mixture was degassed with argon for 10 min. Tetrakis(triphenylphosphine)palladium(0) (3.40 g, 2.94 mmol, 0.1 equiv.) was then added at 25 °C, and the reaction mixture was stirred at 80 °C for 16 h. The progress of the reaction was monitored by TLC and LC-MS. Upon completion, the reaction mixture was cooled to room temperature and filtered through a celite bed. The filtrate was concentrated under reduced pressure to obtain the crude product. The crude compound was purified by reversed-phase chromatography using a Combi Flash C18 column (330 g) with a gradient of 0.1% formic acid in water and acetonitrile at a flow rate of 30 mL/min. The pure fractions were concentrated under reduced pressure to yield tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (**3-b**). LCMS: m/z: MM-ES+APCI, positive [M+H]+ 455.3; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.09 (d, J = 7.9 Hz, 1H), 7.69-7.48 (m, 2H), 6.06 (d, J = 14.1 Hz, 1H), 5.18 (dd, J = 5.0, 13.3 Hz, 1H), 4.53 (d, J = 17.8 Hz, 1H), 4.34 (d, J = 17.6 Hz, 1H), 4.07 (br s, 2H), 3.38-3.31 (m, 1H), 3.00-2.85 (m, 1H), 2.66-2.56 (m, 1H), 2.47-2.35 (m, 1H), 2.09-1.97 (m, 1H), 1.44 (s, 9H), 1.19 (s, 6H).

Step 3: **Synthesis of tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (3-c):**

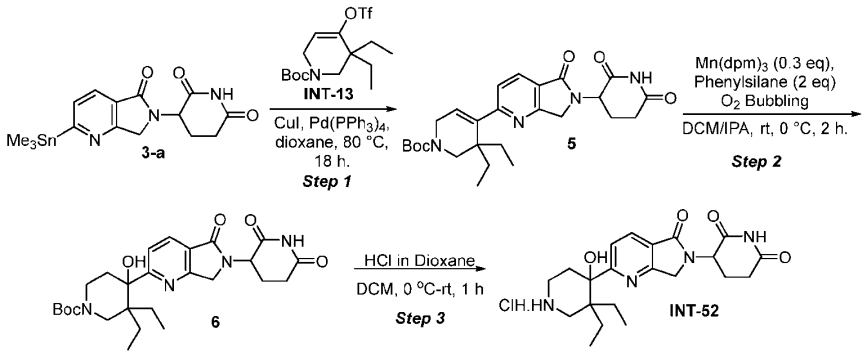
To a stirred solution of tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (**3-b**, 2.4 g, 4.70 mmol) in dichloromethane (15 mL) and IPA (15 mL) was added phenyl silane (1.27 g, 11.75 mmol) and Mn(dpm)3 (0.57 g, 0.94 mmol) at 0 °C and stirred at 25 °C for under oxygen bubbling for 2 h. The

progress of the reaction was monitored by TLC and LC-MS. Upon completion, the reaction mixture was cooled to room temperature and filtered through a celite bed. The filtrate was concentrated under reduced pressure to obtain the crude product. The crude compound was purified by reversed-phase chromatography using a Combi Flash C18 column (330 g) with a gradient of 0.1% formic acid in water and acetonitrile at a flow rate of 30 mL/min. The pure fractions were concentrated under reduced pressure to yield tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (**3-c**). LCMS: m/z: MM-ES+APCI, negative $[M-H]^-$ 471.2; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (br s, 1H), 8.13 (d, J = 8.1 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 5.40 (br s, 1H), 5.18 (dd, J = 4.9, 13.4 Hz, 1H), 4.58-4.42 (m, 1H), 4.39-4.27 (m, 1H), 3.59-3.44 (m, 1H), 3.28-2.72 (m, 6H), 2.61 (dd, J = 2.1, 15.3 Hz, 1H), 2.43 (dd, J = 4.5, 13.2 Hz, 1H), 2.10-2.00 (m, 1H), 1.42 (s, 9H), 0.73 (s, 6H).

Step 4: **Synthesis of 3-(2-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione hydrochloride (INT-51):**

To a stirred solution of tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (**3-c**, 3.7 g, 7.28 mmol) in dichloromethane (20 mL), 4 M hydrochloric acid in dioxane (20 mL, 80 mmol, 10.2 equiv.) was added at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The progress of the reaction was monitored by TLC and LC-MS. Upon completion, the reaction mixture was concentrated under reduced pressure and subsequently lyophilized to afford 3-(2-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione hydrochloride (**INT-51**). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 373.1; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H), 9.42 (d, J = 10.2 Hz, 1H), 8.83-8.44 (m, 1H), 8.17 (d, J = 8.1 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 5.18 (dd, J = 5.0, 13.3 Hz, 1H), 4.61-4.44 (m, 1H), 4.41-4.30 (m, 2H), 3.30-2.80 (m, 6H), 2.62 (d, J = 17.0 Hz, 1H), 2.46-2.36 (m, 1H), 2.12-1.93 (m, 1H), 1.77-1.62 (m, 1H), 0.95-0.71 (m, 6H)

Example 55: Synthesis of 3-(2-(3,3-diethyl-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione hydrochloride (INT-52)



Step 1: **Synthesis of tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-diethyl-3,6-dihydropyridine-1(2H)-carboxylate**

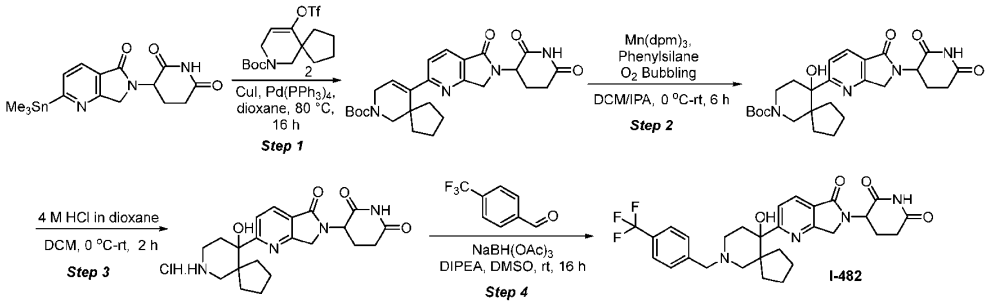
To a stirred solution of 3-(5-oxo-2-(trimethylstannyl)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (5.9 g, 14.46 mmol) and tert-butyl 3,3-diethyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (**INT-13**, 5.60 g, 14.46 mmol) in dioxane (90 mL, 15 vol.), copper(I) iodide (0.55 g, 2.89 mmol) was added at 25 °C. The reaction mixture was degassed with nitrogen for 10 minutes. Tetrakis(triphenylphosphine)-palladium(0) (1.67 g, 1.45 mmol) was added at 25 °C. The resulting reaction mixture was stirred at 80 °C for 18 h. The reaction mixture was concentrated under reduced pressure to obtain the crude product. The crude product was purified by silica gel chromatography (60-120 mesh) with an eluent of ethyl acetate in hexane (0 to 50%). Pure fractions were concentrated under reduced pressure to afford tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-diethyl-3,6-dihydropyridine-1(2H)-carboxylate. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 483.6; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.10 (d, J = 8.1 Hz, 1H), 7.67-7.60 (m, 1H), 6.26 (d, J = 13.8 Hz, 1H), 5.17 (dd, J = 5.1, 13.4 Hz, 1H), 4.63-4.18 (m, 2H), 4.12-3.89 (m, 2H), 3.40 (br s, 2H), 3.02-2.84 (m, 1H), 2.61 (d, J = 16.5 Hz, 1H), 2.47-2.36 (m, 1H), 2.08-2.00 (m, 1H), 1.75 (d, J = 6.5 Hz, 4H), 1.44 (s, 9H), 0.71 (t, J = 7.4 Hz, 6H).

Step 2: **Synthesis of tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-diethyl-4-hydroxypiperidine-1-carboxylate:** To a stirred solution of tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-diethyl-3,6-dihydropyridine-1(2H)-carboxylate (1.75 g, 3.63 mmol) in dichloromethane (60 mL, 30 vol.) and isopropyl alcohol (30.0 mL, 15 vol.), Mn(dpm)3 (0.66 g, 1.09 mmol) and phenylsilane (0.89 mL, 7.25 mmol) were added at 25 °C. The reaction mixture was degassed with O_2 and stirred at 25 °C for 2 h under an O_2 atmosphere. The reaction mixture was concentrated under reduced pressure to obtain the crude product. The crude product was purified by reverse-phase column chromatography using a C18 cartridge (330 g), and the compound was eluted with 35% acetonitrile in 0.01% formic acid in water. Pure fractions were collected, concentrated under reduced pressure, and afforded tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-diethyl-4-hydroxypiperidine-1-carboxylate. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 501.3; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 8.12 (d, J = 8.3 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 5.44 (br s, 1H), 5.17 (dd, J = 4.8, 13.0 Hz, 1H), 4.58-4.43 (m, 1H), 4.39-4.23 (m, 1H), 4.03-3.49 (m, 2H), 2.99-2.82 (m, 1H), 3.24-2.82 (m, 2H), 2.73-2.55 (m, 2H), 2.47-2.36 (m, 1H), 2.08-1.95 (m, 1H), 1.61-1.46 (m, 2H), 1.42 (s, 9H), 1.34-1.18 (m, 2H), 0.64 (br s, 3H), 0.51-0.35 (m, 3H).

Step 3: **Synthesis of 3-(2-(3,3-diethyl-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione hydrochloride (INT-52)**

To a stirred solution of tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-diethyl-4-hydroxypiperidine-1-carboxylate (1.8 g, 3.60 mmol) in dichloromethane (30 mL, 16 vol.) was treated with 4M HCl in dioxane (13.48 mL, 53.9 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to obtain the crude residue. The crude residue was washed with methyl tert-butyl ether (50 mL), filtered, and dried under reduced pressure to afford 3-(2-(3,3-diethyl-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione hydrochloride (**INT-52**). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 401.3; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 9.29 (d, J = 9.9 Hz, 1H), 8.59 (br s, 1H), 8.16 (d, J = 8.1 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 6.07-5.58 (m, 1H), 5.34-4.99 (m, 1H), 4.60-4.47 (m, 1H), 3.29-2.83 (m, 6H), 2.62 (d, J = 16.8 Hz, 1H), 2.46-2.35 (m, 1H), 2.09-1.95 (m, 1H), 1.88-1.72 (m, 1H), 1.73-1.48 (m, 2H), 1.45-1.18 (m, 2H), 0.66-0.40 (m, 6H).

Example 56: Synthesis of 3-(2-(10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-482)



Step 1: **Synthesis of tert-butyl 10-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-7-azaspiro[4.5]dec-9-ene-7-carboxylate**

To a stirred solution of 3-(5-oxo-2-(trimethylstannyl)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (500 mg, 1.225 mmol, 1.0 equiv.) and tert-butyl 10-(((trifluoromethyl)sulfonyl)oxy)-7-azaspiro[4.5]dec-9-ene-7-carboxylate (472 mg, 1.23 mmol, 1.0 equiv.) in dioxane (16 mL) was added copper(I) iodide (46.7 mg, 0.245 mmol, 0.2 equiv.) at 25 °C. The reaction mixture was purged with argon for 5 min. Tetrakis(triphenylphosphine) palladium(0) (142 mg, 0.12 mmol, 0.1 equiv.) was then added. The resulting mixture was stirred at 80 °C for 16 h. The progress of the reaction was monitored by LCMS. Upon completion, the reaction mixture was allowed to cool to room temperature and was then filtered through a celite bed. The filtrate was concentrated under reduced pressure to obtain the crude product. The crude material was purified by reversed-phase chromatography using a Combi Flash C18 column (330 g) with a gradient of 0.1% formic acid in water and acetonitrile at a flow rate of 30 mL/min. The pure fractions were collected and evaporated to afford tert-butyl 10-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-7-azaspiro[4.5]dec-9-ene-7-

carboxylate. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 481.4; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.15-8.07 (m, 1H), 8.03-7.91 (m, 1H), 7.41 (d, J = 7.9 Hz, 1H), 6.14-5.84 (m, 1H), 5.40-5.14 (m, 1H), 4.63-4.29 (m, 2H), 4.22-4.00 (m, 2H), 3.51 (s, 1H), 3.45-3.39 (m, 1H), 3.38-3.30 (m, 1H), 3.02-2.80 (m, 2H), 2.52-2.21 (m, 2H), 2.01-1.83 (m, 2H), 1.75 (br s, 4H), 1.52 (s, 10H).

Step 2: **Synthesis of tert-butyl 10-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-10-hydroxy-7-azaspiro[4.5]decane-7-carboxylate**

To a stirred solution of tert-butyl 10-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-7-azaspiro[4.5]dec-9-ene-7-carboxylate (300 mg, 0.62 mmol, 1.0 equiv.) in DCM (10 mL) and 2-propanol (10 mL) were added $Mn(dpm)_3$ (76 mg, 0.13 mmol, 0.2 equiv.) and phenylsilane (0.192 mL, 1.56 mmol, 2.5 equiv.) at 0 °C. The reaction mixture was stirred at 25 °C under oxygen bubbling for 6 h. The progress of the reaction was monitored by LCMS. Upon completion, the reaction mixture was filtered through a celite bed. The filtrate was concentrated under reduced pressure to obtain the crude product. The crude compound was purified by reversed-phase chromatography using a Biotage Isolera C18 column (350 g) with a gradient of 0.1% formic acid in water and acetonitrile at a flow rate of 30 mL/min. The pure fractions were collected and evaporated to afford tert-butyl 10-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-10-hydroxy-7-azaspiro[4.5]decane-7-carboxylate. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 499.4; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.17-10.44 (m, 1H), 8.14 (d, J = 8.1 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 5.41 (d, J = 3.7 Hz, 1H), 5.27-5.08 (m, 1H), 4.70-4.59 (m, 1H), 4.56-4.42 (m, 1H), 4.40-4.26 (m, 1H), 4.10-3.83 (m, 1H), 3.76-3.40 (m, 2H), 3.24-2.83 (m, 3H), 2.66-2.56 (m, 2H), 2.47-2.36 (m, 1H), 2.11-1.98 (m, 1H), 1.76-1.62 (m, 2H), 1.56-1.46 (m, 2H), 1.46-1.36 (m, 10H), 1.02-0.74 (m, 2H).

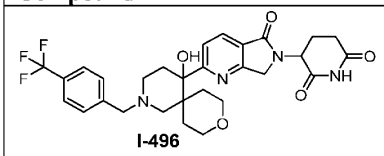
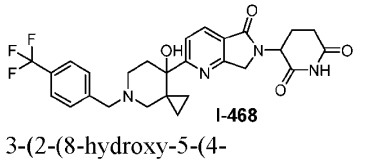
Step 3: **Synthesis of 3-(2-(10-hydroxy-7-azaspiro[4.5]decan-10-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione hydrochloride**

To a stirred solution of tert-butyl 10-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-10-hydroxy-7-azaspiro[4.5]decane-7-carboxylate (80 mg, 0.16 mmol, 1.0 equiv.) in DCM (4 mL) was added 4.0 M HCl in dioxane (0.201 mL, 0.80 mmol, 5.0 equiv.) at 0 °C and stirred the reaction mixture at 25 °C for 2 h. The progress of the reaction was monitored by LCMS. Upon completion, the reaction mixture was concentrated under reduced pressure to afford 3-(2-(10-hydroxy-7-azaspiro[4.5]decan-10-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 399.1; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H), 9.04-8.81 (m, 1H), 8.41-8.36 (m, 1H), 8.18 (d, J = 8.3 Hz, 1H), 7.95 (d, J = 8.1 Hz, 1H), 5.87-5.77 (m, 1H), 5.24-5.12 (m, 1H), 4.59-4.45 (m, 1H), 4.43-4.27 (m, 1H), 3.28-3.16 (m, 1H), 2.62 (d, J = 15.1 Hz, 2H), 2.46-2.38 (m, 2H), 2.13-2.03 (m, 1H), 1.94-1.52 (m, 7H), 1.47-1.28 (m, 3H), 0.95-0.74 (m, 2H).

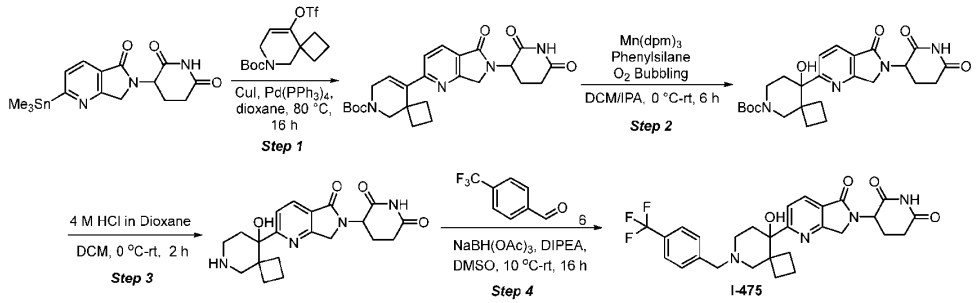
Step 4: **Synthesis of 3-(2-(10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-482)**

To a stirred solution of 3-(2-(10-hydroxy-7-azaspiro[4.5]decan-10-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione hydrochloride (50 mg, 0.106 mmol, 1.0 equiv.) in DMSO (2.0 mL) were added DIPEA (0.028 mL, 0.159 mmol) and 4-(trifluoromethyl)benzaldehyde (18.47 mg, 0.106 mmol, 1.0 equiv.) and stirred the reaction mixture for 1 h at 25 °C. Sodium triacetoxyborohydride (67.4 mg, 0.318 mmol, 1.0 equiv.) was added at 10 °C, and the mixture was allowed to stir at 25 °C for 16 h. The progress of the reaction was monitored by LCMS. Upon completion of the reaction, the reaction mixture was quenched with water and extracted with EtOAc (2 × 100 mL), then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude. The crude compound was purified by Biotage isolera C18 (40 g) using 0.05% hydrochloric acid in H_2O, acetonitrile, flow rate: 15 mL/min). The pure fractions were lyophilized to afford 3-(2-(10-hydroxy-7-(4-(trifluoromethyl) benzyl)-7-azaspiro [4.5] decan-10-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b] pyridin-6-yl) piperidine-2,6-dione (**I-482**). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 557.2; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.30-10.56 (m, 1H), 9.87-9.27 (m, 1H), 8.24-8.11 (m, 1H), 7.98-7.83 (m, 5H), 5.92-5.78 (m, 1H), 5.12 (d, J = 5.6 Hz, 1H), 4.60-4.46 (m, 3H), 4.41-4.28 (m, 1H), 3.31-3.26 (m, 1H), 3.13-2.84 (m, 3H), 2.62 (d, J = 17.2 Hz, 2H), 2.45-2.35 (m, 2H), 2.12-1.68 (m, 5H), 1.39-1.09 (m, 3H), 0.92-0.62 (m, 2H).

The following compounds were synthesized in a similar fashion to **Example 56 (I-482)**.

Compound	Characterization
 **I-496** 3-(2-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-9-oxa-2-azaspiro[5.5]undecan-5-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-496**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 573.2; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.06-11.00 (m, 1H), 10.43-10.21 (m, 1H), 8.20 (d, J = 8.3 Hz, 1H), 8.03-7.96 (m, 2H), 7.94-7.88 (m, 2H), 7.84 (d, J = 8.1 Hz, 1H), 5.91 (d, J = 2.4 Hz, 1H), 5.26-5.13 (m, 1H), 4.64-4.50 (m, 3H), 4.47-4.29 (m, 1H), 3.91-3.80 (m, 1H), 3.59-3.47 (m, 3H), 3.38-3.11 (m, 6H), 3.01-2.85 (m, 1H), 2.66-2.58 (m, 1H), 2.46-2.37 (m, 1H), 1.97 (d, J = 1.4 Hz, 1H), 1.72 (dd, J = 7.7, 13.9 Hz, 1H), 1.55 (d, J = 13.5 Hz, 1H), 1.38-1.15 (m, 2H).
 **I-468** 3-(2-(8-hydroxy-5-(4-(trifluoromethyl)benzyl)-5-azaspiro[2.5]octan-8-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-468**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 529.1; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.23-10.92 (m, 1H), 10.23 (d, J = 3.0 Hz, 1H), 8.25-8.12 (m, 1H), 7.92-7.75 (m, 5H), 6.07 (br s, 1H), 5.30-5.12 (m, 1H), 4.58-4.22 (m, 4H), 3.93-3.64 (m, 1H), 3.21-2.86 (m, 2H), 3.22-2.76 (m, 2H), 2.65-2.57 (m, 1H), 2.48-2.35 (m, 2H), 2.09-1.96 (m, 1H), 1.91-1.80 (m, 1H), 1.13-0.24 (m, 4H).

Example 57: Synthesis of 3-(2-(9-hydroxy-6-(4-(trifluoromethyl)benzyl)-6-azaspiro[3.5]nonan-9-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-475)



Step 1: **Synthesis of tert-butyl 9-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-6-azaspiro[3.5]non-8-ene-6-carboxylate**

To a stirred solution of 3-(5-oxo-2-(trimethylstannyl)-5,7-dihydro-6H-pyrrolo[3,4-b]-pyridin-6-yl)piperidine-2,6-dione (500 mg, 1.23 mmol, 1.0 equiv.) and tert-butyl 9-(((trifluoromethyl)sulfonyl)oxy)-6-azaspiro[3.5]non-8-ene-6-carboxylate (455 mg, 1.23 mmol, 1.0 equiv.) in dioxane (16 mL) under a nitrogen atmosphere, copper(I) iodide (46.7 mg, 0.25 mmol, 0.2 equiv.) was added at 25 °C. The reaction mixture was degassed with argon for 5 min. Tetrakis(triphenylphosphine)palladium(0) (142 mg, 0.12 mmol, 0.1 equiv.) was then introduced. The resulting mixture was stirred at 80 °C for 16 h. The progress of the reaction was monitored by LCMS. Upon completion, the reaction mixture was allowed to cool to room temperature and was filtered through a Celite bed. The filtrate was concentrated under reduced pressure to obtain the crude product. The crude compound was purified by reversed-phase chromatography using a Combi Flash C18 column (330 g) with a gradient of 0.1% formic acid in water and acetonitrile at a flow rate of 30 mL/min. The pure fractions were collected and evaporated to afford tert-butyl 9-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-6-azaspiro[3.5] non-8-ene-6-carboxylate. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 467.4; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.13 (d, J = 8.1 Hz, 1H), 7.57-7.53 (m, 1H), 6.05 (br d, J = 3.3 Hz, 1H), 5.20 (dd, J = 5.2, 13.3 Hz, 1H), 4.56 (d, J = 17.6 Hz, 1H), 4.43-4.33 (m, 1H), 4.03 (br s, 2H), 3.62 (br d, J = 3.5 Hz, 2H), 3.00-2.86 (m, 1H), 2.66-2.58 (m, 1H), 2.46-2.39 (m, 1H), 2.10-1.95 (m, 2H), 1.94-1.86 (m, 1H), 1.80-1.69 (m, 2H), 1.53-1.34 (m, 11H).

Step 2: **Synthesis of tert-butyl 9-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-9-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate**

To a stirred solution of tert-butyl 9-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-6-azaspiro[3.5]non-8-ene-6-carboxylate (200 mg, 0.429 mmol, 1.0 equiv.) in dichloromethane (10 mL) and 2-propanol (10 mL) were added $Mn(dpm)_3$ (51.8 mg, 0.086 mmol, 0.2 equiv.) and phenylsilane (0.13 mL, 1.07 mmol, 2.5 equiv.) at 0 °C. The reaction mixture was stirred at 25

°C under an oxygen atmosphere for 6 h. The progress of the reaction was monitored by LCMS. Upon completion, the reaction mixture was filtered through a celite bed. The filtrate was concentrated under reduced pressure to obtain the crude product. The crude compound was purified by reversed-phase chromatography using a Combi Flash C18 column (330 g) with a gradient of 0.1% formic acid in water and acetonitrile at a flow rate of 30 mL/min. The pure fractions were collected and evaporated to afford tert-butyl 9-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-9-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 485.4; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.24-10.79 (m, 1H), 8.18 (d, J = 8.1 Hz, 1H), 7.95 (d, J = 8.1 Hz, 1H), 5.44 (d, J = 2.1 Hz, 1H), 5.25-5.12 (m, 1H), 4.60-4.48 (m, 1H), 4.36 (dd, J = 11.8, 17.6 Hz, 1H), 3.98-3.77 (m, 2H), 3.17 (d, J = 5.2 Hz, 2H), 3.01-2.81 (m, 2H), 2.62 (br d, J = 18.0 Hz, 2H), 2.47-2.39 (m, 2H), 2.13-1.99 (m, 2H), 1.95-1.81 (m, 1H), 1.70-1.53 (m, 2H), 1.43 (s, 9H).

Step 3: **Synthesis of 3-(2-(9-hydroxy-6-azaspiro[3.5]nonan-9-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione**

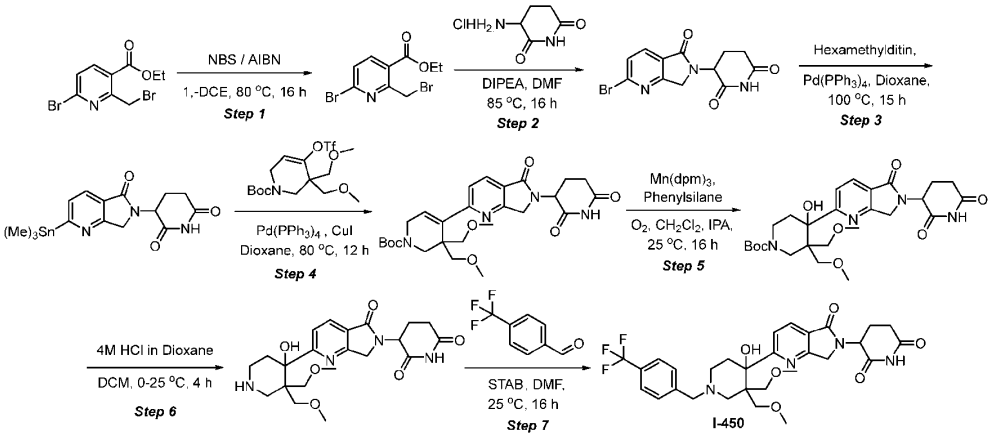
To a stirred solution of tert-butyl 9-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-9-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (70 mg, 0.144 mmol, 1.0 equiv.) in DCM (4 mL) was added 4.0 M HCl in dioxane (0.18 mL, 0.72 mmol, 5.0 equiv.) at 0 °C and stirred the reaction mixture at 25 °C for 2 h. The progress of the reaction was monitored by LCMS. Upon completion, the mixture was concentrated under reduced pressure to afford 3-(2-(9-hydroxy-6-azaspiro[3.5]nonan-9-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl) piperidine-2,6-dione. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 385.2.

Step 4: **Synthesis of 3-(2-(9-hydroxy-6-(4-(trifluoromethyl)benzyl)-6-azaspiro[3.5]nonan-9-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-475)**

To a stirred solution of 3-(2-(9-hydroxy-6-azaspiro[3.5]nonan-9-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione hydrochloride (55 mg, 0.12 mmol, 1.0 equiv.) in dimethyl sulfoxide (5 mL) were added DIPEA (0.032 mL, 0.18 mmol, 1.5 equiv.) and 4-(trifluoromethyl)benzaldehyde (20.94 mg, 0.12 mmol, 1.0 equiv.). The reaction mixture was stirred at 25 °C for 1 h. Sodium triacetoxyborohydride (76 mg, 0.361 mmol, 3.0 equiv.) was added at 10 °C, and the mixture was allowed to stir at 25 °C for 16 h. The progress of the reaction was monitored by LCMS. Upon completion, the reaction mixture was quenched with water and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain the crude product. The crude compound was purified by reversed-phase column chromatography using a C18 cartridge (40 g), with a gradient of 20% acetonitrile in 0.1% formic acid in water as the eluent. The pure fractions were collected and concentrated under reduced pressure to afford the salt-free compound. The salt-free compound was then subjected to HCl salt formation using

reversed-phase column chromatography on a C18 cartridge (40 g) with acetonitrile and 0.05% HCl in water as the eluent. The pure fractions were lyophilized to afford 3-(2-(9-hydroxy-6-(4-(trifluoromethyl)benzyl)-6-azaspiro[3.5]nonan-9-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-475**). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 543.3; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.25-10.90 (m, 1H), 10.12-9.64 (m, 1H), 8.24 (dd, J = 1.6, 8.1 Hz, 1H), 8.01 (d, J = 7.9 Hz, 1H), 7.95-7.84 (m, 4H), 5.94-5.79 (m, 1H), 5.27-5.16 (m, 1H), 4.66-4.33 (m, 4H), 3.39-3.18 (m, 4H), 3.06-2.87 (m, 2H), 2.62 (d, J = 15.7 Hz, 1H), 2.48-2.37 (m, 2H), 2.24-1.88 (m, 4H), 1.73 (br dd, J = 7.5, 14.8 Hz, 1H), 1.60-1.42 (m, 2H).

Example 58: Synthesis of 3-(2-(4-hydroxy-3,3-bis(methoxymethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-450)



Step 1: **Synthesis of ethyl 6-bromo-2-(bromomethyl)nicotinate**

To a stirred solution of ethyl 6-bromo-2-methylnicotinate (36 g, 147.4 mmol) in DCE (360 mL) was added AIBN (4.84 g, 29.5 mmol), followed by the addition of NBS (28.88 g, 162 mmol) portion wise at room temperature under nitrogen atmosphere. The reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was concentrated to get crude compound which was dissolved in DCM (300 mL) and washed with water (200 mLx2). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to obtain 50 g of crude compound. This crude was purified by Flash column chromatography using SiO_2/60-120 mesh; 5-10% Ethyl acetate in hexanes). The pure fractions were concentrated under reduced pressure to afford ethyl 6-bromo-2-(bromomethyl)nicotinate. LCMS: m/z MM-ES+APCI, Positive $[M+H]^-$ 323.9.

Step 2: **Synthesis of 3-(2-bromo-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione**

To the stirred solution of ethyl 6-bromo-2-(bromomethyl)nicotinate (41 g, 69.8 mmol) in DMF (300 mL) was added 3-aminopiperidine-2,6-dione hydrochloride (17.24 g, 105 mmol) and DIPEA (36.6

mL, 209 mmol) at 25 °C under nitrogen atmosphere and reaction mixture was stirred at 85 °C for 16 h. After completion of the reaction, the reaction mixture was quenched with ice cold water (2000 mL) and stirred for 15 minutes and extracted with MTBE (500 mL). The aqueous layer was filtered through a Buchner funnel and the obtained solids were dried under vacuum to obtain crude compound (20 g). This crude material was suspended in methanol (200 mL), stirred for 15 minutes, and filtered. The obtained solid was dried under reduced pressure to afford 3-(2-bromo-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione. LCMS: m/z MM-ES+APCI, Positive $[M/M+2]^+$ 323.9/325.9. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 5.18 (q, J = 5.2 Hz, 1H), 4.56 (d, J = 18.0 Hz, 1H), 4.40 (d, J = 18.4 Hz, 1H), 2.97-2.88 (m, 1H), 2.63 (t, J = 1.6 Hz, 1H), 2.50-2.40 (m, 1H), 2.05-2.00 (m, 1H).

Step 3: **3-(5-oxo-2-(trimethylstannyl)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione**

To a stirred solution of 3-(2-bromo-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (500 mg, 1.54 mmol) in 1,4-dioxane (10 mL) under nitrogen blanket, hexamethylditin (657 mg, 2.005 mmol) was added at 25 °C. The reaction mixture was purged with N_2 for 10 min. After 10 min, tetrakis(triphenylphosphine)palladium(0) (178 mg, 0.15 mmol) was added to reaction mass followed by N_2 purging. The resulting reaction mixture was irradiated at 100 °C for 15 h. The reaction mixture was concentrated under reduced pressure to afford a crude residue. This crude was triturated with MTBE and concentrated under reduced pressure to afford 3-(5-oxo-2-(trimethylstannyl)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione. LCMS: m/z MM-ES+APCI, Negative $[M-H]^-$ 407.8 ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 7.97 (d, J = 13.2 Hz, 1H), 7.69 (d, J = 30.0 Hz, 1H), 5.18 (q, J = 5.2 Hz, 1H), 4.55 (d, J = 17.6 Hz, 1H), 4.36 (d, J = 17.6 Hz, 1H), 2.99-2.85 (m, 1H), 2.70-2.50 (m, 1H), 2.48-2.31 (m, 1H), 2.06-2.03 (m, 1H), 0.41 (s, 9H).

Step 4: **Synthesis of tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-bis(methoxymethyl)-3,6-dihydropyridine-1(2H)-carboxylate**

To a stirred solution of 3-(5-oxo-2-(trimethylstannyl)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (450 mg, 1.10 mmol) in 1,4-dioxane (6 mL) was added tert-butyl 3,3-bis(methoxymethyl)-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (462 mg, 1.1 mmol), CuI (42 mg, 0.22 mmol) at 25 °C. The reaction mixture was degassed with argon for 10 min, followed by the addition tetrakis(triphenylphosphine)-palladium(0) (127 mg, 0.11 mmol). The resulting reaction mixture was stirred at 80 °C for 12 h. After completion, the reaction mixture was concentrated under reduced pressure to afford crude compound. This crude compound was purified by Column chromatography using Isolera (silica gel, 230-400 mesh) in 70% EtOAc in hexane as eluent to afford tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-

bis(methoxymethyl)-3,6-dihydropyridine-1(2H)-carboxylate. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 515.4. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 5.21-5.16 (m, 1H), 4.54 (d, J = 17.6 Hz, 1H), 4.35 (d, J = 17.6 Hz, 1H), 4.04 (t, J = 14.0 Hz, 3H), 3.77-3.64 (m, 4H), 3.39 (d, J = 53.2 Hz, 2H), 3.06 (s, 6H), 2.92-2.93 (m, 1H), 2.64-2.60 (m, 1H), 2.46-2.42 (m, 1H), 2.09-2.00 (m, 1H), 1.4 (s, 9H).

Step 5: **Synthesis of tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-4-hydroxy-3,3-bis(methoxymethyl)piperidine-1-carboxylate**

A stirred solution of tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-bis(methoxymethyl)-3,6-dihydropyridine-1(2H)-carboxylate (350 mg, 0.68 mmol) in DCM (10 mL) and IPA (5 mL) was degassed with O_2 for 5 min. Then $Mn(dpm)_3$ (206 mg, 0.34 mmol) and phenylsilane (0.17 mL, 1.36 mmol) were added to the reaction mixture and stirred at 25 °C for 6 h with continuous oxygen bubbling. After completion, the reaction mixture was concentrated under reduced pressure to afford a crude compound. The crude material was purified by flash chromatography (SiO_2/230-400 mesh) with 100% ethyl acetate to 5% IPA in DCM as eluent to afford tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-4-hydroxy-3,3-bis(methoxymethyl)piperidine-1-carboxylate. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 533.4 ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 5.76 (s, 1H), 5.19-5.16 (m, 1H), 4.49 (dd, J = 7.6, 17.6 Hz, 1H), 4.32 (dd, J = 8.4, 17.6 Hz, 1H), 4.05-3.95 (m, 2H), 3.42 (q, J = 3.6 Hz, 3H), 3.32-3.17 (m, 3H), 3.05-2.97 (m, 3H), 2.96-2.92 (m, 2H), 2.75-2.66 (m, 1H), 2.65-2.55 (m, 2H), 2.49-2.41 (m, 2H), 2.10-2.00 (m, 2H), 1.4 (s, 9H).

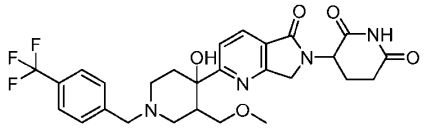
Step 6: **Synthesis of 3-(2-(4-hydroxy-3,3-bis(methoxymethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione**

To a stirred solution of tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-4-hydroxy-3,3-bis(methoxymethyl)piperidine-1-carboxylate (90 mg, 0.17 mmol) in 1,4-dioxane (1 mL) was added 4M HCl in dioxane (0.42 mL, 1.69 mmol) dropwise at 0 °C. The resulting reaction mixture was slowly allowed to stir at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and azeotroped with toluene (3 × 6 mL) to afford a crude compound. This crude compound was triturated with a mixture of DCM and hexane to afford 3-(2-(4-hydroxy-3,3-bis (methoxymethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 433.4. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 5.13 (d, J = 13.2 Hz, 1H), 4.53 (d, J = 29.2 Hz, 1H), 4.35 (d, J = 17.6 Hz, 1H), 3.45 (d, J = 24.0 Hz, 1H), 3.33-3.12 (m, 8H), 3.10-2.99 (m, 5H), 2.86 (t, J = 24.0 Hz, 1H), 2.70-2.65 (m, 2H), 2.45-2.38 (m, 2H), 2.14-1.98 (m, 1H), 1.65 (t, J = 40.0 Hz, 1H), 1.33-0.99 (m, 2H).

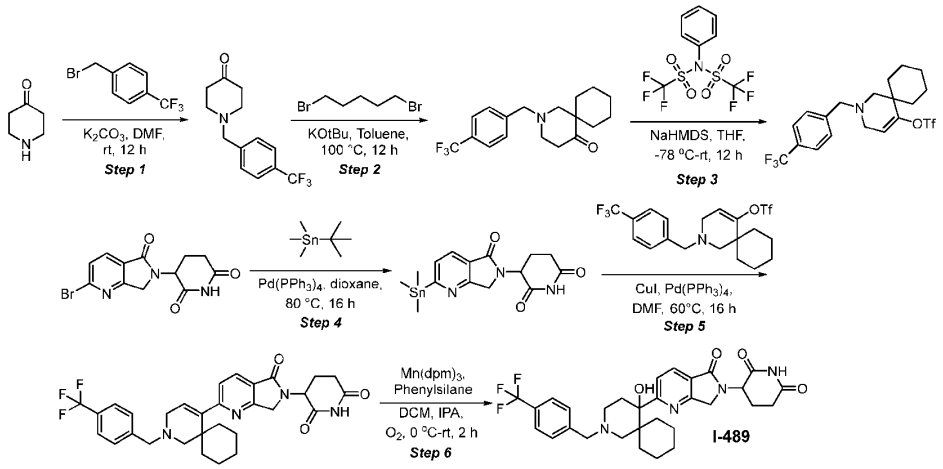
Step 7: **Synthesis of 3-(2-(4-hydroxy-3,3-bis(methoxymethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-450)**

To a stirred solution of 3-(2-(4-hydroxy-3,3-bis(methoxymethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione hydrochloride (60 mg, 0.13 mmol) in DMF (2 mL) was added 4-(trifluoromethyl)benzaldehyde (29.0 mg, 0.17 mmol)) at 25 °C and stirred at 25 °C for 30 min, followed by the addition of STAB (81 mg, 0.38 mmol) at 25 °C. The resulting reaction mixture was stirred at 25 °C for 16 h. The reaction mixture was concentrated under reduced pressure to afford crude compound. This crude compound was triturated with a mixture of DCM in hexane to give crude compound. The obtained crude was purified by prep HPLC [**Method**: X Select C18(250 × 19 mm), Mobile phase A: 0.05% HCl in H_2O, Mobile phase B: ACN, flow rate: 14 mL/min, RT:12.8] and then repurified by prep HPLC [**Method**: X Select C18(250 × 19 mm), Mobile phase A: 10% Ammonium Acetate in H_2O, Mobile phase B: ACN, flow rate: 15 mL/min, RT: 10.0]. The obtained pure fractions were lyophilized to afford 3-(2-(4-hydroxy-3,3-bis(methoxymethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-450**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 591.1 ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.0 Hz, 2H), 5.40 (d, J = 7.2 Hz, 1H), 5.21-5.12 (m, 1H), 4.52 (d, J = 32.0 Hz, 1H), 4.34 (d, J = 40.0 Hz, 1H), 3.81-3.67 (m, 2H), 3.50 (d, J = 48.0 Hz, 1H), 3.41-3.35 (m, 2H), 3.28-2.85 (m, 6H), 2.81-2.65 (m, 3H), 2.38 (d, J = 24.00 Hz, 2H), 2.2 (t, J = 16.0 Hz, 2H), 2.13-1.98 (m, 2H), 1.5 (d, J = 20.0 Hz, 2H).

The following compound was synthesized in a similar fashion to **Example 58 (I-450)**.

