SUBSTITUTED (PIPERIDIN-4-YL)-1,5-NAPHTHYRIDINE AND (PIPERIDIN-4-YL)QUINOLINE DERIVATIVES AND USES THEREOF

CLAIM OF PRIORITY

The present application claims priority to U.S. Application No. 63/547,059, filed November 2, 2023, and U.S. Application No. 63/547,060, filed November 2, 2023. The entire contents of each of the foregoing applications are incorporated by reference in their entirety.

FIELD OF THE DISCLOSURE

The present disclosure relates to substituted (piperidin-4-yl)-1,5-naphthyridine and (piperidin-4-yl)quinoline compounds and compositions for modulation of hypoxia inducible factor 1 beta (HIF-1b) and their use for the treatment of HIF-1b-dependent diseases or disorders or where reduction of HIF-1b 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-1b, also known as ARNT) and either of the two HIF-a isoforms, HIF-1a or HIF-2a. HIF-1b 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-a 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-a proteins are then translocated to the nucleus, where they interact with HIF-1b to form a heterodimeric transcription factor (Kallio et al., *Embo* J, 1998, 17, 6573-65, 86). The dimerization step has been shown in HIF-1b 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-1b protein levels, the abundance of the HIF-a 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-2a/HIF-1b 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-1b heterodimer directly associates with the estrogen receptors ER-a and ER-b 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).

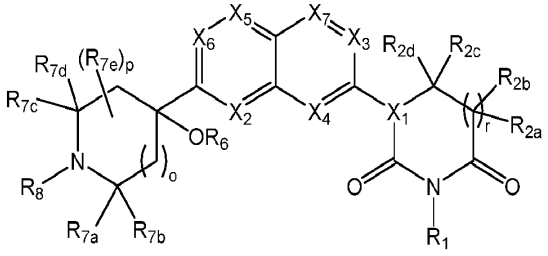
In summary, HIF-1b plays an important role in both the hypoxia-induced and AHR signaling pathways, which have been linked to various forms of malignancies (Harris, *Nat. Rev. Cancer*, 2002, 2, 8-47; *Safe Toxicol. Lett.*, 2001, 120, 1-7). The angiogenic promoting capabilities of HIF-1b also make it a

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-1b 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-1b.

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 disorders (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-1b-related diseases. In one aspect, the compounds of the disclosure have HIF-1b degrader activity. In some embodiments, the HIF-1b degrader activity is at or below the 50 μM level, and more preferably at or below the 10 μM level, when administered to a cell or subject. 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.

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 X_1 is N or CR_3; X_2 is N, N(O), or CR_5; X_3 is N or CR_{4a}; X_4 is N or CR_{4b}; X_5 is N or $CR_{4b'}$; X_6 is N or CR_5; X_7 is N or N(O); wherein no more than three of X_2, X_3, X_4, X_5, X_6 and X_7 is simultaneously N; R_1 is H, D, $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, $-CH_2OP(O)(R_{12})_2$, $-CH_2OC(O)CH_2NHC(O)CH_2NH_2$, $-CH_2OC(O)CH(R_{12'})NHR_{12'}$, $-CH_2OC(O)(CH_2)_q$-

$C(O)OR_{12'}$, 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, halogen, or -OH, 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; R_{4a}, R_{4b}, and $R_{4b'}$ are each independently 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, or $-NR_9R_{10}$; wherein each alkyl, deuteroalkyl, haloalkyl, alkoxy, deuteoalkoxy, haloalkoxy, and carbocyclyl is optionally substituted with one or more R_{40} $R_{4a'}$ are each independently H, D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, or halogen; R_5 and $R_{5'}$ are each independently 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, $(C_3$-$C_7)$carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; halogen, -OH, or $-NR_9R_{10}$; wherein each alkyl, deuteroalkyl, haloalkyl, alkoxy, deuteoalkoxy, haloalkoxy, and carbocyclyl is optionally substituted with one or more R_{40} $R_{4a'}$ are each independently H, D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, or halogen; R_6 is H, D, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$halohydroxyalkyl, $(C_1$-$C_6)$aminoalkyl, $(C_1$-$C_6)$alkyl-O-$(C_1$-$C_6)$hydroxyalkyl, $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$; R_{7a}, R_{7b}, R_{7c}, and R_{7d} are each independently H, D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl; or two of R_{7a}, R_{7b}, R_{7c}, and R_{7d} are taken together with the carbon atoms to which they are attached form a $(C_3$-$C_7)$carbocyclyl, $(C_3$-$C_7)$spirocarbocyclyl, or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one or more substituents independently selected from D, $(C_1$-$C_6)$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, $-C(O)OR_{13'}$, $-C(O)R_{13}$, and $-C(O)NR_{13'}R_{13'}$; each R_{7e} is independently at each occurrence D, $(C_1$-$C_6)$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_{19}, the aryl and heteroaryl are optionally substituted with one or more R_{21}, and the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{22}; or two R_{7e} together with the carbon atom to which they are attached form a $(C_3$-$C_7)$carbocyclyl, $(C_3$-$C_7)$spirocarbocyclyl, or a 4- to 7-membered spiroheterocyclyl comprising 1 to 4 heteroatoms selected from

O, N, NH, and S, wherein the carbocyclyl, spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one or more substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$; one R_{7e} is taken together with any one of R_{7a}, R_{7b}, R_{7c}, and R_{7d} 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_{22}; R_8 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)$NR_{32}R_{33}$, 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 $R_{15'}$; R_9 and R_{10} are each independently at each occurrence H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, or (C_1-C_6)haloalkyl; 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} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; $R_{13'}$ is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; 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} and $R_{15'}$ 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_{16}, -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 alkyl, alkoxy,"" 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, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{29}$, $SO_2NR_{30}R_{31}$, -CN, and R_{19}; or two R_{15}, 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_{17}; two $R_{15'}$, 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_{17}; or two $R_{15'}$ 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_{17}; or two $R_{15'}$ when on the same carbon atom form C=(O); R_{16} is H, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl; R_{17} is independently at each occurrence D, $(C_1$-$C_6)$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, $-NH_2$, $-SF_5$, $-SR_{18}$, or -CN; R_{18} is H, $(C_1$-$C_6)$alkyl, or $(C_1$-$C_6)$haloalkyl; each R_{19} is independently at each occurrence $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $-NR_{20}R_{20'}$, -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 or more R_{23} and the aryl and heteroaryl are optionally substituted with one or more R_{24}; or R_{19} when on the same carbon atom form C=(O); or two R_{19} 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_{17}; R_{20} and $R_{20'}$ are each independently at each occurrence H or $(C_1$-$C_6)$alkyl; 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, $-NH_2$, $-SF_5$, $-SR_{25}$, -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_{21}, 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_{15}; 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, $-NH_2$, $-SF_5$, $-SR_{26}$, -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_{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_{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; 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; each R_{24} 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_{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; 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 D, (C_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_{16}, -CN, -C(O)$NR_{32}R_{33}$, -C(O)OR_{32}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl; o is 1 or 2; p is 0, 1, 2, 3 or 4; q is 1, 2, or 3; and r is 0 or 1.

In one aspect of the disclosure, the hydrogens in the Compound of Formula (I) 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), 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-1b-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), 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-1b-dependent disease or disorder by reducing HIF-1b protein levels wherein reduction of HIF-1b protein levels treats the HIF-1b-dependent disease or disorder. The

pharmaceutical composition is useful in the treatment of HIF-1b-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), 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-1b 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-1b, comprising administering to a patient in need thereof an effective amount of a Compound of Formula (I), 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-1b levels comprising administering to a patient in need thereof an effective amount of a Compound of Formula (I), 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), 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-1b levels, comprising administering to a patient in need thereof a therapeutically effective amount of a Compound of Formula (I), 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), 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-1b levels, comprising administering to a subject in need thereof a therapeutically effective amount of a Compound of Formula (I), 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), 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), 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), 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-1b 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-1b protein levels, and in the treatment HIF-1b-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-1b 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-1b protein levels, and in the treatment HIF-1b-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-1b proteins.

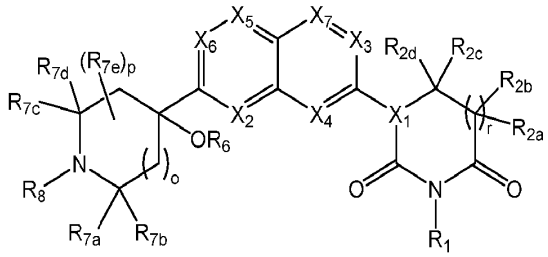
DETAILED DESCRIPTION OF THE DISCLOSURE

The present disclosure relates to compounds and compositions that are capable of modulating HIF-1b protein levels. The disclosure features methods of treating, preventing, or ameliorating a disease or disorder in which HIF-1b plays a role by administering to a patient in need thereof a therapeutically effective amount of a Compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. The methods of the present disclosure can be used in the treatment of a variety of HIF-1b-dependent diseases and disorders by modulating HIF-1b protein levels. Modulation of HIF-1b 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-1b-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-1b-related diseases. In one aspect, the compounds of the disclosure have HIF-1b 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-1b 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-1b-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_1, R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_6, R_{7a}, R_{7b}, R_{7c}, R_{7d}, R_{7e}, R_8, X_1, X_2, X_3, X_4, X_5, X_6, X_7, o, p, 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, $(C_1\text{-}C_{10})$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.

"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.

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

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

"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.

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

"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.

"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)-.

"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)) 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" mean 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 structure 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 stereoisomers, 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" mean 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), (Ia), (Ib), (Ic), (Id), (Ie), (If), (lg), (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), (Iaaa), (Ibbb), (Iccc), (Iddd), (Ieee), (Ifff), (Iggg), (Ihhh), (Iiii), (Ijjj), and (Ikkk), 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), 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), 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), 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), 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), 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), 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-1b-dependent disease or disorder" means any disease or disorder which is directly or indirectly affected by the modulation of HIF-1b protein levels.

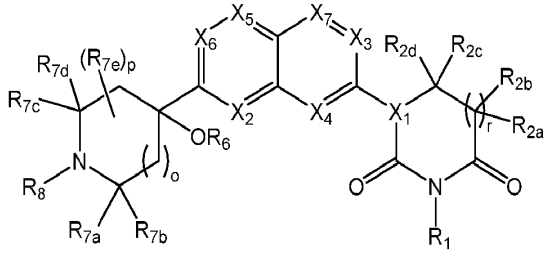
The term "von Hippel-Lindau disease" or "VHL disease" or "VHL syndrome" or "von Hippel-Lindau syndrome", as used herein, refers to a rare disease caused by a mutation in the von Hippel-Lindau (VHL) tumor suppressor leading to an aberrant non-functional VHL protein and to an absence of VHL protein. VHL 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-1b protein levels, which are useful for the treatment of diseases and disorders associated with modulation of HIF-1b 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-1b protein levels.

The present disclosure features compounds of Formula (I):



(I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein X_1 is N or $C(R_3)_2$; X_2 is N, N(O), or CR_5; X_3 is N or CR_{4a}; X_4 is N or CR_{4b}; X_5 is N or $CR_{4b'}$; X_6 is N or CR_5; X_7 is N or N(O); wherein no more than three of X_2, X_3, X_4, X_5, X_6 and X_7 is simultaneously N; R_1 is H, D, $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, $-CH_2OP(O)(R_{12})_2$, $-CH_2OC(O)CH_2NHC(O)CH_2NH_2$, $-CH_2OC(O)CH(R_{12'})NHR_{12'}$, $-CH_2OC(O)(CH_2)_q-$

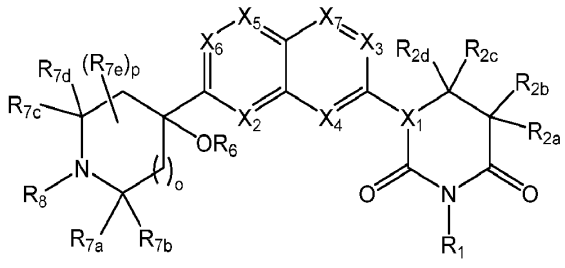
$C(O)OR_{12'}$, or $-CH_2OC(O)$-(5- or 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S); R_{2a}, R_{2b}, R_{2c}, and R_{2d} are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, halogen, or -OH, wherein two of R_{2a}, R_{2b}, R_{2c}, and R_{2d} may be taken 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, halogen, or -OH, 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; R_{4a}, R_{4b}, and $R_{4b'}$ are each independently 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, or $-NR_9R_{10}$; wherein each alkyl, deuteroalkyl, haloalkyl, alkoxy, deuteoalkoxy, haloalkoxy, and carbocyclyl is optionally substituted with one or more $R_{40}R_{4a'}$ are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, or halogen; R_5 and $R_{5'}$ are each independently 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, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; halogen, -OH, or $-NR_9R_{10}$;, wherein each alkyl, deuteroalkyl, haloalkyl, alkoxy, deuteoalkoxy, haloalkoxy, and carbocyclyl is optionally substituted with one or more $R_{40}R_{4a'}$ are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, or halogen; R_6 is H, D, (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, $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$; R_{7a}, R_{7b}, R_{7c}, and R_{7d} are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, or(C_1-C_2)haloalkyl; or two of R_{7a}, R_{7b}, R_{7c}, and R_{7d} are taken together with the carbon atoms to which they are attached form a (C_3-C_7)carbocyclyl, (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 carbocyclyl, spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one or more substituents independently selected from D, (C_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, $-C(O)OR_{13'}$, $-C(O)R_{13}$, and $-C(O)NR_{13'}R_{13'}$; each R_{7e} is independently at each occurrence D, (C_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_{19}, the aryl and heteroaryl are optionally substituted with one or more R_{21}, and the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{22}; or two R_{7e} together with the carbon atom to which they are attached form a (C_3-C_7)carbocyclyl, (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 carbocyclyl, spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one or more substituents independently selected from D, $(C_1$-$C_6)$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, $-C(O)OR_{13'}$, $-C(O)R_{13}$, and $-C(O)NR_{13'}R_{13'}$; one R_{7e} is taken together with any one of R_{7a}, R_{7b}, R_{7c}, and R_{7d} 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_{22}; R_8 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, $-SF_5$, $-SR_{14a}$, $-NR_{14}R_{14'}$, $-C(O)NR_{32}R_{33}$, 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 $R_{15'}$; R_9 and R_{10} are each independently at each occurrence H, D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, or $(C_1$-$C_6)$haloalkyl; 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} is independently at each occurrence $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl; $R_{13'}$ is independently at each occurrence H, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$ haloalkyl; 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} and $R_{15'}$ 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, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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 alkyl, alkoxy,"" 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_{29}, $SO_2NR_{30}R_{31}$, -CN, and R_{19}; or two R_{15}, 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_{17}; two $R_{15'}$, 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_{17}; or two $R_{15'}$ 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_{17}; or two $R_{15'}$ when on the same carbon atom form C=(O); R_{16} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{17} is independently at each occurrence D, (C_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_{18}, or -CN; R_{18} is H, (C_1-C_6)alkyl, or (C_1-C_6)haloalkyl;
each R_{19} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{20}R_{20'}$, -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 or more R_{23} and the aryl and heteroaryl are optionally substituted with one or more R_{24}; or R_{19} when on the same carbon atom form C=(O); or two R_{19} 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_{17}; R_{20} and $R_{20'}$ are each independently at each occurrence H or (C_1-C_6)alkyl; 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_{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_{21}, 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_{15}; 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_{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_{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_{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; 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; each R_{24} 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_{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; 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 D, (C_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_{16}, -CN, -C(O)$NR_{32}R_{33}$, -C(O)OR_{32}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl; o is 1 or 2; p is 0, 1, 2, 3 or 4; q is 1, 2, or 3; and r is 0 or 1.

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



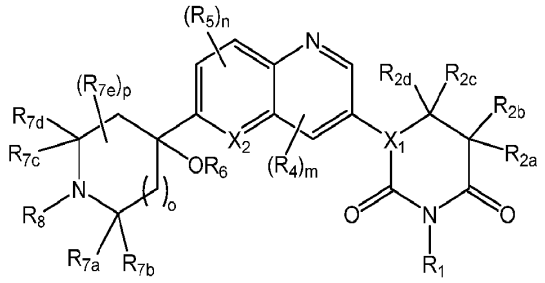
(I-a), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein X_1 is N or CR_3; X_2 is N or $CR_{4a'}$; X_3 is N or CR_{4a}; X_4 is N or CR_{4b}; X_5 is N or $CR_{4b'}$; X_6 is N or CR_5; X_7 is N or $CR_{5'}$; wherein no more than three of X_2, X_3, X_4, X_5, X_6 and X_7 is simultaneously N; 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}, -

$CH_2OP(O)(R_{12})_2$, $-CH_2OC(O)CH_2NHC(O)CH_2NH_2$, $-CH_2OC(O)CH(R_{12'})NHR_{12'}$, $-CH_2OC(O)(CH_2)q-C(O)OR_{12'}$, 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; R_{4a} and R_{4b} are each independently 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, or $-NR_9R_{10}$; $R_{4a'}$ are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, or halogen; $R_{4b'}$ 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, or $-NR_9R_{10}$; R_5 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, or $-NR_9R_{10}$; $R_{5'}$ 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, or $-NR_9R_{10}$; R_6 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_{7a}, R_{7b}, R_{7c}, and R_{7d} are each independently H, D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl; each R_{7e} is independently at each occurrence D, (C_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_{19}, the aryl and heteroaryl are optionally substituted with one or more R_{21}, and the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{22}; or two R_{7e}, 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 substituents independently selected from D, (C_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, $-C(O)OR_{13'}$, $-C(O)R_{13}$, and $-C(O)NR_{13'}R_{13'}$; R_8 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, 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 $R_{15'}$; R_9 and R_{10} are each independently at each occurrence H, D, (C_1-C_6)alkyl, or (C_1-C_6)deuteroalkyl; 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} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; $R_{13'}$ is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; 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} and $R_{15'}$ 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_{16}, -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_{29}, and -CN; or two R_{15}, 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_{17}; two $R_{15'}$, 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_{17}; or two $R_{15'}$ 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_{17}; or two $R_{15'}$ when on the same carbon atom form C=(O); R_{16} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{17} is independently at each occurrence D, (C_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_{18}, or -CN; R_{18} is H, (C_1-C_6)alkyl, or (C_1-C_6)haloalkyl; each R_{19} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{20}R_{20'}$, -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 or more R_{23} and the aryl and heteroaryl are optionally substituted with one or more R_{24}; R_{20} and $R_{20'}$ are each independently at each occurrence H or $(C_1\text{-}C_6)$alkyl; each R_{21} 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, $-NH_2$, $-SF_5$, $-SR_{25}$, -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; or two R_{21}, 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_{22} 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, $-NH_2$, $-SF_5$, $-SR_{26}$, -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, $-NH_2$, $-SF_5$, $-SR_{27}$, -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_{23} 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_{24} 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, $-NH_2$, $-SF_5$, $-SR_{28}$, -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_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each independently at each occurrence H, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$haloalkyl; R_{30} and R_{31} are each independently at each occurrence H, $(C_1\text{-}C_6)$alkyl, or $-C(O)R_{34}$; R_{32}, R_{33}, and R_{34} are each independently at each occurrence H or $(C_1\text{-}C_6)$alkyl; R_{35} and R_{36} are each independently at each occurrence H, $(C_1\text{-}C_6)$alkyl, or $-C(O)R_{39}$; R_{37}, R_{38}, and R_{39} are each independently at each occurrence H or $(C_1\text{-}C_6)$alkyl; o is 1 or 2; p is 0, 1, 2, 3 or 4; and q is 1, 2, or 3.

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



(I-b),

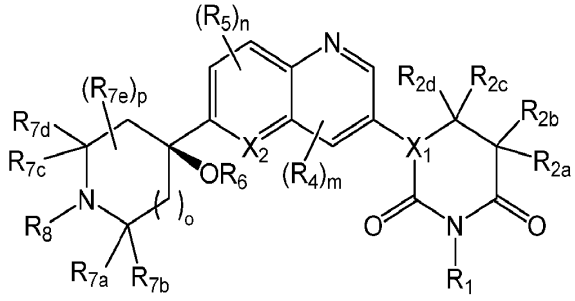
or a pharmaceutically accept-able salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein X_1 is N or CR_3; X_2 is N or $CR_{5'}$; R_1 is H, D, $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, $-CH_2OP(O)(R_{12})_2$, $-CH_2OC(O)CH_2NHC(O)CH_2NH_2$, $-CH_2OC(O)CH(R_{12'})NHR_{12'}$, $-CH_2OC(O)(CH_2)_qC(O)OR_{12'}$, 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, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, or $-NR_9R_{10}$; each R_5 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, or $-NR_9R_{10}$; $R_{5'}$ is H, D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, halogen, -OH, or $-NR_9R_{10}$; R_6 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_{7a}, R_{7b}, R_{7c}, and R_{7d} are each independently H, D, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl; each R_{7e} is independently at each occurrence D, $(C_1$-$C_6)$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_{19}, the aryl and heteroaryl are optionally substituted with one or more R_{21}, and the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{22}; or two R_{7e}, 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 substituents independently selected from D, $(C_1$-$C_6)$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, $-C(O)OR_{13'}$, $-C(O)R_{13}$, and $-C(O)NR_{13'}R_{13''}$; R_8 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, 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 $R_{15'}$; R_9 and R_{10} are each independently at each occurrence H, D, (C_1-C_6)alkyl, or (C_1-C_6)deuteroalkyl; 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} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; $R_{13'}$ is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; 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} and $R_{15'}$ 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_{16}, -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_{29}, and -CN; or two R_{15}, 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_{17}; two $R_{15'}$, 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 SO, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{17}; or two $R_{15'}$ together with

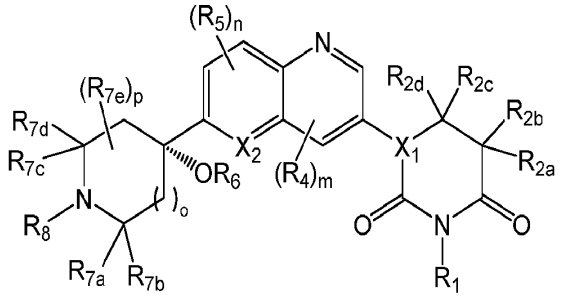
the atoms to which they are attached form a (C_3-C_7)carbocyclyl or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{17}; or two $R_{15'}$ when on the same carbon atom form C=(O); R_{16} is H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl; R_{17} is independently at each occurrence D, (C_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_{18}, or -CN; R_{18} is H, (C_1-C_6)alkyl, or (C_1-C_6)haloalkyl; each R_{19} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{20}R_{20'}$, -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 or more R_{23} and the aryl and heteroaryl are optionally substituted with one or more R_{24}; R_{20} and $R_{20'}$ are each independently at each occurrence H or (C_1-C_6)alkyl; 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_{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; two R_{21}, 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_{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_{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_{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_{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; 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; each R_{24} 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_{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; 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; o is 1 or 2; m and n are each independently 0, 1 or 2; p is 0, 1, 2, 3 or 4; and q is 1, 2, or 3.

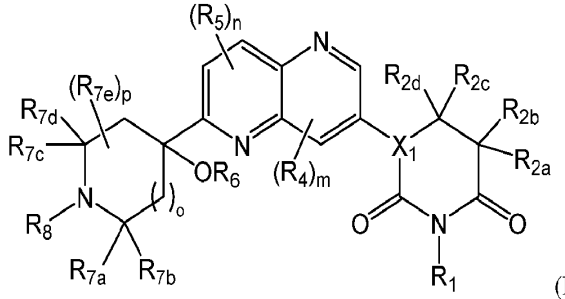
In one embodiment, the compounds of Formula (I) have the structure of Formula (I-c):



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

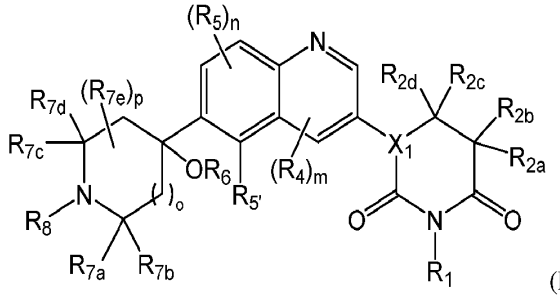


(I-d), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (I-e):



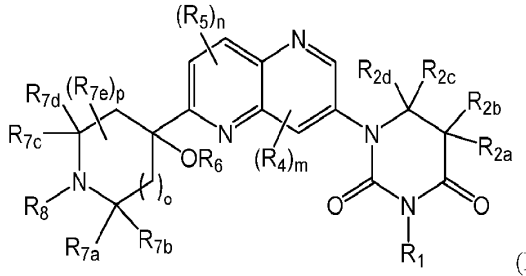
(I-e), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In yet another embodiment, the compounds of Formula (I) have the structure of Formula (I-f):



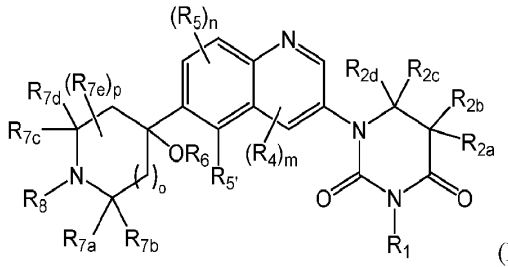
(I-f), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (I-g)



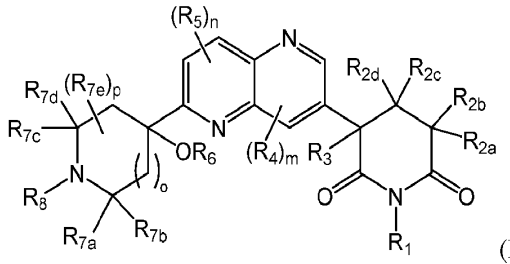
(I-g), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

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



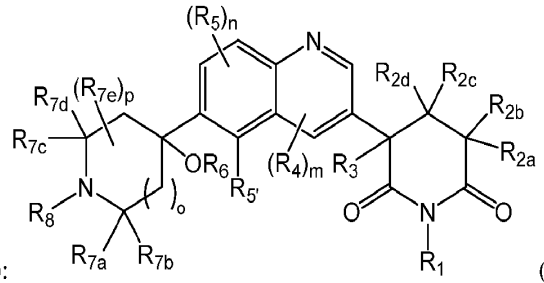
(I-h), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

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

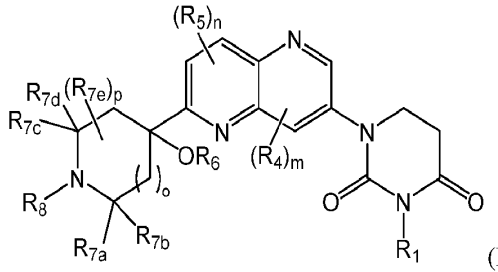


(I-i), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In yet another embodiment, the compounds of

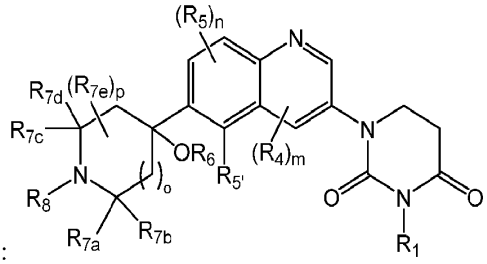
Formula (I) have the structure of Formula (I-j):



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

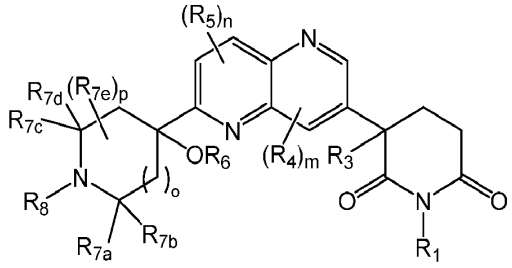


(I-k), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (I-l):

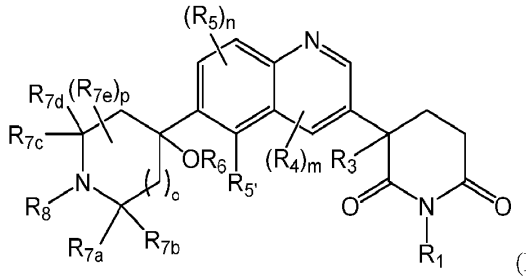


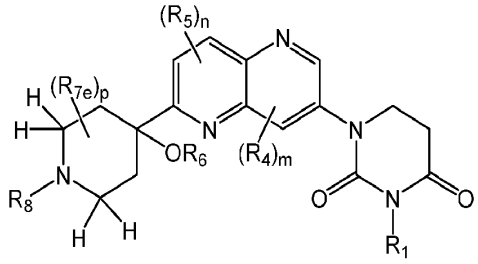
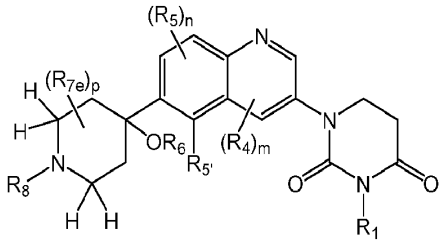
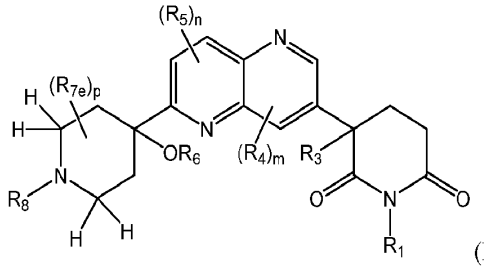
(I-l), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

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

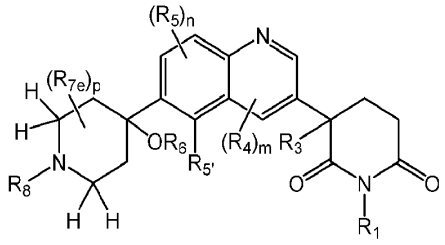


(I-m), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of

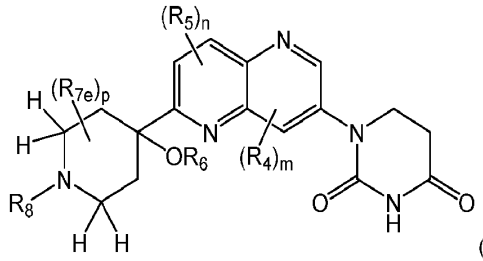
Formula (I) have the structure of Formula (I-n):  (I-n), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

In another embodiment, the compounds of Formula (I) have the structure of Formula (I-o):  (I-o), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In yet another embodiment, the compounds of Formula (I) have the structure of Formula (I-p):  (I-p), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (I-q):  (I-q), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

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

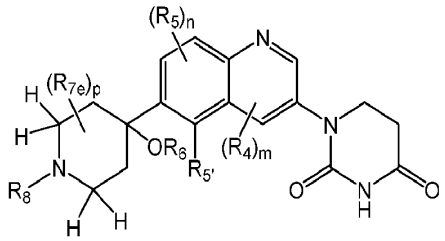


(I-r), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (I-s):

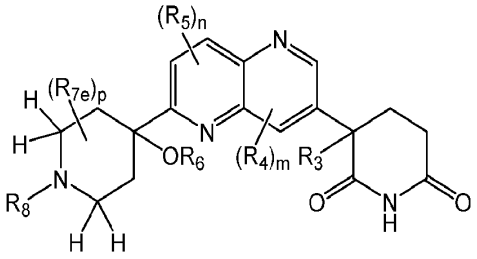


(Is), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

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

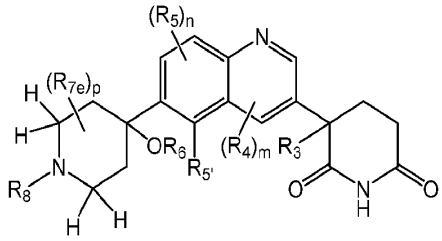


(Iu), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Iv):

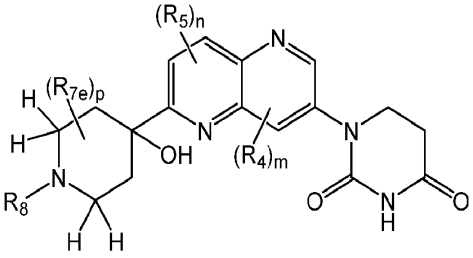


(Iv), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

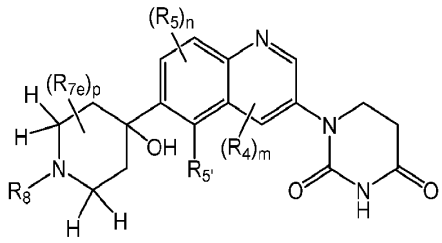
In another embodiment, the compounds of Formula (I) have the structure of Formula (Iw):



(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):

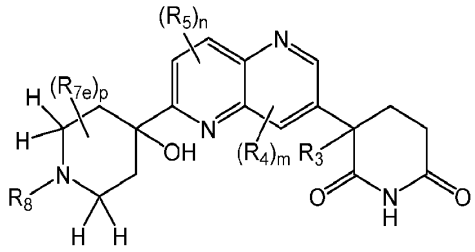


(Ix), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Iy):

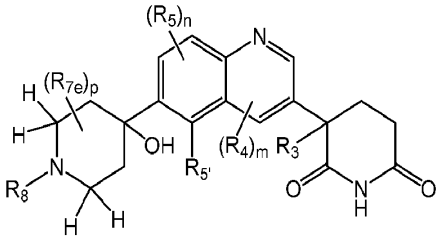
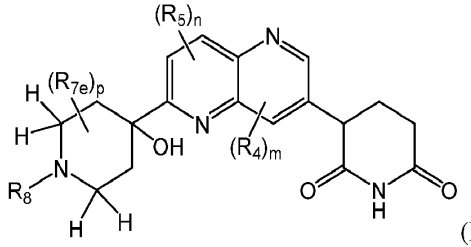
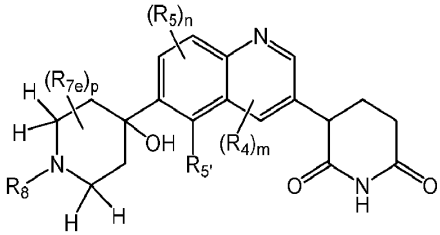


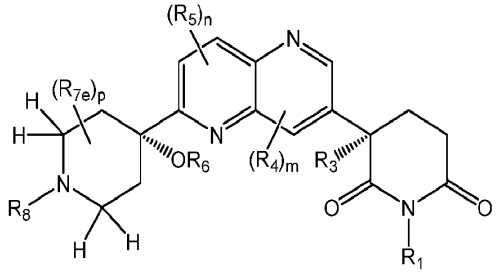
(Iy), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

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

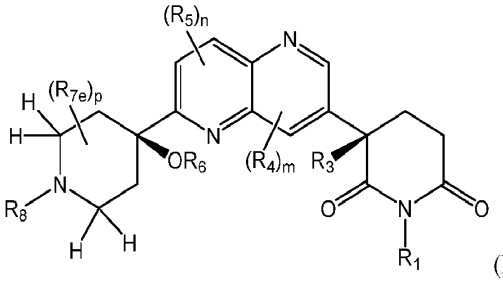


(Iz), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of

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 yet 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.

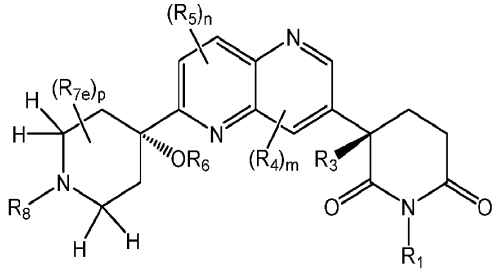
In another embodiment, the compounds of Formula (I) have the structure of Formula (Idd):  (Idd), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of

Formula (I) have the structure of Formula (Iee):

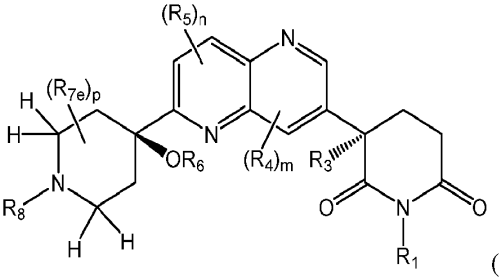


(Iee), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

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

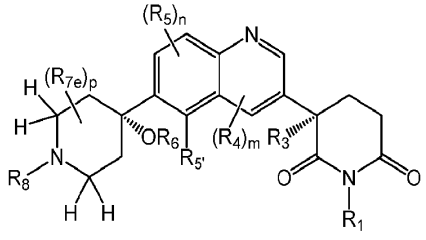


(Iff), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Igg):

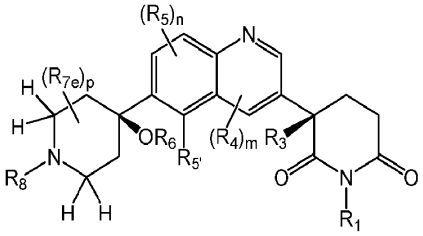


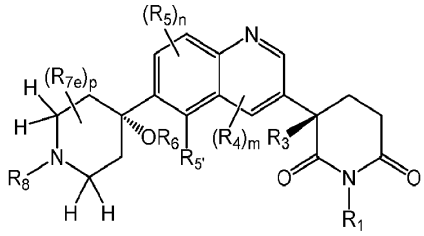
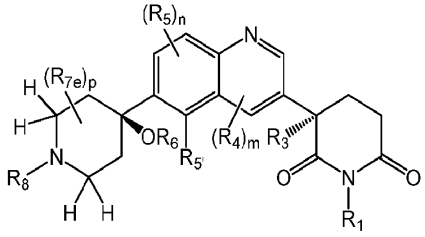
(Igg), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

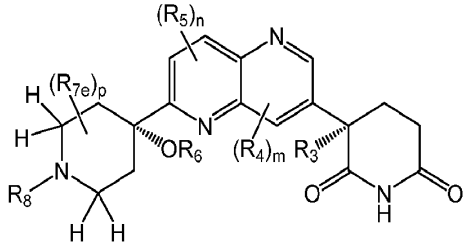
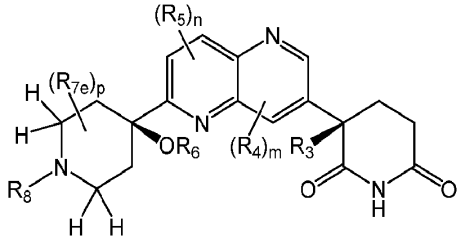
In another embodiment, the compounds of Formula (I) have the structure of Formula (Ihh):



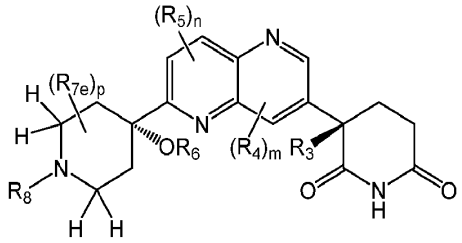
(Ihh), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have

the structure of Formula (Iii):  (Iii), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

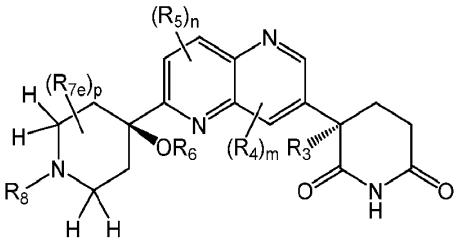
In another embodiment, the compounds of Formula (I) have the structure of Formula (Ijj):  (Ijj), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Ikk):  (Ikk), or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

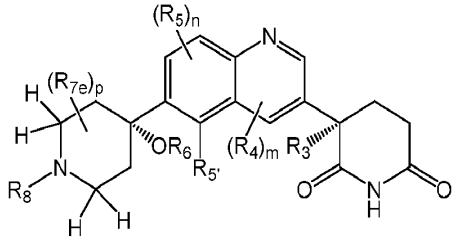


(Ipp), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Iqq):

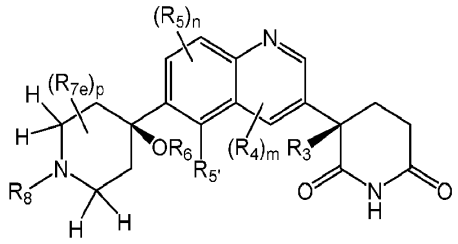


(Iqq), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

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

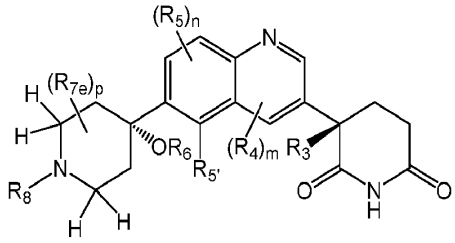


(Irr), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Iss):

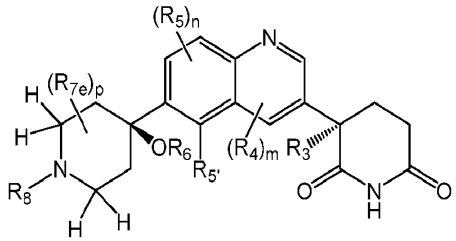


(Iss), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

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

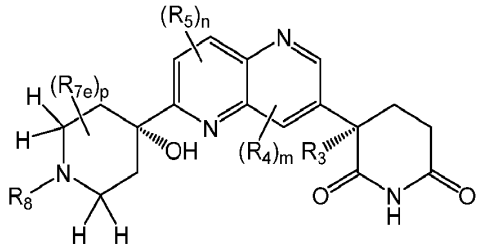


(Itt), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Iuu):

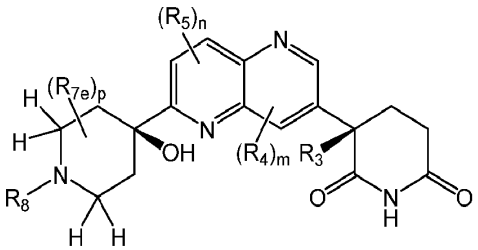


(Iuu), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

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

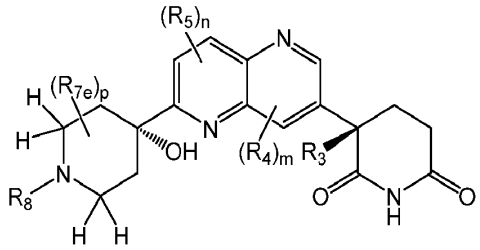


(Ivv), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Iww):

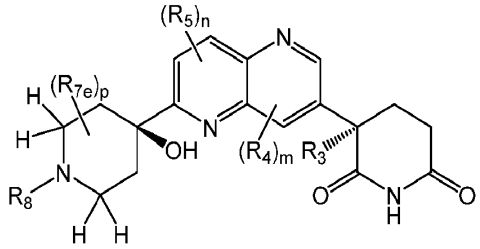


(Iww), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

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

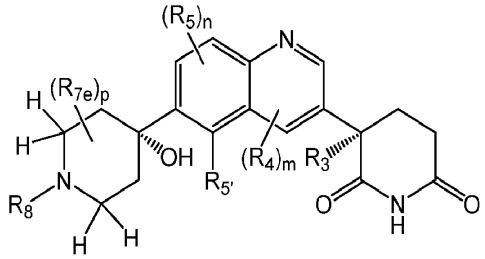


(Ixx), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Iyy):

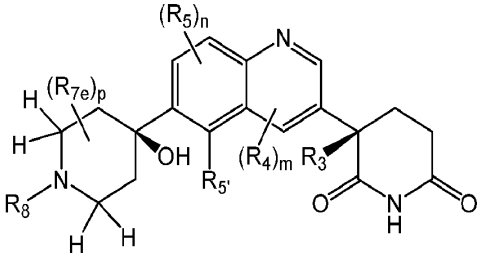


(Iyy), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

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

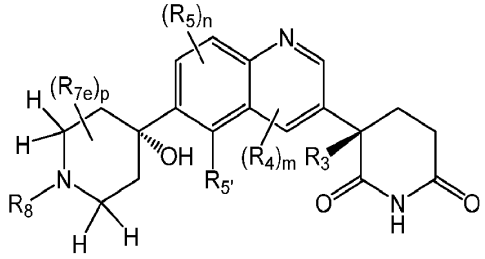


(Izz), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Iaaa):

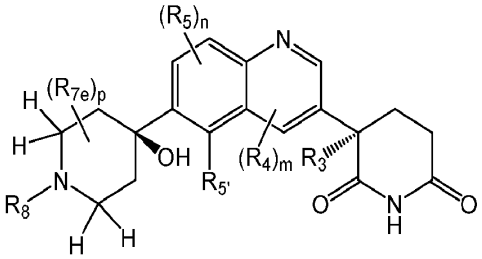


(Iaaa), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

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

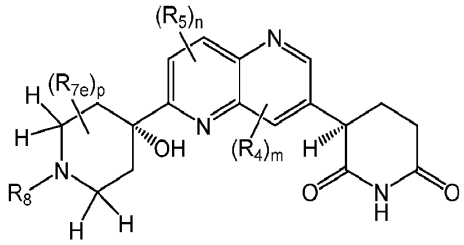


(Ibbb), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Iccc):

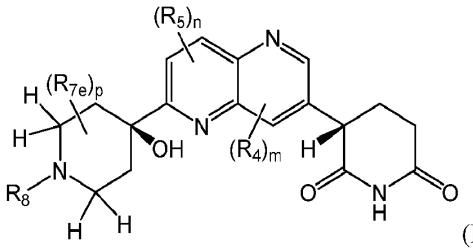


(Iccc), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

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

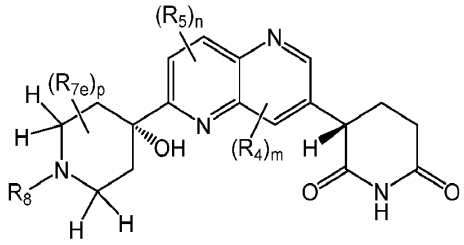


(Iddd), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Ieee):

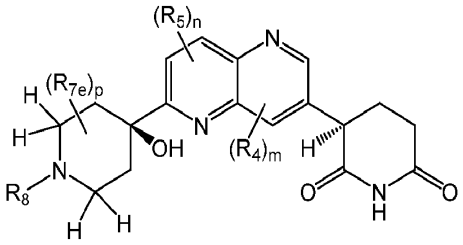


(Ieee), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

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

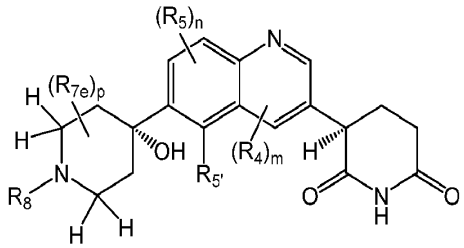


(Ifff), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Iggg):

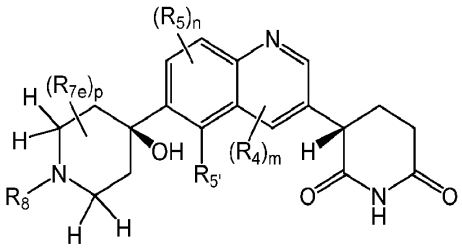


(Iggg), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

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

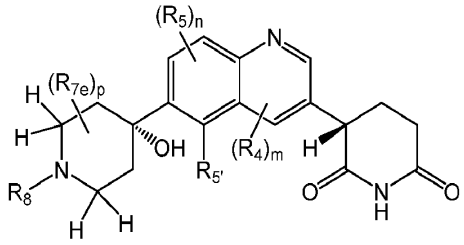


(Ihhh), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof. In another embodiment, the compounds of Formula (I) have the structure of Formula (Iiii):

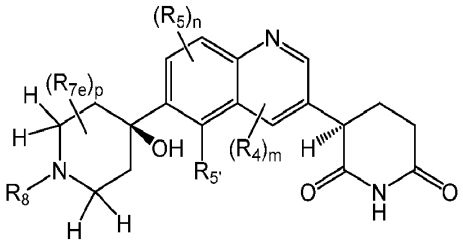


(Iiii), or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

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



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



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

In some embodiments of the formulae above (*e.g.*, Formula (I), Formula (Ia), Formula (Ib) Formula (Ie), 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 (Iaaa), Formula (Ibbb), Formula (Iccc), Formula (Iddd), Formula (Ieee), Formula (Ifff), Formula (Iggg), Formula (Ihhh), Formula (Iiii), Formula (Ijjj), and/or Formula (Ikkk)), wherein:

X_1 is N or CR_3;

X_2 is N or $CR_{5'}$;

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, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, or -NR_9R_{10};

each R_5 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl,

(C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, or -NR_9R_{10};

$R_{5'}$ is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, halogen, -OH, or -NR_9R_{10};

R_6 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_{7a}, R_{7b}, R_{7c}, and R_{7d} are each independently H, D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl;

each R_{7e} is independently at each occurrence D, (C_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_{19}, the aryl and heteroaryl are optionally substituted with one to four R_{21}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22}; or

two R_{7e}, 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 substituents independently selected from D, (C_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, -$C(O)OR_{13'}$, -$C(O)R_{13}$, and -$C(O)NR_{13'}R_{13'}$;

R_8 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, 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_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$;

R_9 and R_{10} are each independently at each occurrence H, D, (C_1-C_6)alkyl, or (C_1-C_6)deuteroalkyl;

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

$R_{13'}$ is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

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} and $R_{15'}$ 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_{16}, -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_{29}, and -CN; or

two R_{15}, 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_{17};

two $R_{15'}$, 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 SO, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one to four R_{17}; or

two $R_{15'}$ 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_{17}; or

two $R_{15'}$ when on the same carbon atom form C=(O);

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

R_{17} is independently at each occurrence D, (C_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_{18}, or -CN;

R_{18} is H, (C_1-C_6)alkyl, or (C_1-C_6)haloalkyl;

each R_{19} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{20}R_{20'}$, -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_{23} and the aryl and heteroaryl are optionally substituted with one to four R_{24};

R_{20} and $R_{20'}$ are each independently at each occurrence H or (C_1-C_6)alkyl;

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_{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;

two R_{21}, 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_{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_{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_{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_{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; 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;

each R_{24} 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_{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;

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;

o is 1 or 2;

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

p is 0, 1, 2, 3 or 4; and

q is 1, 2, or 3.

In some embodiments of the formulae above, X_1 is N. In another embodiment, X_1 is CR_3. In yet another embodiment, X_1 is CD. In another embodiment, X_1 is CH.

In some embodiments of the formulae above, X_2 is N. In another embodiment, X_2 is $CR_{5'}$.

In some embodiments of the formulae above, R_1 is H, D, $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, $-CH_2OP(O)(R_{12})_2$, $-CH_2OC(O)CH_2NHC(O)CH_2NH_2$, $-CH_2OC(O)CH(R_{12'})NHR_{12'}$, $-CH_2OC(O)(CH_2)_qC(O)OR_{12'}$, 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 the formulae above, R_1 is $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, $-CH_2OP(O)(R_{12})_2$, $-CH_2OC(O)CH_2NHC(O)CH_2NH_2$, $-CH_2OC(O)CH(R_{12'})NHR_{12'}$, $-CH_2OC(O)(CH_2)_qC(O)OR_{12'}$, 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 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, each R_4 is independently at each occurrence D, (C_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, or -NR_9R_{10}. In another embodiment, each R_4 is independently at each occurrence D, (C_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, or -OH. In yet another embodiment, each R_4 is independently at each occurrence D, (C_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, or -NR_9R_{10}. In another embodiment, each R_4 is independently at each occurrence D, (C_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, or -NR_9R_{10}. In yet another embodiment, each R_4 is independently 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, -OH, or -NR_9R_{10}. In another embodiment, each R_4 is 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, -OH, or -NR_9R_{10}.

In another embodiment, each R_4 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, halogen, -OH, or -NR_9R_{10}. In yet another embodiment, each R_4 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, or -NR_9R_{10}. In another embodiment, each R_4 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, -OH, or -NR_9R_{10}. In yet another embodiment, each R_4 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, -OH, or -NR_9R_{10}.

In another embodiment, each R_4 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, or (C_1-C_6)haloalkoxy. In yet another embodiment, each R_4 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, halogen, -OH, or -NR_9R_{10}. In another embodiment, each R_4 is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, or -NR_9R_{10}. In another embodiment, each R_4 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)alkoxy, halogen, -OH, or -NR_9R_{10}. In yet another embodiment, each R_4 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-

C_6)alkoxy, halogen, or -NR_9R_{10}. In another embodiment, each R_4 is independently at each occurrence D, (C_1-C_3)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_3)alkoxy, halogen, or -NR_9R_{10}.

In another embodiment, each R_4 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, or (C_1-C_6)haloalkoxy. In yet another embodiment, each R_4 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, halogen, -OH, or -NR_9R_{10}. In another embodiment, each R_4 is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, or -NR_9R_{10}. In another embodiment, each R_4 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, -OH, or -NR_9R_{10}. In yet another embodiment, each R_4 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, or -NR_9R_{10}. In another embodiment, each R_4 is independently at each occurrence D, (C_1-C_3)alkyl, (C_1-C_3)alkoxy, halogen, or -NR_9R_{10}.

In another embodiment, each R_4 is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, or (C_1-C_6)haloalkoxy. In yet another embodiment, each R_4 is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, halogen, -OH, or -NR_9R_{10}. In another embodiment, each R_4 is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, or -NR_9R_{10}. In another embodiment, each R_4 is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, -OH, or -NR_9R_{10}. In yet another embodiment, each R_4 is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, or -NR_9R_{10}. In another embodiment, each R_4 is independently at each occurrence (C_1-C_3)alkyl, (C_1-C_3)alkoxy, halogen, or -NR_9R_{10}.

In some embodiments of the formulae above, each R_5 is independently at each occurrence D, (C_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, or -NR_9R_{10}. In another embodiment, each R_5 is independently at each occurrence D, (C_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, or -OH. In yet another embodiment, each R_5 is independently at each occurrence D, (C_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, or -NR_9R_{10}. In another embodiment, each R_5 is independently at each occurrence D, (C_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, or -NR_9R_{10}. In yet another embodiment, each R_5 is independently 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, -OH, or -NR_9R_{10}. In another embodiment, each R_5 is 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, -OH, or -NR_9R_{10}.

In another embodiment, each R_5 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, halogen, -OH, or -NR_9R_{10}. In yet another embodiment, each R_5 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, or -NR_9R_{10}. In another embodiment, each R_5 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, -OH, or

$-NR_9R_{10}$. In yet another embodiment, each R_5 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, -OH, or $-NR_9R_{10}$.

In another embodiment, each R_5 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, or (C_1-C_6)haloalkoxy. In yet another embodiment, each R_5 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, halogen, -OH, or $-NR_9R_{10}$. In another embodiment, each R_5 is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, or $-NR_9R_{10}$. In another embodiment, each R_5 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)alkoxy, halogen, -OH, or $-NR_9R_{10}$. In yet another embodiment, each R_5 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)alkoxy, halogen, or $-NR_9R_{10}$. In another embodiment, each R_5 is independently at each occurrence D, (C_1-C_3)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_3)alkoxy, halogen, or $-NR_9R_{10}$.

In another embodiment, each R_5 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, or (C_1-C_6)haloalkoxy. In yet another embodiment, each R_5 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, halogen, -OH, or $-NR_9R_{10}$. In another embodiment, each R_5 is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, or $-NR_9R_{10}$. In another embodiment, each R_5 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, -OH, or $-NR_9R_{10}$. In yet another embodiment, each R_5 is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, or $-NR_9R_{10}$. In another embodiment, each R_5 is independently at each occurrence D, (C_1-C_3)alkyl, (C_1-C_3)alkoxy, halogen, or $-NR_9R_{10}$.

In another embodiment, each R_5 is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, or (C_1-C_6)haloalkoxy. In yet another embodiment, each R_5 is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, halogen, -OH, or $-NR_9R_{10}$. In another embodiment, each R_5 is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, halogen, -OH, or $-NR_9R_{10}$. In another embodiment, each R_5 is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, -OH, or $-NR_9R_{10}$. In yet another embodiment, each R_5 is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, or $-NR_9R_{10}$. In another embodiment, each R_5 is independently at each occurrence (C_1-C_3)alkyl, (C_1-C_3)alkoxy, halogen, or $-NR_9R_{10}$.

In some embodiments of the formulae above, $R_{5'}$ is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, halogen, -OH, or $-NR_9R_{10}$. In another embodiment, $R_{5'}$ is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, halogen, or -OH. In yet another embodiment, $R_{5'}$ is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, halogen, or $-NR_9R_{10}$. In another embodiment, $R_{5'}$ is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, -OH, or $-NR_9R_{10}$. In yet another embodiment, $R_{5'}$ is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, halogen, -OH, or $-NR_9R_{10}$. In another embodiment, $R_{5'}$ is H, D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, halogen, -OH, or $-NR_9R_{10}$. In yet another embodiment, $R_{5'}$ is H, D, $(C_1-$

C_6)deuteroalkyl, (C_1-C_6)haloalkyl, halogen, -OH, or -NR_9R_{10}. In another embodiment, $R_{5'}$ is H, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, halogen, -OH, or -NR_9R_{10}. In yet another embodiment, $R_{5'}$ is D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, halogen, -OH, or -NR_9R_{10}. In another embodiment, $R_{5'}$ is H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, halogen, or -NR_9R_{10}. In yet another embodiment, $R_{5'}$ is H, D, (C_1-C_3)alkyl, (C_1-C_6)deuteroalkyl, halogen, or -NR_9R_{10}. In another embodiment, $R_{5'}$ is H, D, (C_1-C_6)alkyl, halogen, or -NR_9R_{10}. In yet another embodiment, $R_{5'}$ is H, D, (C_1-C_3)alkyl, halogen, or -NR_9R_{10}. In another embodiment, $R_{5'}$ is H, (C_1-C_6)alkyl, halogen, or -NR_9R_{10}. In yet another embodiment, $R_{5'}$ is H, (C_1-C_3)alkyl, halogen, or -NR_9R_{10}.

In some embodiments of the formulae above, R_6 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_6 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_6 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_6 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_6 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_6 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_6 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_6 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_6 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_6 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_6 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_6 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_6 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_6 is H or D. In yet another embodiment, R_6 is D. In another embodiment, R_6 is H.

In some embodiments of the formulae above, R_{7a} is H, D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{7a} is H, D, (C_1-C_2)alkyl, or (C_1-C_2)deuteroalkyl. In yet another embodiment, R_{7a} is H, D, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{7a} is H, D, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{7a} is H, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{7a} is D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{7a} is H, D, or (C_1-C_2)alkyl. In another embodiment, R_{7a}

is H, D, or (C_1-C_2)deuteroalkyl. In yet another embodiment, R_{7a} is H, D, or (C_1-C_2)haloalkyl. In another embodiment, R_{7a} is H, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{7a} is D, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{7a} is (C_1-C_2)alkyl or (C_1-C_2)haloalkyl. In another embodiment, R_{7a} is H or D. In yet another embodiment, R_{7a} is D. In another embodiment, R_{7a} is H.

In some embodiments of the formulae above, R_{7b} is H, D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{7b} is H, D, (C_1-C_2)alkyl, or (C_1-C_2)deuteroalkyl. In yet another embodiment, R_{7b} is H, D, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{7b} is H, D, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{7b} is H, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{7b} is D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{7b} is H, D, or (C_1-C_2)alkyl. In another embodiment, R_{7b} is H, D, or (C_1-C_2)deuteroalkyl. In yet another embodiment, R_{7b} is H, D, or (C_1-C_2)haloalkyl. In another embodiment, R_{7b} is H, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{7b} is D, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{7b} is (C_1-C_2)alkyl or (C_1-C_2)haloalkyl. In another embodiment, R_{7b} is H or D. In yet another embodiment, R_{7b} is D. In another embodiment, R_{7b} is H.