Compound	Characterization
 **I-451** 3-(2-(4-hydroxy-3-(methoxymethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-451**)	The title compound was isolated as a mixture of diastereomers. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 547.3; 1H-NMR (400 MHz, DMSO-d_6): δ 11.48-11.15 (m, 1H), 11.14-10.91 (m, 1H), 8.17 (dd, *J* = 8.1, 18.3 Hz, 1H), 8.03-7.70 (m, 5H), 5.28-5.12 (m, 1H), 4.68-4.22 (m, 4H), 3.87-3.29 (m, 5H), 3.27-3.17 (m, 1H), 3.11-2.98 (m, 3H), 2.98-2.86 (m, 1H), 2.79-2.56 (m, 3H), 2.46-2.23 (m, 2H), 2.10-1.95 (m, 2H).

Example 59: Synthesis of 3-(2-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-489)



Step 1: **Synthesis of 1-(4-(trifluoromethyl)benzyl)piperidin-4-one**

To a stirred solution of piperidin-4-one (12 g, 121 mmol) and potassium carbonate (33.5 g, 242 mmol) in DMF (100 mL) under nitrogen at room temperature was added 1-(bromomethyl)-4-(trifluoromethyl)benzene (28.9 g, 121 mmol). The reaction mixture was stirred at room temperature for 12 h under N_2 atmosphere. The reaction mixture was quenched with water at 0 °C and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude compound. The crude compound was purified by Biotage Isolera (silica gel 230-400 mesh) and a linear gradient of 0-10% ethyl acetate in hexane as an eluent to afford 1-(4-(trifluoromethyl)benzyl)-piperidin-4-one. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 258.3. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 8.00 Hz, 2H), 7.52 (d, J = 8.00 Hz, 2H), 3.70 (s, 2H), 2.78 (t, J = 6.40 Hz, 4H), 2.49 (t, J = 6.00 Hz, 4H).

Step 2: **Synthesis of 2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-one**

To a stirred solution of 1-(4-(trifluoromethyl)benzyl)piperidin-4-one (10 g, 38.9 mmol) in Toluene (100 mL) was added potassium tert-butoxide (8.72 g, 78 mmol) at 25 °C under N_2 atmosphere and stirred for 1 h, then 1,5-dibromopentane (8.35 mL, 58.3 mmol) was added. The reaction mixture was heated and stirred at 100 °C for 12 h under N_2 atmosphere. The reaction mixture was quenched with sat. NH_4Cl at 0 °C and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude residue. The crude residue was purified by Biotage Isolera (silica gel 230-400 mesh) and a linear gradient of 0-10% EtOAc in hexane as eluents to afford 2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-one. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 326.3. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 8.00 Hz, 2H), 7.53 (d, J = 8.00 Hz, 2H), 3.63 (s, 2H), 2.76 (t, J = 6.40 Hz, 2H), 2.55 (t, J = 6.40 Hz, 2H), 2.49 (s, 2H), 1.85-1.92 (m, 2H), 1.47-1.54 (m, 4H), 1.33-1.40 (m, 2H).

Step 3: **Synthesis of 2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl trifluoromethanesulfonate**

To a stirred solution of 2-(4-(trifluoromethyl) benzyl)-2-azaspiro[5.5]undecan-5-one (5.5 g, 16.90 mmol) in THF (20 mL) was added NaHMDS (33.8 mL, 33.8 mmol) at -78 °C under N_2 atmosphere and stirred for 1 h. The reaction mixture was again cooled to -78°C and added 1,1,1-trifluoro-N-phenyl-*N*-((trifluoromethyl)sulfonyl)methanesulfonamide (7.25 g, 20.28 mmol) in THF (20 mL). The reaction mixture was stirred at -78 °C for 2 h under N_2 atmosphere. The reaction mixture was quenched with sat. NH_4Cl at 0 °C and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude residue. The crude residue was purified by Biotage Isolera (silica gel 100-200 mesh) and a linear gradient of 0-10% EtOAc in hexane to afford 2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl trifluoromethanesulfonate. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.00 Hz, 2H), 7.50 (d, J = 8.00 Hz, 2H), 5.71 (t, J = 3.60 Hz, 1H), 3.68 (s, 2H), 3.16 (d, J = 3.60 Hz, 2H), 2.57 (s, 2H), 1.52-1.71 (m, 6H), 1.09-1.12 (m, 4H).

Step 4: **Synthesis of 3-(5-oxo-2-(trimethylstannyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione**

To a stirred solution of 3-(2-bromo-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (500 mg, 1.54 mmol) and hexamethylditin (0.32 mL, 1.543 mmol) in 1,4-dioxane (10 mL) was purged with N_2 at room temperature over 10 minutes. To this resulting mixture was added tetrakis(triphenylphosphine)palladium(0) (178 mg, 0.154 mmol) and the reaction mixture was again purged with N_2 for 10 min. The reaction mixture was stirred at 80 °C for 16 h under N_2 atmosphere. Upon completion of the reaction as confirmed by TLC, the reaction mixture was cooled to room temperature and concentrated under reduced pressure to get crude compound. The crude compound was triturated with MTBE (20 mL × 2) and dried to under reduced pressure to afford 3-(5-oxo-2-(trimethylstannyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 410.3. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 7.96 (d, J = 6.40 Hz, 1H), 7.74 (d, J = 6.40 Hz, 1H), 5.16 (dd, J = 5.20, Hz, 1H), 4.55 (d, J = 17.60 Hz, 1H), 4.40 (d, J = 15.20 Hz, 1H), 2.88-2.96 (m, 1H), 2.59-2.67 (m, 1H), 2.33-2.50 (m, 1H), 2.01-2.05 (m, 1H), 0.34 (s, 9H).

Step 5: **Synthesis of 3-(5-oxo-2-(2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione**

A solution of 3-(5-oxo-2-(trimethylstannyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione (300 mg, 0.74 mmol), and 2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl trifluoromethanesulfonate (504 mg, 1.10 mmol) in 1,4-dioxane (10 mL) was purged with N_2 at room temperature over 10 minutes. To this mixture was added copper(I) iodide (28.0 mg, 0.15 mmol) and tetrakis(triphenylphosphine)palladium(0) (85 mg, 0.074 mmol) in one lot and the reaction mixture was

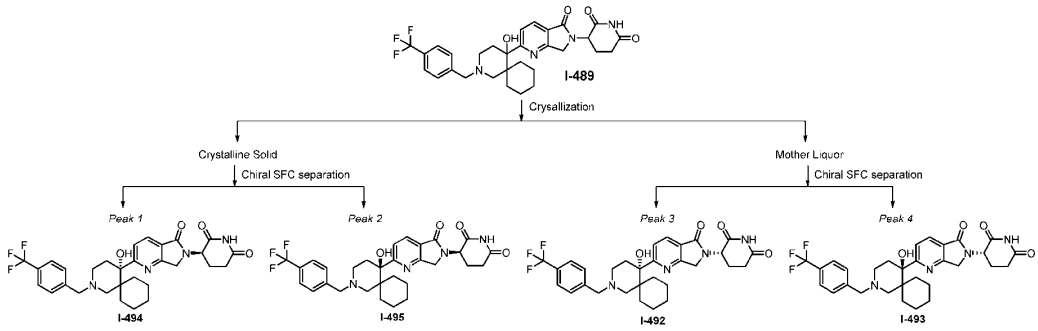
again purged with N_2 for 10 min. This resulting reaction mixture was stirred at 60 °C for 16 h. The reaction mixture was filtered through a pad of celite and washed with ethyl acetate (30 mL). The filtrate was concentrated under reduced pressure and was purified by flash column chromatography using Biotage Isolera (silica gel 100-200 mesh) and a linear gradient of 0-15% IPA in DCM as eluents to afford 3-(5-oxo-2-(2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione. LCMS: m/z MM-ES+APCI, Positive $[M+H]^-$ 553.1. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.07 (d, J = 7.60 Hz, 1H), 7.73 (d, J = 8.40 Hz, 2H), 7.63 (d, J = 8.00 Hz, 2H), 7.43 (d, J = 8.00 Hz, 1H), 5.89 (t, J = 3.20 Hz, 1H), 5.17 (dd, J = 4.80, Hz, 1H), 4.53 (d, J = 17.60 Hz, 1H), 4.35 (d, J = 17.60 Hz, 1H), 3.73 (s, 2H), 3.40-3.55 (m, 1H), 3.15 (d, J = 3.20 Hz, 2H), 2.85-2.99 (m, 1H), 2.53-2.55 (m, 2H), 2.45-2.50 (m, 2H), 2.01-2.09 (m, 1H), 1.91-2.00 (m, 2H), 1.58-1.61 (m, 2H), 1.35-1.38 (m, 2H), 0.96-1.20 (m, 1H), 0.84-0.87 (m, 1H).

Step 6: **Synthesis of 3-(2-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-489)**

A solution of 3-(5-oxo-2-(2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione (80 mg, 0.15 mmol) in DCM (10 mL) and 2-propanol (2.00 mL) was purged with O_2 at 0 °C over 10 minutes. To this reaction mixture was added $Mn(dpm)_3$ (88 mg, 0.145 mmol) and phenyl silane (78 mg, 0.724 mmol) under O_2 at 0 °C and the reaction mixture was again purged with O_2 for 10 min. This resulting reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, triturated with pentane (10 mL × 2), dried to under reduced pressure, and purified by preparative-HPLC [Method: (Column:X select (C18 150 mm × 19)5 µm, Mobile phase A: 0.05% HCl in H_2O, Mobile phase B: ACN, flow rate: 15 mL/min)]. Pure fractions were lyophilized to afford 3-(2-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **(I-489)**. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 571.4. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (d, J = 3.20 Hz, 1H), 9.96 (s, 1H), 8.17 (d, J = 7.20 Hz, 1H), 7.90-7.99 (m, 4H), 7.82 (d, J = 8.40 Hz, 1H), 5.78 (s, 1H), 5.18 (dd, J = 4.80, 13.20 Hz, 1H), 4.51-4.60 (m, 2H), 4.31-4.41 (m, 1H), 3.53-3.55 (m, 1H), 3.12-3.39 (m, 3H), 2.93 (t, J = Hz, 1H), 2.60-2.68 (m, 1H), 2.31-2.44 (m, 2H), 2.04-2.28 (m, 1H), 2.01-2.09 (m, 1H), 1.71-1.82 (m, 2H), 1.35-1.42 (m, 3H), 0.73 (m, 2H).

Example 60: Synthesis of (S)-3-(2-((S)-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-495), (R)-3-(2-((R)-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-492), (R)-3-(2-((S)-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-494), (S)-3-(2-((R)-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-

azaspiro[5.5]undecan-5-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-493)



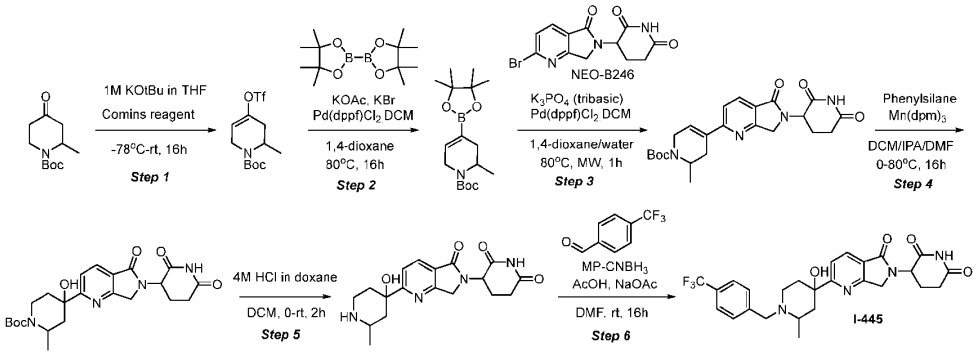
Crude 3-(2-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **(I-489)** was washed with n-hexane (2 × 10 mL) and dried to yield 3-(2-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione as a diastereomeric mixture. This crude diastereomeric mixture was crystallized using IPA (10 mL) in DCM (90 mL) (1:9) and stirred at room temperature for 10 min. After 10 min precipitate was formed. The solid was filtered and dried under vacuum to get first diastereomeric pair and the filtrate was concentrated under reduced pressure to get the second diastereomeric pair as semi-solid. Both diastereomeric pairs were further purified by reverse phase using Grace instrument (40g-C18 column and ACN and 0.1% FA in H_2O as an eluent) followed by SFC separation (Instrument: PIC-22-027; Column: RR WHELK-(250 × 30) mm, 5µm; mobile phase as CO2: 100% IPA [60:40]) to get four individual diastereomers as mentioned below.

The first pair of diastereomers obtained from solid was subjected to achiral reverse phase purification followed by chiral SFC separation to yield peak 1 as (R)-3-(2-((S)-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **(I-494)**: LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 571.9; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 8.11 (d, J = 8.00 Hz, 1H), 7.82 (d, J = 8.00 Hz, 1H), 7.70 (d, J = 8.00 Hz, 2H), 7.60 (d, J = 8.00 Hz, 2H), 5.20-5.16 (m, 1H), 5.07 (s, 1H), 4.52-4.30 (m, 2H), 3.62 (q, J = 13.20 Hz, 2H), 3.00-2.85 (m, 3H), 2.70-2.60 (m, 2H), 2.50-2.43 (m, 1H), 2.34-2.27 (m, 2H), 2.06-2.04 (m, 1H), 1.75 (d, J = 13.20 Hz, 1H), 1.44-1.27 (m, 5H), 1.07-1.04 (m, 2H), 0.90-0.52 (m, 3H), and peak 2 as (S)-3-(2-((S)-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **(I-495)**. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 571.9; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 8.11 (d, J = 8.00 Hz, 1H), 7.82 (d, J = 8.00 Hz, 1H), 7.70 (d, J = 8.00 Hz, 2H), 7.60 (d, J = 8.00 Hz, 2H), 5.20-5.16 (m, 1H), 5.07 (s, 1H), 4.52-4.30 (m, 2H), 3.62 (q, J = 13.20 Hz, 2H), 3.00-2.85 (m, 3H), 2.70-2.60 (m, 2H), 2.50-2.43 (m, 1H), 2.34-2.27 (m,

2H), 2.06-2.04 (m, 1H), 1.75 (d, J = 13.20 Hz, 1H), 1.44-1.27 (m, 5H), 1.07-1.04 (m, 2H), 0.90-0.52 (m, 3H).

The first pair of diastereomers obtained from filtrate was subjected to achiral reverse phase purification followed by chiral SFC separation to yield peak 3 as (R)-3-(2-((R)-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **(I-492)**. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 571.9; 1H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 8.11 (d, J = 8.00 Hz, 1H), 7.83 (d, J = 8.40 Hz, 1H), 7.71 (d, J = 7.60 Hz, 2H), 7.60 (d, J = 7.60 Hz, 2H), 5.20-5.16 (m, 1H), 5.06 (s, 1H), 4.54-4.34 (m, 2H), 3.62 (q, J = 13.20 Hz, 2H), 2.99-2.90 (m, 3H), 2.68-2.60 (m, 2H), 2.50-2.43 (m, 1H), 2.33-2.24 (m, 2H), 2.06-2.04 (m, 1H), 1.75 (d, J = 13.20 Hz, 1H), 1.44-1.27 (m, 4H), 1.07-1.04 (m, 2H), 0.86 (m, 2H), 0.06 (s, 2H), and peak 3 as (S)-3-(2-((R)-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **(I-493)**. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 571.9; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.11 (d, J = 8.00 Hz, 1H), 7.83 (d, J = 8.40 Hz, 1H), 7.71 (d, J = 7.60 Hz, 2H), 7.60 (d, J = 7.60 Hz, 2H), 5.20-5.16 (m, 1H), 5.06 (s, 1H), 4.54-4.34 (m, 2H), 3.62 (q, J = 13.20 Hz, 2H), 2.99-2.90 (m, 3H), 2.68-2.60 (m, 2H), 2.50-2.43 (m, 1H), 2.33-2.24 (m, 2H), 2.06-2.04 (m, 1H), 1.75 (d, J = 13.20 Hz, 1H), 1.44-1.27 (m, 5H), 1.07-1.04 (m, 2H), 0.86-0.52 (m, 3H).

Example 61: Synthesis of 3-(2-(4-hydroxy-2-methyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-445):



Step 1: **Synthesis of tert-butyl 2-methyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2*H*)-carboxylate**

To a stirred solution of tert-butyl 2-methyl-4-oxopiperidine-1-carboxylate (5 g, 23.44 mmol) in THF (50 mL) was added potassium tert-butoxide solution (30.5 mL, 30.5 mmol) at -78 °C under N_2 atmosphere and stirred for 1 h. The reaction mixture was again cooled to -78°C and added Comins reagent (13.81 g, 35.2 mmol) in THF (50 mL). The reaction mixture was stirred at room temperature for 16 h under N_2 atmosphere. The progress of reaction was monitored by TLC. Upon completion of the

reaction as confirmed by TLC, the reaction mixture was quenched with sat. NH_4Cl at 0 °C and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude residue. The crude residue was purified by Biotage Isolera (silica gel 100-200 mesh) and a linear gradient of 0-10% EtOAc in hexane as eluents to afford tert-butyl 2-methyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2*H*)-carboxylate. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.76 (d, J = 14.40 Hz, 1H), 4.42-4.69 (m, 2H), 3.66 (d, *J* = 2.00 Hz, 0.5H), 2.90-3.10 (m, 0.5H), 2.80-2.86 (m, 0.5H), 2.60-2.61 (m, 0.5H), 2.23 (dd, *J* = 4.00, 16.80 Hz, 0.5H), 2.09 (d, *J* = 1.20 Hz, 0.5H), 1.63-1.65 (m, 9H), 1.23 (dd, J = 3.20, 13.80 Hz, 3H).

Step 2: **Synthesis of tert-butyl 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate**

To a stirred solution of tert-butyl 2-methyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2*H*)-carboxylate (1 g, 2.90 mmol), bis(pinacolato)diboron (0.88 g, 3.47 mmol), potassium bromide (0.379 g, 3.19 mmol) and potassium acetate (0.85 g, 8.69 mmol) in 1,4-dioxane (10 mL) was purged with N_2 at room temperature over 10 minutes. To this resulting mixture was added $PdCl_2$(dppf)-CH_2Cl_2 (0.236 g, 0.29 mmol) and the reaction mixture was again purged with N_2 for 10 min. This resulting reaction mixture was subjected to react under microwave irradiation at 80 °C for 16 h. The reaction mixture was filtered through a pad of celite and washed with ethyl acetate (10 mL) and the filtrate was concentrated under reduced pressure. The crude compound was purified by flash column chromatography using Biotage Isolera (silica gel 100-200 mesh) and a linear gradient of 0-10% ethyl acetate in hexane to afford tert-butyl 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.45 (d, *J* = 31.60 Hz, 1H), 4.09-4.48 (m, 2H), 3.62 (d, *J* = 2.00 Hz, 0.5H), 2.76 (m, 0.5H), 2.47-2.49 (m, 0.5H), 2.19-2.24 (m, 1.5H), 1.61 (s, 9H), 1.29 (s, 12H), 1.21 (dd, J = 6.80, Hz, 3H).

Step 3: **Synthesis of tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-2-yl)-2-methyl-3,6-dihydropyridine-1(2*H*)-carboxylate**

A stirred solution of tert-butyl 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (0.4 g, 1.24 mmol), 3-(2-bromo-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione (0.40 g, 1.24 mmol) and potassium phosphate tribasic (0.79 g, 3.71 mmol) in 1,4-dioxane (10 mL) and water (0.1 mL) was purged with N_2 at room temperature over 10 minutes. To this resulting mixture was added $PdCl_2$(dppf)-CH_2Cl_2 (0.101 g, 0.12 mmol) in one lot and the reaction mixture was again purged with N_2 for 10 min. This resulting reaction mixture was subjected to react under microwave irradiation at 80 °C for 1 h. under microwave irradiation. The progress of reaction was monitored by TLC/LCMS. The reaction mixture was filtered through a pad of celite and washed with ethyl acetate (10 mL); the filtrate was concentrated under reduced pressure. The crude compound was

purified by reverse phase column [C18, 40 g, (Mobile phase A: 0.1% FA in H_2O, Mobile phase B: ACN, flow rate: 15 mL/min), RT: 8.5]. Pure fractions were collected and lyophilized to afford tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-2-methyl-3,6-dihydropyridine-1(2H)-carboxylate LCMS: m/z MM-ES+APCI, Negative $[M-H]^-$ 439.2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.13 (d, J = 1.20 Hz, 1H), 7.73 (d, J = 8.40 Hz, 1H), 6.86 (d, J = 14.80 Hz, 1H), 5.18 (dd, J = 5.20, 13.00 Hz, 1H), 4.49-4.59 (m, 3H), 3.75-4.49 (m, 3H), 2.89-2.98 (m, 1H), 2.64-2.73 (m, 3H), 2.42-2.50 (m, 1H), 2.02-2.05 (m, 2H), 1.44 (s, 9H), 1.15 (dd, J = 7.20, 40.00 Hz, 3H).

Step 4: **Synthesis of tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-2-yl)-4-hydroxy-2-methylpiperidine-1-carboxylate**

A solution of tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-2-yl)-2-methyl-3,6-dihydropyridine-1(2*H*)-carboxylate (0.25 g, 0.57 mmol) in DCM (5 mL), DMF (2 mL) and 2-propanol (5.00 mL) was purged with O_2 at room temperature over 10 minutes at 0 °C. To this resulting mixture was added $Mn(dpm)_3$ (0.104 g, 0.17 mmol) and phenyl silane (0.092 g, 0.851 mmol) under O_2 at 0 °C and the reaction mixture was again purged with O_2 for 10 min. This resulting reaction mixture was stirred at room temperature for 16 h and then concentrated under reduced pressure. The crude compound was purified by reverse phase HPLC [Method: (Column:X select (C1, 40 g, Mobile phase A: 0.1% FA in H_2O, Mobile phase B: ACN, flow rate: 15 mL/min)]. Pure fractions were lyophilized to afford tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-4-hydroxy-2-methylpiperidine-1-carboxylate. LCMS: m/z MM-ES+APCI, Negative $[M-H]^-$ 457.1. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.15 (d, J = 4.40 Hz, 1H), 7.82 (d, J = 8.40 Hz, 1H), 5.47 (s, 1H), 5.18 (dd, J = 4.80, 13.20 Hz, 1H), 4.52 (dd, J = 4.80, 17.60 Hz, 1H), 4.33 (dd, J = 4.80, 17.80 Hz, 1H), 4.04-4.06 (m, 1H), 3.73-3.77 (m, 1H), 2.90-2.93 (m, 1H), 2.60-2.68 (m, 3H), 2.40-2.45 (m, 2H), 2.30-2.34 (m, 1H), 2.12-2.18 (m, 1H), 1.42 (s, 9H), 0.98 (t, J = 6.40 Hz, 3H).

Step 5: **Synthesis of 3-(2-(4-hydroxy-2-methylpiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione**

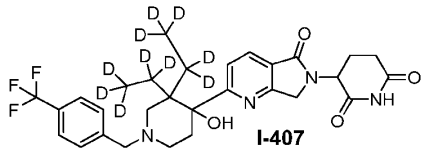
To a stirred solution of tert-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-2-yl)-2-methyl-3,6-dihydropyridine-1(2*H*)-carboxylate (80 mg, 0.182 mmol) in DCM (1 mL) was added 4 M HCl in dioxane (0.227 mL, 0.908 mmol) at 0 °C. The reaction stirred for 2 h. The reaction mixture was directly concentrated under reduced pressure, triturated with MTBE (2 × 5 mL), and dried under vacuum to afford 3-(2-(4-hydroxy-2-methylpiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione hydrochloride. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 359.1. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H), 9.01-9.04 (m, 1H), 8.46-8.49 (m, 1H), 8.21 (d, *J* = 4.40 Hz, 1H), 7.86 (d, *J* = 4.40 Hz, 1H), 5.20 (dd, *J* = 4.80, 13.20 Hz, 1H), 4.53 (d, *J* = 2.00

Hz, 1H), 4.35 (d, *J* = 19.20 Hz, 1H), 3.29-3.57 (m, 3H), 2.91-2.94 (m, 1H), 2.51-2.68 (m, 2H), 2.35-2.50 (m, 3H), 2.02-2.17 (m, 2H), 1.26 (d, *J* = 6.40 Hz, 3H).

Step 6: **Synthesis of 3-(2-(4-hydroxy-2-methyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione (I-445)**

To a stirred solution of 3-(2-(4-hydroxy-2-methylpiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione hydrochloride (0.08 g, 0.203 mmol), 4-(trifluoromethyl)benzaldehyde (0.035 g, 0.203 mmol), acetic acid (0.037 g, 0.608 mmol) and sodium acetate (0.083 g, 1.013 mmol) in DMF (1 mL) was added MP-$CNBH_3$ (0.08 g, 0.203 mmol) and stirred at 25 °C for 16 h. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by MD prep [Zorbax C18,150 mm X 19, (Mobile phase A: 0.1% HCl in H_2O, Mobile phase B: ACN, flow rate: 15 mL/min), RT: 8.5]. Pure fractions were lyophilized to afford 33-(2-(4-hydroxy-2-methyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 517.5. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (d, *J* = 1.60 Hz, 1H), 10.36 (s, 1H), 8.23 (d, *J* = 7.60 Hz, 1H), 7.84-7.96 (m, 5H), 5.99 (s, 1H), 5.19 (dd, *J* = 4.80, 13.20 Hz, 1H), 4.84 (d, *J* = 11.60 Hz, 1H), 4.53-4.36 (m, 3H), 3.53-3.67 (m, 2H), 3.05-3.28 (m, 1H), 2.90-3.05 (m, 2H), 2.60-2.68 (m, 1H), 2.39-2.50 (m, 1H), 2.01-2.04 (m, 2H), 1.72-1.81 (m, 1H), 1.57 (d, *J* = 7.60 Hz, 3H).

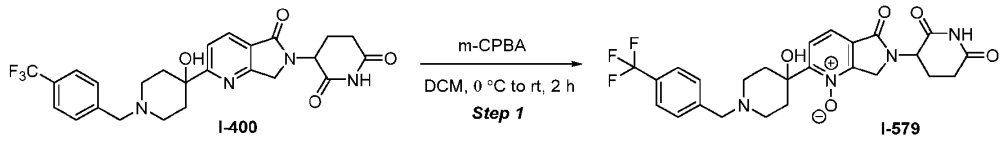
Example 62: Synthesis of 3-(2-(3,3-bis(ethyl-d5)-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-407)



I-407

The title compound was synthesized in a similar fashion to **I-424** and was isolated as a mixture of diastereomers. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 569.95. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 10.98-11.06 (m, 1H), 8.09 (d, *J*=7.94 Hz, 1H), 7.88 (dd, *J*=8.21, 1.92 Hz, 1H), 7.70 (d, *J*=8.21 Hz, 2H), 7.58 (d, *J*=8.21 Hz, 2H), 5.10-5.24 (m, 2H), 4.44-4.56 (m, 1H), 4.26-4.39 (m, 1H), 3.52-3.59 (m, 2H), 2.86-3.01 (m, 2H), 2.57-2.72 (m, 2H), 2.31-2.42 (m, 3H), 1.94-2.09 (m, 1H), 1.35-1.46 (m, 1H).

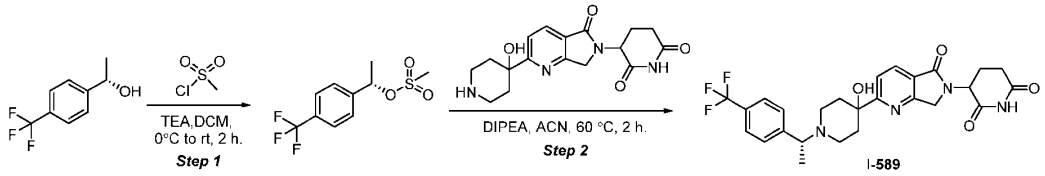
Example 63: Synthesis of 6-(2,6-dioxopiperidin-3-yl)-2-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine (I-579)



I-400 **I-579**

Step 1: Synthesis of 6-(2,6-dioxopiperidin-3-yl)-2-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-b]pyridine 1-oxide, Formic Acid: To a stirred solution of 3-(2-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-400**, 100 mg, 0.19 mmol) in DCM (3 mL) was added mCPBA (86 mg, 0.49 mmol) at 0 °C. The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was quenched with sodium hypochlorite solution (5 mL) and extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated to obtain the crude product. The crude product was purified by reverse-phase chromatography (C18 column) with an eluent of 20% ACN in water (0.1% formic acid). The pure fractions were concentrated to afford 6-(2,6-dioxopiperidin-3-yl)-2-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine 1-oxide (**I-579**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 519.1. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.17 (d, J = 8.00 Hz, 1H), 7.91 (d, J = 8.40 Hz, 2H), 7.85 (d, J = 8.00 Hz, 1H), 7.79 (d, J = 8.00 Hz, 2H), 5.69 (s, 1H), 5.19-5.15 (m, 1H), 4.63 (s, 2H), 4.51 (d, J = 17.60 Hz, 1H), 4.34 (d, J = 18.00 Hz, 1H), 3.69 (t, J = 11.20 Hz, 2H), 2.99-2.89 (m, 5H), 2.51-2.51 (m, 2H), 2.04-2.02 (m, 1H), 1.55-1.52 (m, 2H).

Example 64: Synthesis of 3-(2-(4-hydroxy-1-((R)-1-(4-(trifluoromethyl)phenyl)ethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-589)



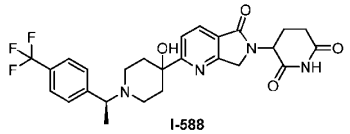
Step 1: **Synthesis of (*S*)-1-(4-(trifluoromethyl)phenyl)ethyl methanesulfonate**

To a stirred solution of (*S*)-1-(4-(trifluoromethyl)phenyl)ethan-1-ol (200 mg, 1.05 mmol) in DCM (3 mL) was added triethylamine (0.44 mL, 3.16 mmol). The reaction mixture was cooled to 0 °C then added methanesulfonyl chloride (0.123 mL, 1.58 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with saturated aqueous sodium bicarbonate solution (10 mL) and extracted with DCM (20 mL × 2). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get crude residue. The crude was purified by flash chromatography using Biotage Isolera (Silica gel 100-200 mesh) and a linear gradient of 0-10% EtOAc in hexane as eluents to afford (*S*)-1-(4-(trifluoromethyl)phenyl)ethyl methanesulfonate. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 7.60 Hz, 2H), 7.63 (d, J = 8.40 Hz, 2H), 5.81 (q, J = 6.80 Hz, 1H), 2.87 (s, 3H), 1.75 (d, J = 6.80 Hz, 3H).

Step 2: **Synthesis of 3-(2-(4-hydroxy-1-((R)-1-(4-(trifluoromethyl)phenyl)ethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-589)**

To a stirred solution of 3-(2-(4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione hydrochloride (70 mg, 0.18 mmol) in acetonitrile (1 mL) was added (*S*)-1-(4-(trifluoromethyl)phenyl)ethyl methanesulfonate (59.2 mg, 0.22 mmol) followed by DIPEA (0.096 mL, 0.55 mmol) at room temperature. The reaction mixture was stirred at 60 °C for 2 h. The reaction mixture was concentrated under reduced and purified by preparative high-performance liquid chromatography (HPLC) using an Agilent Pursuit XR C18 column (30 × 150 mm, 5 μm), with a mobile phase of 0.1% formic acid in water (A) and acetonitrile (B), at a flow rate of 15 mL/min and a retention time of 12.0 minutes. The collected acetonitrile/water mixture was lyophilized to afford 3-(2-(4-hydroxy-1-((*R*)-1-(4-(trifluoromethyl)phenyl)ethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione (**I-589**). LCMS: m/z MM-ES+APCI, $[M+H]^+$ 517.3 ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.13 (d, J = 8.00 Hz, 1H), 7.83 (q, J = 8.00 Hz, 1H), 7.70 (d, J = 8.00 Hz, 2H), 7.60 (d, J = 8.40 Hz, 2H), 5.21-5.15 (m, 2H), 4.51 (d, J = 18.00 Hz, 1H), 4.34 (d, J = 17.60 Hz, 1H), 3.62 (d, J = 5.20 Hz, 1H), 2.93 (m, 2H), 2.68-2.64 (m, 2H), 2.50-2.42 (m, 3H), 2.27-2.22 (m, 2H), 2.05-2.03 (m, 1H), 1.49 (m, 2H), 1.35 (d, J = 6.80 Hz, 3H).

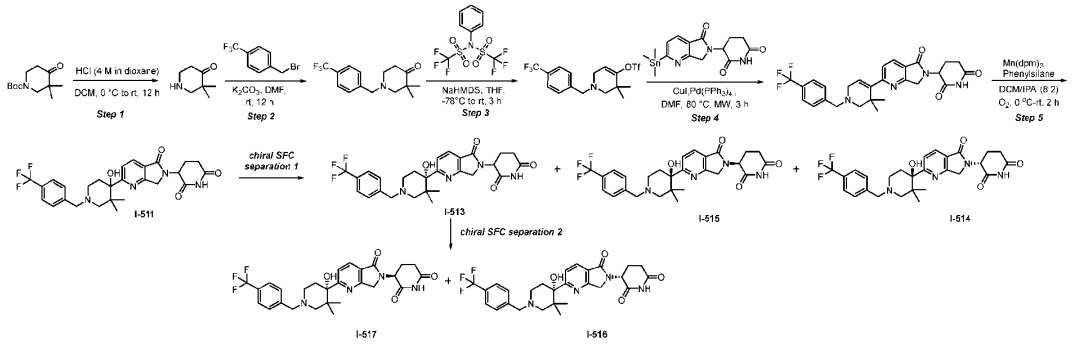
Example 65: Synthesis of 3-(2-(4-hydroxy-1-((S)-1-(4-(trifluoromethyl)phenyl)ethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-588)



I-588

This compound was synthesized in a similar fashion to Example 64 (**I-589**). LCMS: m/z MM-ES+APCI, $[M+H]^+$ 517.3 ^{1}H-NMR (400 MHz, DMSO-d_6): 11.02 (s, 1H), 8.13 (d, J = 8.40 Hz, 1H), 7.83 (d, J = 8.00 Hz, 1H), 7.70 (d, J = 8.00 Hz, 2H), 7.60 (d, J = 8.00 Hz, 2H), 5.21-5.15 (m, 2H), 4.53-4.31 (m, 2H), 3.62 (d, J = 5.20 Hz, 1H), 2.93-2.81 (m, 1H), 2.81-2.68 (m, 1H), 2.64-2.51 (m, 2H), 2.50-2.42 (m, 3H), 2.39-2.24 (m, 2H), 2.05-2.02 (m, 1H), 1.59-1.50 (m, 2H), 1.35 (d, J = 6.80 Hz, 3H).

Example 66: Synthesis of 3-(2-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-511), (S)-3-(2-((R)-4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-515), (R)-3-(2-((R)-4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-514), (S)-3-(2-((S)-4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-517), (R)-3-(2-((S)-4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-516)



Step 1: **Synthesis of 3,3-dimethylpiperidin-4-one hydrochloride**

To a stirred solution of tert-butyl 3,3-dimethyl-4-oxopiperidine-1-carboxylate (5 g, 22.00 mmol) in DCM (25 mL) was added HCl (4M in 1,4-dioxane) (11.00 mL, 44.0 mmol) at 0°C under nitrogen atmosphere and the reaction mixture was allowed to stir at room temperature for 12 h. The solution was concentrated under reduced pressure to afford 3,3-dimethylpiperidin-4-one hydrochloride. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 128.1.

Step 2: **Synthesis of 3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-one**

To a stirred solution of 3,3-dimethylpiperidin-4-one hydrochloride (2.6 g, 20.44 mmol) in DMF (25 mL) was added potassium carbonate (5.65 g, 40.9 mmol) and 1-(bromomethyl)-4-(trifluoromethyl)benzene (5.38 g, 22.49 mmol) at 25°C. The reaction mixture was allowed to stir at 25°C for 12 h. The reaction mixture was quenched with ice-cold water (50 mL) and extracted with EtOAc (2 × 200 mL). The organic layer was dried over sodium sulphate, filtered, concentrated, and purified by flash column chromatography using Biotage isolera with silica gel (100-200 mesh) and 0 to 10% EtOAc in *n*-hexane as eluent to afford 3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-one. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 286.1, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.72 (d, *J* = 8.00 Hz, 2H), 7.62 (d, *J* = 8.00 Hz, 2H), 3.67 (s, 2H), 2.70 (t, *J* = 6.00 Hz, 2H), 2.46 (t, *J* = 6.00 Hz, 2H), 2.40 (s, 2H), 1.06 (d, *J* = Hz, 6H

Step 3: **Synthesis of 3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate**

To a stirred solution of 3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-one (3.3 g, 11.57 mmol) in THF (20 mL) was added NaHMDS (1 M in THF) (23.13 mL, 23.13 mmol) at -78°C and the reaction mixture was stirred at -78°C for 35 min. To this resulting solution was added 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (5.37 g, 15.04 mmol) dissolved in THF (5 mL) dropwise at -78°C and the reaction mixture was allowed to stir at room temperature for 3 h. The reaction mixture was quenched with aq. ammonium chloride solution (50 mL) and extracted with ethyl acetate (2 × 200 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated

under reduced pressure to afford crude product. The crude material was purified by flash column chromatography using Biotage isolera with silica gel (100-200 mesh) and 0-10% ethyl acetate in *n*-hexane as eluents to afford 3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate . LCMS: m/z MM-ES+APCI, Positive ES+APCI, Positive $[M+H]^+$ 418.1, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.72 (d, *J* = 8.00 Hz, 2H), 7.58 (d, *J* = 8.00 Hz, 2H), 5.79-5.76 (m, 1H), 3.70 (s, 2H), 3.11 (s, 2H), 2.33 (s, 2H), 1.09 (s, 6H).

Step 4: **Synthesis of 3-(2-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione**

A solution of 3-(5-oxo-2-(trimethylstannyl)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (200 mg, 0.49 mmol), 3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (205 mg, 0.49 mmol) and copper(I) iodide (28.0 mg, 0.147 mmol) in 1,4-dioxane (3 mL) was purged with N_2 for 10 min at room temperature. To this resulting mixture was added tetrakis(triphenylphosphine)palladium (56.6 mg, 0.049 mmol) at room temperature and again purged with N_2 for 10 min. This resulting reaction mixture was subjected to microwave irradiation at 80 °C for 3 h. The reaction mixture was cooled to room temperature, filtered on a celite pad and washed with EtOAC (20 mL). The filtrate was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by Biotage isolera (silica gel 100-200 mesh) and a linear gradient of 0-100% EtOAc in hexane. This resulting material was repurified by reverse phase chromatography using a C18 column [Mobile phase A: 0.1% FA in H_2O, Mobile phase B: ACN, flow rate: 10 mL/min)]. Fractions were combined to afford 3-(2-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione. LCMS: m/z MM- ES+APCI, Positive $[M+H]^+$ 513.4, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.002 (s, 1H), 8.06 (d, J = 8.40 Hz, 1H), 7.73 (d, J = 8.00 Hz, 2H), 7.53-7.65 (m, 2H), 7.47 (d, J = 6.40 Hz, 1H), 6.10 (t, J = 3.60 Hz, 1H), 5.17 (dd, J = 4.80, 13.20 Hz, 1H), 4.52 (d, J = 17.60 Hz, 1H), 4.34 (d, J = 17.60 Hz, 1H), 3.72 (s, 2H), 3.17 (d, J = 3.20 Hz, 2H), 2.93-2.90 (m, 1H), 2.64-2.60 (m, 1H), 2.64-2.60 (m, 3H), 2.06-2.03 (m, 1H), 1.24 (s, 6H).

Step 5: **Synthesis of 3-(2-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-511)**

To a stirred solution of 3-(2-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (400 mg, 0.78 mmol) in DCM (15 mL) and 2-propanol (3.75 mL) was added phenyl silane (0.29 mL, 2.34 mmol) and Mn(dpm)3 (472 mg, 0.78 mmol) at 0 °C. The reaction mixture was allowed to stir under O_2 atmosphere at room temperature for 2 h. The reaction mixture was concentrated, and the resulting residue was washed with hexane (2 × 10 mL). The crude compound was purified by preparative-HPLC

[(Column:X select (C18 150 mm × 19)5 μm, Mobile phase A: 0.05% HCl in H_2O, Mobile phase B: ACN, flow rate: 15 mL/min)]. Pure fractions were combined to afford 3-(2-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-511**). LCMS: m/z MM- ES+APCI, Positive $[M+H]^+$ 531.1, ^1H NMR (400 MHz, DMSO-d6): δ 11.02 (s, 1H), 10.01 (s, 1H), 8.18 (d, J = 0.8 Hz, 1H), 7.95-7.92 (m, 5H), 5.85 (s, 1H), 5.18 (q, J = 4.8 Hz, 1H), 4.56-4.52 (m, 3H), 4.38-4.36 (m, 1H), 3.38-3.15 (m, 4H), 2.89-2.86 (m, 2H), 2.68-2.59 (m, 1H), 2.42 (d, J = 8.4 Hz, 1H), 2.05 (t, J = 20.00 Hz, 1H), 1.76 (t, J = 1.20 Hz, 1H), 0.94 (s, 3H), 0.8 (s, 3H).

Chiral SFC separation:

3-(2-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-511**, 250 mg) was purified by SFC-chiral purification, [Column: Whelk-(R,R) and Co-Solvent Name: IPA:ACN (4:6), Injected Volume: 15 μl, FlowRate: 3 mL/min)] to afford:

Peak 3: (S)-3-(2-((R)-4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-515**, 28.2 mg). LCMS: m/z MM-ES+APCI, Positive$[M+H]^+$ 531.1, 1H-NMR (400 MHz, DMSO-d6): δ 11.03 (s, 1H), 8.12 (d, J = 8.00 Hz, 1H), 7.84 (d, J = 8.00 Hz, 1H), 7.70 (d, J = 8.00 Hz, 2H), 7.59 (d, J = 8.00 Hz, 2H), 5.20-5.16 (m, 1H), 5.12 (s, 1H), 4.53-4.31 (m, 2H), 3.66-3.33 (m, 2H), 2.98-2.93 (m, 2H), 2.60-2.44 (m, 5H), 2.15 (d, J = 10.40 Hz, 1H), 2.10-2.01 (m, 1H), 1.48 (d, J = 13.60 Hz, 1H), 0.91 (s, 3H), 0.68 (s, 3H).

Peak 4: R)-3-(2-((R)-4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-514**, 30.3 mg). LCMS: m/z MM-ES+APCI, Positive$[M+H]^+$ 531.2, 1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 8.12 (d, J = 8.00 Hz, 1H), 7.84 (d, J = 8.00 Hz, 1H), 7.70 (d, J = 8.00 Hz, 2H), 7.59 (d, J = 8.00 Hz, 2H), 5.20-5.16 (m, 1H), 5.11 (s, 1H), 4.54-4.32 (m, 2H), 3.63-3.54 (m, 2H), 3.01-2.98 (m, 2H), 2.64-2.46 (m, 5H), 2.15 (d, J = 10.40 Hz, 1H), 2.05 (m, 1H), 1.47 (d, J = 13.60 Hz, 1H), 0.91 (s, 3H), 0.69 (s, 3H).

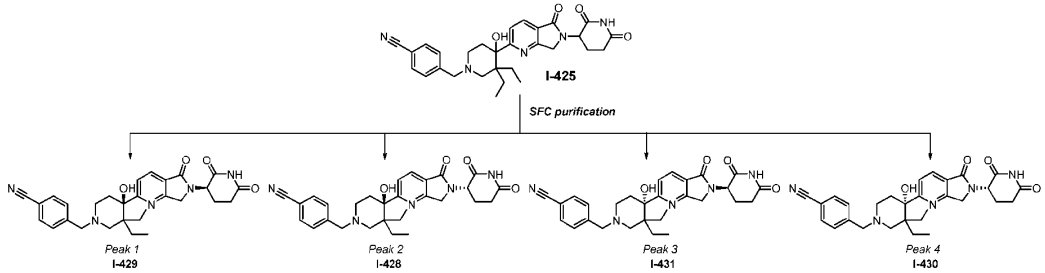
Peak 1 and *Peak 2* coeluted in the first purification and were subjected to a second chiral SFC purification using I-cellulose-B column, IPA 30% as co-solvent, [Column: I-cellulose-B column, IPA 30% as co-solvent, Injected Volume: 15 μl, Flow Rate: 3 mL/min)] to afford:

Peak 1: (S)-3-(2-((S)-4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-517**, 35 mg). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 531.8, ^1H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 5.20-5.16 (m, 1H), 5.12 (s, 1H), 4.50 (d, J = 17.6 Hz, 1H), 4.32 (d, J = 17.6 Hz, 1H), 3.65-3.33 (m, 2H), 3.01-2.90 (m, 2H), 2.70-2.67 (m, 1H), 2.63-2.59 (m, 1H), 2.50-2.42 (m, 3H), 2.33-2.32 (m, 1H), 2.15-2.02 (m, 1H), 1.47 (d, J = 14 Hz, 1H), 0.90 (s, 3H), 0.67 (s, 3H).

Peak 2: (R)-3-(2-((S)-4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-516**, 39 mg). LCMS: m/z MM-ES+APCI, Positive$[M+H]^+$ 531.6, 1H-NMR (400 MHz, DMSO-d6): δ 11.03 (s, 1H), 8.12 (d, J = 8.00 Hz, 1H), 7.84 (d, J = 8.00 Hz, 1H), 7.70 (d, J = 8.40 Hz, 2H), 7.59 (d, J = 8.00 Hz, 2H), 5.19-5.13 (m, 2H), 4.54-4.50 (m, 1H), 4.36-4.31 (m, 1H), 3.62-3.38 (m, 1H), 3.38-3.29 (m, 1H), 3.04-2.92 (m, 2H), 2.64-2.51 (m, 3H), 2.50-2.44 (m, 2H), 2.14 (d, J = 10.40 Hz, 1H), 2.05-2.02 (m, 1H), 1.47 (d, J = 13.60 Hz, 1H), 0.90 (s, 3H), 0.68 (s, 3H).

Note: stereochemistry of all four diastereomers was arbitrarily assigned.

Example 67: Synthesis of 4-(((R)-4-(6-((S)-2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile (I-429), 4-(((R)-4-(6-((R)-2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile (I-428), 4-(((S)-4-(6-((S)-2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile (I-431), 4-(((S)-4-(6-((R)-2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile (I-430)



Chiral SFC purification:

4-((4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile (**I-425**, 480 mg) was purified using the instrument: PIC 175* [22-027]; column: IA- (250 × 30) mm, 5 μm; mobile Phase: CO_2: 0.2% FA in 2-propanol: acetonitrile; gradient [CO_2:Co-solvent]: [55:45]; total Flow: 120 mL/min; back pressure: 100 bar; wavelength: 254 nm; cycle time: 11 min. The pure fractions were concentrated under reduced pressure and lyophilized to afford 200 mg of *Peak 3* and *Peak 4* mixture and 200 mg of *Peak 1* and *Peak 2* mixture. These mixtures were submitted to second SFC purifications using the following methods:

Chiral SFC purification of Peak 1 and Peak 2:

Instrument: PIC 175* [22-027]; column: I cellulose J-(250 × 30) mm, 5 μm; mobile Phase: CO_2:0.2%FA IPA:ACN (1:1); gradient [CO_2:Co-solvent]: [70:30]; total Flow: 120 mL/min; back pressure: 120 bar; wavelength: 274 nm; cycle time: 12 min. The pure fractions were concentrated under reduced pressure and lyophilized to afford:

Peak 1: 4-(((R)-4-(6-((S)-2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile (**I-429**, 43 mg). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 516.4; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.05-10.98 (m, 1H), 10.30-10.15 (m, 1H), 8.16 (d, *J* = 8.1 Hz, 1H), 8.04-7.97 (m, 4H), 7.90 (d, *J* = 8.1 Hz, 1H), 6.06-5.79 (m, 1H), 5.17 (dd, *J* = 5.1, 13.4 Hz, 1H), 4.59-4.50 (m, 2H), 4.47-4.33 (m, 2H), 3.31-3.13 (m, 3H), 3.00-2.85 (m, 1H), 2.75 (d, *J* = 12.4 Hz, 1H), 2.66-2.56 (m, 1H), 2.41 (dd, *J* = 4.8, 13.2 Hz, 1H), 2.07-1.98 (m, 2H), 1.68 (d, *J* = 12.1 Hz, 1H), 1.54 (qd, *J* = 7.4, 14.8 Hz, 1H), 1.25-1.15 (m, 3H), 0.45-0.34 (m, 6H).

Peak 2: 4-(((R)-4-(6-((R)-2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile (**I-428,** 49 mg). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 516.4; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H), 10.50-9.89 (m, 1H), 8.16 (d, *J* = 8.1 Hz, 1H), 8.06-7.88 (m, 5H), 6.37-5.53 (m, 1H), 5.18 (dd, *J* = 5.2, 13.1 Hz, 1H), 4.61-4.48 (m, 1H), 4.46-4.33 (m, 1H), 3.46-3.08 (m, 4H), 3.02-2.85 (m, 1H), 2.74 (d, *J* = 13.0 Hz, 1H), 2.67-2.58 (m, 1H), 2.45-2.36 (m, 1H), 2.14-1.95 (m, 2H), 1.68 (d, *J* = 13.2 Hz, 1H), 1.59-1.46 (m, 1H), 1.30-1.10 (m, 4H), 0.40 (td, *J* = 7.4, 15.0 Hz, 6H).

Chiral SFC purification of Peak 3 and Peak 4:

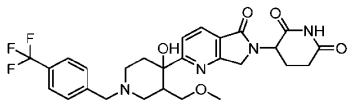
Instrument: PIC 175* [22-028]; column: RR whelk-(250 × 30)mm, 5μm; mobile phase: CO_2:IPA; gradient [CO_2:co-solvent]: [50:50]; total flow: 100 mL/min; back pressure: 120 bar; wavelength: 274 nm; cycle time: 11 min. The pure fractions were concentrated under reduced pressure and lyophilized to afford:

Peak 3: 4-(((S)-4-(6-((S)-2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile (**I-431,** 68 mg). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 516.4; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.13-10.82 (m, 1H), 10.30-9.68 (m, 1H), 8.16 (d, *J* = 8.1 Hz, 1H), 8.00 (s, 4H), 7.95-7.86 (m, 1H), 6.07-5.71 (m, 1H), 5.30-4.95 (m, 1H), 4.64-4.50 (m, 2H), 4.48-4.24 (m, 2H), 3.45-3.37 (m, 1H), 3.32-3.13 (m, 3H), 3.02-2.86 (m, 1H), 2.80-2.70 (m, 1H), 2.66-2.57 (m, 1H), 2.46-2.36 (m, 1H), 2.09-1.96 (m, 2H), 1.76-1.65 (m, 1H), 1.61-1.47 (m, 1H), 1.29-1.09 (m, 2H), 0.49-0.31 (m, 6H).

Peak 4: 4-(((S)-4-(6-((R)-2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile (**I-430**, 46 mg). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 516.4; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H), 10.50-9.89 (m, 1H), 8.16 (d, *J* = 8.1 Hz, 1H), 8.06-7.88 (m, 5H), 6.37-5.53 (m, 1H), 5.18 (dd, *J* = 5.2, 13.1 Hz, 1H), 4.61-4.48 (m, 1H), 4.46-4.33 (m, 1H), 3.46-3.08 (m, 4H), 3.02-2.85 (m, 1H), 2.74 (d, *J* = 13.0 Hz, 1H), 2.67-2.58 (m, 1H), 2.45-2.36 (m, 1H), 2.14-1.95 (m, 2H), 1.68 (d, *J* = 13.2 Hz, 1H), 1.59-1.46 (m, 1H), 1.30-1.10 (m, 4H), 0.40 (td, *J* = 7.4, 15.0 Hz, 6H).

Note: stereochemistry for all 4 diastereomers was arbitrarily assigned.

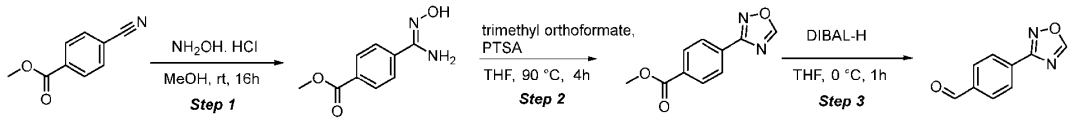
Example 68: Synthesis of 3-(2-(4-hydroxy-3-(methoxymethyl)-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (I-451)



I-451

The title compound was synthesized in a similar fashion to **Example 58 (I-450)** and was isolated as a mixture of diastereomers. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 547.3; 1H-NMR (400 MHz, DMSO-d_6): δ 11.48 - 11.15 (m, 1H), 11.14 - 10.91 (m, 1H), 8.17 (dd, J = 8.1, 18.3 Hz, 1H), 8.03 - 7.70 (m, 5H), 5.28 - 5.12 (m, 1H), 4.68 - 4.22 (m, 4H), 3.87 - 3.29 (m, 5H), 3.27 - 3.17 (m, 1H), 3.11 - 2.98 (m, 3H), 2.98 - 2.86 (m, 1H), 2.79 - 2.56 (m, 3H), 2.46 - 2.23 (m, 2H), 2.10 - 1.95 (m, 2H).

Example 69: Synthesis of 4-(1,2,4-oxadiazol-3-yl)benzaldehyde (ALD-1)



Step 1: **Synthesis of methyl 4-(1,2,4-oxadiazol-3-yl)benzoate**

To a stirred solution of hydroxylamine hydrochloride (8.56 g, 124 mmol) in water (25 mL) was added sodium hydrogen carbonate (10.42 g, 124 mmol) at room temperature and stirred for 15 min. After that methyl-4-cyanobenzoate (10 g, 62.1 mmol) in MeOH (100 mL) was added to the above reaction mixture and stirred at room temperature for 16 h. The reaction mixture was filtered, and the solid was collected. The solid was dried under reduced pressure to afford methyl 4-(N'-hydroxycarbamimidoyl)benzoate. LCMS: ES+APCI, Positive $[M+H]^+$ 194.19. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.91 (s, 1H), 7.96 (d, J = 8.80 Hz, 2H), 7.82 (d, J = 8.80 Hz, 2H), 5.94 (s, 2H, 3.87 (s, 3H).

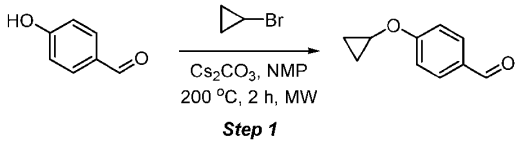
Step 2: **Synthesis of methyl 4-(1,2,4-oxadiazol-3-yl)benzoate**

To the stirred solution of methyl 4-(N'-hydroxycarbamimidoyl)benzoate (9 g, 46 mmol) in THF (50 mL), trimethyl orthoformate (25.3 mL, 232 mmol) and toluene-4-sulfonic acid monohydrate (0.88 g, 4.63 mmol) were added at room temperature and the reaction mixture was stirred at 90 °C for 4 h. The reaction mixture was cooled and the excess solvent from the reaction mixture was evaporated under reduced pressure. Water was then added and precipitation was observed. The formed solid was filtered and dried under reduced pressure to afford methyl 4-(1,2,4-oxadiazol-3-yl)benzoate. LCMS: ES+APCI, Positive $[M+H]^+$ 205.10. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.80 (s, 1H), 8.21-8.14 (m, 4H), 3.91 (s, 3H).

Step 3: **Synthesis of 4-(1,2,4-oxadiazol-3-yl)benzaldehyde (ALD-1)**

To a stirred solution of morpholine (0.98 g, 11.26 mmol) in THF (25 mL) was added DIBAL-H (1.0M in THF) (10.77 mL, 10.77 mmol) at 0 °C and stirred for 3 h. To this resulting mixture was added methyl 4-(1,2,4-oxadiazol-3-yl)benzoate (1 g, 4.90 mmol) in THF (25 mL) at 0 °C and stirred for 10 min. DIBAL-H (1.0M in THF) (5.88 mL, 5.88 mmol) was then added at 0 °C and the reaction mixture was stirred for 1 h. After completion of the reaction, the reaction was quenched with 1N HCl (100 mL) and excess THF was removed under reduced pressure. The resulting solid was collected by filtration and dried to afford 4-(1,2,4-oxadiazol-3-yl)benzaldehyde (**ALD-1**). LCMS: ES+APCI, Positive $[M+H]^+$ 175.0. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.15 (s, 1H), 9.82 (s, 1H), 8.29 (t, J = 8.40 Hz, 2H), 8.11 (t, J = 6.80 Hz, 2H).

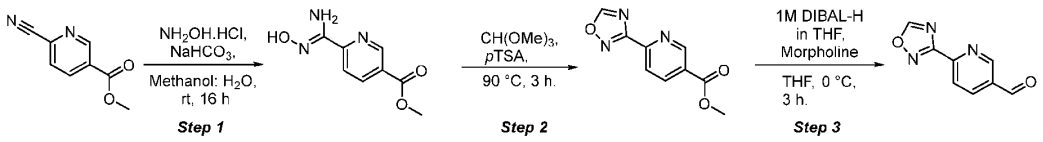
Example 70: Synthesis of 4-cyclopropoxybenzaldehyde (ALD-2)



Step 1: **Synthesis of 4-cyclopropoxybenzaldehyde (ALD-2)**

To a stirred solution of 4-hydroxybenzaldehyde (0.5 g, 4.09 mmol) and bromocyclopropane (0.743 g, 6.14 mmol) in NMP (5 mL) was added cesium carbonate (2.67 g, 8.19 mmol) and the reaction mixture was irradiated under microwave at 200 °C for 2h. The reaction mixture was quenched with H_2O (50 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by Biotage column chromatography (100-200 silica) and ethyl acetate and hexane (0-100%) as eluent. The pure fractions containing product were collected and concentrated to afford 4-cyclopropoxybenzaldehyde (**ALD-2**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 163.1. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.89 (s, 1H), 7.89 (d, J = 2.40 Hz, 2H), 7.25 (d, J = 2.00 Hz, 2H), 4.01-3.98 (m, 1H), 0.88-0.85 (m, 2H), 0.73-0.71 (m, 2H).

Example 71: Synthesis of 6-(1,2,4-oxadiazol-3-yl)nicotinaldehyde (ALD-4)



Step 1: **Synthesis of methyl (Z)-6-(N'-hydroxycarbamimidoyl)nicotinate**

To a stirred solution of hydroxylamine hydrochloride (0.429 g, 6.17 mmol, 2 equiv) in water (5 mL) at 25 °C was added sodium bicarbonate (0.518 g, 6.17 mmol, 2 equiv). The mixture was stirred for 15

min. A solution of methyl 6-cyanonicotinate (0.5 g, 3.08 mmol, 1 equiv) in methanol (5 mL) was then added at 25 °C. The reaction was stirred for 16 h and then filtered to remove the solid byproduct. The filtrate was concentrated under reduced pressure to afford methyl 6-(N-hydroxycarbamimidoyl)nicotinate. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 196.1; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.24 (s, 1H), 9.06 (d, J = 1.4 Hz, 1H), 8.28 (dd, J = 2.2, 8.4 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 5.95 (br. s, 2H), 4.02-3.75 (m, 3H).

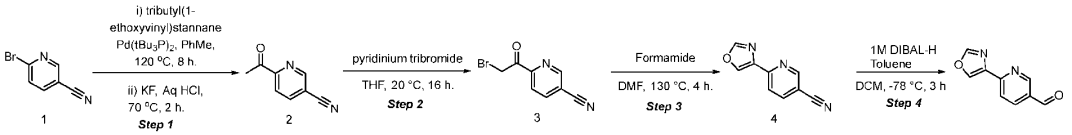
Step 2: **Synthesis of methyl 6-(1,2,4-oxadiazol-3-yl)nicotinate**

To a stirred solution of methyl 6-(N-hydroxycarbamimidoyl)nicotinate (2.00 g, 10.25 mmol, 1 equiv) in trimethyl orthoformate (8.50 mL, 77.0 mmol, 7.5 equiv) was added toluene-4-sulfonic acid monohydrate (0.195 g, 1.03 mmol, 0.1 equiv) at 25 °C. The reaction mixture was then heated to 90 °C and stirred for 3 h. The volatiles were evaporated under reduced pressure and the crude residue was was diluted with ice-cold water, resulting in the formation of a solid. This solid was filtered and dried under reduced pressure to afford methyl 6-(1,2,4-oxadiazol-3-yl)nicotinate. LCMS: m/z: MM-ES+APCI, positive $[M+H]^-$ 206.2; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.86 (s, 1H), 9.25 (d, J = 1.7 Hz, 1H), 8.53 (dd, J = 2.1, 8.2 Hz, 1H), 8.27 (d, J = 8.1 Hz, 1H), 3.94 (s, 4H).

Step 3: **Synthesis of 6-(1,2,4-oxadiazol-3-yl)nicotinaldehyde (ALD-4)**

To a stirred solution of morpholine (0.97 mL, 11.21 mmol, 2.3 equiv) in THF (12.5 mL) at 0 °C was added DIBAL-H (10.72 mL, 10.72 mmol, 2.2 equiv). The reaction mixture was stirred at 0 °C for 2 h. Then, a solution of methyl 6-(1,2,4-oxadiazol-3-yl)nicotinate (1.00 g, 4.80 mmol, 1 equiv) in THF (12.5 mL) was added to the reaction mixture, which was then stirred at 0 °C for 1 hour. After that, DIBAL-H (5.85 mL, 5.85 mmol, 1.1 equiv) was added and the reaction stirred at 0 °C for an additional 1 h. Upon completion, the mixture was slowly quenched with 1.5 N HCl (~100 mL) at 0 °C and extracted with ethyl acetate (EtOAc, 2 × 100 mL). The pooled organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure, The crude compound was purified using a Biotage Isolera system with a 100-200 mesh silica gel cartridge (120 g), eluting with a gradient of ethyl acetate in hexane (40%-80%). This provided 6-(1,2,4-oxadiazol-3-yl)nicotinaldehyde (**ALD-4**). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 176.0; ^{1}H NMR (400 MHz, DMSO-d_6): δ ^{1}H NMR (401 MHz, DMSO-d_6) δ = 10.28-10.15 (m, 1H), 9.87 (s, 1H), 9.36-9.12 (m, 1H), 8.49 (dd, J = 2.1, 8.1 Hz, 1H), 8.34 (d, J = 7.9 Hz, 1H).

Example 72: Synthesis of 6-(oxazol-4-yl)nicotinaldehyde (ALD-5)



Step 1: **Synthesis of 6-acetylnicotinonitrile**

To a stirred solution of 6-bromonicotinonitrile (5.00 g, 27.3 mmol, 1.00 equiv) in toluene (40 mL) was added tributyl(1-ethoxyvinyl)stannane (10.15 mL, 30.1 mmol, 1.10 equiv) at 25 °C. The reaction mixture was degassed with argon for 5 min. Bis(triphenylphosphine)palladium(II) dichloride (0.959 g, 1.37 mmol, 0.05 equiv) was added at 25 °C, and the mixture was stirred at 120 °C for 8 h. The reaction mixture was then cooled to room temperature, and aqueous potassium fluoride (25 mL) was added and stirred for 30 min. Aqueous hydrochloric acid (50 mL) was then added, and the mixture was heated to 70 °C for 2 h. After cooling to room temperature, the mixture was extracted with ethyl acetate (2 × 200 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate, and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (100-200 mesh) using a gradient of ethyl acetate in hexane (0-20%) as the eluent to afford 6-acetylnicotinonitrile. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 147.0; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.31-9.09 (m, 1H), 8.52 (dd, J = 2.1, 8.1 Hz, 1H), 8.08 (dd, J = 0.8, 8.1 Hz, 1H), 3.32 (s, 1H), 2.67 (s, 3H).

Step 2: **Synthesis of 6-(2-bromoacetyl)nicotinonitrile**

To a stirred solution of 6-acetylnicotinonitrile (3.40 g, 23.26 mmol, 1.00 equiv) in tetrahydrofuran (4 mL) was added pyridinium tribromide (7.44 g, 23.26 mmol, 1.00 equiv) at 25 °C. The reaction mixture was stirred at 25 °C for 16 h. The reaction mixture was quenched with aqueous saturated sodium thiosulfate (50 mL). The aqueous layer was extracted with ethyl acetate (2 × 200 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (100-200 mesh) using a gradient of ethyl acetate in hexane (0-20%) as the eluent to yield 6-(2-bromoacetyl)nicotinonitrile. LCMS: m/z: MM-ES+APCI, positive $[M+2H]^+$ 224.9; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.22 (dd, J = 1.0, 2.1 Hz, 1H), 8.57 (dd, J = 2.1, 8.1 Hz, 1H), 8.17 (dd, J = 0.9, 8.2 Hz, 1H), 5.04 (s, 2H).

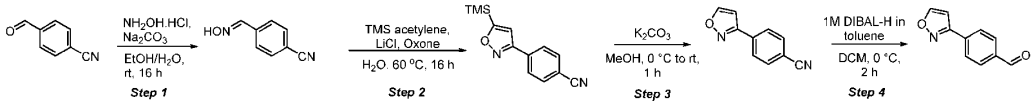
Step 3: **Synthesis of 6-(oxazol-4-yl)nicotinonitrile**

To a stirred solution of 6-(2-bromoacetyl)nicotinonitrile (2.57 g, 11.42 mmol, 1.00 equiv) in DMF (12.5 mL) at 25 °C, formamide (12.79 mL, 322 mmol, 28.2 equiv) was added. The reaction mixture was heated to 130 °C and stirred for 4 h. The reaction mixture was concentrated under reduced pressure and the crude material was purified by reverse-phase column chromatography using a C18 cartridge (330 g), with a gradient elution of 0.1% ammonium acetate in water and acetonitrile. The pure fractions were concentrated under reduced pressure to afford 6-(oxazol-4-yl)nicotinonitrile. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 171.2; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.92 (d, J = 1.4 Hz, 1H), 8.25 (dd, J = 2.1, 8.3 Hz, 1H), 8.00 (d, J = 8.3 Hz, 1H), 7.87 (dd, J = 0.8, 18.0 Hz, 2H).

Step 4: **Synthesis of 6-(oxazol-4-yl)nicotinaldehyde (ALD-5)**

To a stirred solution of 6-(oxazol-4-yl)nicotinonitrile (0.470 g, 2.47 mmol, 1 equiv) in DCM (15 mL) was added DIBAL-H in toluene (7.2 mL, 7.4 mmol, 3 equiv) at 0 °C and stirred at 25 °C for 1 h. The progress of the reaction was monitored by LCMS. Upon completion, the reaction mixture was quenched with ethyl acetate (10 mL). The mixture was then concentrated under reduced pressure and the crude material was purified by reverse-phase column chromatography on a C18 cartridge, eluted with a gradient of 0.1% ammonium acetate in water and acetonitrile. Pure fractions were concentrated under reduced pressure to yield 6-(oxazol-4-yl)nicotinaldehyde (**ALD-5**). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 175.1.

Example 73: Synthesis of 4-(isoxazol-3-yl)benzaldehyde (ALD-6)



Step 1: **Synthesis of (Z)-4-((hydroxyimino)methyl)benzonitrile**

To a stirred solution of sodium carbonate (4.85 g, 45.8 mmol, 1.2 equiv) in water (50 mL) was added hydroxylamine hydrochloride (3.18 g, 45.8 mmol, 1.2 equiv), followed by the addition of 4-formylbenzonitrile (5 g, 38.1 mmol, 1 equiv) in ethanol (50 mL) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated and the aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford crude (Z)-4-((hydroxyimino)methyl)benzonitrile. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 147.0; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.25 (s, 1H), 7.90-7.83 (m, 2H), 7.81-7.72 (m, 2H).

Step 2: **Synthesis of 4-(5-(trimethylsilyl)isoxazol-3-yl)benzonitrile**

In a 100 mL two-neck round-bottom flask, trimethylsilyl acetylene (2.88 mL, 20.53 mmol, 1.5 equiv) was added to a solution of (Z)-4-((hydroxyimino)methyl)benzonitrile (2 g, 13.68 mmol, 1 equiv) in water (30 mL). Lithium chloride (0.580 g, 13.68 mmol, 1 equiv) was added portion-wise, followed by oxone (12.62 g, 20.53 mmol, 1.5 equiv) under a nitrogen atmosphere at 60 °C. The reaction mixture was stirred for 16 h. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain the crude product. The crude product was purified by flash column chromatography (100-200 mesh size) using (0 to 10%) hexane ethyl acetate as the eluent to obtain the desired product. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 243.0; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.14-8.05 (m, 2H), 8.02-7.94 (m, 2H), 7.45 (s, 1H), 0.42-0.32 (m, 9H).

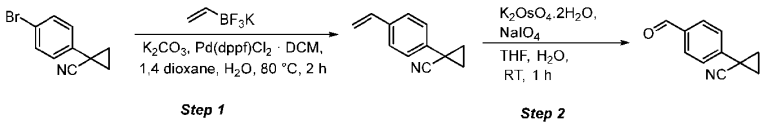
Step 3: **Synthesis of 4-(isoxazol-3-yl)benzonitrile**

To a stirred solution of 4-(5-(trimethylsilyl)isoxazol-3-yl)benzonitrile (1.3 g, 5.36 mmol, 1 equiv) in methanol (17 mL) at 0 °C under a nitrogen atmosphere, potassium carbonate (1.11 g, 8.05 mmol, 1.5 equiv) was added. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under vacuum to afford the crude product. The crude product was then dissolved in water (10 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to yield 4-(isoxazol-3-yl)benzonitrile. Quantitative yield was assumed. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 170.9; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.19-9.00 (m, 1H), 8.14-8.07 (m, 2H), 8.04-7.98 (m, 2H), 7.30 (d, J = 1.6 Hz, 1H).

Step 4: **Synthesis of 4-(isoxazol-3-yl)benzaldehyde (ALD-6)**

To a stirred solution of 4-(isoxazol-3-yl)benzonitrile (0.4 g, 2.35 mmol, 1 equiv) in DCM (5 mL) at 0 °C under a nitrogen atmosphere was added dropwise a solution of DIBAL-H (2.35 mL, 2.35 mmol, 1 M in toluene, 1 equiv). The reaction mixture was stirred at room temperature for 1 h, after which an additional portion of DIBAL-H (2.35 mL, 2.35 mmol, 1 M in toluene, 1 equiv) was added. The reaction mixture was stirred at room temperature for an additional 2 h. The reaction mixture was quenched with 1.5 N HCl solution (50 mL) and extracted with DCM (2 × 100 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude product. The crude compound was purified by flash chromatography on a Biotage Isolera system using a silica gel cartridge (120 g) and eluting with ethyl acetate in hexane (2-4%). The pure fractions were concentrated to afford 4-(isoxazol-3-yl)benzaldehyde (**ALD-6**, 0.2 g, 1.15 mmol, 49% yield). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 174.0; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.10 (s, 1H), 8.55 (d, J = 1.7 Hz, 1H), 8.17-7.75 (m, 4H), 6.77 (d, J = 1.7 Hz, 1H).

Example 74: Synthesis of 1-(4-formylphenyl) cyclopropane-1-carbonitrile (ALD-7)



Step 1: **Synthesis of 1-(4-vinylphenyl) cyclopropane-1-carbonitrile**

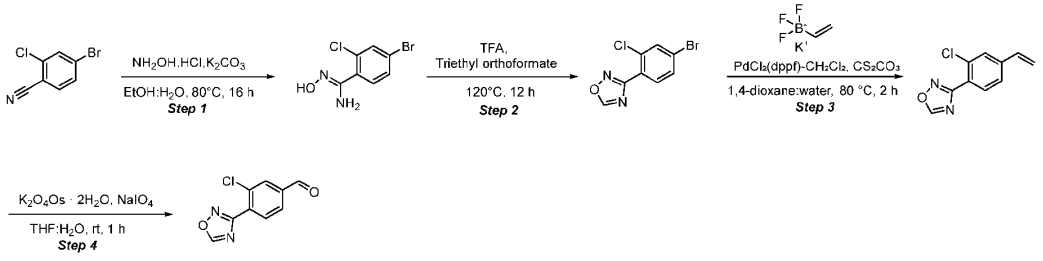
To a stirred solution of 4-bromo-2-(2-methoxyethoxy) benzonitrile and trifluoro(vinyl)-λ⁴-borane, potassium salt (379 mg, 2.83 mmol) in 1,4-dioxane (0.9 mL) and water (0.1 mL), was added potassium carbonate (622 mg, 4.50 mmol) at room temperature and degassed with N_2 for 10 minutes. 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium (II) dichloromethane complex (165 mg, 0.23 mmol) was then added and the mixture was degassed with N_2 for another 10 minutes. The reaction mixture was then stirred at 80 °C for 2 h. The reaction mixture was filtered through a pad of Celite and washed with

ethyl acetate (2 × 30 mL). The organic layer was combined with the previous batch and concentrated under reduced pressure to obtain the crude product. The crude compound was purified by flash column chromatography using Biotage Isolera using a 100-200 mesh silica gel cartridge (10 g) with 2-5% ethyl acetate in hexane as the eluent. The pure fractions were concentrated under reduced pressure to obtain 1-(4-vinylphenyl) cyclopropane-1-carbonitrile. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.52 (d, J = 10.00 Hz, 2H), 7.46 (d, J = 2.00 Hz, 2H), 6.68-6.75 (m, 1H), 5.77 (d, J = 9.60 Hz, 1H), 5.29 (d, J = 9.60 Hz, 1H), 1.71-1.78 (m, 2H), 1.39-1.44 (m, 2H).

Step 2: **Synthesis of 1-(4-formylphenyl) cyclopropane-1-carbonitrile (ALD-7)**

To a stirred solution of 1-(4-vinylphenyl) cyclopropane-1-carbonitrile (350 mg, 2.07 mmol) in THF (1 mL) and water (0.2 mL) was added sodium periodate (403 mg, 1.89 mmol) and potassium osmate dihydrate (19.05 mg, 0.052 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was quenched with water (30 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by flash column chromatography (Biotage Isolera) using a 100-200 mesh silica gel cartridge (10 g) with 5-10% ethyl acetate in n-hexane as the eluent. The pure fractions were collected and concentrated under reduced pressure to afford 1-(4-formylphenyl) cyclopropane-1-carbonitrile (**ALD-7**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 172.0; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.03 (s, 1H), 7.90 (d, J = 2.00 Hz, 2H), 7.46 (d, J = 1.60 Hz, 2H), 1.87-1.91 (m, 2H), 1.53-1.58 (m, 2H).

Example 75: Synthesis of 3-chloro-4-(1,2,4-oxadiazol-3-yl)benzaldehyde (ALD-8)



Step 1: **Synthesis of (Z)-4-bromo-2-chloro-N'-hydroxybenzimidamide**

To a stirred solution of 4-bromo-2-chlorobenzonitrile (1 g, 4.62 mmol) in ethanol (10 mL) and water (1 mL), hydroxylamine hydrochloride (0.963 g, 13.86 mmol) and K_2CO_3 (3.19 g, 23.10 mmol) were added at 25 °C. The resulting reaction mixture was stirred at 80 °C for 12 h. The reaction mixture was poured into water to precipitate the compound. The precipitate was filtered through a Büchner funnel and

washed with MTBE. LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2H]^+$ 248.9, 250.9, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.51 (s, 1H), 7.66-7.57 (m, 1H), 7.41-7.34 (m, 2H), 5.87 (s, 2H).

Step 2: **Synthesis of 3-(4-bromo-2-chlorophenyl)-1,2,4-oxadiazole**

To a stirred solution of 4-bromo-2-chloro-N-hydroxybenzimidamide (0.45 g, 1.80 mmol) in triethyl orthoformate (13.37 g, 90 mmol) was added TFA (0.206 g, 1.804 mmol). The resulting reaction mixture was stirred at 120 °C for 12 h. The solvent was concentrated under reduced pressure. The crude product was quenched with $NaHCO_3$ (50 mL) and extracted with ethyl acetate (2 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (100-200 mesh), eluting with 12% ethyl acetate in hexane. The collected pure fractions were concentrated under reduced pressure to afford 3-(4-bromo-2-chlorophenyl)-1,2,4-oxadiazole. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.82 (s, 1H), 8.02 (s, 1H), 7.90 (d, J = 8.40 Hz, 1H), 7.79 (d, J = 2.00 Hz, 1H).

Step 3: **Synthesis of 3-(2-chloro-4-vinylphenyl)-1,2,4-oxadiazole**

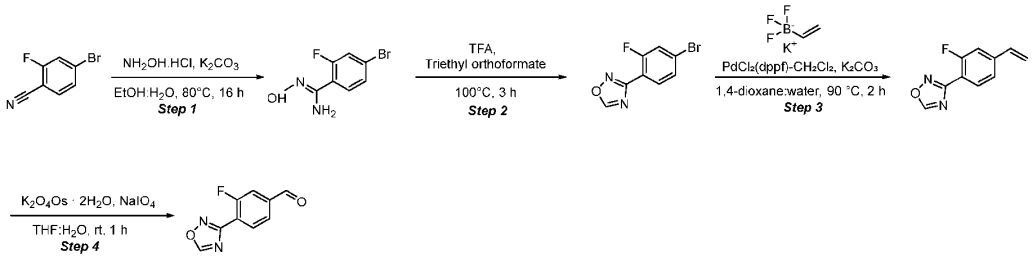
To a stirred solution of 3-(4-bromo-2-chlorophenyl)-1,2,4-oxadiazole (500 mg, 1.93 mmol) and potassium trifluorovinyl borate (310 mg, 2.31 mmol) in 1,4-dioxane (7 mL) and water (0.7 mL), was added cesium carbonate (1.26 g, 3.85 mmol) at rt and the mixture was purged with N_2 gas for 10 min. Then, $PdCl_2$(dppf)-CH_2Cl_2 adduct (157 mg, 0.19 mmol) was added and the mixture was further purged for 5 min. The reaction mixture was heated to 80 °C for 2 h. The solvent was concentrated under reduced pressure and purified by column chromatography using (100-200 silica mesh) eluting with 16 % of ethyl in hexane. Pure fractions were concentrated under reduced pressure to afford 3-(2-chloro-4-vinylphenyl)-1,2,4-oxadiazole. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.81 (t, J = 8.40 Hz, 1H), 7.93 (t, J = 6.00 Hz, 1H), 7.68 (d, J = 1.20 Hz, 2H), 6.88-6.82 (m, 1H), 6.12-6.08 (m, 1H), 5.51-5.48 (m, 1H).

Step 4: **Synthesis of 3-chloro-4-(1,2,4-oxadiazol-3-yl)benzaldehyde (ALD-8)**

To a stirred solution of 3-(2-chloro-4-vinylphenyl)-1,2,4-oxadiazole (500 mg, 2.42 mmol) in THF (7 mL) and water (2.33 mL) was added sodium periodate (776 mg, 3.63 mmol) and potassium osmate dihydrate (22.29 mg, 0.060 mmol) at 0 °C. The resulting reaction mixture was stirred at 25 °C for 1 h. The solvent was concentrated under reduced pressure and the residue was quenched with water (50 mL) and extracted with ethyl acetate (2 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (100-200 mesh), eluting with 14% ethyl acetate in hexane. The collected pure fractions were concentrated under reduced pressure to afford 3-chloro-4-(1,2,4-oxadiazol-3-yl) benzaldehyde (**ALD-8**).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.10 (s, 1H), 9.88 (s, 1H), 8.19 (d, J = 8.00 Hz, 2H), 8.05 (d, J = 1.60 Hz, 1H).

Example 76: Synthesis of 3-fluoro-4-(1,2,4-oxadiazol-3-yl)benzaldehyde (ALD-9)



Step 1: **Synthesis of (Z)-4-bromo-2-fluoro-N'-hydroxybenzimidamide**

To a stirred solution of 4-bromo-2-fluorobenzonitrile (5 g, 25 mmol) in ethanol (20 mL) and water (2 mL), hydroxylamine hydrochloride (5.21 g, 75.0 mmol) and K_2CO_3 (17.27 g, 125 mmol) were added at 25 °C. The resulting reaction mixture was stirred at 80 °C for 16 h. The reaction was concentrated and quenched with ice water. The obtained solid was filtered and dried to yield (Z)-4-bromo-2-fluoro-N'-hydroxybenzimidamide. LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2H]^+$ 232.8, 234.9, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.73 (s, 1H), 7.70-7.62 (m, 1H), 7.52-7.45 (m, 2H), 5.85 (s, 2H).

Step 2: **Synthesis of 3-(4-bromo-2-fluorophenyl)-1,2,4-oxadiazole**

To a stirred solution of 4-bromo-2-fluoro-N-hydroxybenzimidamide (500 mg, 2.15 mmol) in triethyl orthoformate (7 mL, 2.146 mmol) was added TFA (0.5 mL, 2.15 mmol) at room temperature. The resulting reaction mixture was stirred at 100 °C for 3 h. The reaction mixture was poured into a saturated $NaHCO_3$ solution (100 mL) and extracted with ethyl acetate (2 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. This crude product was purified by Isolera Biotage column chromatography using silica gel (100-200 mesh), eluting with 50% ethyl acetate in petroleum ether. The collected pure fractions were concentrated under reduced pressure to afford 3-(4-bromo-2-fluorophenyl)-1,2,4-oxadiazole. LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2H]^+$ 243, 245, ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.84 (s, 1H), 8.03-7.99 (m, 1H), 7.49 (d, J = 8.40 Hz, 2H).