In some embodiments of the formulae above, R_{7c} is H, D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{7c} is H, D, (C_1-C_2)alkyl, or (C_1-C_2)deuteroalkyl. In yet another embodiment, R_{7c} is H, D, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{7c} is H, D, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{7c} is H, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{7c} is D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{7c} is H, D, or (C_1-C_2)alkyl. In another embodiment, R_{7c} is H, D, or (C_1-C_2)deuteroalkyl. In yet another embodiment, R_{7c} is H, D, or (C_1-C_2)haloalkyl. In another embodiment, R_{7c} is H, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{7c} is D, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{7c} is (C_1-C_2)alkyl or (C_1-C_2)haloalkyl. In another embodiment, R_{7c} is H or D. In yet another embodiment, R_{7c} is D. In another embodiment, R_{7c} is H.

In some embodiments of the formulae above, R_{7d} is H, D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{7d} is H, D, (C_1-C_2)alkyl, or (C_1-C_2)deuteroalkyl. In yet another embodiment, R_{7d} is H, D, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{7d} is H, D, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{7d} is H, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In another embodiment, R_{7d} is D, (C_1-C_2)alkyl, (C_1-C_2)deuteroalkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{7d} is H, D, or (C_1-C_2)alkyl. In another embodiment, R_{7d} is H, D, or (C_1-C_2)deuteroalkyl. In yet another embodiment, R_{7d} is H, D, or (C_1-C_2)haloalkyl. In another embodiment, R_{7d} is H, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{7d} is D, (C_1-C_2)alkyl, or (C_1-C_2)haloalkyl. In yet another embodiment, R_{7d} is (C_1-C_2)alkyl or (C_1-C_2)haloalkyl. In another embodiment, R_{7d} is H or D. In yet another embodiment, R_{7d} is D. In another embodiment, R_{7d} is H.

In some embodiments of the formulae above, each R_{7e} is independently at each occurrence D, (C_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_{19}, the aryl and heteroaryl are optionally substituted with one to six R_{21}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22}. In another embodiment, each R_{7e} is independently at each occurrence D, (C_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_{19}, the aryl and heteroaryl are optionally substituted with one to six R_{21}, and the carbocyclyl is optionally substituted with one to four R_{22}.

In another embodiment, each R_{7e} is independently at each occurrence D, (C_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_{19}, the aryl and heteroaryl are optionally substituted with one to six R_{21}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22}. In another embodiment, each R_{7e} is independently at each occurrence D, (C_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_{19}, the aryl and heteroaryl are optionally substituted with one to six R_{21}, and the heterocyclyl is optionally substituted with one to four R_{22}.

In another embodiment, each R_{7e} is independently at each occurrence D, (C_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 or more R_{19}, the aryl is optionally substituted with one to six R_{21}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22}. In yet another embodiment, each R_{7e} is independently at each occurrence D, (C_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_{19}, the heteroaryl is optionally substituted with one to six R_{21}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22}.

In another embodiment, each R_{7e} is independently at each occurrence D, $(C_1$-$C_6)$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_{19}, the aryl and heteroaryl are optionally substituted with one to six R_{21}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22}. In yet another embodiment, each R_{7e} is independently at each occurrence D, $(C_1$-$C_6)$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_{19}, the aryl and heteroaryl are optionally substituted with one to six R_{21}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22}.

In another embodiment, each R_{7e} is independently at each occurrence D, $(C_1$-$C_6)$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_{19}, the aryl and heteroaryl are optionally substituted with one to six R_{21}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22}. In yet another embodiment, each R_{7e} is independently at each occurrence D, $(C_1$-$C_6)$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_{19}, the aryl and heteroaryl are optionally substituted with one to six R_{21}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22}.

In another embodiment, each R_{7e} is independently at each occurrence D, $(C_1$-$C_6)$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_{19}, the aryl and

heteroaryl are optionally substituted with one to six R_{21}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22}. In yet another embodiment, each R_{7e} is independently 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_{19}, the aryl and heteroaryl are optionally substituted with one to six R_{21}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22}.

In another embodiment, each R_{7e} is 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_{19}, the aryl and heteroaryl are optionally substituted with one to six R_{21}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22}. In yet another embodiment, each R_{7e} 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_{19}, the aryl and heteroaryl are optionally substituted with one to six R_{21}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22}. In another embodiment, each R_{7e} 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_{19}, the aryl and heteroaryl are optionally substituted with one to six R_{21}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22}.

In another embodiment, each R_{7e} 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_{21}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22}. In yet another embodiment, each R_{7e} 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_{19}, the aryl and heteroaryl are optionally substituted with one to six R_{21}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22}.

In another embodiment, each R_{7e} is independently at each occurrence D, (C_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_{19}. In another embodiment, each R_{7e} 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_{21}, and the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{22}.

In another embodiment, each R_{7e} is independently 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_{19}, the aryl is optionally substituted with one to six R_{21}, and the carbocyclyl is optionally substituted with one to four R_{22}. In yet another embodiment, each R_{7e} 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_{19}, the aryl is optionally substituted with one to six R_{21}, and the carbocyclyl is optionally substituted with one to four R_{22}.

In some embodiments of the formulae above, two R_{7e}, 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 substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$. In another embodiment, two R_{7e}, 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 substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$. In yet another embodiment, two R_{7e}, 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 substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$. In another embodiment, two R_{7e}, 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 substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$. In yet another embodiment, two R_{7e}, 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_{7e}, 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 substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$. In yet another embodiment, two R_{7e}, 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 substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$.

In another embodiment, two R_{7e}, 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 substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$. In yet another embodiment, two R_{7e}, 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

substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$.

In another embodiment, two R_{7e}, 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 substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$. In yet another embodiment, two R_{7e}, 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 substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$.

In another embodiment, two R_{7e}, 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 substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$. In yet another embodiment, two R_{7e}, 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 substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$.

In another embodiment, two R_{7e}, 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 substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$. In yet another embodiment, two R_{7e}, 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

substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$.

In another embodiment, two R_{7e}, 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 substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$. In yet another embodiment, two R_{7e}, 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 substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$. In another embodiment, two R_{7e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl. In yet another embodiment, two R_{7e}, 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 halogen.

In another embodiment, two R_{7e}, 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 substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$. In yet another embodiment, two R_{7e}, 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 substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$. In another embodiment, two R_{7e}, 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 yet another embodiment, two R_{7e}, 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 halogen.

In some embodiments of the formulae above, R_8 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_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$. In another embodiment, R_8 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_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$.

In some embodiments of the formulae above, R_8 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_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$. In yet another embodiment, R_8 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, or (C_1-C_6)halohydroxyalkyl. In another embodiment, R_8 is (C_1-C_6)haloalkyl or (C_1-C_6)hydroxyalkyl. In yet another embodiment, R_8 is (C_1-C_6)haloalkyl or (C_1-C_6)halohydroxyalkyl. In another embodiment, R_8 is (C_1-C_6)hydroxyalkyl or (C_1-C_6)halohydroxyalkyl.

In some embodiments of the formulae above, R_8 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_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$. In yet another embodiment, R_8 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_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$.

In some embodiments of the formulae above, R_8 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_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$. In another embodiment, R_8 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_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$. In yet another embodiment, R_8 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_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$.

In some embodiments of the formulae above, R_8 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_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$. In yet another embodiment, R_8 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_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$.

In some embodiments of the formulae above, R_8 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_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to

four $R_{15'}$. In yet another embodiment, R_8 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_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$.

In some embodiments of the formulae above, R_8 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_{15} and the heterocyclyl is optionally substituted with one to four $R_{15'}$. In yet another embodiment, R_8 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 (C_3-C_7)carbocyclyl, wherein the phenyl and heteroaryl are optionally substituted with one to four R_{15} and the carbocyclyl is optionally substituted with one to four $R_{15'}$.

In some embodiments of the formulae above, R_8 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_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$. In yet another embodiment, R_8 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_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$.

In some embodiments of the formulae above, R_8 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_{15} and the carbocyclyl and

heterocyclyl are optionally substituted with one to four $R_{15'}$. In yet another embodiment, R_8 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_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$.

In some embodiments of the formulae above, R_8 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_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$. In yet another embodiment, R_8 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_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$. In another embodiment, R_8 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_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$.

In some embodiments of the formulae above, R_9 is independently at each occurrence H, D, (C_1-C_6)alkyl, or (C_1-C_6)deuteroalkyl. In another embodiment, R_9 is independently at each occurrence D, (C_1-C_6)alkyl, or (C_1-C_6)deuteroalkyl. In yet another embodiment, R_9 is independently at each occurrence H, D, or (C_1-C_6)deuteroalkyl. In another embodiment, R_9 is independently at each occurrence H, D, or (C_1-C_6)alkyl. In yet another embodiment, R_9 is independently at each occurrence H or D. In another embodiment, R_9 is independently at each occurrence D or (C_1-C_6)alkyl. In yet another embodiment, R_9 is independently at each occurrence H or (C_1-C_3)alkyl. In another embodiment, R_9 is independently at each occurrence H or (C_1-C_6)deuteroalkyl. In yet another embodiment, R_9 is independently at each occurrence D or (C_1-C_6)deuteroalkyl. In another embodiment, R_9 is independently at each occurrence (C_1-C_3)alkyl or (C_1-C_6)deuteroalkyl. In yet another embodiment, R_9 is independently at each occurrence D or (C_1-C_3)alkyl. In another embodiment, R_9 is independently at each occurrence (C_1-C_6)deuteroalkyl. In yet another

embodiment, R_9 is independently at each occurrence $(C_1\text{-}C_6)$alkyl. In another embodiment, R_9 is independently at each occurrence D. In yet another embodiment, R_9 is independently at each occurrence H.

In some embodiments of the formulae above, R_{10} is independently at each occurrence H, D, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$deuteroalkyl. In another embodiment, R_{10} is independently at each occurrence D, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$deuteroalkyl. In yet another embodiment, R_{10} is independently at each occurrence H, D, or $(C_1\text{-}C_6)$deuteroalkyl. In another embodiment, R_{10} is independently at each occurrence H, D, or $(C_1\text{-}C_6)$alkyl. In yet another embodiment, R_{10} is independently at each occurrence H or D. In another embodiment, R_{10} is independently at each occurrence D or $(C_1\text{-}C_6)$alkyl. In yet another embodiment, R_{10} is independently at each occurrence H or $(C_1\text{-}C_3)$alkyl. In another embodiment, R_{10} is independently at each occurrence H or $(C_1\text{-}C_6)$deuteroalkyl. In yet another embodiment, R_{10} is independently at each occurrence D or $(C_1\text{-}C_6)$deuteroalkyl. In another embodiment, R_{10} is independently at each occurrence $(C_1\text{-}C_3)$alkyl or $(C_1\text{-}C_6)$deuteroalkyl. In yet another embodiment, R_{10} is independently at each occurrence D or $(C_1\text{-}C_3)$alkyl. In another embodiment, R_{10} is independently at each occurrence $(C_1\text{-}C_6)$deuteroalkyl. In yet another embodiment, R_{10} is independently at each occurrence $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{10} is independently at each occurrence D. In yet another embodiment, R_{10} is independently at each occurrence H.

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

In another embodiment, R_{11} is independently at each occurrence H, $(C_1\text{-}C_6)$alkoxy, $-NH_2$, $-N(H)(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl optionally substituted with one to four substituents independently selected from $(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$hydroxyalkyl, $(C_1\text{-}C_6)$haloalkyl, halogen, -OH, $-NH_2$, and -CN, or $(C_6\text{-}C_{10})$aryl optionally substituted with one to four substituents independently selected from $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$hydroxyalkyl, $(C_1\text{-}C_6)$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 $(C_6$-$C_{10})$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 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, R_{13} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{13} is independently at each occurrence (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In another embodiment, R_{13} is independently at each occurrence (C_1-C_6)haloalkyl. In 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)haloalkyl. In another embodiment, R_{13} is independently at each occurrence (C_1-C_3)alkyl.

In some embodiments of the formulae above, $R_{13'}$ is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, $R_{13'}$ is independently at each occurrence H, (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, $R_{13'}$ 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_6)haloalkyl. In yet another embodiment, $R_{13'}$ is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, $R_{13'}$ is independently at each occurrence (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. 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 another embodiment, $R_{13'}$ is independently at each occurrence (C_1-C_6)haloalkyl. In another embodiment, $R_{13'}$ is independently at each occurrence (C_1-C_3)haloalkyl. In another embodiment, $R_{13'}$ 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, $R_{14'}$ 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 D, (C_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_{16}, -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_{29}, and -CN. In another embodiment, 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, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{16}, -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_{29}, and -CN.

In another embodiment, 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, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{16}, -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_{29}, and -CN. In yet another embodiment, 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, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{16}, -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_{29}, and -CN.

In another embodiment, 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, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{16}, -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 D, (C_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, -$NR_{35}R_{36}$, -C(O)$NR_{37}R_{38}$, -C(O)R_{37}, -C(O)OR_{37}, -SF_5, -SR_{29}, and -CN. In yet another embodiment, 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, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{16}, -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_{29}, and -CN.

In another embodiment, 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, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{16}, -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_{29}, and -CN. In yet another embodiment, 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, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{16}, -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_{29}, and -CN.

In another embodiment, 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, -OH,

$-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{29}$, and -CN. In yet another embodiment, 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, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{29}$, and -CN.

In another embodiment, 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, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{29}$, and -CN. In yet another embodiment, 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, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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_{29}, and -CN.

In another embodiment, 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, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{16}, -$C(O)NR_{32}R_{33}$, -$C(O)OR_{32}$, (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_{29}, and -CN. In yet another embodiment, 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, -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_{29}, and -CN.

In another embodiment, 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, -OH, -$NR_{30}R_{31}$, -SR_{16}, -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_{29}, and -CN. In yet another embodiment, 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, -OH, -SF_5, -SR_{16}, -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_{29}, and -CN.

In another embodiment, 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, -$NR_{30}R_{31}$, -SF_5, -SR_{16}, -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_{29}, and -CN. In yet another embodiment, 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, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{16}, -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_{29}, and -CN.

In another embodiment, 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, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{29}$, and -CN. In yet another embodiment, 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, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{29}$, and -CN.

In another embodiment, 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, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{29}$, and -CN. In yet another embodiment, 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, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{29}$, and -CN.

In another embodiment, 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, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{29}$, and -CN. In yet another embodiment, 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, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{29}$, and -CN.

In another embodiment, 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, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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_{29}, and -CN. In yet another embodiment, 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, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{16}, -CN, -$C(O)NR_{32}R_{33}$, or -$C(O)OR_{32}$. In yet another embodiment, 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, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{16}, -CN, -$C(O)NR_{32}R_{33}$, or -$C(O)OR_{32}$.

In another embodiment, R_{15} 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_{29}, and -CN.

In yet another embodiment, R_{15} 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_{29}, and -CN.

In some embodiments of the formulae above, $R_{15'}$ 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, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{16}, -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_{29}, and -CN. In another embodiment, $R_{15'}$ 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, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{16}, -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_{29}, and -CN.

In another embodiment, $R_{15'}$ 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, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{16}, -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_{29}, and -CN. In yet another embodiment, $R_{15'}$ 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, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{16}, -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_{29}, and -CN.

In another embodiment, $R_{15'}$ 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, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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 D, $(C_1$-$C_6)$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, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{29}$, and -CN. In yet another embodiment, $R_{15'}$ 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, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{29}$, and -CN.

In another embodiment, $R_{15'}$ 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, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{29}$, and -CN. In yet another embodiment, $R_{15'}$ 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, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{29}$, and -CN.

In another embodiment, $R_{15'}$ 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, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{29}$, and -CN. In yet another embodiment, $R_{15'}$ 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, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{29}$, and -CN.

In another embodiment, $R_{15'}$ 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, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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_{29}, and -CN. In yet another embodiment, $R_{15'}$ 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, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{16}, -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_{29}, and -CN.

In another embodiment, $R_{15'}$ 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, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{16}, -$C(O)NR_{32}R_{33}$, -$C(O)OR_{32}$, $(C_3$-$C_7)$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_{29}, and -CN. In yet another embodiment, $R_{15'}$ 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, -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_{29}, and -CN.

In another embodiment, $R_{15'}$ 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, -OH, $-NR_{30}R_{31}$, $-SR_{16}$, -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, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{29}$, and -CN. In yet another embodiment, $R_{15'}$ 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, -OH, $-SF_5$, $-SR_{16}$, -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, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{29}$, and -CN.

In another embodiment, $R_{15'}$ 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, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{29}$, and -CN. In yet another embodiment, $R_{15'}$ 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, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{29}$, and -CN.

In another embodiment, $R_{15'}$ 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, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{29}$, and -CN. In yet another embodiment, $R_{15'}$ 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, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{29}$, and -CN.

In another embodiment, $R_{15'}$ 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, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{29}$, and -CN. In yet another embodiment, $R_{15'}$ 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, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{29}$, and -CN.

In another embodiment, $R_{15'}$ 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, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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, $-NR_{35}R_{36}$, $-C(O)NR_{37}R_{38}$, $-C(O)R_{37}$, $-C(O)OR_{37}$, $-SF_5$, $-SR_{29}$, and -CN. In yet another embodiment, $R_{15'}$ 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, -OH, $-NR_{30}R_{31}$, $-SF_5$, $-SR_{16}$, -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_{29}, and -CN.

In another embodiment, $R_{15'}$ 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, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{16}, -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_{29}, and -CN. In yet another embodiment, $R_{15'}$ 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, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{16}, -CN, -C(O)$NR_{32}R_{33}$, or -C(O)OR_{32}. In yet another embodiment, $R_{15'}$ 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, halogen, -OH, -$NR_{30}R_{31}$, -SF_5, -SR_{16}, -CN, -C(O)$NR_{32}R_{33}$, or -C(O)OR_{32}.

In another embodiment, $R_{15'}$ 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_{29}, and -CN.

In yet another embodiment, $R_{15'}$ 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_{29}, and -CN.

In some embodiments of the formulae above, two R_{15}, 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_{17}. In another embodiment, two R_{15}, 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_{17}. In another embodiment, two R_{15}, 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_{17}.

In another embodiment, two R_{15}, 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_{17}. In yet another embodiment, two R_{15}, 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_{17}. In another embodiment, two R_{15}, 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_{17}.

In another embodiment, two R_{15}, 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_{17}. In yet another embodiment, two R_{15}, 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_{17}. In another embodiment, two R_{15}, 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_{17}. In yet another embodiment, two R_{15}, 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_{17}.

In another embodiment, two R_{15}, 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_{17}. In yet another embodiment, two R_{15}, 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_{17}. In another embodiment, two R_{15}, when on adjacent atoms, together with the atoms to which they are attached form a $(C_3\text{-}C_7)$carbocyclyl, wherein the carbocyclyl is optionally substituted with one to four R_{17}. In yet another embodiment, two R_{15}, 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_{17}.

In some embodiments of the formulae above, two $R_{15'}$, 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_{17}. In another embodiment, two $R_{15'}$, 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_{17}. In yet another embodiment, two $R_{15'}$, 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_{17} and the heteroaryl is substituted with one to four R_{17}. In another embodiment, two $R_{15'}$, 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_{17} and the heteroaryl is optionally substituted with one to four R_{17}.

In another embodiment, two $R_{15'}$, 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_{17}. In yet another embodiment, two $R_{15'}$, 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_{17}. In another embodiment, two $R_{15'}$, 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_{17}. In yet another embodiment, two $R_{15'}$, 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_{17}.

In some embodiments of the formulae above, two $R_{15'}$ 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_{17}. In yet another embodiment, two $R_{15'}$ 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_{17}. In another embodiment, two $R_{15'}$ 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_{17} and the heterocyclyl is to optionally substituted with one to four R_{17}. In yet another embodiment, two $R_{15'}$ 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_{17} and the heterocyclyl is to optionally substituted with one to four R_{17}. In another embodiment, two $R_{15'}$ 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_{17} and the heterocyclyl is substituted with one to four R_{17}. In yet another embodiment, two $R_{15'}$ 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_{17} and the heterocyclyl is substituted with one to four R_{17}.

In another embodiment, two $R_{15'}$ 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_{17}. In yet another embodiment, two $R_{15'}$ 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_{17}. In another embodiment, two $R_{15'}$ 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_{17}. In another embodiment, two $R_{15'}$ 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_{17}. In another embodiment, two $R_{15'}$ 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_{17}. In yet another embodiment, two $R_{15'}$ 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_{17}.

In another embodiment, two $R_{15'}$ 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_{17} and the heterocyclyl is optionally substituted with one to four R_{17}. In yet another embodiment, two $R_{15'}$ 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_{17} and the heterocyclyl is optionally substituted with one to four R_{17}. In another embodiment, two $R_{15'}$ 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_{17} and the heterocyclyl is optionally substituted with one to four R_{17}.

In another embodiment, two $R_{15'}$ 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_{17} and the heterocyclyl is substituted with one to four R_{17}. In yet another embodiment, two $R_{15'}$ 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_{17} and the heterocyclyl is substituted with one to four R_{17}. In another embodiment, two $R_{15'}$ 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_{17} and the heterocyclyl is substituted with one to four R_{17}.

In another embodiment, two $R_{15'}$ 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_{17}. In yet another embodiment, two $R_{15'}$ 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_{17}. In another embodiment, two $R_{15'}$ 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_{17}. In yet another embodiment, two $R_{15'}$ 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_{17}.

In another embodiment, two R_{15}, 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_{17}. In yet another embodiment, two R_{15}, 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_{17}. In another embodiment, two R_{15}, 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_{17}.

In another embodiment, two R_{15}, 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_{17} and the heterocyclyl is optionally substituted with one to four R_{17}. In yet another embodiment, two R_{15}, 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_{17} and the heterocyclyl is optionally substituted with one to four R_{17}. In another embodiment, two R_{15}, 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_{17} and the heterocyclyl is optionally substituted with one to four R_{17}. In yet another embodiment, two R_{15}, 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_{17} and the heterocyclyl is optionally substituted with one to four R_{17}.

In another embodiment, two R_{15}, 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_{17} and the heterocyclyl is optionally substituted with one to four R_{17}. In yet another embodiment, two R_{15}, 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_{17} and the heterocyclyl is optionally substituted with one to four R_{17}. In another embodiment, two R_{15}, 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_{17} and the heterocyclyl is optionally substituted with one to four R_{17}.

In another embodiment, two R_{15}, 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_{17} and the heterocyclyl is substituted with one to four R_{17}. In yet another embodiment, two R_{15}, 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_{17} and the heterocyclyl is substituted with one to four R_{17}. In another embodiment, two R_{15}, 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_{17} and the heterocyclyl is substituted with one to four R_{17}. In yet another embodiment, two R_{15}, 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_{17} and the heterocyclyl is substituted with one to four R_{17}.

In another embodiment, two R_{15}, 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_{17} and the heterocyclyl is substituted with one to four R_{17}. In yet another embodiment, two R_{15}, 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_{17} and the heterocyclyl is substituted with one to four R_{17}. In another embodiment, two R_{15}, 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_{17} and the heterocyclyl is substituted with one to four R_{17}.

In another embodiment, two R_{15}, 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_{17}. In yet another embodiment, two R_{15}, 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_{17}. In another embodiment, two R_{15}, 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_{17}. In yet another embodiment, two R_{15}, 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_{17}.

In another embodiment, two R_{15}, 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_{17}. In yet another

embodiment, two $R_{15'}$ 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_{17}. In another embodiment, two $R_{15'}$ 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_{17}. In yet another embodiment, two $R_{15'}$ 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_{17}.

In another embodiment, two $R_{15'}$ 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_{17}. In yet another embodiment, two $R_{15'}$ 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_{17}. In another embodiment, two $R_{15'}$ 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_{17}. In yet another embodiment, two $R_{15'}$ 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_{17}.

In another embodiment, two $R_{15'}$ 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_{17}. In yet another embodiment, two $R_{15'}$ 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_{17}. In another embodiment, two $R_{15'}$ 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_{17}. In yet another embodiment, two $R_{15'}$ 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_{17}. In another embodiment, two $R_{15'}$ 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_{17}. In yet another embodiment, two $R_{15'}$ 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_{17}.

In another embodiment, two $R_{15'}$ 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_{17}. In yet another embodiment, two $R_{15'}$ 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_{17}. In another embodiment, two $R_{15'}$ 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_{17}. In yet another embodiment, two $R_{15'}$ 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_{17}.

In another embodiment, two $R_{15'}$ 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_{17}. In yet another embodiment, two $R_{15'}$ 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_{17}. In another embodiment, two $R_{15'}$ 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_{17}. In yet another embodiment, two $R_{15'}$ 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_{17}.

In another embodiment, two $R_{15'}$ 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_{17}. In yet another embodiment, two $R_{15'}$ 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_{17}. In another embodiment, two $R_{15'}$ 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_{17}. In yet another embodiment, two $R_{15'}$ 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_{17}.

In some embodiments of the formulae above, two $R_{15'}$ when on the same carbon atom form C=(O);

In some embodiments of the formulae above, R_{16} is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{16} is independently at each occurrence H, (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. In yet another embodiment, 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_6)haloalkyl. In yet another embodiment, R_{16} is independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)haloalkyl. In another embodiment, R_{16} is independently at each occurrence (C_1-C_3)alkyl or (C_1-C_3)haloalkyl. 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 (C_1-C_6)haloalkyl. In another embodiment, R_{16} is independently at each occurrence (C_1-C_3)haloalkyl. In another embodiment, R_{16} is independently at each occurrence H.

In some embodiments of the formulae above, R_{17} is independently at each occurrence D, (C_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, $-NH_2$, $-SF_5$, $-SR_{18}$, or -CN. In another embodiment, R_{17} is independently at each occurrence

D, (C_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 $-SR_{18}$. In yet another embodiment, R_{17} is independently at each occurrence D, (C_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_{17} is independently at each occurrence D, (C_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, $-NH_2$, $-SR_{18}$, or -CN. In another embodiment, R_{17} is independently at each occurrence D, (C_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, $-SF_5$, $-SR_{18}$, or -CN. In yet another embodiment, R_{17} is independently at each occurrence D, (C_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, $-NH_2$, $-SF_5$, $-SR_{18}$, or -CN. In another embodiment, R_{17} is independently at each occurrence D, (C_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, $-NH_2$, $-SF_5$, $-SR_{18}$, or -CN. In yet another embodiment, R_{17} is independently at each occurrence D, (C_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, $-NH_2$, $-SF_5$, $-SR_{18}$, or -CN.

In another embodiment, R_{17} is independently at each occurrence D, (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, $-NH_2$, $-SF_5$, $-SR_{18}$, or -CN. In yet another embodiment, R_{17} is 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, $-NH_2$, $-SF_5$, $-SR_{18}$, or -CN. In another embodiment, R_{17} 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, $-NH_2$, $-SF_5$, $-SR_{18}$, or -CN. In yet another embodiment, R_{17} 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, $-NH_2$, $-SF_5$, $-SR_{18}$, or -CN. In another embodiment, R_{17} 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, $-NH_2$, $-SF_5$, $-SR_{18}$, or -CN. In yet another embodiment, R_{17} 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, $-NH_2$, $-SF_5$, $-SR_{18}$, or -CN.

In another embodiment, R_{17} is independently at each occurrence D, (C_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_{17} is 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, $-NH_2$, $-SF_5$, $-SR_{18}$, or -CN. In another embodiment, R_{17} is independently at each occurrence D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, (C_1-C_6)haloalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{18}$, or -CN. In yet another embodiment, R_{17} is 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

another embodiment, R_{17} is 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 yet another embodiment, R_{17} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, halogen, or -CN.

In another embodiment, R_{17} 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_{17} is independently at each occurrence halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{18}$, or -CN. In another embodiment, R_{17} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$hydroxyalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{18}$, or -CN. In yet another embodiment, R_{17} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, halogen, -OH, $-NH_2$, $-SF_5$, $-SR_{18}$, or -CN. In another embodiment, R_{17} 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_{17} 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_{17} 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_{18} is H, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{18} is H, $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$haloalkyl. In yet another embodiment, R_{18} is H or $(C_1$-$C_6)$alkyl. In another embodiment, R_{18} is H or $(C_1$-$C_6)$haloalkyl. In yet another embodiment, R_{18} is $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{18} is $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$haloalkyl. In yet another embodiment, R_{18} is $(C_1$-$C_6)$alkyl. In another embodiment, R_{18} is $(C_1$-$C_3)$alkyl. In another embodiment, R_{18} is $(C_1$-$C_6)$haloalkyl. In another embodiment, R_{18} is $(C_1$-$C_3)$haloalkyl. In another embodiment, R_{18} is H.

In some embodiments of the formulae above, each R_{19} is independently at each occurrence $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $-NR_{20}R_{20'}$, -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_{23} and the aryl and heteroaryl are optionally substituted with one to four R_{24}. In another embodiment, each R_{19} is independently at each occurrence $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $-NR_{20}R_{20'}$, -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_{23} and the aryl and heteroaryl are optionally substituted with one to four R_{24}. In yet another embodiment, each R_{19} is independently at each occurrence $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, $-NR_{20}R_{20'}$, -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_{23} and the aryl and heteroaryl are substituted with one to four R_{24}.

In another embodiment, each R_{19} is independently at each occurrence $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, $-NR_{20}R_{20'}$, -CN, $(C_3\text{-}C_7)$carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, or $(C_6\text{-}C_{10})$ aryl, wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{23} and the aryl is optionally substituted with one to four R_{24}. In yet another embodiment, each R_{19} is independently at each occurrence $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, $-NR_{20}R_{20'}$, -CN, $(C_3\text{-}C_7)$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_{23} and the heteroaryl is optionally substituted with one to four R_{24}.

In another embodiment, each R_{19} is independently at each occurrence $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, $-NR_{20}R_{20'}$, -CN, $(C_3\text{-}C_7)$carbocyclyl, $(C_6\text{-}C_{10})$ aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein carbocyclyl is optionally substituted with one to four R_{23} and the aryl and heteroaryl are optionally substituted with one to four R_{24}. In yet another embodiment, each R_{19} is independently at each occurrence $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, $-NR_{20}R_{20'}$, -CN, 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 heterocyclyl is optionally substituted with one to four R_{23} and the aryl and heteroaryl are optionally substituted with one to four R_{24}.

In another embodiment, each R_{19} is independently at each occurrence $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, -CN, $(C_3\text{-}C_7)$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_{23} and the aryl and heteroaryl are optionally substituted with one to four R_{24}. In another embodiment, each R_{19} is independently at each occurrence $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, $-NR_{20}R_{20'}$, $(C_3\text{-}C_7)$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_{23} and the aryl and heteroaryl are optionally substituted with one to four R_{24}. In yet another embodiment, each R_{19} is independently at each occurrence $(C_1\text{-}C_6)$alkoxy, $-NR_{20}R_{20'}$, -CN, $(C_3\text{-}C_7)$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_{23} and the aryl and heteroaryl are optionally substituted with one to four R_{24}.

In another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)haloalkoxy, -$NR_{20}R_{20'}$, -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_{23} and the aryl and heteroaryl are optionally substituted with one to four R_{24}. In yet another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{20}R_{20'}$, or -CN. In yet another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, or -$NR_{20}R_{20'}$.

In another embodiment, each R_{19} 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_{23} and the aryl and heteroaryl are optionally substituted with one to four R_{24}. In yet another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{20}R_{20'}$, -CN, (C_3-C_7)carbocyclyl, or 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, (C_6-C_{10}), wherein the carbocyclyl and heterocyclyl are optionally substituted with one to four R_{23}.

In another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{20}R_{20'}$, -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_{24}. In yet another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{20}R_{20'}$, -CN, (C_3-C_7)carbocyclyl, or (C_6-C_{10}) aryl, wherein the carbocyclyl is optionally substituted with one to four R_{23} and the aryl is optionally substituted with one to four R_{24}. In another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{20}R_{20'}$, -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_{23} and the heteroaryl is optionally substituted with one to four R_{24}.

In another embodiment, each R_{19} is independently at each occurrence (C_1-C_6)alkoxy, -$NR_{20}R_{20'}$, -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_{23} and the aryl and heteroaryl are optionally substituted with one to four R_{24}.

In yet another embodiment, each R_{19} is independently at each occurrence $(C_1\text{-}C_6)$alkoxy, $-NR_{20}R_{20'}$, -CN, $(C_3\text{-}C_7)$carbocyclyl, or $(C_6\text{-}C_{10})$ aryl, wherein the carbocyclyl is substituted with one to four R_{23} and the aryl is optionally substituted with one to four R_{24}.

In another embodiment, each R_{19} is independently at each occurrence $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, $-NR_{20}R_{20'}$, $(C_6\text{-}C_{10})$ aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl comprising 1 to 4 heteroatoms selected from O, N, NH, and S, wherein the aryl and heteroaryl are optionally substituted with one to four R_{24}. In yet another embodiment, each R_{19} is independently at each occurrence $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, $-NR_{20}R_{20'}$, $(C_3\text{-}C_7)$carbocyclyl, or $(C_6\text{-}C_{10})$ aryl, wherein the carbocyclyl is optionally substituted with one to four R_{23} and the aryl is optionally substituted with one to four R_{24}. In another embodiment, each R_{19} is independently at each occurrence $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, $-NR_{20}R_{20'}$, 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_{23} and the heteroaryl is optionally substituted with one to four R_{24}.

In another embodiment, each R_{19} is independently at each occurrence $(C_1\text{-}C_6)$alkoxy, $-NR_{20}R_{20'}$, $(C_3\text{-}C_7)$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_{23} and the aryl and heteroaryl are optionally substituted with one to four R_{24}. In yet another embodiment, each R_{19} is independently at each occurrence $(C_1\text{-}C_6)$alkoxy, $-NR_{20}R_{20'}$, $(C_3\text{-}C_7)$carbocyclyl, or $(C_6\text{-}C_{10})$ aryl, wherein the carbocyclyl is substituted with one to four R_{23} and the aryl is optionally substituted with one to four R_{24}.

In some embodiments of the formulae above, R_{20} is independently at each occurrence H or $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{20} is independently at each occurrence H or $(C_1\text{-}C_3)$alkyl. In yet another embodiment, R_{20} is independently at each occurrence $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{20} is independently at each occurrence $(C_1\text{-}C_3)$alkyl. In yet another embodiment, R_{20} is independently at each occurrence H.

In some embodiments of the formulae above, $R_{20'}$ is independently at each occurrence H or $(C_1\text{-}C_6)$alkyl. In another embodiment, $R_{20'}$ is independently at each occurrence H or $(C_1\text{-}C_3)$alkyl. In yet another embodiment, $R_{20'}$ is independently at each occurrence $(C_1\text{-}C_6)$alkyl. In another embodiment, $R_{20'}$ is independently at each occurrence $(C_1\text{-}C_3)$alkyl. In yet another embodiment, $R_{20'}$ is independently at each occurrence H.

In some embodiments of the formulae above, each R_{21} 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_{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_{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_{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_{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_{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_{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_{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_{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_{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_{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_{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_{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, -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, -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_{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, -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_{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, $-NH_2$, $-SF_5$, $-SR_{25}$, -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_{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, -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_{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, 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_{21} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$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_{21} 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_{21} 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 another embodiment, each R_{21} 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 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, $-NH_2$, $-SF_5$, $-SR_{25}$, or -CN. In yet another embodiment, each R_{21} 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_{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_{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_{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_{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_{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 the formulae above, two R_{21}, 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_{21}, when on adjacent atoms, together with the atoms to which they are attached form a phenyl. In yet another embodiment, two R_{21}, 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_{21}, 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_{21}, 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_{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_{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_{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_{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_{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_{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 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_{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_{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_{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_{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_{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 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, -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_{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_{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_{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_{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_{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_{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_{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_{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_{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_{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, $-NH_2$, $-SF_5$, $-SR_{26}$, -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_{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, $-NH_2$, $-SF_5$, $-SR_{26}$, -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_{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, $-NH_2$, $-SF_5$, $-SR_{26}$, -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_{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, $-NH_2$, $-SF_5$, $-SR_{26}$, -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_{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, $-NH_2$, $-SF_5$, $-SR_{26}$, or -CN. In yet another embodiment, each R_{22} 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_{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, $-NH_2$, $-SF_5$, $-SR_{26}$, -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_{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, $-NH_2$, $-SF_5$, $-SR_{26}$, -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_{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_{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_{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_{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_{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_{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 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_{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_{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_{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_{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_{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 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_{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_{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 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_{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_{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_{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_{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_{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_{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_{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_{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, $-NH_2$, $-SF_5$, $-SR_{27}$, -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_{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, $-NH_2$, $-SF_5$, $-SR_{27}$, -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_{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, $-NH_2$, $-SF_5$, $-SR_{27}$, -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_{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, $-NH_2$, $-SF_5$, $-SR_{27}$, -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_{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, $-NH_2$, $-SF_5$, $-SR_{27}$, -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_{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, $-NH_2$, $-SF_5$, $-SR_{27}$, -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_{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, $-NH_2$, $-SF_5$, $-SR_{27}$, or -CN. In yet another embodiment, each R_{23} 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_{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, $-NH_2$, $-SF_5$, $-SR_{27}$, -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_{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, $-NH_2$, $-SF_5$, $-SR_{27}$, -

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_{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, 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_{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_{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_{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_{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, 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 another embodiment, 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 the formulae above, each R_{24} 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_{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_{24} 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_{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_{24} 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_{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 another embodiment, each R_{24} 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_{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_{24} 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_{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_{24} 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_{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 another embodiment, each R_{24} 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_{24} 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_{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_{24} 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, $-SF_5$, $-SR_{28}$, -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_{24} 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, $-NH_2$, $-SF_5$, $-SR_{28}$, -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_{24} 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, $-NH_2$, $-SF_5$, $-SR_{28}$, -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_{24} 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, $-NH_2$, $-SF_5$, $-SR_{28}$, -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_{24} 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, $-NH_2$, $-SF_5$, $-SR_{28}$, -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_{24} 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, $-NH_2$, $-SF_5$, $-SR_{28}$, -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_{24} 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, $-NH_2$, $-SF_5$, $-SR_{28}$, -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_{24} 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, $-NH_2$, $-SF_5$, $-SR_{28}$, -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_{24} 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_{24} 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_{28}, or -CN. In yet another embodiment, each R_{24} 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 yet another embodiment, each R_{24} 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_{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_{24} 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_{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_{24} 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_{24} 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_{24} 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_{24} 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_{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 $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{25} is $(C_1\text{-}C_3)$alkyl. In another embodiment, R_{25} is $(C_1\text{-}C_6)$haloalkyl. In another embodiment, R_{25} is $(C_1\text{-}C_3)$haloalkyl. In another embodiment, R_{25} is H.

In some embodiments of the formulae above, R_{26} is H, $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$haloalkyl. In another embodiment, R_{26} is H, $(C_1\text{-}C_3)$alkyl or $(C_1\text{-}C_3)$haloalkyl. In yet another embodiment, R_{26} is H or $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{26} is H or $(C_1\text{-}C_6)$haloalkyl. In yet another embodiment, R_{26} is $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$haloalkyl. In another embodiment, R_{26} is $(C_1\text{-}C_3)$alkyl or $(C_1\text{-}C_3)$haloalkyl. In yet another embodiment, R_{26} is $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{26} is $(C_1\text{-}C_3)$alkyl. In another embodiment, R_{26} is $(C_1\text{-}C_6)$haloalkyl. In another embodiment, R_{26} is $(C_1\text{-}C_3)$haloalkyl. In another embodiment, R_{26} is H.

In some embodiments of the formulae above, R_{27} is H, $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$haloalkyl. In another embodiment, R_{27} is H, $(C_1\text{-}C_3)$alkyl or $(C_1\text{-}C_3)$haloalkyl. In yet another embodiment, R_{27} is H or $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{27} is H or $(C_1\text{-}C_6)$haloalkyl. In yet another embodiment, R_{27} is $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$haloalkyl. In another embodiment, R_{27} is $(C_1\text{-}C_3)$alkyl or $(C_1\text{-}C_3)$haloalkyl. In yet another embodiment, R_{27} is $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{27} is $(C_1\text{-}C_3)$alkyl. In another embodiment, R_{27} is $(C_1\text{-}C_6)$haloalkyl. In another embodiment, R_{27} is $(C_1\text{-}C_3)$haloalkyl. In another embodiment, R_{27} is H.

In some embodiments of the formulae above, R_{28} is H, $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$haloalkyl. In another embodiment, R_{28} is H, $(C_1\text{-}C_3)$alkyl or $(C_1\text{-}C_3)$haloalkyl. In yet another embodiment, R_{28} is H or $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{28} is H or $(C_1\text{-}C_6)$haloalkyl. In yet another embodiment, R_{28} is $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$haloalkyl. In another embodiment, R_{28} is $(C_1\text{-}C_3)$alkyl or $(C_1\text{-}C_3)$haloalkyl. In yet another embodiment, R_{28} is $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{28} is $(C_1\text{-}C_3)$alkyl. In another embodiment, R_{28} is $(C_1\text{-}C_6)$haloalkyl. In another embodiment, R_{28} is $(C_1\text{-}C_3)$haloalkyl. In another embodiment, R_{28} is H.

In some embodiments of the formulae above, R_{29} is H, $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$haloalkyl. In another embodiment, R_{29} is H, $(C_1\text{-}C_3)$alkyl or $(C_1\text{-}C_3)$haloalkyl. In yet another embodiment, R_{29} is H or $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{29} is H or $(C_1\text{-}C_6)$haloalkyl. In yet another embodiment, R_{29} is $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$haloalkyl. In another embodiment, R_{29} is $(C_1\text{-}C_3)$alkyl or $(C_1\text{-}C_3)$haloalkyl. In yet another embodiment, R_{29} is $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{29} is $(C_1\text{-}C_3)$alkyl. In another embodiment, R_{29} is $(C_1\text{-}C_6)$haloalkyl. In another embodiment, R_{29} is $(C_1\text{-}C_3)$haloalkyl. In another embodiment, R_{29} is H.

In some embodiments of the formulae above, R_{30} is H, $(C_1\text{-}C_6)$alkyl, or $-C(O)R_{34}$. In another embodiment, R_{30} is H, $(C_1\text{-}C_3)$alkyl, or $-C(O)R_{34}$. In yet another embodiment, R_{30} is H or $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{30} is H or $-C(O)R_{34}$. In yet another embodiment, R_{30} is $(C_1\text{-}C_3)$alkyl or $-C(O)R_{34}$. In another embodiment, R_{30} is $(C_1\text{-}C_3)$alkyl. In yet another embodiment, R_{30} is $-C(O)R_{34}$. In another embodiment, R_{30} is H.

In some embodiments of the formulae above, R_{31} is H, $(C_1\text{-}C_6)$alkyl, or $-C(O)R_{34}$. In another embodiment, R_{31} is H, $(C_1\text{-}C_3)$alkyl, or $-C(O)R_{34}$. In yet another embodiment, R_{31} is H or $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{31} is H or $-C(O)R_{34}$. In yet another embodiment, R_{31} is $(C_1\text{-}C_3)$alkyl or $-C(O)R_{34}$. In

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

In some embodiments of the formulae above, R_{32} is H or $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{32} is H or $(C_1\text{-}C_3)$alkyl. In yet another embodiment, R_{32} is $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{32} is $(C_1\text{-}C_3)$alkyl. In yet another embodiment, R_{32} is H.

In some embodiments of the formulae above, R_{33} is H or $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{33} is H or $(C_1\text{-}C_3)$alkyl. In yet another embodiment, R_{33} is $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{33} is $(C_1\text{-}C_3)$alkyl. In yet another embodiment, R_{33} is H.

In some embodiments of the formulae above, R_{34} is H or $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{34} is H or $(C_1\text{-}C_3)$alkyl. In yet another embodiment, R_{34} is $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{34} is $(C_1\text{-}C_3)$alkyl. In yet another embodiment, R_{34} is H.

In some embodiments of the formulae above, R_{35} is H, $(C_1\text{-}C_6)$alkyl, or $-C(O)R_{39}$. In another embodiment, R_{35} is H, $(C_1\text{-}C_3)$alkyl, or $-C(O)R_{39}$. In yet another embodiment, R_{35} is H or $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{35} is H or $-C(O)R_{39}$. In yet another embodiment, R_{35} is $(C_1\text{-}C_3)$alkyl or $-C(O)R_{39}$. In another embodiment, R_{35} is $(C_1\text{-}C_3)$alkyl. In yet another embodiment, R_{35} is $-C(O)R_{39}$. In another embodiment, R_{35} is H.

In some embodiments of the formulae above, R_{36} is H, $(C_1\text{-}C_6)$alkyl, or $-C(O)R_{39}$. In another embodiment, R_{36} is H, $(C_1\text{-}C_3)$alkyl, or $-C(O)R_{39}$. In yet another embodiment, R_{36} is H or $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{36} is H or $-C(O)R_{39}$. In yet another embodiment, R_{36} is $(C_1\text{-}C_3)$alkyl or $-C(O)R_{39}$. In another embodiment, R_{36} is $(C_1\text{-}C_3)$alkyl. In yet another embodiment, R_{36} is $-C(O)R_{39}$. In another embodiment, R_{36} is H.

In some embodiments of the formulae above, R_{37} is H or $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{37} is H or $(C_1\text{-}C_3)$alkyl. In yet another embodiment, R_{37} is $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{37} is $(C_1\text{-}C_3)$alkyl. In yet another embodiment, R_{37} is H.

In some embodiments of the formulae above, R_{38} is H or $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{38} is H or $(C_1\text{-}C_3)$alkyl. In yet another embodiment, R_{38} is $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{38} is $(C_1\text{-}C_3)$alkyl. In yet another embodiment, R_{38} is H.

In some embodiments of the formulae above, R_{39} is H or $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{39} is H or $(C_1\text{-}C_3)$alkyl. In yet another embodiment, R_{39} is independently at each occurrence $(C_1\text{-}C_6)$alkyl. In another embodiment, R_{39} is $(C_1\text{-}C_3)$alkyl. In yet another embodiment, R_{39} is H.

In some embodiments of the formulae above, o is 1 or 2. In another embodiment, o is 1. In another embodiment, o is 2.

In some embodiments of the formulae above, m is 0, 1 or 2. In another embodiment, m is 0 or 2. In yet another embodiment, m is 0 or 1. In another embodiment, m is 1 or 2. In yet another embodiment, m is 0. In another embodiment, m is 1. In yet another embodiment, m is 2.

In some embodiments of the formulae above, n is 0, 1 or 2. In another embodiment, n is 0 or 2. In yet another embodiment, n is 0 or 1. In another embodiment, n is 1 or 2. In yet another embodiment, n is 0. In another embodiment, n is 1. In yet another embodiment, n is 2.

In some embodiments of the formulae above, p is 0, 1, 2, 3, or 4. In another embodiment, p is 0, 1, 2, or 3. In yet another embodiment, p is 0, 1, 2, or 4. In another embodiment, p is 0, 1, 3 or 4. In yet another embodiment, p is 0, 2, 3, or 4. In another embodiment, p is 1, 2, 3 or 4. In yet another embodiment, p is 0, 1, or 2. In another embodiment, p is 2, 3, or 4. In yet another embodiment, p is 1, 2, or 3. In another embodiment, p is 0 or 1. In yet another embodiment, p is 1 or 2. In another embodiment, p is 2 or 3. In yet another embodiment, p is 3 or 4. In another embodiment, p is 0 or 2. In yet another embodiment, p is 0 or 3. In another embodiment, p is 0 or 4. In yet another embodiment, p is 1 or 2. In another embodiment, p is 1 or 3. In yet another embodiment, p is 1 or 4. In another embodiment, p is 0 or 2. In yet another embodiment, p is 2 or 4. In another embodiment, p is 0. In yet another embodiment, p is 1. In another embodiment, p is 2. In yet another embodiment, p is 4.

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, X_1 is N or CR_3. In another embodiment, X_1 is N or CR_3 and X_2 is N or $CR_{5'}$. In yet another embodiment, X_1 is N or CR_3, X_2 is N or $CR_{5'}$, and R_1 is H. In another embodiment, X_1 is N or CR_3, X_2 is N or $CR_{5'}$, R_1 is H, and R_{2a} is H. In yet another embodiment, X_1 is N or CR_3, X_2 is N or $CR_{5'}$, R_1 is H, R_{2a} is H and R_{2b} is H. In another embodiment, X_1 is N or CR_3, X_2 is N or $CR_{5'}$, R_1 is H, R_{2a} is H, R_{2b} is H, and R_{2c} is H. In yet another embodiment, X_1 is N or CR_3, X_2 is N or $CR_{5'}$, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, and R_{2d} is H. In another embodiment, X_1 is N or CR_3, X_2 is N or $CR_{5'}$, 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 yet another embodiment, X_1 is N or CR_3, X_2 is N or $CR_{5'}$, 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_6 is H. In yet another embodiment, X_1 is N or CR_3, X_2 is N or $CR_{5'}$, 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_6 is H, and R_{7a} is H. In another embodiment, X_1 is N or CR_3, X_2 is N or $CR_{5'}$, 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_6 is H, R_{7a} is H, and R_{7b} is H. In yet another embodiment, X_1 is N or CR_3, X_2 is N or $CR_{5'}$, 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_6 is H, R_{7a} is H, R_{7b} is H, and R_{7c} is H.

In another embodiment, X_1 is N or CR_3, X_2 is N or $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, and R_{7d} is H. In another embodiment, X_1 is N or CR_3, X_2 is N or $CR_{5'}$ 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is

H, R_{7d} is H, and n is 0 or 1. In yet another embodiment, X_1 is N or CR_3, X_2 is N or $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, and n is 0.In another embodiment, X_1 is N or CR_3, X_2 is N or $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, and m is 0, 1, or 2.

In yet another embodiment, X_1 is N or CR_3, X_2 is N or $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, and each R_4 is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halogen, or $-NR_9R_{10}$. In another embodiment, X_1 is N or CR_3, X_2 is N or $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halogen, or $-NR_9R_{10}$, and $R_{5'}$ is H, $(C_1\text{-}C_6)$alkyl, halogen, or $-NR_9R_{10}$. In yet another embodiment, X_1 is N or CR_3, X_2 is N or $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halogen, or $-NR_9R_{10}$, $R_{5'}$ is H, $(C_1\text{-}C_6)$alkyl, halogen, or $-NR_9R_{10}$, and p is 0, 1, 2, or 3.

In another embodiment, X_1 is N or CR_3, X_2 is N or $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halogen, or $-NR_9R_{10}$, $R_{5'}$ is H, $(C_1\text{-}C_6)$alkyl, halogen, or $-NR_9R_{10}$, p is 0, 1, 2, or 3, and each R_{7e} is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, halogen, $(C_1\text{-}C_6)$hydroxyalkyl, -OH, $(C_6\text{-}C_{10})$ aryl, or $(C_3\text{-}C_7)$carbocyclyl, wherein the alkyl is optionally substituted with one to six R_{19}, the aryl is optionally substituted with one to four R_{21}, and the carbocyclyl is optionally substituted with one to four R_{22}; or two R_{7e}, when on the same carbon atom, together with the carbon atom to which they are attached form a $(C_3\text{-}C_7)$spirocarbocyclyl, wherein the spirocarbocyclyl is optionally substituted with one or more substituents independently selected from D, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$deuteroalkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, $(C_1\text{-}C_6)$hydroxyalkyl, halogen, $-C(O)OR_{13'}$, $-C(O)R_{13}$, and $-C(O)NR_{13'}R_{13'}$.

In yet another embodiment, X_1 is N or CR_3, X_2 is N or $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halogen, or $-NR_9R_{10}$, $R_{5'}$ is H, $(C_1\text{-}C_6)$alkyl, halogen, or $-NR_9R_{10}$, p is 0, 1, 2, or 3, each R_{7e} is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, halogen, $(C_1\text{-}C_6)$hydroxyalkyl, -OH, $(C_6\text{-}C_{10})$ aryl, or $(C_3\text{-}C_7)$carbocyclyl, wherein the alkyl is optionally substituted with one to six R_{19}, the aryl is optionally substituted with one to four R_{21}, and the carbocyclyl is optionally substituted with one to four R_{22}; or two R_{7e}, when on the same carbon atom, together with the carbon atom to which they are attached form a $(C_3\text{-}C_7)$spirocarbocyclyl, wherein the spirocarbocyclyl is optionally substituted with one or more substituents independently selected

from D, $(C_1$-$C_6)$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, $-C(O)OR_{13'}$, $-C(O)R_{13}$, and $-C(O)NR_{13'}R_{13'}$, and R_8 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, 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_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$.

In another embodiment, X_1 is N or CR_3, X_2 is N or $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, halogen, or $-NR_9R_{10}$, $R_{5'}$ is H, $(C_1$-$C_6)$alkyl, halogen, or $-NR_9R_{10}$, p is 0, 1, 2, or 3, each R_{7e} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$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_{19}, the aryl is optionally substituted with one to four R_{21}, and the carbocyclyl is optionally substituted with one to four R_{22}; or two R_{7e}, 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 or more substituents independently selected from D, $(C_1$-$C_6)$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, $-C(O)OR_{13'}$, $-C(O)R_{13}$, and $-C(O)NR_{13'}R_{13'}$, and R_8 is $(C_1$-$C_6)$haloalkyl 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, 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_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$.In yet another embodiment, X_1 is N or CR_3, X_2 is N or $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, halogen, or $-NR_9R_{10}$, $R_{5'}$ is H, $(C_1$-$C_6)$alkyl, halogen, or $-NR_9R_{10}$, p is 0, 1, 2, or 3, each R_{7e} is independently at each occurrence $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$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_{19}, the aryl is optionally substituted with one to four R_{21}, and the carbocyclyl is optionally substituted with one to four R_{22}; or two R_{7e}, 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 or more substituents independently selected from D, $(C_1$-$C_6)$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, $-C(O)OR_{13'}$, $-C(O)R_{13}$, and $-C(O)NR_{13'}R_{13'}$, and R_8 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 to four R_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$.

In some embodiments of the formulae above, X_1 is N or CR_3. In another embodiment, X_1 is N or CR_3 and X_2 is N. In yet another embodiment, X_1 is N or CR_3, X_2 is N, and R_1 is H. In another embodiment, X_1 is N or CR_3, X_2 is N, R_1 is H, and R_{2a} is H. In yet another embodiment, X_1 is N or CR_3, X_2 is N, R_1 is H, R_{2a} is H and R_{2b} is H. In another embodiment, X_1 is N or CR_3, X_2 is N, R_1 is H, R_{2a} is H, R_{2b} is H, and R_{2c} is H. In yet another embodiment, X_1 is N or CR_3, X_2 is N, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, and R_{2d} is H. In another embodiment, X_1 is N or CR_3, X_2 is N, 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 yet another embodiment, X_1 is N or CR_3, X_2 is N, 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_6 is H. In yet another embodiment, X_1 is N or CR_3, X_2 is N, 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_6 is H, and R_{7a} is H. In another embodiment, X_1 is N or CR_3, X_2 is N, 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_6 is H, R_{7a} is H, and R_{7b} is H. In yet another embodiment, X_1 is N or CR_3, X_2 is N, 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_6 is H, R_{7a} is H, R_{7b} is H, and R_{7c} is H.

In another embodiment, X_1 is N or CR_3, X_2 is N, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, and R_{7d} is H. In another embodiment, X_1 is N or CR_3, X_2 is N, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, and n is 0 or 1. In yet another embodiment, X_1 is N or CR_3, X_2 is N, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, and n is 0. In another embodiment, X_1 is N or CR_3, X_2 is N, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, and m is 0, 1, or 2.

In yet another embodiment, X_1 is N or CR_3, X_2 is N, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, and each R_4 is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, or -NR_9R_{10}. In another embodiment, X_1 is N or CR_3, X_2 is N, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, or -NR_9R_{10}, and $R_{5'}$ is H, (C_1-C_6)alkyl, halogen, or -NR_9R_{10}. In yet another embodiment, X_1 is N or CR_3, X_2 is N, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, or -NR_9R_{10}, $R_{5'}$ is H, (C_1-C_6)alkyl, halogen, or -NR_9R_{10}, and p is 0, 1, 2, or 3.

In another embodiment, X_1 is N or CR_3, X_2 is N, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at

each occurrence (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, or -NR_9R_{10}, $R_{5'}$ is H, (C_1-C_6)alkyl, halogen, or -NR_9R_{10}, p is 0, 1, 2, or 3, and each R_{7e} is independently at each occurrence (C_1-C_6)alkyl, (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_{19}, the aryl is optionally substituted with one to four R_{21}, and the carbocyclyl is optionally substituted with one to four R_{22}; or two R_{7e}, 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 or more substituents independently selected from D, (C_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, -$C(O)OR_{13'}$, -$C(O)R_{13}$, and -$C(O)NR_{13'}R_{13'}$.

In yet another embodiment, X_1 is N or CR_3, X_2 is N, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, or -NR_9R_{10}, $R_{5'}$ is H, (C_1-C_6)alkyl, halogen, or -NR_9R_{10}, p is 0, 1, 2, or 3, each R_{7e} is independently at each occurrence (C_1-C_6)alkyl, (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_{19}, the aryl is optionally substituted with one to four R_{21}, and the carbocyclyl is optionally substituted with one to four R_{22}; or two R_{7e}, 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 or more substituents independently selected from D, (C_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, -$C(O)OR_{13'}$, -$C(O)R_{13}$, and -$C(O)NR_{13'}R_{13'}$, and R_8 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 to four R_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$.

In some embodiments of the formulae above, X_1 is N or CR_3. In another embodiment, X_1 is N or CR_3 and X_2 is $CR_{5'}$. In yet another embodiment, X_1 is N or CR_3, X_2 is $CR_{5'}$, and R_1 is H. In another embodiment, X_1 is N or CR_3, X_2 is $CR_{5'}$, R_1 is H, and R_{2a} is H. In yet another embodiment, X_1 is N or CR_3, X_2 is $CR_{5'}$, R_1 is H, R_{2a} is H and R_{2b} is H. In another embodiment, X_1 is N or CR_3, X_2 is $CR_{5'}$, R_1 is H, R_{2a} is H, R_{2b} is H, and R_{2c} is H. In yet another embodiment, X_1 is N or CR_3, X_2 is $CR_{5'}$, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, and R_{2d} is H. In another embodiment, X_1 is N or CR_3, X_2 is $CR_{5'}$, 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 yet another embodiment, X_1 is N or CR_3, X_2 is $CR_{5'}$, 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_6 is H. In yet another embodiment, X_1 is N or CR_3, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H. In another embodiment, X_1 is N or CR_3, X_2 is $CR_{5'}$, 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_6 is H, R_{7a} is H, and R_{7b} is H. In yet another embodiment, X_1 is N or CR_3, X_2 is $CR_{5'}$, 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_6 is H, R_{7a} is H, R_{7b} is H, and R_{7c} is H.

In another embodiment, X_1 is N or CR_3, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, and R_{7d} is H. In another embodiment, X_1 is N or CR_3, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, and n is 0 or 1. In yet another embodiment, X_1 is N or CR_3, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, and n is 0. In another embodiment, X_1 is N or CR_3, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, and m is 0, 1, or 2.