Step 3: **Synthesis of 3-(2-fluoro-4-vinylphenyl)-1,2,4-oxadiazole**

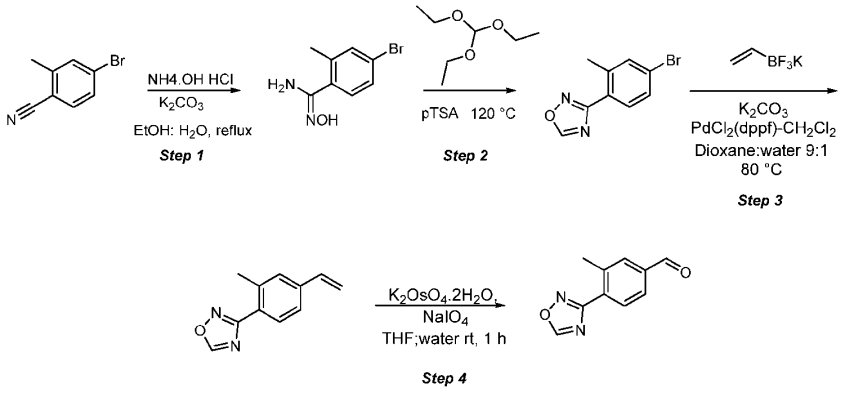
To a stirred solution of 3-(4-bromo-2-fluorophenyl)-1,2,4-oxadiazole 3-(4-bromo-2-fluorophenyl)-1,2,4-oxadiazole (50 mg, 0.21 mmol) and potassium vinyltrifluoroborate (41.3 mg, 0.31 mmol) in 1,4-dioxane (2 mL) and water (0.25 mL) was added K_2CO_3 (56.9 mg, 0.41 mmol). The resulting reaction mixture was degassed with argon for 15 min. Then, $PdCl_2$(dppf)-CH_2Cl_2 adduct (16.80 mg, 0.021 mmol) was added and the mixture was degassed with argon for another 15 min. The reaction mixture was heated

at 90 °C for 2 h. The reaction mixture was filtered through a celite bed, washed with ethyl acetate (50 mL), and extracted with water (2 × 20 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by normal phase column chromatography using silica gel (100-200 mesh), eluting with 15% ethyl acetate in hexane. The collected pure fractions were concentrated under reduced pressure to afford 3-(2-fluoro-4-vinylphenyl)-1,2,4-oxadiazole. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 191.0, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.83 (s, 1H), 8.09-8.05 (m, 1H), 7.47-7.28 (m, 2H), 6.79-5.93 (m, 1H), 5.91 (d, J = 17.60 Hz, 1H), 5.46 (d, J = 10.80 Hz, 1H).

Step 4: **Synthesis of 3-fluoro-4-(1,2,4-oxadiazol-3-yl)benzaldehyde (ALD-9)**

To a stirred solution of 3-(2-fluoro-4-vinylphenyl)-1,2,4-oxadiazole (190 mg, 0.99 mmol) in THF (9 mL) and water (3 mL) was added sodium periodate (321 mg, 1.49 mmol) and potassium osmate dihydrate (9.20 mg, 0.025 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 1 h. The reaction mixture was poured into cooled water (100 mL) and extracted with ethyl acetate (2 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. This crude product was purified by Isolera Biotage column chromatography using neutral alumina mesh, eluting with 30% ethyl acetate in petroleum ether. Pure fractions were concentrated under reduced pressure to afford 3-fluoro-4-(1,2,4-oxadiazol-3-yl)benzaldehyde (**ALD-9**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 193.0, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.10 (s, 1H), 8.90 (s, 1H), 8.36-8.32 (m, 1H), 7.78 (d, J = 1.60 Hz, 1H), 7.28 (m 1H).

Example 77: Synthesis of 3-methyl-4-(1,2,4-oxadiazol-3-yl)benzaldehyde (ALD-10)



Step 1: **Synthesis of (E)-4-bromo-N'-hydroxy-2-methylbenzimidamide**

To a stirred solution of 4-bromo-2-methylbenzonitrile (5 g, 25.5 mmol) in ethanol (40 mL) and water (4 mL) was added hydroxylamine hydrochloride (5.32 g, 77 mmol) and K_2CO_3 (17.62 g, 128 mmol)

at 25 °C. The resulting reaction mixture was stirred at 80 °C for 12 h. The reaction mixture was concentrated under reduced pressure to obtain the crude product. The crude compound was extracted with ethyl acetate (2 × 50 mL) and washed with brine solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was triturated with hexane (10 mL) and dried under vacuum to afford (E)-4-bromo-N'-hydroxy-2-methylbenzimidamide. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 231.1; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.41 (s, 1H), 7.76-7.43 (m, 2H), 7.22 (d, J = 8.00 Hz, 1H), 5.77 (s, 2H), 2.34 (s, 3H).

Step 2: **Synthesis of 3-(4-bromo-2-methylphenyl)-1,2,4-oxadiazole**

To a stirred solution of (E)-4-bromo-N'-hydroxy-2-methylbenzimidamide (2 g, 8.73 mmol) in triethyl orthoformate (64.7 g, 437 mmol) at 25 °C was added pyridinium p-toluene sulfonate (1.09 g, 4.37 mmol). The resulting reaction mixture was stirred at 120 °C for 12 h. The reaction mixture was concentrated under reduced pressure to obtain the crude product. The crude compound was extracted with ethyl acetate (2 × 100 mL) and washed with brine solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by Isolera Biotage column chromatography using 100-200 mesh silica gel, eluted with 5% ethyl acetate in hexane. The collected pure fractions were concentrated to yield 3-(4-bromo-2-methylphenyl)-1,2,4-oxadiazole. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.75 (s, 1H), 7.89 (dd, J = 8.00 Hz, 1H), 7.71 (s, 1H), 7.61 (s, 1H), 2.57 (s, 3H),

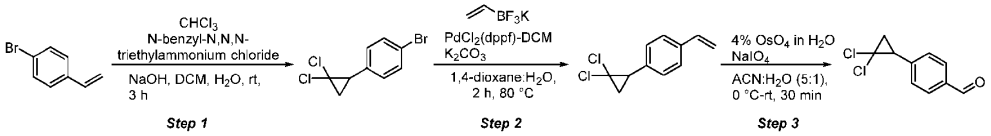
Step 3: **Synthesis of 3-(4-bromo-2-methylphenyl)-1,2,4-oxadiazole**

A stirred solution of 3-(4-bromo-2-methylphenyl)-1,2,4-oxadiazole (1.5 g, 6.27 mmol), potassium trifluoroborate (1.185 g, 9.41 mmol), K_2CO_3 (2.168 g, 15.69 mmol) in 1,4-dioxane (9.5 mL) and water (0.5 mL) was degassed with N_2 at room temperature. $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.512 g, 0.627 mmol) was added and the reaction mixture was stirred at 85 °C for 1 hour in a microwave reactor. The reaction mixture was concentrated under reduced pressure to obtain the crude product. The crude compound was extracted with ethyl acetate (2 × 100 mL) and washed with brine solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by Isolera Biotage column chromatography using 100-200 mesh silica gel, eluted with 5% ethyl acetate in hexane. The collected pure fractions were concentrated under reduced pressure to yield 3-(2-methyl-4-vinylphenyl)-1,2,4-oxadiazole. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 187.2; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.71 (s, 1H), 7.95 (d, J = 8.00 Hz, 1H), 7.54-7.50 (m, 2H), 6.79 (dd, J = 10.80, 17.60 Hz, 1H), 5.99 (d, J = 0.40 Hz, 1H), 5.40 (d, J = 11.20 Hz, 1H), 2.59 (s, 1H),

Step 4: **Synthesis of 3-methyl-4-(1,2,4-oxadiazol-3-yl) benzaldehyde (ALD-10)**

To a stirred solution of 3-(2-methyl-4-vinylphenyl)-1,2,4-oxadiazole (870 mg, 4.67 mmol) in THF (20 mL) and water (4.00 mL) was added sodium periodate (1499 mg, 7.01 mmol) at 25 °C. Potassium osmate dihydrate (43.0 mg, 0.12 mmol) was then added to the reaction mixture, which was stirred at 25 °C for 1 hour. The reaction mixture was directly concentrated under reduced pressure to obtain the crude product. The crude compound was purified by Isolera Biotage column chromatography using 100-200 mesh silica gel, eluted with 5% ethyl acetate in hexane. The collected pure fractions were concentrated under reduced pressure to yield 3-methyl-4-(1,2,4-oxadiazol-3-yl) benzaldehyde (**ALD-10**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 189; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.09 (s, 1H), 9.81 (s, 1H), 8.17 (d, J = 8.00 Hz, 1H), 7.97 (s, 1H), 7.93 (d, J = 8.00 Hz, 1H), 2.67 (s, 3H).

Example 78: Synthesis of 4-(2,2-dichlorocyclopropyl) benzaldehyde (ALD-12)



Step 1: **Synthesis of 1-bromo-4-(2,2-dichlorocyclopropyl) benzene**

To a stirred solution of 1-bromo-4-vinylbenzene (3.57 mL, 27.3 mmol) in chloroform (60 mL) under a nitrogen atmosphere was added benzyltriethylammonium chloride (0.18 g, 0.82 mmol) at 0 °C. Sodium hydroxide (NaOH, 32.8 g, 819 mmol) was then added at 0 °C. The resulting reaction mixture was stirred at room temperature for 3 h. After completion of reaction, the reaction mixture was quenched with saturated aqueous ammonium chloride solution (100 mL). The aqueous layer was extracted with dichloromethane (3 × 200 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered. The solvent was concentrated under reduced pressure to obtain the crude compound. The crude product was purified by flash column chromatography using hexane (100%) as the eluent to obtain the desired product, 1-bromo-4-(2,2-dichlorocyclopropyl) benzene. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.58 (dd, J = 14.20, 5.20 Hz, 2H), 7.40 (dd, J = 15.20, 2.80 Hz, 2H), 3.14 (t, J = 8.40 Hz, 1H), 2.20-2.12 (m, 1H), 2.10-2.07 (m, 1H).

Step 2: **Synthesis of 1-(2,2-dichlorocyclopropyl)-4-vinylbenzene**

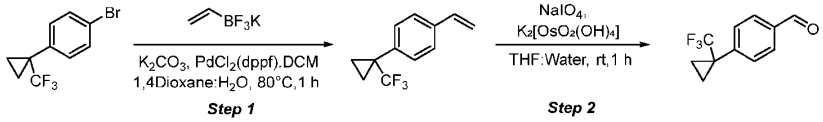
To a stirred solution of 1-bromo-4-(2,2-dichlorocyclopropyl)benzene (2 g, 7.52 mmol), trifluoro(vinyl)-l4-borane, potassium salt (1.51 g, 11.28 mmol), K_2CO_3 (3.12 g, 22.56 mmol) in 1,4-dioxane (20 mL) and water (2.22 mL) was added $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.61 g, 0.75 mmol) at room temperature and the reaction mixture was stirred at 80 °C for 2 h. The reaction mixture was quenched with water (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain the crude compound. The crude product was purified by flash column chromatography using hexane (100%) as the eluent to

afford 1-(2,2-dichlorocyclopropyl)-4-vinylbenzene. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.42 (d, J = 8.0 Hz, 2H), 7.23 (dd, J = 8.40, Hz, 2H), 6.73 (t, J = 17.6, 10.80 Hz, 1H), 5.78 (d, J = 17.6 Hz, 1H), 5.29 (d, J = 11.20 Hz, 1H), 2.93 (dd, J =10.4, 8.4 Hz, 1H), 2.02-199 (m, 1H), 1.88-182 (m, 1H).

Step 3: **Synthesis of 4-(2,2-dichlorocyclopropyl) benzaldehyde (ALD-12)**

To a stirred solution 1-(2,2-dichlorocyclopropyl)-4-vinylbenzene (0.50 g, 1.92 mmol), in water (0.056 mL) and acetonitrile (0.5 mL) was added sodium periodate (0.42 g, 1.92 mmol) and osmium (VIII) oxide (0.29 mL, 0.038 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (50 mL), extracted with DCM (3x 50 mL). The combined organic layer was dried, over sodium sulphate and concentrated under reduced pressure to obtain the crude compound. The crude compound was purified by flash column chromatography using ethyl acetate in hexane (10 to 12%) as an eluent to obtain desired product 4-(2,2-dichlorocyclopropyl) benzaldehyde (**ALD-12**). LCMS m/z: MM-ES+APCI, positive $[M+2H]^+$ 216.2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.05 (s, 1H), 7.91 (dd, J = 8.00 Hz, 2H), 7.45 (dd, J =8.40 Hz, 2H), 3.02-2.92 (m, 1H), 2.11-2.07 (m, 1H), 1.98-1.95 (m, 1H).

Example 79: Synthesis of 4-(1-(trifluoromethyl)cyclopropyl)benzaldehyde (ALD-13)



Step 1: **Synthesis of 1-(1-(trifluoromethyl)cyclopropyl)-4-vinylbenzene**

To a stirred solution of 1-bromo-4-(1-(trifluoromethyl)cyclopropyl)benzene (0.10 g, 0.37 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was added trifluoro(vinyl)-λ_4-borane potassium salt (0.061 g, 0.45 mmol) and K_2CO_3 (0.078 g, 0.56 mmol) at 25 °C. The mixture was purged with N_2 for 5 minutes. To this reaction mixture, $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.031 g, 0.038 mmol) was added and purged with N_2 for another 5 min. The resulting reaction mixture was heated at 80 °C for 1 h. After completion of the reaction as confirmed by TLC, the reaction mass was filtered through a Celite bed and washed with ethyl acetate (20 mL) and water (10 mL). The organic layer was concentrated under reduced pressure to afford the crude product 1-(1-(trifluoromethyl)cyclopropyl)-4-vinylbenzene, which was carried forward without purification. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.48-7.34 (m, 4H), 6.73 (q, J = 10.80 Hz, 1H), 5.78 (d, J = 17.60 Hz, 1H), 5.29 (d, J = 10.80 Hz, 1H), 1.37-1.37 (m, 2H), 1.04-1.02 (m, 2H).

Step 2: **Synthesis of 4-(1-(trifluoromethyl)cyclopropyl)benzaldehyde (ALD-13)**

To a stirred solution of 1-(1-(trifluoromethyl)cyclopropyl)-4-vinylbenzene (100 mg, 0.47 mmol) in THF (0.6 mL) and water (0.2 mL) was added potassium osmate dihydrate (17.36 mg, 0.047 mmol) and

sodium periodate (302 mg, 1.41 mmol) at 25 °C. The resulting reaction mixture was stirred at 25 °C for 1 h. The reaction was concentrated under reduced pressure and extracted with ethyl acetate (20 mL), then washed with water (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford the crude product 4-(1-(trifluoromethyl)cyclopropyl)benzaldehyde (**ALD-13**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 215.

Example 80: General procedure A- Reductive amination

To a stirred solution of the amine or the amine hydrochloride (0.1 mmol, 1.0 equiv) in DMF (1 mL) and the aldehyde (0.12 mmol, 1.2 equiv) was added sodium triacetoxyborohydride (0.3 mmol, 3.0 equiv) and the resulting mixture was stirred for 16 h. The reaction mixture was then concentrated under reduced pressure to afford crude compound, which was purified by reverse phase chromatography [(Column: X select (150 mm × 19) 5 μm, eluting with Mobile phase A: 0.05% FA or HCl in H_2O, Mobile phase B: ACN, flow rate: 15 mL/min)]. The fractions containing pure product were combined and concentrated via lyophilization to afford the desired product as the formic acid salt, the hydrochloric salt, or the free amine.

The following compounds in Table 3 were prepared from corresponding amine or amine hydrochloride and aldehyde according to a reductive amination procedure described in General Procedure A.

Table 3:

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
INT-2	4-formylbenzonitrile	4-((4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-4-hydroxy-piperidin-1-yl)methyl)benzonitrile, AcOH (**I-10**)	Positive $[M+H]^+$ = 477	^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.96 (br s, 1H), 7.86-7.80 (m, 3H), 7.59-7.55 (m, 3H), 5.30 (s, 1H), 5.14-5.09 (m, 1H), 4.55 (d, J = 17.20 Hz, 1H), 4.37 (d, J = 17.20 Hz, 1H), 3.62 (s, 2H), 2.95-2.87 (m, 1H), 2.63-2.59 (m, 3H), 2.43-2.42 (m, 3H), 2.30-2.24 (m, 2H), 2.03-1.99 (m, 1H), 1.88 (s, 2H), 1.64-1.60 (m, 2H).
INT-2	4-(trifluoromet	3-(4-fluoro-5-(4-hydroxy-1-(4-	Positive $[M+H]^+$ = 520	^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 10.38 (s, 1H), 7.89-7.81 (m,

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
	hyl)benzaldehyde	(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-2**)		5H), 7.63 (dd, *J* = 8.00, Hz, 1H), 5.11-5.10 (m, 1H), 4.59-4.37 (m, 4H), 3.36 (s, 4H), 2.95-2.88 (m, 1H), 2.68-2.59 (m, 3H), 2.47-2.45 (m, 2H), 2.02-1.99 (m, 1H), 1.88 (d, *J* = 15.20 Hz, 2H).
INT-2	4-(trifluoromethoxy)benzaldehyde	3-(4-fluoro-5-(4-hydroxy-1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-12**)	Positive $[M+H]^+$ = 536.1	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 10.41 (br s, 1H), 7.84-7.78 (m, 3H), 7.63 (d, *J* = 8.00 Hz, 1H), 7.51 (d, *J* = 8.00 Hz, 2H), 5.99 (s, 1H), 5.12 (dd, *J* = 5.20, 13.20 Hz, 1H), 4.56 (d, *J* = 17.60 Hz, 1H), 4.44 (d, *J* = 5.20 Hz, 2H), 4.39 (d, *J* = 17.60 Hz, 1H), 3.46-3.35 (m, 4H), 2.93-2.88 (m, 1H), 2.68-2.55 (m, 3H), 2.51-2.50 (m, 1H), 2.46-2.34 (m, 1H), 2.34-2.02 (m, 2H).
INT-8	4-(1,2,4-oxadiazol-3-yl)benzaldehyde (**ALD-1**)	3-(5-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-182**)	Negative $[M-H]^-$ = 546.39	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 9.78 (s, 1H), 9.68 (bs, 1H), 8.17 (d, J = 8.00 Hz, 2H), 7.88 (d, J = 12.00 Hz, 3H), 7.63 (d, J = 8.00 Hz, 1H), 5.89 (d, J = 6.40 Hz, 1H), 5.14-5.11 (m, 1H), 4.57-4.51 (m, 3H), 4.51-4.37 (m, 1H), 3.34-3.26 (m, 4H), 2.97-2.92 (m, 2H), 2.68-2.63 (m, 1H), 2.59-2.50 (m, 2H), 2.02-1.95 (m, 2H), 1.05 (s, 3H), 0.76 (s, 3H).
INT-5	4-(trifluoromethyl)benzaldehyde	3-(5-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-	Negative $[M-H]^-$ = 528.6	^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 9.65 (br s, 1H), 7.92-7.88 (m, 4H), 7.73-7.66 (m, 2H), 7.61-7.56 (m, 1H), 5.61 (d, J = 4.4 Hz, 1H), 5.12 (dd, J =

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
		oxoisoindolin-2-yl)piperidine-2,6-dione (**I-36**)		5.20, 13.20 Hz, 1H), 4.53-4.44 (m, 3H), 4.35-4.33 (m, 1H), 3.38-3.33 (m, 3H), 2.94-2.89 (m, 3H), 2.68-2.63 (m, 1H), 2.43-2.38 (m, 1H), 2.18-2.2.12 (m, 1H), 1.74-1.68 (m, 1H), 0.93 (s, 3H), 0.75 (s, 3H).
INT-9	4-cyclopropoxybenzaldehyde (**ALD-2**)	3-(5-(1-(4-cyclopropoxybenzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-142**)	Positive $[M+H]^+$ = 564.61	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 7.87-7.84 (m, 1H), 7.54 (d, J = 8.00 Hz, 1H), 7.25 (d, J = 8.40 Hz, 2H), 7.00 (d, J = 8.00 Hz, 2H), 5.08-5.06 (m, 2H), 4.54-4.34 (m, 2H), 3.82-3.80 (m, 1H), 3.42-3.33 (m, 4H), 2.68-2.64 (m, 2H), 2.60-2.56 (m, 2H), 2.52-2.50 (m, 2H), 2.45-2.42 (m, 2H), 2.34-2.27 (m, 2H), 1.86-1.76 (m, 2H), 0.78-0.76 (m, 2H), 0.65-0.63 (m, 2H), 0.58-0.56 (m, 3H), 0.48-0.44 (m, 3H)
INT-9	4-cyclopropylbenzaldehyde	3-(5-(1-(4-cyclopropylbenzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-138**)	Positive $[M+H]^+$ = 548.8	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 8.18 (s, 1H), 8.01 (s, 1H), 7.54 (d, J = 8.00 Hz, 1H), 7.20 (d, J = 8.00 Hz, 2H), 7.03 (d, J = 8.00, Hz, 2H), 5.08-5.06 (m, 2H), 4.54-4.37 (m, 2H), 3.43-35 (m, 5H), 3.02-2.98 (m, 2H), 2.62-2.34 (m, 5H), 2.03-1.97 (m, 2H), 1.91-1.87 (m, 1H), 1.02-0.96 (m, 2H), 0.94-0.91 (m, 2H), 0.66-0.63 (m, 2H), 0.58-0.54 (m, 3H), 0.47-0.43 (m, 3H).
INT-9	benzaldehyde	3-(5-(1-benzyl-3,3-diethyl-4-hydroxypiperidin-4-yl)-4-	Positive $[M+H]^+$ = 508.57	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 7.99-7.97 (m, 1H), 7.54 (d, J = 8.40 Hz, 1H), 7.37-7.33

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
		fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-128**)		(m, 4H), 7.26-7.23 (m, 1H), 5.13-5.10 (m, 2H), 4.54 (t, J = 17.20 Hz, 1H), 4.35 (t, J = 17.20 Hz, 1H), 3.50-3.38 (m, 1H), 3.33-2.92 (m, 1H), 2.92-2.68 (m, 2H), 2.63-2.59 (m, 2H), 2.52-2.45 (m, 2H), 2.34-2.29 (m, 2H), 2.27 (m, 2H), 1.52 (m, 2H), 1.10 (m, 2H), 0.57-0.52 (m, 3H), 0.47-0.41 (m, 3H).
INT-9	4-(1,2,4-oxadiazol-3-yl)benzaldehyde (**ALD-1**)	3-(5-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-131**)	Positive $[M+H]^+$ = 576.59	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 9.70 (s, 1H), 8.01 (d, J = 12.00 Hz, 3H), 7.56 (t, J = 7.60 Hz, 3H), 5.13-5.08 (m, 2H), 4.52 (t, J = 17.60 Hz, 1H), 4.38 (t, J = 17.60 Hz, 1H), 3.60 (d, J = 13.20 Hz, 1H), 3.47 (d, J = 22.40 Hz, 1H), 3.13-3.01 (m, 1H), 2.98-2.88 (m, 1H), 2.68-2.62 (m, 2H), 2.51-2.42 (m, 2H), 2.01-2.00 (m, 2H), 1.55-1.48 (m, 3H), 1.12-1.06 (m, 3H), 0.59-0.56 (m, 3H), 0.48-0.42 (m, 3H).
INT-9	4-chlorobenzaldehyde	3-(5-(1-(4-chlorobenzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-160**)	Positive $[M+H]^+$ = 542.53	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 9.43 (s, 1H), 7.96 (t, J = 7.20 Hz, 1H), 7.72 (d, J = 8.40 Hz, 2H), 7.61 (t, J = 8.80 Hz, 3H), 5.93 (d, J = 7.60 Hz, 1H), 5.14-5.10 (m, 1H), 4.56-4.38 (m, 4H), 3.29-3.28 (m, 3H), 3.16-2.85 (m, 2H), 2.59-2.45 (m, 3H), 2.33-2.03 (m, 2H), 1.87 (m, 1H), 1.59 (m, 1H), 1.15-1.11 (m, 2H), 0.54-0.48 (m, 3H), 0.46-0.42 (m, 3H).

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
INT-9	4-(trifluoromethyl)benzaldehyde	3-(5-(3,3-diethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-82**)	Positive $[M+H]^+$ = 576.56	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 7.89-7.97 (m, 5H), 7.62 (d, J = 8.00 Hz, 1H), 5.94 (d, J = 7.60 Hz, 1H), 5.13-5.13 (m, 1H), 4.50-4.56 (m, 3H), 4.38-4.43 (m, 1H), 3.20-3.33 (m, 1H), 2.63-2.68 (m, 2H), 2.50-2.59 (m, 1H), 2.45-2.50 (m, 1H), 2.02-2.03 (m, 1H), 1.98-2.00 (m, 1H), 1.80-1.88 (m, 1H), 1.60-1.65 (m, 1H), 1.08-1.18 (m, 1H), 0.51-0.55 (m, 3H), 0.43-0.47 (m, 3H).
INT-9	6-(trifluoromethyl)nicotinaldehyde	3-(5-(3,3-diethyl-4-hydroxy-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-146**)	Positive $[M+H]^+$ = 577.55	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 10.29 (s, 1H), 9.10 (s, 1H), 8.54 (d, J = 8.00 Hz, 1H), 8.09 (d, J = 8.00 Hz, 1H), 7.95-7.99 (m, 1H), 7.61 (d, J = 8.00 Hz, 1H), 5.95 (d, J = 6.80 Hz, 1H), 5.10-5.14 (m, 1H), 4.52-4.58 (m, 3H), 4.34-4.43 (m, 1H), 3.23-3.39 (m, 2H), 2.87-2.91 (m, 2H), 2.59-2.68 (m, 2H), 2.50-2.59 (m, 1H), 2.33-2.34 (m, 1H), 2.00-2.02 (m, 1H), 1.82-1.87 (m, 1H), 1.13-1.17 (m, 2H), 0.55 (q, J = 7.20 Hz, 3H), 0.45 (q, J = 7.60 Hz, 3H).
INT-9	1-methyl-1H-pyrazole-5-carbaldehyde	3-(5-(3,3-diethyl-4-hydroxy-1-((1-methyl-1H-pyrazol-5-yl)methyl)piperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-	Positive $[M+H]^+$ = 512.53	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 10.07 (s, 1H), 7.97 (t, J = 7.20 Hz, 1H), 7.62 (d, J = 8.00 Hz, 1H), 7.53 (s, 1H), 6.75 (s, 1H), 5.93 (s, 1H), 5.12 (dd, J = 5.20, 13.40 Hz, 1H), 4.52-4.56 (m, 3H), 4.41 (d, J = 17.60 Hz, 1H), 3.97 (s, 3H), 3.19-3.50 (m,

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
		2,6-dione (**I-173**)		2H), 2.63-2.91 (m, 1H), 2.42-2.51 (m, 1H), 1.99-2.19 (m, 1H), 1.86 (d, J = 12.80 Hz, 1H), 1.58-1.62 (m, 1H), 1.14-1.19 (m, 2H), 0.58 (t, J = 7.20 Hz, 3H), 0.48 (t, J = 7.60 Hz, 3H).
INT-9	4-(difluoromethyl)benzaldehyde	3-(5-(1-(4-(difluoromethyl)benzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-129**)	Positive $[M+H]^+$ = 558.54	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 9.61 (s, 1H), 7.96 (t, J = 2.40 Hz, 1H), 7.85 (d, J = 8.00 Hz, 2H), 7.71 (d, J = 8.00 Hz, 2H), 7.62 (d, J = 8.00 Hz, 1H), 7.11 (t, J = 55.60 Hz, 1H), 5.93 (d, J = 7.60 Hz, 1H), 5.12 (dd, J = 2.00, 11.80 Hz, 1H), 4.60-4.33 (m, 4H), 3.42-3.25 (m, 2H), 2.98-2.78 (m 2H), 2.51-2.33 (m, 3H), 2.21-2.03 (m, 2H), 1.89-1.85 (m, 1H), 1.63-1.55 (m, 1H), 1.15-1.09 (m, 2H), 0.55-0.41 (m, 6H).
INT-9	3-formyl-1H-indole-7-carbonitrile	3-((4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)-1H-indole-7-carbonitrile (**I-163**)	Positive $[M+H]^+$ = 572.53	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.81 (s, 1H), 11.0 (s, 1H), 8.05 (d, J = 8.0 Hz 1H), 7.98-7.94 (m, 1H), 7.58 (d, J = 7.2 Hz 1H), 7.53 (d, J = 8.4 Hz 1H), 7.41 (s, 1H), 7.20-7.16 (m, 1H), 5.11-5.03 (m, 2H), 4.52 (t, J = 16 Hz 1H), 4.33 (t, J = 16 Hz 1H), 3.65 (s, 1H), 2.99-2.91 (m, 1H), 2.62-2.57 (m, 2H), 2.51-2.33 (m, 4H), 2.26-2.01 (m, 2H), 1.81(s, 3H), 1.76-1.51 (m, 2H), 1.20-0.95 (m, 2H), 0.50-0.41 (m, 6H).
INT-11	4-chlorobenzaldehyde	3-(5-(1-(4-chlorobenzyl)-3,3-diethyl-4-	Positive $[M+2H]^+$ =	^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 9.50 (s, 1H), 7.47-7.58 (m,

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
		hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-114**)	525.4	7H), 5.64 (d, J = 4.0 Hz, 1H), 5.14-5.09 (m, 1H), 4.49-4.32 (m, 4H), 3.34-3.18 (m, 3H), 2.95-2.80 (m, 3H), 2.67-2.58 (m, 1H), 2.49-2.37 (m, 1H), 2.02-1.19 (m, 2H), 1.74-1.71 (m, 1H), 1.71-1.50 (m, 1H), 1.14-1.11 (m, 2H), 0.49-0.42 (m, 6H).
INT-11	4-(1,2,4-oxadiazol-3-yl)benzaldehyde (**ALD-1**)	3-(5-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-196**)	Positive $[M+H]^+$ = 558.6	^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 9.83-9.78 (m, 2H), 8.17 (d, J = 8.40 Hz, 2H), 7.95 (d, J = 8.00 Hz, 2H), 7.72-7.62 (m, 3H), 5.66-5.64 (m, 1H), 5.14-5.10 (m, 1H), 4.50-4.32 (m, 4H), 3.36-3.32 (m, 2H), 3.22-3.14 (m, 1H), 3.02-2.78 (m, 3H), 2.62-2.58 (m, 1H), 2.42-2.36 (m, 1H), 2.08-1.84 (m, 2H), 1.78-1.69 (m, 1H), 1.61-1.42 (m, 1H), 1.22-1.04 (m, 2H), 0.48-0.43 (m, 6H).
INT-11	4-(trifluoromethoxy)benzaldehyde	3-(5-(3,3-diethyl-4-hydroxy-1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-100**)	Positive $[M+H]^+$ = 574.6	^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.998 (s, 1H), δ 9.55 (s, 1H), 7.86 (d, J = 8.00 Hz, 2H), 7.72-7.62 (m, 3H), 7.53 (d, J = 8.00 Hz, 2H), 5.66-5.64 (m, 1H), 5.14-5.10 (m, 1H), 4.50-4.32 (m, 4H), 3.22-3.14 (m, 1H), 3.02-2.78 (m, 3H), 2.62-2.58 (m, 1H), 2.42-2.36 (m, 1H), 2.08-1.84 (m, 2H), 1.78-1.69 (m, 1H), 1.61-1.42 (m, 1H), 1.22-1.04 (m, 2H), 0.48-0.43 (m, 6H).
INT-11	5-formylpicolinonitrile	5-((4-(2-(2,6-dioxopiperidin-3-yl)-1-	Positive $[M+H]^+$ =	^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.98 (s, 1H), 8.75 (s, 1H), 8.05-8.00 (m,

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
		oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)picolinonitrile (**I-99**)	516.4	2H), 7.74-7.62 (m, 3H), 5.12 (t, J = 8.00 Hz, 1H), 4.86 (d, J = 5.20 Hz, 1H), 4.46 (d, J = 2.80 Hz, 1H), 4.42 (d, J = 2.00 Hz, 1H), 3.62 (d, J = 4.80 Hz, 2H), 2.92 (m, 1H), 2.68-2.62 (m, 1H), 2.62-2.58 (m, 2H), 2.43-2.34 (m, 3H), 2.31-2.01 (m, 2H), 2.00-1.98 (m, 1H), 2.00-1.89 (m, 2H), 1.44-1.41 (m, 1H), 1.39-1.17 (m, 1H), 0.53-0.45 (m, 6H).
INT-11	4-(difluoromethyl)benzaldehyde	3-(5-(1-(4-(difluoromethyl)benzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-119**)	Positive $[M+H]^+$ = 540.6	^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.14 (s, 1H), 7.75-7.68 (m, 2H), 7.63 (d, J = 8.00 Hz, 1H), 7.56-7.49 (m, 4H), 7.03 (s, 1H), 5.13-5.09 (m, 1H), 4.83 (s, 1H), 4.46 (d, J = 2.80 Hz, 1H), 4.42 (d, J = 2.80 Hz, 1H), 3.54-3.33 (m, 2H), 2.92-2.68 (m, 1H), 2.92-2.68 (m, 1H), 2.58-2.41 (m, 2H), 2.58-2.41 (m, 4H), 2.02-1.98 (m, 2H), 1.45-1.43 (m, 2H), 1.41-1.39 (m, 1H), 1.18-1.16 (m, 1H), 0.55-0.48 (m, 3H), 0.48-0.44 (m, 3H).
INT-11	4-formylbenzonitrile	4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile (**I-103**)	Positive $[M+H]^+$ = 515.3	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 9.83 (s, 1H), 8.01 (d, J = 8.40 Hz, 2H), 7.95 (d, J = 8.00 Hz, 2H), 7.72-7.62 (m, 3H), 5.66 (d, J = 5.60 Hz, 1H), 5.12 (dd, J = 5.20, 13.20 Hz, 1H), 4.55-4.45 (m, 3H), 4.34 (d, J = 17.60 Hz, 1H), 3.44-3.33 (m, 1H), 3.21 (t, J = 11.60 Hz, 1H), 2.95-2.92 (m, 2H), 2.78 (d, J

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
				= 12.00 Hz, 1H), 2.61 (d, J = 17.20 Hz, 1H), 2.41-2.40 (m, 1H), 2.03-2.00 (m, 2H), 1.73 (d, J = 13.60 Hz, 1H), 1.53-1.51 (m, 1H), 1.15-1.10 (m, 2H), 0.48-0.42 (m, 6H).
INT-11	3-formyl-1H-indole-7-carbonitrile	3-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)-1H-indole-7-carbonitrile (**I-162**)	Positive $[M+H]^+$ = 554.4	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.81 (s, 1H), 10.98 (s, 1H), 8.18 (s, 1H), 8.06 (d, J = 7.60 Hz, 1H), 7.72-7.66 (m, 2H), 7.60 (t, J = 7.60 Hz, 2H), 7.42 (d, J = 2.40 Hz, 1H), 7.18 (t, J = 8.00 Hz, 1H), 5.10 (dd, J = 5.20, 13.20 Hz, 1H), 4.76 (d, J = 5.20 Hz, 1H), 4.43 (dd, J = 2.40, 17.20 Hz, 1H), 4.29 (d, J = 16.80 Hz, 1H), 3.67 (d, J = 3.60 Hz, 2H), 2.91-2.88 (m, 1H), 2.71-2.68 (m, 2H), 2.62-2.58 (m, 1H), 2.45-2.38 (m, 3H), 2.34-2.31 (m, 1H), 2.02-1.91 (m, 2H), 1.42-1.38 (m, 2H), 1.18-1.16 (m, 1H), 1.10-0.85 (m, 1H), 0.48-0.45 (m, 6H).
INT-11	3-methoxy-4-(trifluoromethyl)benzaldehyde	3-(5-(3,3-diethyl-4-hydroxy-1-(3-methoxy-4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-126**)	Positive $[M+H]^+$ = 588.6	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.07 (s, 1H), 7.76-7.69 (m, 2H), 7.64 (d, J = 8.00 Hz, 1H), 7.57 (d, J = 8.00 Hz, 1H), 7.25 (s, 1H), 7.09 (d, J = 8.00 Hz, 1H), 4.84 (s, 1H), 4.43 (d, J = 3.20 Hz, 1H), 4.33 (d, J = 1.60 Hz, 1H), 3.90 (s, 3H), 3.59 (d, J = 13.60 Hz, 1H), 3.49 (d, J = 13.60 Hz, 1H), 2.69-2.63 (m, 2H), 2.63-2.53 (m, 2H), 2.50-2.35 (m, 3H), 2.03-1.99 (m, 2H), 1.99 (s, 3H), 1.44-1.42 (m,

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
				2H), 1.41 (m, 1H), 1.40 (m, 1H), 0.57-0.49 (m, 3H), 0.47-0.44 (m, 3H).
INT-11	4-(difluoromethyl)-3-methoxybenzaldehyde	3-(5-(1-(4-(difluoromethyl)-3-methoxybenzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-102**)	Positive $[M+H]^+$ = 570.3	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 9.89 (s, 1H), 7.71-7.61 (m, 5H), 7.37 (d, J = 8.00 Hz, 1H), 7.12 (t, J = 54.80 Hz, 1H), 5.66 (d, J = 5.60 Hz, 1H), 5.12 (dd, J = 4.80, 13.40 Hz, 1H), 4.50-4.37 (m, 4H), 3.91 (s, 3H), 3.39-3.21 (m, 3H), 2.92-2.75 (m, 2H), 2.68-2.63 (m, 2H), 2.50-2.50 (m, 1H), 2.04-2.01 (m, 2H), 1.76 (d, J = Hz, 1H), 1.57 (m, 1H), 1.14-1.09 (m, 2H), 0.50-0.41 (m, 6H).
INT-11	4-cyclopropoxybenzaldehyde (**ALD-2**)	3-(5-(1-(4-cyclopropoxybenzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-125**)	Positive $[M+H]^+$ = 546.8	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 9,57 (br s, 1H), 7.72-7.63 (m, 5H), 7.15 (d, J = 8.80 Hz, 2H), 5.61 (d, J = 5.60 Hz, 1H), 5.12 (dd, J = 5.20, 13.20 Hz, 1H), 4.50-4.36 (m, 4H), 3.91-3.88 (m, 1H), 3.13-2.92 (m, 3H), 2.84-2.81 (m, 3H), 2.63-2.59 (m, 1H), 2.50-2.50 (m, 1H), 2.015 (m, 2H), 1.74 (m, 2H), 1.12-1.10 (m, 2H), 0.81 (q, J = 5.60 Hz, 2H), 0.68 (q, J = 7.20 Hz, 2H), 0.49-0.43 (m, 6H).
INT-11	4-cyclopropylbenzaldehyde	3-(5-(1-(4-cyclopropylbenzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-	Positive $[M+H]^+$ = 530.55	^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (br,s, 1H, D2O exchangeable), 8.93 (br s, 1H, D2O exchangeable), 7.72-7.61 (m, 3H), 7.50 (d, J = 8.00 Hz, 2H), 7.20 (d, J = 8.00 Hz, 2H), 5.61 (d, J = 5.20

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
		2,6-dione (**I-121**)		Hz, 1H), 5.14-5.10 (m, 1H), 4.45-4.32 (m, 4H), 3.33-3.16 (m, 1H), 2.92-2.88 (m, 3H), 2.59 (s, 2H), 2.51 (s, 2H), 2.50-2.41 (m, 2H), 2.00-1.92 (m, 2H), 1.24-1.00 (m, 2H), 1.00-0.99 (m, 2H), 0.74-0.72 (m, 1H), 0.50-0.46 (m, 2H), 0.45 (t, J = 3.60 Hz, 6H).
INT-11	tetrahydro-2H-pyran-4-carbaldehyde	3-(5-(3,3-diethyl-4-hydroxy-1-((tetrahydro-2H-pyran-4-yl)methyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-117**)	Positive $[M+H]^+$ = 498.6	^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (br s, 1H, D2O exchangeable), 8.17 (s, 1H), 7.74-7.62 (m, 3H), 5.14-5.10 (m, 1H), 5.09 (s, 1H), 4.42 (d, J = 2.80 Hz, 1H), 4.30 (d, J = 17.20 Hz, 1H), 3.86-3.83 (m, 2H), 3.34-3.26 (m, 2H), 2.67-2.63 (m, 1H), 2.51-2.50 (m, 3H), 2.40-2.35 (m, 4H), 2.30-2.27 (m, 2H), 2.15-2.12 (m, 2H), 1.69-1.66 (m, 3H), 1.44-1.41 (m, 2H), 1.20-1.13 (m, 4H), 0.64 (t, J = 7.60 Hz, 3H), 0.52 (t, J = 3.20 Hz, 3H).
INT-11	4-(2,2-difluoroethoxy)benzaldehyde	3-(5-(1-(4-(2,2-difluoroethoxy)benzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-123**)	Positive $[M+H]^+$ = 570.8	^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.988 (br s, 1H, D2O exchange), 7.74-7.61 (m, 3H), 7.27 (d, J = 8.40 Hz, 2H), 6.97 (d, J = 8.40 Hz, 2H), 6.52-6.24 (m, 1H), 5.13-5.09 (m, 1H), 4.79-4.78 (m, 1H), 4.42-4.41 (m, 1H), 4.34-4.28 (m, 3H), 3.46-3.38 (m, 2H), 3.00-2.85 (m, 1H), 2.68-2.62 (m, 1H), 2.58-2.53 (m, 2H), 2.45-2.28 (m, 4H), 2.05-1.95 (m, 2H), 1.884 (s, 3H), 1.15-1.38 (m, 2H),

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
				0.92-0.98 (m, 1H), 0.52-0.44 (m, 6H).
INT-11	benzaldehyde	3-(5-(1-benzyl-3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-118**)	Positive $[M+H]^+$ = 490.8	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 9.75 (bs, 1H), 7.74-7.72 (m, 5H), 7.70-7.49 (m, 3H), 5.63 (s, 1H), 5.12 (t, J = 5.20 Hz, 1H), 4.48 (d, J = 9.20 Hz, 2H), 4.34 (d, J = 5.20 Hz, 2H), 3.52-3.43 (m, 1H), 3.43-3.40 (m, 2H), 2.79-2.76 (m, 1H), 2.68-2.63 (m, 2H), 2.52 (m, 1H), 2.51-2.50 (m, 2H), 2.50 (m, 1H), 2.34-2.33 (m, 1H), 2.03-2.00 (m, 2H), 0.43 (s, 6H).
INT-11	4,4-difluorocyclohexane-1-carbaldehyde	3-(5-(1-((4,4-difluorocyclohexyl)methyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-98**)	Positive $[M+H]^+$ = 532.6	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 9.05 (s, 1H), 7.74-7.66 (m, 3H), 6.32 (d, J = 6.00 Hz, 1H), 5.13 (t, J = 5.20 Hz, 1H), 4.49 (d, J = 17.60 Hz, 1H), 4.35 (d, J = 17.60 Hz, 1H), 3.34-3.19 (m, 8H), 2.68-2.64 (m, 1H), 2.51-2.51 (m, 1H), 2.04-1.83 (m, 12H), 1.59-1.27 (m, 4H), 0.60 (t, J = 3.60 Hz, 3H), 0.53 (t, J = 3.60 Hz, 3H).
INT-11	4-(difluoromethoxy)benzaldehyde	3-(5-(1-(4-(difluoromethoxy)benzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-120**)	Positive $[M+H]^+$ = 556.6	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 9.57 (s, 1H), 7.77 (d, J = 8.40 Hz, 2H), 7.71 (d, J = 8.00 Hz, 1H), 7.67-7.62 (m, 1H), 7.53-7.16 (m, 4H), 5.63 (d, J = 5.20 Hz, 1H), 5.14-5.10 (m, 1H), 4.50-4.45 (m, 2H), 4.38-4.32 (m, 2H), 3.40-3.27 (m, 2H), 3.17-3.14 (m, 1H), 2.97-2.92 (m, 2H), 2.84-2.81 (m, 1H), 2.63-2.59 (m, 1H),

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
				2.41-2.37 (m, 1H), 2.03-2.00 (m, 2H), 1.73 (d, J = 12.80 Hz, 1H), 1.75-1.72 (m, 1H), 1.51-1.09 (m, 2H), 0.49-0.43 (m, 6H).
INT-11	6-(trifluoromethyl)nicotinaldehyde	3-(5-(3,3-diethyl-4-hydroxy-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-97**)	Positive $[M+H]^+$ = 559.6	^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 8.75 (s, 1H), 8.05 (d, J = 9.20 Hz, 1H), 7.90 (d, J = 8.00 Hz, 1H), 7.74-7.62 (m, 3H), 5.12-5.10 (m, 1H), 4.86 (s, 1H), 4.42-4.28 (m, 2H), 3.63-3.62 (m, 2H), 2.68-2.94 (m, 2H), 2.52-2.50 (m, 3H), 2.44-2.33 (m, 3H), 2.00-1.98 (m, 2H), 1.41 (t, J = 6.80 Hz, 2H), 0.75-0.94 (m, 2H), 0.53-0.45 (m, 6H).
INT-9	5-formylpicolinonitrile	5-((4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)picolinonitrile (**I-161**)	Positive $[M+H]^+$ = 534.5	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 9.87 (s, 1H), 9.05 (s, 1H), 8.44 (d, J = 8.00 Hz, 1H), 8.22 (d, J = 8.00 Hz, 1H), 7.97 (d, J = 6.80 Hz, 1H), 7.62 (d, J = 8.00 Hz, 1H), 5.96 (d, J = 7.60 Hz, 1H), 5.12 (d, J = 12.00 Hz, 1H), 4.59-4.38 (m, 4H), 3.39-3.21 (m, 4H), 2.92-2.89 (m, 2H), 2.68-2.50 (m, 1H), 2.45-2.02 (m, 4H), 1.19-1.15 (m, 2H), 0.52 (dd, J = 7.60, 17.20 Hz, 6H).
INT-5	benzaldehyde	3-(5-(1-benzyl-4-hydroxy-3,3-dimethylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-29**)	Positive $[M+H]^+$ = 462.1	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 9.28 (s, 1H), 7.68-7.56 (m, 5H), 7.52-7.50 (m, 3H), 5.58 (d, J = 4 Hz, 1H), 5.13 (dd, J = 4.80, 13.20 Hz, 1H), 4.49-4.36 (m, 4H), 3.25-3.22 (m, 2H), 2.94-2.88 (m, 3H), 2.60 (d, J =

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
				7.20 Hz, 2H), 2.41 (d, J = 4.00 Hz, 1H), 2.02 (d, J = 7.20 Hz, 1H), 1.80 (d, J = 14.00 Hz, 1H), 0.91 (s, 3H), 0.75 (s, 3H).
INT-8	4-(pentafluoro-λ^6-sulfanyl)-benzaldehyde	3-(4-fluoro-5-(4-hydroxy-3,3-dimethyl-1-(4-(pentafluoro-λ^6-sulfaneyl) benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-174**)	positive $[M+H]^+$ = 606.3	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.17-10.87 (m, 1H), 9.94-9.48 (m, 1H), 8.08 (d, J = 8.7 Hz, 2H), 7.98-7.83 (m, 3H), 7.63 (d, J = 8.1 Hz, 1H), 5.90 (d, J = 6.5 Hz, 1H), 5.13 (ddd, J = 2.8, 4.9, 13.2 Hz, 1H), 4.59-4.48 (m, 3H), 4.43-4.34 (m, 1H), 3.31-3.23 (m, 3H), 3.01-2.87 (m, 2H), 2.61 (d, J = 17.2 Hz, 1H), 2.46 (m, 2H), 2.06-1.88 (m, 2H), 1.06 (br. s, 3H), 0.76 (d, J = 8.3 Hz, 3H)
INT-9	4-formylbenzonitrile	4-((4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile (**I-145**)	positive $[M+H]^+$ = 533.5	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 10.27 (br. s, 1H), 8.09-7.86 (m, 5H), 7.61 (d, J = 8.1 Hz, 1H), 6.00-5.77 (m, 1H), 5.26-4.96 (m, 1H), 4.69-4.18 (m, 4H), 3.17 (t, J = 11.8 Hz, 1H), 2.99-2.83 (m, 1H), 2.72 (d, J = 12.2 Hz, 1H), 2.61 (d, J = 16.8 Hz, 2H), 2.47-2.37 (m, 1H), 2.22 (dd, J = 6.8, 11.4 Hz, 1H), 2.06-1.95 (m, 1H), 1.93-1.78 (m, 1H), 1.66-1.47 (m, 1H), 1.26-0.95 (m, 4H), 0.58-0.31 (m, 6H). *Note: ^{1}H NMR Integration given for one diastereomer.
INT-9	4-(2H-1,2,3-triazol-2-yl)benzaldehyde	3-(5-(1-(4-(2H-1,2,3-triazol-2-yl)benzyl)-3,3-diethyl-4-hydroxypiperidi	positive $[M+H]^+$ = 575.5	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 9.69 (d, J = 2.2 Hz, 1H), 8.19 (s, 2H), 8.15 (d, J = 8.6 Hz, 2H), 8.03-7.85 (m, 3H),

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
		n-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-190**)		7.61 (d, *J* = 8.1 Hz, 1H), 5.94 (d, *J* = 7.3 Hz, 1H), 5.18-5.04 (m, 1H), 4.67-4.29 (m, 4H), 3.25-3.12 (m, 1H), 2.99-2.78 (m, 2H), 2.66-2.56 (m, 1H), 2.47-2.37 (m, 1H), 2.23-1.81 (m, 4H), 1.67-1.49 (m, 1H), 1.23-1.04 (m, 4H), 0.59-0.35 (m, 6H). **Note: ^{1}H NMR Integration given for one diastereomer.*
INT-9	1H-pyrrole-2-carbaldehyde	3-(5-(1-((1H-pyrrol-2-yl)methyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-191**)	negative $[M-H]^-$ = 495.5	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.20 (d, J = 2.2 Hz, 1H), 11.02 (s, 1H), 9.74-9.59 (m, 1H), 7.99-7.89 (m, 1H), 7.61 (d, J = 8.1 Hz, 1H), 6.97-6.90 (m, 1H), 6.33 (t, J = 3.4 Hz, 1H), 6.11 (q, J = 2.5 Hz, 1H), 5.86 (d, J = 7.0 Hz, 1H), 5.12 (ddd, J = 2.9, 4.9, 13.2 Hz, 1H), 4.62-4.49 (m, 1H), 4.45-4.23 (m, 3H), 3.30-3.16 (m, 3H), 3.12-3.01 (m, 1H), 3.00-2.82 (m, 2H), 2.66-2.56 (m, 1H), 2.47-2.36 (m, 1H), 2.24-1.95 (m, 2H), 1.85 (t, J = 10.5 Hz, 1H), 1.65-1.48 (m, 1H), 1.22-1.04 (m, 2H), 0.64-0.38 (m, 6H). **Note: ^{1}H NMR Integration given for one diastereomer.*
INT-8	6-(oxazol-4-yl)nicotinaldehyde (**ALD-5**)	3-(4-fluoro-5-(4-hydroxy-3,3-dimethyl-1-((6-(oxazol-4-yl)pyridin-3-yl)methyl)piperidin-4-yl)-1-oxoisoindolin-	Positive $[M+H]^+$ = 547.4	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.10-10.93 (m, 1H), 10.36-10.00 (m, 1H), 8.99-8.89 (m, 1H), 8.45-8.22 (m, 2H), 8.10 (d, *J* = 8.1 Hz, 1H), 7.88 (t, *J* = 7.1 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 5.90 (d, *J* = 5.2

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
		2-yl)piperidine-2,6-dione (**I-212**)		Hz, 1H), 5.12 (ddd, *J* = 2.3, 4.9, 13.2 Hz, 1H), 4.62-4.33 (m, 4H), 3.27-3.21 (m, 2H), 2.99-2.86 (m, 2H), 2.66-2.55 (m, 3H), 2.42 (s, 2H), 2.08-1.89 (m, 2H), 1.07 (s, 3H), 0.75 (d, *J* = 7.5 Hz, 3H).
INT-11	isobutyraldehyde	3-(5-(3,3-diethyl-4-hydroxy-1-isobutylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-101**)	Positive $[M+H]^+$ = 456.4	^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 8.20 (s, 1H), 7.75-7.61 (m, 3H), 5.17-5.09 (m, 1H), 4.76 (d, J = 5.20 Hz, 1H), 4.48-4.28 (m, 2H), 2.93-2.87 (m, 1H), 2.78-2.73 (m, 1H), 2.68-2.52 (m, 4H), 2.49-2.33 (m, 2H), 2.26 (d, J = 10.80 Hz, 1H), 2.07-1.93 (m, 4H), 1.81-1.73 (m, 1H), 1.42-1.38 (m, 2H), 1.26-1.12 (m, 1H), 0.91-0.88 (m, 6H), 0.65 (t, J = 7.20 Hz, 3H), 0.53-0.48 (m, 3H).
INT-2	4-(4-(trifluoromethyl)phenoxy)benzaldehyde	3-(4-fluoro-5-(4-hydroxy-1-(4-(4-(trifluoromethyl)phenoxy)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-11**)	Positive $[M+H]^+$ = 612.1	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 10.2 (s, 1H), 7.84 (t, J = 7.20 Hz, 1H), 7.79 (d, J = 8.80 Hz, 2H), 7.70 (d, J = 8.80 Hz, 2H), 7.64 (d, J = 7.60 Hz, 1H), 7.26-7.21 (m, 4H), 6.00 (s, 1H), 5.15-5.11 (m, 1H), 4.59-4.37 (m, 4H), 3.34 (s, 4H), 2.96-2.91 (m, 1H), 2.73-2.63 (m, 3H), 2.48-2.45 (m, 1H), 2.02-2.00 (m, 1H), 1.89 (d, J = 14.40 Hz, 2H).
INT-2	4-phenoxybenzaldehyde	3-(4-fluoro-5-(4-hydroxy-1-(4-phenoxybenzyl)piperidin-4-yl)-1-	Positive $[M+H]^+$ = 544	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 7.83 (t, J = 7.60 Hz, 1H), 7.66-7.65 (m, 3H), 7.45 (t, J = 2.40 Hz, 2H), 7.23 (t, J = 0.80 Hz, 1H), 7.21-7.19 (m,

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
		oxoisoindolin-2-yl)piperidine-2,6-dione (**I-9**)		4H), 5.99 (s, 1H), 5.15-5.10 (m, 1H), 4.56 (d, J = 17.20 Hz, 1H), 4.41-4.36 (m, 3H), 3.32 (s, 4H), 2.97-2.92 (m, 1H), 2.62-2.45 (m, 4H), 1.99 (m, 1H), 1.89 (d, J = 2.00 Hz, 2H).
INT-2	benzaldehyde	3-(5-(1-benzyl-4-hydroxypiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-1**)	Positive $[M+H]^+$ = 452.2	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 7.84 (t, J = 7.60 Hz, 1H), 7.58 (d, J = 8.00 Hz, 1H), 7.35-7.31 (m, 4H), 7.28-7.24 (m, 1H), 5.29 (s, 1H), 5.14-5.09 (m, 1H), 4.54 (d, J = 17.20 Hz, 1H), 4.37 (d, J = 17.20 Hz, 1H), 3.53 (s, 2H), 2.93-2.89 (m, 1H), 2.68-2.63 (m, 3H), 2.51-2.43 (m, 3H), 2.25 (t, J = 12.00 Hz, 2H), 2.02-2.00 (m, 1H), 1.62 (d, J = 2.40 Hz, 2H).
INT-18	benzaldehyde	3-(5-(1-benzyl-4-hydroxypiperidin-4-yl)-1-oxo-4-(trifluoromethoxy)isoindolin-2-yl)piperidine-2,6-dione **(I-44)**	Positive $[M+H]^+$ = 518.3	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 10.11 (s, 1H), 7.80 (d, J = 8.00 Hz, 1H), 7.74 (d, J = 8.00 Hz, 1H), 7.62 (dd, J = 2.00, 6.60 Hz, 2H), 7.51-7.49 (m, 3H), 5.81 (s, 1H), 5.13 (dd, J = 5.20, 13.20 Hz, 1H), 4.55 (d, J = 17.60 Hz, 1H), 4.44-4.38 (m, 2H), 3.332-3.337 (m, 5H), 2.85-2.94 (m, 1H), 2.25-2.61 (m, 6H)
INT-18	4-(trifluoromethyl)benzaldehyde	3-(5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxo-4-(trifluoromethoxy)isoindolin-2-	Positive $[M+H]^+$ = 586.4	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 10.16 (s, 1H), 7.73-7.91 (m, 6H), 5.83 (d, J = 6.40 Hz, 1H), 5.13 (dd, J = 5.20, 13.20 Hz, 1H), 4.40-4.57 (m, 4H), 3.49-3.34 (m, 2H), 2.85-2.91 (m, 1H), 1.99-

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
		yl)piperidine-2,6-dione **(I-43)**		2.57 (m, 7H), (one aliphatic proton overlapped with deuterated solvent)
INT-17	4-(trifluoromethyl)benzaldehyde	3-(5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1-oxo-4-(trifluoromethyl)isoindolin-2-yl)piperidine-2,6-dione **(I-27)**	Positive $[M+H]^+$ = = 570.2	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 8.05 (d, J = 8.00 Hz, 1H), 7.90 (d, J = 8.00 Hz, 2H), 7.88 (d, J = 8.00 Hz, 2H), 7.77 (d, J = 8.00 Hz, 3H), 5.70 (s, 1H), 5.16-5.12 (m, 1H), 4.66-4.56 (m, 1H), 4.52-4.51 (m, 3H), 3.42-3.39 (m, 4H), 2.91-2.90 (m, 1H), 2.68-2.67 (m, 2H), 2.57-2.50 (m, 1H), 2.10-2.03 (m, 2H).
INT-50	4-(trifluoromethoxy)benzaldehyde	3-(2-(4-hydroxy-1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-411**)	Positive $[M+H]^+$ = 518.9	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 9.99 (s, 1H), 8.21 (d, J = 8.40 Hz, 1H), 7.86 (d, J = 8.00 Hz, 1H), 7.75 (d, J = 8.80 Hz, 2H), 7.51 (d, J = 8.00 Hz, 2H), 5.98 (s, 1H), 5.21-5.16 (m, 1H), 4.49-4.31 (m, 4H), 3.63-31 (m, 4H), 2.93-2.90 (m, 1H), 2.68-2.59 (m, 1H), 2.51-2.39 (m, 3H), 2.04-2.01 (m, 1H), 1.85-1.84 (m, 2H).
INT-50	4-(trifluoromethyl)benzaldehyde	3-(2-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-400**)	Positive $[M+H]^+$ = 503.0	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 10.40 (s, 1H), 8.21 (d, J = 8.40 Hz, 1H), 7.90-7.85 (m, 5H), 5.40 (br s, 1H), 5.18 (d, J = 5.20 Hz, 1H), 4.54-4.32 (m, 4H), 3.46 (s, 4H), 3.00-2.80 (m, 1H), 2.70-38 (m, 4H), 2.04-2.03 (m, 1H), 1.85-1.81 (m, 2H).
INT-50	3-(trifluoromet	3-(2-(4-hydroxy-1-(3-(trifluoromethyl	Positive $[M+H]^+$ = 503	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 10.06 (s, 1H), 8.23-8.20 (m,

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
	hyl)benzaldehyde	)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-412**)		1H), 8.05 (s, 1H), 7.93-7.86 (m, 3H), 7.76-7.72 (m, 1H), 5.96 (br s, 1H), 5.21-5.16 (m, 1H), 4.53-4.49 (m, 3H), 4.36-4.31 (m, 1H), 3.47-3.35 (m, 4H), 2.93-2.90 (m, 1H), 2.68-2.59 (m, 2H), 2.45-2.41 (m, 2H), 2.04-2.01 (m, 1H), 1.86-1.76 (m, 2H).
INT-50	4-(2,2,2-trifluoroethyl)benzaldehyde	3-(2-(4-hydroxy-1-(4-(2,2,2-trifluoroethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-446**)	Negative $[M-H]^-$ = 515.5	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 10.40 (br s, 1H), 8.20 (d, J = 8.00 Hz, 1H), 7.85 (d, J = 8.00 Hz, 1H), 7.66 (d, J = 8.40 Hz, 2H), 7.48 (d, J = 8.00 Hz, 2H), 5.80 (br s, 1H), 5.21-5.16 (m, 1H), 4.54-4.32 (m, 4H), 3.74-3.68 (m, 2H), 3.31-3.28 (m, 4H), 3.00-2.80 (m, 1H), 2.69-2.53 (m, 2H), 2.51-2.42 (m, 2H), 2.04-2.03 (m, 1H), 1.85-1.81 (m, 2H).
INT-50	benzaldehyde	3-(2-(1-benzyl-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-444**)	Positive $[M+H]^+$ = 435.5	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 9.91 (s, 1H), 8.21 (d, J = 8.00 Hz, 1H), 7.86 (d, J = 8.40 Hz, 1H), 7.60 (q, J = 2.00 Hz, 2H), 7.52-7.49 (m, 3H), 5.79 (s, 1H), 5.19 (q, J = 4.80 Hz, 1H), 4.46 (d, J = 4.80 Hz, 1H), 4.39 (d, J = 16.00 Hz, 2H), 4.32 (s, 1H), 3.34 (s, 2H), 3.29-3.26 (m, 3H), 2.98-2.90 (m, 1H), 2.89-2.63 (m, 1H), 2.46-2.41 (m, 2H), 2.03 (q, J = 2.00 Hz, 1H), 1.84-1.76 (m, 2H)

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
INT-51	4-(1,2,4-oxadiazol-3-yl)benzaldehyde (**ALD-1**)	3-(2-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-518**)	Positive $[M+H]^+$ = 531.8	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H), 9.78 (s, 1H), 9.61 (s, 1H), 8.20-8.16 (m, 3H), 7.88-7.83 (m, 3H), 5.85 (s, 1H), 5.21-5.17 (m, 1H), 4.56-4.48 (m, 3H), 4.38-4.32 (m, 1H), 3.32-3.22 (m, 3H), 2.93-2.90 (m, 2H), 2.64-2.56 (m, 1H), 2.45-2.38 (m, 2H), 2.05-2.02 (m, 1H), 1.81-1.75 (m, 1H), 0.93 (s, 3H), 0.79 (d, J = 6.40 Hz, 3H).
INT-52	acetaldehyde	3-(5-oxo-2-(1,3,3-triethyl-4-hydroxy-piperidin-4-yl)-5,7-dihydro-6H-pyrrolo-[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-432**)	Positive $[M+H]^+$ = 429.4	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H), 8.17 (d, J = 8.40 Hz, 1H), 7.93 (d, J = 8.00 Hz, 1H), 5.90 (s, 1H), 5.21-5.17 (m, 1H), 4.51-4.36 (m, 1H), 4.38 (t, J = 18.00 Hz, 1H), 3.28-3.11 (m, 7H), 2.93 (m, 1H), 2.64-2.51 (m, 1H), 2.06-2.04 (m, 1H), 1.91 (m, 1H), 1.60-1.57 (m, 2H), 1.34-1.29 (m, 6H), 0.59-0.50 (m, 6H).
INT-52	1-methyl-1H-pyrazole-5-carbaldehyde	3-(2-(3,3-diethyl-4-hydroxy-1-((1-methyl-1H-pyrazol-5-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **(I-533)**	Positive $[M+H]^+$ = 495.54	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H), 8.15 (d, J = 0.80 Hz, 1H), 7.91 (d, J = 8.00 Hz, 1H), 7.54 (d, J = 1.60 Hz, 1H), 6.74 (t, J = 2.40 Hz, 1H), 5.33-5.13 (m, 1H), 4.55-4.51 (m, 3H), 4.35 (t, J = 18.00 Hz, 1H), 3.97 (s, 3H), 3.42-3.23 (m, 3H), 2.95-2.90 (m, 2H), 2.68-2.64 (m, 1H), 2.44-2.41 (m, 1H), 2.05-2.02 (m, 2H), 1.75-1.65 (m, 1H), 1.57-1.55 (m, 1H), 1.29-1.23 (m, 2H), 0.50-0.42 (m, 6H).

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
INT-52	4-formylbenzonitrile	4-((4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo-[3,4-b]pyridin-2-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile (**I-425**)	Positive $[M+H]^+$ = 516.5	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H), 8.19-8.15 (m, 1H), 8.00-7.89 (m, 4H), 7.89-7.56 (m, 1H), 5.91 (d, J = 2.80 Hz, 1H), 5.20-5.16 (m, 1H), 4.55-4.48 (m, 3H), 3.41-3.33 (m, 1H), 3.27-3.19 (m, 2H), 2.93-2.64 (m, 2H), 2.60-2.51 (m, 1H), 2.43-2.33 (m, 2H), 2.05-2.00 (m, 2H), 1.53-1.20 (m, 2H), 1.24-1.20 (m, 2H), 0.46-0.38 (m, 6H).
INT-52	tetrahydro-2H-pyran-4-carbaldehyde	3-(2-(3,3-diethyl-4-hydroxy-1-((tetrahydro-2H-pyran-4-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]-pyridin-6-yl)-piperidine-2,6-dione (**I-449**)	Positive $[M+H]^+$ = 499.8	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.05 (s, 1H), 8.97 (s, 1H), 8.19 (d, J = 8.00 Hz, 1H), 7.93 (d, J = 1.60 Hz, 1H), 5.91 (s, 1H), 5.22-5.18 (m, 1H), 4.54-4.40 (m, 1H), 4.36 (t, J = 17.60 Hz, 1H), 3.86 (d, J = 11.20 Hz, 2H), 3.43-3.33 (m, 8H), 3.23-3.15 (m, 2H), 2.64 (t, J = 17.20 Hz, 1H), 2.45-2.41 (m, 1H), 1.74-1.64 (m, 4H), 1.38-1.29 (m, 4H), 0.56-0.50 (m, 6H).
INT-52	4,4-difluorocyclohexane-1-carbaldehyde	3-(2-(1-((4,4-difluorocyclohexyl)methyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-448**)	Positive $[M+H]^+$ = 533.5	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H), 9.22 (s, 1H), 8.17 (d, J = 8.00 Hz, 1H), 7.92 (d, J = 1.60 Hz, 1H), 6.92 (s, 1H), 5.21-5.18 (m, 1H), 4.59-4.51 (m, 1H), 4.36 (t, J = 18.40 Hz, 1H), 3.36-2.64 (m, 8H), 2.52-2.50 (m, 1H), 2.50-2.44 (m, 1H), 2.06-1.84 (m, 9H), 1.65-1.60 (m, 2H), 1.37-1.30 (m, 4H), 0.57-0.51 (m, 6H).

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
INT-52	4-chlorobenzaldehyde	3-(2-(1-(4-chlorobenzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-443**)	Positive $[M+H]^+$ = 526.5	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 9.46 (s, 1H), 8.16 (d, J = 1.20 Hz, 1H), 7.91 (d, J = 8.40 Hz, 1H), 7.74 (d, J = 6.40 Hz, 2H), 7.60 (d, J = 8.40 Hz, 2H), 5.90 (s, 1H), 5.18 (q, J = 4.80 Hz, 1H), 4.53-4.35 (m, 4H), 3.24-3.16 (m, 3H), 2.96 (m, 2H), 2.64-2.44 (m, 4H), 2.08-1.92 (m, 2H), 1.53 (m, 2H), 1.26-1.20 (m, 2H), 0.41-0.37 (m, 6H).
INT-52	4-(1,2,4-oxadiazol-3-yl)benzaldehyde (**ALD-1**)	3-(2-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-525**)	Positive $[M+H]^+$ = 559.5	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H), 8.20-8.14 (m, 3H), 7.97-7.90 (m, 3H), 5.91 (s, 1H), 5.18 (q, J = 3.20 Hz, 1H), 4.58-4.31 (m, 4H), 3.44-3.20 (m, 4H), 2.88-2.64 (m, 2H), 2.51-2.41 (m, 2H), 2.05-2.00 (m, 2H), 1.77 (t, J = Hz, 1H), 1.54 (q, J = 7.20 Hz, 1H), 1.24-1.19 (m, 2H), 0.41-0.37 (m, 6H).
INT-52	4-(trifluoromethyl)benzaldehyde	3-(2-(3,3-diethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-424**)	Positive $[M+H]^+$ = 559.6	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.10 (d, J = 8.40 Hz, 2H), 7.89 (dd, J = 1.60, 8.20 Hz, 1H), 7.71 (d, J = 8.40 Hz, 2H), 7.59 (d, J = 8.00 Hz, 1H), 5.20 (s, 1H), 5.17 (t, J = 5.20 Hz, 1H), 4.53-4.49 (m, 1H), 4.48-4.29 (m, 1H), 3.57 (s, 4H), 2.68-2.59 (m, 2H), 2.47-2.34 (m, 4H), 2.33-2.03 (m, 2H), 1.47-1.43 (m, 2H), 1.19-1.23 (m, 2H), 0.51-0.45 (m, 6H).

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
INT-52	5-formylpicolinonitrile	5-((4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)picolinonitrile (**I-442**)	Positive $[M+H]^+$ = 517.7	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 8.74 (s, 1H), 8.16 (s, 1H), 8.10 (d, J = 8.00 Hz, 1H), 8.03 (t, J = 2.00 Hz, 1H), 7.90-7.88 (m, 1H), 5.20 (s, 1H), 5.20-5.18 (m, 1H), 4.47-4.36 (m, 2H), 3.62 (s, 2H), 3.33 (s, 2H), 3.09-3.33 (m, 2H), 2.68-2.67 (m, 2H), 2.52-2.50 (m, 2H), 2.50-2.43 (m, 2H), 2.33-2.08 (m, 2H), 1.37-1.43 (m, 1H), 1.32-1.36 (m, 1H), 0.48-0.42 (m, 6H).
INT-52	isobutyraldehyde	3-(2-(3,3-diethyl-4-hydroxy-1-isobutylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-434**)	Positive $[M+H]^+$ = 457.5	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H), 8.60 (s, 1H), 8.20 (dd, J = 8.00, 17.00 Hz, 1H), 7.93 (dd, J = 1.60, 8.00 Hz, 1H), 5.91 (s, 1H), 5.22-5.19 (m, 1H), 4.53-4.51 (m, 1H), 4.40-4.36 (m, 1H), 3.40-3.24 (m, 2H), 3.18-3.13 (m, 2H), 2.97-2.91 (m, 2H), 2.68-2.60 (m, 1H), 2.51-2.50 (m, 2H), 2.44-2.41 (m, 1H), 2.34-2.34 (m, 2H), 1.59-1.78 (m, 2H), 1.38-1.33 (m, 2H), 1.05-0.99 (m, 6H), 0.58-0.50 (m, 6H).
INT-52	formaldehyde	3-(2-(3,3-diethyl-4-hydroxy-1-methylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-433**)	Positive $[M+H]^+$ = 415.5	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.05 (s, 1H), 9.28 (br s, 1H), 8.22-8.15 (m, 1H), 7.99-7.91 (m, 1H), 5.89 (d, *J* = 2.80 Hz, 1H), 5.18-5.10 (m, 1H), 4.57-4.53 (m, 1H), 4.50-4.39 (m, 1H), 3.33-3.16 (m, 5H), 2.89-2.87 (m, 4H), 2.68-2.55 (m, 1H), 2.44-2.41 (m, 1H), 2.36-2.32 (m, 1H), 2.00-1.86 (m, 1H), 1.77-

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
				1.73 (m, 1H), 1.55-1.53 (m, 1H), 1.36-1.31 (m, 2H), 0.61-0.54 (m, 6H).
INT-52	6-(trifluoromethyl) nicotinaldehyde	3-(2-(3,3-diethyl-4-hydroxy-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-435**)	Positive $[M+H]^+$ = 560.8	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 10.47 (br s, 1H), 9.13-9.09 (m, 1H), 8.60-8.58 (m, 1H), 8.19-8.08 (m, 2H), 7.96-7.90 (m, 1H), 5.90 (br s, 1H), 5.20-5.16 (m, 1H), 4.59-4.51 (m, 3H), 4.35 (t, J = 18.00 Hz, 1H), 3.40 (br s, 1H), 3.28-3.20 (m, 3H), 2.89-2.87 (m, 2H), 2.64-2.50 (m, 1H), 2.43-2.40 (m, 1H), 2.08-2.02 (m, 2H), 1.69-1.56 (m, 2H), 1.26-1.20 (m, 2H), 0.47-0.38 (m, 6H).

Example 81: General procedure B- Reductive amination

To a stirred solution of the amine or the amine hydrochloride (0.1 mmol, 1.0 equiv) in DMF (1 mL) and the aldehyde (0.12 mmol, 1.2 equiv) and DIPEA (0.3 mmol, 3.0 equiv) is added sodium triacetoxyborohydride (0.3 mmol, 3.0 equiv) and the resulting mixture is stirred for 16 h. The reaction mixture is then filtered and the filtrate is concentrated under reduced pressure to afford the crude compound, which is purified by reverse phase chromatography [(Column: X select (150 mm × 19) 5 µm, eluting with Mobile phase A: 0.05% FA or HCl in H_2O, Mobile phase B: ACN, flow rate: 15 mL/min)]. The fractions containing pure product are combined and concentrated via lyophilization to afford the desired product as the formic acid salt, the hydrochloric salt, or the free amine.

The following compounds in Table 2 were prepared from corresponding amine or amine hydrochloride and aldehyde according to a reductive amination procedure described in General Procedure B.

Table 2:

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
INT-10	5-methyl-1H-pyrrole-2-carbaldehyde	3-(5-(5-hydroxy-2-((5-methyl-1H-pyrrol-2-yl)methyl)-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-77**)	Positive $[M+H]^+$ = 505.9	^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 10.28 (s, 1H), 7.67-7.57 (m, 3H), 5.73 (s, 1H), 5.60 (s, 1H), 5.12 (d, J = 4.80 Hz, 1H), 4.67 (s, 1H), 4.44 (q, J = 11.60 Hz, 1H), 4.34 (q, J = 10.00 Hz, 1H), 3.46-3.43 (m, 1H), 2.94-2.91 (m, 2H), 2.68-2.63 (m, 4H), 2.53-2.51 (m, 1H), 2.50-2.33 (m, 5H), 2.17 (m, 1H), 2.13 (d, J = 12.00 Hz, 1H), 1.91 (t, J = Hz, 2H), 1.40 (m, 4H), 1.24 (m, 1H), 0.59 (m, 2H).
INT-10	1-methyl-1H-pyrrole-2-carbaldehyde	3-(5-(5-hydroxy-2-((1-methyl-1H-pyrrol-2-yl)methyl)-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-76**)	Positive $[M+H]^+$ = 505.41	^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 7.68-7.59 (m, 3H), 6.66 (t, J = 2.00 Hz, 1H), 5.90-5.87 (m, 2H), 5.12 (dd, J = 4.80, 13.40 Hz, 2H), 4.73 (d, J = 3.60 Hz, 1H), 4.45-4.33 (m, 2H), 3.64 (s, 3H), 3.37 (d, J = 35.60 Hz, 2H), 2.96-2.92 (m, 2H), 2.68-2.51 (m, 3H), 2.44-2.33 (m, 2H), 2.19-2.01 (m, 3H), 1.72-1.61 (m, 1H), 1.43-1.07 (m, 6H), 0.62-0.59 (m, 3H).
INT-10	5-amino-1-phenyl-1H-pyrazole-4-carbaldehyde	3-(5-(2-((5-amino-1-phenyl-1H-pyrazol-4-yl)methyl)-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-71**)	Positive $[M+H]^+$ = 583.8	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 9.48 (s, 1H), 7.73 (d, J = 8.40 Hz, 1H), 7.67-7.59 (m, 7H), 7.41 (t, J = 5.20 Hz, 1H), 5.53 (s, 3H), 5.15-5.11 (m, 1H), 4.52-4.46 (m, 1H), 4.37-4.24 (m, 3H), 3.67 (d, J = 12.00 Hz, 1H), 3.35-3.11 (m, 3H), 2.94-2.90 (m, 2H), 2.68-2.64 (m, 1H), 2.50-2.34 (m, 2H), 2.02 (s, 1H), 1.77 (t, J = 14.80 Hz, 2H),

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
				1.46-1.37 (m, 5H), 0.76-0.73 (m, 3H).
INT-8	6-(1,2,4-oxadiazol-3-yl)nicotinaldehyde (**ALD-4**)	3-(5-(1-((6-(1,2,4-oxadiazol-3-yl)pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-204**)	Positive $[M+H]^+$ = 549.3	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 10.62 (s, 1H), 9.83 (s, 1H), 9.08 (s, 1H), 8.45 (d, J = 8.1 Hz, 1H), 8.23 (d, J = 8.1 Hz, 1H), 7.88 (t, J = 7.2 Hz, 1H), 7.62 (d, J = 7.9 Hz, 1H), 6.04-5.77 (m, 1H), 5.12 (ddd, J = 2.5, 4.8, 13.2 Hz, 1H), 4.66-4.44 (m, 3H), 4.43-4.33 (m, 1H), 3.45-3.23 (m, 4H), 2.98-2.84 (m, 2H), 2.61 (d, J = 16.8 Hz, 1H), 2.47-2.38 (m, 1H), 2.07-1.87 (m, 2H), 1.09 (br s, 3H), 0.75 (d, J = 7.8 Hz, 3H)
INT-8	4-(3,3-difluorocyclobutyl)benzaldehyde (**ALD-109**)	3-(5-(1-(4-(3,3-difluorocyclobutyl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-189**)	positive $[M+H]^+$ = 570.5	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 9.73-9.35 (m, 1H), 7.87 (t, J = 7.4 Hz, 1H), 7.66-7.59 (m, 3H), 7.45 (d, J = 8.1 Hz, 2H), 5.89-5.81 (m, 1H), 5.18-5.05 (m, 1H), 4.61-4.50 (m, 1H), 4.45-4.30 (m, 3H), 3.54-3.44 (m, 1H), 3.27-3.15 (m, 3H), 3.11-2.84 (m, 4H), 2.81-2.69 (m, 2H), 2.65-2.56 (m, 1H), 2.47-2.36 (m, 1H), 2.06-1.87 (m, 2H), 1.04 (br. s, 3H), 0.79-0.68 (m, 3H)
INT-8	4-(isoxazol-3-yl)benzaldehyde (**ALD-6**)	3-(4-fluoro-5-(4-hydroxy-1-(4-(isoxazol-3-yl)benzyl)-3,3-dimethylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-	positive $[M+H]^+$ = 547.4	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 9.91-9.58 (m, 1H), 9.07 (d, J = 1.6 Hz, 1H), 8.03 (d, J = 8.4 Hz, 2H), 7.92-7.77 (m, 3H), 7.62 (d, J = 8.1 Hz, 1H), 7.23 (d, J = 1.7 Hz, 1H), 5.87 (d, J = 6.4 Hz, 1H), 5.19-5.04 (m, 1H),

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
		2,6-dione (**I-211**)		4.62-4.31 (m, 4H), 3.37 (br s, 2H), 3.28-3.20 (m, 2H), 2.99-2.84 (m, 2H), 2.65-2.56 (m, 1H), 2.47-2.36 (m, 1H), 2.04-1.88 (m, 2H), 1.06 (br s, 3H), 0.74 (d, *J* = 8.1 Hz, 3H).
INT-51	4-(isoxazol-3-yl)benzaldehyde (**ALD-6**)	3-(2-(4-hydroxy-1-(4-(isoxazol-3-yl)benzyl)-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-542**)	Positive $[M+H]^+$ = 530.2	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.15-10.89 (m, 1H), 9.98-9.59 (m, 1H), 9.07 (d, *J* = 1.6 Hz, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 8.03 (d, *J* = 8.3 Hz, 2H), 7.87-7.78 (m, 3H), 7.23 (d, *J* = 1.6 Hz, 1H), 5.84 (br s, 1H), 5.15 (s, 1H), 4.61-4.27 (m, 4H), 3.32-3.20 (m, 3H), 2.99-2.83 (m, 2H), 2.55 (br s, 2H), 2.46-2.36 (m, 1H), 2.09-1.98 (m, 1H), 1.84-1.70 (m, 1H), 0.94 (s, 3H), 0.78 (d, *J* = 6.2 Hz, 3H).
INT-51	4-(1,3,4-oxadiazol-2-yl)benzaldehyde	3-(2-(1-(4-(1,3,4-oxadiazol-2-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-558**)	Positive $[M+H]^+$ = 531.4	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 9.34 (s, 1H), 8.12 (dd, *J* = 0.6, 8.1 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 5.23-5.07 (m, 2H), 4.52 (dd, *J* = 4.3, 17.6 Hz, 1H), 4.34 (dd, *J* = 3.7, 17.7 Hz, 1H), 3.73-3.49 (m, 2H), 3.08-2.86 (m, 2H), 2.79-2.57 (m, 2H), 2.55-2.52 (m, 2H), 2.49-2.39 (m, 2H), 2.17 (d, *J* = 10.5 Hz, 1H), 2.09-1.98 (m, 1H), 1.54-1.43 (m, 1H), 0.92 (s, 3H), 0.69 (d, *J* = 3.5 Hz, 3H)
INT-51	4-chlorobenzaldehyde	3-(2-(1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperid	Positive $[M+H]^+$ = 497.3	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 10.35-9.82 (m, 1H), 8.17 (dd, *J* = 0.7, 8.2 Hz, 1H),