In yet another embodiment, X_1 is N or CR_3, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, and each R_4 is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halogen, or $-NR_9R_{10}$. In another embodiment, X_1 is N or CR_3, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halogen, or $-NR_9R_{10}$, and $R_{5'}$ is H, $(C_1\text{-}C_6)$alkyl, halogen, or $-NR_9R_{10}$. In yet another embodiment, X_1 is N or CR_3, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halogen, or $-NR_9R_{10}$, $R_{5'}$ is H, $(C_1\text{-}C_6)$alkyl, halogen, or $-NR_9R_{10}$, and p is 0, 1, 2, or 3.

In another embodiment, X_1 is N or CR_3, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halogen, or $-NR_9R_{10}$, $R_{5'}$ is H, $(C_1\text{-}C_6)$alkyl, halogen, or $-NR_9R_{10}$, p is 0, 1, 2, or 3, and each R_{7e} is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, halogen, $(C_1\text{-}C_6)$hydroxyalkyl, -OH, $(C_6\text{-}C_{10})$ aryl, or $(C_3\text{-}C_7)$carbocyclyl, wherein the alkyl is optionally substituted with one to six R_{19}, the aryl is optionally substituted with one to four R_{21}, and the carbocyclyl is optionally substituted with one to four R_{22}; or two R_{7e}, when on the same carbon atom, together with the carbon atom to which they are attached form a $(C_3\text{-}C_7)$spirocarbocyclyl, wherein the spirocarbocyclyl is optionally substituted with one or more substituents independently selected from D, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$deuteroalkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, $(C_1\text{-}C_6)$hydroxyalkyl, halogen, $-C(O)OR_{13'}$, $-C(O)R_{13}$, and $-C(O)NR_{13'}R_{13'}$.

In yet another embodiment, X_1 is N or CR_3, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently

at each occurrence (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, or -NR_9R_{10}, $R_{5'}$ is H, (C_1-C_6)alkyl, halogen, or -NR_9R_{10}, p is 0, 1, 2, or 3, each R_{7e} is independently at each occurrence (C_1-C_6)alkyl, (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_{19}, the aryl is optionally substituted with one to four R_{21}, and the carbocyclyl is optionally substituted with one to four R_{22}; or two R_{7e}, 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 or more substituents independently selected from D, (C_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, -$C(O)OR_{13'}$, -$C(O)R_{13}$, and -$C(O)NR_{13'}R_{13'}$, and R_8 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 to four R_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$.

In some embodiments of the formulae above, X_1 is N. In another embodiment, X_1 is N and X_2 is N. In yet another embodiment, X_1 is N, X_2 is N, and R_1 is H. In another embodiment, X_1 is N, X_2 is N, R_1 is H, and R_{2a} is H. In yet another embodiment, X_1 is N, X_2 is N, R_1 is H, R_{2a} is H and R_{2b} is H. In another embodiment, X_1 is N, X_2 is N, R_1 is H, R_{2a} is H, R_{2b} is H, and R_{2c} is H. In yet another embodiment, X_1 is N, X_2 is N, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, and R_{2d} is H. In another embodiment, X_1 is N, X_2 is N, 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 yet another embodiment, X_1 is N, X_2 is N, 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_6 is H. In yet another embodiment, X_1 is N, X_2 is N, 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_6 is H, and R_{7a} is H. In another embodiment, X_1 is N, X_2 is N, 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_6 is H, R_{7a} is H, and R_{7b} is H. In yet another embodiment, X_1 is N, X_2 is N, 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_6 is H, R_{7a} is H, R_{7b} is H, and R_{7c} is H.

In another embodiment, X_1 is N, X_2 is N, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, and R_{7d} is H. In another embodiment, X_1 is N, X_2 is N, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, and n is 0 or 1. In yet another embodiment, X_1 is N, X_2 is N, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, and n is 0. In another embodiment, X_1 is N, X_2 is N, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, and m is 0, 1, or 2.

In yet another embodiment, X_1 is N, X_2 is N, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, and each R_4 is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halogen, or $-NR_9R_{10}$. In another embodiment, X_1 is N, X_2 is N, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halogen, or $-NR_9R_{10}$, and $R_{5'}$ is H, $(C_1\text{-}C_6)$alkyl, halogen, or $-NR_9R_{10}$. In yet another embodiment, X_1 is N, X_2 is N, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halogen, or $-NR_9R_{10}$, $R_{5'}$ is H, $(C_1\text{-}C_6)$alkyl, halogen, or $-NR_9R_{10}$, and p is 0, 1, 2, or 3.

In another embodiment, X_1 is N, X_2 is N, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halogen, or $-NR_9R_{10}$, $R_{5'}$ is H, $(C_1\text{-}C_6)$alkyl, halogen, or $-NR_9R_{10}$, p is 0, 1, 2, or 3, and each R_{7e} is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, halogen, $(C_1\text{-}C_6)$hydroxyalkyl, -OH, $(C_6\text{-}C_{10})$ aryl, or $(C_3\text{-}C_7)$carbocyclyl, wherein the alkyl is optionally substituted with one to six R_{19}, the aryl is optionally substituted with one to four R_{21}, and the carbocyclyl is optionally substituted with one to four R_{22}; or two R_{7e}, when on the same carbon atom, together with the carbon atom to which they are attached form a $(C_3\text{-}C_7)$spirocarbocyclyl, wherein the spirocarbocyclyl is optionally substituted with one or more substituents independently selected from D, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$deuteroalkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, $(C_1\text{-}C_6)$hydroxyalkyl, halogen, $-C(O)OR_{13'}$, $-C(O)R_{13}$, and $-C(O)NR_{13'}R_{13'}$.

In yet another embodiment, X_1 is N, X_2 is N, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halogen, or $-NR_9R_{10}$, $R_{5'}$ is H, $(C_1\text{-}C_6)$alkyl, halogen, or $-NR_9R_{10}$, p is 0, 1, 2, or 3, each R_{7e} is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, halogen, $(C_1\text{-}C_6)$hydroxyalkyl, -OH, $(C_6\text{-}C_{10})$ aryl, or $(C_3\text{-}C_7)$carbocyclyl, wherein the alkyl is optionally substituted with one to six R_{19}, the aryl is optionally substituted with one to four R_{21}, and the carbocyclyl is optionally substituted with one to four R_{22}; or two R_{7e}, when on the same carbon atom, together with the carbon atom to which they are attached form a $(C_3\text{-}C_7)$spirocarbocyclyl, wherein the spirocarbocyclyl is optionally substituted with one or more substituents independently selected from D, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$deuteroalkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, $(C_1\text{-}C_6)$hydroxyalkyl, halogen, $-C(O)OR_{13'}$, $-C(O)R_{13}$, and $-C(O)NR_{13'}R_{13'}$, and R_8 is $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$hydroxyalkyl, $(C_1\text{-}C_6)$halohydroxyalkyl, or $(C_1\text{-}C_6)$alkyl optionally substituted with one or more substituents independently selected from D, $(C_1\text{-}C_6)$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, $(C_3\text{-}C_7)$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_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$.

In some embodiments of the formulae above, X_1 is CR_3. In another embodiment, X_1 is CR_3 and X_2 is $CR_{5'}$. In yet another embodiment, X_1 is CR_3, X_2 is $CR_{5'}$, and R_1 is H. In another embodiment, X_1 is CR_3, X_2 is $CR_{5'}$, R_1 is H, and R_{2a} is H. In yet another embodiment, X_1 is CR_3, X_2 is $CR_{5'}$, R_1 is H, R_{2a} is H and R_{2b} is H. In another embodiment, X_1 is CR_3, X_2 is $CR_{5'}$, R_1 is H, R_{2a} is H, R_{2b} is H, and R_{2c} is H. In yet another embodiment, X_1 is CR_3, X_2 is $CR_{5'}$, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, and R_{2d} is H. In another embodiment, X_1 is CR_3, X_2 is $CR_{5'}$, 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 yet another embodiment, X_1 is CR_3, X_2 is $CR_{5'}$, 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_6 is H. In yet another embodiment, X_1 is CR_3, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H. In another embodiment, X_1 is CR_3, X_2 is $CR_{5'}$, 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_6 is H, R_{7a} is H, and R_{7b} is H. In yet another embodiment, X_1 is CR_3, X_2 is $CR_{5'}$, 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_6 is H, R_{7a} is H, R_{7b} is H, and R_{7c} is H.

In another embodiment, X_1 is CR_3, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, and R_{7d} is H. In another embodiment, X_1 is CR_3, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, and n is 0 or 1. In yet another embodiment, X_1 is CR_3, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, and n is 0. In another embodiment, X_1 is CR_3, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, and m is 0, 1, or 2.

In yet another embodiment, X_1 is CR_3, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, and each R_4 is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halogen, or $-NR_9R_{10}$. In another embodiment, X_1 is CR_3, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halogen, or $-NR_9R_{10}$, and $R_{5'}$ is H, $(C_1\text{-}C_6)$alkyl, halogen, or $-NR_9R_{10}$. In yet another embodiment, X_1 is CR_3, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halogen, or $-NR_9R_{10}$, $R_{5'}$ is H, $(C_1\text{-}C_6)$alkyl, halogen, or $-NR_9R_{10}$, and p is 0, 1, 2, or 3.

In another embodiment, X_1 is CR_3, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halogen, or $-NR_9R_{10}$, $R_{5'}$ is H, $(C_1\text{-}C_6)$alkyl, halogen, or $-NR_9R_{10}$, p is 0, 1, 2, or 3, and each R_{7e} is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}$

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_{19}, the aryl is optionally substituted with one to four R_{21}, and the carbocyclyl is optionally substituted with one to four R_{22}; or two R_{7e}, 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 or more substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$.

In yet another embodiment, X_1 is CR_3, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, or -NR_9R_{10}, $R_{5'}$ is H, (C_1-C_6)alkyl, halogen, or -NR_9R_{10}, p is 0, 1, 2, or 3, each R_{7e} is independently at each occurrence (C_1-C_6)alkyl, (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_{19}, the aryl is optionally substituted with one to four R_{21}, and the carbocyclyl is optionally substituted with one to four R_{22}; or two R_{7e}, 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 or more substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$, and R_8 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 to four R_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$.

In some embodiments of the formulae above, X_1 is N. In another embodiment, X_1 is N and X_2 is $CR_{5'}$. In yet another embodiment, X_1 is N, X_2 is $CR_{5'}$, and R_1 is H. In another embodiment, X_1 is N, X_2 is $CR_{5'}$, R_1 is H, and R_{2a} is H. In yet another embodiment, X_1 is N, X_2 is $CR_{5'}$, R_1 is H, R_{2a} is H and R_{2b} is H. In another embodiment, X_1 is N, X_2 is $CR_{5'}$, R_1 is H, R_{2a} is H, R_{2b} is H, and R_{2c} is H. In yet another embodiment, X_1 is N, X_2 is $CR_{5'}$, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, and R_{2d} is H. In another embodiment, X_1 is N, X_2 is $CR_{5'}$, 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 yet another embodiment, X_1 is N, X_2 is $CR_{5'}$, 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_6 is H. In yet another embodiment, X_1 is N, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H. In another embodiment, X_1 is N, X_2 is $CR_{5'}$, 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_6 is

H, R_{7a} is H, and R_{7b} is H. In yet another embodiment, X_1 is N, X_2 is $CR_{5'}$, 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_6 is H, R_{7a} is H, R_{7b} is H, and R_{7c} is H.

In another embodiment, X_1 is N, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, and R_{7d} is H. In another embodiment, X_1 is N, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, and n is 0 or 1. In yet another embodiment, X_1 is N, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, and n is 0. In another embodiment, X_1 is N, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, and m is 0, 1, or 2.

In yet another embodiment, X_1 is N, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, and each R_4 is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halogen, or $-NR_9R_{10}$. In another embodiment, X_1 is N, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halogen, or $-NR_9R_{10}$, and $R_{5'}$ is H, $(C_1\text{-}C_6)$alkyl, halogen, or $-NR_9R_{10}$. In yet another embodiment, X_1 is N, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halogen, or $-NR_9R_{10}$, $R_{5'}$ is H, $(C_1\text{-}C_6)$alkyl, halogen, or $-NR_9R_{10}$, and p is 0, 1, 2, or 3.

In another embodiment, X_1 is N, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halogen, or $-NR_9R_{10}$, $R_{5'}$ is H, $(C_1\text{-}C_6)$alkyl, halogen, or $-NR_9R_{10}$, p is 0, 1, 2, or 3, and each R_{7e} is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, halogen, $(C_1\text{-}C_6)$hydroxyalkyl, -OH, $(C_6\text{-}C_{10})$ aryl, or $(C_3\text{-}C_7)$carbocyclyl, wherein the alkyl is optionally substituted with one to six R_{19}, the aryl is optionally substituted with one to four R_{21}, and the carbocyclyl is optionally substituted with one to four R_{22}; or two R_{7e}, when on the same carbon atom, together with the carbon atom to which they are attached form a $(C_3\text{-}C_7)$spirocarbocyclyl, wherein the spirocarbocyclyl is optionally substituted with one or more substituents independently selected from D, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$deuteroalkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, $(C_1\text{-}C_6)$hydroxyalkyl, halogen, $-C(O)OR_{13'}$, $-C(O)R_{13}$, and $-C(O)NR_{13'}R_{13'}$.

In yet another embodiment, X_1 is N, X_2 is $CR_{5'}$, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halogen, or $-NR_9R_{10}$, $R_{5'}$ is H, $(C_1\text{-}C_6)$alkyl, halogen, or $-NR_9R_{10}$, p is 0, 1, 2, or 3, each R_{7e} is independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, halogen, $(C_1\text{-}C_6)$hydroxyalkyl, -OH, $(C_6\text{-}C_{10})$ aryl, or $(C_3\text{-}C_7)$carbocyclyl, wherein the alkyl is optionally

substituted with one to six R_{19}, the aryl is optionally substituted with one to four R_{21}, and the carbocyclyl is optionally substituted with one to four R_{22}; or two R_{7e}, 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 or more substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$, and R_8 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 to four R_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$.

In some embodiments of the formulae above, X_1 is CR_3. In another embodiment, X_1 is CR_3 and X_2 is N. In yet another embodiment, X_1 is CR_3, X_2 is N, and R_1 is H. In another embodiment, X_1 is CR_3, X_2 is N, R_1 is H, and R_{2a} is H. In yet another embodiment, X_1 is CR_3, X_2 is N, R_1 is H, R_{2a} is H and R_{2b} is H. In another embodiment, X_1 is CR_3, X_2 is N, R_1 is H, R_{2a} is H, R_{2b} is H, and R_{2c} is H. In yet another embodiment, X_1 is CR_3, X_2 is N, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, and R_{2d} is H. In another embodiment, X_1 is CR_3, X_2 is N, 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 yet another embodiment, X_1 is CR_3, X_2 is N, 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_6 is H. In yet another embodiment, X_1 is CR_3, X_2 is N, 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_6 is H, and R_{7a} is H. In another embodiment, X_1 is CR_3, X_2 is N, 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_6 is H, R_{7a} is H, and R_{7b} is H. In yet another embodiment, X_1 is CR_3, X_2 is N, 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_6 is H, R_{7a} is H, R_{7b} is H, and R_{7c} is H.

In another embodiment, X_1 is CR_3, X_2 is N, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, and R_{7d} is H. In another embodiment, X_1 is CR_3, X_2 is N, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, and n is 0 or 1. In yet another embodiment, X_1 is CR_3, X_2 is N, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, and n is 0. In another embodiment, X_1 is CR_3, X_2 is N, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, and m is 0, 1, or 2.

In yet another embodiment, X_1 is CR_3, X_2 is N, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, and each R_4 is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, or -NR_9R_{10}. In another embodiment, X_1 is CR_3, X_2 is N, 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_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is

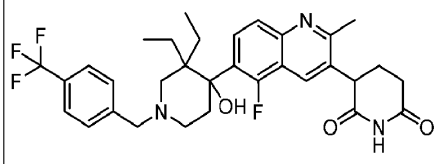
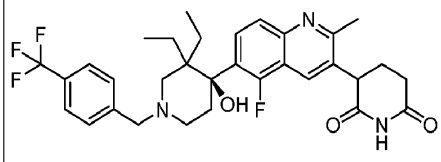
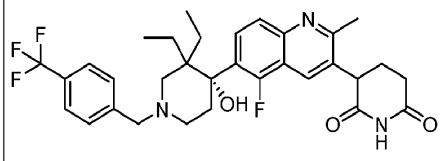
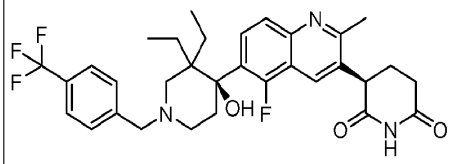
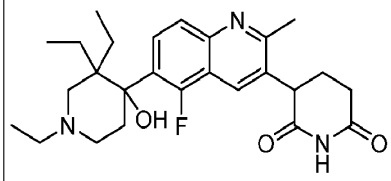
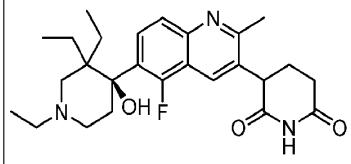
H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, or -NR_9R_{10}, and $R_{5'}$ is H, (C_1-C_6)alkyl, halogen, or -NR_9R_{10}. In yet another embodiment, X_1 is CR_3, X_2 is N, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, or -NR_9R_{10}, $R_{5'}$ is H, (C_1-C_6)alkyl, halogen, or -NR_9R_{10}, and p is 0, 1, 2, or 3.

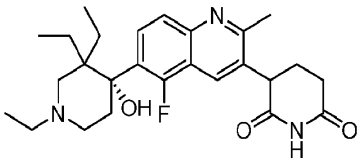
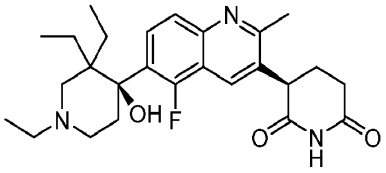
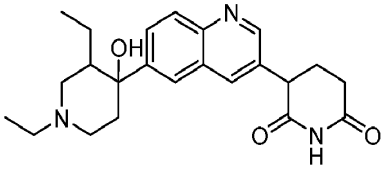
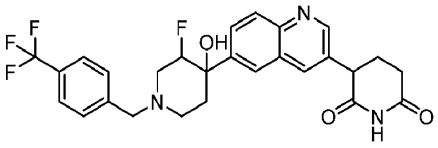
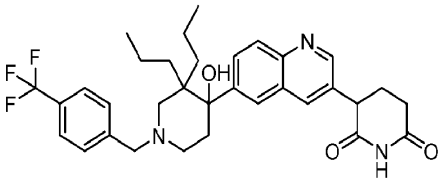
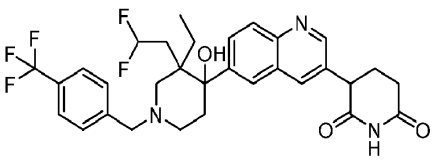
In another embodiment, X_1 is CR_3, X_2 is N, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, or -NR_9R_{10}, $R_{5'}$ is H, (C_1-C_6)alkyl, halogen, or -NR_9R_{10}, p is 0, 1, 2, or 3, and each R_{7e} is independently at each occurrence (C_1-C_6)alkyl, (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_{19}, the aryl is optionally substituted with one to four R_{21}, and the carbocyclyl is optionally substituted with one to four R_{22}; or two R_{7e}, 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 or more substituents independently selected from D, (C_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, -$C(O)OR_{13'}$, -$C(O)R_{13}$, and -$C(O)NR_{13'}R_{13'}$.

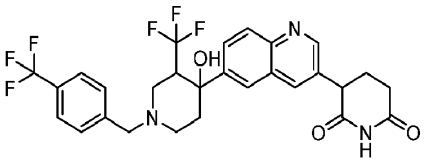
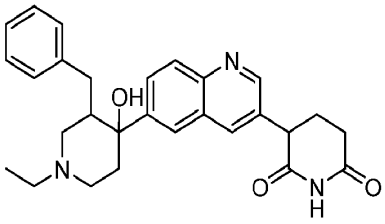
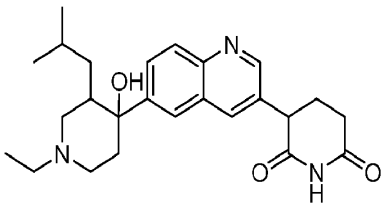
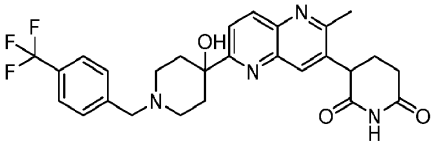
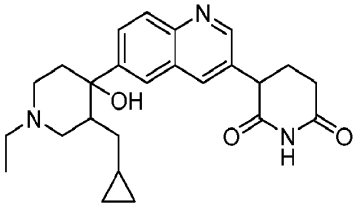
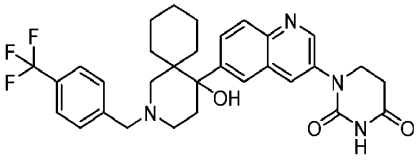
In yet another embodiment, X_1 is CR_3, X_2 is N, R_1 is H, R_{2a} is H, R_{2b} is H, R_{2c} is H, R_{2d} is H, R_3 is H, R_6 is H, and R_{7a} is H, R_{7b} is H, R_{7c} is H, R_{7d} is H, n is 0, m is 0, 1, or 2, each R_4 is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, or -NR_9R_{10}, $R_{5'}$ is H, (C_1-C_6)alkyl, halogen, or -NR_9R_{10}, p is 0, 1, 2, or 3, each R_{7e} is independently at each occurrence (C_1-C_6)alkyl, (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_{19}, the aryl is optionally substituted with one to four R_{21}, and the carbocyclyl is optionally substituted with one to four R_{22}; or two R_{7e}, 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 or more substituents independently selected from D, (C_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, -$C(O)OR_{13'}$, -$C(O)R_{13}$, and -$C(O)NR_{13'}R_{13'}$, and R_8 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 to four R_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to four $R_{15'}$.

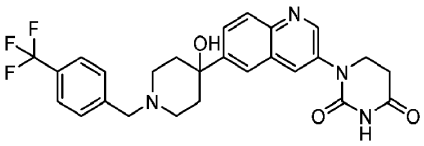
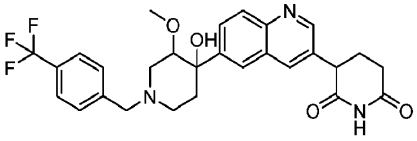
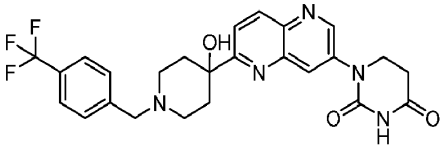
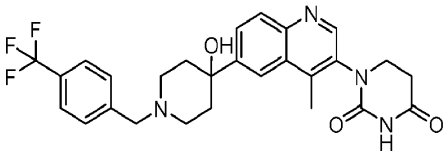
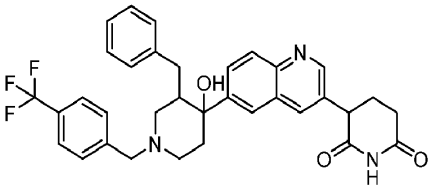
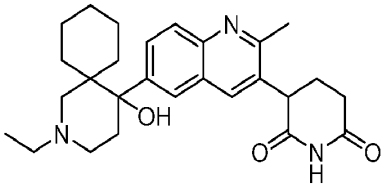
Non-limiting illustrative compounds of the disclosure include the compounds in Table 1:

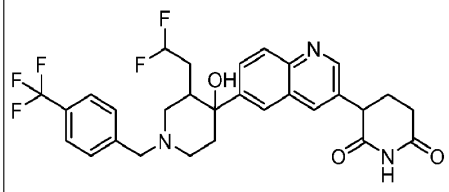
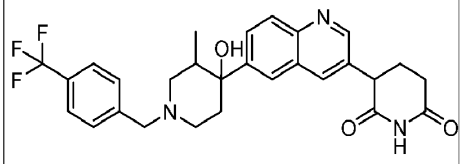
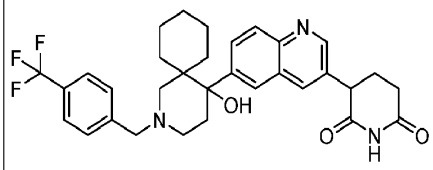
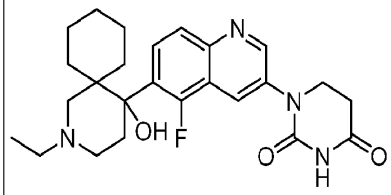
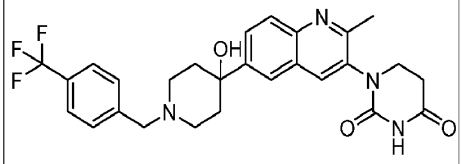
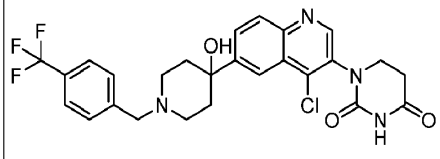
Table 1:

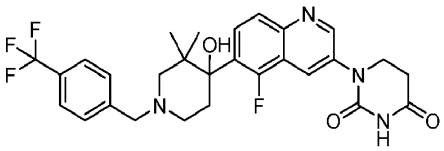
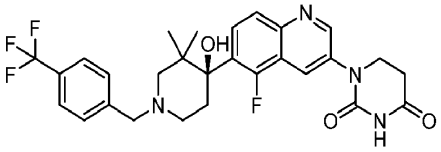
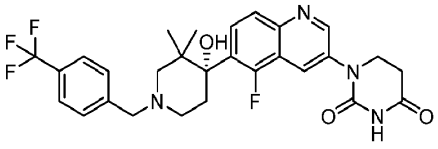
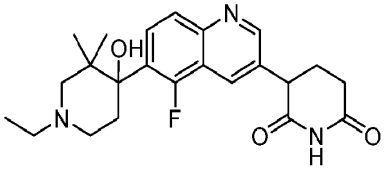
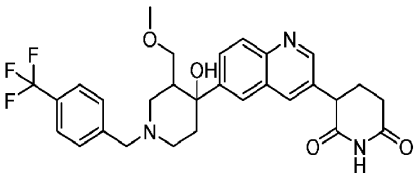
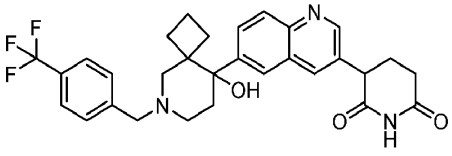
Cmpd No.	Compound Structure
I-1	
I-2	
I-3	
I-4	
I-5	
I-6	

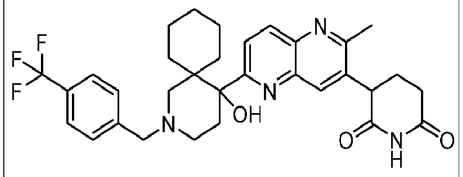
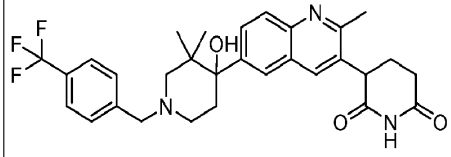
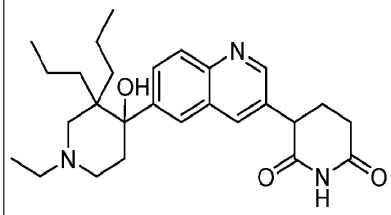
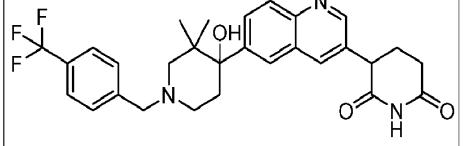
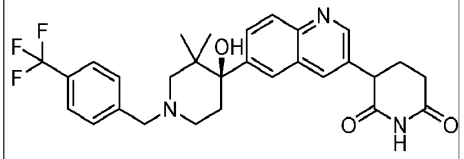
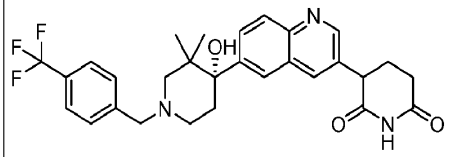
Cmpd No.	Compound Structure
I-7	
I-8	
I-9	
I-10	
I-11	
I-12	

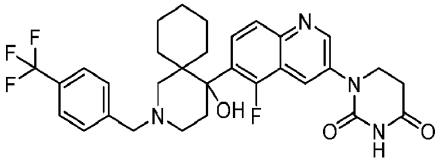
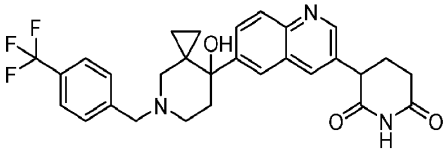
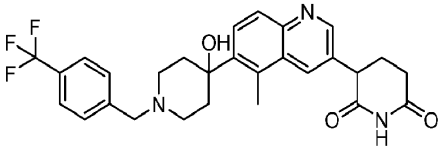
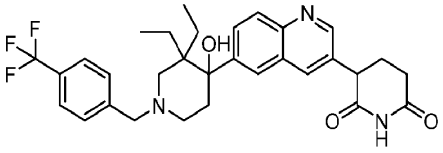
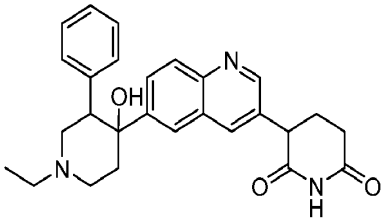
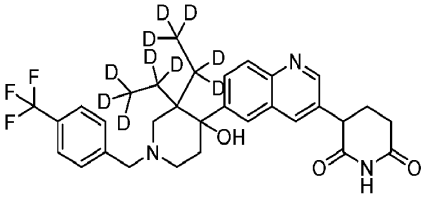
Cmpd No.	Compound Structure
I-13	
I-14	
I-15	
I-16	
I-17	
I-18	

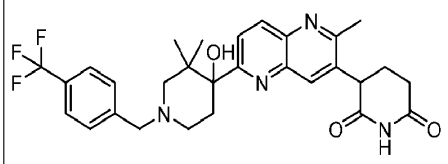
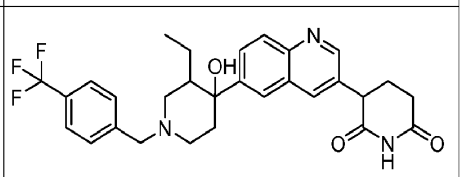
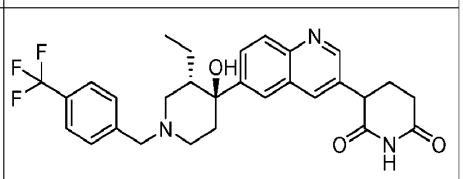
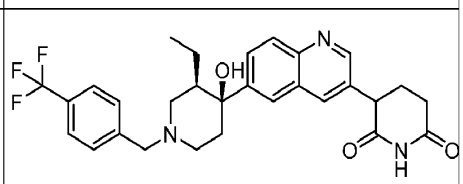
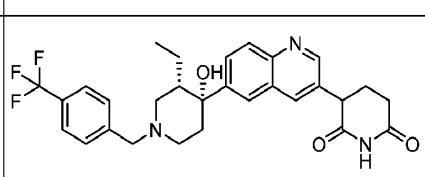
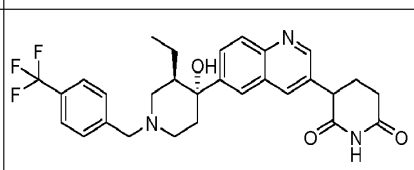
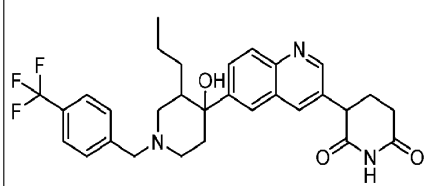
Cmpd No.	Compound Structure
I-19	
I-20	
I-21	
I-22	
I-23	
I-24	

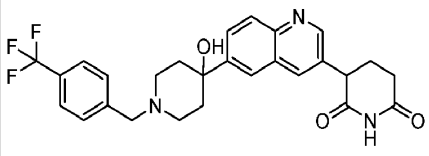
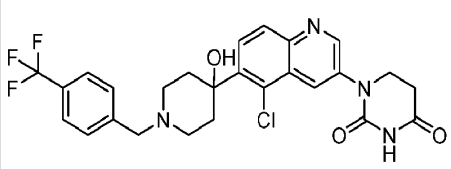
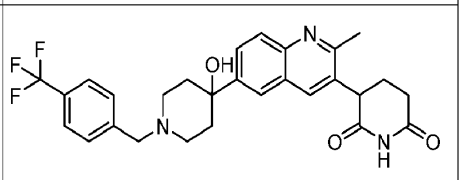
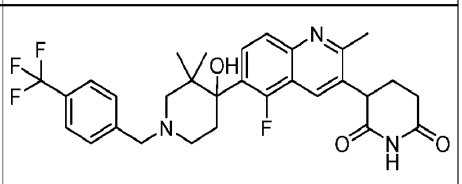
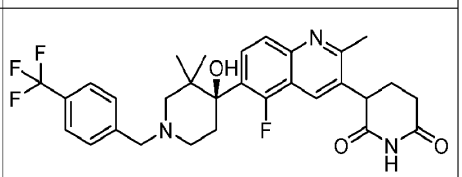
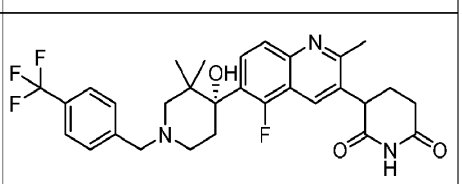
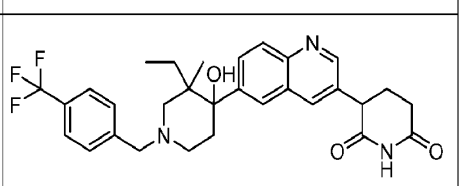
Cmpd No.	Compound Structure
I-25	
I-26	
I-27	
I-28	
I-29	
I-30	

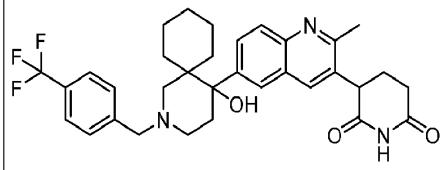
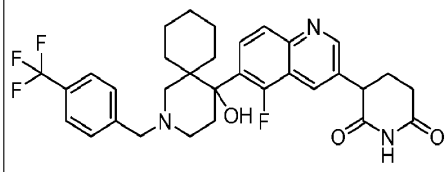
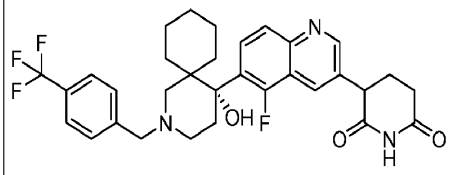
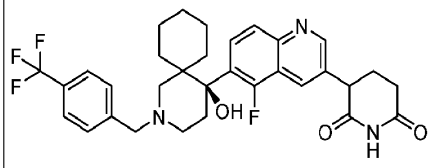
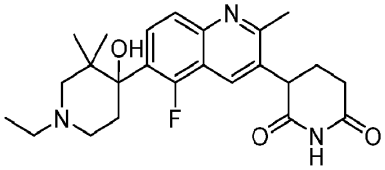
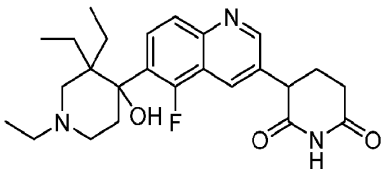
Cmpd No.	Compound Structure
I-31	
I-32	
I-33	
I-34	
I-35	
I-36	

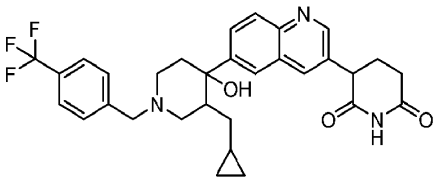
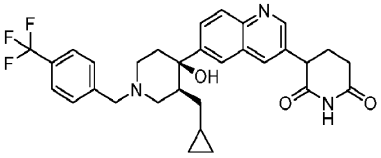
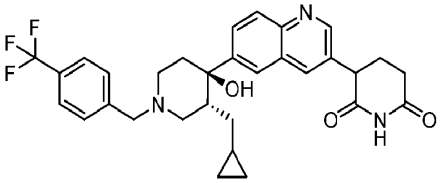
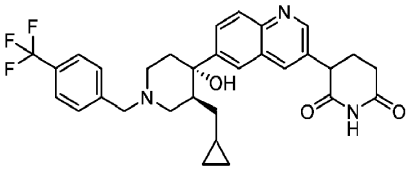
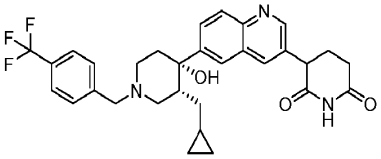
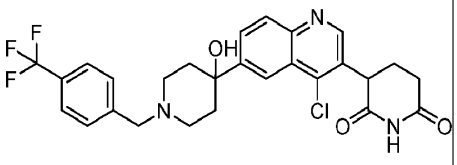
Cmpd No.	Compound Structure
I-37	
I-38	
I-39	
I-40	
I-41	
I-42	

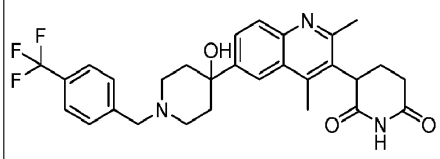
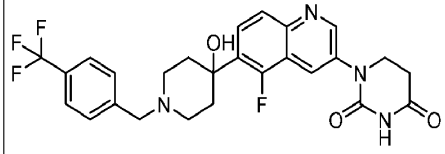
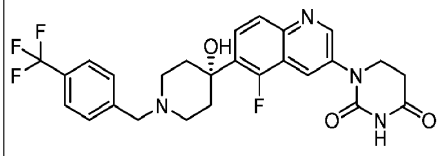
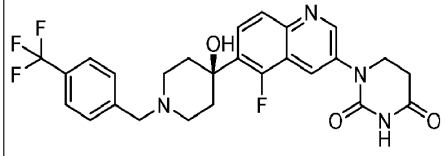
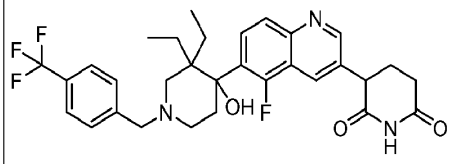
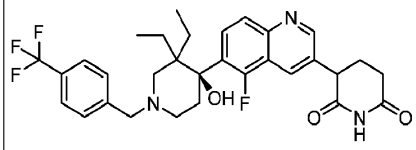
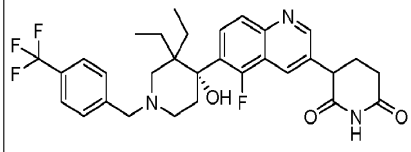
Cmpd No.	Compound Structure
I-43	
I-44	
I-45	
I-46	
I-47	
I-48	

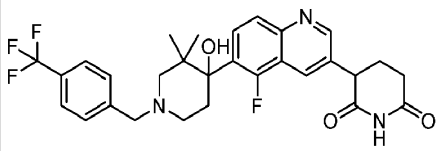
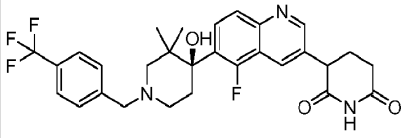
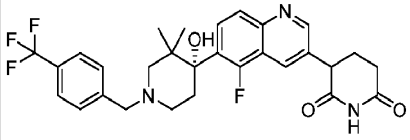
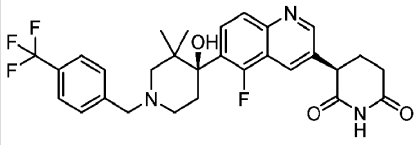
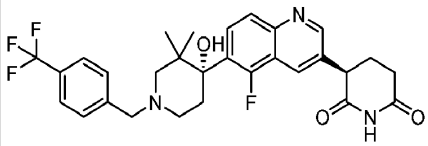
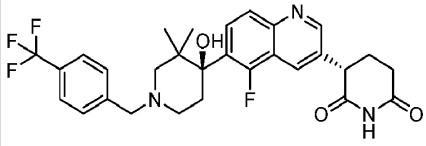
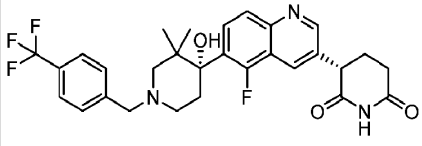
Cmpd No.	Compound Structure
I-49	
I-50	
I-51	
I-52	
I-53	
I-54	
I-55	

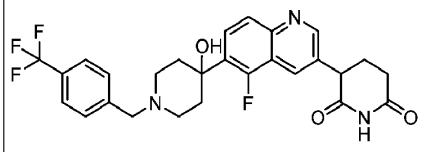
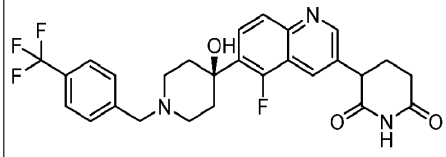
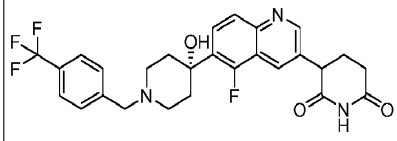
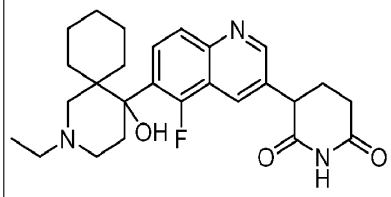
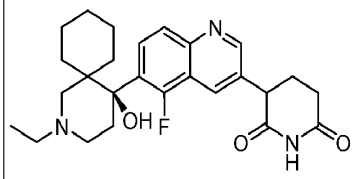
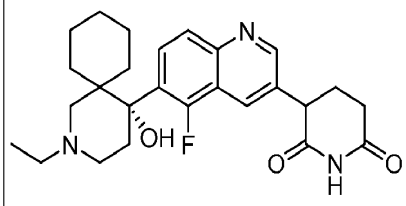
Cmpd No.	Compound Structure
I-56	
I-57	
I-58	
I-59	
I-60	
I-61	
I-62	

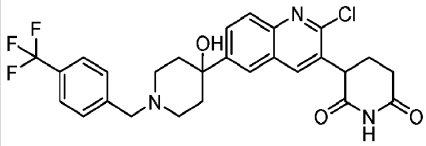
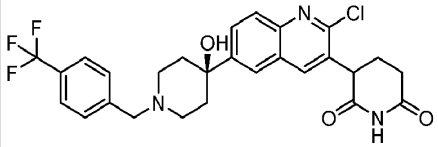
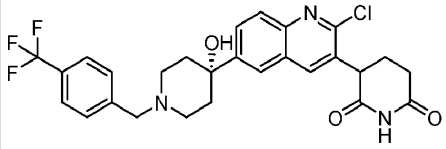
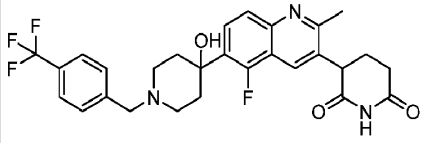
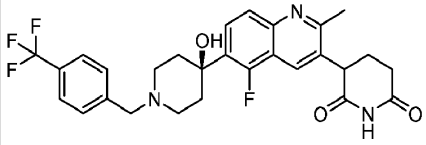
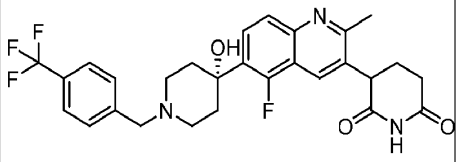
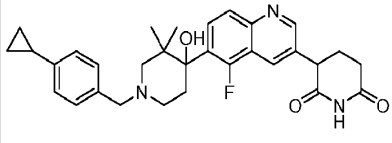
Cmpd No.	Compound Structure
I-63	
I-64	
I-65	
I-66	
I-67	
I-68	

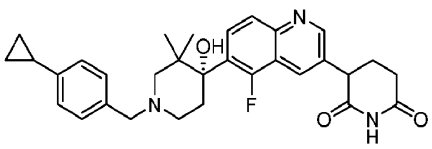
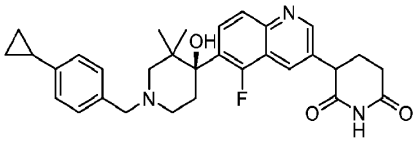
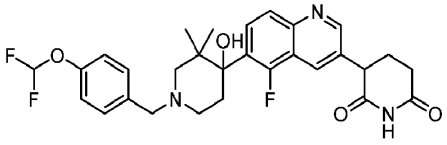
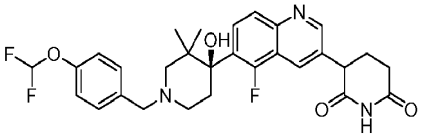
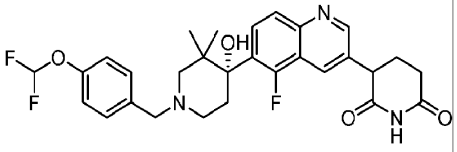
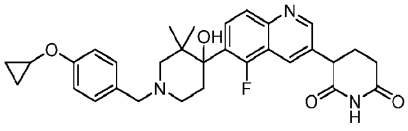
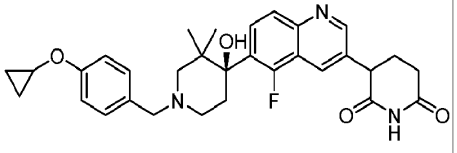
Cmpd No.	Compound Structure
I-69	
I-70	
I-71	
I-72	
I-73	
I-74	

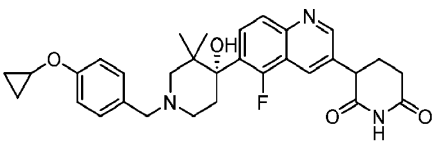
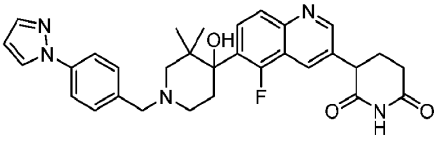
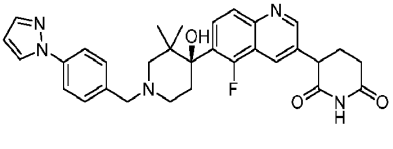
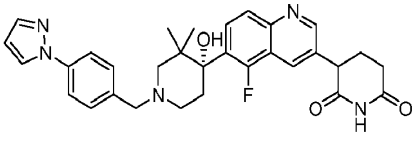
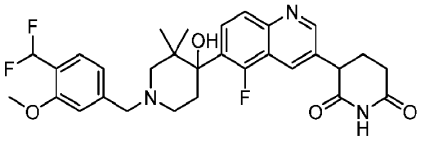
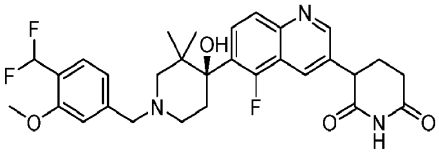
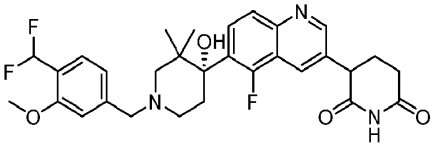
Cmpd No.	Compound Structure
I-75	
I-76	
I-77	
I-78	
I-79	
I-80	
I-81	

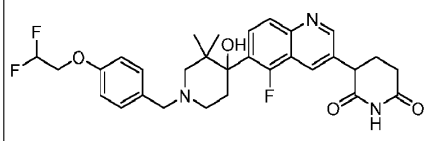
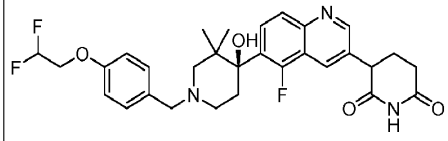
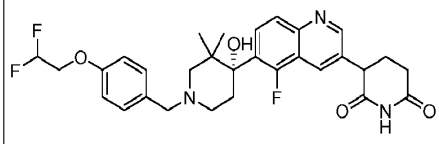
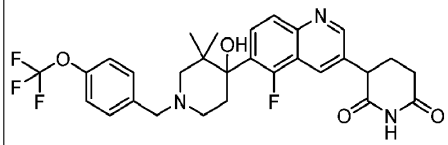
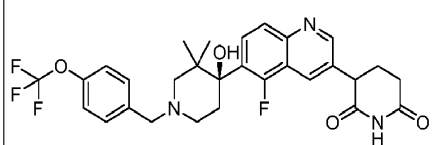
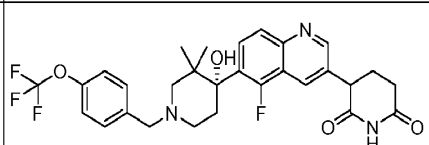
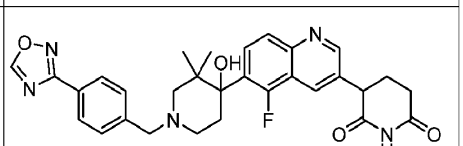
Cmpd No.	Compound Structure
I-82	
I-83	
I-84	
I-85	
I-86	
I-87	
I-88	

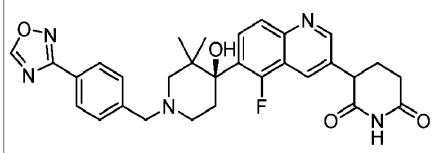
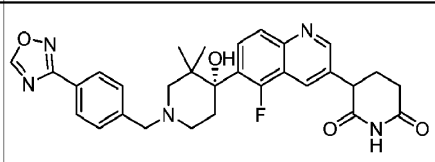
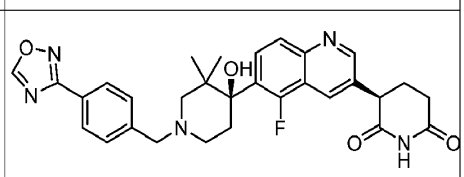
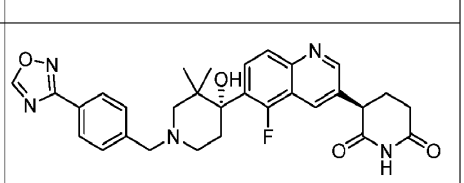
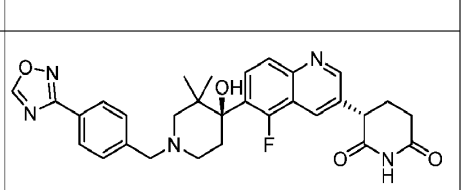
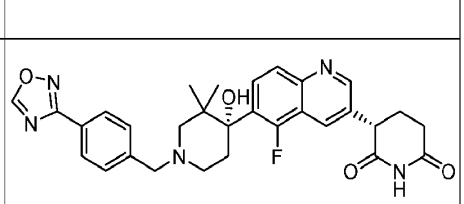
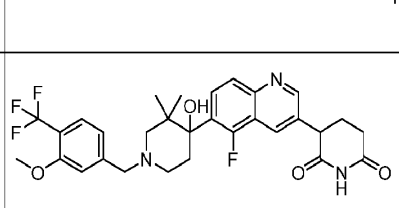
Cmpd No.	Compound Structure
I-89	
I-90	
I-91	
I-92	
I-93	
I-94	

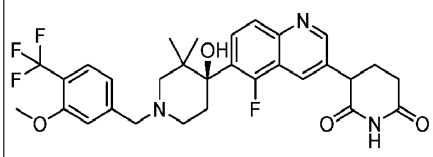
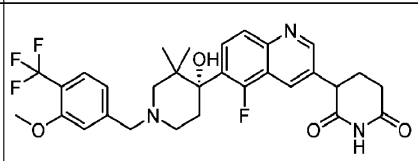
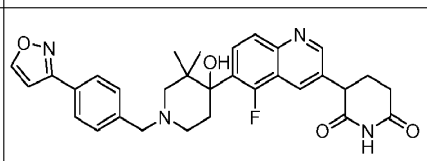
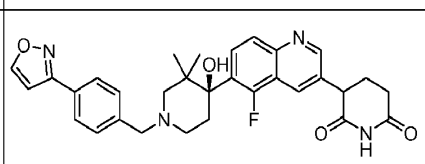
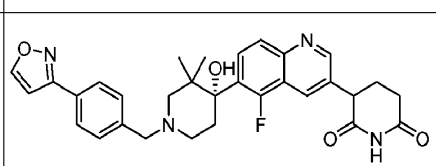
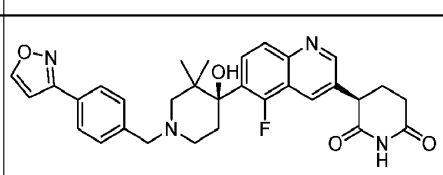
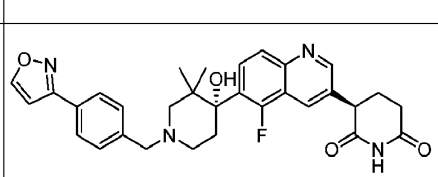
Cmpd No.	Compound Structure
I-95	
I-96	
I-97	
I-98	
I-99	
I-100	
I-101	

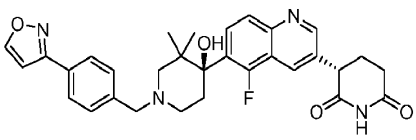
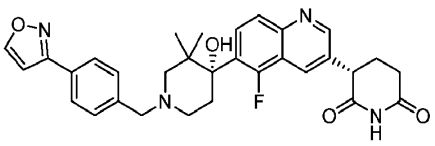
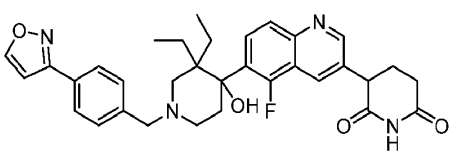
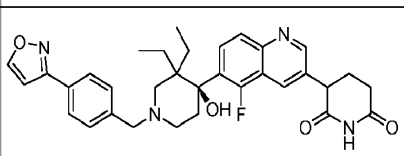
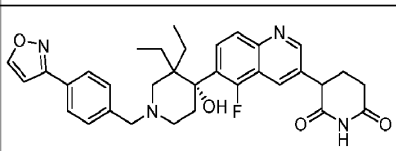
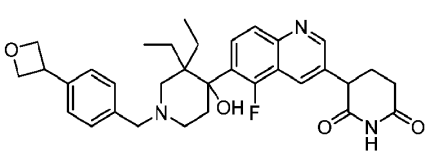
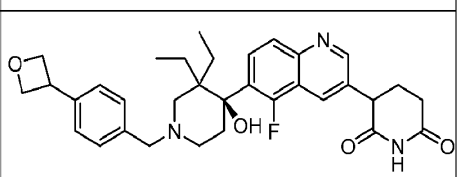
Cmpd No.	Compound Structure
I-102	
I-103	
I-104	
I-105	
I-106	
I-107	
I-108	

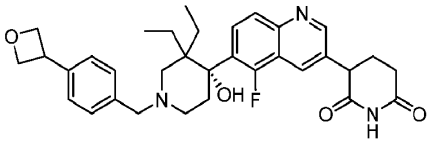
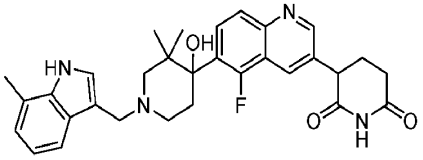
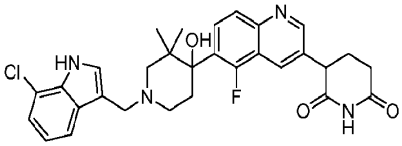
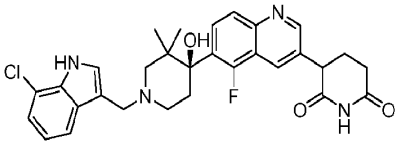
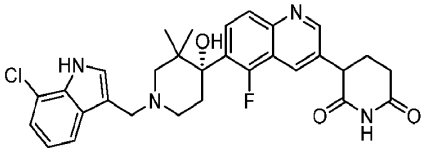
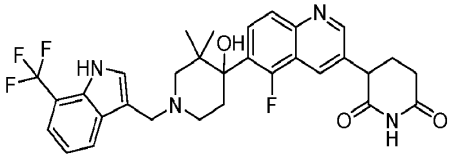
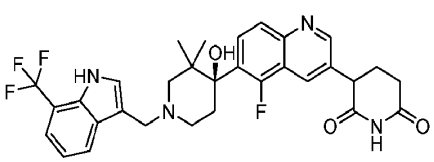
Cmpd No.	Compound Structure
I-109	
I-110	
I-111	
I-112	
I-113	
I-114	
I-115	

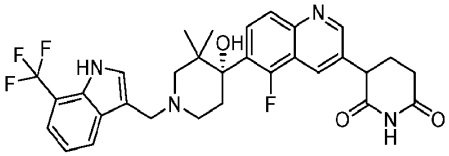
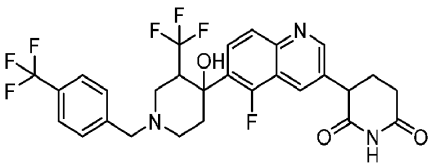
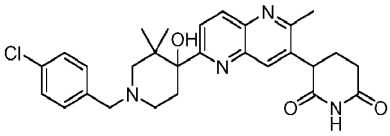
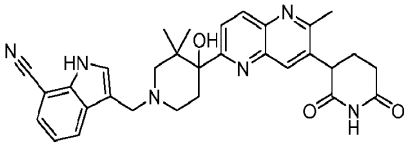
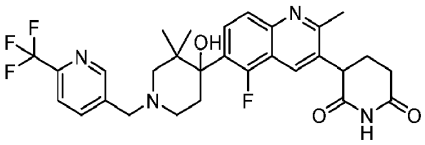
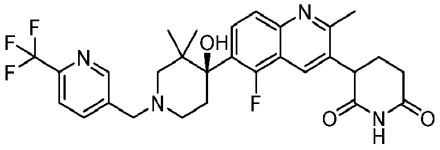
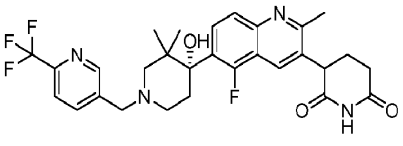
Cmpd No.	Compound Structure
I-116	
I-117	
I-118	
I-119	
I-120	
I-121	
I-122	

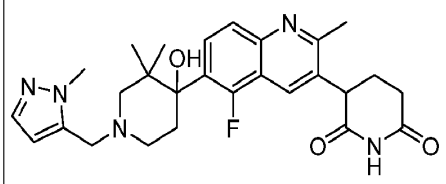
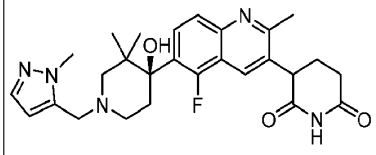
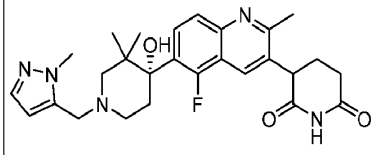
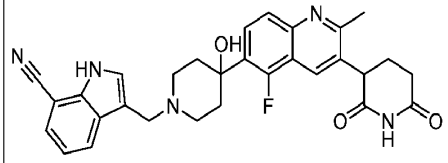
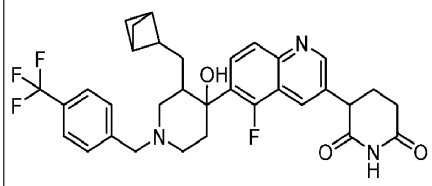
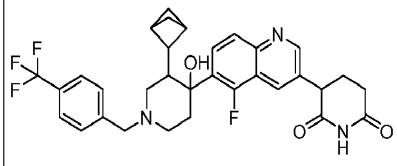
Cmpd No.	Compound Structure
I-123	
I-124	
I-125	
I-126	
I-127	
I-128	
I-129	