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
		in-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-452**)		7.84 (d, *J* = 8.1 Hz, 1H), 7.75 (dd, *J* = 3.0, 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 5.83 (br s, 1H), 5.24-5.08 (m, 1H), 4.62-4.23 (m, 4H), 3.31-3.12 (m, 3H), 3.03-2.86 (m, 1H), 2.79 (t, *J* = 11.4 Hz, 1H), 2.62 (d, *J* = 16.8 Hz, 1H), 2.48-2.35 (m, 2H), 2.08-1.97 (m, 1H), 1.81-1.68 (m, 1H), 0.94 (s, 3H), 0.77 (d, *J* = 5.6 Hz, 3H)
INT-51	4-formylbenzonitrile	4-((4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)benzonitrile (**I-459**)	Positive $[M+H]^+$ = 488.1	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 10.36-9.80 (m, 1H), 8.17 (d, *J* = 8.1 Hz, 1H), 8.01-7.96 (m, 2H), 7.96-7.90 (m, 2H), 7.84 (d, *J* = 8.1 Hz, 1H), 5.91-5.77 (m, 1H), 5.18 (br dd, *J* = 3.8, 13.0 Hz, 1H), 4.59-4.30 (m, 4H), 3.41 (br s, 1H), 3.32-3.16 (m, 3H), 3.02-2.75 (m, 2H), 2.62 (br d, *J* = 16.1 Hz, 1H), 2.45-2.36 (m, 1H), 2.13-1.94 (m, 1H), 1.82-1.70 (m, 1H), 0.94 (s, 3H), 0.76 (d, *J* = 5.7 Hz, 3H)
INT-51	4-(trifluoromethoxy)benzaldehyde	3-(2-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-467**)	Positive $[M+H]^+$ = 547.1	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H), 10.10-9.42 (m, 1H), 8.18 (dd, *J* = 0.8, 8.1 Hz, 1H), 7.89-7.76 (m, 3H), 7.51 (d, *J* = 8.3 Hz, 2H), 5.84 (br s, 1H), 5.25-5.07 (m, 1H), 4.59-4.29 (m, 4H), 3.41-3.34 (m, 2H), 3.32-3.17 (m, 3H), 3.03-2.75 (m, 2H), 2.62 (d, *J* = 16.8 Hz, 1H), 2.46-2.36 (m, 1H), 2.09-1.96 (m, 1H), 1.77 (dd, *J* = 6.7, 10.8 Hz, 1H), 0.94 (s,

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
				3H), 0.78 (d, *J* = 5.7 Hz, 3H)
INT-51	4-(1,1-difluoroethyl)benzaldehyde	3-(2-(1-(4-(1,1-difluoroethyl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-510**)	Positive $[M+H]^+$ = 527.1	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 11.03 (s, 1H), 9.94-9.29 (m, 1H), 8.18 (dd, *J* = 0.7, 8.2 Hz, 1H), 7.88-7.63 (m, 5H), 5.83 (d, *J* = 2.7 Hz, 1H), 5.19 (dd, *J* = 5.0, 13.3 Hz, 1H), 4.59-4.29 (m, 4H), 3.30-3.14 (m, 3H), 3.00-2.82 (m, 2H), 2.66-2.55 (m, 2H), 2.46-2.36 (m, 1H), 2.01 (t, *J* = 18.9 Hz, 4H), 1.77 (dd, *J* = 6.5, 12.2 Hz, 1H), 0.93 (s, 3H), 0.78 (d, *J* = 6.0 Hz, 3H)
INT-51	6-(1,2,4-oxadiazol-3-yl)nicotinaldehyde (**ALD-4**)	3-(2-(1-((6-(1,2,4-oxadiazol-3-yl)pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-535**)	positive $[M+H]^+$ = 532.4	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 11.01 (s, 1H), 9.77 (s, 1H), 8.74 (d, *J* = 1.4 Hz, 1H), 8.19 (s, 1H), 8.11 (dd, *J* = 4.7, 8.0 Hz, 2H), 8.00 (dd, *J* = 1.6, 8.1 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 5.23-5.10 (m, 2H), 4.64-4.24 (m, 2H), 3.78-3.53 (m, 2H), 3.15-2.57 (m, 5H), 2.47-2.36 (m, 2H), 2.21-1.94 (m, 2H), 1.49 (dd, *J* = 2.6, 13.6 Hz, 1H), 0.90 (s, 3H), 0.69 (d, *J* = 3.7 Hz, 3H)
INT-51	3-methyl-4-(1,2,4-oxadiazol-3-yl)benzaldehyde (**ALD-10**)	3-(2-(4-hydroxy-3,3-dimethyl-1-(3-methyl-4-(1,2,4-oxadiazol-3-yl)benzyl) piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-	positive $[M+H]^+$ = 545.1	1H NMR (400 MHz, DMSO-*d*$_6$, 298 K) δ (ppm): 11.01 (s, 1H), 9.70 (s, 1H), 8.20 (s, 1H), 8.12 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.44-7.35 (m, 2H), 5.18 (dd, *J* = 5.1, 13.2 Hz, 1H), 5.11 (br s, 1H), 4.59-4.44 (m, 1H), 4.39-4.27 (m, 1H), 3.67-3.47 (m, 3H), 3.08-2.86 (m, 2H), 2.75 (d,

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
		yl)piperidine-2,6-dione **(I-534)**		*J* = 9.5 Hz, 1H), 2.62 (d, *J* = 18.0 Hz, 1H), 2.57 (s, 3H), 2.48-2.39 (m, 2H), 2.18 (d, *J* = 10.5 Hz, 1H), 2.10-1.99 (m, 1H), 1.48 (dd, *J* = 2.1, 13.5 Hz, 1H), 0.92 (s, 3H), 0.68 (d, *J* = 3.7 Hz, 3H).
INT-51	6-(oxazol-4-yl)nicotinaldehyde (**ALD-5**)	3-(2-(4-hydroxy-3,3-dimethyl-1-((6-(oxazol-4-yl)pyridin-3-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **(I-549)**	positive $[M+]^+$ = 530.2	1H NMR (400 MHz, DMSO-*d*$_6$, 298 K) δ (ppm): 11.02 (s, 1H), 8.45 (br s, 1H), 8.17 (s, 1H), 8.14-8.09 (m, 1H), 7.84 (d, *J* = 8.1 Hz, 2H), 7.77-7.70 (m, 2H), 5.27-5.05 (m, 2H), 4.57-4.46 (m, 1H), 4.40-4.24 (m, 1H), 3.63-3.57 (m, 1H), 3.47 (d, *J* = 13.8 Hz, 2H), 3.00-2.88 (m, 2H), 2.81-2.72 (m, 1H), 2.66-2.58 (m, 1H), 2.48-2.44 (m, 2H), 2.19-2.13 (m, 1H), 2.08-1.98 (m, 1H), 1.57-1.38 (m, 1H), 0.88 (s, 3H), 0.68 (d, *J* = 3.5 Hz, 3H).

Example 82: General procedure C- Reductive amination

To a stirred solution of the amine or the amine hydrochloride (0.1 mmol, 1.0 equiv) in DMF (1 mL) and the aldehyde (0.12 mmol, 1.2 equiv) at 25 °C is added acetic acid (0.1 mmol, 1.0 equiv) and the resulting mixture is stirred for 0.5 to 1 h. Sodium triacetoxyborohydride (0.3 mmol, 3.0 equiv) is then added and stirring is continued for 16 h. The reaction mixture is then concentrated under reduced pressure to afford crude compound, which is purified by reverse phase chromatography [(Column: X select (150 mm × 19) 5 µm, eluting with Mobile phase A: 0.05% FA or HCl in H_2O, Mobile phase B: ACN, flow rate: 15 mL/min)]. The fractions containing pure product are combined and concentrated via lyophilization to afford the desired product the formic acid salt, the hydrochloric salt, or the free amine.

The following compounds in Table 3 were prepared from corresponding amine or amine hydrochloride and aldehyde according to a reductive amination procedure described in General Procedure C.

Table 3:

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
INT-10	3-methyl-1H-pyrrole-2-carbaldehyde	3-(5-(5-hydroxy-2-((3-methyl-1H-pyrrol-2-yl)methyl)-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-81**)	positive $[M+H]^+$ = 505.8	^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 10.32 (s, 1H), 8.19 (s, 1H), 7.67-7.56 (m, 3H), 6.53 (t, J = 2.40 Hz, 1H), 5.80 (t, J = 2.40 Hz, 1H), 5.14-5.09 (m, 1H), 4.68 (d, J = 3.20 Hz, 1H), 4.45-4.42 (m, 1H), 4.35-4.33 (m, 1H), 3.45-3.33 (m, 2H), 2.90-2.63 (m, 2H), 2.58-2.50 (m, 3H), 2.42-2.41 (m, 1H), 2.34-2.31 (m, 2H), 2.17 (s, 3H), 2.14-2.02 (m, 1H), 1.43-1.10 (m, 7H), 0.48-0.58 (m, 3H).

Example 83: General procedure D- Reductive amination

To a stirred solution of the amine or the amine hydrochloride (0.1 mmol, 1.0 equiv) in DMF (1 mL) and the aldehyde (0.12 mmol, 1.2 equiv) at 25 °C was added sodium acetate (0.5 mmol, 5.0 equiv) and acetic acid (0.3 mmol, 3.0 equiv) and the resulting mixture was stirred for 30 min. MP-Cyanoborohydride (0.15 mmol) was then added and stirring was continued for 16 h. (If reaction was not complete after 16 h, temperature was raised to 60 °C). The reaction mixture was then filtered, and the filtrate was concentrated under reduced pressure to afford crude compound, which was purified by reverse phase chromatography [(Column: X select (150 mm × 19) 5 µm, eluting with Mobile phase A: 0.05% FA or HCl in H_2O, Mobile phase B: ACN, flow rate: 15 mL/min)]. The fractions containing pure product were combined and concentrated via lyophilization to afford the desired product as the formic acid salt, the hydrochloric salt, or the free amine.

The following compounds in Table 4 were prepared from corresponding amine or amine hydrochloride and aldehyde according to a reductive amination procedure described in General Procedure D.

Table 4:

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
INT-1	benzaldehyde	3-(5-(1-benzyl-4-hydroxypiperidin-4-yl)-4-methoxy-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-23**)	Positive $[M+H]^+$ = 464.0	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 10.30 (s, 1H), 7.78 (d, J = 8.00 Hz, 1H), 7.68-7.64 (m, 2H), 7.50-7.43 (m, 4H), 5.63 (s, 1H), 5.12 (d, J = 4.80 Hz, 1H), 4.69 (d, J = 17.20 Hz, 1H), 4.51 (d, J = 16.80 Hz, 1H), 4.38 (d, J = 4.40 Hz, 2H), 4.01 (s, 3H), 3.27 (br s, 4H), 2.96-2.89 (m, 1H), 2.70-2.30 (m, 4H), 2.02-1.99 (m, 1H), 1.70 (d, J = 13.20 Hz, 2H).
INT-1	4-(trifluoromethyl)benzaldehyde	3-(5-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-methoxy-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-22**)	Positive $[M+H]^+$ = 532	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 10.57 (s, 1H), 7.94-7.87 (m, 4H), 7.78 (d, J = 8.00 Hz, 1H), 7.44 (d, J = 8.00 Hz, 1H), 5.65 (s, 1H), 5.14-5.09 (m, 1H), 4.69 (d, J = 16.80 Hz, 1H), 4.53-4.49 (m, 3H), 4.01 (s, 3H), 3.73-3.29 (m, 4H), 2.97-2.87 (m, 1H), 2.69-2.33 (m, 4H), 2.02-2.00 (m, 1H), 1.69 (d, J = 14.80 Hz, 2H).
INT-10	2-amino-6-(trifluoromethyl)nicotinaldehyde	3-(5-(2-((2-amino-6-(trifluoromethyl)pyridin-3-yl)methyl)-5-hydroxy-2-azaspiro[5.5]un	Positive $[M+H]^+$ = 586.5	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 7.68-7.56 (m, 4H), 6.96 (d, J = 7.60 Hz, 1H), 6.71 (d, J = 4.80 Hz, 2H), 5.14-5.10 (m, 1H), 4.85 (d, J = 4.40 Hz, 1H), 4.50-

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
		decan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-74**)		4.43 (m, 1H), 4.36-4.30 (m, 1H), 3.49 (s, 2H), 2.92-2.90 (m, 2H), 2.87-2.67 (m, 3H), 2.50-2.30 (m, 2H), 1.98-2.08 (m, 2H), 1.71 (d, J = 13.20 Hz, 1H), 1.46 (d, J = 11.60 Hz, 1H), 1.45-1.26 (m, 5H), 0.69-0.99 (m, 3H).
INT-17	benzaldehyde	3-(5-(1-benzyl-4-hydroxypiperidin-4-yl)-1-oxo-4-(trifluoromethyl)isoindolin-2-yl)piperidine-2,6-dione **(I-26)**	Positive $[M+H]^+$ = 502.1	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 10.35 (s, 1H), 8.04 (d, J = 8.00 Hz, 1H), 7.77 (d, J = 8.00 Hz, 1H), 7.64 (d, J = 8.00 Hz, 2H), 7.51 (d, J = 8.00 Hz, 3H), 5.76 (s, 1H), 5.16-5.12 (m, 1H), 4.77-4.60 (m, 2H), 4.38-4.37 (m, 2H), 4.35 (s, 2H), 3.38-3.34 (m, 2H), 3.31-3.27 (m, 2H), 2.91-2.81 (m, 1H), 2.68-2.62 (m, 1H), 2.09-2.02 (m, 4H)
INT-50	nicotinaldehyde	3-(2-(4-hydroxy-1-(pyridin-3-ylmethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-418**)	Positive $[M+H]^+$ = 436.4	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 10.49 (s, 1H), 8.92 (s, 1H), 8.78 (s, 1H), 8.31 (s, 1H), 8.21 (d, J = 8.00 Hz, 1H), 7.87 (d, J − 8.00 Hz, 1H), 7.72 (s, 1H), 5.21-5.16 (m, 1H), 4.54-4.50 (m, 3H), 4.40 (s, 1H), 3.69-3.33 (m, 4H), 2.98-2.90 (m, 1H), 2.68-2.43 (m, 5H), 2.04-2.03 (m, 1H), 1.86-1.76 (m, 2H),
INT-50	4-(4-fluorophenoxy)benzaldehyde	3-(2-(1-(4-(4-fluorophenoxy)benzyl)-4-hydroxypiperidin-4-yl)-5-oxo-	Positive $[M+H]^+$ = 545.3	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 9.83 (br s, 1H), 8.22-8.20 (m, 1H), 7.86 (d, J = 8.00 Hz, 1H), 7.58 (d, J −

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
		5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-410**)		8.40 Hz, 2H), 7.30-7.25 (m, 2H), 7.17-7.14 (m, 2H), 7.14 (d, *J* = 2.40 Hz, 2H), 5.97 (br s), 5.21-5.17 (m, 1H), 4.53-4.49 (m, 1H), 4.38-4.32 (m, 3H), 3.45-3.27 (m, 4H), 2.93-2.90 (m, 1H), 2.71-2.60 (m, 2H), 2.51-2.50 (m, 2H), 2.04-2.01 (m, 1H), 1.84-1.81 (m, 2H).
INT-50	isonicotinaldehyde	3-(2-(4-hydroxy-1-(pyridin-4-ylmethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-409**)	Positive $[M+H]^+$ = 436.0	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 11.02 (s, 1H), 10.681 (br,s 1H), 8.82 (d, *J* = 5.20 Hz, 2H), 8.21 (d, *J* = 8.00 Hz, 1H), 7.87 (d, *J* = 8.00 Hz, 3H), 5.21-5.17 (m, 1H), 4.55-4.50 (m, 3H), 4.37-4.32 (m, 2H), 3.83-3.35 (m, 4H), 2.95-2.89 (m, 1H), 2.68-2.51 (m, 1H), 2.51-2.39 (m, 2H), 2.08-2.02 (m, 2H), 1.85-1.76 (m, 2H).
INT-50	4-(1,1,2,2-tetrafluoroethoxy)benzaldehyde	3-(2-(4-hydroxy-1-(4-(1,1,2,2-tetrafluoroethoxy)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-423**)	Negative $[M-H]^-$ = 549.4	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 11.02 (s, 1H), 10.38 (s, 1H), 8.21 (d, *J* = 8.1 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.76 (d, *J* = 8.7 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 6.85 (m, 1H), 5.9 (br s, 1H), 5.18 (q, *J* = 6.1 Hz, 1H), 4.52-4.43 (m, 4H), 3.31 (d, *J* = 10.3 Hz, 4H), 2.93 (m, 1H), 2.61-2.42 (m, 4H), 2.03 (t, *J* = 5.4 Hz, 1H), 1.84 (t, *J* = 4.9 Hz, 2H).
INT-50	4-((trifluoromet	3-(2-(4-hydroxy-1-(4-((trifluoromethy	Positive $[M+H]^+$ = 535.3	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 11.02 (s, 1H), 10.35 (s, 1H), 8.21

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
	hyl)thio)benzaldehyde	l)thio)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-422**)		(d, *J* = 8.1 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 3H), 7.80 (t, *J* = 4.2 Hz, 2H), 5.99 (s, 1H), 5.19 (q, *J* = 6.1 Hz, 1H), 4.50 (q, *J* = 8.7 Hz, 3H), 4.34 (d, *J* = 7.8 Hz, 1H), 3.34 (m, 4H), 2.93 (m, 2H), 2.62 (t, *J* = 9.4 Hz, 1H), 2.43 (t, *J* = 6.5 Hz, 2H), 2.03 (m, 1H), 1.84 (q, *J* = 6.0 Hz, 2H).
INT-50	4-formylbenzonitrile	4-((4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-4-hydroxypiperidin-1-yl)methyl)benzonitrile (**I-421**)	Positive $[M+H]^+$ = 460.3	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 11.02 (s, 1H), 10.36 (s, 1H), 8.21 (d, *J* = 8.00 Hz, 1H), 7.98 (d, *J* = 11.20 Hz, 2H), 7.85 (t, *J* = 6.40 Hz, 3H), 5.92 (br s, 1H), 5.19 (dd, *J* − 8.00, Hz, 1H), 4.51 (d, *J* = 5.60 Hz, 3H), 4.34 (d, *J* = 17.60 Hz, 1H), 3.33 (s, 4H), 2.93-2.90 (m, 1H), 2.57-2.43 (m, 4H), 2.04-2.01 (m, 1H), 1.85-1.80 (m, 2H).
INT-50	3-methoxy-4-(trifluoromethoxy)benzaldehyde	3-(2-(4-hydroxy-1-(3-methoxy-4-(trifluoromethoxy)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-419**)	Positive $[M+H]^+$ = 549.3	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 11.02 (s, 1H), 10.62 (s, 1H), 8.21 (t, *J* = 8.00 Hz, 1H), 7.86 (t, *J* = 8.00 Hz, 1H), 7.70 (t, *J* − 2.00 Hz, 1H), 7.47-7.44 (m, 1H), 7.28-7.25 (m, 1H), 5.18 (dd, *J* = 5.20, 13.40 Hz, 1H), 4.55-4.28 (m, 4H), 3.91 (s, 3H), 3.36-3.28 (m, 4H), 2.96-2.90 (m, 1H), 2.50-2.33 (m, 5H), 2.05-2.01 (m, 1H), 1.87-1.82 (m, 2H).
INT-50	4-fluorobenzaldehyde	3-(2-(1-(4-fluorobenzyl)-4-hydroxypiperidi	Positive $[M+H]^+$ = 453.6	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 11.02 (s, 1H), 10.09 (s, 1H), 8.21 (d, *J* − 8.40 Hz, 1H), 7.86

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
		n-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-417**)		(d, *J* = 8.40 Hz, 1H), 7.67 (q, *J* = 2.00 Hz, 2H), 7.33 (t, *J* = 2.80 Hz, 2H), 5.90 (br s, 1H), 5.19 (dd, *J* = 5.20, 13.20 Hz, 1H), 4.52 (d, *J* = 17.60 Hz, 1H), 4.40-4.32 (m, 3H), 3.32-3.27 (m, 4H), 2.93 (t, *J* = 8.40 Hz, 1H), 2.67-2.44 (m, 4H), 2.05-2.01 (m, 1H), 1.85-1.81 (m, 2H).
INT-50	3-methoxy-4-(trifluoromethyl)benzaldehyde	3-(2-(4-hydroxy-1-(3-methoxy-4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-416**)	Positive $[M+H]^+$ = 533.0	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 11.03 (s, 1H), 10.44 (s, 1H), 8.21 (d, *J* = 8.00 Hz, 1H), 7.87 (d, *J* = 8.00 Hz, 1H), 7.71 (dd, *J* = 12.80, 16.40 Hz, 2H), 7.32 (d, *J* = 8.00 Hz, 1H), 5.90 (s, 1H), 5.19 (dd, *J* = 5.20, 13.20 Hz, 1H), 4.54-4.46 (m, 3H), 4.34 (d, *J* = 18.00 Hz, 1H), 3.95 (s, 3H), 3.34 (s, 4H), 2.93-2.86 (m, 1H), 2.65 (d, *J* = 13.60 Hz, 2H), 2.46-2.41 (m, 2H), 2.05-2.01 (m, 1H), 1.86-1.81 (m, 2H).
INT-50	4-(difluoromethoxy)benzaldehyde	3-(2-(1-(4-(difluoromethoxy)benzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-415**)	Positive $[M+H]^+$ = 501.2	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 11.02 (s, 1H), 10.11 (s, 1H), 8.21 (d, *J* = 8.00 Hz, 1H), 7.86 (d, *J* = 8.40 Hz, 1H), 7.67 (d, *J* = 8.80 Hz, 2H), 7.31 (t, *J* = 8.40 Hz, 3H), 5.95 (s, 1H), 5.19 (dd, *J* = 5.20, 13.20 Hz, 1H), 4.51 (d, *J* = 18.00 Hz, 1H), 4.40-4.32 (m, 3H), 3.28 (s, 4H), 2.98-2.89 (m, 1H), 2.61 (d, *J* = 17.20 Hz, 2H), 2.41 (d, *J* = 4.40 Hz, 2H), 2.05-2.01 (m, 1H),

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
				1.83 (dd, *J* = 6.40, 14.00 Hz, 2H).
INT-50	4-methylbenzaldehyde	3-(2-(4-hydroxy-1-(4-methylbenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-414**)	Positive $[M+H]^+$ = 449.2	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 11.02 (s, 1H), 10.01 (s, 1H), 8.20 (d, *J* = 8.40 Hz, 1H), 7.85 (d, *J* = 8.00 Hz, 1H), 7.48 (d, *J* = 7.60 Hz, 2H), 7.30 (d, *J* = 8.00 Hz, 2H), 5.96 (br s, 1H), 5.21-5.16 (m, 1H), 4.51 (d, *J* = 18.00 Hz, 1H), 4.36-4.32 (m, 3H), 3.31-3.22 (m, 4H), 2.98-2.89 (m, 1H), 2.63 (m, 1H), 2.51-2.50 (m, 2H), 2.42-2.35 (m, 3H), 2.08-1.91 (m, 2H), 1.83-1.76 (m, 2H).
INT-50	4-chlorobenzaldehyde	3-(2-(1-(4-chlorobenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-413**)	Positive $[M+H, M+2H]^+$ = 469.2, 471.2	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 11.02 (s, 1H), 10.13 (s, 1H), 8.21 (d, *J* = 8.00 Hz, 1H), 7.86 (d, *J* = 8.00 Hz, 1H), 7.65 (d, *J* = 6.80 Hz, 2H), 7.57 (d, *J* = 2.40 Hz, 2H), 5.95 (br s, 1H), 5.21-5.16 (m, 1H), 4.54-4.49 (m, 1H), 4.41-4.32 (m, 3H), 3.32-3.27 (m, 4H), 2.98-2.89 (m, 1H), 2.64-2.60 (m, 2H), 2.45-2.41 (m, 2H), 2.04-2.00 (m, 1H), 1.85-1.80 (m, 2H).
INT-50	4-(1,1-difluoroethyl)benzaldehyde	3-(2-(1-(4-(1,1-difluoroethyl)benzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-	Positive $[M+H]^+$ = 499.3	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 11.02 (s, 1H), 10.07 (s, 1H), 8.22-8.20 (m, 1H), 7.87-7.85 (m, 1H), 7.74-7.69 (m, 4H), 5.97 (br s, 1H), 5.21-5.17 (m, 1H), 4.54-4.46 (m, 3H), 4.36-4.32 (m, 1H), 3.50-3.34 (m, 4H), 2.97-2.89 (m, 1H), 2.64-

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
		2,6-dione (**I-408**)		2.60 (m, 1H), 2.46-2.38 (m, 3H), 2.05-2.00 (m, 4H), 1.96-1.81 (m, 2H).

Example 84: General procedure E- Reductive amination

To a stirred solution of the amine or the amine hydrochloride (0.1 mmol, 1.0 equiv) in DMF (1 mL) was added acetic acid (0.1 mmol, 0.1 equiv) and triethylamine (0.5 mmol, 5.0 equi)) followed by and aldehyde (0.12 mmol, 1.2 equiv) at 25°C. The resulting mixture is stirred for 4 h. Sodium cyanoborohydride (0.5 mmol, 5.0 equiv) is then added and stirring is continued for 16 h. The reaction mixture is concentrated under reduced pressure to afford crude compound, which is purified by reverse phase chromatography [(Column: X select (150 mm × 19) 5 µm, eluting with Mobile phase A: 0.05% FA or HCl in H_2O, Mobile phase B: ACN, flow rate: 15 mL/min)]. The fractions containing pure product are combined and concentrated via lyophilization to afford the desired product as the formic acid salt, the hydrochloric salt, or the free amine.

The following compounds in Table 5 were prepared from corresponding amine or amine hydrochloride and aldehyde according to a reductive amination procedure described in General Procedure E.

Table 5:

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
INT-10	2-chloro-4-formylbenzonitrile	2-chloro-4-((5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-5-hydroxy-2-azaspiro[5.5]undecan-2-yl)methyl)benzonitrile (**I-73**)	Positive $[M+H]^+$ = 561.3	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 7.96 (d, J = 8.00, Hz, 1H), 7.75 (d, J = 1.80 Hz, 1H), 7.69-7.63 (m, 3H), 7.55 (d, J = 8.00 Hz, 1H), 5.15-5.11 (m, 1H), 4.79 (d, J = 4.40 Hz, 1H), 4.50-4.29 (m, 2H), 3.69 (d, J = 14.40 Hz, 1H), 3.58 (d, J = 14.40 Hz, 1H), 2.93-2.90 (m, 1H), 2.81-2.79 (m, 2H), 2.68-2.63 (m, 5H), 2.55-2.46 (m, 1H), 2.25-2.02 (m, 1H),

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
				1.70-1.67 (m, 1H), 1.46-1.43 (m, 4H), 1.34-1.24 (m, 2H), 1.06-0.84 (m, 3H).
INT-10	3-chloro-4-methoxybenzaldehyde	3-(5-(2-(3-chloro-4-methoxybenzyl)-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-72**)	Positive $[M+H]^+$ = 567.6	^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 7.70-7.62 (m, 3H), 7.41 (d, J = 1.60 Hz, 1H), 7.26 (d, J = 10.00 Hz, 1H), 7.10 (d, J = 8.40 Hz, 1H), 5.14-5.10 (m, 1H), 4.74 (d, J = 4.00 Hz, 1H), 4.46-4.43 (m, 1H), 4.36-4.33 (m, 1H), 3.85 (s, 3H), 3.54 (d, J = 13.20 Hz, 1H), 2.92-2.74 (m, 4H), 2.38-2.21 (m, 2H), 2.19-2.01 (m, 1H), 1.87 (s, 1H), 1.70 (d, J = 34.40 Hz, 1H), 1.44 (d, J = 12.00 Hz, 1H), 1.32-1.24 (m, 4H), 1.24-0.55 (m, 6H).

Example 85: General procedure F-Reductive amination

To a stirred solution of the amine or the amine hydrochloride (0.1 mmol, 1.0 equiv) in DMF (1 mL) and the aldehyde (0.12 mmol, 1.2 equiv) was added MP-cyanoborohydride (0.1 mmol, 1.0 equiv) at 25°C. The resulting mixture was stirred at 80 °C for 12 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to afford crude compound, which was purified by reverse phase chromatography [(Column: X select (150 mm × 19) 5 µm, eluting with Mobile phase A: 0.05% FA or HCl in H_2O, Mobile phase B: ACN, flow rate: 15 mL/min)]. The fractions containing pure product were combined and concentrated via lyophilization to afford the desired product as the formic acid salt, the hydrochloride salt, or the free amine.

The following compounds in Table 6 were prepared from corresponding amine or amine hydrochloride and aldehyde according to a reductive amination procedure described in General Procedure F.

Table 6:

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
INT-5	4-(2,2-dichlorocyclopropyl)benzaldehyde (**ALD-12**)	3-(5-(1-(4-(2,2-dichlorocyclopropyl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-309**)	Positive $[M+H]^+$ = 570.1	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 10.99 (s, 1H), 7.71 (s, 1H), 7.65 (s, 2H), 7.34 (d, J = 8.40 Hz, 2H), 7.27 (d, J = 8.00 Hz, 2H), 5.14-5.11 (m, 1H), 4.79 (s, 1H), 4.49-4.42 (m, 1H), 4.35-4.33 (m, 1H), 3.54-3.43 (m, 2H), 3.08-2.92 (m, 1H), 2.75-2.68 (m, 2H), 2.63-2.51 (m, 2H), 2.16-2.12 (m, 5H), 1.91 (s, 2H), 1.50-1.14 (m, 1H), 0.88 (s, 3H), 0.64 (s, 3H).
INT-8	1-(4-formylphenyl)cyclopropane-1-carbonitrile (**ALD-7**)	1-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)-phenyl)cyclopropane-1-carbonitrile (**I-311**)	Positive $[M+H]^+$ = 545.3	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 11.01 (s, 1H), 7.89 (s, 1H), 7.56 (d, J = 8.00 Hz, 1H), 7.36 (d, J = 8.00 Hz, 2H), 7.30 (d, J = 8.40 Hz, 2H), 5.14-5.06 (m, 2H), 4.54 (d, J = 14.80 Hz, 1H), 4.38 (d, J = 5.60 Hz, 1H), 3.56-3.42 (m, 2H), 3.10-2.98 (m, 2H), 2.68-2.67 (m, 2H), 2.46-2.34 (m, 2H), 2.15 (d, J = 10.40 Hz, 1H), 2.08 (m, 1H), 1.75-1.74 (m, 2H), 1.49 (d, J = 12.00 Hz, 1H), 1.63-1.62 (m, 1H), 1.49-1.48 (m, 2H), 0.97 (s, 3H), 0.63 (s, 3H).
INT-8	4-(5-methyl-1,3,4-oxadiazol-2-yl)benzaldehyde	3-(4-fluoro-5-(4-hydroxy-3,3-dimethyl-1-(4-(5-methyl-1,3,4-oxadiazol-2-yl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-335**)	Positive $[M+H]^+$ = 562.5	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 11.01 (s, 1H), 7.95 (d, J = 8.40 Hz, 1H), 7.90 (t, J = 5.60 Hz, 2H), 7.58-7.56 (m, 3H), 5.14-5.10 (m, 2H), 4.57-4.57 (m, 1H), 4.53-4.52 (m, 1H), 3.67-3.52 (m, 2H), 2.92 (m, 2H), 2.68-2.67 (m, 2H), 2.63 (s, 3H),

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
				2.47-2.42 (m, 3H), 2.17 (d, J = 10.40 Hz, 1H), 2.03-2.01 (m, 1H), 1.79-1.76 (m, 1H), 1.00 (s, 3H), 0.65 (s, 3H).
INT-8	3-fluoro-4-(1,2,4-oxadiazol-3-yl)benzaldehyde (**ALD-9**)	3-(4-fluoro-5-(1-(3-fluoro-4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-337**)	Positive $[M+H]^+$ = 566.3	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 9.77 (s, 1H), 8.03 (t, J = 8.00 Hz, 1H), 7.92-7.88 (m, 1H), 7.57 (d, J = 8.00 Hz, 1H), 7.44-7.41 (m, 2H), 5.13-5.11 (m, 2H), 4.57 (d, J = 2.80 Hz, 1H), 4.46 (d, J = 50.00 Hz, 1H), 3.69-3.54 (m, 2H), 3.08-3.04 (m, 1H), 2.92 (m, 1H), 2.68-2.63 (m, 4H), 2.47-2.42 (m, 1H), 2.18 (d, J = 10.40 Hz, 1H), 2.01 (m, 1H), 1.79-1.75 (m, 1H), 1.02 (s, 3H), 0.66 (s, 3H).
INT-8	benzaldehyde	3-(5-(1-benzyl-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-344**)	Positive $[M+H]^+$ = 480.2	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 7.89 (t, J = 2.00 Hz, 1H), 7.56 (d, J = 8.00 Hz, 1H), 7.35-7.31 (m, 4H), 7.26-7.24 (m, 1H), 5.10-5.08 (m, 2H), 4.56 (d, J = 2.80 Hz, 1H), 4.52 (d, J = 2.80 Hz, 1H), 3.58-3.54 (m, 1H), 3.05 (m, 3H), 2.68-2.67 (m, 2H), 2.46-2.45 (m, 3H), 2.17 (d, J = 10.80 Hz, 1H), 2.03 (m, 1H), 1.80-1.75 (m, 1H), 0.98 (s, 3H), 0.64 (s, 3H).
INT-5	4-(1,2,4-oxadiazol-3-yl)benzaldehyde (**ALD-1**)	3-(5-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-1-oxoisoindolin-2-	Positive $[M+H]^+$ = 530.2	^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 9.70 (s, 1H), 8.02 (d, J = 8.00 Hz, 2H), 7.72 (d, J = 4.80 Hz, 1H), 7.66 (d, J = 2.40 Hz, 2H), 7.57 (d, J = 8.40 Hz, 2H), 5.14-5.11

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
		yl)piperidine-2,6-dione (**I-351**)		(m, 1H), 4.82 (s, 1H), 4.49-4.35 (m, 1H), 4.33-4.29 (m, 1H), 3.67-3.56 (m, 2H), 2.92 (m, 1H), 2.75-2.71 (m, 2H), 2.67-2.58 (m, 2H), 2.38-2.33 (m, 2H), 2.19-2.16 (m, 1H), 2.02-2.01 (m, 1H), 1.52-1.50 (m, 1H), 0.91 (s, 3H), 0.65 (s, 3H).
INT-5	4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzaldehyde	3-(5-(4-hydroxy-3,3-dimethyl-1-(4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-365**)	Positive $[M+H]^+$ = 598.1	^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 8.05 (d, J = 8.40 Hz, 2H), 7.72 (d, J = 4.80 Hz, 1H), 7.66 (d, J = 2.40 Hz, 2H), 7.62 (d, J = 8.40 Hz, 2H), 5.13-5.10 (m, 1H), 4.83 (d, J = 4.00 Hz, 1H), 4.49-4.42 (m, 1H), 4.35-4.29 (m, 1H), 3.67 (d, J = 14.00 Hz, 1H), 3.57-3.55 (m, 1H), 2.95-2.89 (m, 1H), 2.78-2.75 (m, 2H), 2.51-2.39 (m, 4H), 2.18-2.16 (m, 1H), 2.02-2.01 (m, 1H), 1.52-1.50 (m, 1H), 0.91 (s, 3H), 0.65 (s, 3H).
INT-5	1-(4-formylphenyl)cyclopropane-1-carbonitrile (**ALD-7**)	1-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)phenyl)cyclopropane-1-carbonitrile (**I-300**)	Positive $[M+H]^+$ = 527.1	^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 7.71 (d, J = 5.20 Hz, 1H), 7.66 (d, J = 6.80 Hz, 2H), 7.36 (d, J = 8.40 Hz, 2H), 7.29 (d, J = 8.40 Hz, 2H), 5.13-5.09 (m, 1H), 4.79 (d, J = 3.60 Hz, 1H), 4.44-4.42 (m, 1H), 4.35-4.33 (m, 1H), 3.55 (d, J = 13.60 Hz, 1H), 3.44 (d, J = 13.60 Hz, 1H), 2.99-2.79 (m, 1H), 2.70-2.67 (m, 3H), 2.34-2.33 (m, 3H), 2.14 (d, J = 10.40 Hz, 1H),

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
				2.01 (m, 1H), 1.75-1.72 (m, 2H), 1.51-1.48 (m, 3H), 0.88 (s, 3H), 0.64 (s, 3H).
INT-5	6-(1,2,4-oxadiazol-3-yl)nicotinaldehyde (**ALD-4**)	3-(5-(1-((6-(1,2,4-oxadiazol-3-yl)pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-285**)	Positive $[M+H]^+$ = 531.1	^{1}H-NMR (400 MHz, DMSO-*d6*): δ 10.99 (s, 1H), 9.77 (s, 1H), 8.75 (d, J = 1.60 Hz, 1H), 8.11 (d, J = 8.00 Hz, 1H), 7.99 (d, J = 2.00 Hz, 1H), 7.72 (d, J = 5.20 Hz, 1H), 7.66 (d, J = 2.00 Hz, 2H), 5.14-5.10 (m, 1H), 4.84 (d, J = 3.60 Hz, 1H), 4.49-4.43 (m, 1H), 4.35-4.29 (m, 1H), 3.71 (d, J = 14.00 Hz, 1H), 3.60 (d, J = 14.00 Hz, 1H), 2.92 (m, 1H), 2.79-2.73 (m, 2H), 2.68-2.62 (m, 2H), 2.51-2.42 (m, 2H), 2.18-2.16 (m, 1H), 2.03-2.01 (m, 1H), 1.53-1.51 (m, 1H), 0.90 (s, 3H), 0.66 (s, 3H).
INT-5	4-(5-methyl-1,3,4-oxadiazol-2-yl)benzaldehyde	3-(5-(4-hydroxy-3,3-dimethyl-1-(4-(5-methyl-1,3,4-oxadiazol-2-yl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-299**)	Positive $[M+H]^+$ = 544.2	^{1}H-NMR (400 MHz, DMSO-*d6*): δ 10.99 (s, 1H), 7.96 (d, J = 8.40 Hz, 2H), 7.72 (d, J = 5.20 Hz, 1H), 7.65 (s, 2H), 7.57 (d, J = 8.40 Hz, 2H), 5.14-5.10 (m, 1H), 4.82 (d, J = 3.60 Hz, 1H), 4.49-4.45 (m, 1H), 4.35-4.29 (m, 1H), 3.67-3.52 (m, 2H), 2.92-2.67 (m, 5H), 2.63 (s, 3H), 2.50-2.33 (m, 2H), 2.17-2.15 (m, 1H), 2.02-2.01 (m, 1H), 1.52-1.49 (m, 1H), 0.91 (s, 3H), 0.65 (s, 3H).
INT-5	6-(trifluoromet	3-(5-(4-hydroxy-3,3-dimethyl-1-((6-	Positive $[M+H]^+$ = 531.0	^{1}H-NMR (400 MHz, DMSO-*d6*): δ 10.99 (s, 1H), 8.75 (s, 1H), 8.05 (d, J

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
	hyl)nicotinaldehyde	(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-283**)		= 8.40 Hz, 1H), 7.90 (d, J = 8.00 Hz, 1H), 7.71 (d, J = 5.20 Hz, 2H), 7.66 (s, 1H), 5.14-5.10 (m, 1H), 4.85 (d, J = 4.00 Hz, 1H), 4.47-4.31 (m, 2H), 3.73-3.60 (m, 2H), 2.93-2.78 (m, 4H), 2.73-2.51 (m, 3H), 2.17-2.16 (m, 1H), 2.03-2.01 (m, 1H), 1.53-1.49 (m, 1H), 0.89 (s, 3H), 0.66 (s, 3H).
INT-51	3-chloro-4-(1,2,4-oxadiazol-3-yl)benzaldehyde (**ALD-8**)	3-(2-(1-(3-chloro-4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-581**)	Positive $[M+H]^+$ = 565.1	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 9.79 (s, 1H), 8.13 (d, J = 8.00 Hz, 1H), 7.92 (d, J = 8.00 Hz, 1H), 7.86 (d, J = 8.00 Hz, 1H), 7.68 (s, 1H), 7.54 (d, J = 8.00 Hz, 1H), 5.21-5.14 (m, 2H), 4.52 (d, J = 4.00 Hz, 1H), 4.34 (d, J = 3.60 Hz, 1H), 3.65-3.59 (m, 2H), 3.02-2.94 (m, 2H), 2.75 (s, 1H), 2.68-2.60 (m, 2H), 2.47-2.34 (m, 2H), 2.19-2.03 (m, 2H), 1.50 (d, J = 14.00 Hz, 1H), 0.93 (s, 3H), 0.70 (s, 3H).
INT-51	3-fluoro-4-(1,2,4-oxadiazol-3-yl)benzaldehyde (**ALD-9**)	3-(2-(1-(3-fluoro-4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-590**)	Positive $[M+H]^+$ = 549.3	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 9.77 (s, 1H), 8.12 (d, J = 8.00 Hz, 1H), 8.02 (t, J = 8.00 Hz, 1H), 7.85 (d, J = 8.00 Hz, 1H), 7.45-7.42 (m, 2H), 5.19-5.13 (m, 2H), 4.52 (dd, J = 4.00, 17.60 Hz, 1H), 4.34 (dd, J = 4.00, 17.60 Hz, 1H), 3.67 (d, J = 14.40 Hz, 1H), 3.57 (d, J = 14.40 Hz, 1H), 3.03-2.94 (m, 2H), 2.75 (s, 1H), 2.68-2.67 (m, 2H), 2.51-

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
				2.43 (m, 2H), 2.20-2.16 (m, 1H), 2.08-2.05 (m, 1H), 1.48 (d, J = 2.40 Hz, 1H), 0.93 (s, 3H), 0.70 (s, 3H).
INT-51	benzaldehyde	3-(2-(1-benzyl-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-597**)	Positive $[M+H]^+$ = 463.1	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.11 (d, J = 8.00 Hz, 1H), 7.84 (d, J = 8.40 Hz, 1H), 7.33-7.26 (m, 5H), 5.18 (dd, J = 5.20, 13.40 Hz, 1H), 5.09 (s, 1H), 4.51 (d, J = 4.40 Hz, 1H), 4.33 (d, J = 2.80 Hz, 1H), 3.56 (d, J = 13.60 Hz, 1H), 3.46 (d, J = 13.60 Hz, 1H), 2.99-2.94 (m, 2H), 2.74-2.67 (m, 2H), 2.44 (d, J = 10.80 Hz, 3H), 2.16 (d, J = 10.80 Hz, 1H), 2.04 (s, 1H), 1.47 (d, J = 14.00 Hz, 1H), 0.89 (s, 3H), 0.68 (s, 3H).
INT-51	4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzaldehyde	3-(2-(4-hydroxy-3,3-dimethyl-1-(4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-604**)	Positive $[M+H]^+$ = 599.2	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.12 (d, J = 7.60 Hz, 1H), 8.05 (d, J = 8.40 Hz, 2H), 7.85 (d, J = 8.00 Hz, 1H), 7.62 (d, J = 8.40 Hz, 2H), 5.19-5.12 (m, 2H), 4.53 (d, J = 14.80 Hz, 1H), 4.33 (d, J = 4.40 Hz, 1H), 3.68-3.59 (m, 2H), 3.02-2.91 (m, 2H), 2.64-2.52 (m, 4H), 2.17 (d, J = 10.40 Hz, 1H), 2.08-2.02 (m, 1H), 1.90 (s, 1H), 1.48 (d, J = 12.80 Hz, 1H), 0.92 (s, 3H), 0.69 (s, 3H).
INT-51	4-(5-methyl-1,3,4-oxadiazol-2-yl)benzaldehyde	3-(2-(4-hydroxy-3,3-dimethyl-1-(4-(5-methyl-1,3,4-oxadiazol-2-	Positive $[M+H]^+$ = 545.2	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.12 (d, J = 8.00 Hz, 1H), 7.95 (d, J = 8.00 Hz, 2H), 7.85 (d, J = 8.00 Hz,

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
		yl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-612**)		1H), 7.58 (d, J = 8.00 Hz, 2H), 5.21-5.12 (m, 2H), 4.54 (d, J = 4.00 Hz, 1H), 4.34 (d, J = 14.00 Hz, 1H), 3.66-3.54 (m, 2H), 3.01-2.91 (m, 2H), 2.75-2.64 (m, 3H), 2.51-2.44 (m, 5H), 2.19-2.15(m, 1H), 2.06-2.00 (m, 1H), 1.51-1.47 (m, 1H), 0.91 (s, 3H), 0.69 (s, 3H).
INT-51	1-(4-formylphenyl)cyclopropane-1-carbonitrile (**ALD-7**)	1-(4-((4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)phenyl)cyclopropane-1-carbonitrile (**I-614**)	Positive $[M+H]^+$ = 528.1	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ 11.02 (s, 1H), 11.02 (d, J = Hz, 1H), 7.84 (d, J = 8.00 Hz, 1H), 7.37 (d, J = 8.40 Hz, 2H), 7.29 (d, J = 8.40 Hz, 2H), 5.20-5.16 (m, 1H), 5.09 (s, 1H), 4.49 (d, J = 3.60 Hz, 1H), 4.35 (d, J = 3.60 Hz, 1H), 3.56-3.43 (m, 2H), 2.98-2.94 (m, 2H), 2.69-2.64 (m, 2H), 2.51-2.45 (m, 3H), 2.16-2.12 (m, 1H), 2.18 (s, 1H), 1.75-1.74 (m, 2H), 1.51-1.50 (m, 3H), 0.89 (s, 3H), 0.68 (s, 3H).
INT-51	6-(trifluoromethyl)nicotinaldehyde	3-(2-(4-hydroxy-3,3-dimethyl-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-621**)	Positive $[M+H]^+$ = 532.1	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ 11.02 (s, 1H), 8.74 (s, 1H), 8.12 (d, J = 8.00 Hz, 1H), 8.05 (d, J = 8.40 Hz, 1H), 7.90 (d, J = 8.00 Hz, 1H), 7.85 (d, J = 8.00 Hz, 1H), 5.20-5.16 (m, 2H), 4.51 (d, J = 15.60 Hz, 1H), 4.33 (d, J = 12.80 Hz, 1H), 3.68-3.64 (m, 2H), 3.00-2.93 (m, 3H), 2.68-2.67 (m, 2H), 2.47-2.44 (m, 2H), 2.33 (d, J = 1.60 Hz, 1H), 2.16-2.13 (m, 1H), 1.51-1.49 (m,

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
				1H), 0.90 (s, 3H), 0.69 (s, 3H).
INT-51	4-(2,2-dichlorocyclopropyl)benzaldehyde (**ALD-12**)	3-(2-(1-(4-(2,2-dichlorocyclopropyl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-628**)	Positive $[M+H]^+$ = 571.5	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.11 (d, J = 8.00 Hz, 1H), 7.84 (d, J = 8.40 Hz, 1H), 7.31 (q, J = 8.00 Hz, 4H), 5.20-5.16 (m, 1H), 5.09 (s, 1H), 4.49 (d, J = 3.60 Hz, 1H), 4.35 (d, J = 3.20 Hz, 1H), 3.57-3.45 (m, 2H), 3.11-3.06 (m, 1H), 2.98 (m, 2H), 2.70-2.67 (m, 1H), 2.60-2.51 (m, 1H), 2.46-2.34 (m, 3H), 2.14-2.08 (m, 4H), 1.44 (d, J = 4.40 Hz, 1H), 0.89 (s, 3H), 0.68 (s, 3H).
INT-51	4-(1-(trifluoromethyl)cyclopropyl)benzaldehyde (**ALD-13**)	3-(2-(4-hydroxy-3,3-dimethyl-1-(4-(1-(trifluoromethyl)cyclopropyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-629**)	Positive $[M+H]^+$ = 571.6	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.11 (d, J = 8.00 Hz, 1H), 7.84 (d, J = 8.00 Hz, 1H), 7.43-7.36 (m, 4H), 5.20-5.16 (m, 1H), 5.09 (s, 1H), 4.53-4.49 (m, 1H), 4.31 (d, J = 4.80 Hz, 1H), 3.52-3.33 (m, 2H), 2.98-2.94 (m, 2H), 2.68-2.64 (m, 3H), 2.46-2.35 (m, 2H), 2.19-2.15 (m, 1H), 2.11 (s, 1H), 1.45 (m, 1H), 1.33 (s, 2H), 1.12 (s, 2H), 0.90 (s, 3H), 0.68 (s, 3H).

Example 86: General procedure G- Reductive amination

To a stirred solution of the amine or the amine hydrochloride (0.1 mmol, 1.0 equiv) and the aldehyde (0.12 mmol, 1.2 equiv) in DMF (1 mL) was added acetic acid (0.1 mmol, 0.1 equiv) and triethylamine (0.2 mmol, 2.0 equiv) followed by MP cyanoborohydride (0.1 mmol, 1.0 equiv) at 25°C. The resulting mixture was stirred at 80 °C for 5 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to afford crude compound,

which was purified by reverse phase chromatography [(Column: X select (150 mm × 19) 5 µm, eluting with Mobile phase A: 0.05% FA or HCl in H_2O, Mobile phase B: ACN, flow rate: 15 mL/min)]. The fractions containing pure product were combined and concentrated via lyophilization to afford the desired product as the formic acid salt, the hydrochloride salt, or the free amine.

The following compounds in Table 7 were prepared from corresponding amine or amine hydrochloride and aldehyde according to a reductive amination procedure described in General Procedure G.

Table 7:

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
INT-5	1-methyl-1H-pyrazole-5-carbaldehyde	3-(5-(4-hydroxy-3,3-dimethyl-1-((1-methyl-1H-pyrazol-5-yl)methyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-308**)	Positive $[M+H]^+$ = 466.1	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 10.99 (s, 1H), 7.70-7.65 (m, 3H), 7.31 (d, J = 1.60 Hz, 1H), 6.15 (s, 1H), 5.14-5.09 (m, 1H), 4.83 (d, J = 3.60 Hz, 1H), 4.48-4.41 (m, 1H), 4.34-4.28 (m, 1H), 3.86 (s, 3H), 3.52 (s, 2H), 2.95-2.92 (m, 1H), 2.70-2.59 (m, 3H), 2.46-2.39 (m, 2H), 2.19-2.15 (m, 1H), 2.01 (m, 1H), 1.50-1.46 (m, 2H), 0.85 (s, 3H), 0.67 (s, 3H).
INT-5	3-chloro-4-(1,2,4-oxadiazol-3-yl)benzaldehyde (**ALD-8**)	3-(5-(1-(3-chloro-4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-292**)	Positive $[M+H]^+$ = 564.1	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 10.99 (s, 1H), 9.79 (s, 1H), 7.91 (d, J = 8.00 Hz, 1H), 7.73 (d, J = 4.80 Hz, 1H), 7.68-7.66 (m, 3H), 7.53 (d, J = 8.00 Hz, 1H), 5.14-5.10 (m, 1H), 4.84 (d, J = 3.60 Hz, 1H), 4.45-4.42 (m, 1H), 4.35-4.33 (m, 1H), 3.67 (d, J = 14.40 Hz, 1H), 3.56 (d, J = 14.40 Hz, 1H), 2.90-2.90 (m, 1H), 2.73 (m, 2H), 2.69-2.67 (m, 2H), 2.51-2.50 (m, 2H), 2.18-2.16 (m, 1H), 1.91 (m, 1H), 1.51-1.48 (m, 1H), 0.92 (s, 3H), 0.66 (s, 3H).

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
INT-5	4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)benzaldehyde	3-(5-(1-(4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-307**)	Positive $[M+H]^+$ = 570.2	^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 7.93 (d, J = 8.00 Hz, 2H), 7.72 (d, J = 5.20 Hz, 1H), 7.66 (d, J = 2.80 Hz, 2H), 7.53 (d, J = 8.00 Hz, 2H), 5.13-5.11 (m, 1H), 4.81 (d, J = 3.60 Hz, 1H), 4.44-4.42 (m, 1H), 4.35-4.33 (m, 1H), 3.64 (d, J = 14.00 Hz, 1H), 3.52 (d, J = 14.00 Hz, 1H), 2.74 (m, 1H), 2.68-2.67 (m, 2H), 2.52-2.50 (m, 1H), 2.40-2.38 (m, 3H), 2.16 (d, J = 10.40 Hz, 1H), 2.01-1.99 (m, 1H), 1.89 (s, 1H), 1.50 (d, J = 4.80 Hz, 1H), 1.31-1.29 (m, 2H), 1.20-1.18 (m, 2H), 0.90 (s, 3H), 0.64 (s, 3H).
INT-5	3-fluoro-4-(1,2,4-oxadiazol-3-yl)benzaldehyde (**ALD-9**)	3-(5-(1-(3-fluoro-4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-358**)	Positive $[M+H]^+$ = 548.2	^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 9.77 (s, 1H), 8.03 (t, J = 8.00 Hz, 1H), 7.73 (d, J = 5.20 Hz, 1H), 7.67 (d, J = 2.40 Hz, 2H), 7.46-7.43 (m, 2H), 5.15-5.10 (m, 1H), 4.84 (s, 1H), 4.45-4.43 (m, 1H), 4.36-4.34 (m, 1H), 3.69-3.55 (m, 2H), 2.73-2.63 (m, 5H), 2.42-2.33 (m, 2H), 2.19-2.17 (m, 1H), 1.91 (m, 1H), 1.51 (m, 1H), 0.93 (s, 3H), 0.66 (s, 3H).
INT-8	isobutyraldehyde	3-(4-fluoro-5-(4-hydroxy-1-isobutyl-3,3-dimethylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-336**)	Positive $[M+H]^+$ = 446.3	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 7.92-7.88 (m, 1H), 7.56 (d, J = 8.00 Hz, 1H), 5.13-4.57 (m, 2H), 4.53 (d, J = 2.80 Hz, 1H), 4.36 (d, J = 5.20 Hz, 1H), 2.95-2.60 (m, 2H), 2.59-2.51 (m, 2H), 2.50-2.43 (m, 2H), 2.34 (d, J = 10.80 Hz, 1H), 2.23 (d, J = 10.80

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
				Hz, 1H), 2.06-2.03 (m, 3H), 2.01-2.00 (m, 1H), 1.79 (m, 1H), 0.97 (s, 3H), 0.89 (s, 6H), 0.68 (s, 3H).
INT-5	isobutyraldehyde	3-(5-(4-hydroxy-1-isobutyl-3,3-dimethylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-334**)	Positive $[M+H]^+$ = 428.3	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 10.99 (s, 1H), 7.71 (d, J = 5.60 Hz, 1H), 7.65 (s, 2H), 5.14-5.09 (m, 1H), 4.74 (s, 1H), 4.44-4.42 (m, 1H), 4.35-4.33 (m, 1H), 2.91 (m, 1H), 2.71-2.67 (m, 3H), 2.50-2.38 (m, 3H), 2.16 (d, J = 10.00 Hz, 1H), 2.05-2.03 (m, 3H), 1.76 (m, 1H), 1.47 (d, J = 12.00 Hz, 1H), 0.89 (m, 9H), 0.67 (s, 3H).
INT-5	4-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)benzaldehyde	3-(5-(4-hydroxy-3,3-dimethyl-1-(4-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)benzyl)piperidin-4-yl)-Che1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-333**)	Positive $[M+H]^+$ = 598.4	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 10.73 (s, 1H), 8.21-8.08 (m, 2H), 7.90-7.70 (m, 5H), 5.15-5.10 (m, 1H), 4.50-4.45 (m, 2H), 4.43-4.35 (m, 1H), 3.60-3.59 (m, 1H), 2.97-2.92 (m, 3H), 2.68-2.67 (m, 2H), 2.42-2.35 (m, 2H), 2.03-2.00 (m, 1H), 2.17 (m, 2H), 1.54-1.50 (m, 1H), 0.92 (s, 3H), 0.68 (s, 3H).
INT-5	4-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)benzaldehyde	3-(5-(1-(4-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-332**)	Positive $[M+H]^+$ = 570.3	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 10.99 (s, 1H), 8.14 (s, 1H), 7.94 (d, J = 8.40 Hz, 2H), 7.72-7.56 (m, 5H), 5.14-5.10 (m, 1H), 4.79 (s, 1H), 4.45-4.34 (m, 2H), 3.75-3.68 (m, 2H), 2.92-2.76 (m, 3H), 2.68-2.59 (m, 2H), 2.39-2.34 (m, 2H), 2.17 (m, 1H), 2.03-2.01 (m, 1H), 1.54-1.50 (m, 1H), 1.17-1.13 (m, 4H), 0.90 (s, 3H), 0.65 (s, 3H).
INT-5	4-(1,3,4-oxadiazol-2-	3-(5-(1-(4-(1,3,4-oxadiazol-2-yl)benzyl)-4-	Positive $[M+H]^+$ = 530.1	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 10.99 (s, 1H), 9.34 (s, 1H), 8.01 (d, J = 8.40 Hz,

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
	yl)benzaldehyde	hydroxy-3,3-dimethylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-325**)		2H), 7.72 (d, J = 5.20 Hz, 1H), 7.66 (s, 2H), 7.60 (d, J = 8.40 Hz, 2H), 5.15-5.10 (m, 1H), 4.82 (s, 1H), 4.47-4.43 (m, 1H), 4.36-4.31 (m, 1H), 3.68-3.54 (m, 2H), 2.92 (m, 1H), 2.75-2.67 (m, 2H), 2.63-2.51 (m, 3H), 2.42-2.38 (m, 1H), 2.17 (d, J = 10.40 Hz, 1H), 2.03-2.01 (m, 1H), 1.51 (d, J = 12.00 Hz, 1H), 0.91 (s, 3H), 0.66 (s, 3H).
INT-8	6-(trifluoromethy)nicotinaldehyde	3-(4-fluoro-5-(4-hydroxy-3,3-dimethyl-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-318**)	Positive $[M+H]^+$ = 549.2	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 11.01 (s, 1H), 8.74 (s, 1H), 8.05 (d, J = 8.40 Hz, 1H), 7.89 (d, J = 3.60 Hz, 2H), 7.57 (d, J = 8.00 Hz, 1H), 5.14-5.10 (m, 2H), 4.57 (d, J = 4.00 Hz, 1H), 4.53 (d, J = 3.60 Hz, 1H), 3.72-3.59 (m, 2H), 2.92 (m, 2H), 2.68-2.67 (m, 3H), 2.59-2.53 (m, 1H), 2.34 (d, J = 2.00 Hz, 1H), 2.14 (m, 1H), 1.50-1.45 (m, 1H), 0.99 (m, 1H), 0.64 (s, 3H), 1.49 (s, 3H).
INT-5	4-(1-(trifluoromethyl)cyclopropyl)benzaldehyde (**ALD-13**)	3-(5-(4-hydroxy-3,3-dimethyl-1-(4-(1-(trifluoromethyl)cyclopropyl)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-310**)	Positive $[M+H]^+$ = 570.2	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 10.99 (s, 1H), 7.71 (d, J = 5.60 Hz, 1H), 7.67 (m, 2H), 7.43 (d, J = 8.40 Hz, 2H), 7.36 (d, J = 8.40 Hz, 2H), 5.14-5.10 (m, 1H), 4.80 (s, 1H), 4.44-4.42 (m, 1H), 4.35-4.33 (m, 1H), 3.52-3.33 (m, 2H), 2.98-2.93 (m, 1H), 2.69-2.67 (m, 3H), 2.50-2.38 (m, 3H), 2.21 (d, J = 6.00 Hz, 1H), 2.17 (s, 1H), 1.49 (d, J = 12.00 Hz, 1H), 1.35 (m, 2H), 1.12 (m, 2H), 0.90 (s, 3H), 0.65 (s, 3H).

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
INT-5	4-(isoxazol-3-yl)benzaldehyde (**ALD-6**)	3-(5-(4-hydroxy-1-(4-(isoxazol-3-yl)benzyl)-3,3-dimethylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-284**)	Positive $[M+H]^+$ = 529.1	^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 9.00 (d, J = 1.60 Hz, 1H), 7.87 (d, J = 8.00 Hz, 2H), 7.72 (d, J = 4.80 Hz, 1H), 7.66 (d, J = 2.80 Hz, 2H), 7.50 (d, J = 8.00 Hz, 2H), 7.15 (d, J = 1.60 Hz, 1H), 5.12 (dd, J = 4.80, 13.20 Hz, 1H), 4.82 (s, 1H), 4.49-4.42 (m, 1H), 4.35-4.29 (m, 1H), 3.66-3.50 (m, 2H), 2.78-2.67 (m, 6H), 2.34-2.33 (m, 1H), 2.19-2.17 (m, 1H), 2.02-2.01 (m, 1H), 1.52-1.50 (m, 1H), 0.90 (s, 3H), 0.65 (s, 3H).
INT-12	formaldehyde	3-(5-(5-hydroxy-9-methyl-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-275**)	Positive $[M+H]^+$ = 585.6	
INT-51	isobutyraldehyde	3-(2-(4-hydroxy-1-isobutyl-3,3-dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-613**)	Positive $[M+H]^+$ = 429.3	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ 11.02 (s, 1H), 8.11 (d, J = 8.00 Hz, 1H), 7.84 (d, J = 8.00 Hz, 1H), 5.20-5.17 (m, 1H), 5.06 (m, 1H), 4.50 (d, J = 4.40 Hz, 1H), 4.36-4.30 (m, 1H), 2.96-2.92 (m, 2H), 2.68-2.64 (m, 2H), 2.44-2.36 (m, 3H), 2.18 (d, J = 10.00 Hz, 1H), 2.08-2.04 (m, 3H), 1.81-1.72 (m, 1H), 1.49-1.41 (m, 1H), 0.88 (s, 9H), 0.70 (s, 3H).
INT-51	4-(5-cyclopropyl-1,3,4-oxadiazol-2-	3-(2-(1-(4-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)benzyl)-4-hydroxy-3,3-	Positive $[M+H]^+$ = 571.2	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ 11.02 (s, 1H), 8.12 (d, J = 8.00 Hz, 1H), 7.93 (d, J = 8.40 Hz, 2H), 7.85 (d, J = 8.40 Hz, 1H), 7.56 (d, J =

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
	yl)benzaldehyde	dimethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (**I-611**)		8.00 Hz, 2H), 5.19-5.11 (m, 2H), 4.50 (d, J = 3.60 Hz, 1H), 4.36 (d, J = 4.00 Hz, 1H), 3.61-3.57 (m, 2H), 3.33-2.84 (m, 3H), 2.68-2.67 (m, 1H), 2.53-2.51 (m, 1H), 2.51-2.50 (m, 1H), 2.47-2.44 (m, 1H), 2.32 (d, J = 4.80 Hz, 1H), 1.92 (s, 1H), 1.49-1.45 (m, 1H), 1.17-1.14 (m, 5H), 0.91 (s, 3H), 0.68 (s, 3H).

Example 87: General procedure H-Reductive amination

To a stirred solution of the amine or the amine hydrochloride (0.1 mmol, 1.0 equiv) and the aldehyde (0.11 mmol, 1.1 equiv) in DMF (1 mL) was added decaborane (0.04 mmol, 0.4 equiv) at 25°C. The resulting mixture was stirred at RT overnight or heated to 70 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to afford crude compound, which was purified by reverse phase chromatography [(Phenomenex Luna C18 column (50 × 21.2 mm) 5 μm, eluting with Mobile phase A: 0.1% formic acid in H_2O, Mobile phase B: 0.1% formic acid in acetonitrile, flow rate: 50 mL/min)]. The fractions containing pure product were combined and concentrated via lyophilization to afford the desired product as the formic acid salt, the hydrochloride salt, or the free amine.

The following compounds in Table 8 were prepared from corresponding amine or amine hydrochloride and aldehyde according to a reductive amination procedure described in General Procedure H.

Table 8:

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
INT-9	isobutyraldehyde	3-(5-(3,3-diethyl-4-hydroxy-1-isobutylpiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-	Positive $[M+H]^+$ = 474	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 7.98 (br t, J = 7.4 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 5.11 (br dd, J = 5.2, 13.4 Hz, 1H), 5.06-5.01 (m, 1H),

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
		yl)piperidine-2,6-dione (**I-166**)		4.51 (d, *J* = 17.0 Hz, 1H), 4.37 (d, *J* = 17.5 Hz, 1H), 3.45-3.42 (m, 1H), 3.08-2.97 (m, 1H), 2.95-2.87 (m, 1H), 2.65-2.54 (m, 2H), 2.48-2.39 (m, 1H), 2.38-2.32 (m, 2H), 2.22 (d, *J* = 11.0 Hz, 1H), 2.16-2.05 (m, 1H), 2.05-1.94 (m, 3H), 1.86-1.68 (m, 1H), 1.56-1.46 (m, 2H), 1.24-1.05 (m, 1H), 0.90-0.87 (m, 6H), 0.69 (t, *J* = 7.4 Hz, 3H), 0.52-0.46 (m, 3H).
INT-9	4,4-difluorocyclohexane-1-carbaldehyde	3-(5-(1-((4,4-difluorocyclohexyl)methyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-164**)	Positive $[M+H]^+$ = 550	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 11.01 (s, 1H), 8.01-7.95 (m, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 5.16-5.03 (m, 2H), 4.61-4.46 (m, 1H), 4.40-4.29 (m, 1H), 3.01 (br t, *J* = 11.5 Hz, 1H), 2.96-2.84 (m, 1H), 2.66-2.54 (m, 2H), 2.46-2.32 (m, 3H), 2.24 (d, *J* = 11.5 Hz, 1H), 2.15-1.96 (m, 6H), 1.89-1.69 (m, 4H), 1.69-1.63 (m, 1H), 1.60-1.41 (m, 2H), 1.19-1.06 (m, 3H), 1.06-0.95 (m, 1H), 0.71-0.65 (m, 3H), 0.52-0.46 (m, 3H).
INT-9	tetrahydro-2H-pyran-4-carbaldehyde	3-(5-(3,3-diethyl-4-hydroxy-1-((tetrahydro-2H-pyran-4-yl)methyl)piperidin-4-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**I-165**)	Positive $[M+H]^+$ = 516	^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 11.01 (s, 1H), 8.17 (br s, 1H), 8.00-7.95 (m, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 5.17-5.02 (m, 2H), 4.60-4.46 (m, 1H), 4.40-4.29 (m, 1H), 3.87-3.81 (m, 2H), 3.35-3.24 (m, 2H), 3.05-2.97 (m, 1H), 2.96-2.86 (m, *J* = 1.6 Hz, 1H), 2.65-2.55 (m, 2H), 2.47-2.33 (m, 3H), 2.24 (d, *J* = 11.0 Hz, 1H), 2.16-2.05 (m,

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
				3H), 2.05-1.97 (m, 1H), 1.78-1.71 (m, 1H), 1.70-1.61 (m, 2H), 1.58-1.44 (m, 2H), 1.19-1.07 (m, 3H), 1.05-0.95 (m, 1H), 0.71-0.64 (m, 3H), 0.53-0.44 (m, 3H).
INT-12	acetaldehyde	3-(5-(9-ethyl-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2,9-diazaspiro[5.5]undecan-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione **(I-272)**	Positive $[M+H]^+$ = 599	^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 7.71 (d, J = 8.00 Hz, 4H), 7.67 (d, J = 8.00 Hz, 3H), 5.13 (d, J = 8.40 Hz, 1H), 4.87 (s, 1H), 4.47-4.44 (m, 1H), 4.36-4.34 (m, 1H), 3.66-3.54 (m, 1H), 3.54-3.50 (m, 1H), 2.84-2.62 (m, 2H), 2.58-2.51 (m, 5H), 2.46-2.38 (m, 4H), 2.26-2.13 (m, 2H), 2.02-1.97 (m, 3H), 1.88 (s, 3H), 1.63-1.46 (m, 2H), 1.21-0.93 (m, 2H), 0.75 (t, J = 7.20 Hz, 3H).

Biological Assays and Data

The activity of a compound according to the present disclosure can be assessed by the following *in vitro* methods.

Example 88: Quantification of endogenous ARNT levels in 786-O cells

The HiBiT Protein Tagging System (Promega) was used to develop a high-throughput and quantitative assay to measure changes in endogenous ARNT protein levels following treatment with compounds. The endogenous ARNT gene was tagged by knocking in the HiBiT sequence immediately preceding the ARNT termination codon using CRISPR. Briefly, ARNT-targeting CRISPR ribonucleoprotein complexes (RNP) and a donor template including the 33 nucleotide HiBiT sequence were delivered to 786-O cells using the Nucleofector 4D system (Lonza). Subsequently, single cell clones were isolated and screened for successful knock-in by genomic DNA sequencing and for HiBiT signal using the Nano-Glo® HiBiT Lytic Detection System (Promega).

The level of ARNT degradation following compound treatment was measured as follows:

Day 1. Triplicate 10-point dose-response curves of all compounds were generated by pre-spotting compounds into solid white 384 well plates using a D300e Digital Dispenser (Tecan). All compounds were run in half-log dilution starting from 10 µM final concentration and all wells were normalized to 0.21% DMSO per well. Cells were then lifted from flasks using 0.25% Trypsin EDTA (Gibco) and quenched with normal growth medium containing 10% fetal bovine serum before viable cells were counted using a Countess II instrument (Thermo Fisher). Cells were then diluted to 2.0×10^5 cells/mL in normal growth medium and 25 µL of cells were plated in each well of pre-spotted 384 well plates using a Multidrop Combi Reagent Dispenser (Thermo Fisher). Plates were then incubated in humidified 37°C incubators maintaining 5% CO_2 for 24 h.

Day 2. Plates were removed from incubators and allowed to equilibrate to room temperature for 30 minutes before adding 15 µL of Nano-Glo® HiBiT Lytic Detection System reagent to each well using a Multidrop Combi Reagent Dispenser. Plates were incubated for an additional 10 minutes at room temperature and luminescence was read using a PHERAstar Microplate Reader (BMG Labtech). Data was analyzed and visualized using GraphPad Prism 9 software (Dotmatics).

Tables 9 and 10 show ARNT (HIF-1b) degradation activity of compounds of the disclosure in Pro-label assays in 7860-O. In Table 9 and 10 below, D_{max} is defined as A = >60%; <; B = 30-60%; C = <30% and DC_{50} is defined as A = <0.20 µM; B = 1 µM-0.20 µM; C = >1 µM.

Table 9:

Cmpd No.	ARNT DC_{50} (µM)	ARNT D_{max} (%)
I-1	A	A
I-2	A	A
I-9	A	A
I-10	A	A
I-11	A	A
I-12	A	A
I-13	B	A
I-14	A	A
I-15	A	A
I-22	B	B
I-23	C	C
I-24	A	A

Cmpd No.	ARNT DC_{50} (µM)	ARNT D_{max} (%)
I-25	B	B
I-26	C	C
I-27	B	B
I-28	A	A
I-29	B	A
I-36	A	A
I-43	C	C
I-44	C	A
I-45	A	B
I-46	B	B
I-47	B	B
I-48	A	A

Cmpd No.	ARNT DC_{50} (µM)	ARNT D_{max} (%)
I-55	A	B
I-56	B	B
I-57	A	B
I-59	B	C
I-60	B	B
I-61	A	A
I-63	A	A
I-69	A	B
I-70	B	B
I-71	A	C
I-72	A	A
I-73	A	A

Cmpd No.	ARNT DC_{50} (μM)	ARNT D_{max} (%)
I-74	A	B
I-75	A	B
I-76	A	A
I-77	B	B
I-78	B	B
I-79	B	C
I-80	B	B
I-81	A	B
I-82	A	A
I-90	B	B
I-97	B	B
I-98	C	B
I-99	B	B
I-100	A	A
I-101	C	B
I-102	A	A
I-103	A	A
I-110	B	A
I-112	A	A
I-113	A	A
I-114	A	A
I-115	A	A
I-116	B	C
I-117	C	C
I-118	A	A
I-119	A	A
I-120	A	A
I-121	A	A
I-122	A	A
I-123	A	A
I-124	A	A
I-125	A	A
I-126	A	A
I-128	A	A
I-129	A	A
I-131	A	A
I-138	A	A
I-139	B	B
I-141	A	A
I-142	A	A
I-145	A	A
I-146	A	A
I-153	A	A
I-160	A	A
I-161	A	A

Cmpd No.	ARNT DC_{50} (μM)	ARNT D_{max} (%)
I-162	A	B
I-163	A	A
I-164	B	A
I-165	B	B
I-166	B	A
I-173	A	A
I-180	A	A
I-182	A	A
I-189	A	A
I-190	A	A
I-191	A	A
I-192	A	A
I-194	A	A
I-196	A	A
I-107	A	A
I-106	C	C
I-109	A	A
I-108	B	C
I-204	A	B
I-211	A	A
I-212	B	B
I-214	A	C
I-226	A	A
I-227	B	A
I-225	A	A
I-228	C	B
I-51	C	C
I-54	A	A
I-239	C	C
I-240	C	C
I-241	C	C
I-242	C	C
I-243	B	B
I-244	C	C
I-245	C	C
I-246	C	C
I-247	C	C
I-248	B	B
I-249	B	A
I-250	C	A
I-251	C	C
I-252	C	C
I-253	C	C
I-254	C	C
I-255	C	C

Cmpd No.	ARNT DC_{50} (μM)	ARNT D_{max} (%)
I-256	C	C
I-257	C	C
I-258	C	C
I-261	C	A
I-262	C	C
I-263	C	C
I-264	C	C
I-265	C	C
I-266	B	C
I-268	C	C
I-269	C	C
I-270	C	C
I-271	C	C
I-272	C	C
I-273	C	C
I-274	C	C
I-275	C	C
I-277	A	A
I-278	A	A
I-283	C	C
I-284	B	A
I-292	B	B
I-299	A	A
I-300	A	A
I-307	A	A
I-308	C	C
I-309	B	B
I-310	A	A
I-311	A	A
I-318	B	A
I-325	A	A
I-332	B	A
I-333	A	A
I-334	C	C
I-335	A	A
I-336	B	A
I-337	A	A
I-344	A	A
I-358	B	A
I-365	A	A
I-238	C	C
I-285	B	C
I-351	A	A

Table 10:

Cmpd No.	ARNT DC_{50} (μM)	ARNT D_{max} (%)
I-400	A	A
I-407	A	A
I-408	A	A
I-409	B	B
I-410	A	A
I-411	A	A
I-412	B	A
I-413	B	A
I-414	B	A
I-415	A	A
I-416	B	A
I-417	B	A
I-418	B	B
I-419	A	A
I-420	C	B
I-421	B	B
I-422	B	A
I-423	B	A
I-424	A	A
I-425	A	A
I-432	B	C
I-433	A	B

Cmpd No.	ARNT DC_{50} (μM)	ARNT D_{max} (%)
I-434	B	B
I-435	A	A
I-442	A	A
I-443	A	A
I-444	B	A
I-445	B	A
I-446	B	A
I-448	B	B
I-449	B	C
I-450	A	A
I-459	A	A
I-468	A	A
I-475	A	A
I-482	A	A
I-489	A	A
I-496	A	A
I-511	A	A
I-518	A	A
I-525	A	A
I-533	A	A
I-429	B	C
I-428	C	C

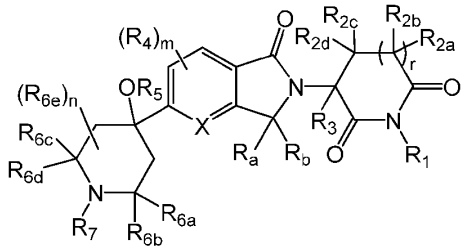
Cmpd No.	ARNT DC_{50} (μM)	ARNT D_{max} (%)
I-431	A	A
I-430	A	A
I-534	A	A
I-535	A	A
I-558	A	A
I-495	A	B
I-492	A	A
I-494	A	A
I-493	A	A
I-579	B	A
I-580	A	B
I-581	A	A
I-590	A	A
I-597	A	A
I-604	A	A
I-611	A	A
I-612	A	A
I-613	B	B
I-614	A	A
I-628	A	A
I-629	A	A
I-621	B	A

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific embodiments described specifically herein. Such equivalents are intended to be encompassed in the scope of the following claims.

CLAIMS

What is claimed is:

1. A compound of Formula (I):



(I),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

R_a and R_b are each independently H, D, or $(C_1$-$C_6)$alkyl;

R_1 is H, D, -C(O)R_{11}, -CH_2OC(O)R_{11}, -CH_2OC(O)NHR_{12}, -CH_2OC(O)OR_{12}, -P(O)$(OR_{12})_2$, -CH_2OP(O)$(OR_{12})_2$, -CH_2OP(O)(OH)OR_{12}, -CH_2OP(O)$(R_{12})_2$, -CH_2OC(O)CH_2NHC(O)CH_2NH_2, -CH_2OC(O)CH($R_{12'}$)N$HR_{12'}$, -CH_2OC(O)$(CH_2)_q$C(O)O$R_{12'}$, or -CH_2OC(O)-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S);

R_{2a}, R_{2b}, R_{2c}, and R_{2d} are each independently H, D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, halogen, or -OH, wherein two of R_{2a}, R_{2b}, R_{2c}, and R_{2d} may be taken together with the carbon atom to which they are attached form a $(C_3$-$C_7)$carbocyclyl or $(C_3$-$C_7)$spirocarbocyclyl;

R_3 is H, D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, or halogen, wherein R_3 may be taken together with one of R_{2a}, R_{2b}, R_{2c}, and R_{2d} with the carbon atom to which they are attached to form a $(C_3$-$C_7)$carbocyclyl or $(C_3$-$C_7)$spirocarbocyclyl;

each R_4 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$halohalkyl, or halogen;

each $R_{4'}$ is independently at each occurrence H, D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$deuteroalkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_3$-$C_7)$carbocyclyl, O$(C_3$-$C_7)$carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$;

R_5 is H, D, $(C_2$-$C_6)$alkyl, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$halohydroxyalkyl, $(C_1$-$C_6)$aminoalkyl, $(C_1$-$C_6)$alkyl-O-$(C_1$-$C_6)$hydroxyalkyl, -C(O)R_{12}, -CH_2OC(O)R_{12}, -CH_2OC(O)N$(R_{12})_2$, -CH_2OC(O)$_2R_{12}$, -P(O)$(OR_{12})_2$, -CH_2OP(O)(OH)OR_{12}, or -CH_2OP(O)$(R_{12})_2$;

R_{6a}, R_{6b}, R_{6c}, and R_{6d} are each independently H, D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy,, or $(C_3$-$C_7)$carbocyclyl; or

two of R_{6a}, R_{6b}, R_{6c}, and R_{6d} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl, (C_3-C_7)spirocarbocyclyl, 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl, heterocyclyl, and spiroheterocyclyl are optionally substituted with one or more R_{10};

each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, -(C_1-C_6)alkylene-O-(C_1-C_6)alkyl, (C_6-C_{10})aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one or more R_{13}, the aryl and heteroaryl are optionally substituted with one or more R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{23}; or

two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)carbocyclyl, (C_3-C_7)spirocarbocyclyl, a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl, heterocyclyl, and spiroheterocyclyl are optionally substituted with one or more R_{15}; or

one R_{6e} is taken together with any one of R_{6a}, R_{6b}, R_{6c}, and R_{6d} and the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{15};

R_7 is (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_3-C_7)carbocyclyl, wherein alkyl, haloalkyl, hydroxyalkyl, halohydroxyalkyl, and carbocyclyl are optionally substituted with one or more substituents independently selected from R_{21}, D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$,-C(O)$NR_{32}R_{33}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$;

when $R_{4'}$ is H, m is 1, n is 0 and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are all simultaneously H, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)alkyl, or (C_3-C_7)carbocyclyl optionally substituted with one or more substituents independently selected from R_{41}, D, (C_1-C_6)alkoxy, -OR_{16a}, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one or more R_8, the

heteroaryl is optionally substituted with one or more R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$.

when $R_{4'}$ is H, m is 0, n is 0, and R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 are not all simultaneously H or when $R_{4'}$ is H, m is 0 or 1, and n is 1, 2, 3, or 4, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)alkyl, or (C_3-C_7)carbocyclyl optionally substituted with one or more substituents independently selected from R_{41}, D, (C_1-C_6)alkoxy, -OR_{16a}, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$;

when $R_{4'}$ is (C_1)alkyl, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one or more R_8, the heteroaryl is optionally substituted with one or more R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$;

when $R_{4'}$ is D, (C_2-C_4)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, -CN, -SH, -$NR_9R_{9'}$, or -$S(O)_pR_{19}$, then R_7 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)alkyl, or (C_3-C_7)carbocyclyl optionally substituted with one or more substituents independently selected from R_{41}, D, (C_1-C_6)alkoxy, -OR_{16a}, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, and 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$;

R_8 and $R_{8'}$ are each independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -$C(O)NR_{32}R_{33}$, -$C(O)OR_{32}$, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the alkyl, deuteroalkyl, haloalkyl, alkoxy, haloalkoxy, hydroalkyl, phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more substituents selected

from $(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$carbocyclyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, –OH, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{40}$, and -CN, and R_{13}; or

two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R_{10};

two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{10}; or

two $R_{8'}$ together with the atoms to which they are attached form a $(C_3$-$C_7)$carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{10}; or

two $R_{8'}$ when on the same carbon atom form C=(O);

each R_9 and $R_{9'}$ are each independently at each occurrence H or $(C_1$-$C_6)$alkyl;

R_{10} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{25}$, -CN, $C(O)OR_9$, $-C(O)R_9$, and $-C(O)NR_9R_{9'}$;

R_{11} is independently at each occurrence H, $(C_1$-$C_6)$alkoxy, $-NH_2$, $-N(H)(C_1$-$C_6)$alkyl, $-N((C_1$-$C_6)$alkyl$)_2$, $(C_1$-$C_6)$alkyl optionally substituted with one or more substituents independently selected from $(C_6$-$C_{10})$aryl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$haloalkyl, halogen, -OH, $-NH_2$, and -CN, or $(C_6$-$C_{10})$aryl optionally substituted with one or more substituents independently selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$haloalkyl, halogen, -OH, $-NH_2$, and -CN;

R_{12} is independently at each occurrence H, $(C_1$-$C_6)$alkyl optionally substituted with one or more substituents independently selected from $(C_6$-$C_{10})$aryl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$haloalkyl, halogen, -OH, $-NH_2$, and -CN, or $(C_6$-$C_{10})$aryl optionally substituted with one or more substituents independently selected from $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$haloalkyl, halogen, -OH, $-NH_2$, and -CN;

$R_{12'}$ is independently at each occurrence H or $(C_1$-$C_6)$alkyl;

each R_{13} is independently at each occurrence $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $-NR_{14}R_{14'}$, -CN, $(C_3$-$C_7)$carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_6$-$C_{10})$ aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms

selected from O, N, NH, and S, wherein carbocyclyl and heterocyclyl are optionally substituted with one or more R_{20} and the aryl and heteroaryl are optionally substituted with one or more R_{21}; or

two R_{13} when on the same carbon atom may be taken together to form C=(O);

R_{14} and $R_{14'}$ are each independently at each occurrence H or $(C_1$-$C_6)$alkyl;

each R_{15} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, $-C(O)OR_{17}$, $-C(O)R_{18}$, or $-C(O)NR_{17}R_{17}$ optionally substituted with one or more R_{20};

R_{16} and $R_{16'}$ are each independently at each occurrence H or $(C_1$-$C_6)$alkyl;

R_{16a} is H, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl;

R_{17} is independently at each occurrence H, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl;

R_{18} is independently at each occurrence $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl;

R_{19} is $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl;

each R_{20} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{26}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{20} together with the atoms to which they are attached form a $(C_3$-$C_7)$carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{21} is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{27}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{22} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{28}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{22}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{23} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{29}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{23} together with the atoms to which they are attached form a $(C_3$-$C_7)$carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each independently at each occurrence H, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl;

R_{30} and R_{31} are each independently at each occurrence H, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_3$-$C_7)$carbocyclyl, -C(O)R_{34}, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl or heteroaryl can be substituted with one or more R_{17};

R_{32}, R_{33}, and R_{34} are each independently at each occurrence H or $(C_1$-$C_6)$alkyl;

R_{35} and R_{36} are each independently at each occurrence H, $(C_1$-$C_6)$alkyl, or -C(O)R_{39};

R_{37}, R_{38}, and R_{39} are each independently at each occurrence H or $(C_1$-$C_6)$alkyl;

R_{40} is H, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl;

two R_{41}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{10}; or

two R_{41} together with the atoms to which they are attached form a $(C_3$-$C_7)$carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{10}; or

m and p are each independently 0, 1, or 2;

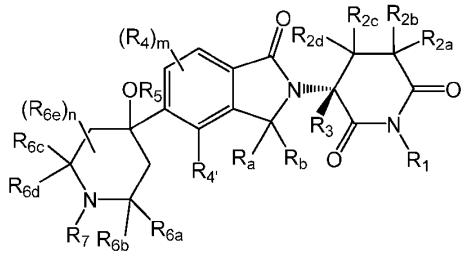
q is 1, 2, or 3;

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

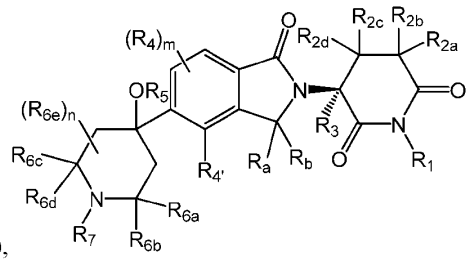
r is 0 or 1.