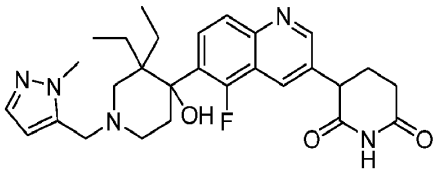
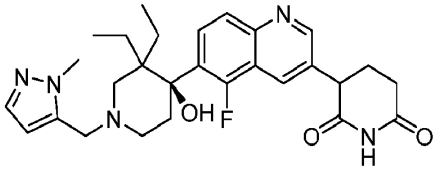
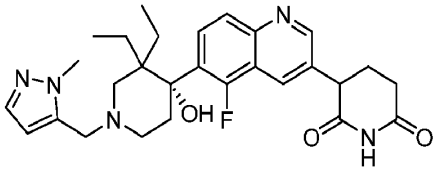
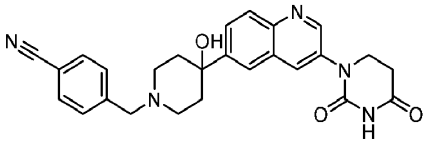
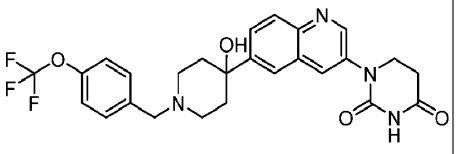
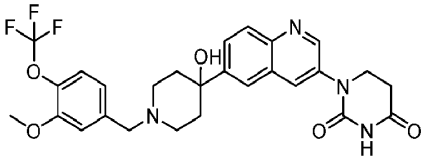
Cmpd No.	Compound Structure
I-130	
I-131	
I-132	
I-133	
I-134	
I-135	
I-136	

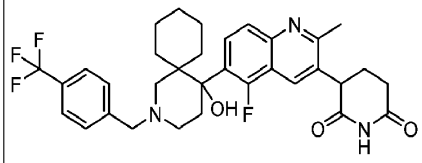
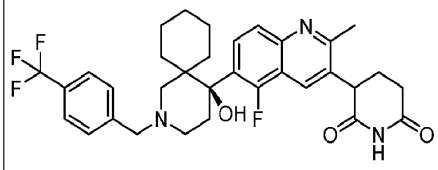
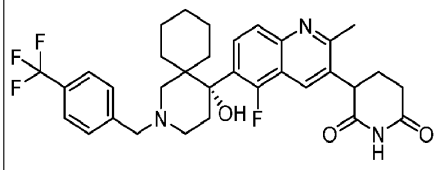
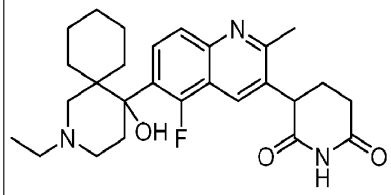
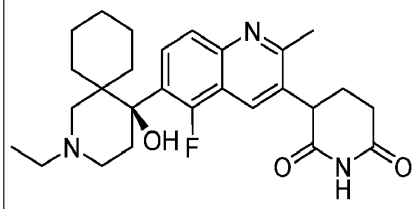
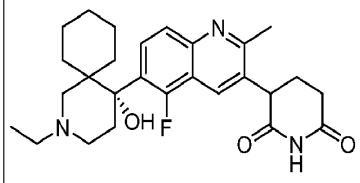
Cmpd No.	Compound Structure
I-137	
I-138	
I-139	
I-140	
I-141	
I-142	
I-143	

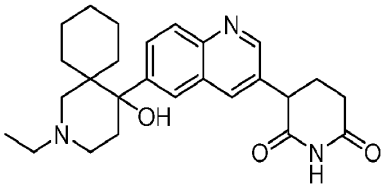
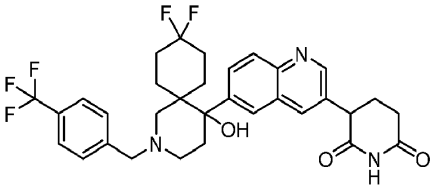
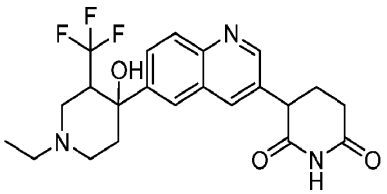
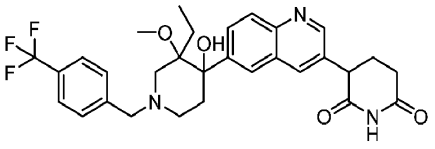
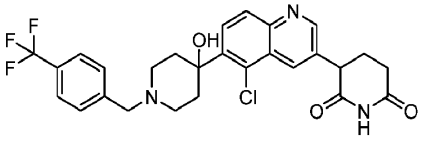
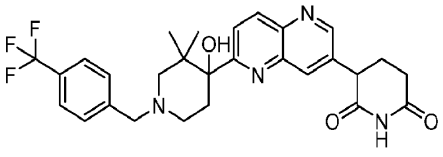
Cmpd No.	Compound Structure
I-144	
I-145	
I-146	
I-147	
I-148	
I-149	
I-150	

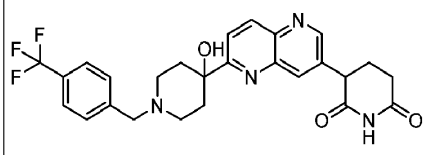
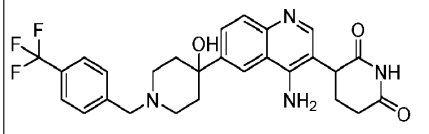
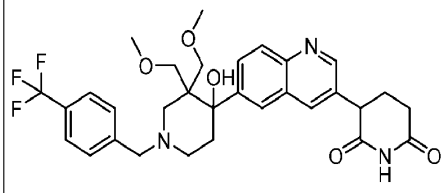
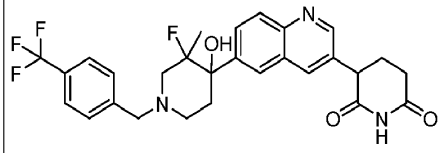
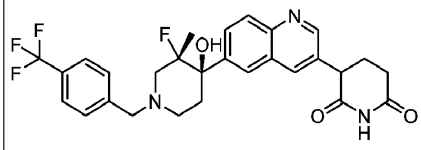
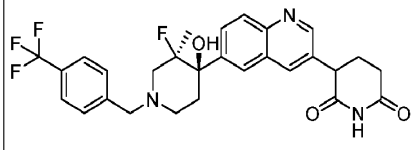
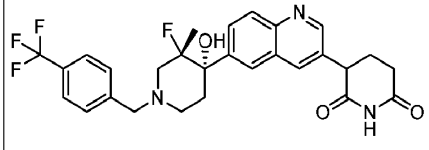
Cmpd No.	Compound Structure
I-151	
I-152	
I-153	
I-154	
I-155	
I-156	
I-157	

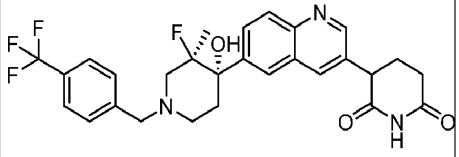
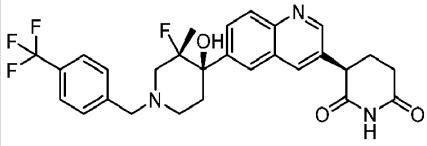
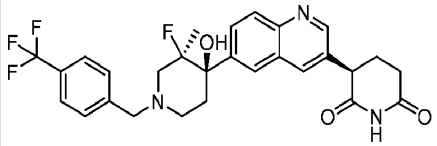
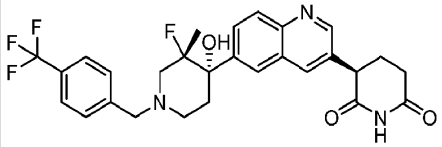
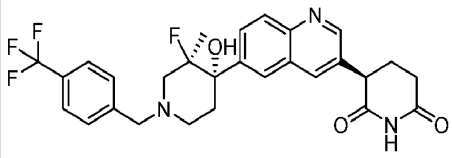
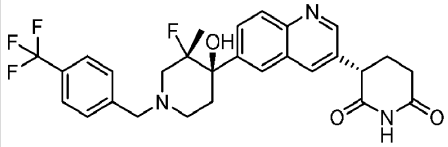
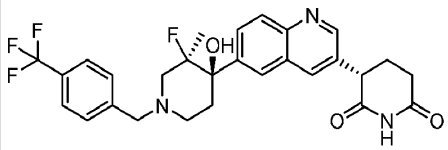
Cmpd No.	Compound Structure
I-158	
I-159	
I-160	
I-161	
I-162	
I-163	

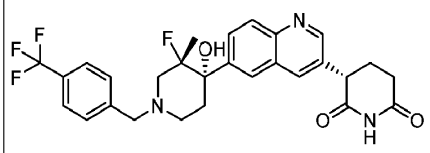
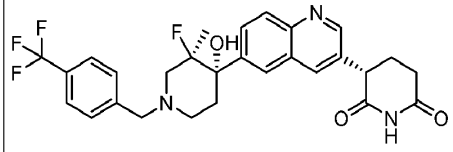
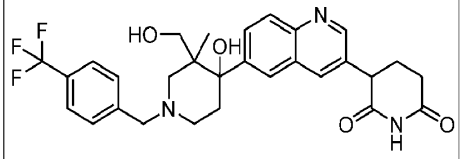
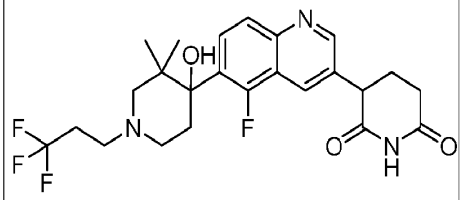
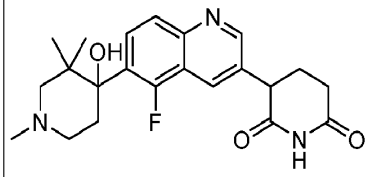
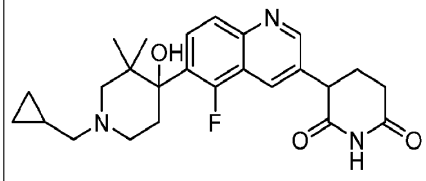
Cmpd No.	Compound Structure
I-164	
I-165	
I-166	
I-167	
I-168	
I-169	

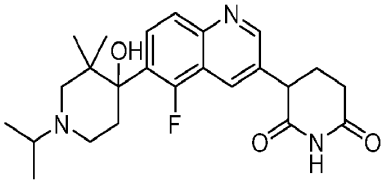
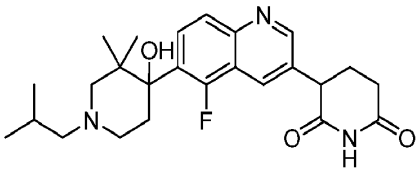
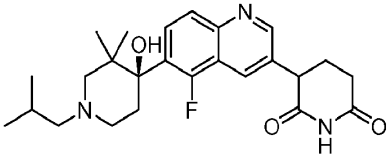
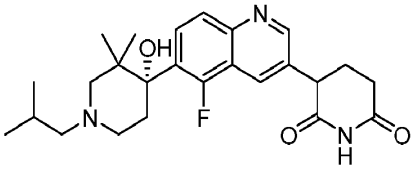
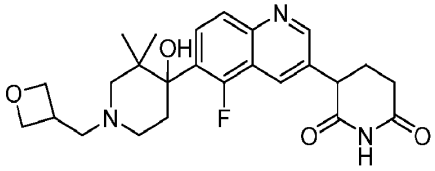
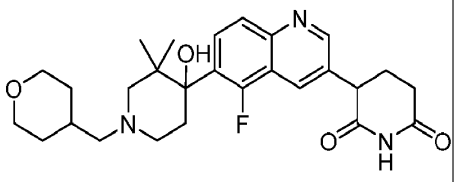
Cmpd No.	Compound Structure
I-170	
I-171	
I-172	
I-173	
I-174	
I-175	

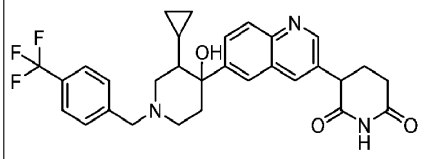
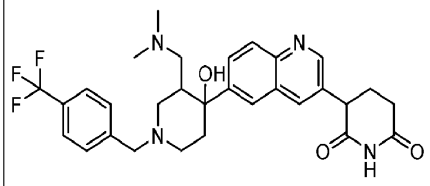
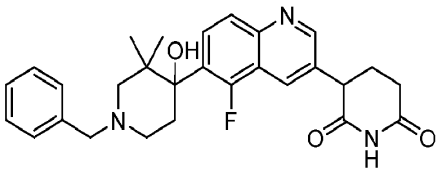
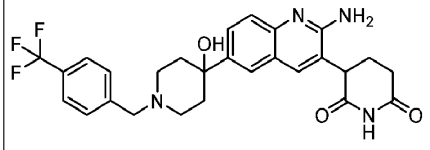
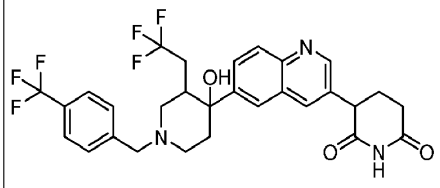
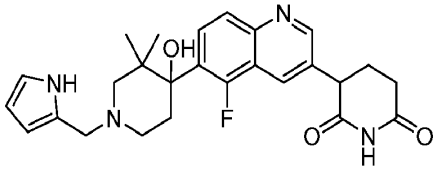
Cmpd No.	Compound Structure
I-176	
I-177	
I-178	
I-179	
I-180	
I-181	

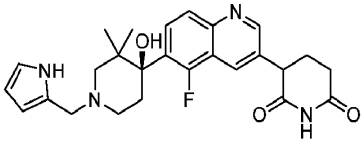
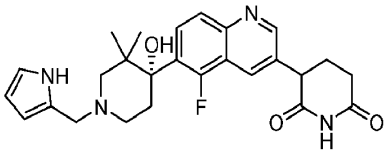
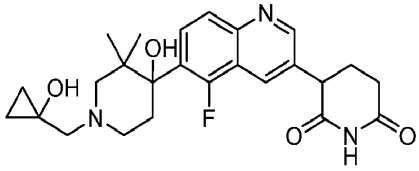
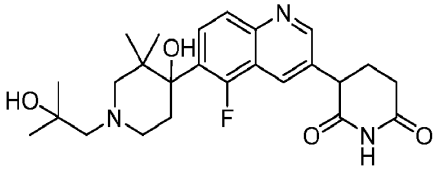
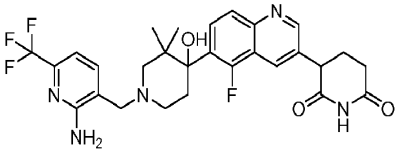
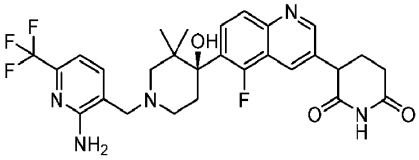
Cmpd No.	Compound Structure
I-182	
I-183	
I-184	
I-185	
I-186	
I-187	
I-188	

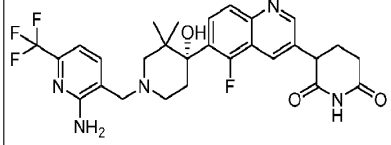
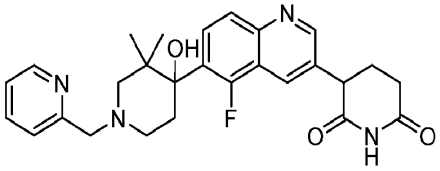
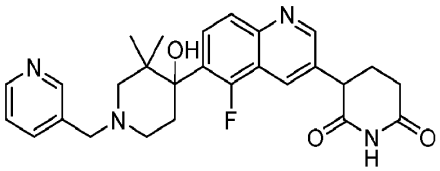
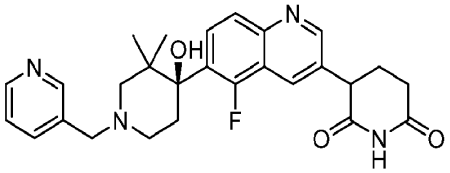
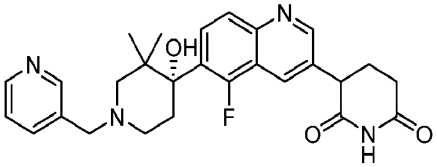
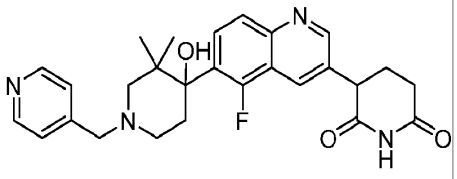
Cmpd No.	Compound Structure
I-189	
I-190	
I-191	
I-192	
I-193	
I-194	
I-195	

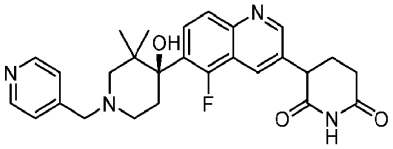
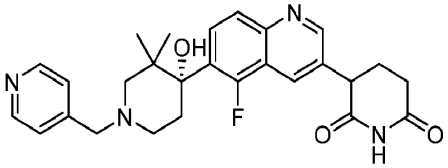
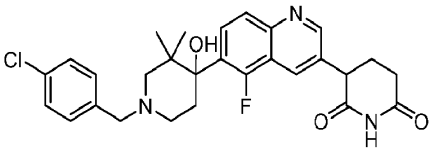
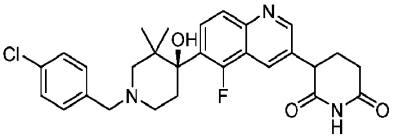
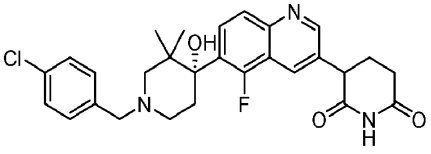
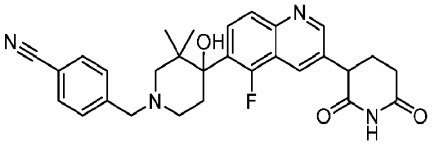
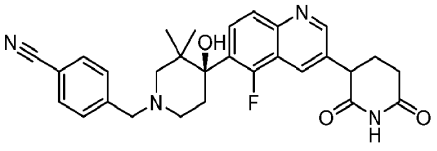
Cmpd No.	Compound Structure
I-196	
I-197	
I-198	
I-199	
I-200	
I-201	

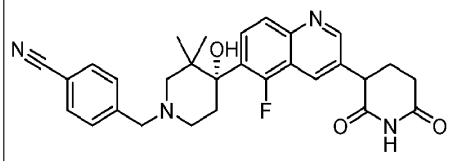
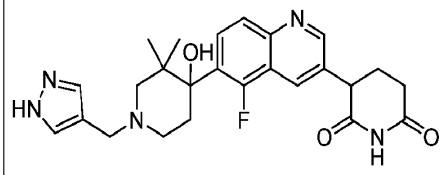
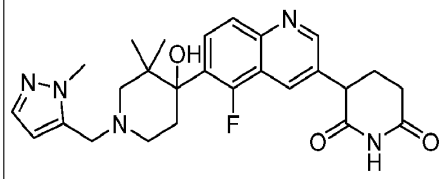
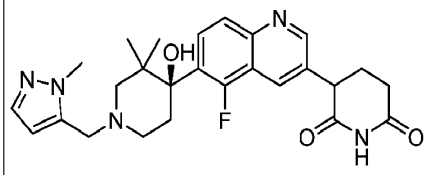
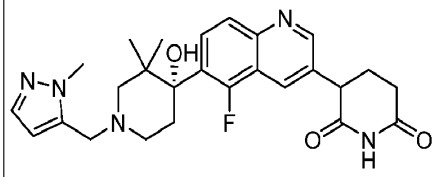
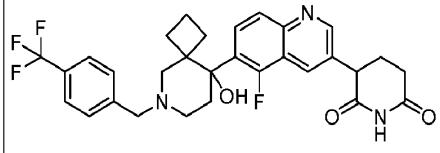
Cmpd No.	Compound Structure
I-202	
I-203	
I-204	
I-205	
I-206	
I-207	

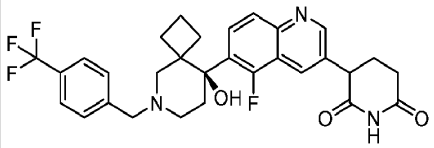
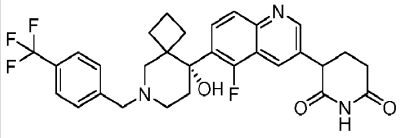
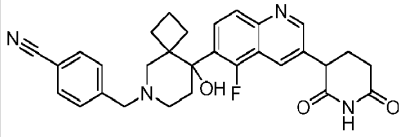
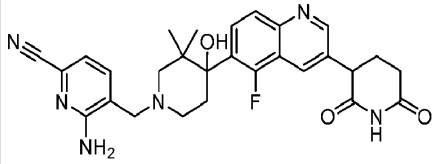
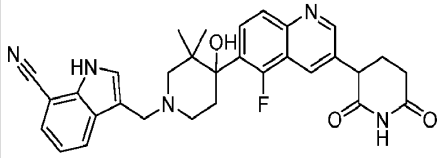
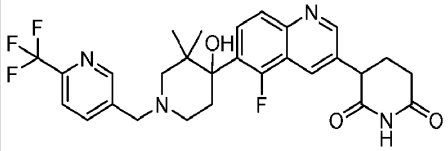
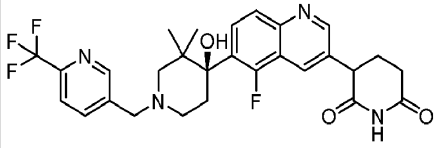
Cmpd No.	Compound Structure
I-208	
I-209	
I-210	
I-211	
I-212	
I-213	

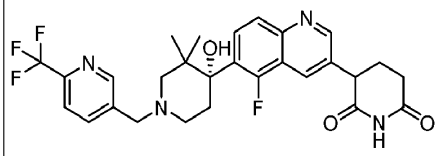
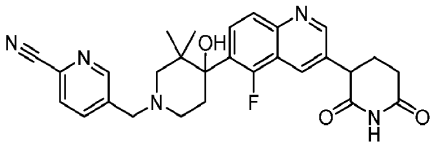
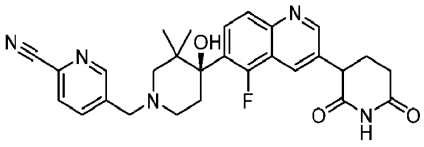
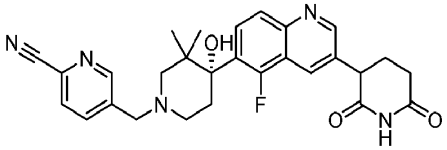
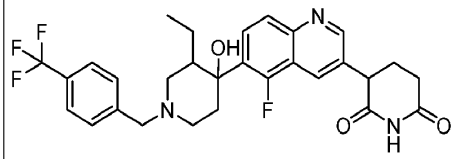
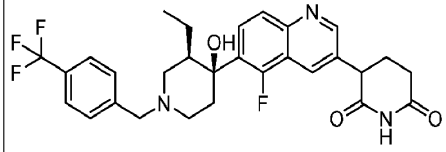
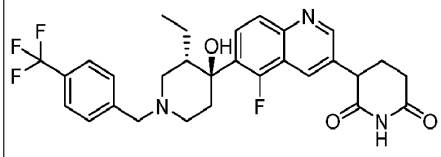
Cmpd No.	Compound Structure
I-214	
I-215	
I-216	
I-217	
I-218	
I-219	

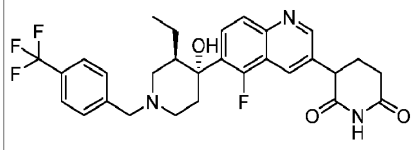
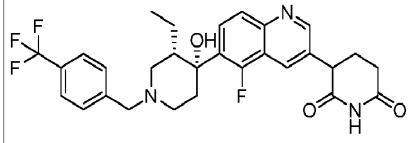
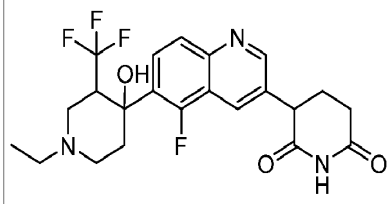
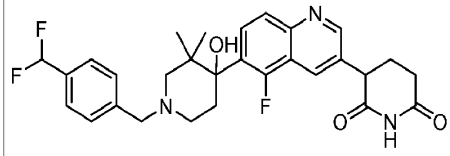
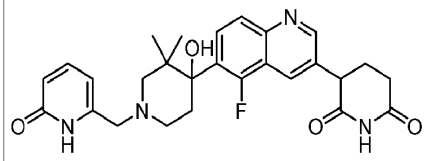
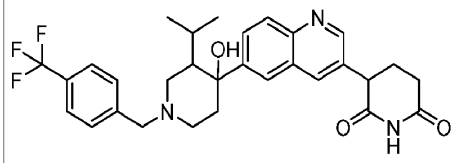
Cmpd No.	Compound Structure
I-220	
I-221	
I-222	
I-223	
I-224	
I-225	

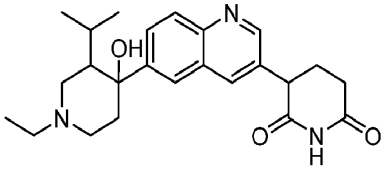
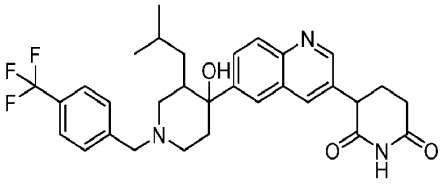
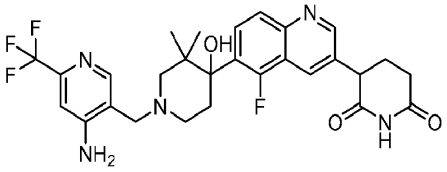
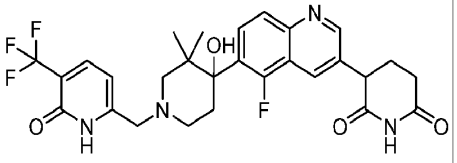
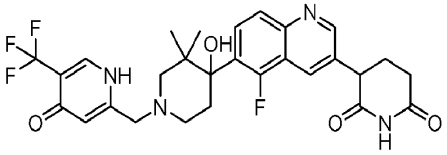
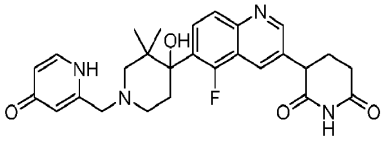
Cmpd No.	Compound Structure
I-226	
I-227	
I-228	
I-229	
I-230	
I-231	
I-232	

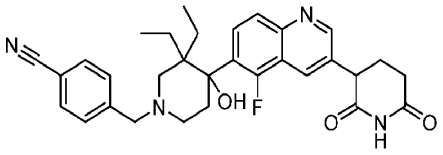
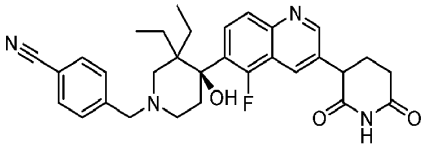
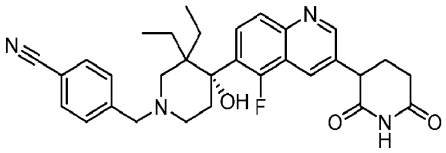
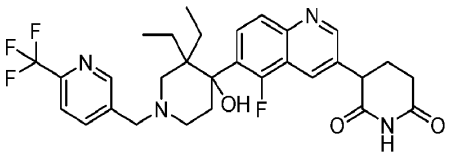
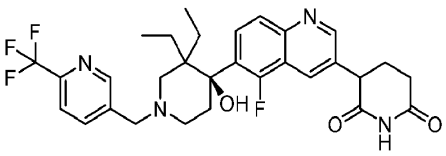
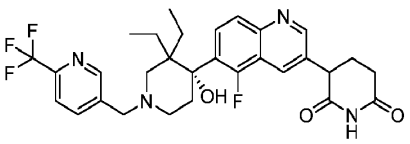
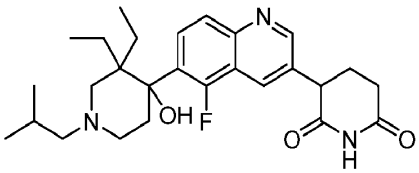
Cmpd No.	Compound Structure
I-233	
I-234	
I-235	
I-236	
I-237	
I-238	

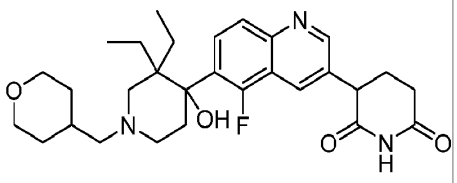
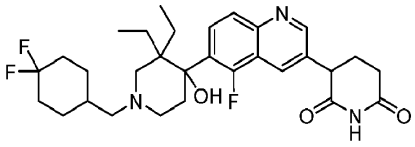
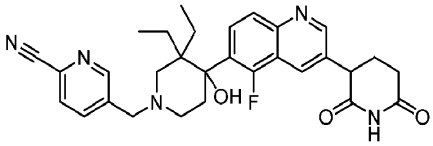
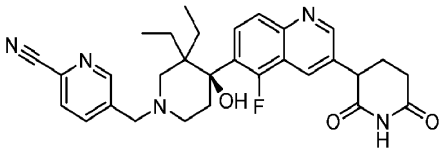
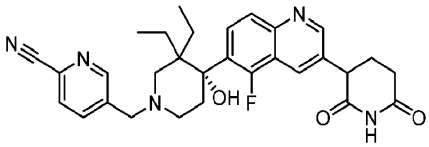
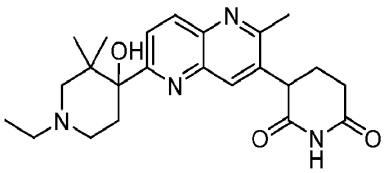
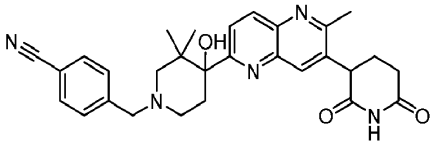
Cmpd No.	Compound Structure
I-239	
I-240	
I-241	
I-242	
I-243	
I-244	
I-245	

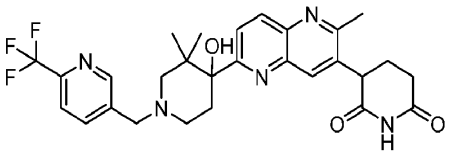
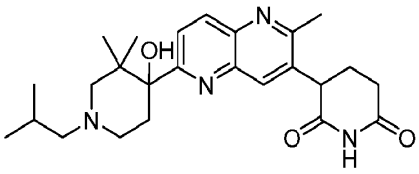
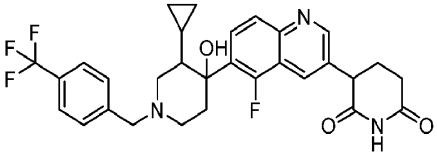
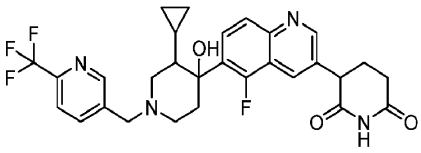
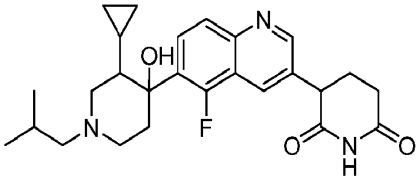
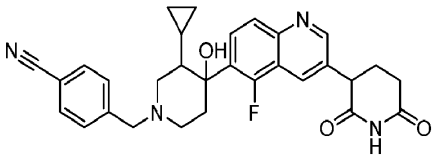
Cmpd No.	Compound Structure
I-246	
I-247	
I-248	
I-249	
I-250	
I-251	
I-252	

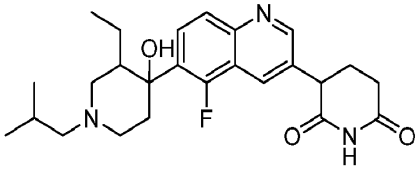
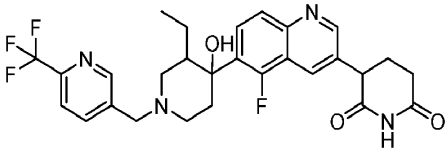
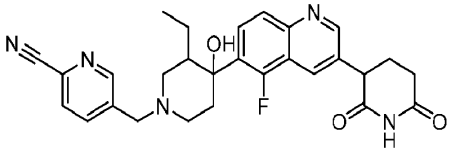
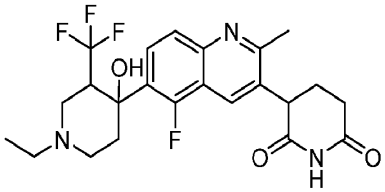
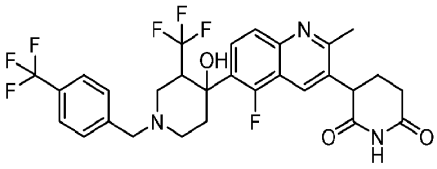
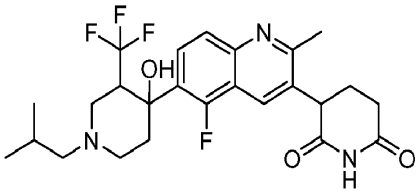
Cmpd No.	Compound Structure
I-253	
I-254	
I-255	
I-256	
I-257	
I-258	

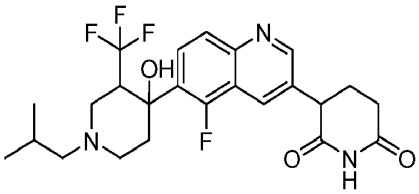
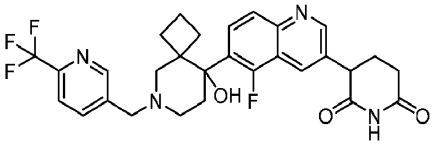
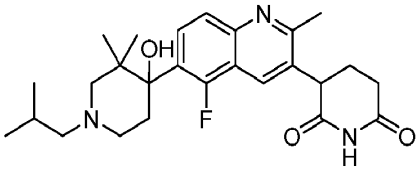
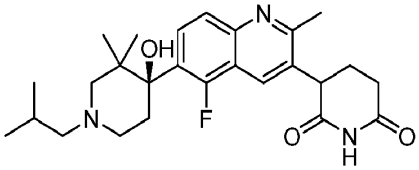
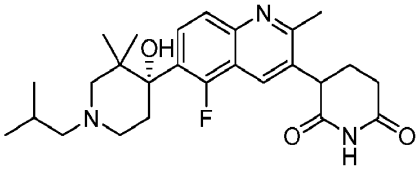
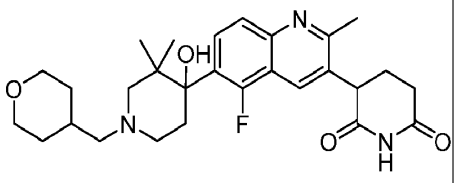
Cmpd No.	Compound Structure
I-259	
I-260	
I-261	
I-262	
I-263	
I-264	

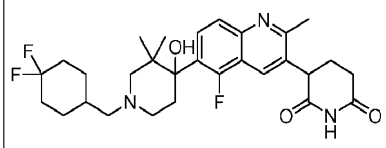
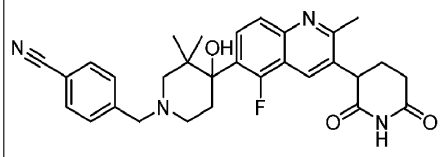
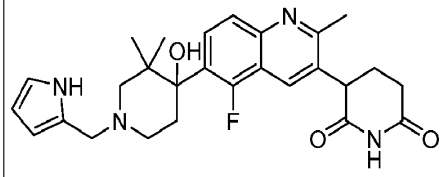
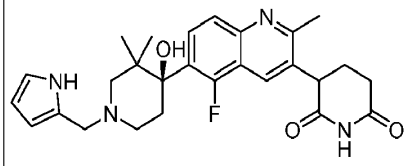
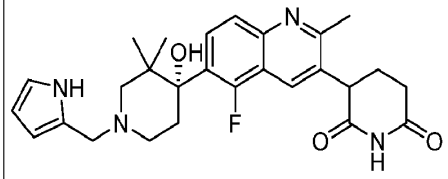
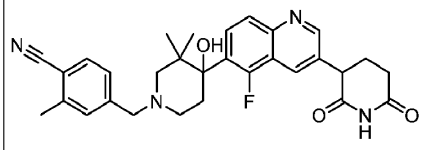
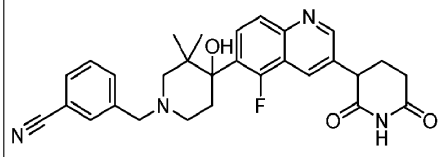
Cmpd No.	Compound Structure
I-265	
I-266	
I-267	
I-268	
I-269	
I-270	
I-271	

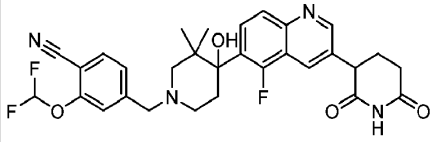
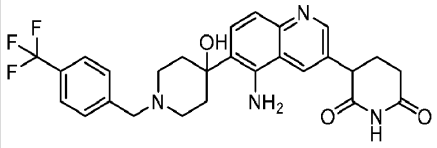
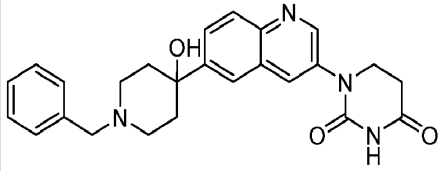
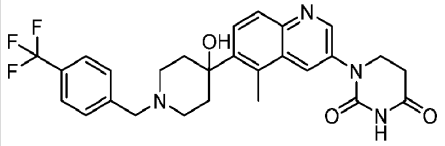
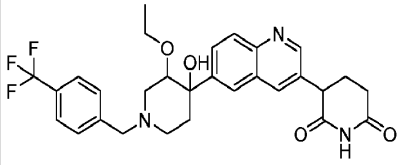
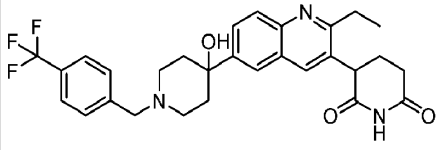
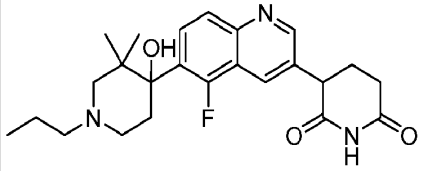
Cmpd No.	Compound Structure
I-272	
I-273	
I-274	
I-275	
I-276	
I-277	
I-278	

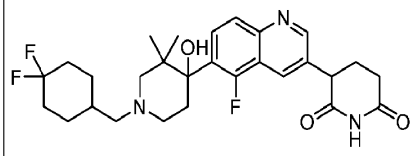
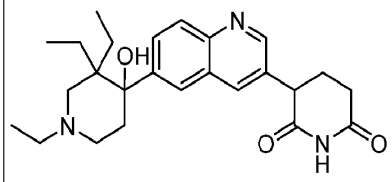
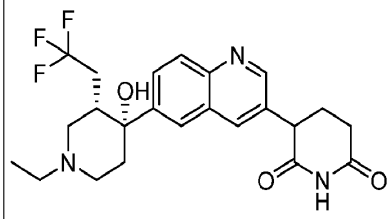
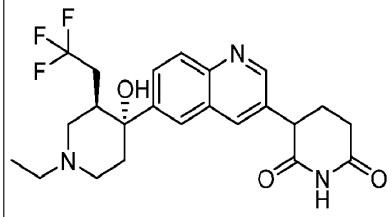
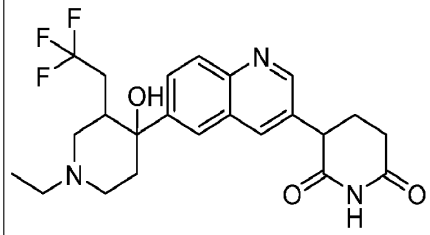
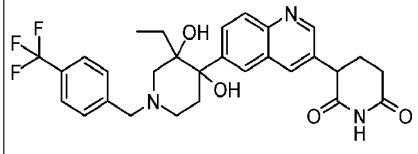
Cmpd No.	Compound Structure
I-279	
I-280	
I-281	
I-282	
I-283	
I-284	

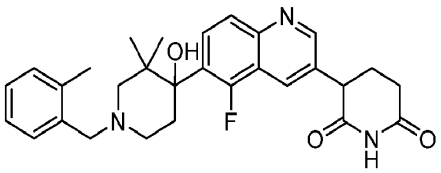
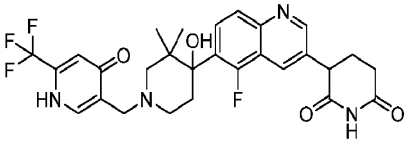
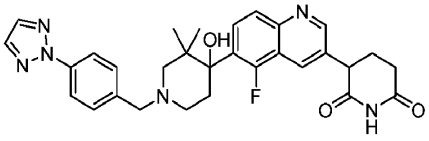
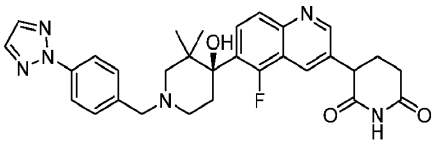
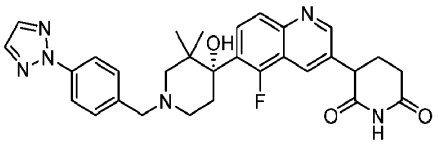
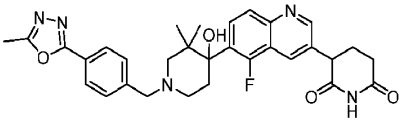
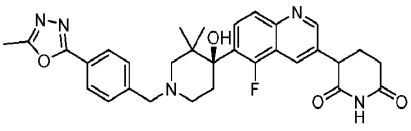
Cmpd No.	Compound Structure
I-285	
I-286	
I-287	
I-288	
I-289	
I-290	

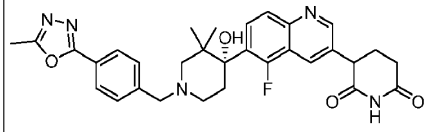
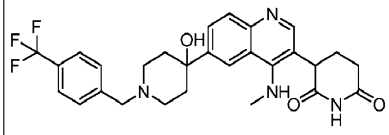
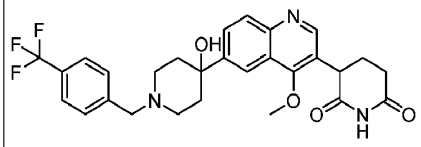
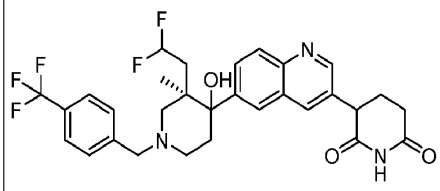
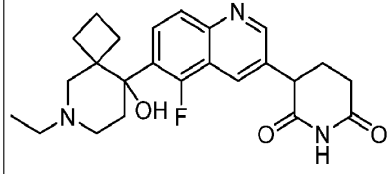
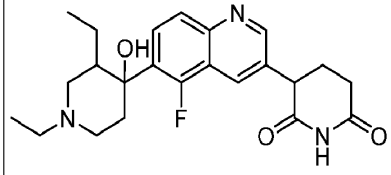
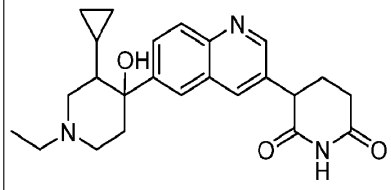
Cmpd No.	Compound Structure
I-291	
I-292	
I-293	
I-294	
I-295	
I-296	

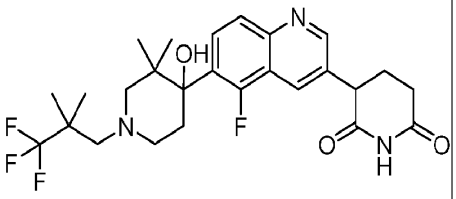
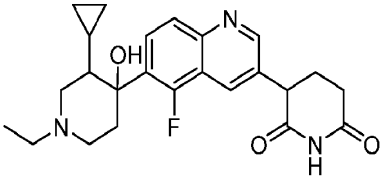
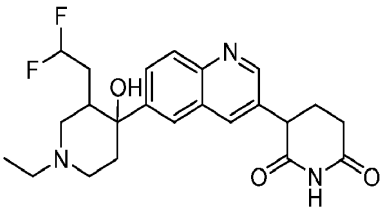
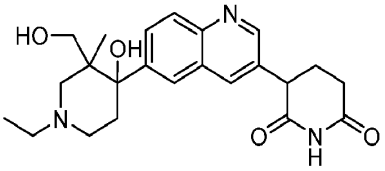
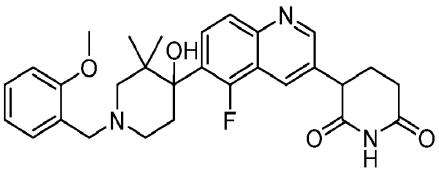
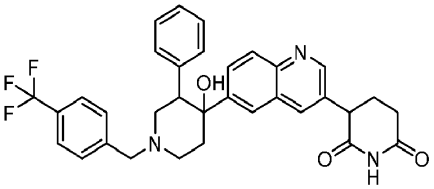
Cmpd No.	Compound Structure
I-297	
I-298	
I-299	
I-300	
I-301	
I-302	
I-303	

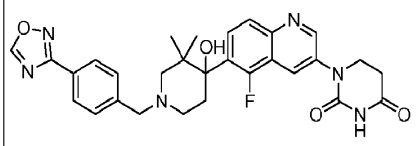
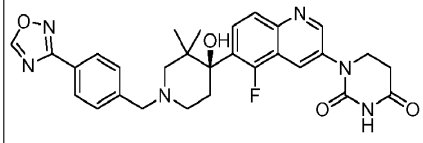
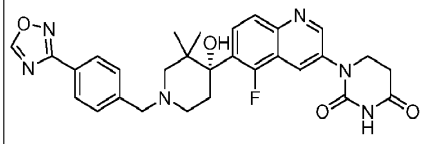
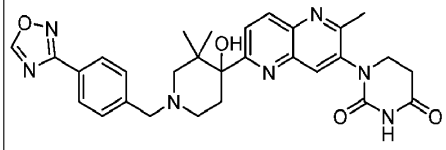
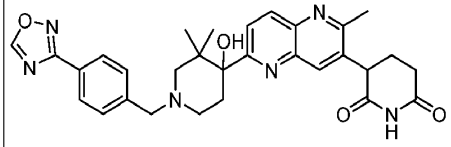
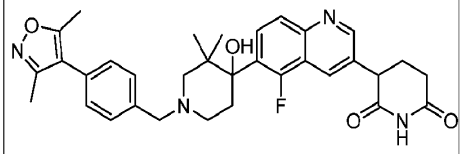
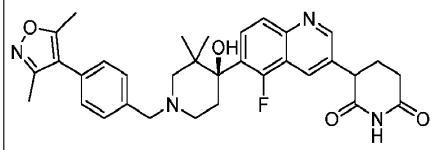
Cmpd No.	Compound Structure
I-304	
I-305	
I-306	
I-307	
I-308	
I-309	
I-310	

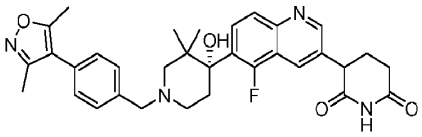
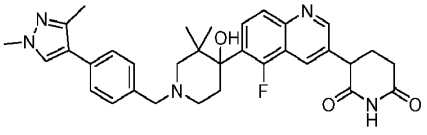
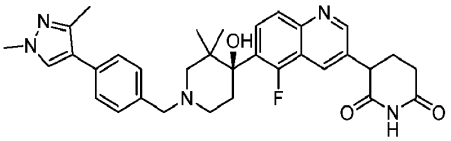
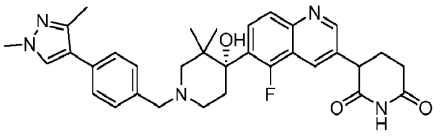
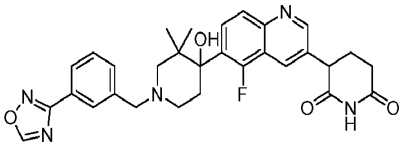
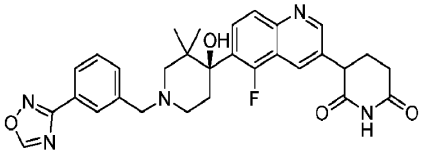
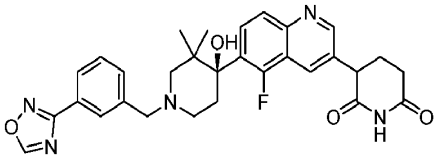
Cmpd No.	Compound Structure
I-311	
I-312	
I-313	
I-314	
I-315	
I-316	

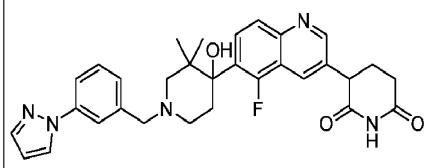
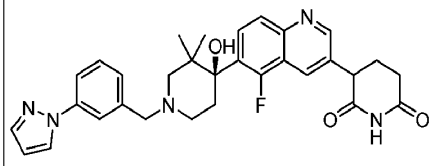
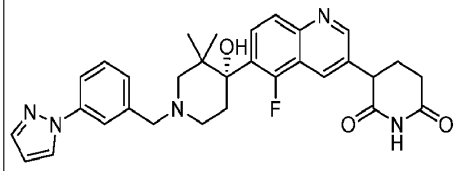
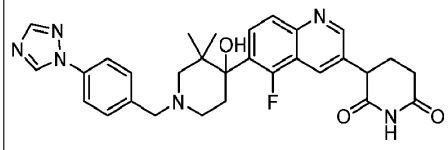
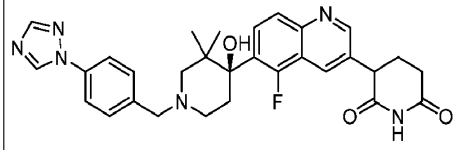
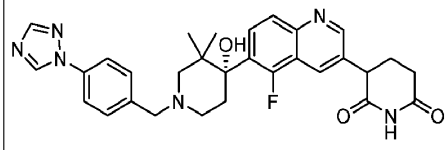
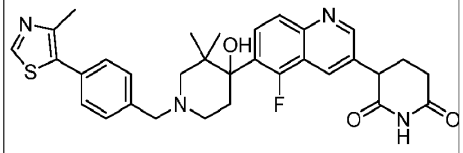
Cmpd No.	Compound Structure
I-317	
I-318	
I-319	
I-320	
I-321	
I-322	
I-323	

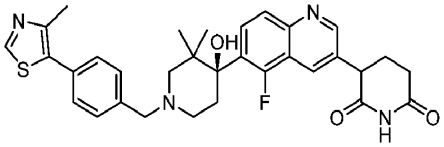
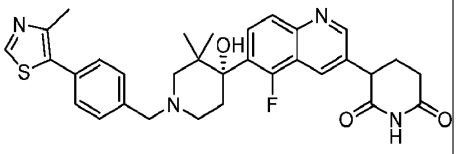
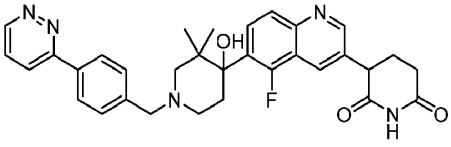
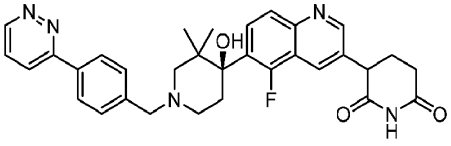
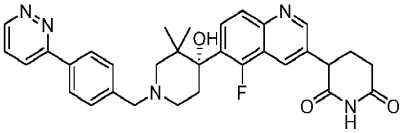
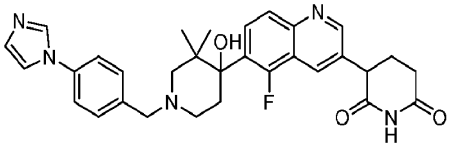
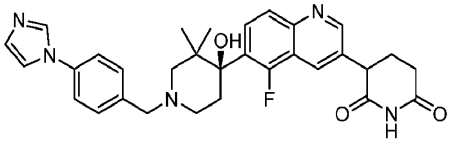
Cmpd No.	Compound Structure
I-324	
I-325	
I-326	
I-327	
I-328	
I-329	
I-330	

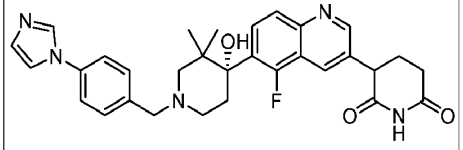
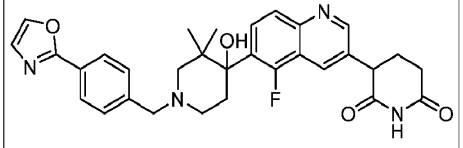
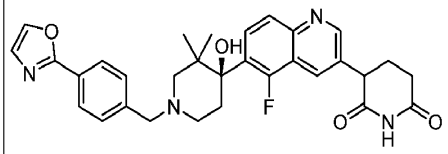
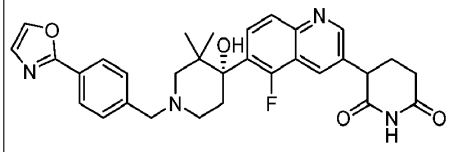
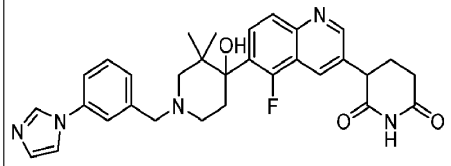
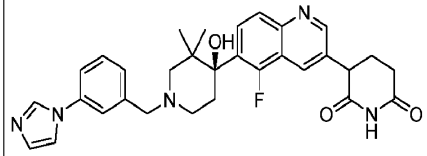
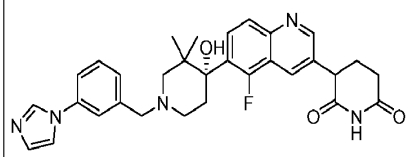
Cmpd No.	Compound Structure
I-331	
I-332	
I-333	
I-334	
I-335	
I-336	

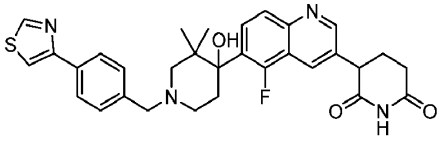
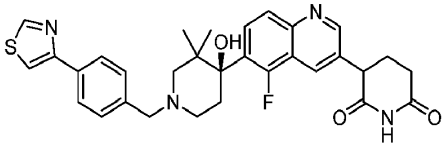
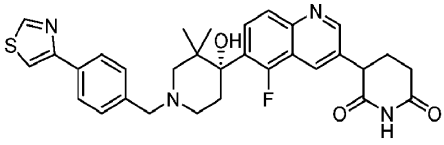
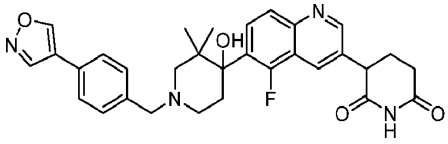
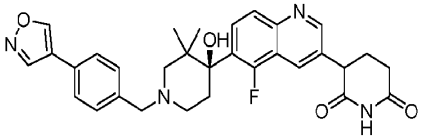
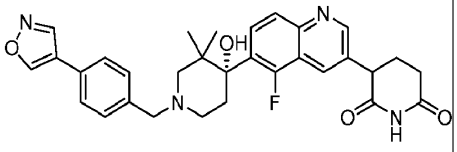
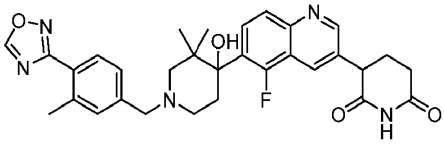
Cmpd No.	Compound Structure
I-337	
I-338	
I-339	
I-340	
I-341	
I-342	
I-343	

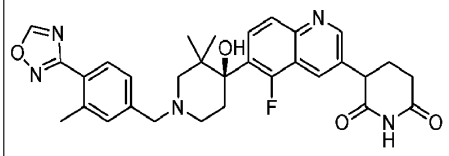
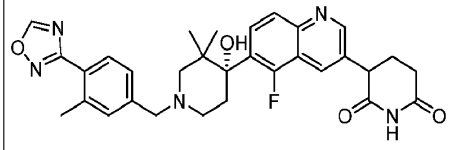
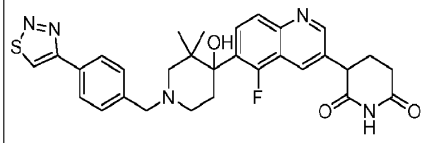
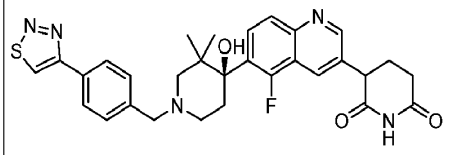
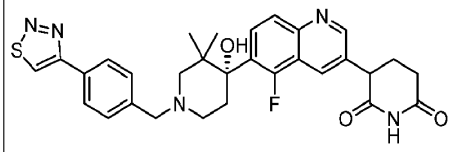
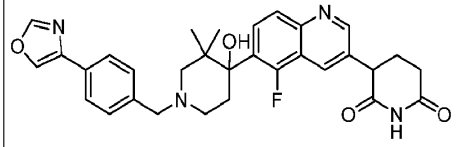
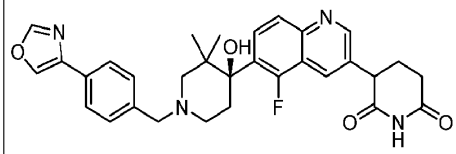
Cmpd No.	Compound Structure
I-344	
I-345	
I-346	
I-347	
I-348	
I-349	
I-350	