.

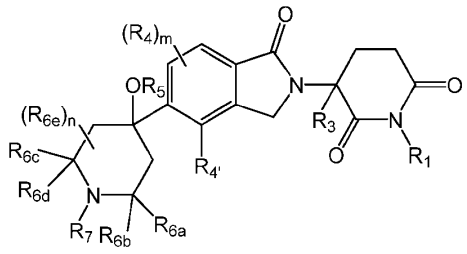
2. The compound according to claim 1, having a Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (Ie), or Formula (If):



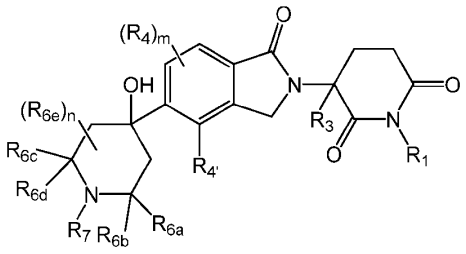
(Ia),



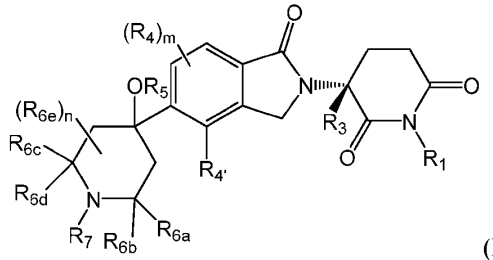
(Ib),



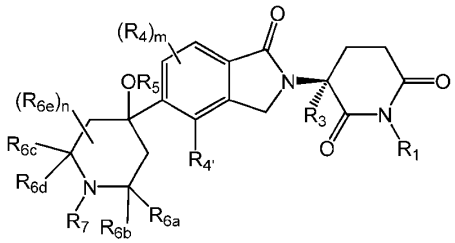
(Ic),



(Id),



(Ie), or



(If),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

3. The compound according to claim 1, wherein R_5 is H.

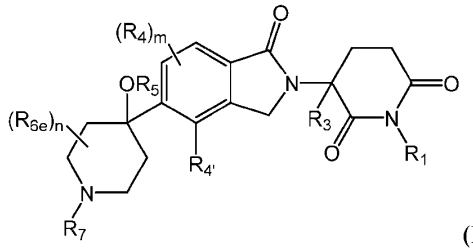
4. The compound according to claim 1, wherein R_{6a} is H.

5. The compound according to claim 1, wherein R_{6b} is H.

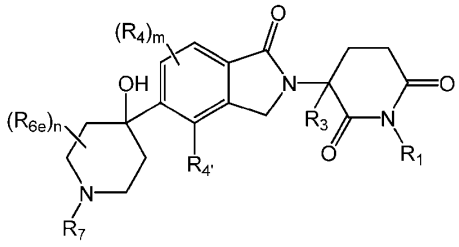
6. The compound according to claim 1, wherein R_{6c} is H.

7. The compound according to claim 1, wherein R_{6d} is H.

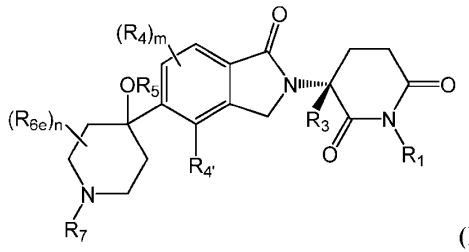
8. The compound according to claim 1, having a Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), or Formula (Im):



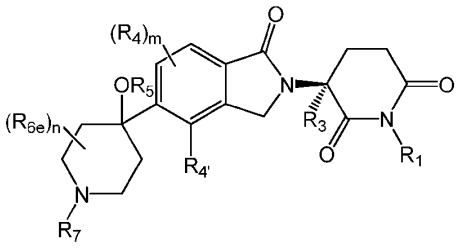
(Ig),



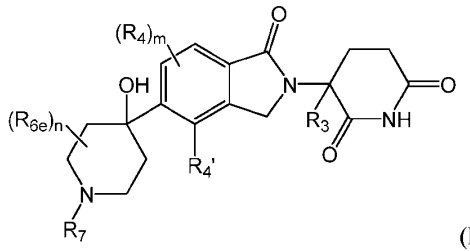
(Ih),



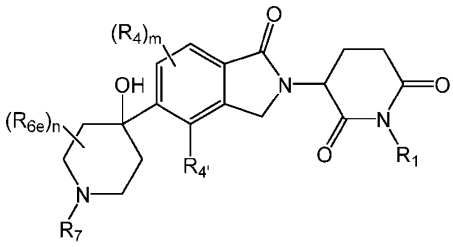
(Ii),



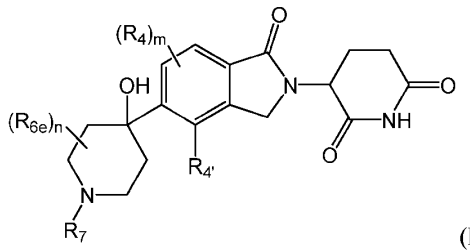
(Ij),



(Ik),



(Il), or



(Im).

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

9. The compound according to claim 1, wherein R_3 is H.

10. The compound according to claim 1, wherein $R_{4'}$ is (C_1)alkyl and R_7 is $(C_1$-$C_6)$alkyl optionally substituted with one to three phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to three R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to three $R_{8'}$.

11. The compound according to claim 1, wherein $R_{4'}$ is $(C_2$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, -CN, -SH, $-NR_9R_{9'}$, or $-S(O)_pR_{19}$ and R_7 is $(C_1$-$C_6)$alkyl optionally substituted with one to three phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3$-$C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to three R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to three $R_{8'}$.

12. The compound according to claim 1, wherein $R_{4'}$ is H.

13. The compound according to claim 1, wherein n is 0 and m is 0.

14. The compound according to claim 1, wherein one of R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_3, and R_5 is not H.

15. The compound according to claim 1, wherein $R_{4'}$ is H.

16. The compound according to claim 1, wherein m is 0 or 1 and n is 1, 2, or 3.

17. The compound according to claim 1, wherein R_7 is (C_1-C_6)alkyl optionally substituted with one to three phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to three R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to three $R_{8'}$.

18. The compound according to claim 1, wherein n is 0 and m is 1.

19. The compound according to claim 1, wherein R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, and R_7 is (C_1-C_6)alkyl optionally substituted with one to three phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl is substituted with one to three R_8, the heteroaryl is optionally substituted with one to three R_8, and the carbocyclyl and heterocyclyl are optionally substituted with one to three $R_{8'}$.

20. The compound according to claim 1, wherein n is 0.

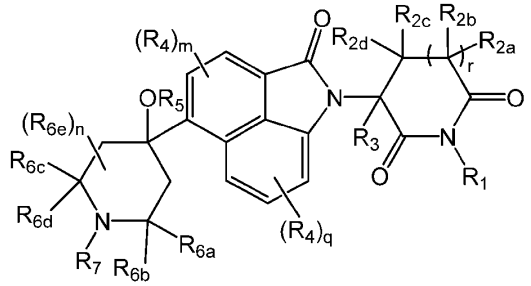
21. The compound according to claim 1, wherein n is 1.

22. The compound according to claim 1, wherein n is 2.

23. The compound according to claim 1, wherein m is 0.

24. The compound according to claim 1, wherein m is 1.

25. A compound of Formula (II):



(II),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

R_1 is H, D, -C(O)R_{11}, -$CH_2OC(O)R_{11}$, -$CH_2OC(O)NHR_{12}$, -$CH_2OC(O)OR_{12}$, -$P(O)(OR_{12})_2$, -$CH_2OP(O)(OR_{12})_2$, -$CH_2OP(O)(OH)OR_{12}$, -$CH_2OP(O)(R_{12})_2$, -$CH_2OC(O)CH_2NHC(O)CH_2NH_2$, -$CH_2OC(O)CH(R_{12'})NHR_{12'}$, -$CH_2OC(O)(CH_2)_qC(O)OR_{12'}$, or -$CH_2OC(O)$-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S);

R_{2a}, R_{2b}, R_{2c}, and R_{2d} are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, halogen, or -OH, wherein two of R_{2a}, R_{2b}, R_{2c}, and R_{2d} may be taken together with the carbon atom to which they are attached form a (C_3-C_7)carbocyclyl or (C_3-C_7)spirocarbocyclyl;

R_3 is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, or halogen, wherein R_3 may be taken together with one of R_{2a}, R_{2b}, R_{2c}, and R_{2d} with the carbon atom to which they are attached to form a (C_3-C_7)carbocyclyl or (C_3-C_7)spirocarbocyclyl;

each R_4 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)halohalkyl, or halogen;

R_5 is H, D, (C_2-C_6)alkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)aminoalkyl, (C_1-C_6)alkyl-O-(C_1-C_6)hydroxyalkyl, -C(O)R_{12}, -$CH_2OC(O)R_{12}$, -$CH_2OC(O)N(R_{12})_2$, -$CH_2OC(O)_2R_{12}$, -$P(O)(OR_{12})_2$, -$CH_2OP(O)(OH)OR_{12}$, or -$CH_2OP(O)(R_{12})_2$;

R_{6a}, R_{6b}, R_{6c}, and R_{6d} are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy,, or (C_3-C_7)carbocyclyl; or

two of R_{6a}, R_{6b}, R_{6c}, and R_{6d} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl, (C_3-C_7)spirocarbocyclyl, 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl, heterocyclyl, and spiroheterocyclyl are optionally substituted with one or more R_{10};

each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, -(C_1-C_6)alkylene-O-(C_1-C_6)alkyl, (C_6-C_{10})aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one or more R_{13}, the aryl and heteroaryl are optionally substituted with one or more R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{23}; or

two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)carbocyclyl, (C_3-C_7)spirocarbocyclyl, a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl, heterocyclyl, and spiroheterocyclyl are optionally substituted with one or more R_{15}; or

one R_{6e} is taken together with any one of R_{6a}, R_{6b}, R_{6c}, and R_{6d} and the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{15};

R_7 is (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_3-C_7)carbocyclyl, wherein alkyl, haloalkyl, hydroxyalkyl, halohydroxyalkyl, and carbocyclyl are optionally substituted with one or more substituents independently selected from R_{21}, D, (C_1-C_6)alkoxy, -SF_5, -SR_{16a}, -$NR_{16}R_{16'}$,-C(O)$NR_{32}R_{33}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$;

R_8 and $R_{8'}$ are each independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{24}, -CN, -C(O)$NR_{32}R_{33}$, -C(O)OR_{32}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the alkyl, deuteroalkyl, haloalkyl, alkoxy, haloalkoxy, hydroalkyl, phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more substituents selected from (C_1-C_6)alkyl, (C_3-C_7)carbocyclyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{35}R_{36}$, -C(O)$NR_{37}R_{38}$, -C(O)R_{37}, -C(O)OR_{37}, -SF_5, -SR_{40}, and -CN, and R_{13}; or

two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R_{10};

two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{10}; or

two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, NH, N, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{10}; or

two $R_{8'}$ when on the same carbon atom form C=(O);

each R_9 and $R_{9'}$ are each independently is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{13}R_{13'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein carbocyclyl and heterocyclyl are optionally substituted with one or more R_{20} and the aryl and heteroaryl are optionally substituted with one or more R_{21};

R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, - OH, -NH_2, -SF_5, -SR_{25}, -CN, C(O)OR_9, -C(O)R_9, and -C(O)NR_9R_9;

R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN;

R_{12} is independently at each occurrence H, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN;

$R_{12'}$ is independently at each occurrence H or (C_1-C_6)alkyl;

R_{13} and $R_{13'}$ are each independently at each occurrence H or (C_1-C_6)alkyl;

each R_{14} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)OR_{17}, -C(O)R_{18}, or -C(O)$NR_{17}R_{17}$;

R_{15} and $R_{15'}$ are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{15a} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

each R_{16} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{24}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{16}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S

R_{17} is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{18} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

each R_{19} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{25}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{19} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{20} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{20} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{21} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{27}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, and R_{27} are each independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{30} and R_{31} are each independently at each occurrence H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_3-C_7)carbocyclyl, -C(O)R_{32}, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl or heteroaryl can be substituted with one or more R_{17};

R_{30}, R_{31}, and R_{32} are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{33} and R_{34} are each independently at each occurrence H, (C_1-C_6)alkyl, or -C(O)R_{37};

R_{35}, R_{36}, and R_{37} are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{38} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

m is 0, 1, or 2;

q is 1, 2, or 3;

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

r is 0 or 1.

26. The compound according to claim 25, wherein R_3 is H.

27. The compound according to claim 25, wherein R_5 is H.

28. The compound according to claim 25, wherein R_{2a} is H.

29. The compound according to claim 25, wherein R_{2b} is H.

30. The compound according to claim 25, wherein R_{2c} is H.

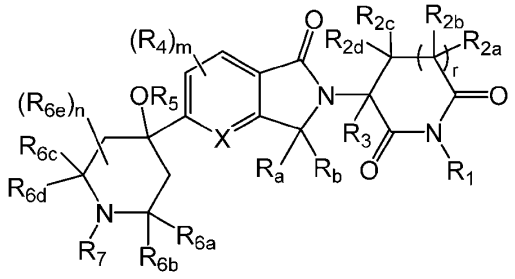
31. The compound according to claim 25, wherein R_{2d} is H.

32. The compound according to claim 25, R_7 is (C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one to three phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to three R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to three $R_{8'}$.

33. The compound according to claim 25, R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one to three phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to three R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to three $R_{8'}$.

34. The compound according to claim 25, wherein the compound of Formula (I) or (II) is a compound provided in Table 1.

35. A compound of Formula (III):



(III),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

X is N or N(O);

R_a and R_b are each independently H, D, or (C_1-C_6)alkyl;

R_1 is H, D, -C(O)R_{11}, -CH_2OC(O)R_{11}, -CH_2OC(O)NHR_{12}, -CH_2OC(O)OR_{12}, -P(O)(OR_{12})$_2$, -CH_2OP(O)(OR_{12})$_2$, -CH_2OP(O)(OH)OR_{12}, -CH_2OP(O)(R_{12})$_2$, -CH_2OC(O)CH_2NHC(O)CH_2NH_2, -CH_2OC(O)CH($R_{12'}$)N$HR_{12'}$, -CH_2OC(O)(CH_2)$_q$C(O)$OR_{12'}$, or -CH_2OC(O)-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S);

R_{2a}, R_{2b}, R_{2c}, and R_{2d} are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, halogen, or -OH, wherein two of R_{2a}, R_{2b}, R_{2c}, and R_{2d} may be taken together with the carbon atom to which they are attached form a (C_3-C_7)carbocyclyl or (C_3-C_7)spirocarbocyclyl;

R_3 is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, or halogen, wherein R_3 may be taken together with one of R_{2a}, R_{2b}, R_{2c}, and R_{2d} with the carbon atom to which they are attached to form a (C_3-C_7)carbocyclyl or (C_3-C_7)spirocarbocyclyl;

each R_4 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, or halogen;

R_5 is H, D, (C_2-C_6)alkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)aminoalkyl, (C_1-C_6)alkyl-O-(C_1-C_6)hydroxyalkyl, $-C(O)R_{12}$, $-CH_2OC(O)R_{12}$, $-CH_2OC(O)N(R_{12})_2$, $-CH_2OC(O)_2R_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$;

R_{6a}, R_{6b}, R_{6c}, and R_{6d} are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy,, or (C_3-C_7)carbocyclyl; or

two of R_{6a}, R_{6b}, R_{6c}, and R_{6d} together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl, (C_3-C_7)spirocarbocyclyl, 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl, heterocyclyl, and spiroheterocyclyl are optionally substituted with one or more R_{10};

each R_{6e} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, (C_1-C_6)hydroxyalkyl, -CN, -OH, -O-(C_1-C_6)hydroxyalkyl, -(C_1-C_6)alkylene-O-(C_1-C_6)alkyl, (C_6-C_{10})aryl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the alkyl is optionally substituted with one or more R_{13}, the aryl and heteroaryl are optionally substituted with one or more R_{22}, and the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{23}; or

two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)carbocyclyl, (C_3-C_7)spirocarbocyclyl, a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl, heterocyclyl, and spiroheterocyclyl are optionally substituted with one or more R_{15}; or

one R_{6e} is taken together with any one of R_{6a}, R_{6b}, R_{6c}, and R_{6d} and the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{15};

R_7 is (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, or (C_3-C_7)carbocyclyl, wherein alkyl, haloalkyl, hydroxyalkyl, halohydroxyalkyl, and carbocyclyl are optionally substituted with one or more substituents independently selected from R_{21}, D, (C_1-C_6)alkoxy, -SF_5, -SR_{14a}, -$NR_{14}R_{14'}$,-C(O)$NR_{29}R_{30}$, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one or more $R_{8'}$;

R_8 and $R_{8'}$ are each independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -$NR_{27}R_{28}$, -SF_5, -SR_9, -CN, -C(O)$NR_{29}R_{30}$, -C(O)OR_{29}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl, -O-phenyl, monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, -O-(monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S or -O-(4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S), wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more substituents selected from (C_1-C_6)alkyl, (C_3-C_7)carbocyclyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy,
(C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, –OH, -$NR_{32}R_{33}$, -C(O)$NR_{34}R_{35}$, -C(O)R_{34}, -C(O)OR_{34}, -SF_5, -SR_{37}, and -CN; or

two R_8, when on adjacent atoms, together with the atoms to which they are attached form a phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R_{10};

two $R_{8'}$, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{10}; or

two $R_{8'}$ together with the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{10}; or

two $R_{8'}$ when on the same carbon atom form C=(O);

R_9 is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{10} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{26}, or -CN;

R_{11} is independently at each occurrence H, (C_1-C_6)alkoxy, -NH_2, -N(H)(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN;

R_{12} is independently at each occurrence H, (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from (C_6-C_{10})aryl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN, or (C_6-C_{10})aryl optionally substituted with one or more substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, (C_1-C_6)haloalkyl, halogen, -OH, -NH_2, and -CN;

$R_{12'}$ is independently at each occurrence H or (C_1-C_6)alkyl;

each R_{13} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -C(O)O$R_{15'}$, -C(O)R_{15}, or -C(O)N$R_{15'}R_{15'}$;

R_{14} and $R_{14'}$ are each independently at each occurrence H or (C_1-C_6)alkyl;

R_{14a} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

R_{15} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

$R_{15'}$ is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

each R_{16} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -N$R_{17}R_{17'}$, -CN, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}) aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein carbocyclyl and heterocyclyl are optionally substituted with one or more R_{22} and the aryl and heteroaryl are optionally substituted with one or more R_{23};

R_{17} and $R_{17'}$ are each independently at each occurrence H or (C_1-C_6)alkyl;

each R_{18} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)hydroxyalkyl, halogen, -OH, -NH_2, -SF_5, -SR_{20}, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{18}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{19} is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, $(C_1\text{-}C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{21}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3\text{-}C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{19} together with the atoms to which they are attached form a $(C_3\text{-}C_7)$carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

R_{20} and R_{21} are each independently at each occurrence H, $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$haloalkyl;

each R_{22} is independently at each occurrence D, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, $(C_1\text{-}C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{24}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3\text{-}C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; or

two R_{22} together with the atoms to which they are attached form a $(C_3\text{-}C_7)$carbocyclyl or a 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

each R_{23} is independently at each occurrence D, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, $(C_1\text{-}C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{25}$, -CN, phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, $(C_3\text{-}C_7)$carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S;

R_{24}, R_{25} and R_{26} are each independently at each occurrence H, $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$haloalkyl;

R_{27} and R_{28} are each independently at each occurrence H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_3\text{-}C_7)$carbocyclyl, $-C(O)R_{31}$, phenyl, or 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl or heteroaryl can be substituted with one or more R_{17};

R_{29}, R_{30}, and R_{31} are each independently at each occurrence H or $(C_1\text{-}C_6)$alkyl;

R_{32} and R_{33} are each independently at each occurrence H, $(C_1\text{-}C_6)$alkyl, or $-C(O)R_{36}$;

R_{34}, R_{35}, and R_{36} are each independently at each occurrence H or $(C_1\text{-}C_6)$alkyl;

R_{37} is H, $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$haloalkyl;

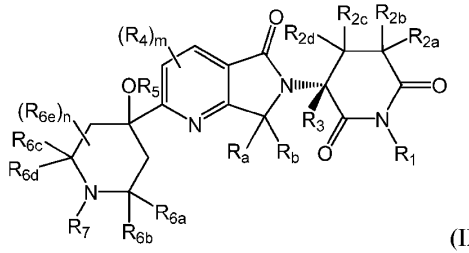
q is 1, 2, or 3;

m is 0, 1 or 2;

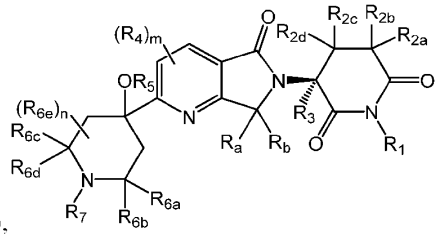
n is 0, 1, 2, 3 or 4;

r is 0 or 1.

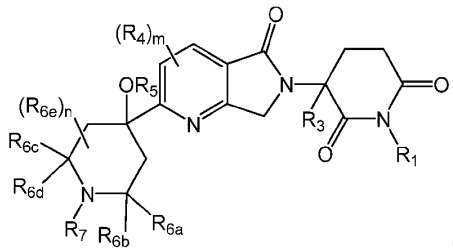
36. The compound according to claim 35, having a Formula (IIIa), Formula (IIIb), Formula (IIIc), Formula (IIId), Formula (IIIe), Formula (IIIf), or Formula (IIIg):



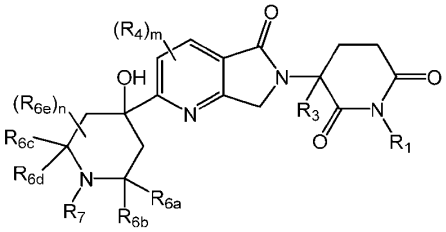
(IIIa),



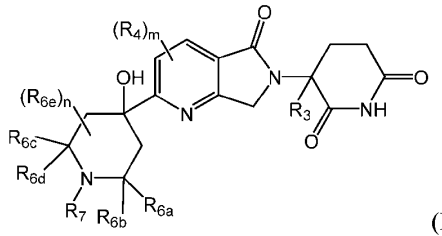
(IIIb),



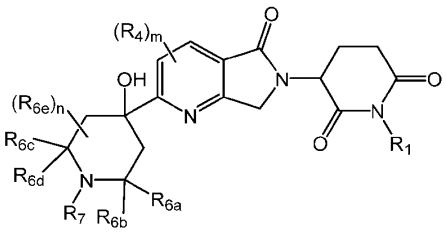
(IIIc),



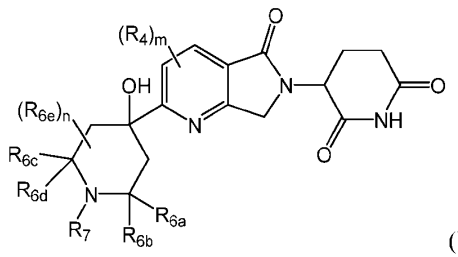
(IIId),



(IIIe),



(IIIf), or



(IIIg),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

37. The compound according to claim 35, wherein R_5 is H.

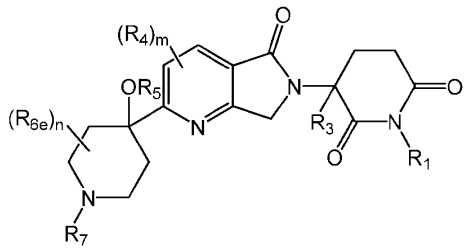
38. The compound according to claim 35, wherein R_{6a} is H.

39. The compound according to claim 35, wherein R_{6b} is H.

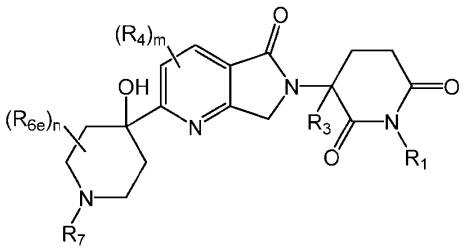
40. The compound according to claim 35, wherein R_{6c} is H.

41. The compound according to claim 35, wherein R_{6d} is H.

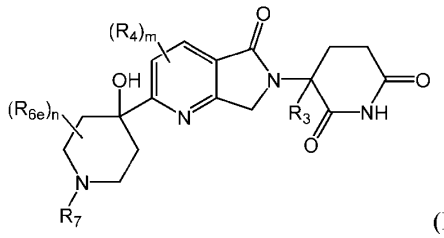
42. The compound according to claim 35, having a Formula (IIIh), Formula (IIIi), Formula (IIIj), Formula (IIIk), or Formula (IIIl):



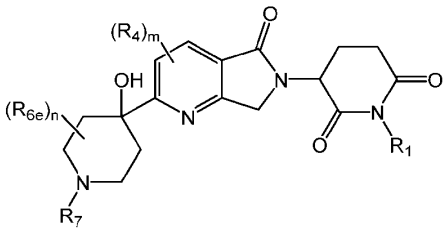
(IIIh),



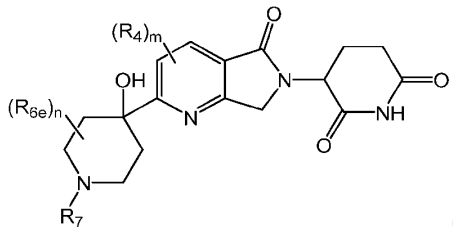
(IIIi),



(IIIj),



(IIIk), or



(IIIl),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

43. The compound according to claim 35, wherein R_1 is H.

44. The compound according to claim 35, wherein R_{2a}, R_{2b}, R_{2c}, and R_{2d} are each H.

45. The compound according to claim 35, wherein R_3 is H, D, or methyl.

46. The compound according to claim 35, wherein R_a and R_b are both H.

47. The compound according to any one of the above claims, wherein m is 0.

48. The compound according to claim 35, wherein R_{6a}, R_{6b}, R_{6c}, and R_{6d} are each independently H or (C_1-C_6)alkyl.

49. The compound according to claim 35, wherein each R_{6e} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl,
-(C_1-C_6)alkylene-O-(C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one or more R_{13}, the aryl is optionally substituted with one or more R_{22}; or

two R_{6e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one or more R_{15}.

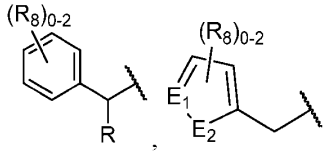
50. The compound according to claim 35, wherein n is 0.

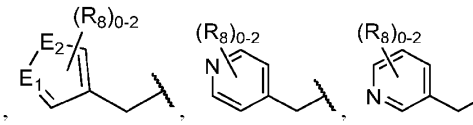
51. The compound according to claim 35, wherein n is 1.

52. The compound according to claim 35, wherein n is 2.

53. The compound according to claim 35, wherein R_7 is (C_1-C_6)alkyl, wherein the alkyl is optionally substituted with one or two phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{8'}$.

54. The compound according to claim 35, wherein R_7 is (C_1-C_6)alkyl, wherein the alkyl is substituted with one or two phenyl, 5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_8 and the carbocyclyl, and heterocyclyl are optionally substituted with one to four $R_{8'}$.

55. The compound according to claim 35, wherein R_7 is selected from 

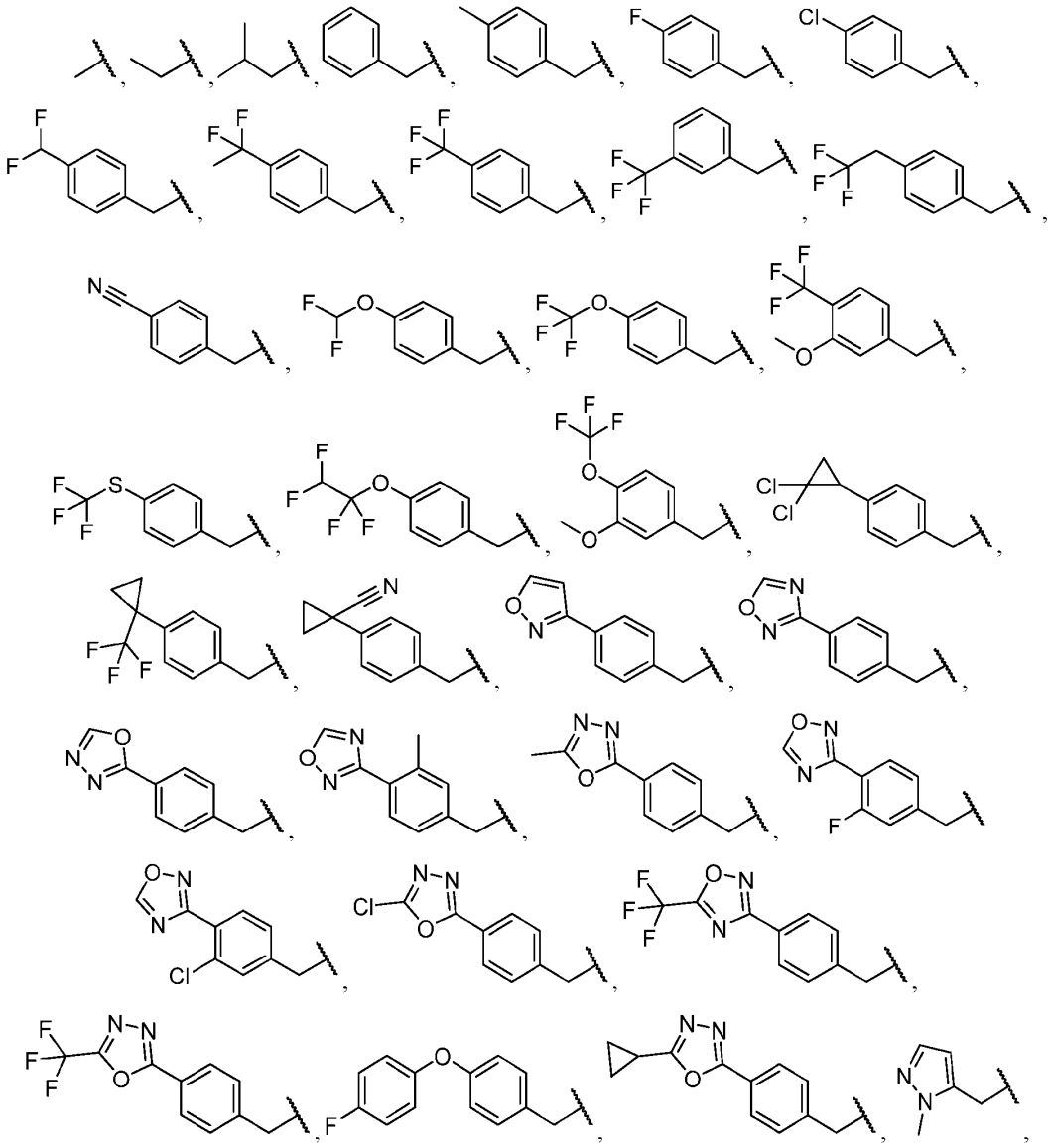
, 

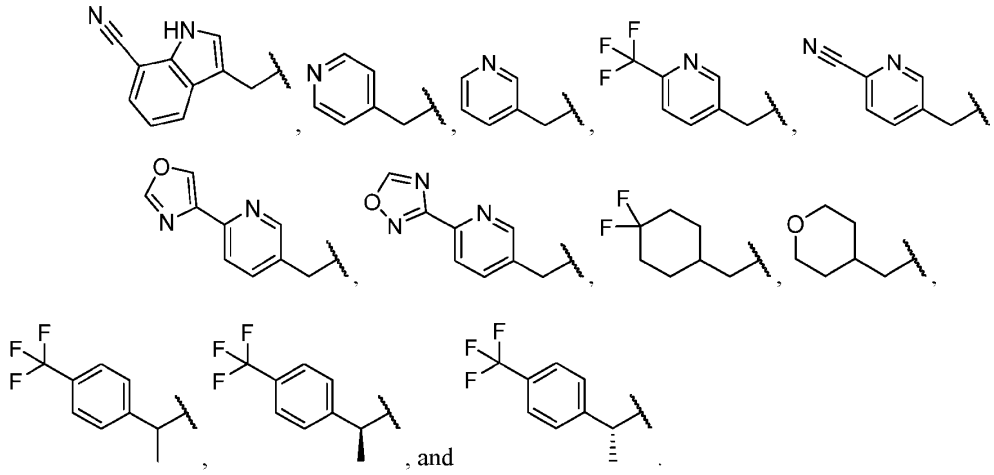
, and

, wherein R is selected from H and (C_1-C_3)alkyl; E_1 is selected from CH and N; E_2 is selected from O, NH, NR_8, and S; and

R_8 and $R_{8'}$ are defined according to the above claim 35.

56. The compound according to claim 35, wherein R_7 is selected from





57. The compound according to claim 35, wherein the compound is provided in Table 2.

58. A pharmaceutical composition according to any one of claims 1-57, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

59. The pharmaceutical composition according to claim 58, further comprising a pharmaceutically acceptable additive or excipient.

60. The pharmaceutical composition according to claim 58, for use in the treatment of a disease or disorder that is affected by the reduction of HIF-1β levels.

61. A method of degrading HIF-1β, comprising administering to a patient in need thereof an effective amount of a compound according to claim 1, 25, or 35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

62. A method of modulating HIF-1β levels comprising administering to a patient in need thereof an effective amount of a compound according to claim 1, 25, or 35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

63. An *in vitro* method of reducing the proliferation of a cell, comprising contacting the cell with an effective amount of a compound according to claim 1, 25, or 35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

64. A method of treating a disease or disorder that is affected by the modulation of HIF-1β levels, comprising administering to a patient in need thereof a therapeutically effective amount of a compound

according to claim 1, 25, or 35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

65. The method according to claim 64, wherein the disease or disorder is selected from cancer, von Hippel-Lindau (VHL) disease, iron overload disorders, cardiovascular diseases, pulmonary diseases, autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, metabolic diseases, neovascular diseases, retinal vascular diseases, fibrosis, endometriosis, preeclampsia, and allergic and genetic diseases.

66. The method according to claim 65, wherein the disease or disorder is selected from renal cell carcinoma (RCC), von Hippel-Lindau disease (VHL), advanced pheochromocytoma/paraganglioma (PPGL), pancreatic neuroendocrine tumor (pNET), pulmonary arterial hypertension (PAH), glioblastoma, colitis, Crohn's disease, ulcerative colitis, T cell leukemia or T cell lymphoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), melanoma, triple-negative breast cancer (TNBC), nasopharyngeal cancer (NPC), microsatellite stable colorectal cancer (mssCRC), thymoma, carcinoid, gastrointestinal stromal tumor (GIST), myeloid leukemia, and coronary heart disease.

67. A method of treating cancer, comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to claim 1, 25, or 35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

68. The method according to claim 67, wherein the cancer is VHL-deficient cancer.

69. The method according to claim 67, wherein the cancer is selected from renal cell carcinoma (RCC), glioblastoma, T cell leukemia or T cell lymphoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), melanoma, triple-negative breast cancer (TNBC), nasopharyngeal cancer (NPC), microsatellite stable colorectal cancer (mssCRC), thymoma, carcinoid, gastrointestinal stromal tumor (GIST), and myeloid leukemia.

70. A method for reducing HIF-1β levels, comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to claim 1, 25, or 35, or a pharmaceutically acceptable salt thereof.

71. A method of treating von Hippel-Lindau (VHL) disease, comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to claim 1, 25, or 35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

72. A method of treating a neoplastic condition, comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to claim 1, 25, or 35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

73. A method of treating renal cell carcinoma (RCC), comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to claim 1, 25, or 35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

74. The method of claim 73, wherein the renal cell carcinoma is clear cell renal cell carcinoma (ccRCC).

74. The method according to claim 64, wherein the administration is oral, parenteral, subcutaneous, by injection, or by infusion.

75. A compound according to claim 1, 25, or 35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in the treatment of a disease or disorder that is affected by the reduction of HIF-1β levels.

76. A compound according to claim 1, 25, or 35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in treating a disease or disorder associated with the reduction of HIF-1β levels.

77. Use of a compound according to claim 1, 25, or 35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for treating a disease or disorder that is affected by the reduction of HIF-1β levels.

78. Use of a compound according to claim 1, 25, or 35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the treatment of a disease or disorder associated with the reduction of HIF-1β levels.

79. The compound for use according to claim 77 or the use according to claim 64, wherein the disease or disorder is selected from cancer, von Hippel-Lindau (VHL) disease, iron overload disorders, cardiovascular diseases, pulmonary arterial hypertension (PAH), autoimmune and inflammatory-related diseases and conditions, neurodegenerative diseases, viral diseases, metabolic diseases, and allergic and genetic diseases.