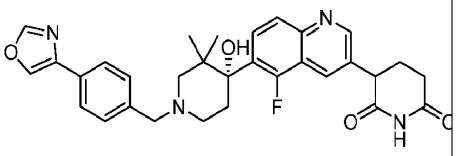
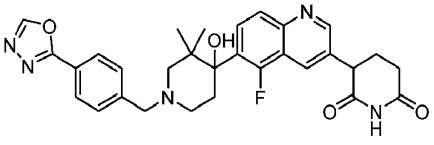
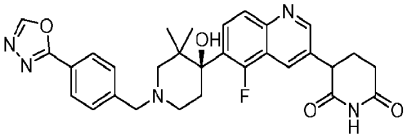
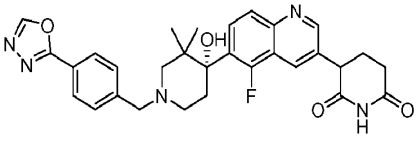
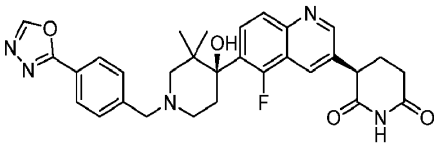
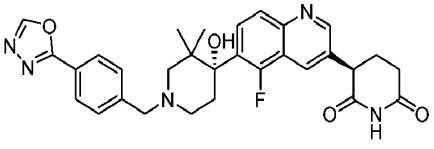
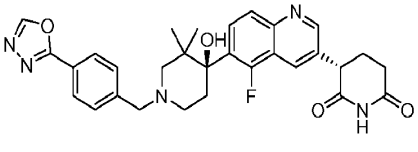
Cmpd No.	Compound Structure
I-351	
I-352	
I-353	
I-354	
I-355	
I-356	
I-357	

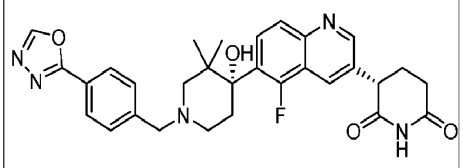
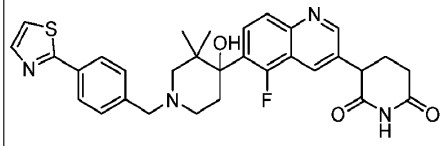
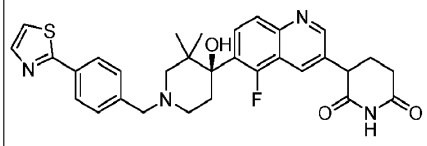
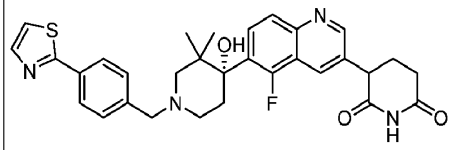
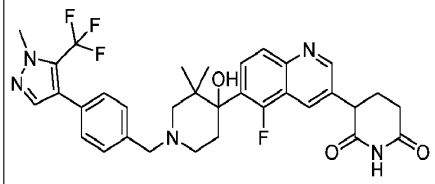
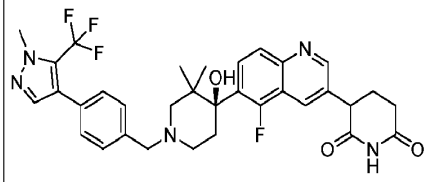
Cmpd No.	Compound Structure
I-358	
I-359	
I-360	
I-361	
I-362	
I-363	
I-364	

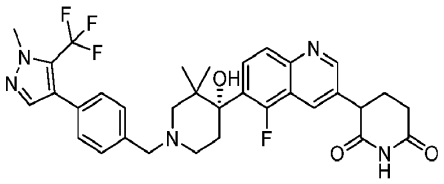
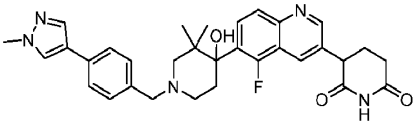
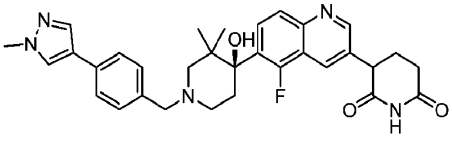
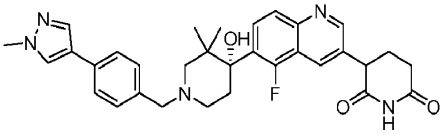
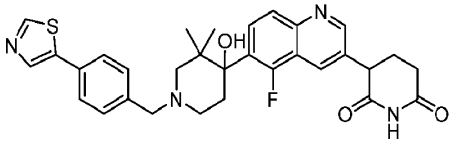
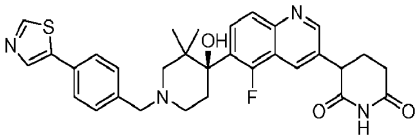
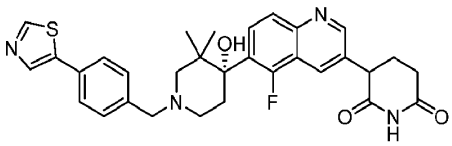
Cmpd No.	Compound Structure
I-365	
I-366	
I-367	
I-368	
I-369	
I-370	
I-371	

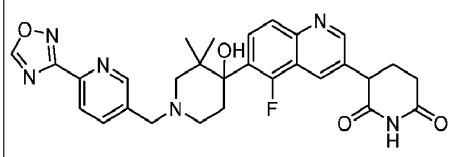
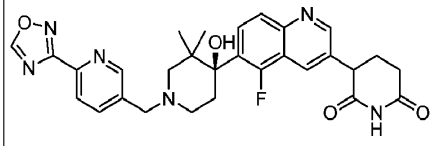
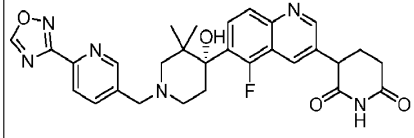
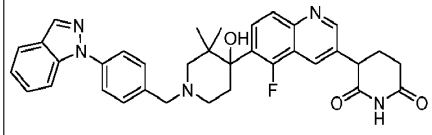
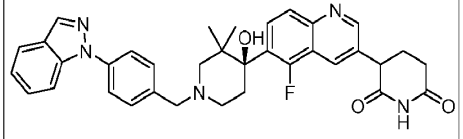
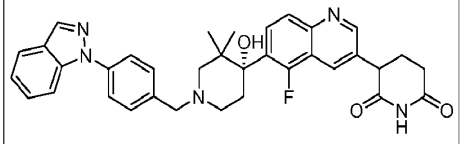
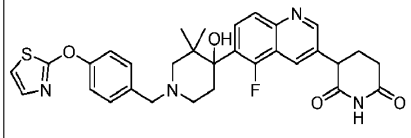
Cmpd No.	Compound Structure
I-372	
I-373	
I-374	
I-375	
I-376	
I-377	
I-378	

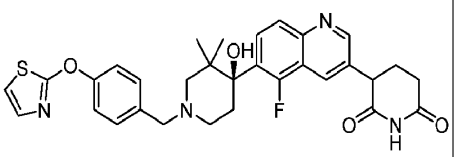
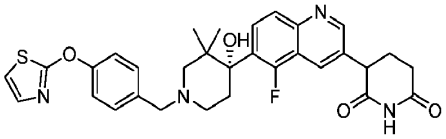
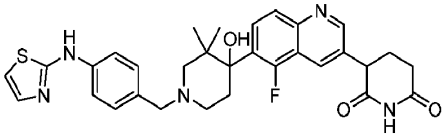
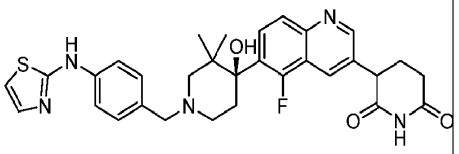
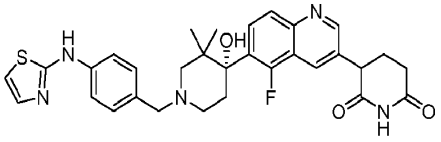
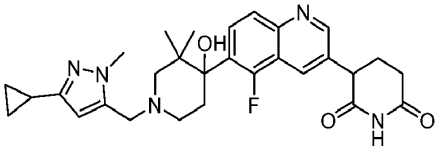
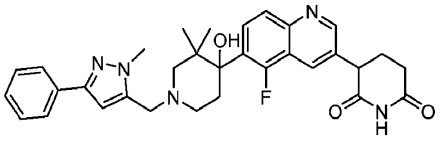
Cmpd No.	Compound Structure
I-379	
I-380	
I-381	
I-382	
I-383	
I-384	
I-385	

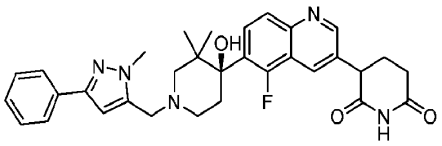
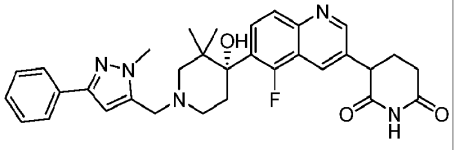
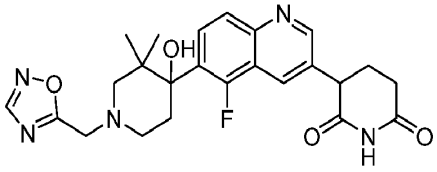
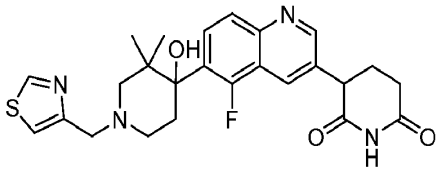
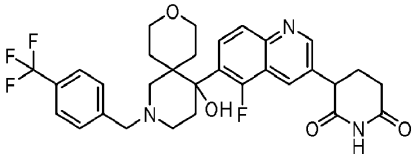
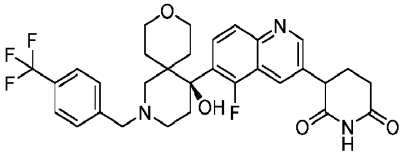
Cmpd No.	Compound Structure
I-386	
I-387	
I-388	
I-389	
I-390	
I-391	
I-392	

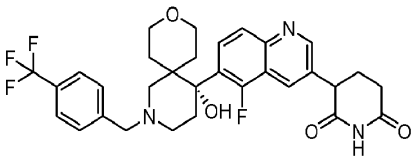
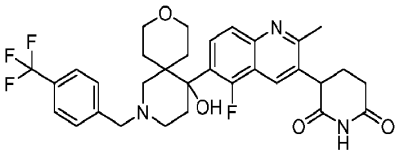
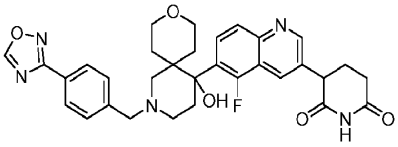
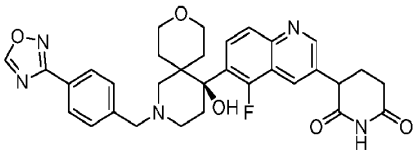
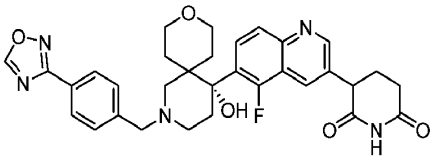
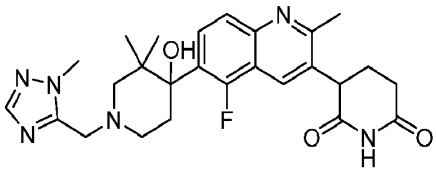
Cmpd No.	Compound Structure
I-393	
I-394	
I-395	
I-396	
I-397	
I-398	

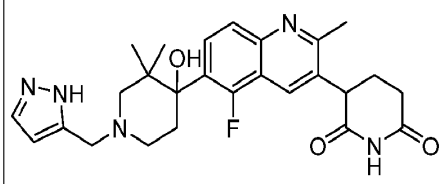
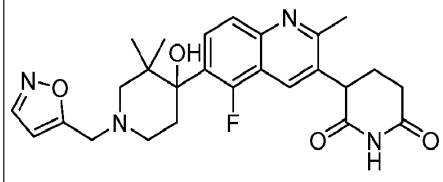
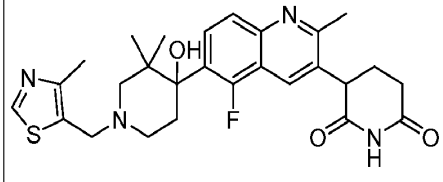
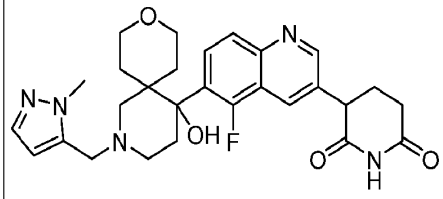
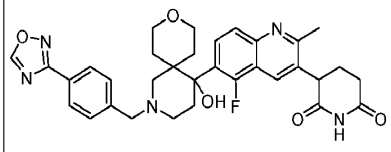
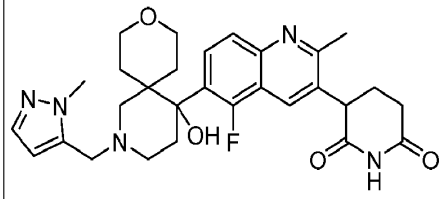
Cmpd No.	Compound Structure
I-399	
I-400	
I-401	
I-402	
I-403	
I-404	
I-405	

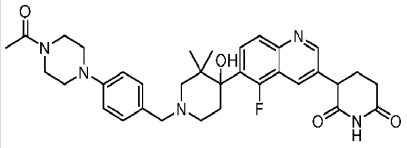
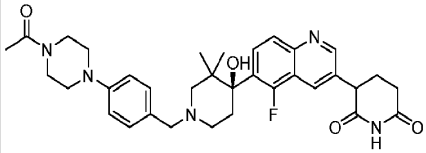
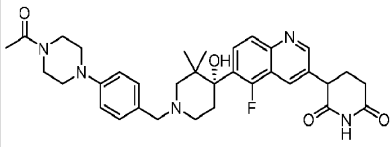
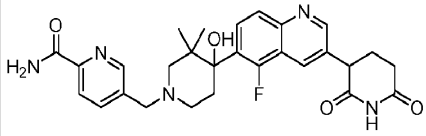
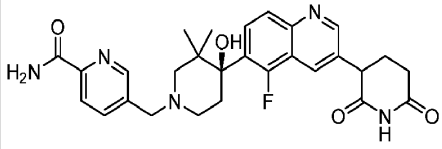
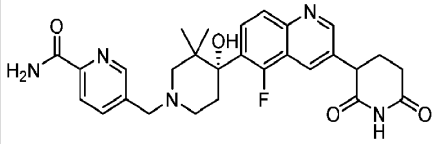
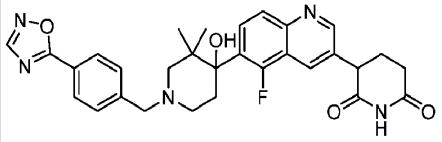
Cmpd No.	Compound Structure
I-406	
I-407	
I-408	
I-409	
I-410	
I-411	
I-412	

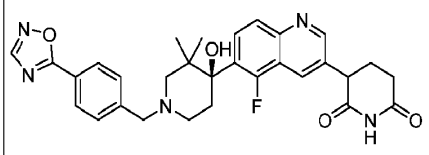
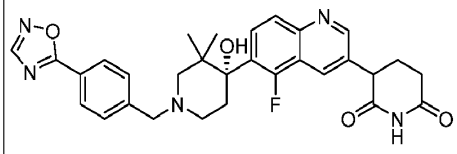
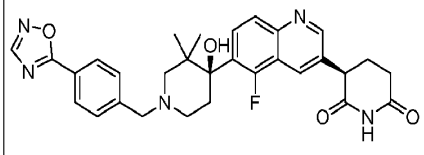
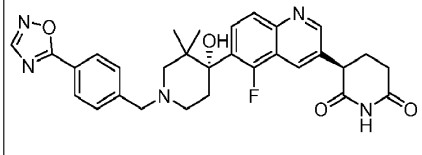
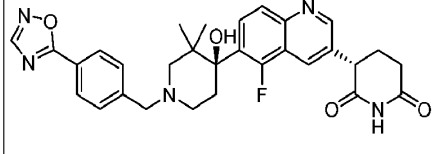
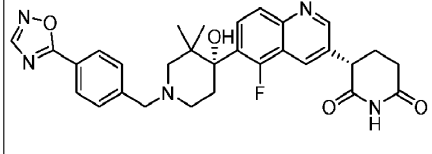
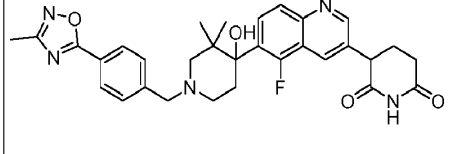
Cmpd No.	Compound Structure
I-413	
I-414	
I-415	
I-416	
I-417	
I-418	
I-419	

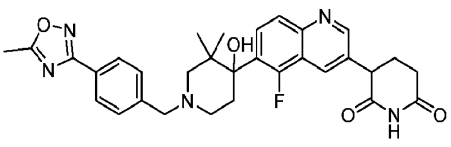
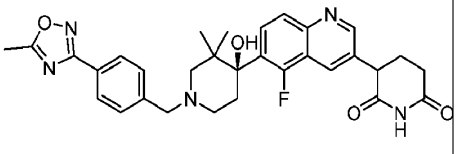
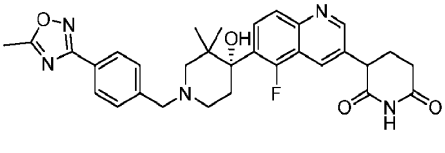
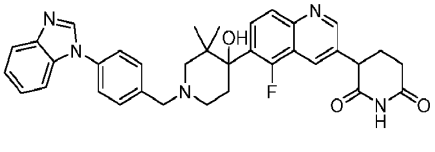
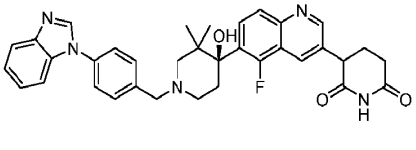
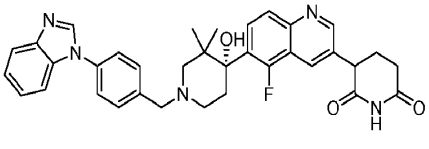
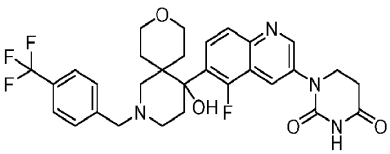
Cmpd No.	Compound Structure
I-420	
I-421	
I-422	
I-423	
I-424	
I-425	

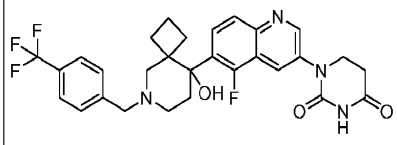
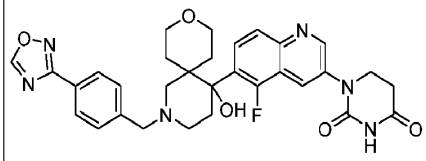
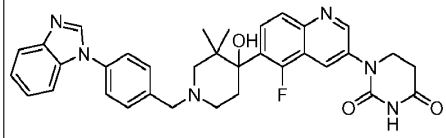
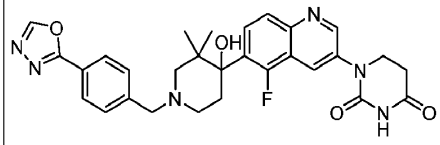
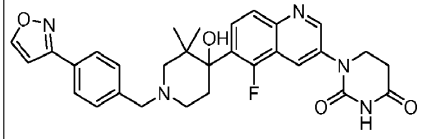
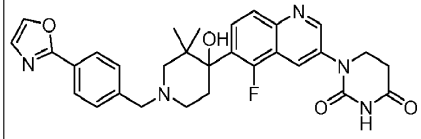
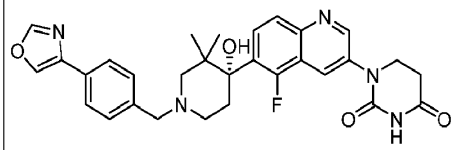
Cmpd No.	Compound Structure
I-426	
I-427	
I-428	
I-429	
I-430	
I-431	

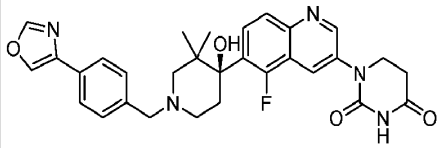
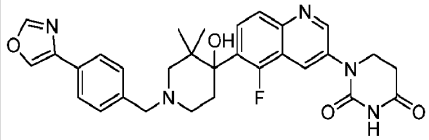
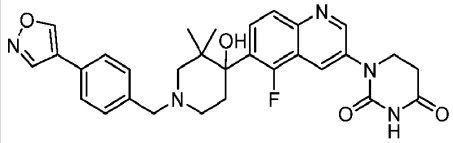
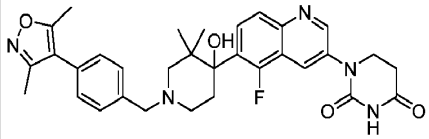
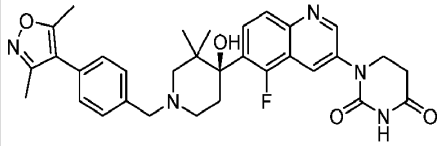
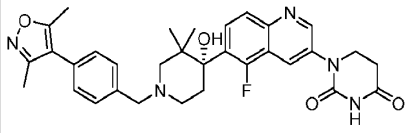
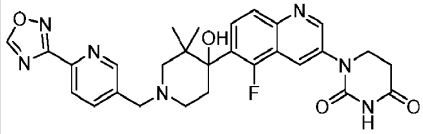
Cmpd No.	Compound Structure
I-432	
I-433	
I-434	
I-435	
I-436	
I-437	

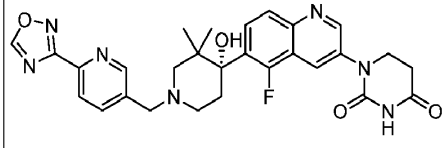
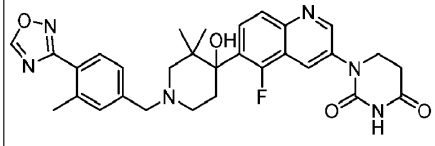
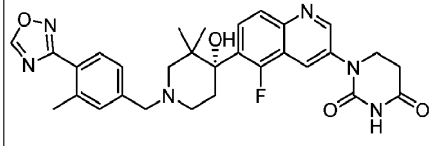
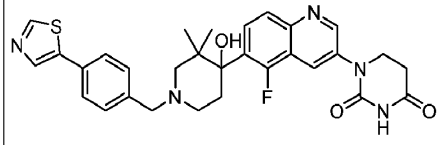
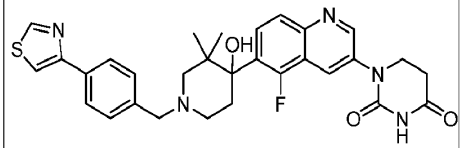
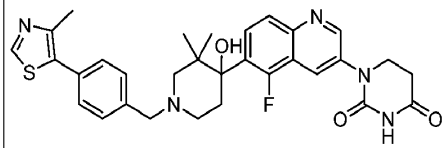
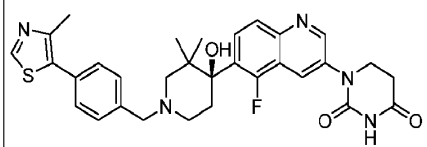
Cmpd No.	Compound Structure
I-438	
I-439	
I-440	
I-441	
I-442	
I-443	
I-444	

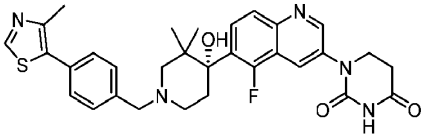
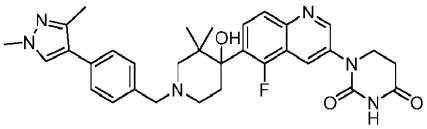
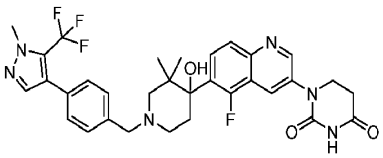
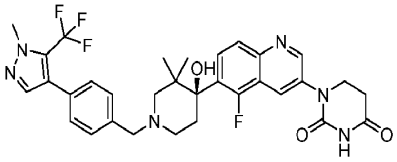
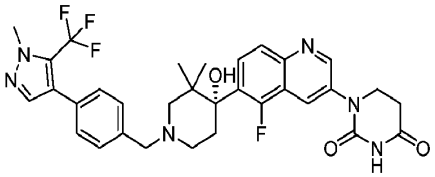
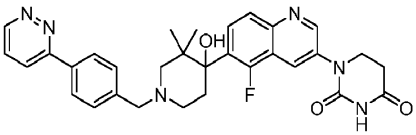
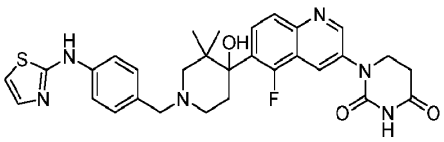
Cmpd No.	Compound Structure
I-445	
I-446	
I-447	
I-448	
I-449	
I-450	
I-451	

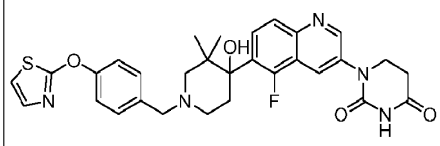
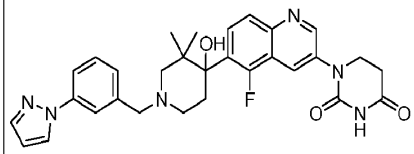
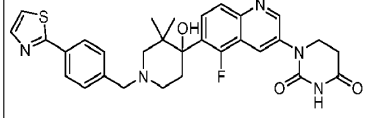
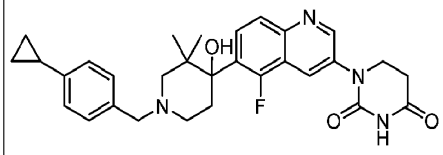
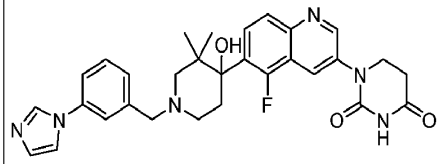
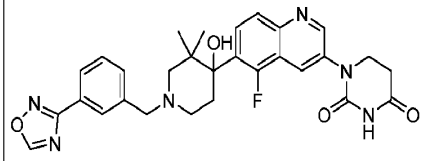
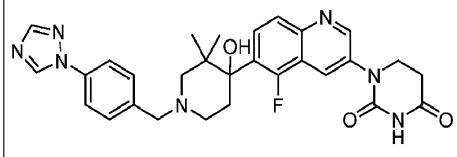
Cmpd No.	Compound Structure
I-452	
I-453	
I-454	
I-455	
I-456	
I-457	
I-458	

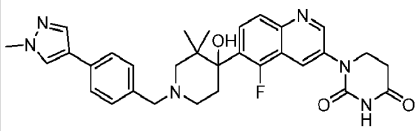
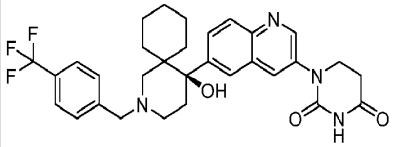
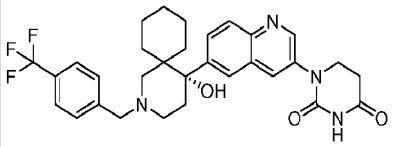
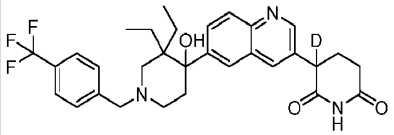
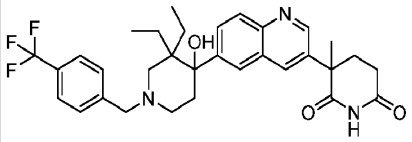
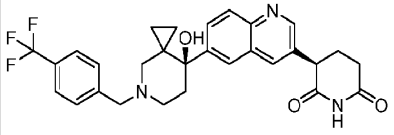
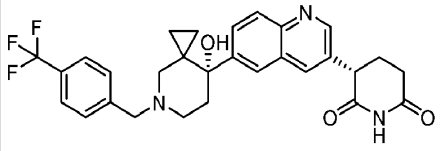
Cmpd No.	Compound Structure
I-459	
I-460	
I-461	
I-462	
I-463	
I-464	
I-465	

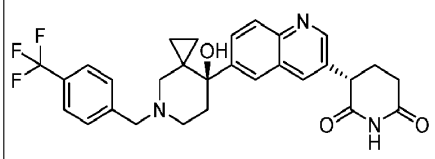
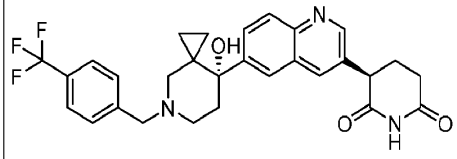
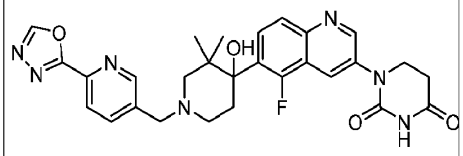
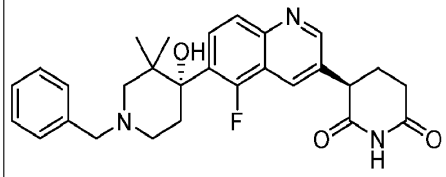
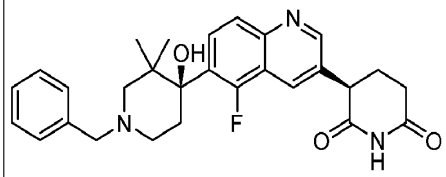
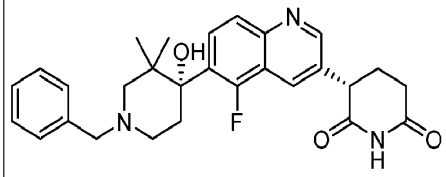
Cmpd No.	Compound Structure
I-466	
I-467	
I-468	
I-469	
I-470	
I-471	
I-472	

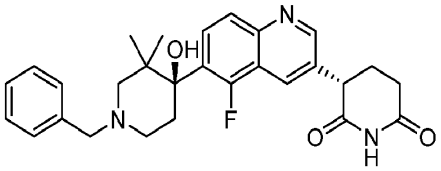
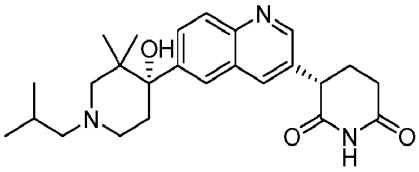
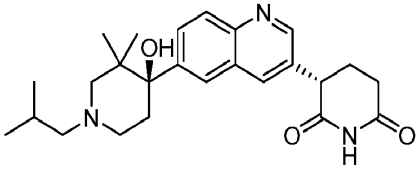
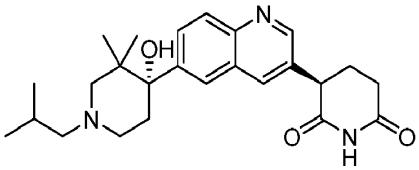
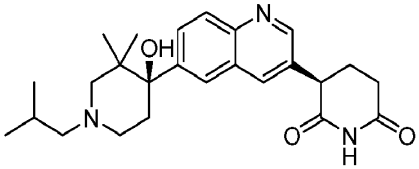
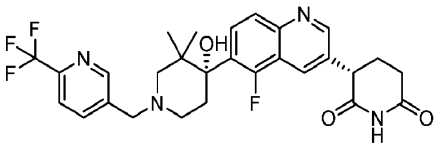
Cmpd No.	Compound Structure
I-473	
I-474	
I-475	
I-476	
I-477	
I-478	
I-479	

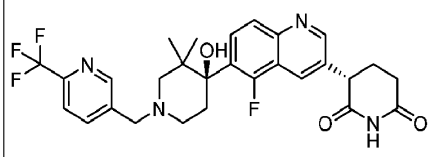
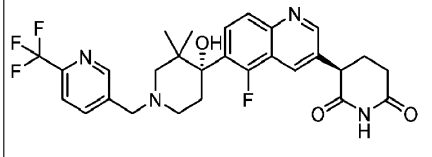
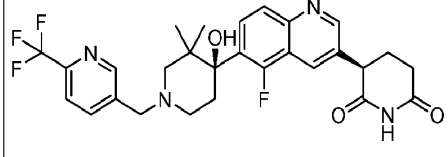
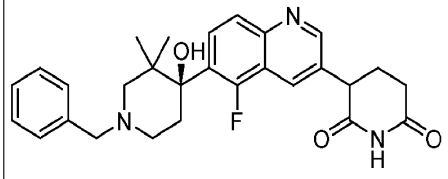
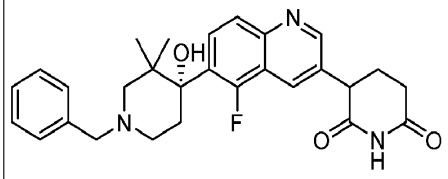
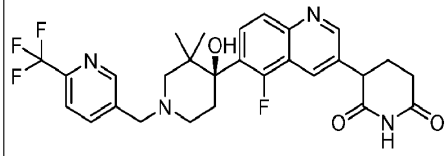
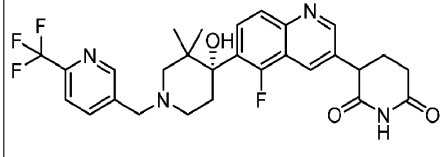
Cmpd No.	Compound Structure
I-480	
I-481	
I-482	
I-483	
I-484	
I-485	
I-486	

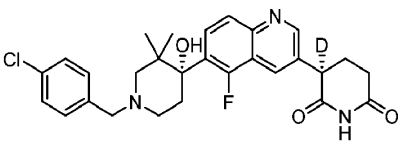
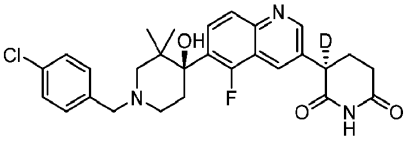
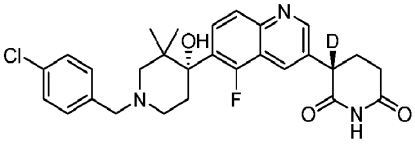
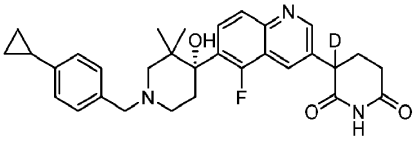
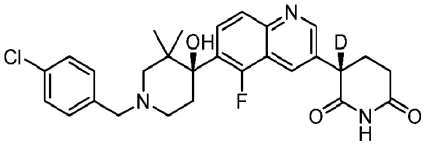
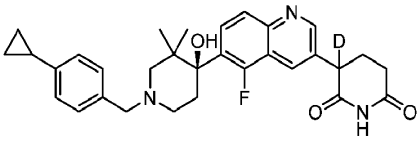
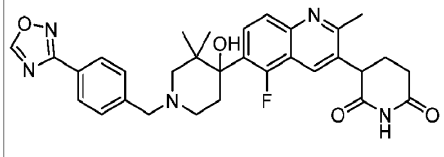
Cmpd No.	Compound Structure
I-487	
I-488	
I-489	
I-490	
I-491	
I-492	
I-493	

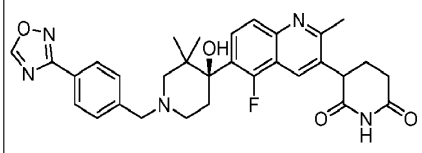
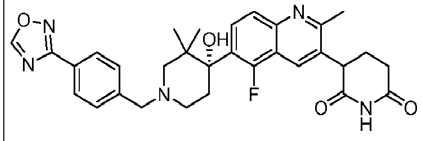
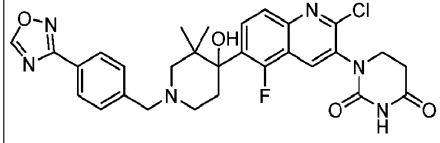
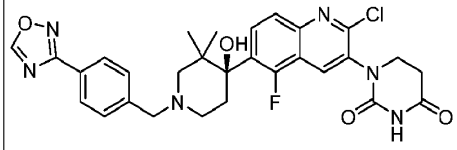
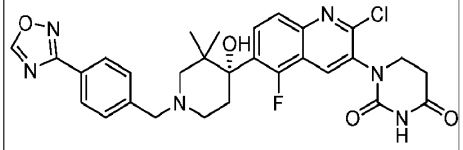
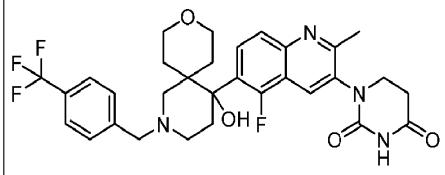
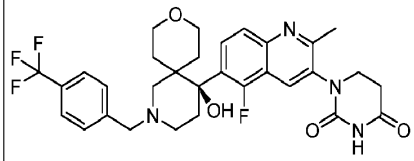
Cmpd No.	Compound Structure
I-494	
I-495	
I-496	
I-497	
I-498	
I-499	
I-500	

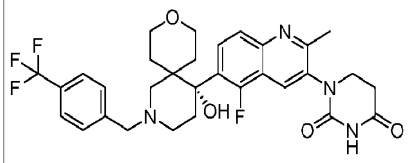
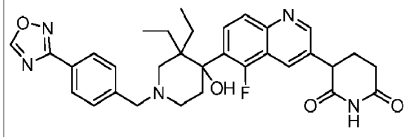
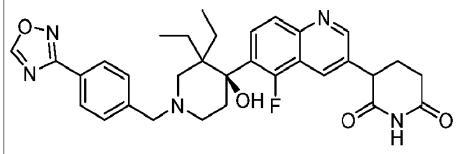
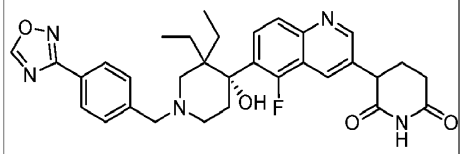
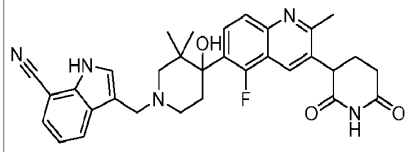
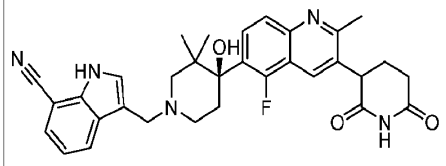
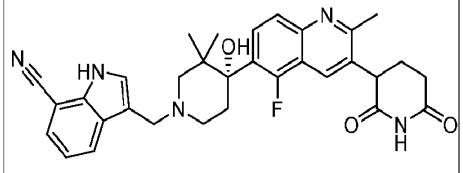
Cmpd No.	Compound Structure
I-501	
I-502	
I-503	
I-504	
I-505	
I-506	

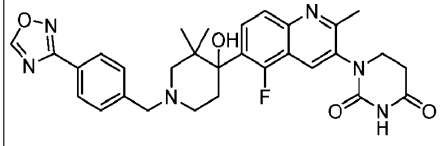
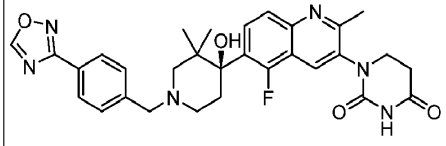
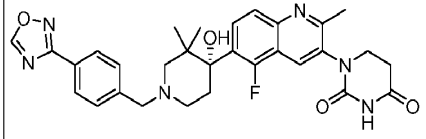
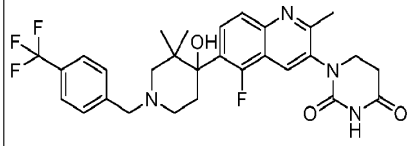
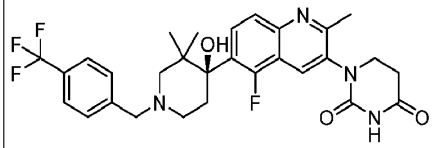
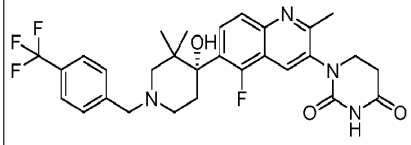
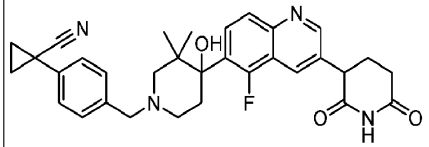
Cmpd No.	Compound Structure
I-507	
I-508	
I-509	
I-510	
I-511	
I-512	

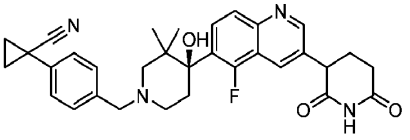
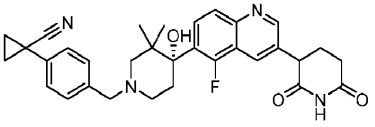
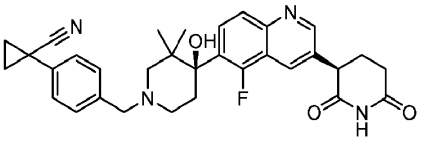
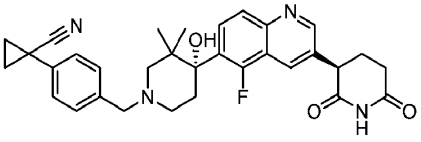
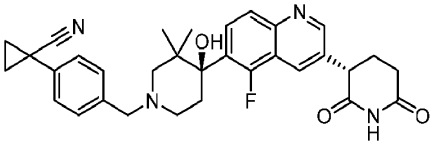
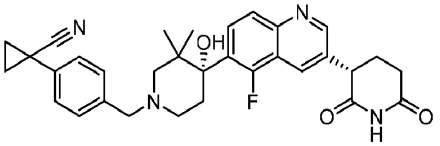
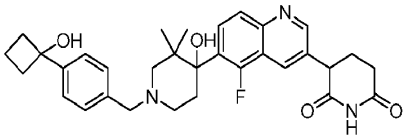
Cmpd No.	Compound Structure
I-513	
I-514	
I-515	
I-516	
I-517	
I-518	
I-519	

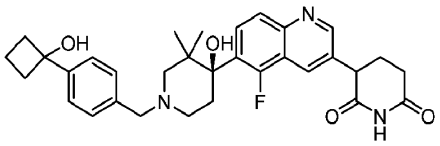
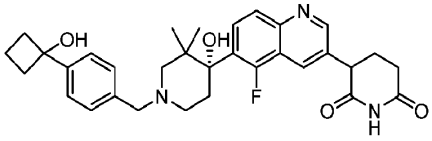
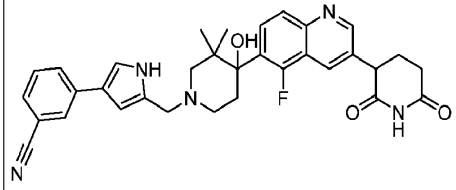
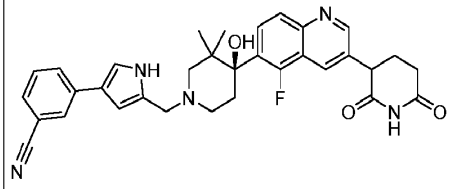
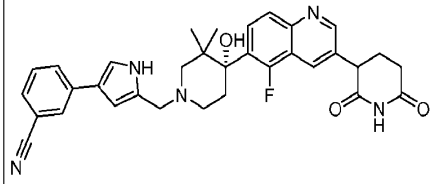
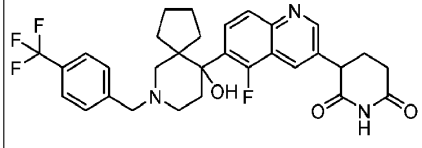
Cmpd No.	Compound Structure
I-520	
I-521	
I-522	
I-523	
I-524	
I-525	
I-526	

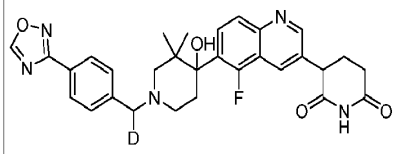
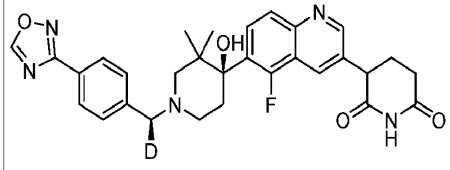
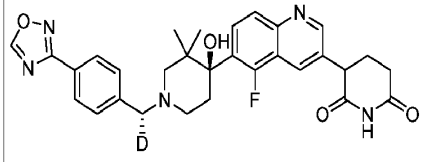
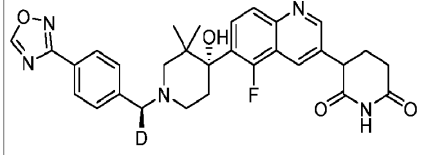
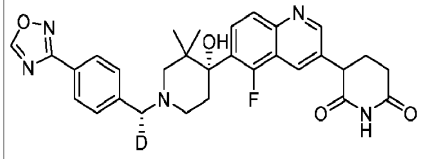
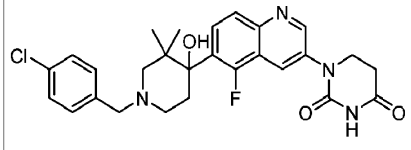
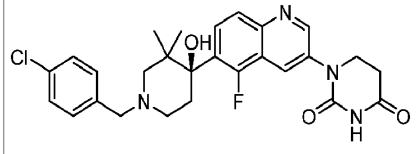
Cmpd No.	Compound Structure
I-527	
I-528	
I-529	
I-530	
I-531	
I-532	
I-533	

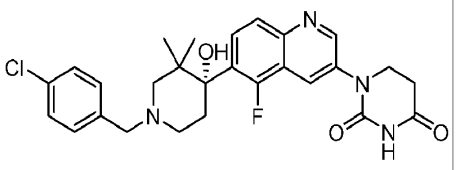
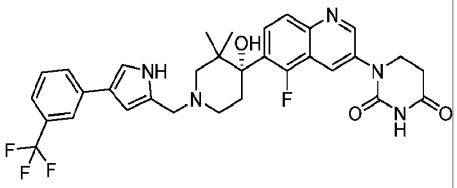
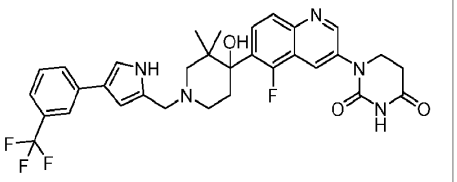
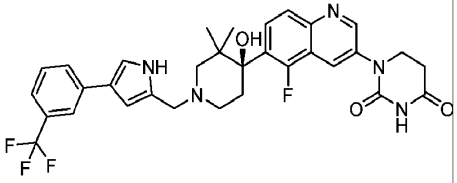
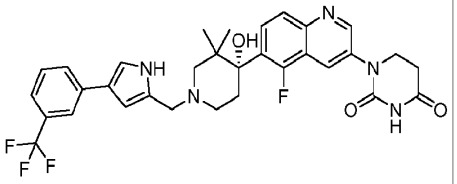
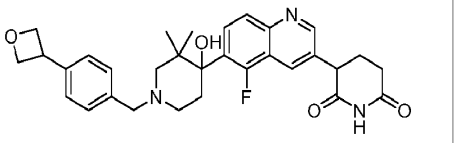
Cmpd No.	Compound Structure
I-534	
I-535	
I-536	
I-537	
I-538	
I-539	
I-540	

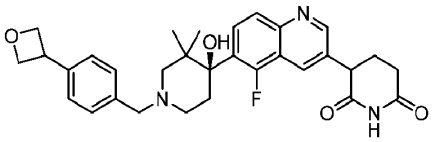
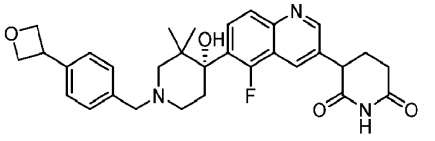
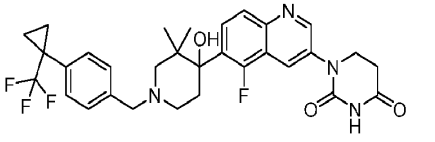
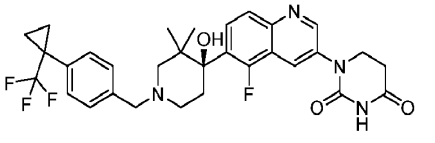
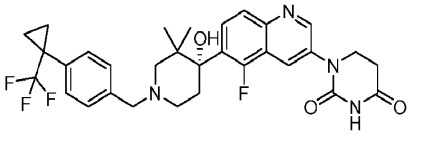
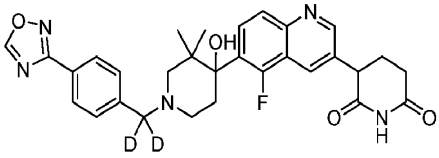
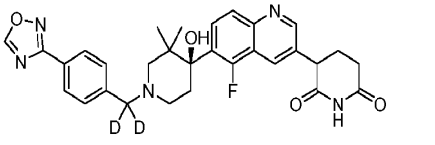
Cmpd No.	Compound Structure
I-541	
I-542	
I-543	
I-544	
I-545	
I-546	
I-547	

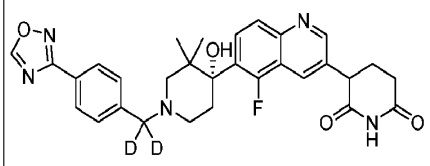
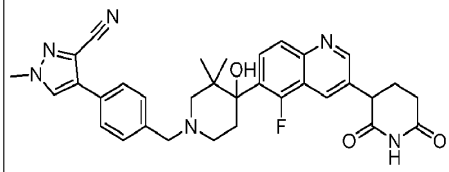
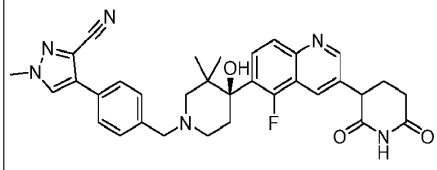
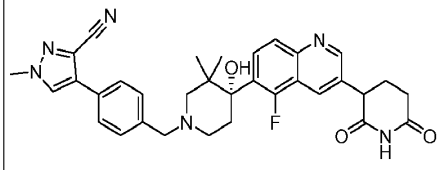
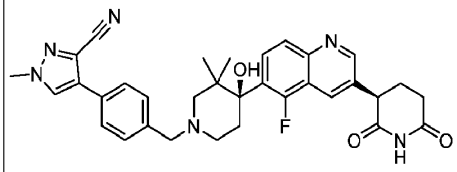
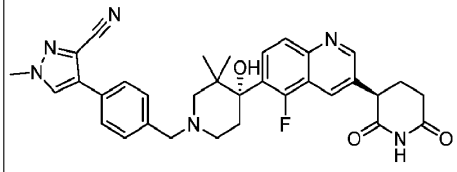
Cmpd No.	Compound Structure
I-548	
I-549	
I-550	
I-551	
I-552	
I-553	
I-554	

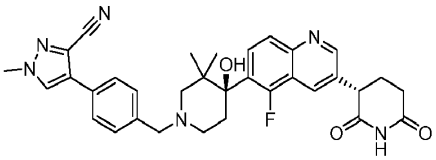
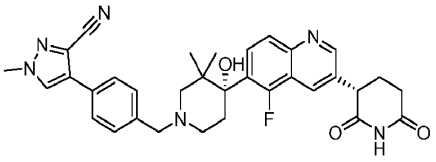
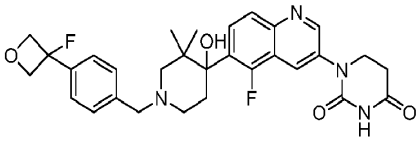
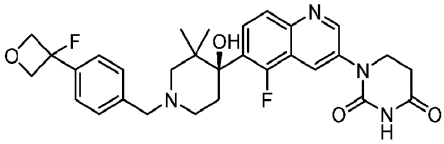
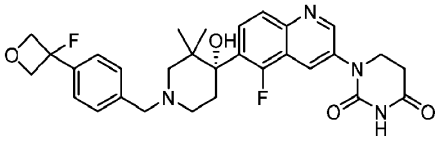
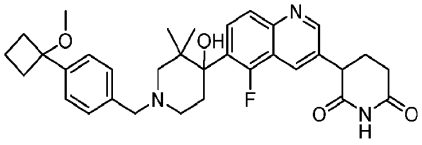
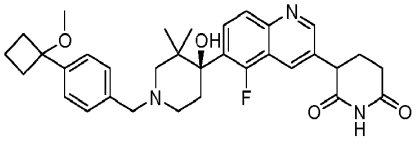
Cmpd No.	Compound Structure
I-555	
I-556	
I-557	
I-558	
I-559	
I-560	

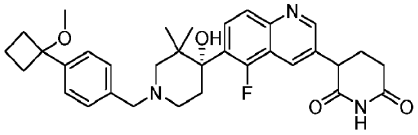
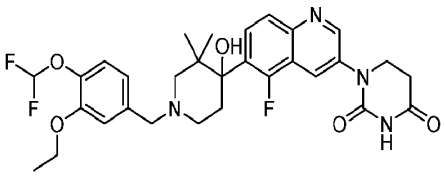
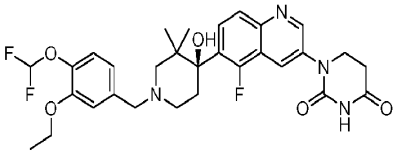
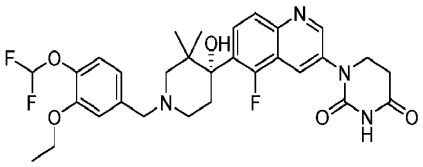
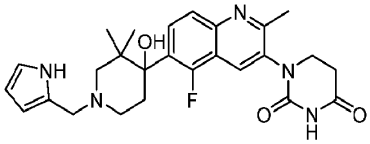
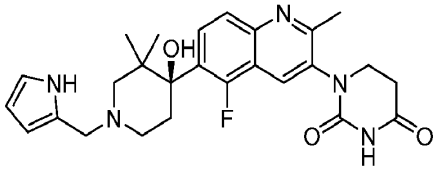
Cmpd No.	Compound Structure
I-561	
I-562	
I-563	
I-564	
I-565	
I-566	
I-567	

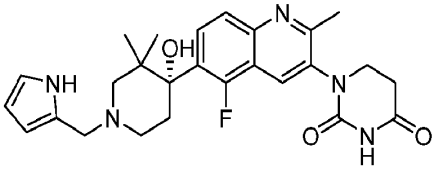
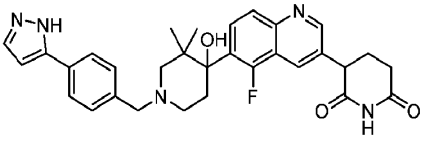
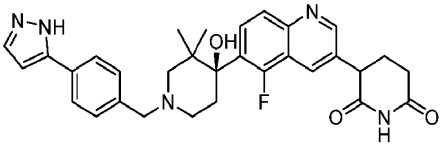
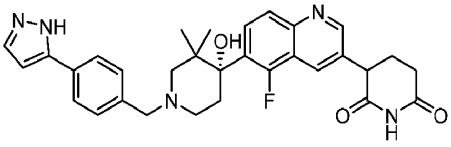
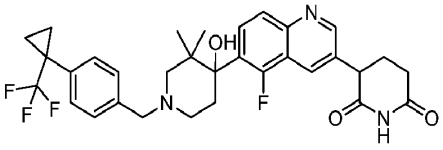
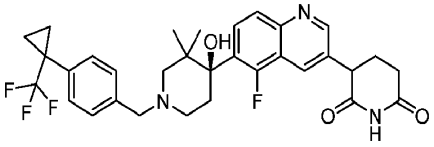
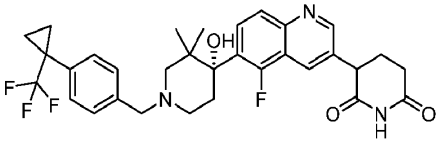
Cmpd No.	Compound Structure
I-568	
I-569	
I-570	
I-571	
I-572	
I-573	

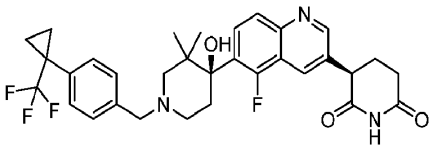
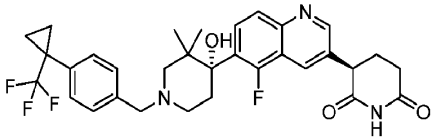
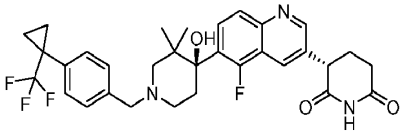
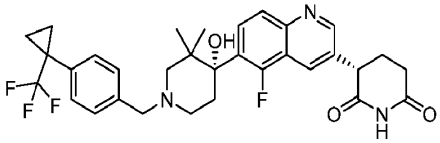
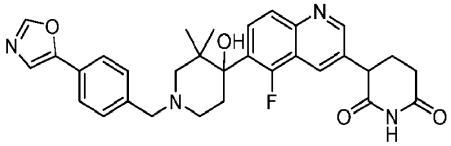
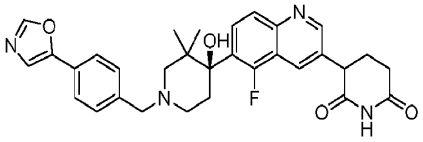
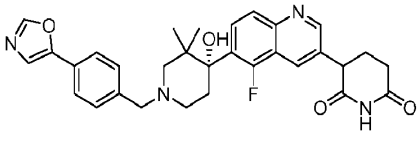
Cmpd No.	Compound Structure
I-574	
I-575	
I-576	
I-577	
I-578	
I-579	
I-580	

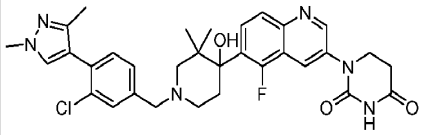
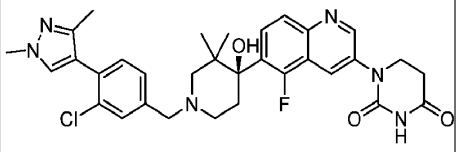
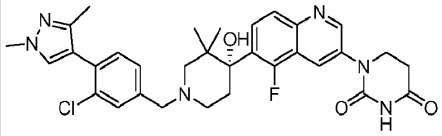
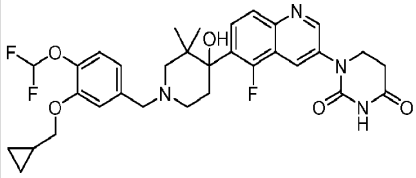
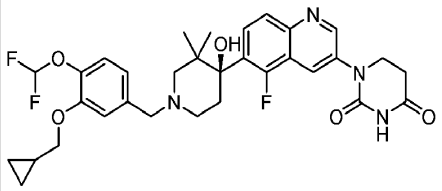
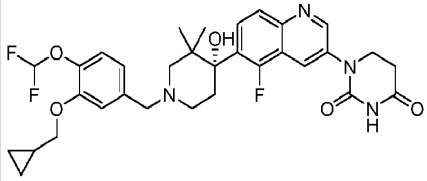
Cmpd No.	Compound Structure
I-581	
I-582	
I-583	
I-584	
I-585	
I-586	

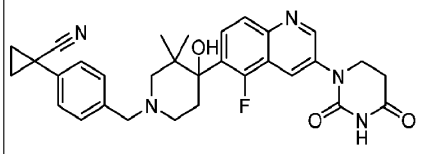
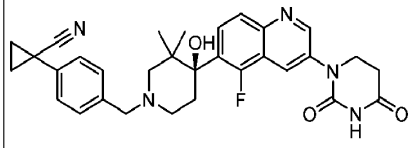
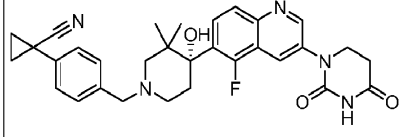
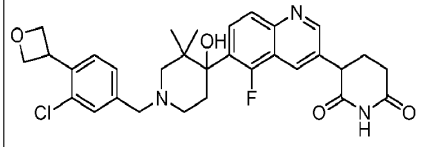
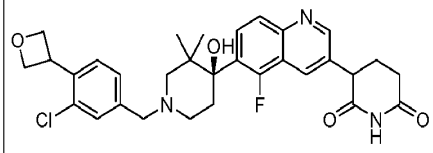
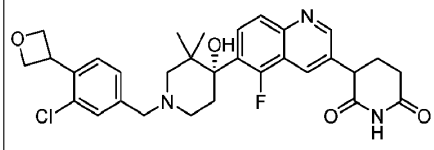
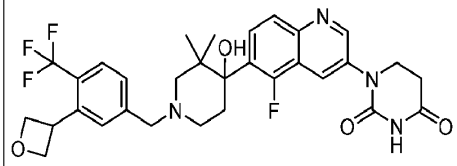
Cmpd No.	Compound Structure
I-587	
I-588	
I-589	
I-590	
I-591	
I-592	
I-593	

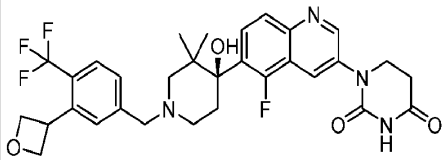
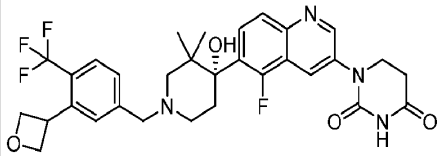
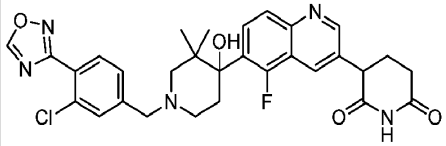
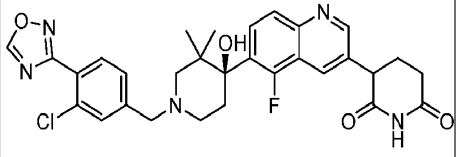
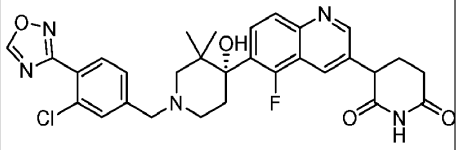
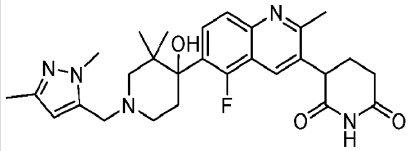
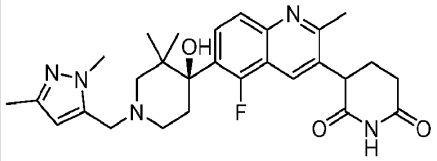
Cmpd No.	Compound Structure
I-594	
I-595	
I-596	
I-597	
I-598	
I-599	

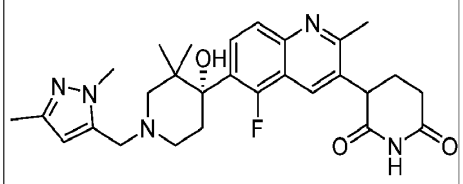
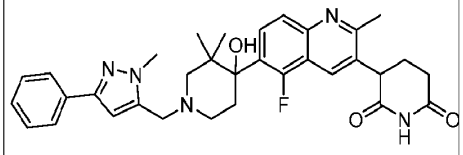
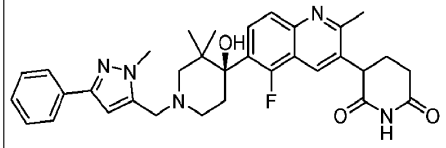
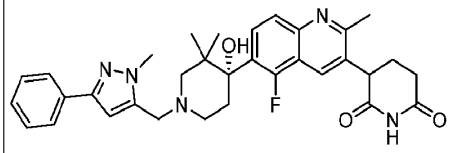
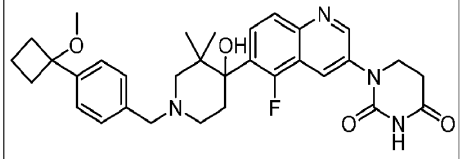
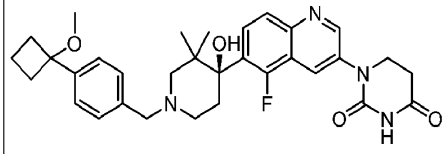
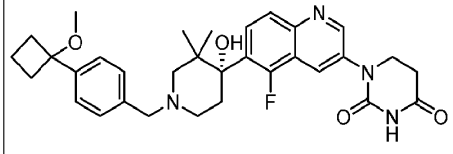
Cmpd No.	Compound Structure
I-600	
I-601	
I-602	
I-603	
I-604	
I-605	
I-606	

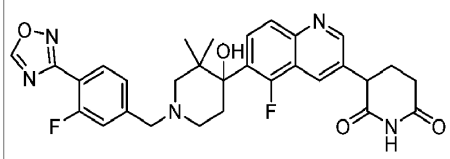
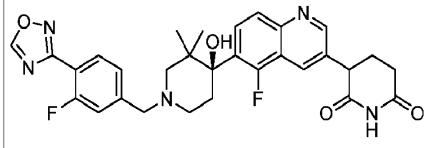
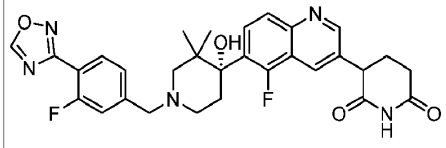
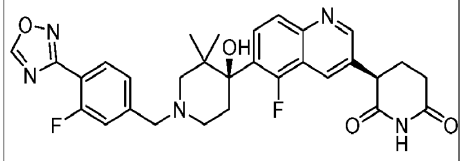
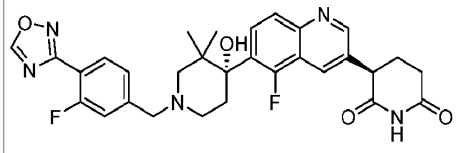
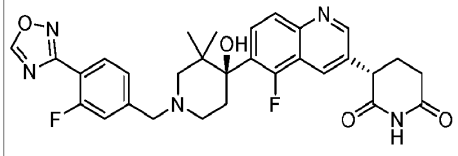
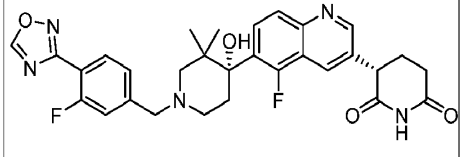
Cmpd No.	Compound Structure
I-607	
I-608	
I-609	
I-610	
I-611	
I-612	
I-613	

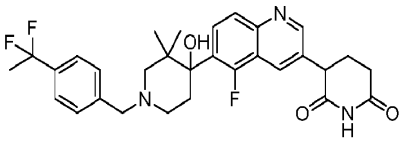
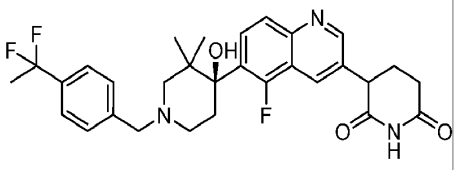
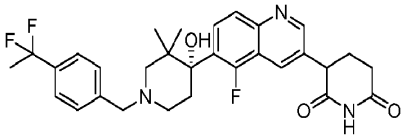
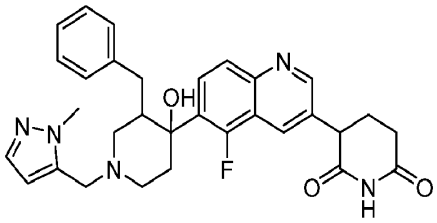
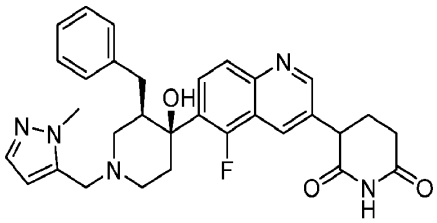
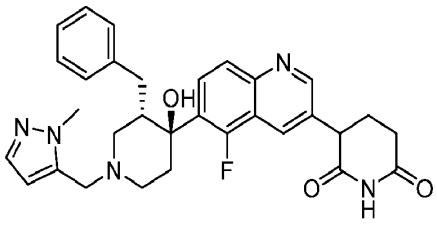
Cmpd No.	Compound Structure
I-614	
I-615	
I-616	
I-617	
I-618	
I-619	

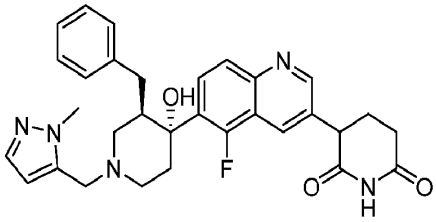
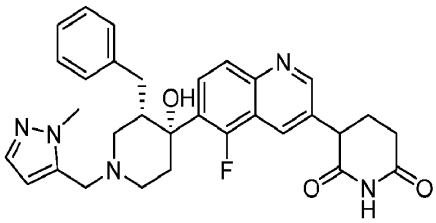
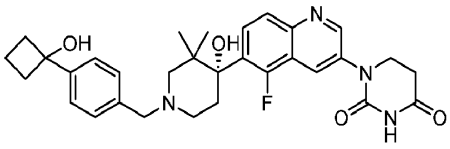
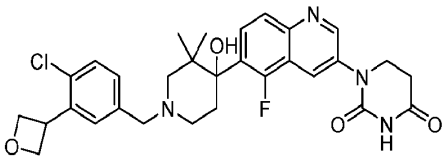
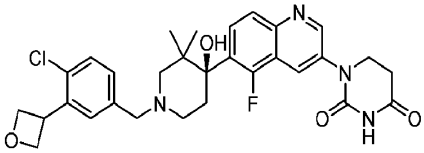
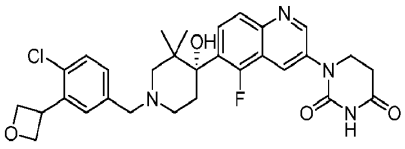
Cmpd No.	Compound Structure
I-620	
I-621	
I-622	
I-623	
I-624	
I-625	
I-626	

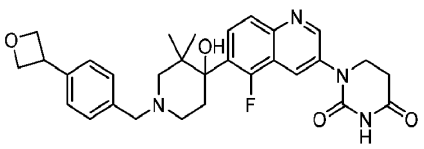
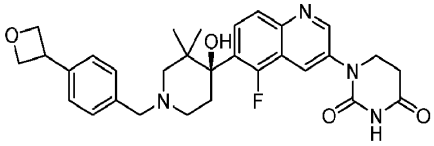
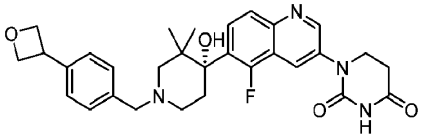
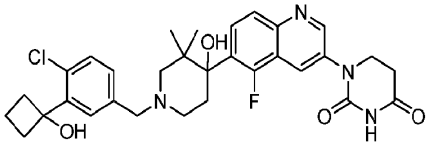
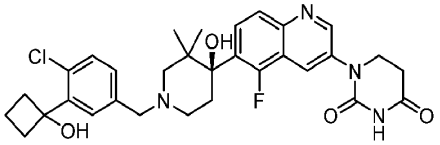
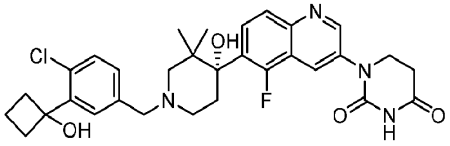
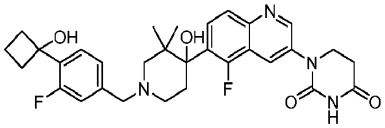
Cmpd No.	Compound Structure
I-627	
I-628	
I-629	
I-630	
I-631	
I-632	
I-633	

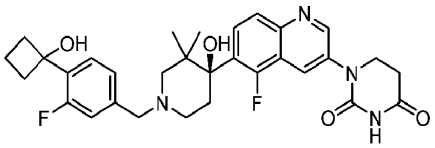
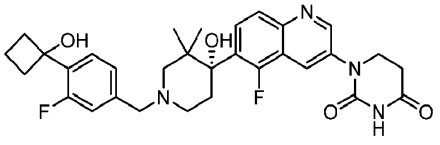
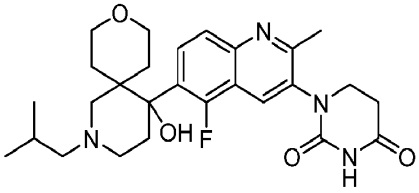
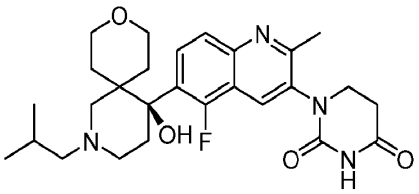
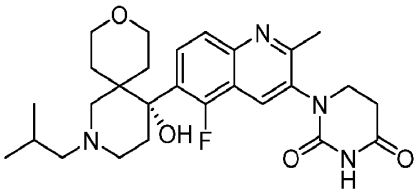
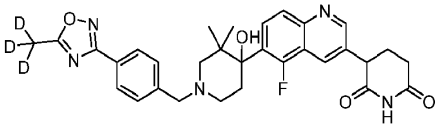
Cmpd No.	Compound Structure
I-634	
I-635	
I-636	
I-637	
I-638	
I-639	
I-640	

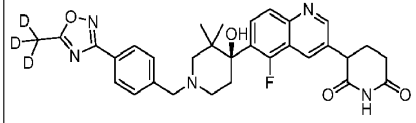
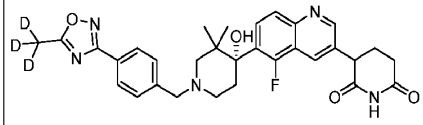
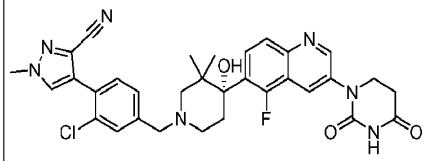
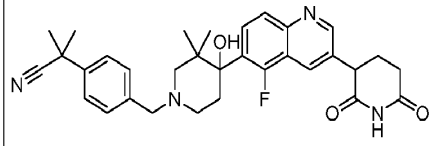
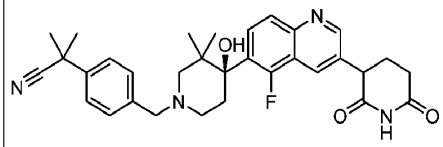
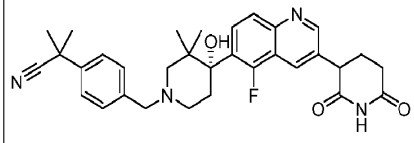
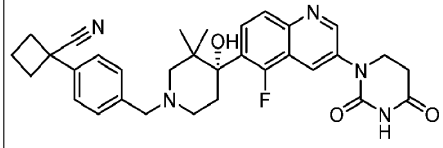
Cmpd No.	Compound Structure
I-641	
I-642	
I-643	
I-644	
I-645	
I-646	
I-647	

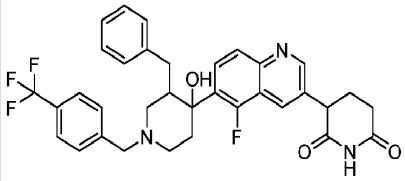
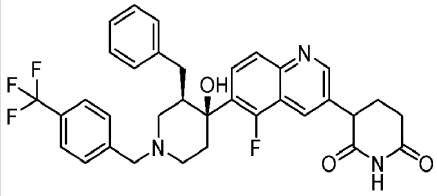
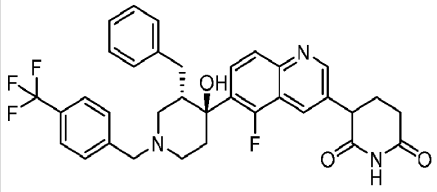
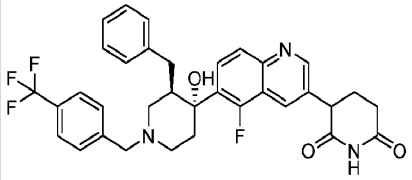
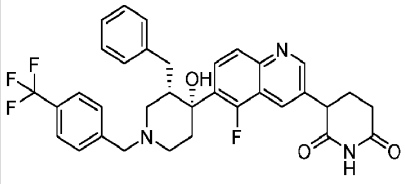
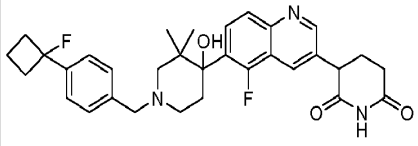
Cmpd No.	Compound Structure
I-648	
I-649	
I-650	
I-651	
I-652	
I-653	

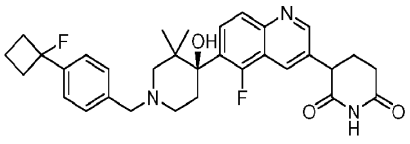
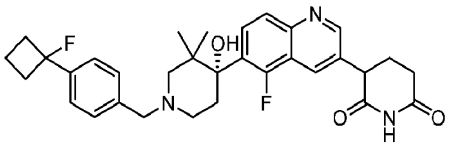
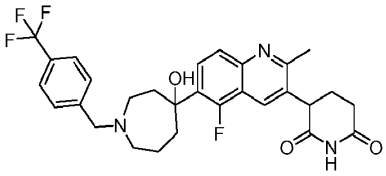
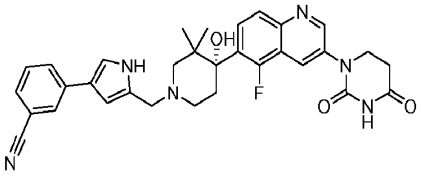
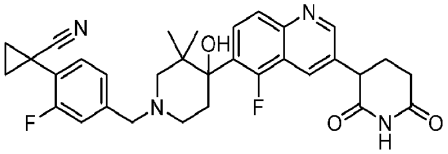
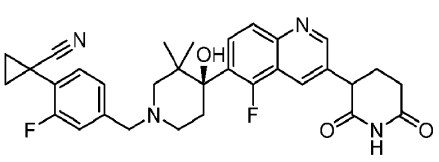
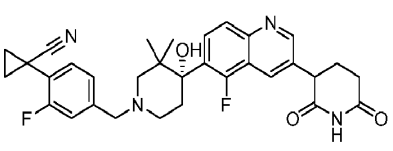
Cmpd No.	Compound Structure
I-654	
I-655	
I-656	
I-657	
I-658	
I-659	

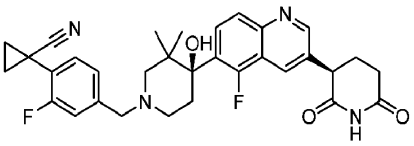
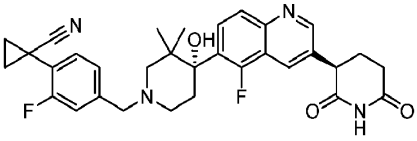
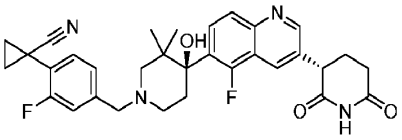
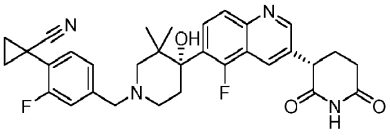
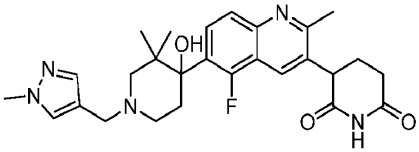
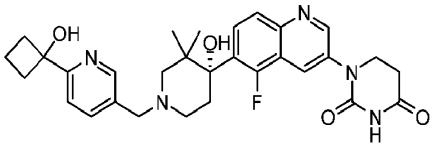
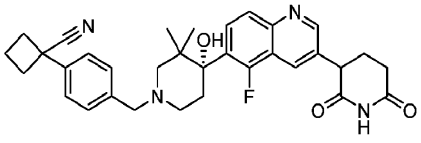
Cmpd No.	Compound Structure
I-660	
I-661	
I-662	
I-663	
I-664	
I-665	
I-666	

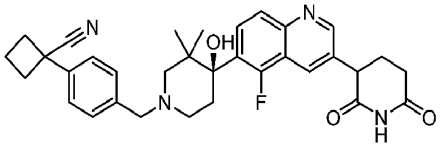
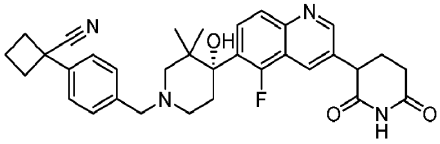
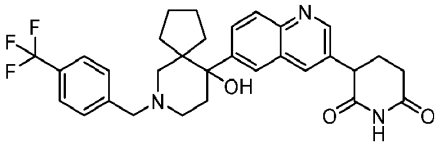
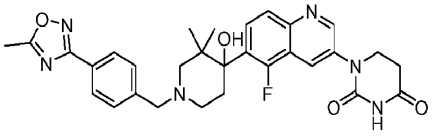
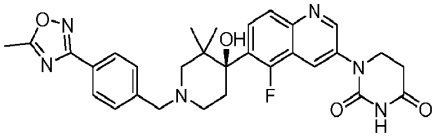
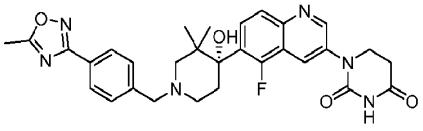
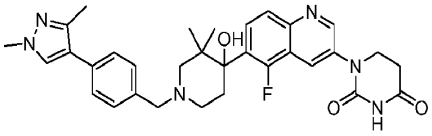
Cmpd No.	Compound Structure
I-667	
I-668	
I-669	
I-670	
I-671	
I-672	

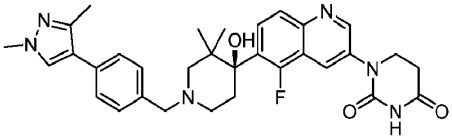
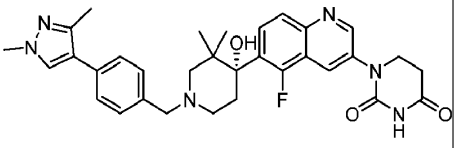
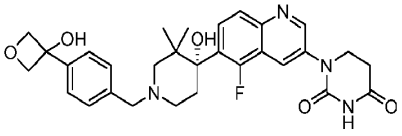
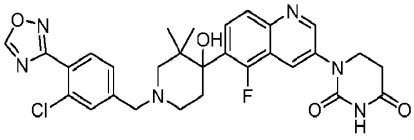
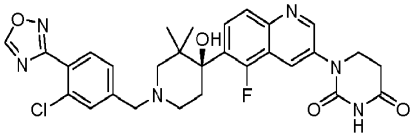
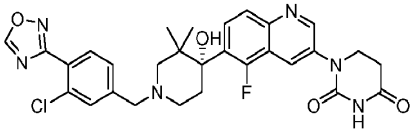
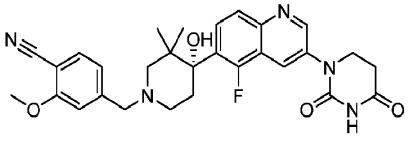
Cmpd No.	Compound Structure
I-673	
I-674	
I-675	
I-676	
I-677	
I-678	
I-679	

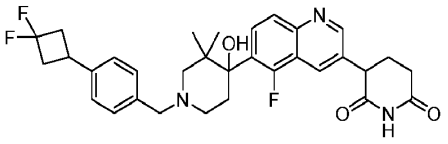
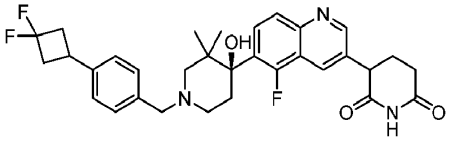
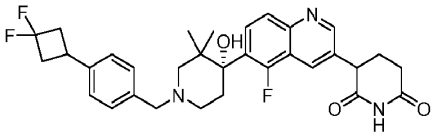
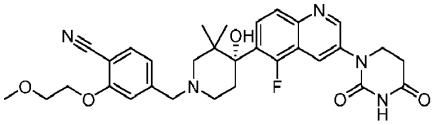
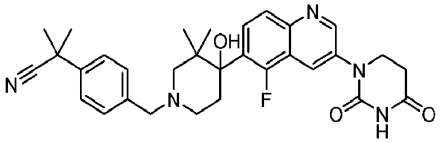
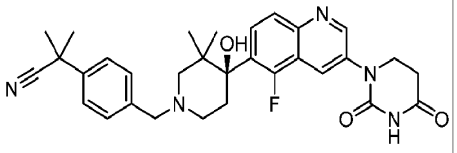
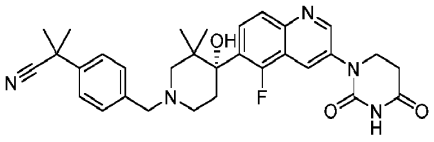
Cmpd No.	Compound Structure
I-680	
I-681	
I-682	
I-683	
I-684	
I-685	

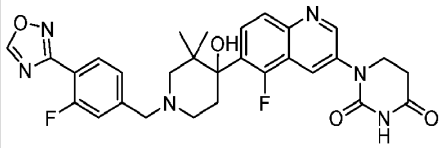
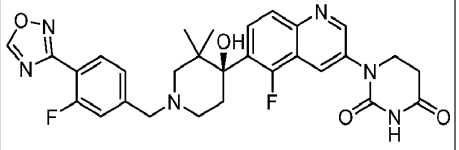
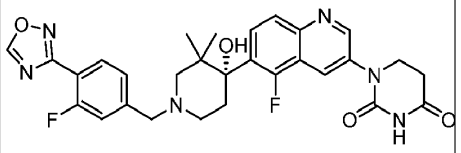
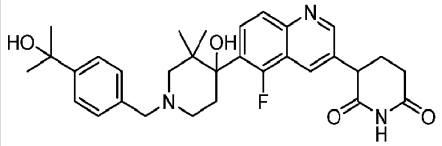
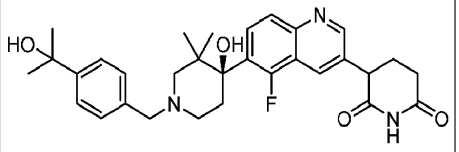
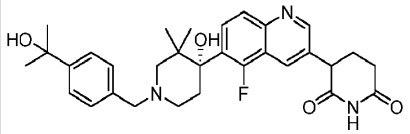
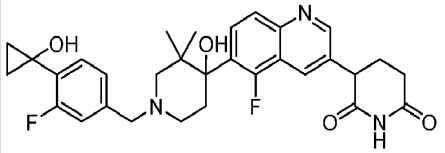
Cmpd No.	Compound Structure
I-686	
I-687	
I-688	
I-689	
I-690	
I-691	
I-692	

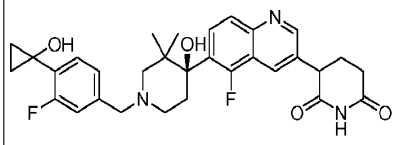
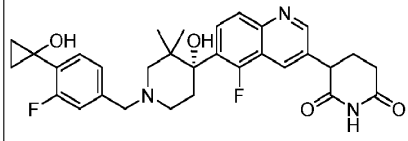
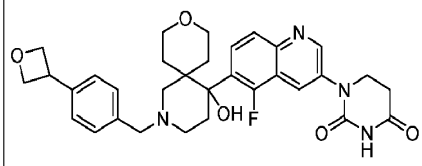
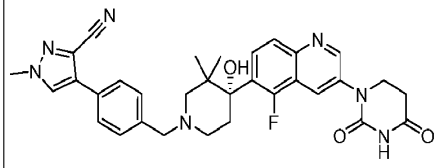
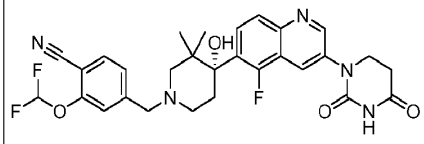
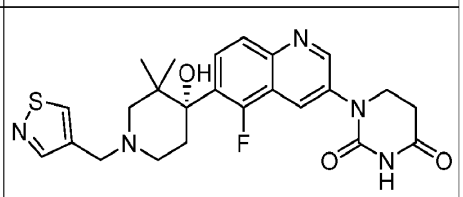
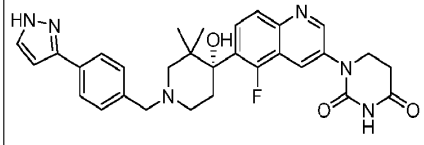
Cmpd No.	Compound Structure
I-693	
I-694	
I-695	
I-696	
I-697	
I-698	
I-699	

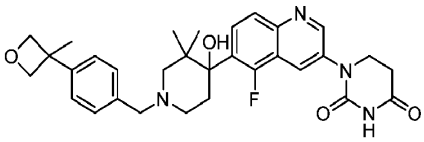
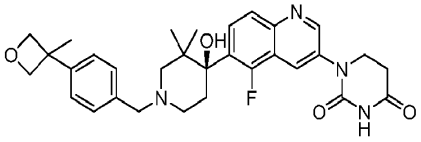
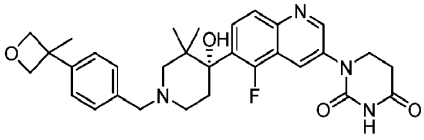
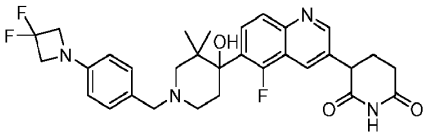
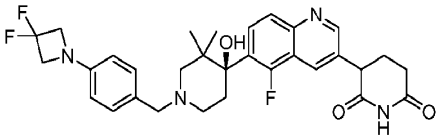
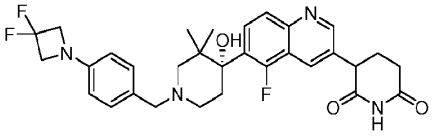
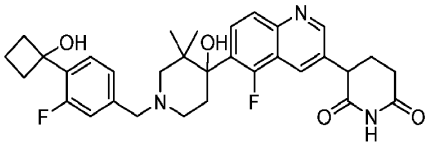
Cmpd No.	Compound Structure
I-700	
I-701	
I-702	
I-703	
I-704	
I-705	
I-706	

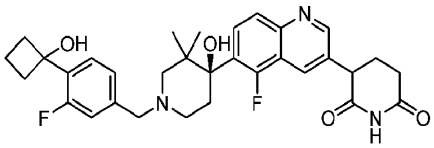
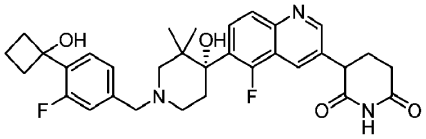
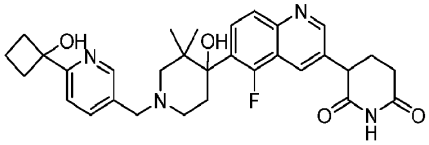
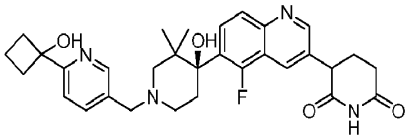
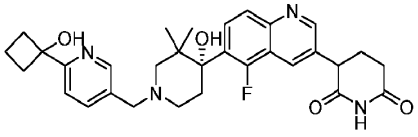
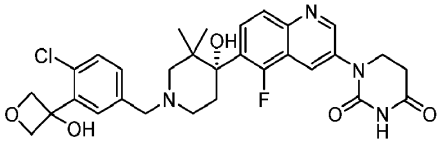
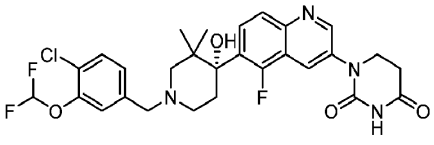
Cmpd No.	Compound Structure
I-707	
I-708	
I-709	
I-710	
I-711	
I-712	
I-713	

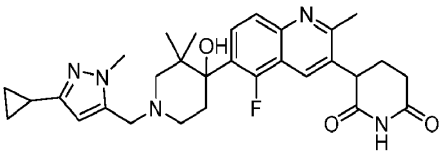
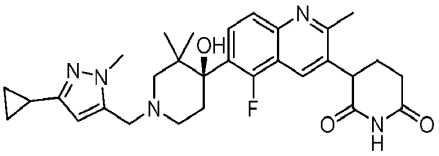
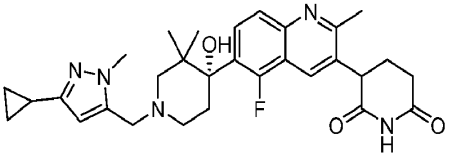
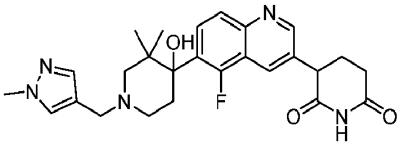
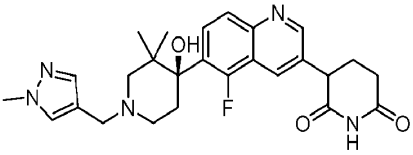
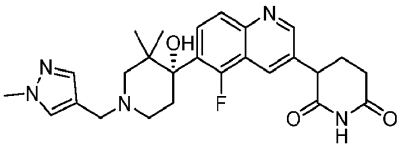
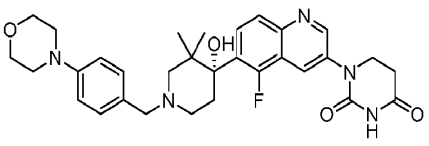
Cmpd No.	Compound Structure
I-714	
I-715	
I-716	
I-717	
I-718	
I-719	
I-720	

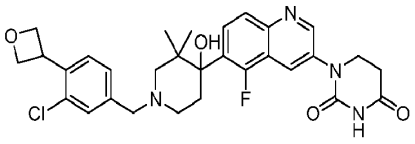
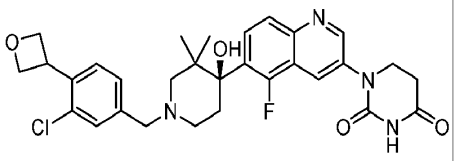
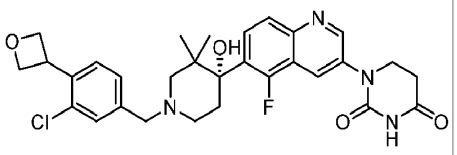
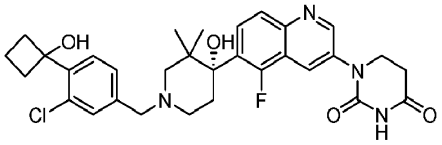
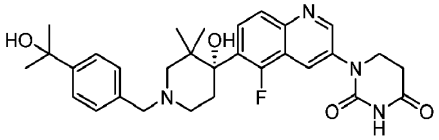
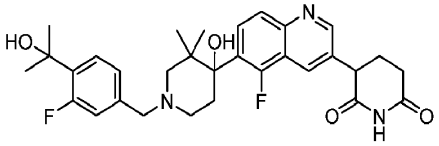
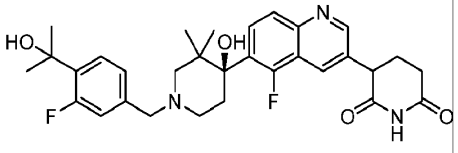
Cmpd No.	Compound Structure
I-721	
I-722	
I-723	
I-724	
I-725	
I-726	
I-727	

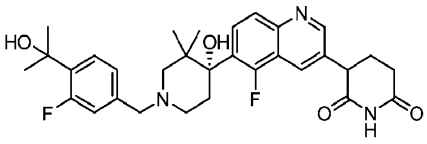
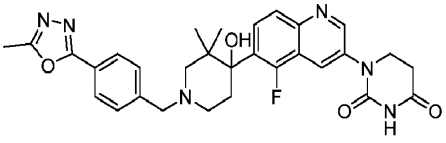
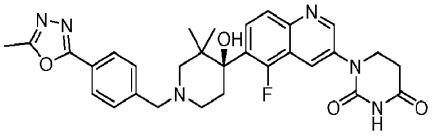
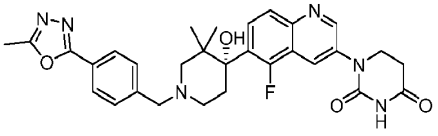
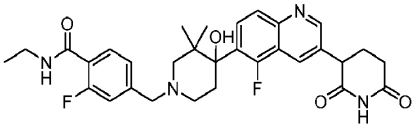
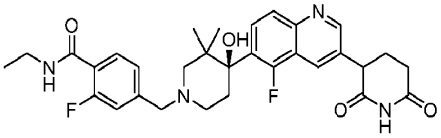
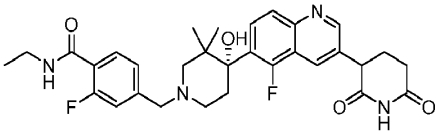
Cmpd No.	Compound Structure
I-728	
I-729	
I-730	
I-731	
I-732	
I-733	
I-734	

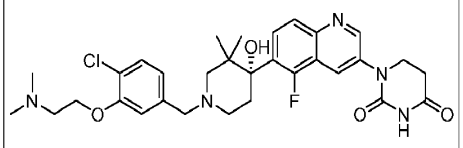
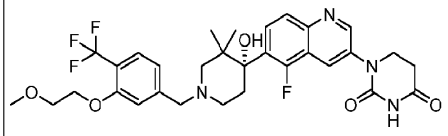
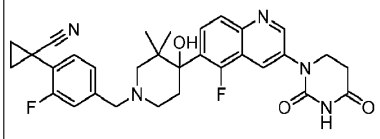
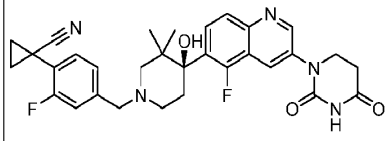
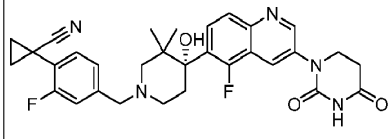
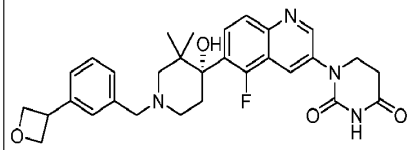
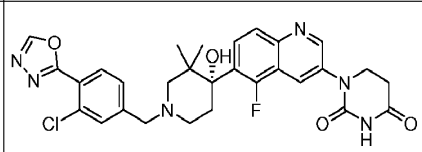
Cmpd No.	Compound Structure
I-735	
I-736	
I-737	
I-738	
I-739	
I-740	
I-741	

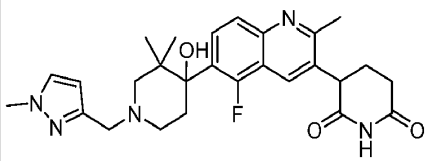
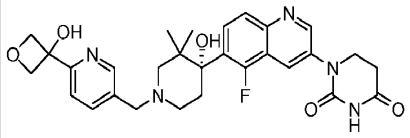
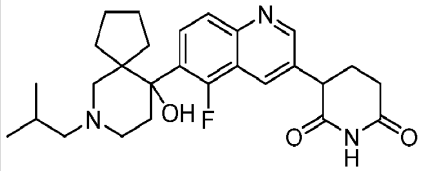
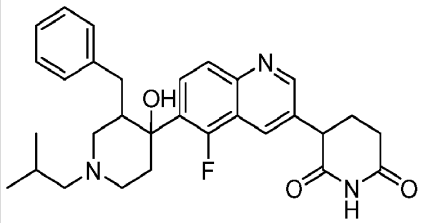
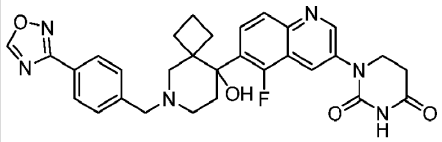
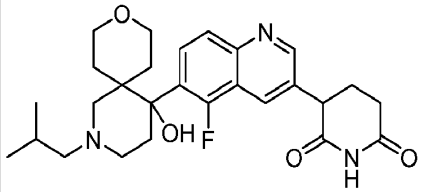
Cmpd No.	Compound Structure
I-742	
I-743	
I-744	
I-745	
I-746	
I-747	
I-748	

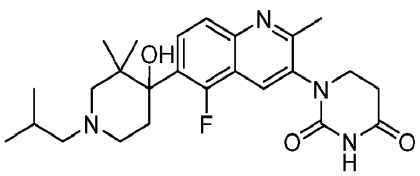
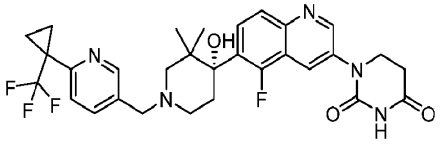
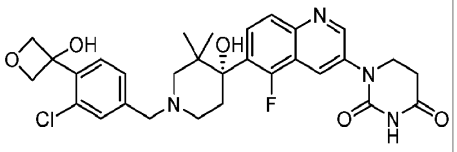
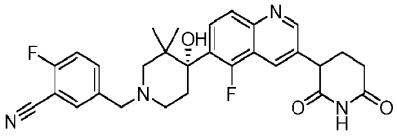
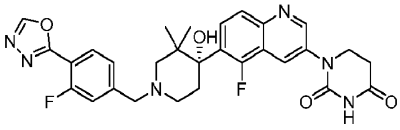
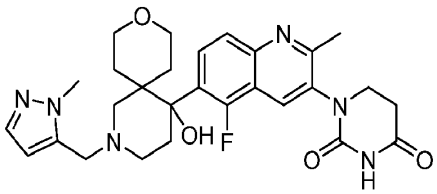
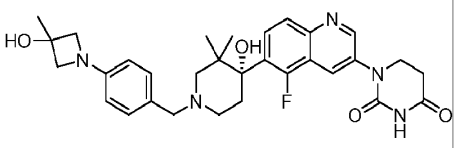
Cmpd No.	Compound Structure
I-749	
I-750	
I-751	
I-752	
I-753	
I-754	
I-755	

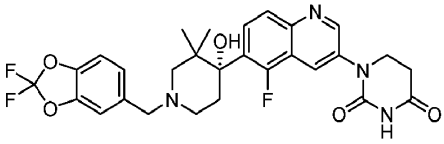
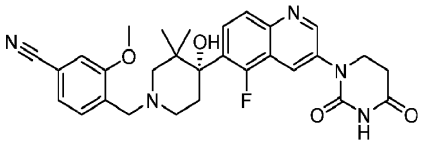
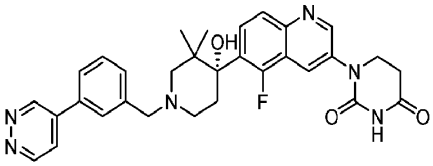
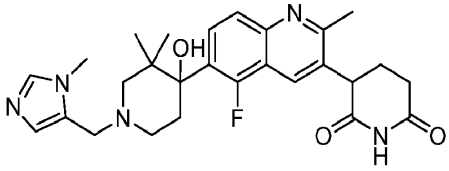
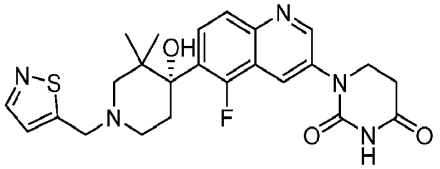
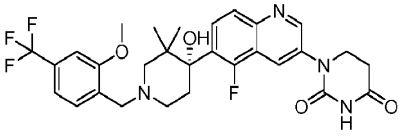
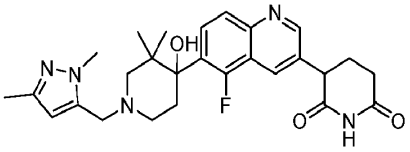
Cmpd No.	Compound Structure
I-756	
I-757	
I-758	
I-759	
I-760	
I-761	
I-762	

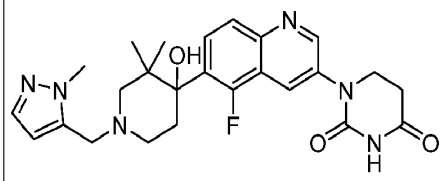
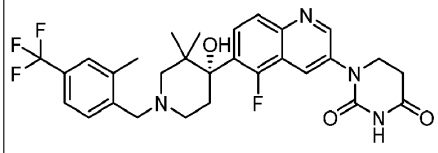
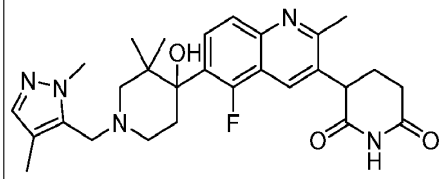
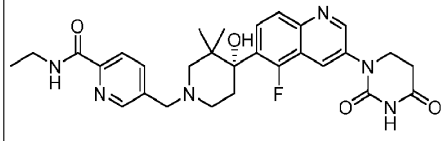
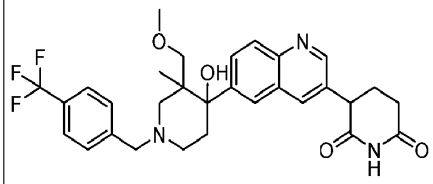
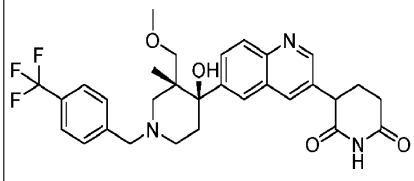
Cmpd No.	Compound Structure
I-763	
I-764	
I-765	
I-766	
I-767	
I-768	
I-769	

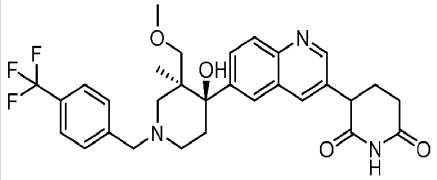
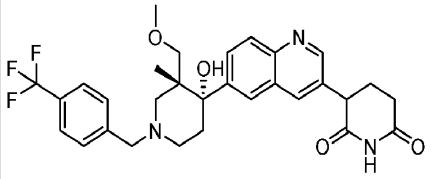
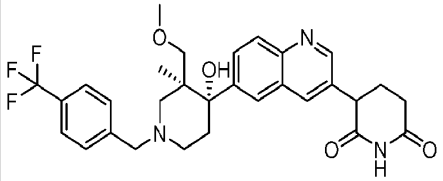
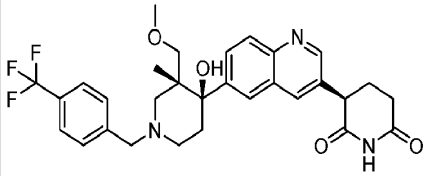
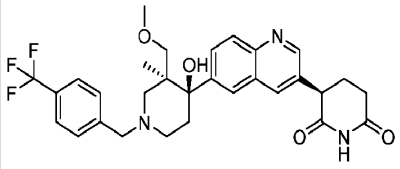
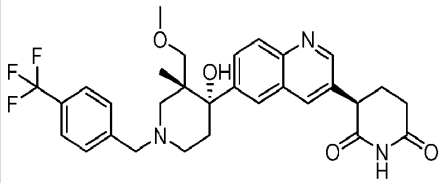
Cmpd No.	Compound Structure
I-770	
I-771	
I-772	
I-773	
I-774	
I-775	
I-776	

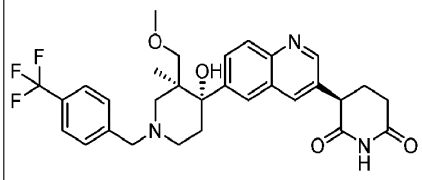
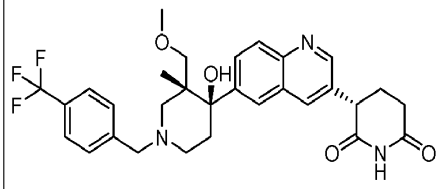
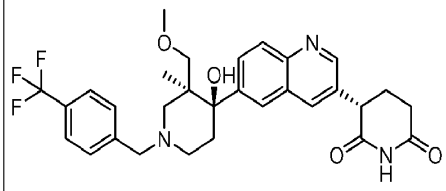
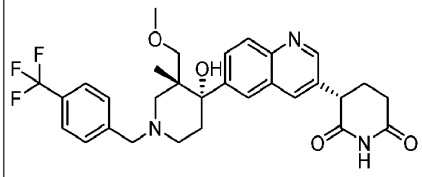
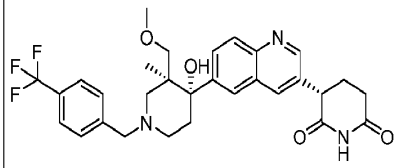
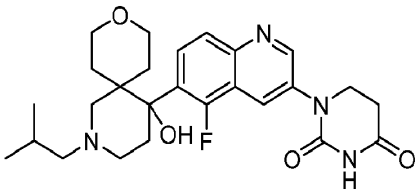
Cmpd No.	Compound Structure
I-777	
I-778	
I-779	
I-780	
I-781	
I-782	

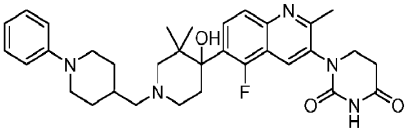
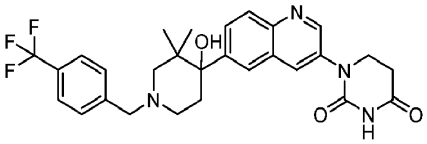
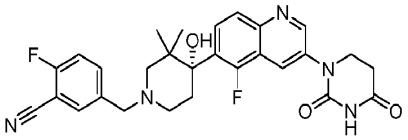
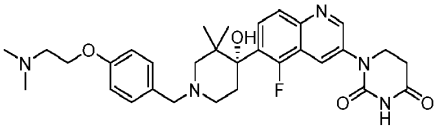
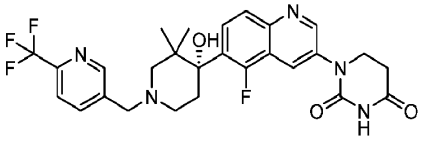
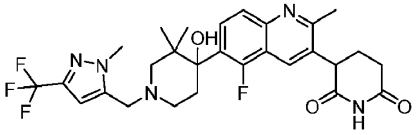
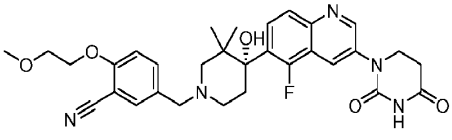
Cmpd No.	Compound Structure
I-783	
I-784	
I-785	
I-786	
I-787	
I-788	
I-789	

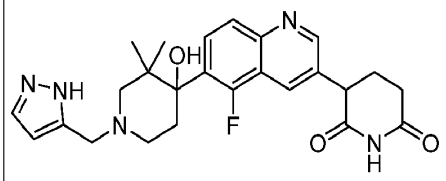
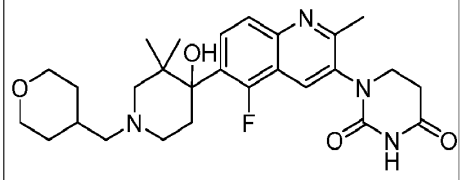
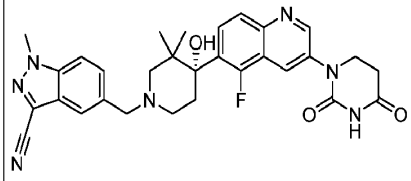
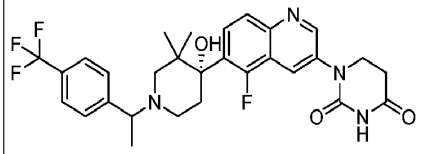
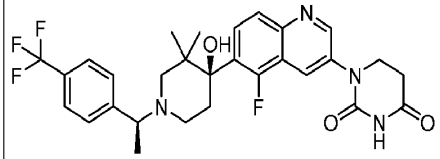
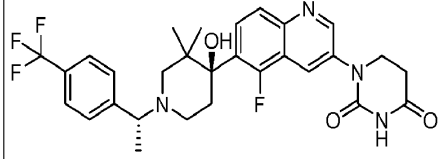
Cmpd No.	Compound Structure
I-790	
I-791	
I-792	
I-793	
I-794	
I-795	
I-796	

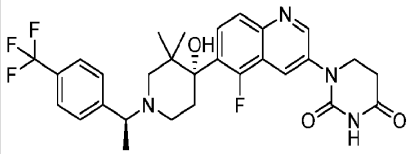
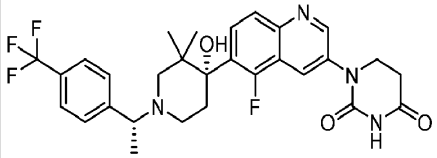
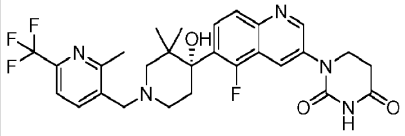
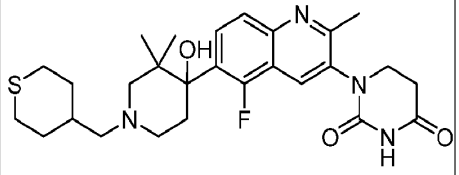
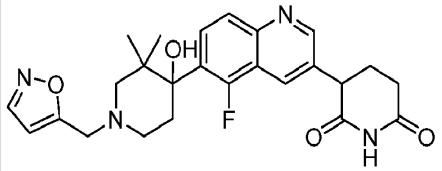
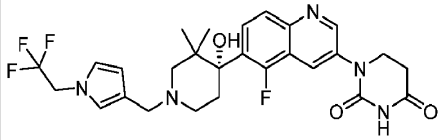
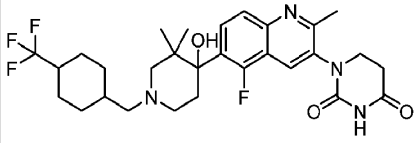
Cmpd No.	Compound Structure
I-797	
I-798	
I-799	
I-800	
I-801	
I-802	

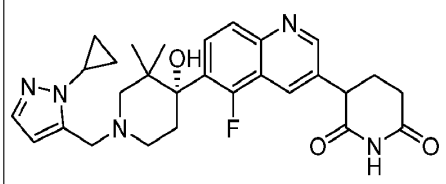
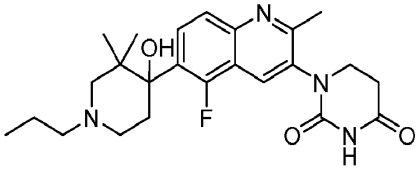
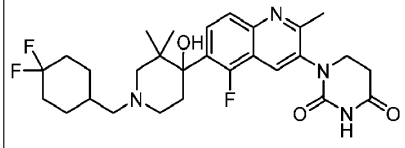
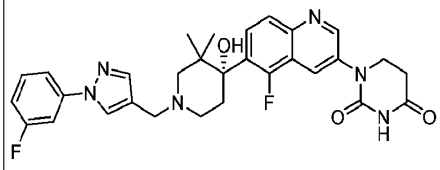
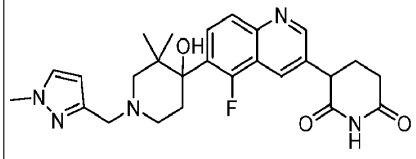
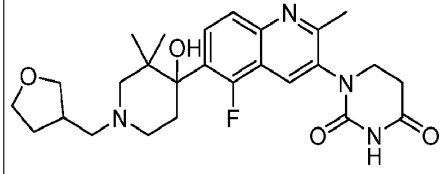
Cmpd No.	Compound Structure
I-803	
I-804	
I-805	
I-806	
I-807	
I-808	

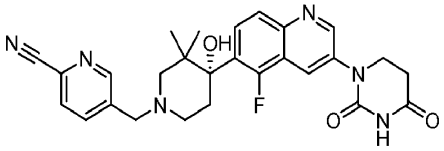
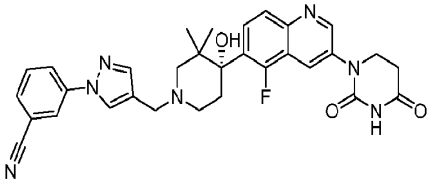
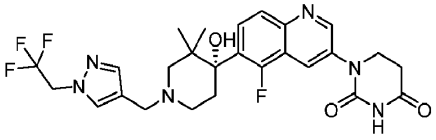
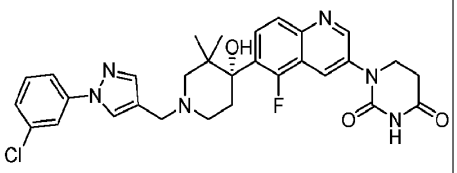
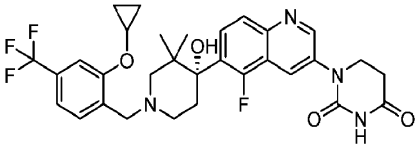
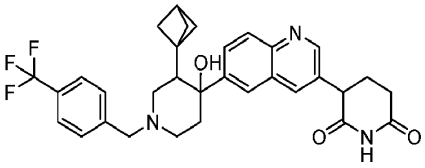
Cmpd No.	Compound Structure
I-809	
I-810	
I-811	
I-812	
I-813	
I-814	

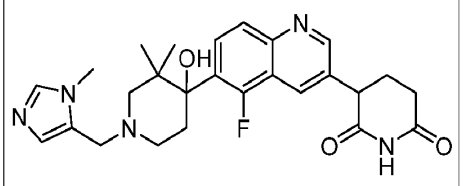
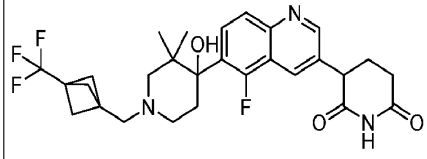
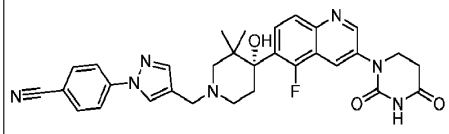
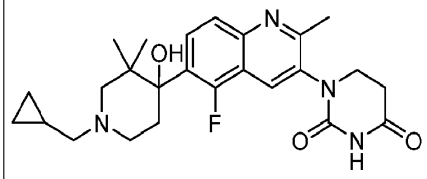
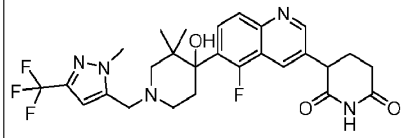
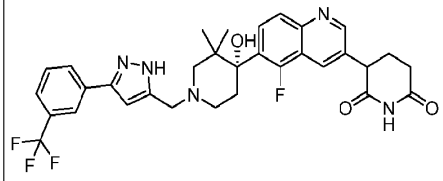
Cmpd No.	Compound Structure
I-815	
I-816	
I-817	
I-818	
I-819	
I-820	
I-821	

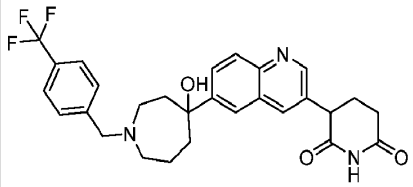
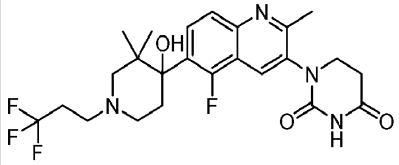
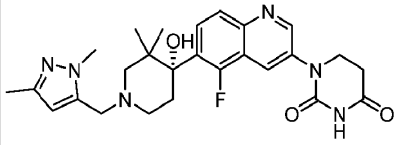
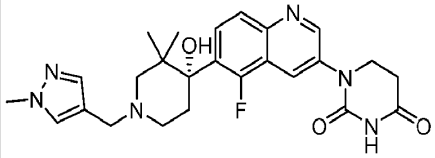
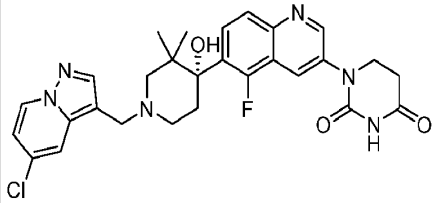
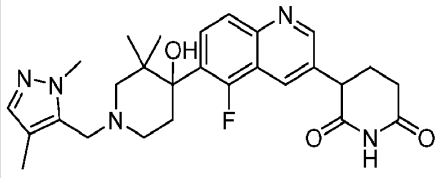
Cmpd No.	Compound Structure
I-822	
I-823	
I-824	
I-825	
I-826	
I-827	

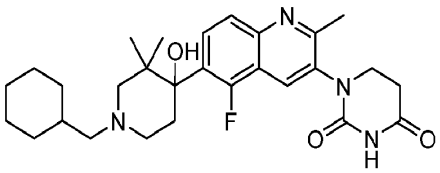
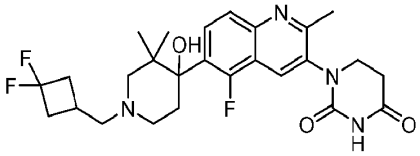
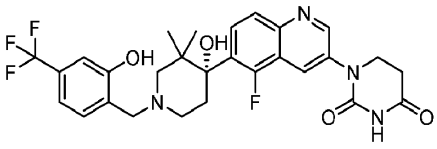
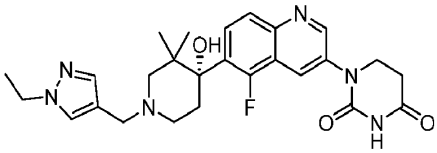
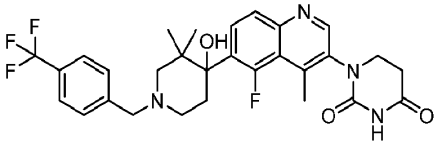
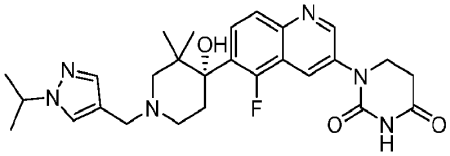
Cmpd No.	Compound Structure
I-828	
I-829	
I-830	
I-831	
I-832	
I-833	
I-834	

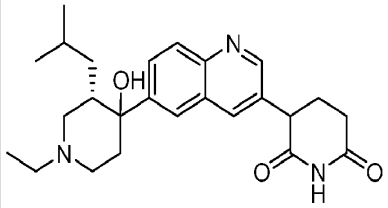
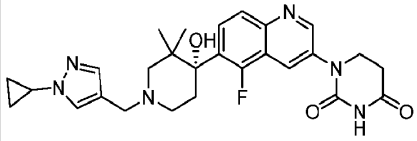
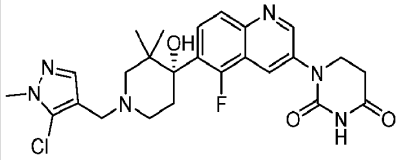
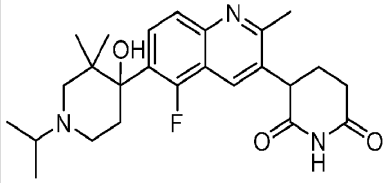
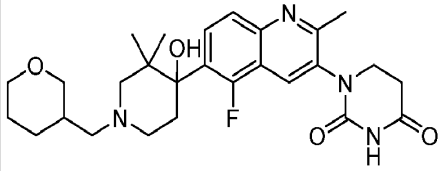
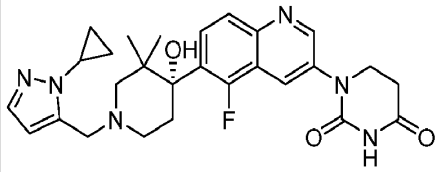
Cmpd No.	Compound Structure
I-835	
I-836	
I-837	
I-838	
I-839	
I-840	

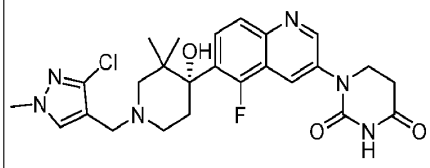
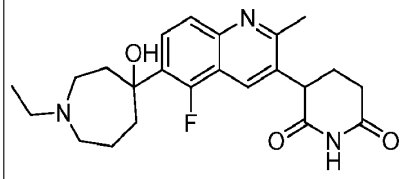
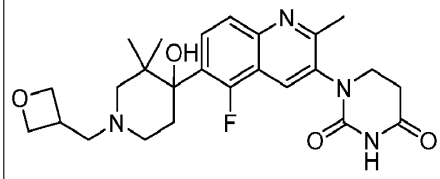
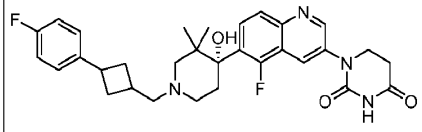
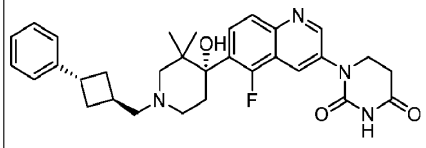
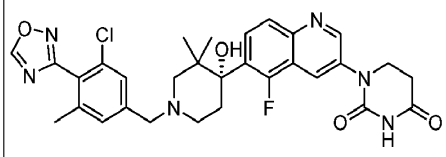
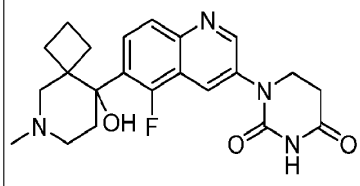
Cmpd No.	Compound Structure
I-841	
I-842	
I-843	
I-844	
I-845	
I-846	

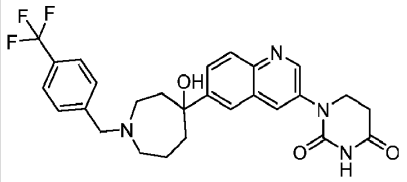
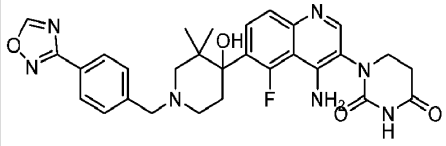
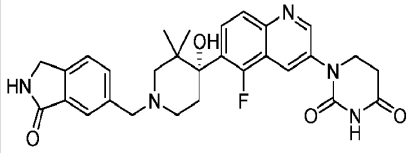
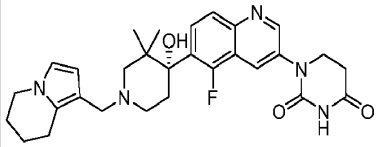
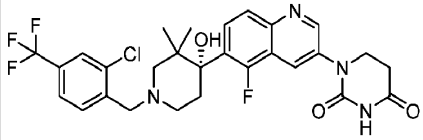
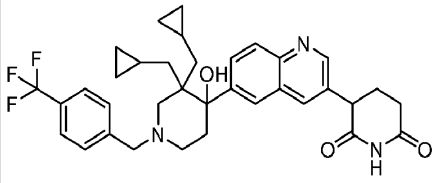
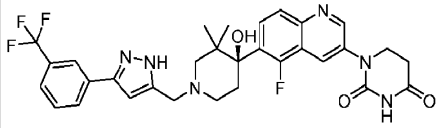
Cmpd No.	Compound Structure
I-847	
I-848	
I-849	
I-850	
I-851	
I-852	

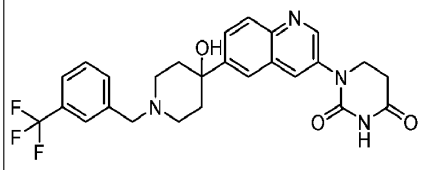
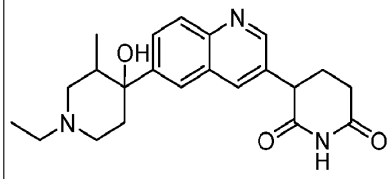
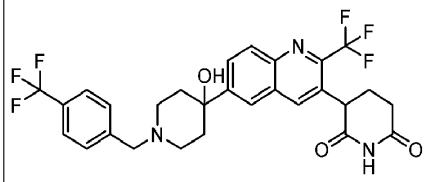
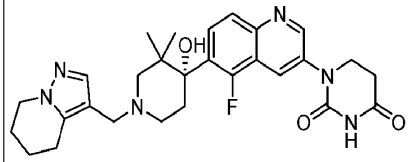
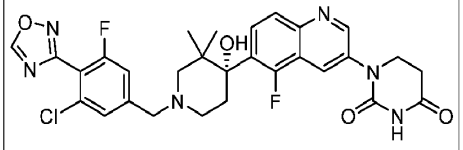
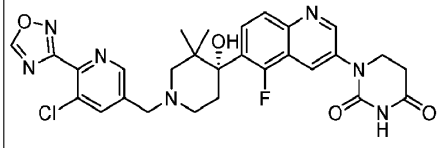
Cmpd No.	Compound Structure
I-853	
I-854	
I-855	
I-856	
I-857	
I-858	

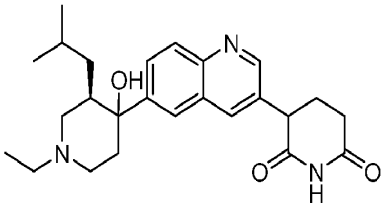
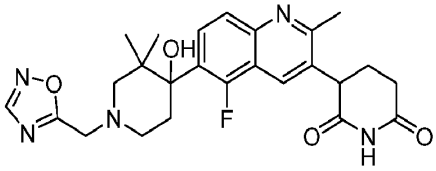
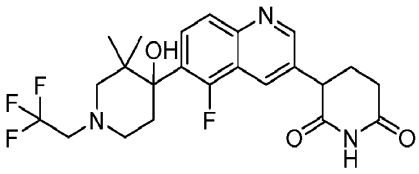
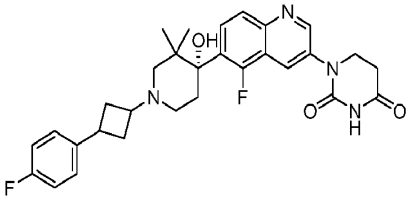
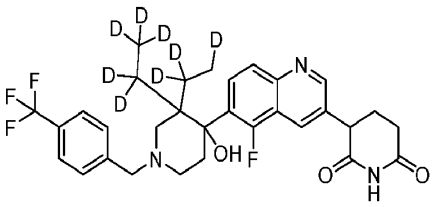
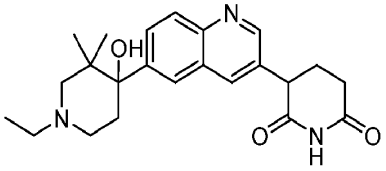
Cmpd No.	Compound Structure
I-859	
I-860	
I-861	
I-862	
I-863	
I-864	

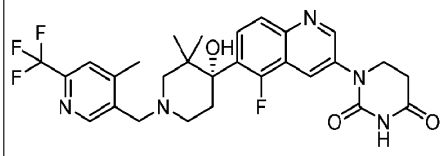
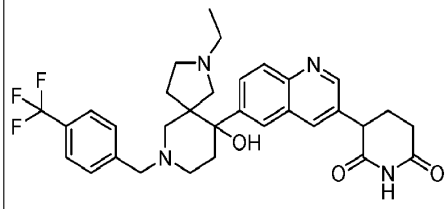
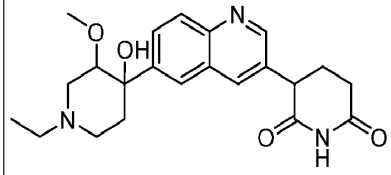
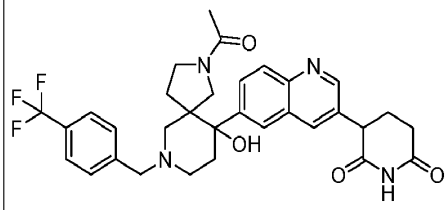
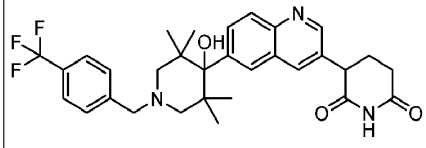
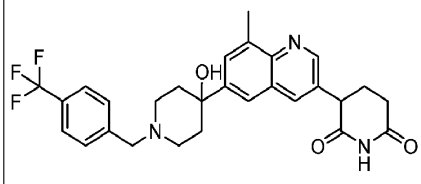
Cmpd No.	Compound Structure
I-865	
I-866	
I-867	
I-868	
I-869	
I-870	

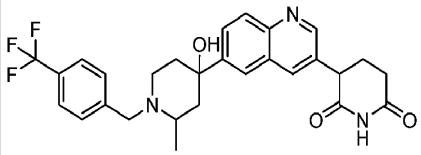
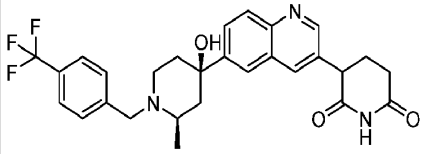
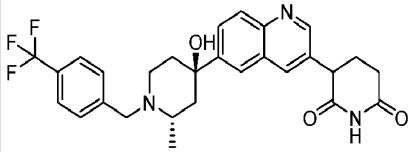
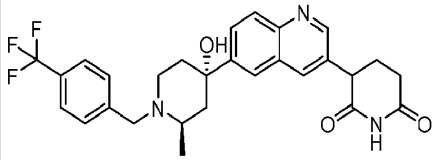
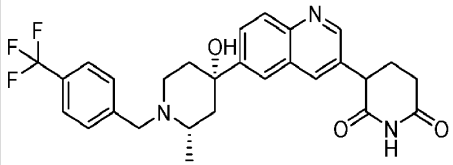
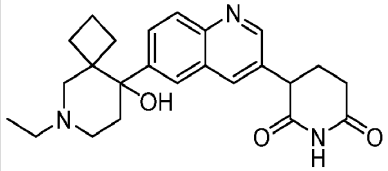
Cmpd No.	Compound Structure
I-871	
I-872	
I-873	
I-874	
I-875	
I-876	
I-877	

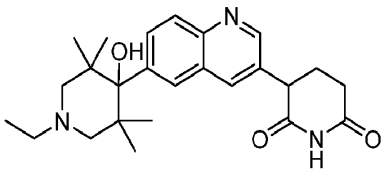
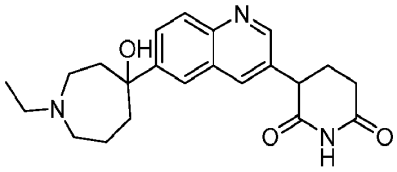
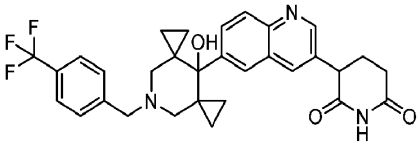
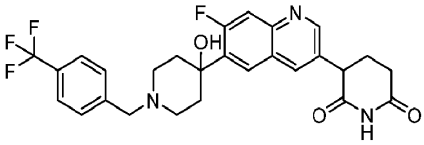
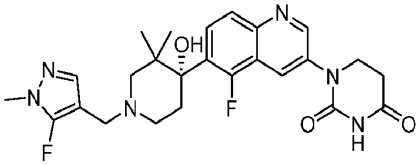
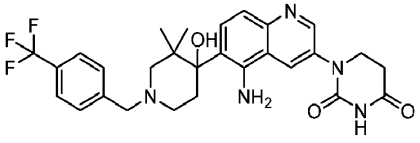
Cmpd No.	Compound Structure
I-878	
I-879	
I-880	
I-881	
I-882	
I-883	
I-884	

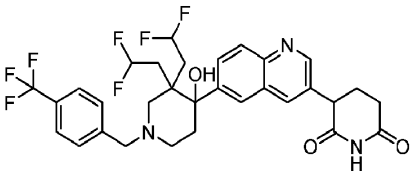
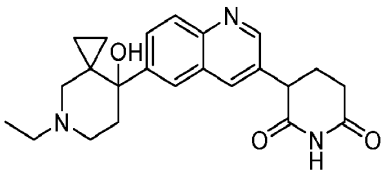
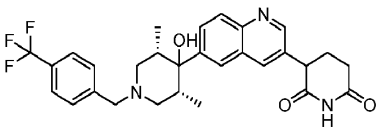
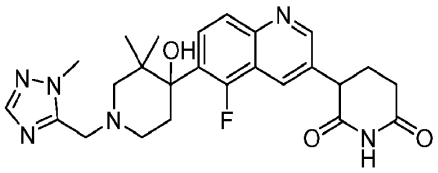
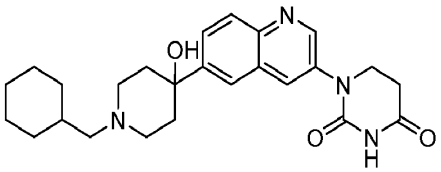
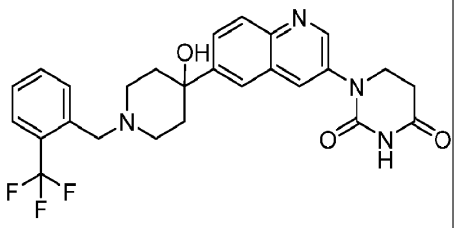
Cmpd No.	Compound Structure
I-885	
I-886	
I-887	
I-888	
I-889	
I-890	

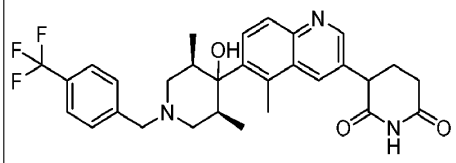
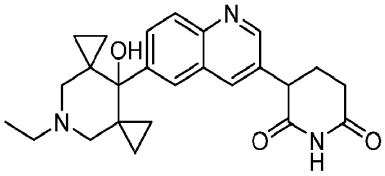
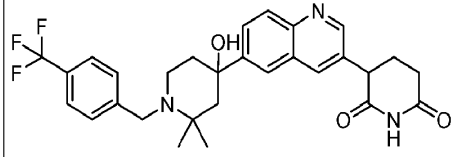
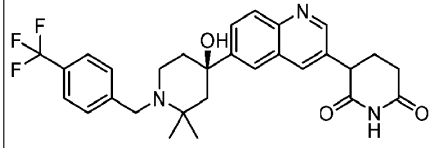
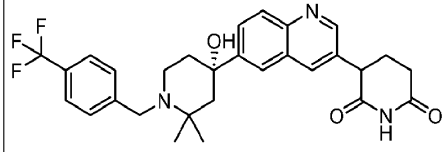
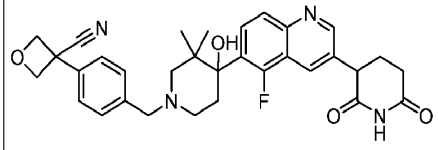
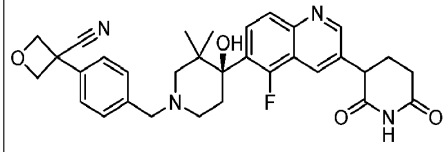
Cmpd No.	Compound Structure
I-891	
I-892	
I-893	
I-894	
I-895	
I-896	

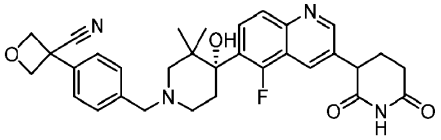
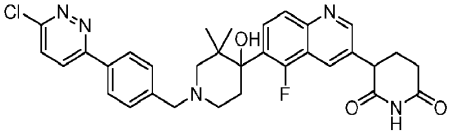
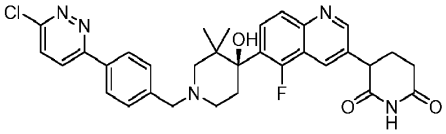
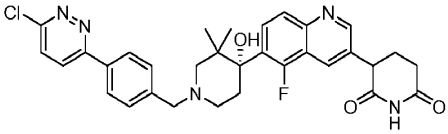
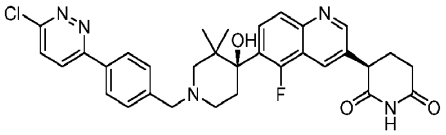
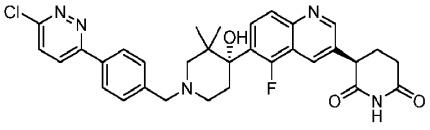
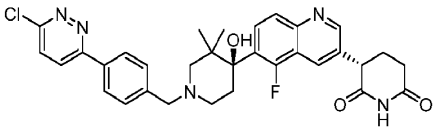
Cmpd No.	Compound Structure
I-897	
I-898	
I-899	
I-900	
I-901	
I-902	

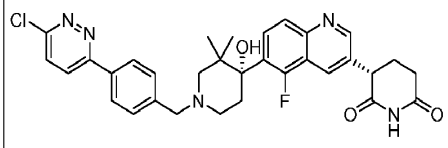
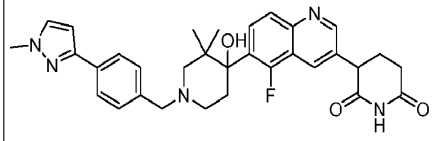
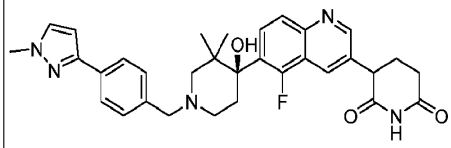
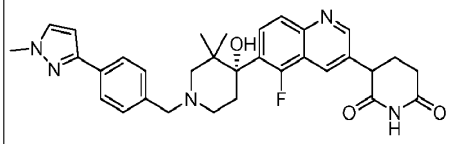
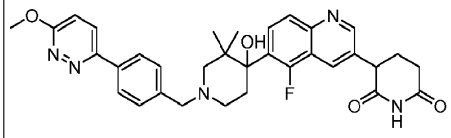
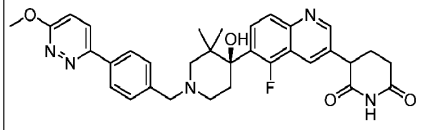
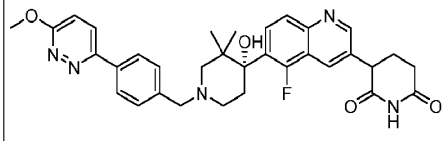
Cmpd No.	Compound Structure
I-903	
I-904	
I-905	
I-906	
I-907	
I-908	

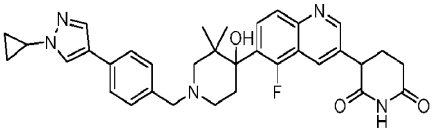
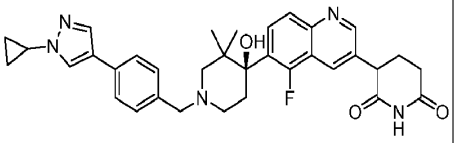
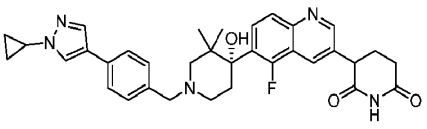
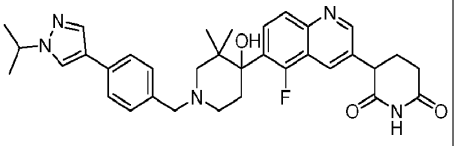
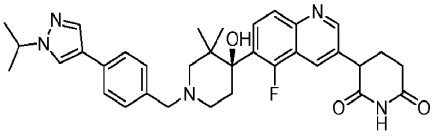
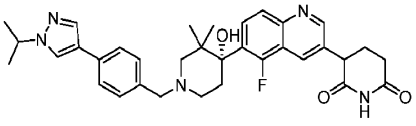
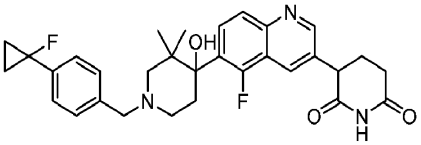
Cmpd No.	Compound Structure
I-909	
I-910	
I-911	
I-912	
I-913	
I-914	

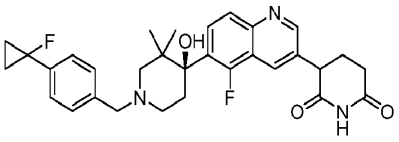
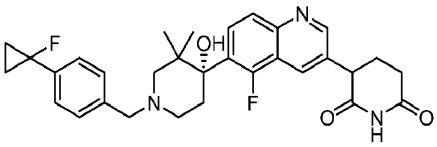
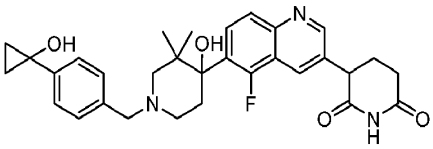
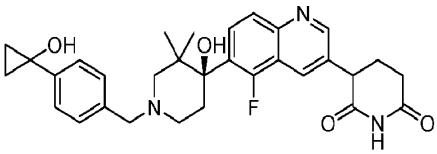
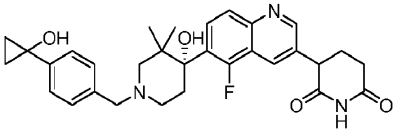
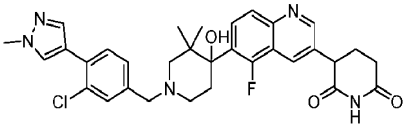
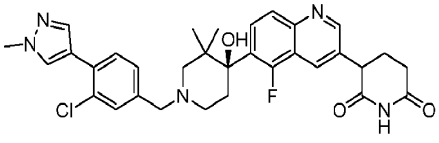
Cmpd No.	Compound Structure
I-915	
I-916	
I-917	
I-918	
I-919	
I-920	

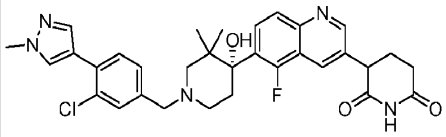
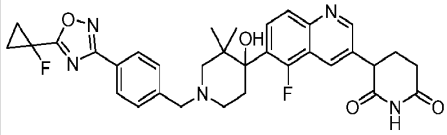
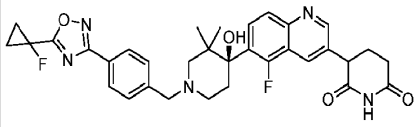
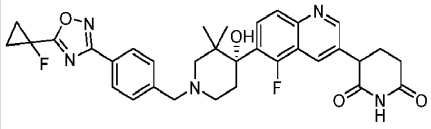
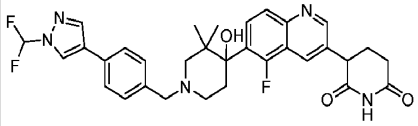
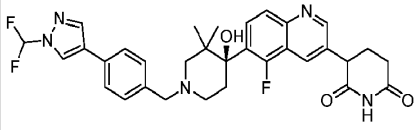
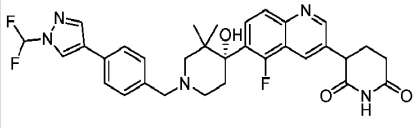
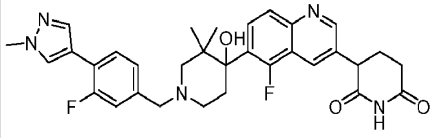
Cmpd No.	Compound Structure
I-921	
I-922	
I-923	
I-924	
I-925	
I-926	
I-927	

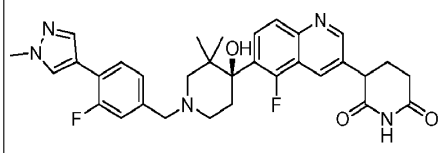
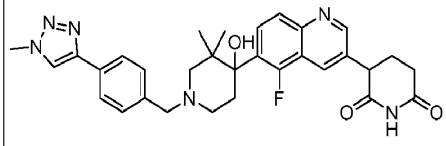
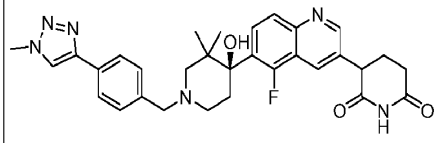
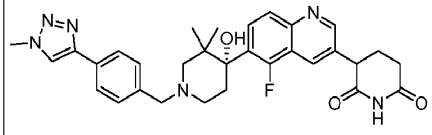
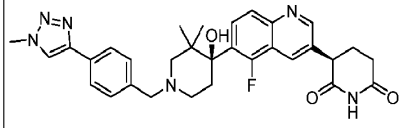
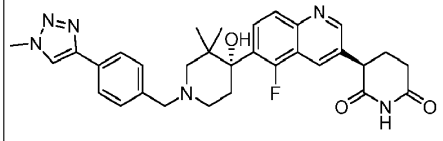
Cmpd No.	Compound Structure
I-928	
I-929	
I-930	
I-931	
I-932	
I-933	
I-934	

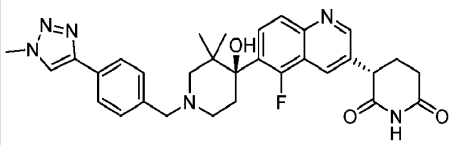
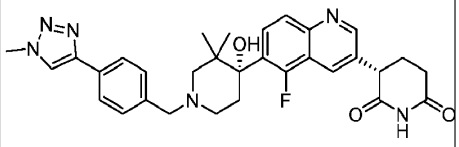
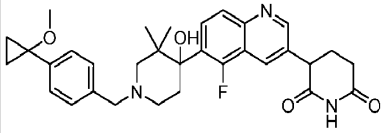
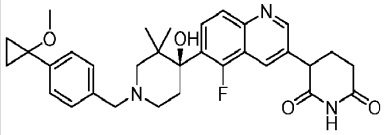
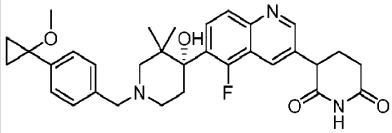
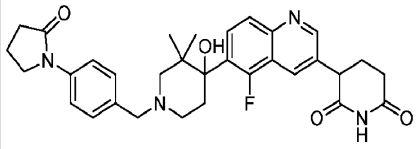
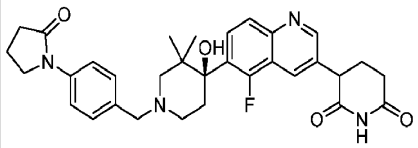
Cmpd No.	Compound Structure
I-935	
I-936	
I-937	
I-938	
I-939	
I-940	
I-941	

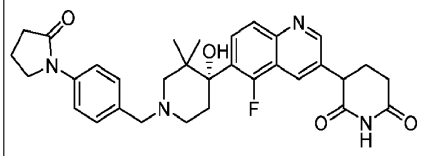
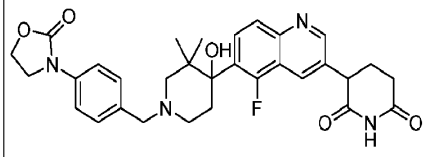
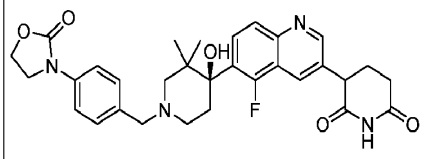
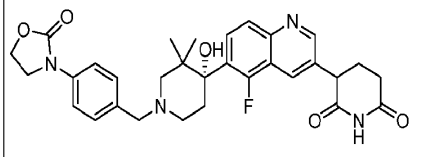
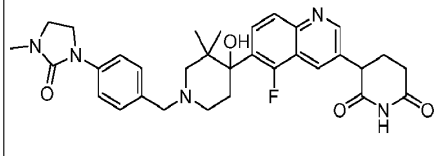
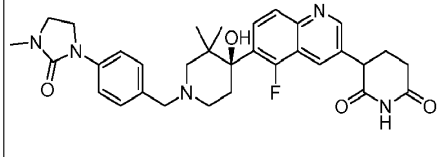
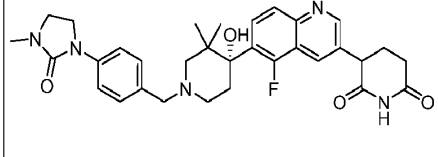
Cmpd No.	Compound Structure
I-942	
I-943	
I-944	
I-945	
I-946	
I-947	
I-948	

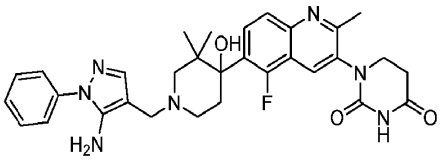
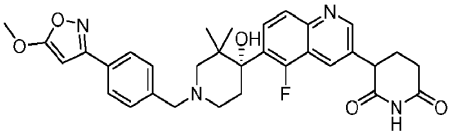
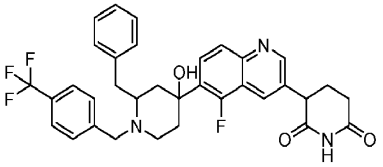
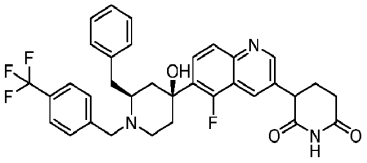
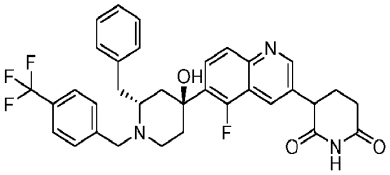
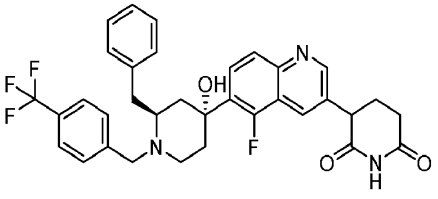
Cmpd No.	Compound Structure
I-949	
I-950	
I-951	
I-952	
I-953	
I-954	
I-955	

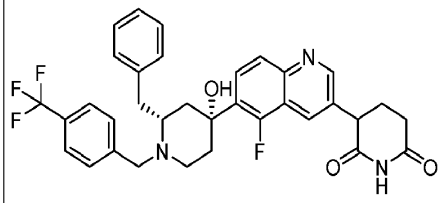
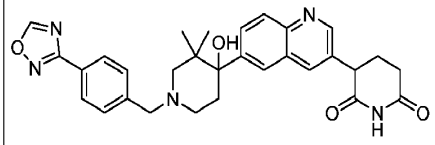
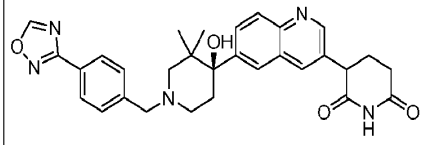
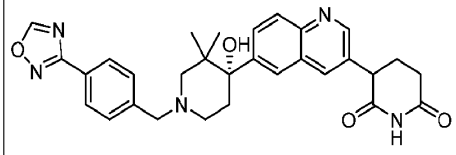
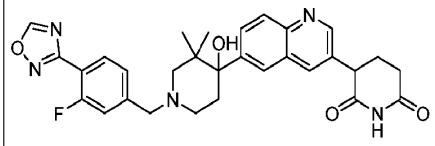
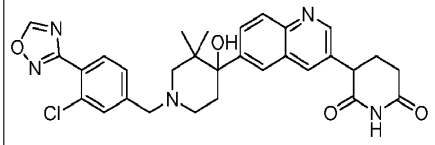
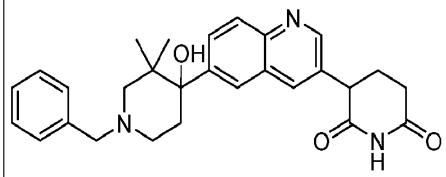
Cmpd No.	Compound Structure
I-956	
I-957	
I-958	
I-959	
I-960	
I-961	
I-962	
I-963	

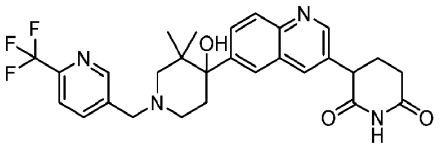
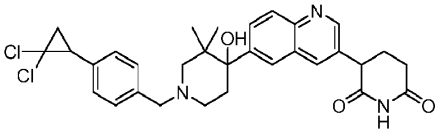
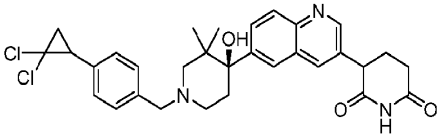
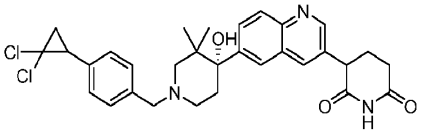
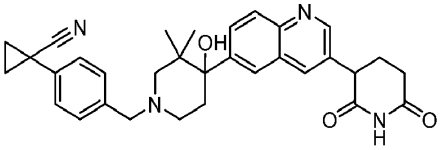
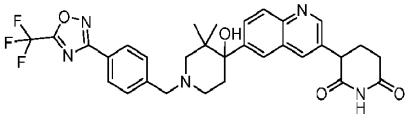
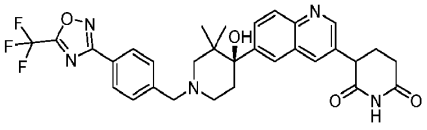
Cmpd No.	Compound Structure
I-964	
I-965	
I-966	
I-967	
I-968	
I-969	
I-970	

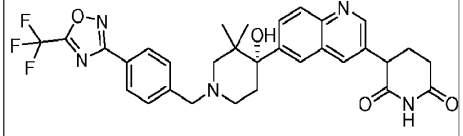
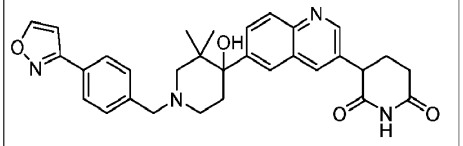
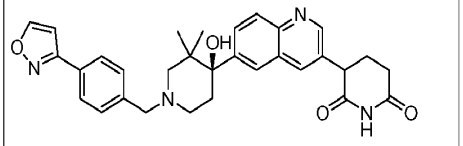
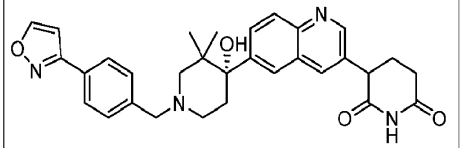
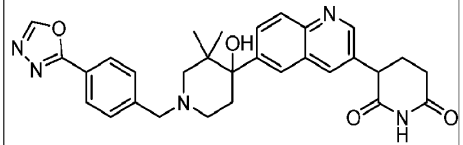
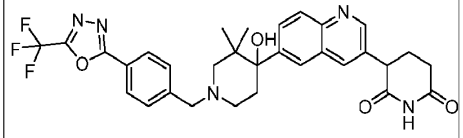
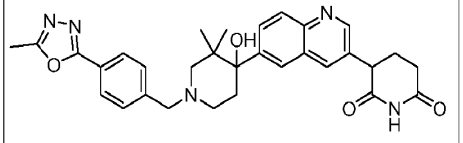
Cmpd No.	Compound Structure
I-971	
I-972	
I-973	
I-974	
I-975	
I-976	
I-977	

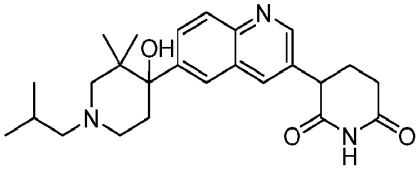
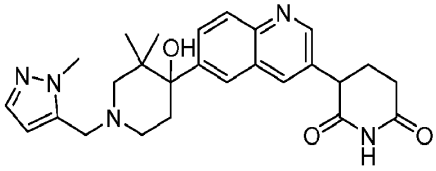
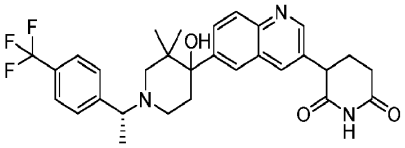
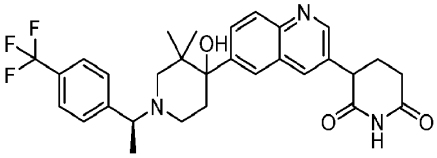
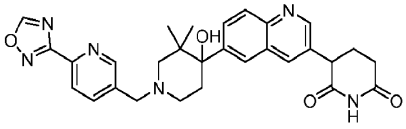
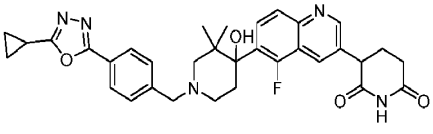
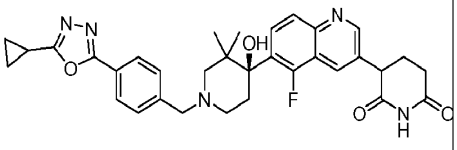
Cmpd No.	Compound Structure
I-978	
I-979	
I-980	
I-981	
I-982	
I-983	
I-984	

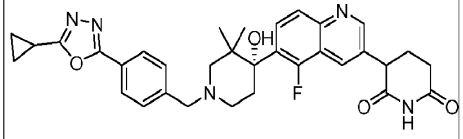
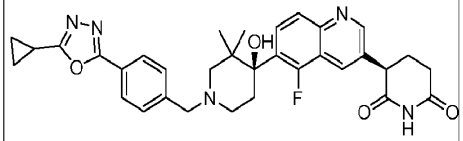
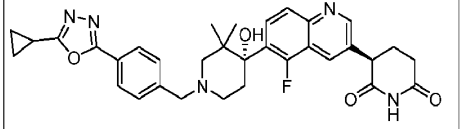
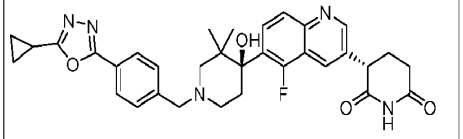
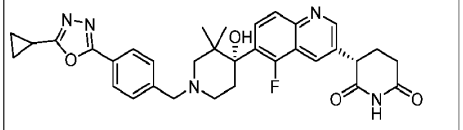
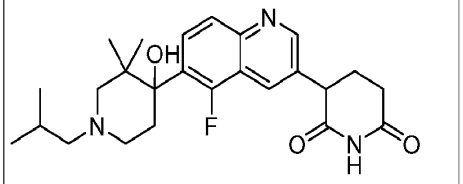
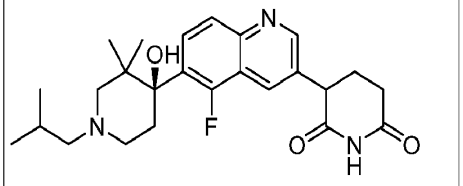
Cmpd No.	Compound Structure
I-985	
I-986	
I-987	
I-988	
I-989	
I-990	

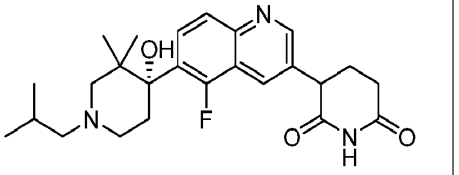
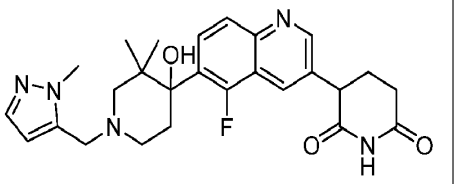
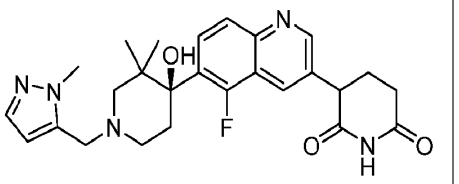
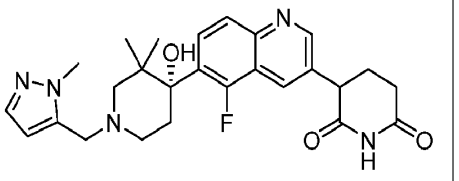
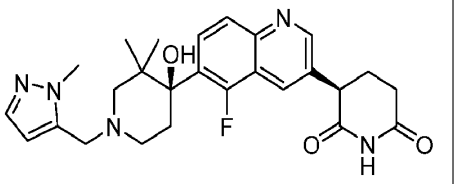
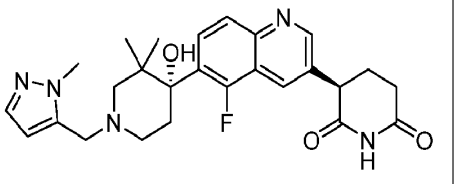
Cmpd No.	Compound Structure
I-991	
I-992	
I-993	
I-994	
I-995	
I-996	
I-997	

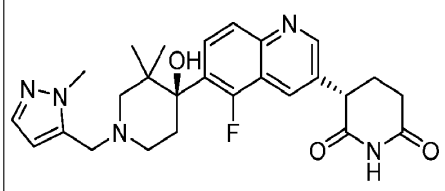
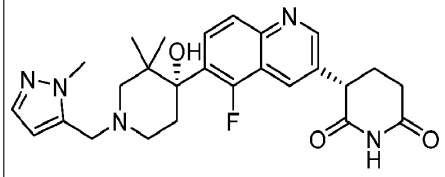
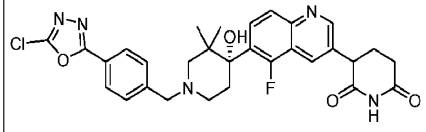
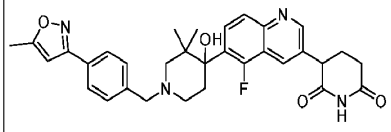
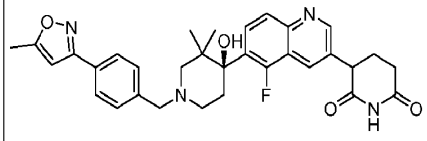
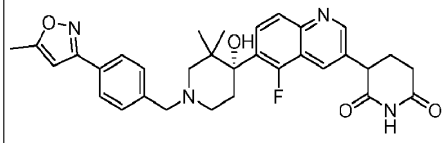
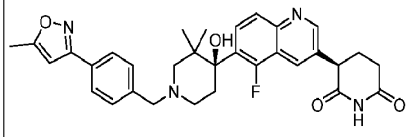
Cmpd No.	Compound Structure
I-998	
I-999	
I-1000	
I-1001	
I-1002	
I-1003	
I-1004	

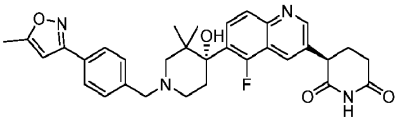
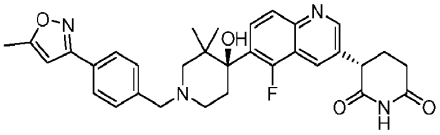
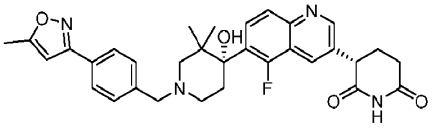
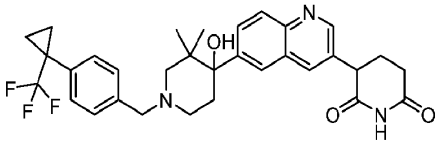
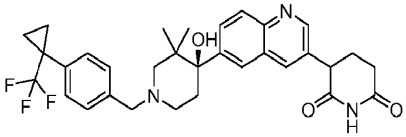
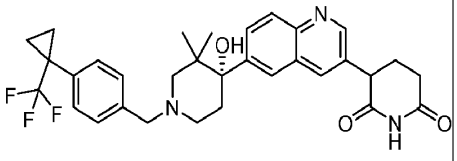
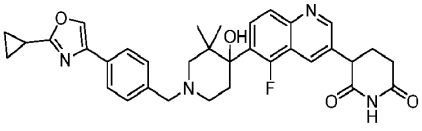
Cmpd No.	Compound Structure
I-1005	
I-1006	
I-1007	
I-1008	
I-1009	
I-1010	
I-1011	

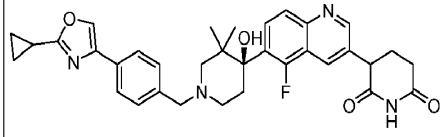
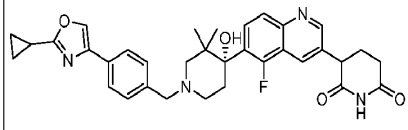
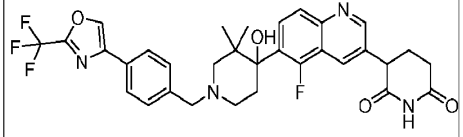
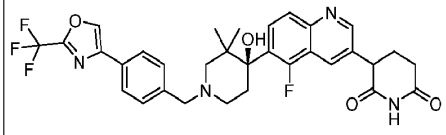
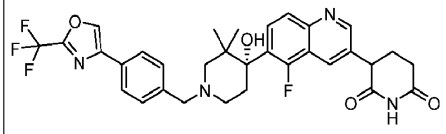
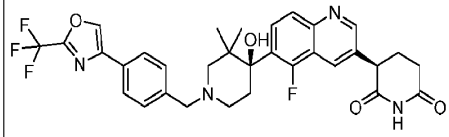
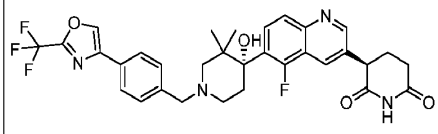
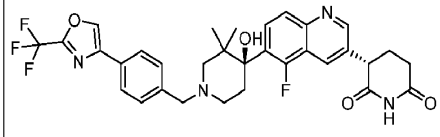
Cmpd No.	Compound Structure
I-1012	
I-1013	
I-1014	
I-1015	
I-1016	
I-1017	
I-1018	

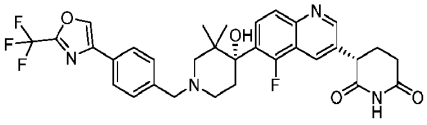
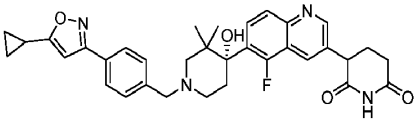
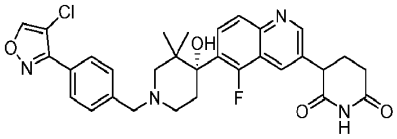
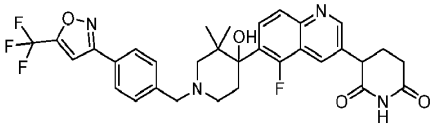
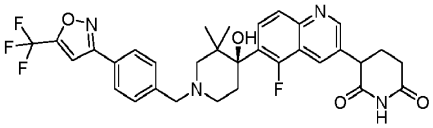
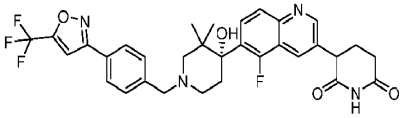
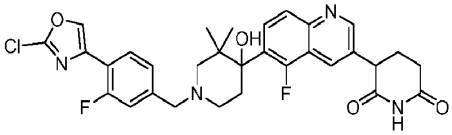
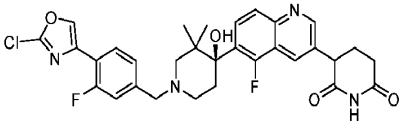
Cmpd No.	Compound Structure
I-1019	
I-1020	
I-1021	
I-1022	
I-1023	
I-1024	
I-1025	

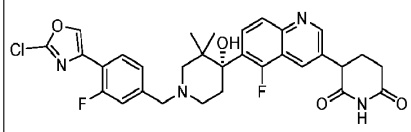
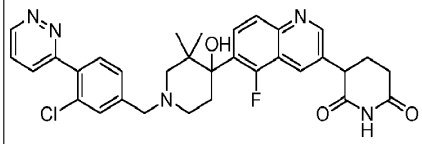
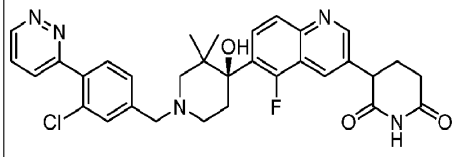
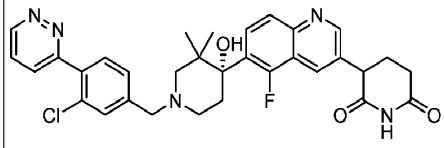
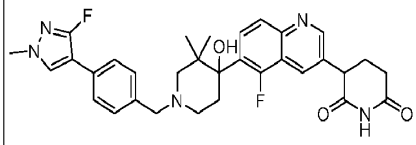
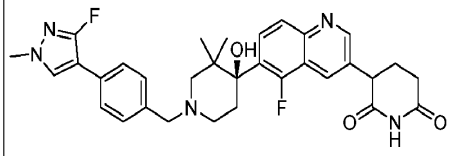
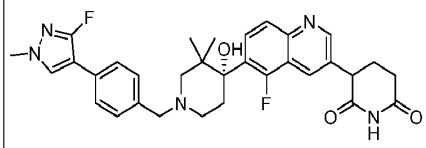
Cmpd No.	Compound Structure
I-1026	
I-1027	
I-1028	
I-1029	
I-1030	
I-1031	

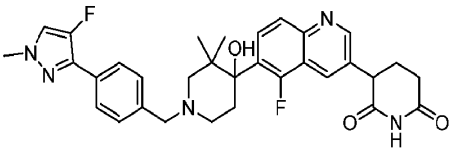
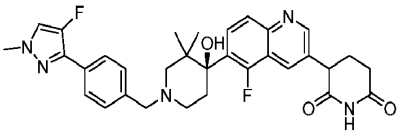
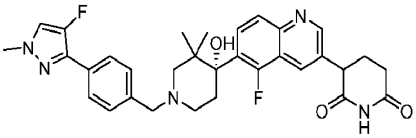
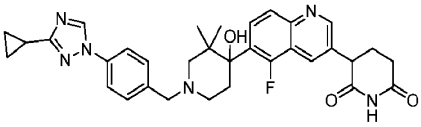
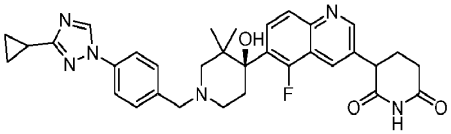
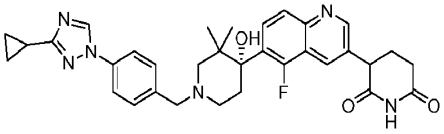
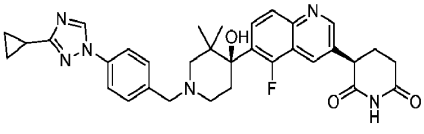
Cmpd No.	Compound Structure
I-1032	
I-1033	
I-1034	
I-1035	
I-1036	
I-1037	
I-1038	

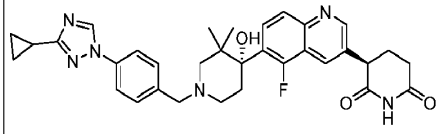
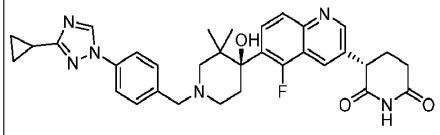
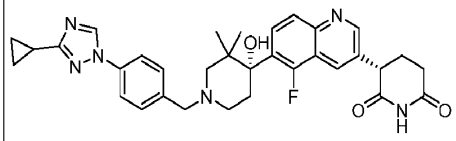
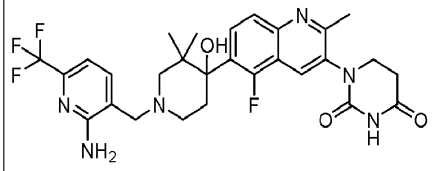
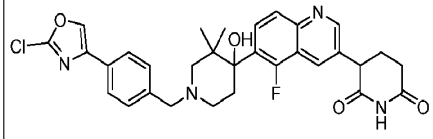
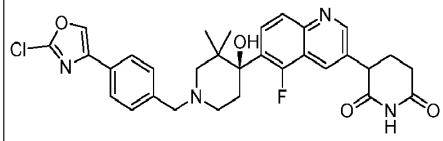
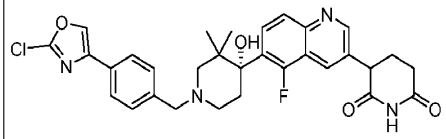
Cmpd No.	Compound Structure
I-1039	
I-1040	
I-1041	
I-1042	
I-1043	
I-1044	
I-1045	

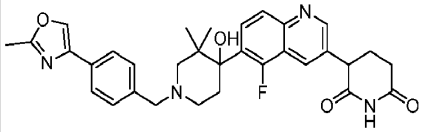
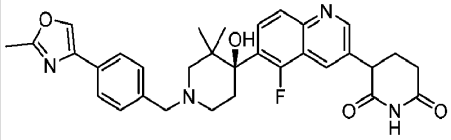
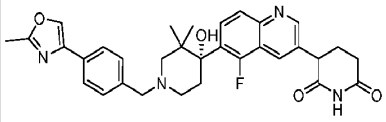
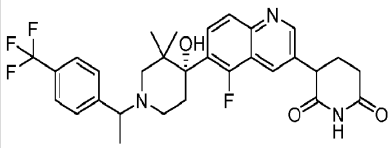
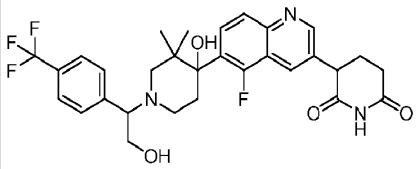
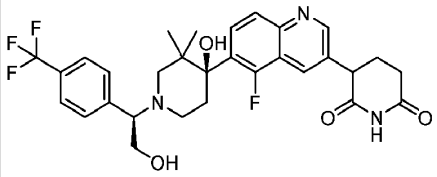
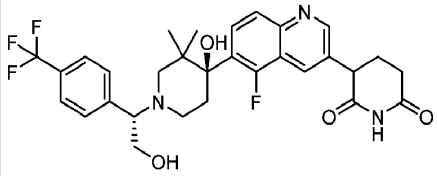
Cmpd No.	Compound Structure
I-1046	
I-1047	
I-1048	
I-1049	
I-1050	
I-1051	
I-1052	
I-1053	

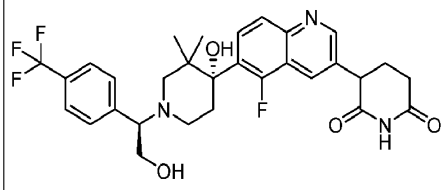
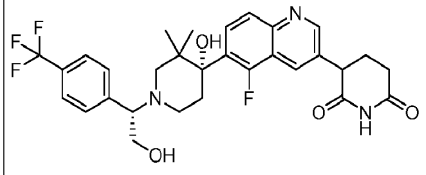
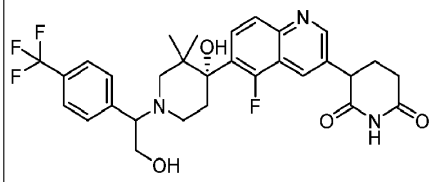
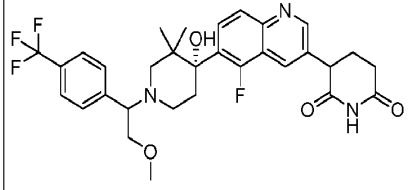
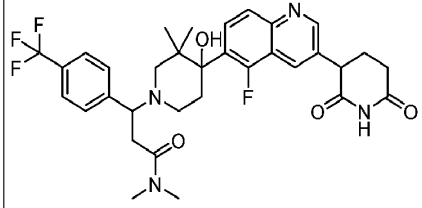
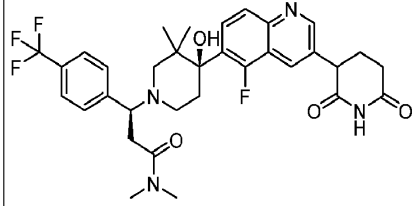
Cmpd No.	Compound Structure
I-1054	
I-1055	
I-1056	
I-1057	
I-1058	
I-1059	
I-1060	
I-1061	

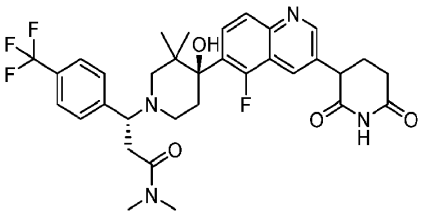
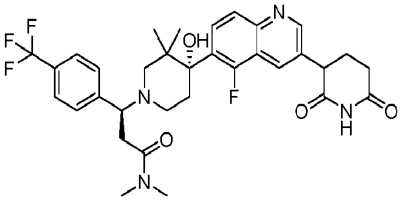
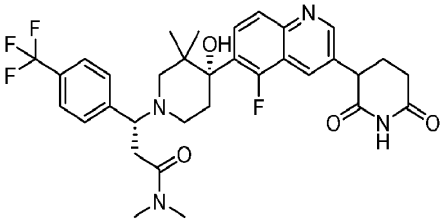
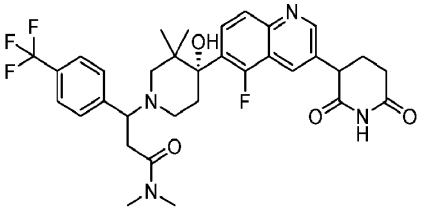
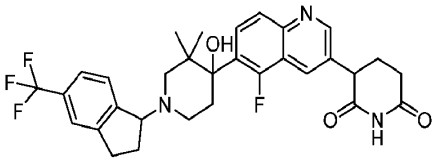
Cmpd No.	Compound Structure
I-1062	
I-1063	
I-1064	
I-1065	
I-1066	
I-1067	
I-1068	

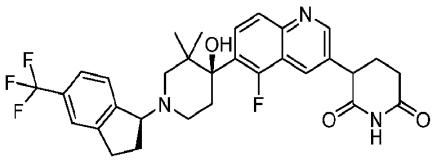
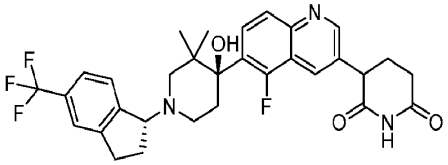
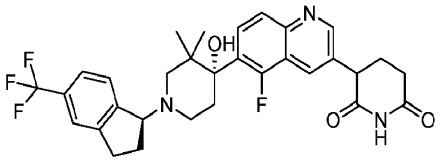
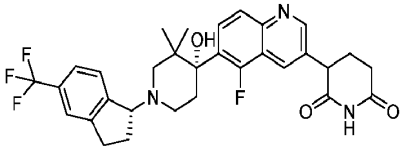
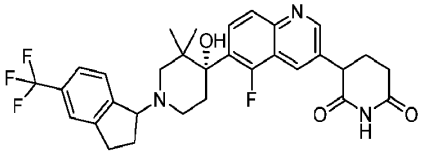
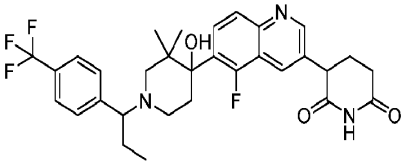
Cmpd No.	Compound Structure
I-1069	
I-1070	
I-1071	
I-1072	
I-1073	
I-1074	
I-1075	

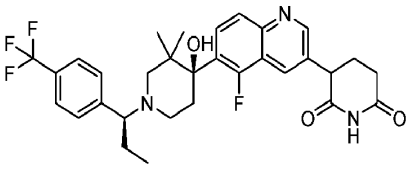
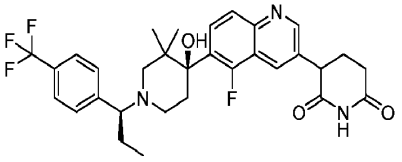
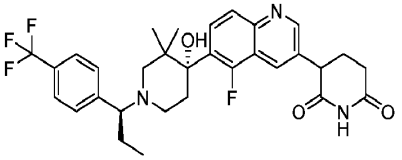
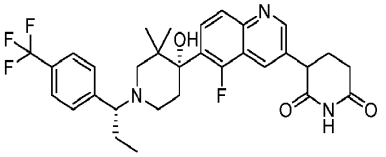
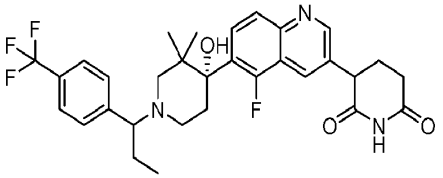
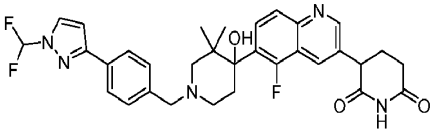
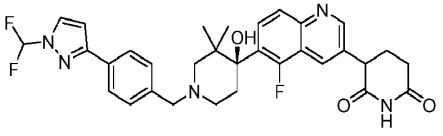
Cmpd No.	Compound Structure
I-1076	
I-1077	
I-1078	
I-1079	
I-1080	
I-1081	
I-1082	

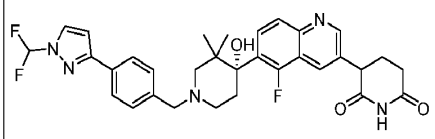
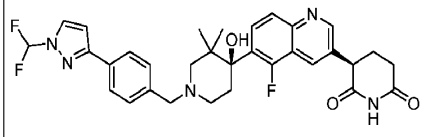
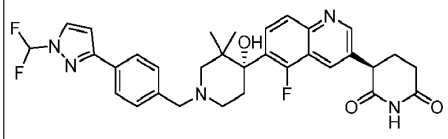
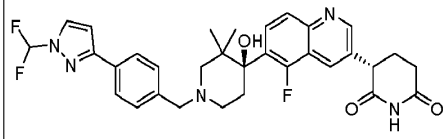
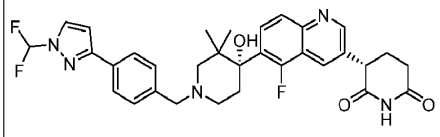
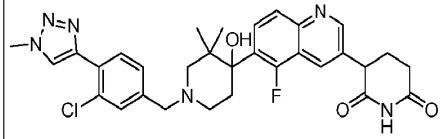
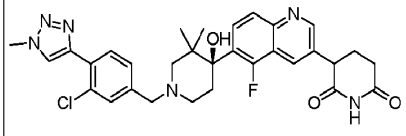
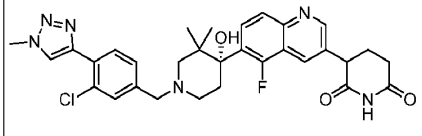
Cmpd No.	Compound Structure
I-1083	
I-1084	
I-1085	
I-1086	
I-1087	
I-1088	
I-1089	

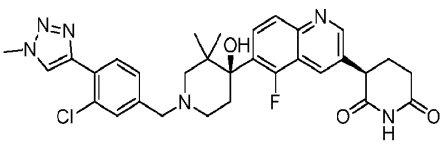
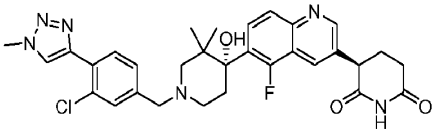
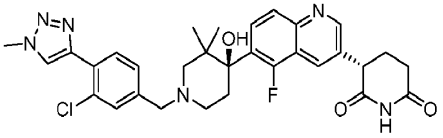
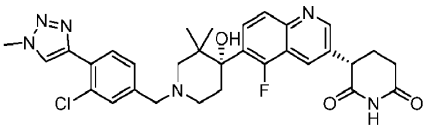
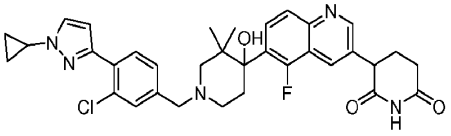
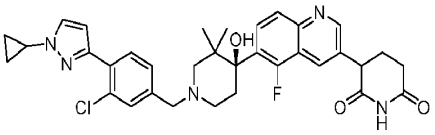
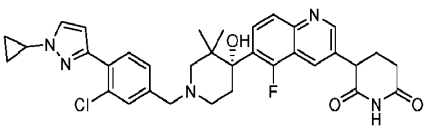
Cmpd No.	Compound Structure
I-1090	
I-1091	
I-1092	
I-1093	
I-1094	
I-1095	

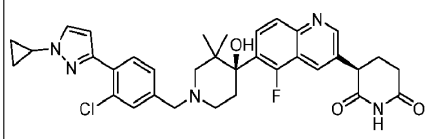
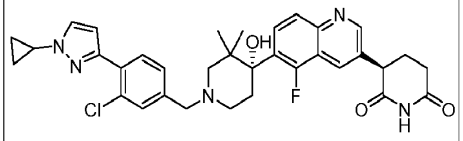
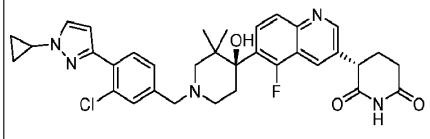
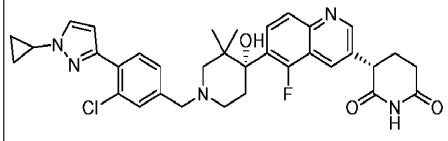
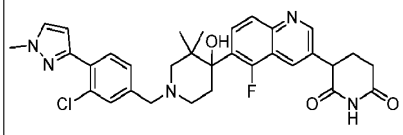
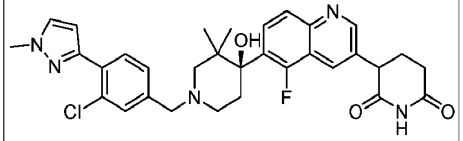
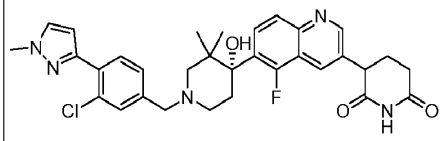
Cmpd No.	Compound Structure
I-1096	
I-1097	
I-1098	
I-1099	
I-1100	

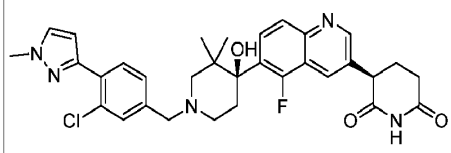
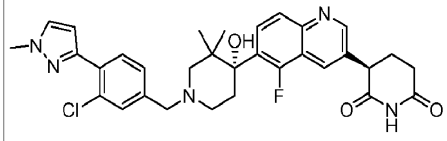
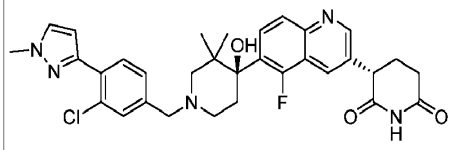
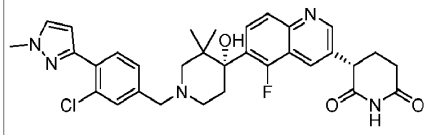
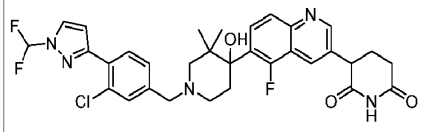
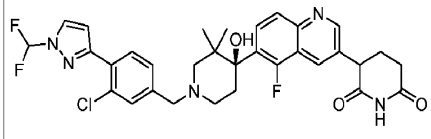
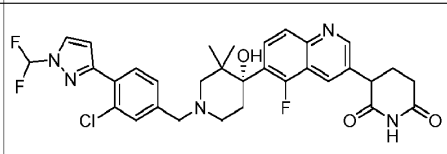
Cmpd No.	Compound Structure
I-1101	
I-1102	
I-1103	
I-1104	
I-1105	
I-1106	

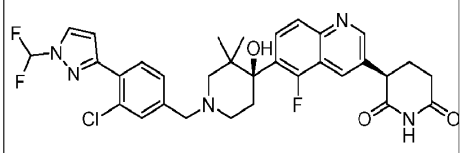
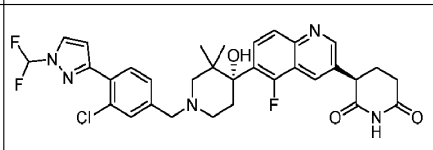
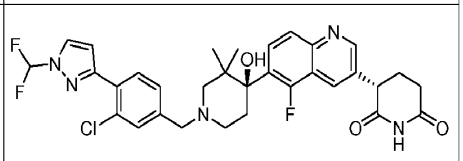
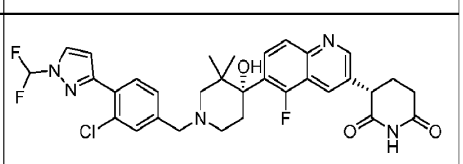
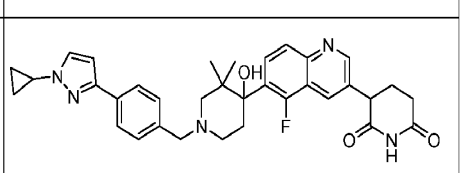
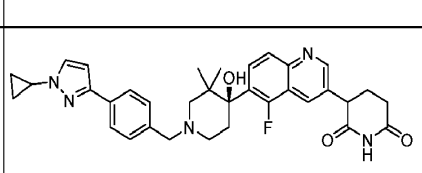
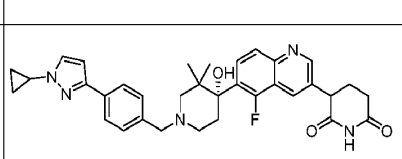
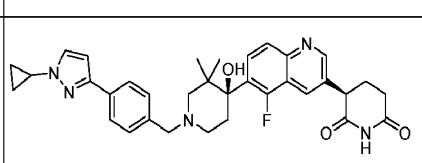
Cmpd No.	Compound Structure
I-1107	
I-1108	
I-1109	
I-1110	
I-1111	
I-1119	
I-1120	

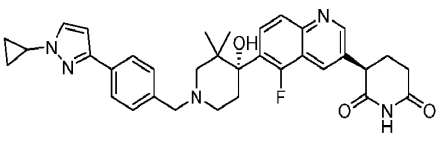
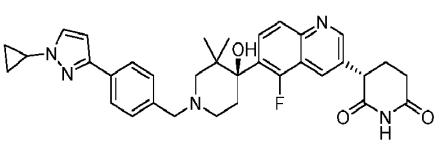
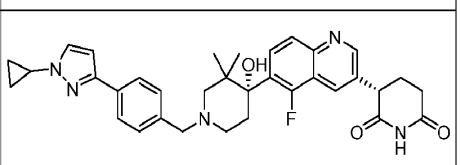
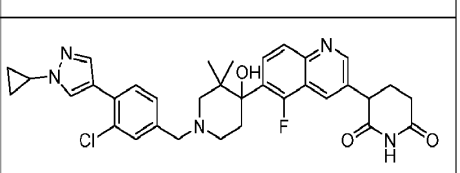
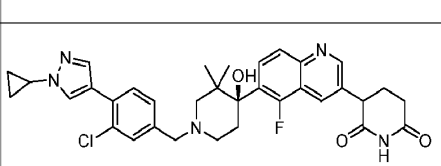
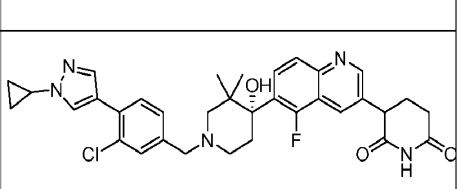
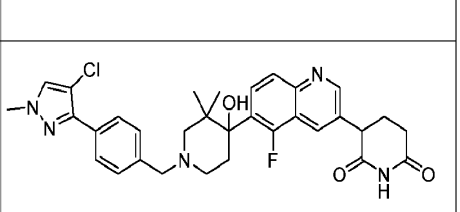
Cmpd No.	Compound Structure
I-1121	
I-1122	
I-1123	
I-1124	
I-1125	
I-1126	
I-1127	
I-1128	

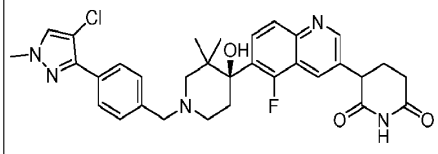
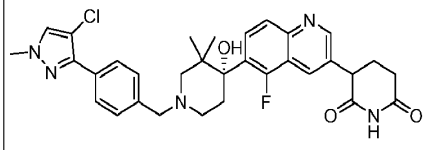
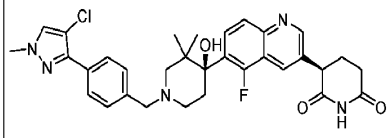
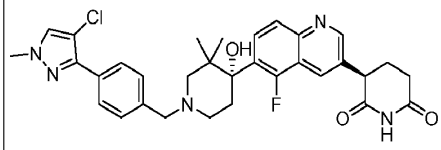
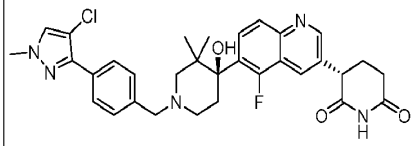
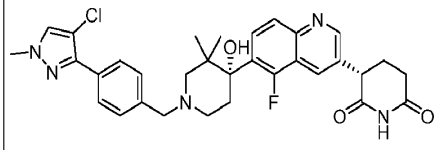
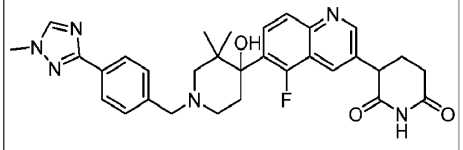
Cmpd No.	Compound Structure
I-1129	
I-1130	
I-1131	
I-1132	
I-1133	
I-1134	
I-1135	

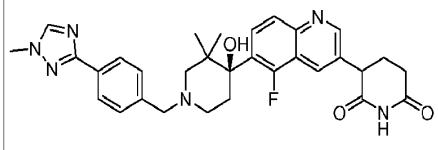
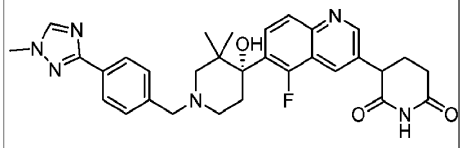
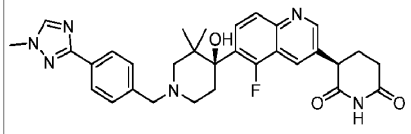
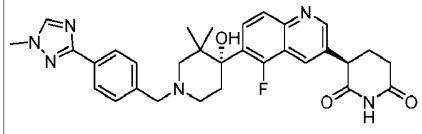
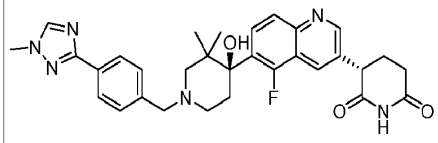
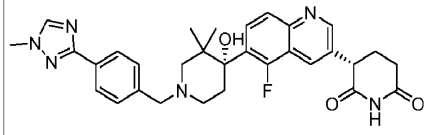
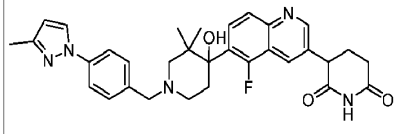
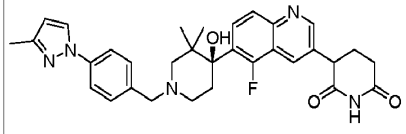
Cmpd No.	Compound Structure
I-1136	
I-1137	
I-1138	
I-1139	
I-1140	
I-1141	
I-1142	

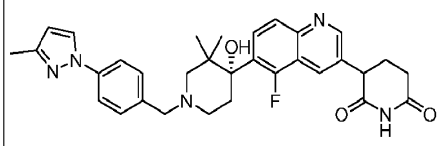
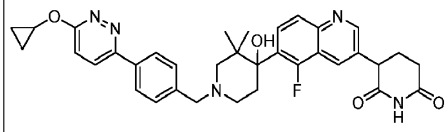
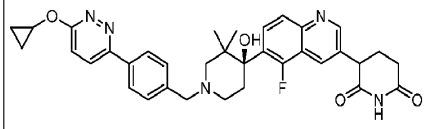
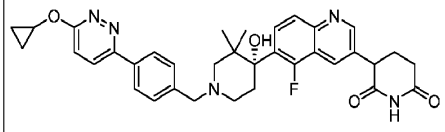
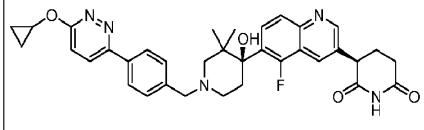
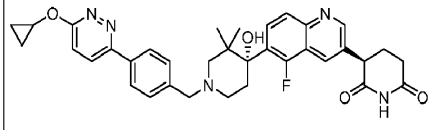
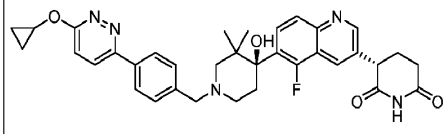
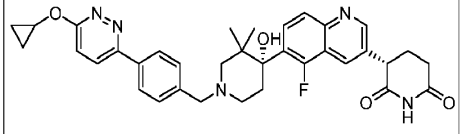
Cmpd No.	Compound Structure
I-1143	
I-1144	
I-1145	
I-1146	
I-1147	
I-1148	
I-1149	

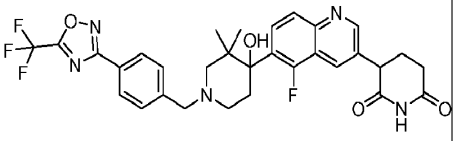
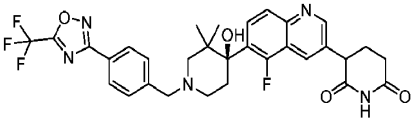
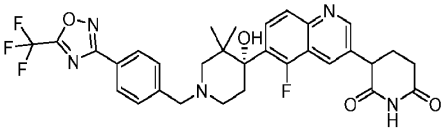
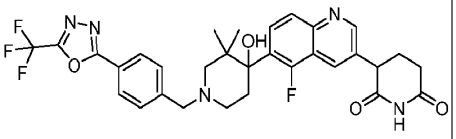
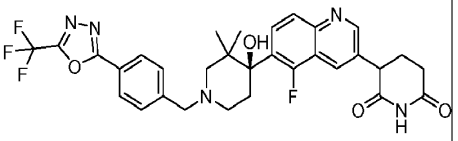
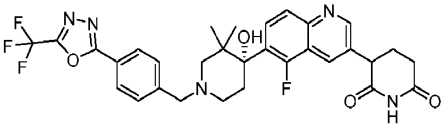
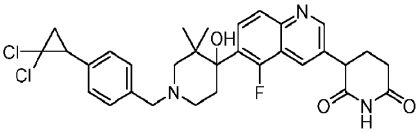
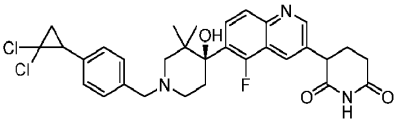
Cmpd No.	Compound Structure
I-1150	
I-1151	
I-1152	
I-1153	
I-1154	
I-1155	
I-1156	
I-1157	

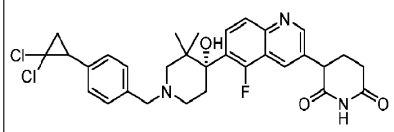
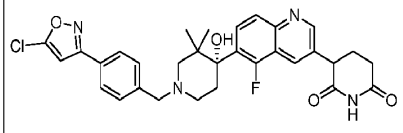
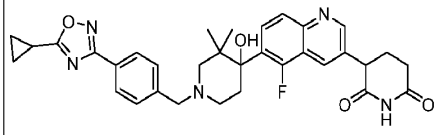
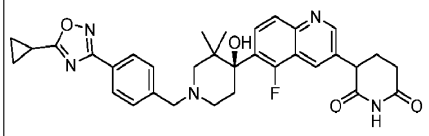
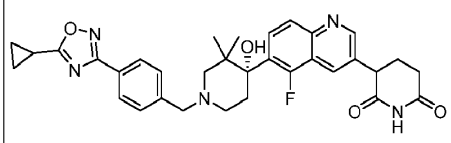
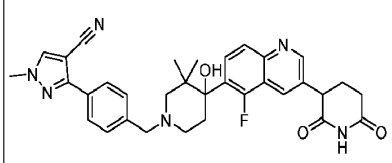
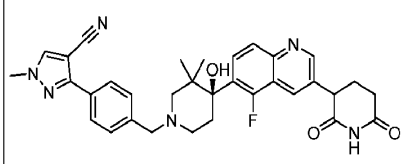
Cmpd No.	Compound Structure
I-1158	
I-1159	
I-1160	
I-1161	
I-1162	
I-1163	
I-1164	

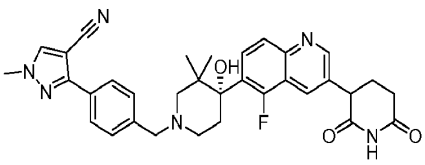
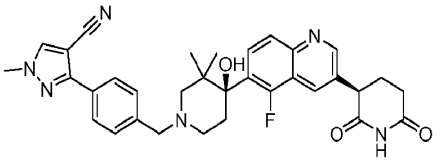
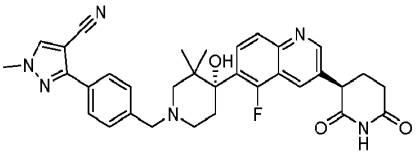
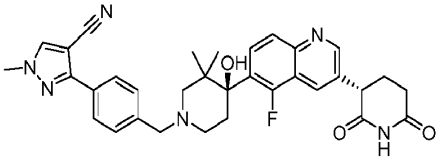
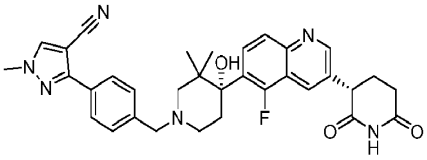
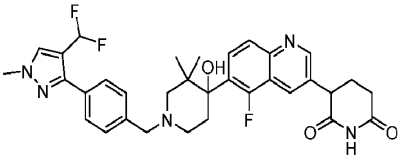
Cmpd No.	Compound Structure
I-1165	
I-1166	
I-1167	
I-1168	
I-1169	
I-1170	
I-1171	

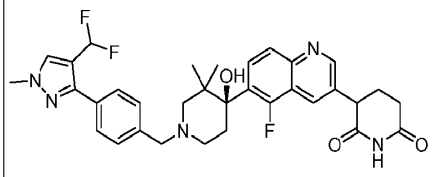
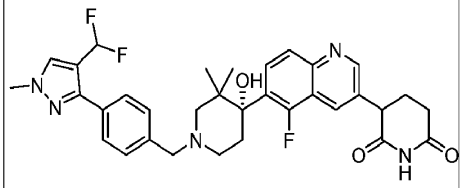
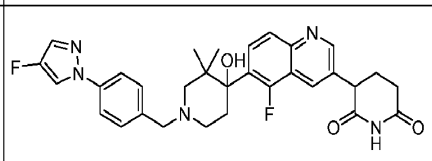
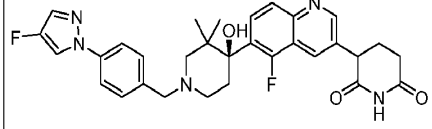
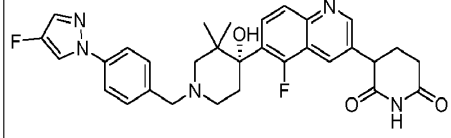
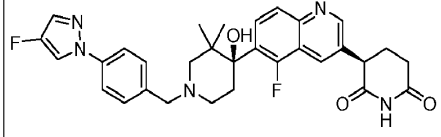
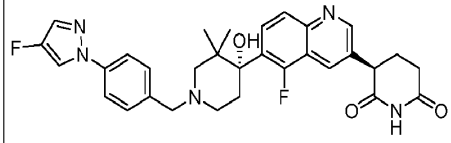
Cmpd No.	Compound Structure
I-1172	
I-1173	
I-1174	
I-1175	
I-1176	
I-1177	
I-1178	
I-1179	

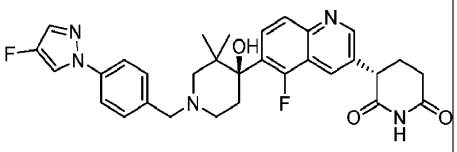
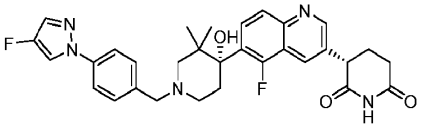
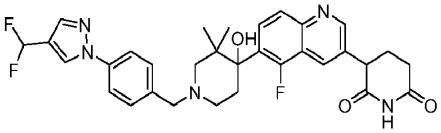
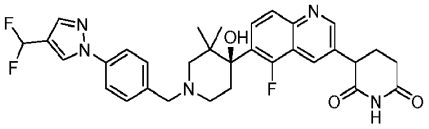
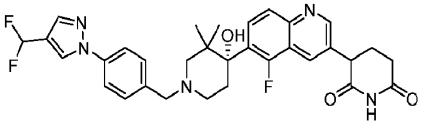
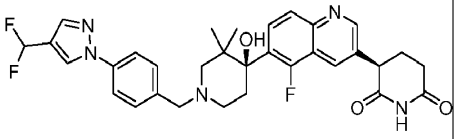
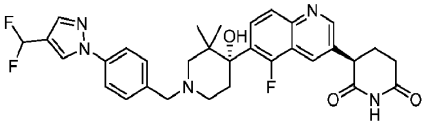
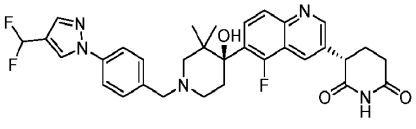
Cmpd No.	Compound Structure
I-1180	
I-1181	
I-1182	
I-1183	
I-1184	
I-1185	
I-1186	
I-1187	

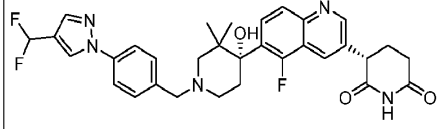
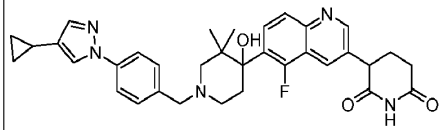
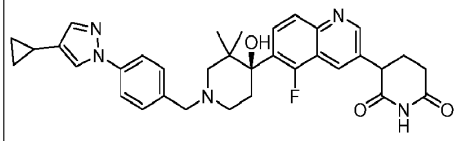
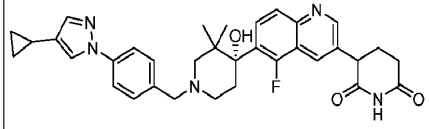
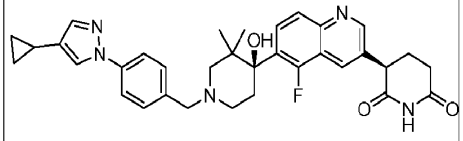
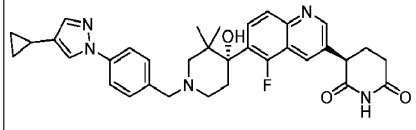
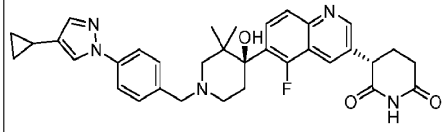
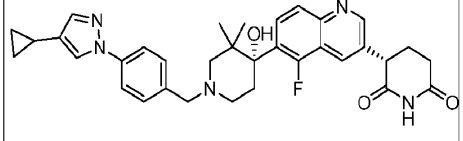
Cmpd No.	Compound Structure
I-1188	
I-1189	
I-1190	
I-1191	
I-1192	
I-1193	
I-1194	
I-1195	

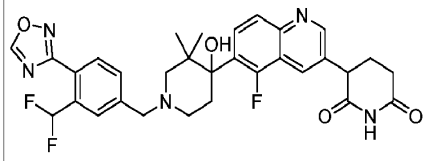
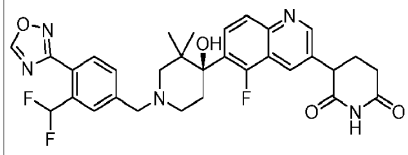
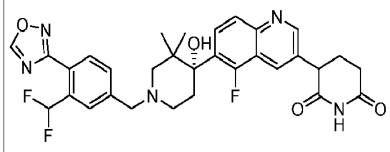
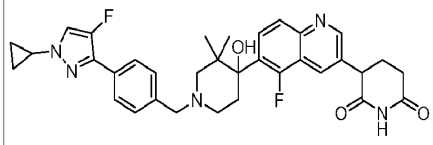
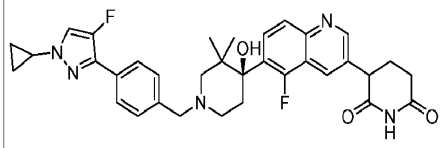
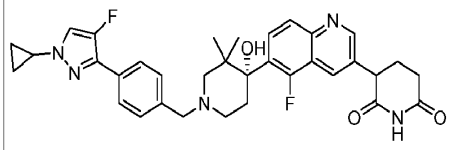
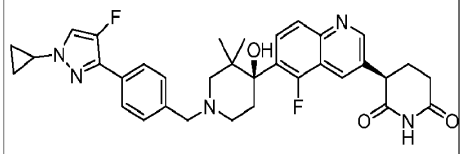
Cmpd No.	Compound Structure
I-1196	
I-1197	
I-1198	
I-1199	
I-1200	
I-1201	
I-1202	

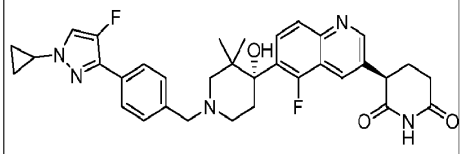
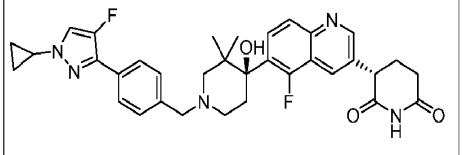
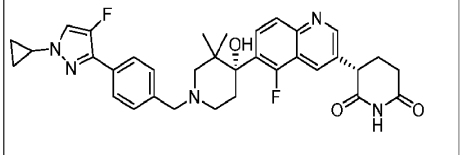
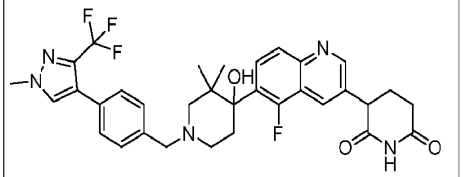
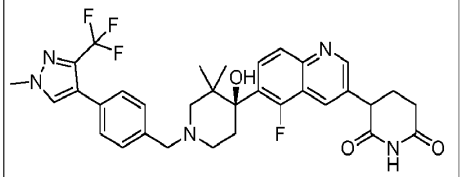
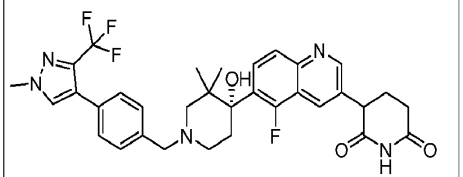
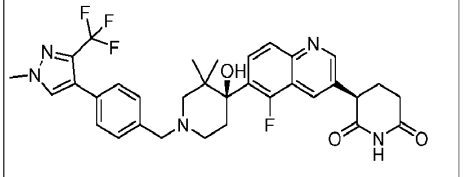
Cmpd No.	Compound Structure
I-1203	
I-1204	
I-1205	
I-1206	
I-1207	
I-1208	

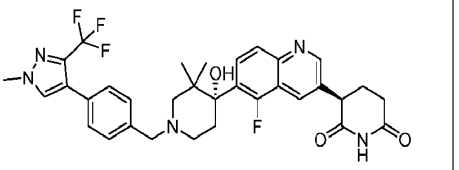
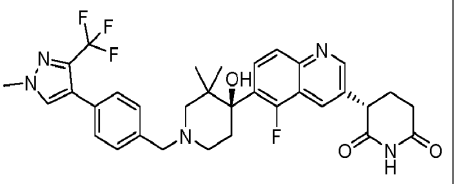
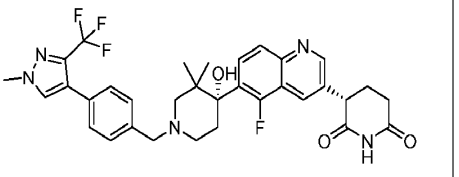
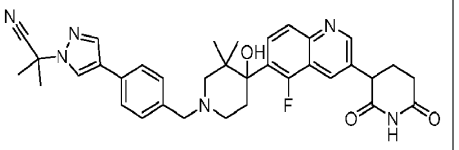
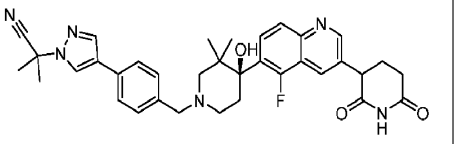
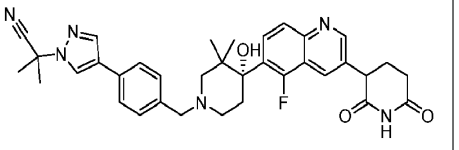
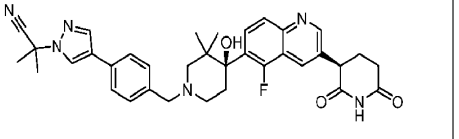
Cmpd No.	Compound Structure
I-1209	
I-1210	
I-1211	
I-1212	
I-1213	
I-1214	
I-1215	

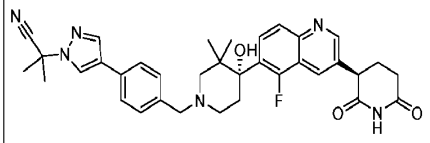
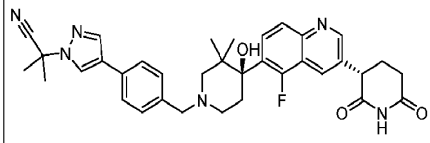
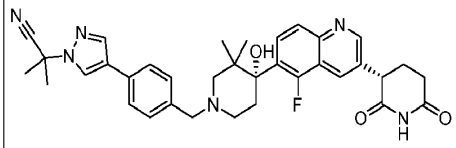
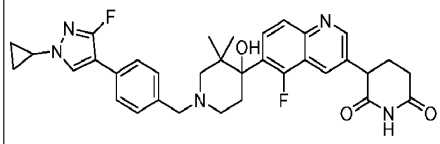
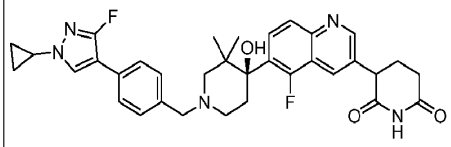
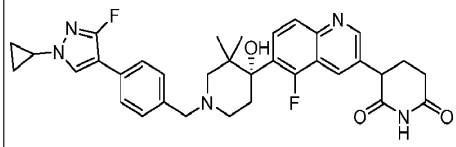
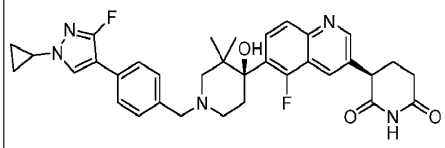
Cmpd No.	Compound Structure
I-1216	
I-1217	
I-1218	
I-1219	
I-1220	
I-1221	
I-1222	
I-1223	

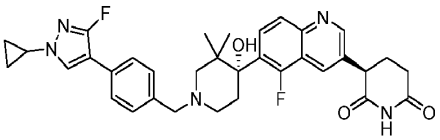
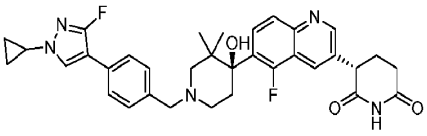
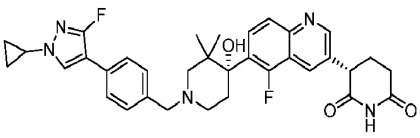
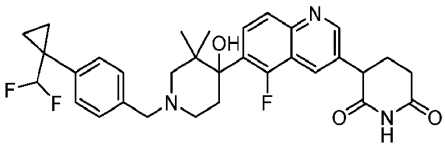
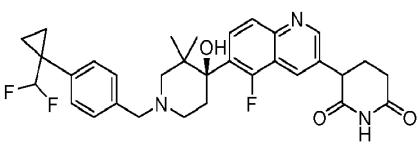
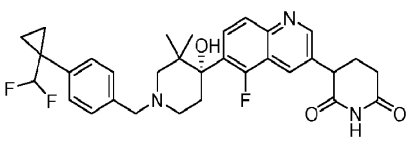
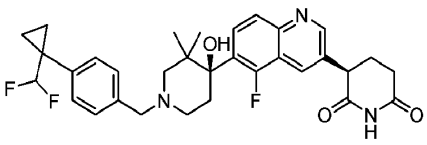
Cmpd No.	Compound Structure
I-1224	
I-1225	
I-1226	
I-1227	
I-1228	
I-1229	
I-1230	
I-1231	

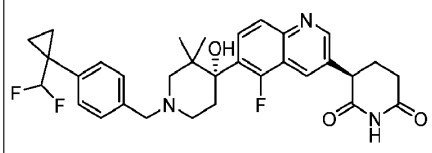
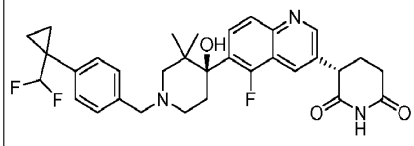
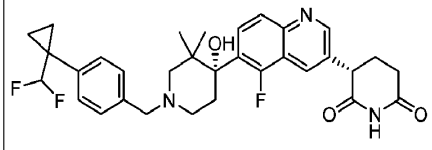
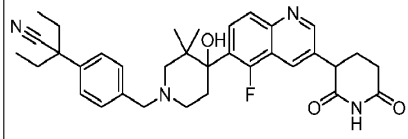
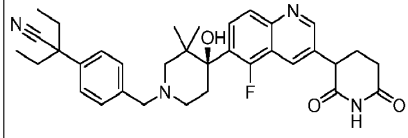
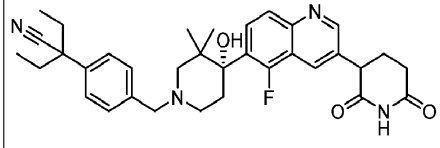
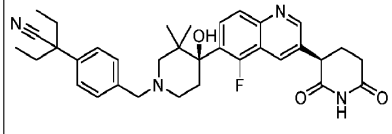
Cmpd No.	Compound Structure
I-1232	
I-1233	
I-1234	
I-1235	
I-1236	
I-1237	
I-1238	

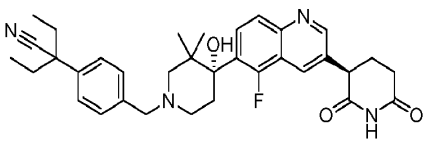
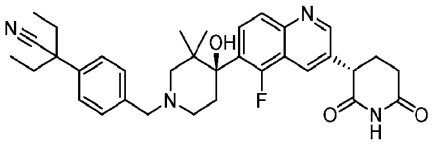
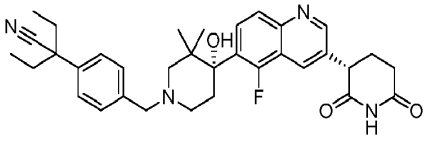
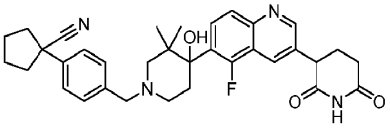
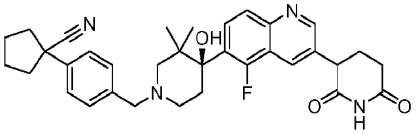
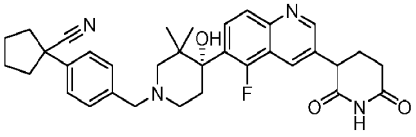
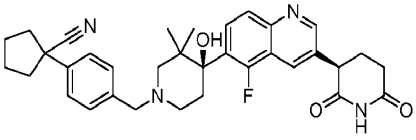
Cmpd No.	Compound Structure
I-1239	
I-1240	
I-1241	
I-1249	
I-1250	
I-1251	
I-1252	

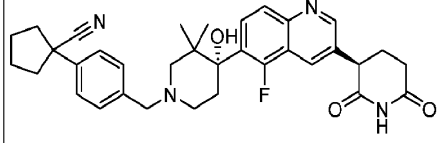
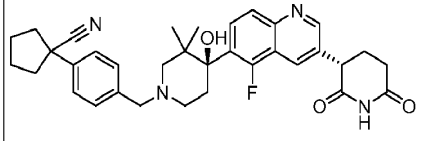
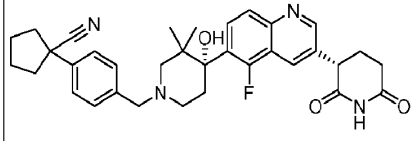
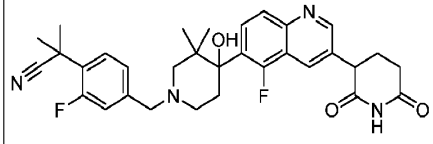
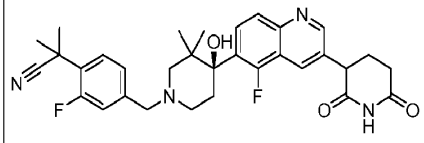
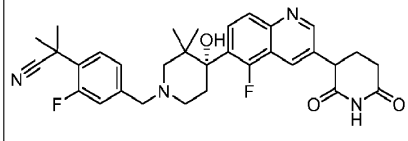
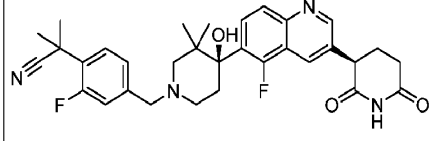
Cmpd No.	Compound Structure
I-1253	
I-1254	
I-1255	
I-1256	
I-1257	
I-1258	
I-1259	

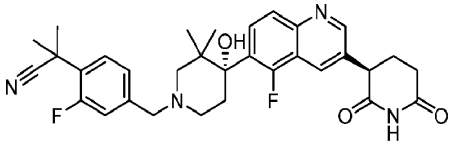
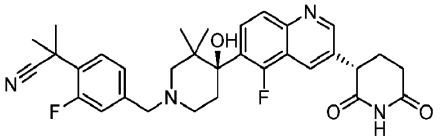
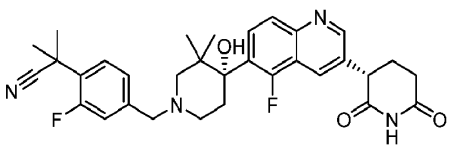
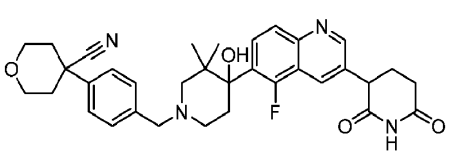
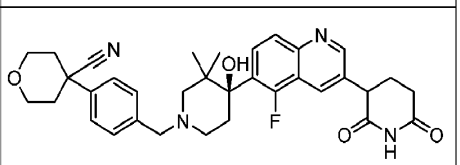
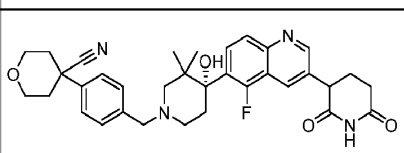
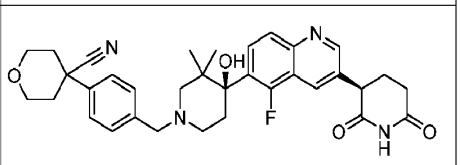
Cmpd No.	Compound Structure
I-1260	
I-1261	
I-1262	
I-1263	
I-1264	
I-1265	
I-1266	

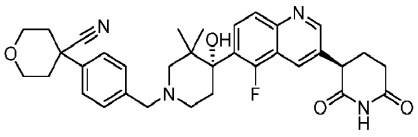
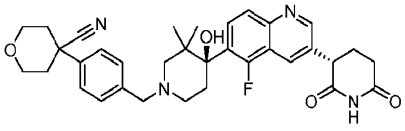
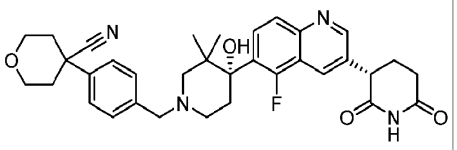
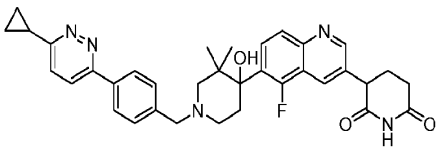
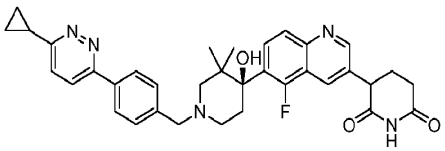
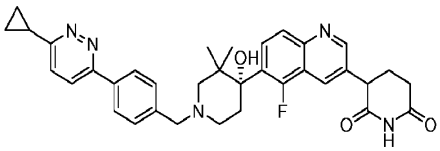
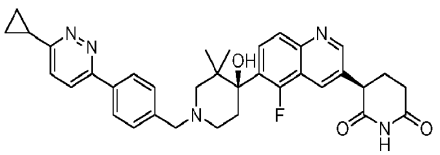
Cmpd No.	Compound Structure
I-1267	
I-1268	
I-1269	
I-1270	
I-1271	
I-1272	
I-1273	

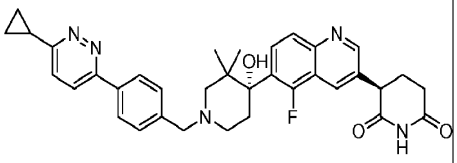
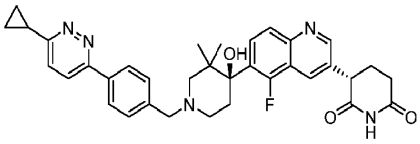
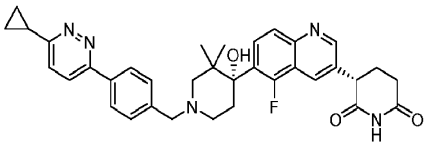
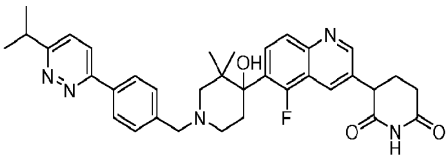
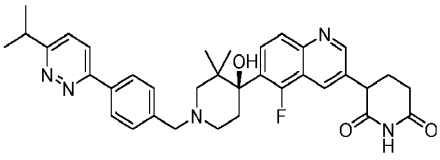
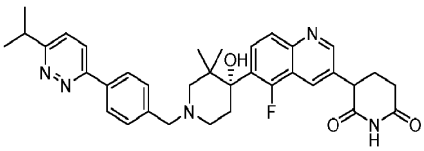
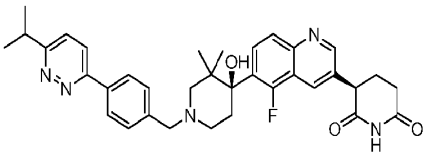
Cmpd No.	Compound Structure
I-1274	
I-1275	
I-1276	
I-1277	
I-1278	
I-1279	
I-1280	

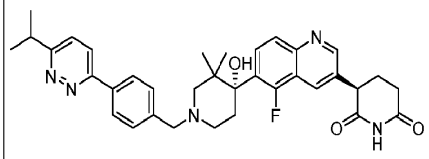
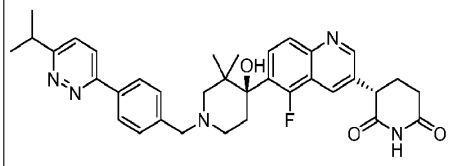
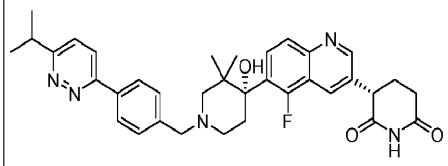
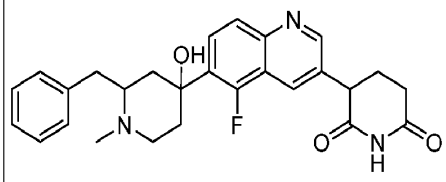
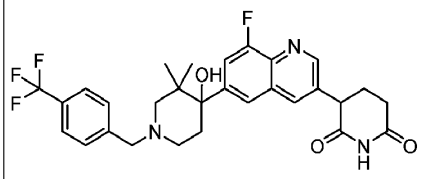
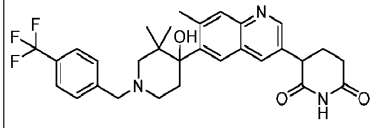
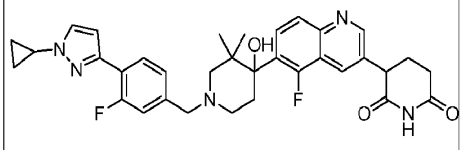
Cmpd No.	Compound Structure
I-1281	
I-1282	
I-1283	
I-1284	
I-1285	
I-1286	
I-1287	

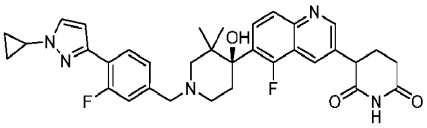
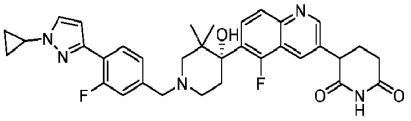
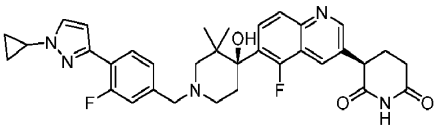
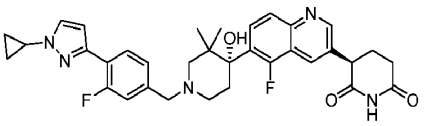
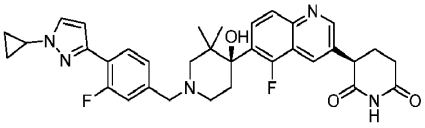
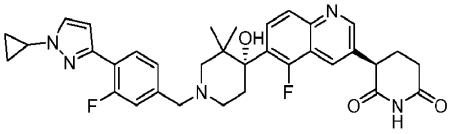
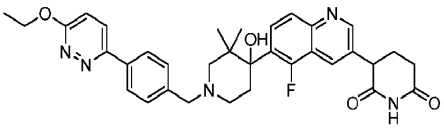
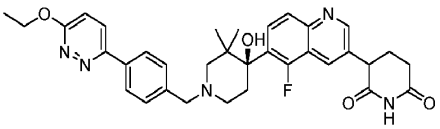
Cmpd No.	Compound Structure
I-1288	
I-1289	
I-1290	
I-1291	
I-1292	
I-1293	
I-1294	

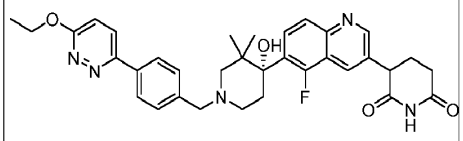
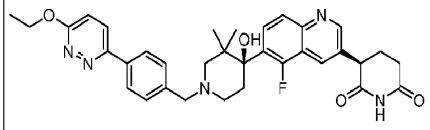
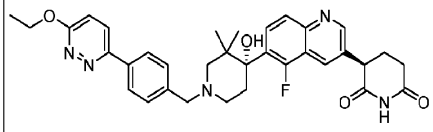
Cmpd No.	Compound Structure
I-1295	
I-1296	
I-1297	
I-1298	
I-1299	
I-1300	
I-1301	

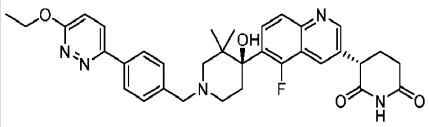
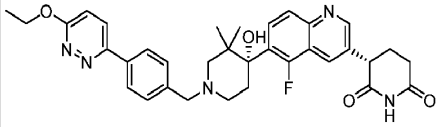
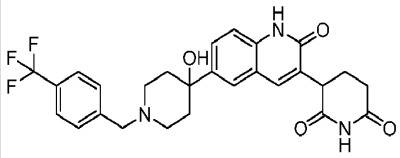
Cmpd No.	Compound Structure
I-1302	
I-1303	
I-1304	
I-1305	
I-1306	
I-1307	
I-1308	

Cmpd No.	Compound Structure
I-1309	
I-1310	
I-1311	
I-1312	
I-1313	
I-1314	
I-1315	

Cmpd No.	Compound Structure
I-1316	
I-1317	
I-1318	
I-1319	
I-1320	
I-1321	
I-1322	

Cmpd No.	Compound Structure
I-1323	
I-1324	
I-1325	
I-1326	
I-1327	
I-1328	
I-1329	
I-1330	

Cmpd No.	Compound Structure
I-1331	
I-1332	
I-1333	

Cmpd No.	Compound Structure
I-1334	
I-1335	
I-1336	

* 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:

X_1 is N or CR_3;

X_2 is N or $CR_{5'}$;

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, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, or $-NR_9R_{10}$;

each R_5 is independently at each occurrence D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$haloalkoxy, halogen, -OH, or $-NR_9R_{10}$;

$R_{5'}$ is H, D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, halogen, -OH, or $-NR_9R_{10}$;

R_6 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_{7a}, R_{7b}, R_{7c}, and R_{7d} are each independently H, D, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$deuteroalkyl, or $(C_1$-$C_2)$haloalkyl;

each R_{7e} is independently at each occurrence D, $(C_1$-$C_6)$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_{19}, the aryl and heteroaryl are optionally substituted with one or more R_{21}, and the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{22}; or

two R_{7e}, 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 substituents independently selected from D, $(C_1$-$C_6)$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, $-C(O)OR_{13'}$, $-C(O)R_{13}$, and $-C(O)NR_{13'}R_{13'}$;

R_8 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, 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 $R_{15'}$;

R_9 and R_{10} are each independently at each occurrence H, D, $(C_1$-$C_6)$alkyl, or $(C_1$-$C_6)$deuteroalkyl;

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

$R_{13'}$ is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

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} and $R_{15'}$ 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_{16}, -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_{29}, and -CN; or

two R_{15}, 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_{17};

two $R_{15'}$, 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 SO, N, NH, and S, wherein the phenyl and heteroaryl are optionally substituted with one or more R_{17}; or

two $R_{15'}$ 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_{17}; or

two $R_{15'}$ when on the same carbon atom form C=(O);

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

R_{17} is independently at each occurrence D, (C_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_{18}, or -CN;

R_{18} is H, (C_1-C_6)alkyl, or (C_1-C_6)haloalkyl;

each R_{19} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{20}R_{20'}$, -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 or more R_{23} and the aryl and heteroaryl are optionally substituted with one or more R_{24};

R_{20} and $R_{20'}$ are each independently at each occurrence H or $(C_1$-$C_6)$alkyl;

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, $-NH_2$, $-SF_5$, $-SR_{25}$, -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;

two R_{21}, 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_{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, $-NH_2$, $-SF_5$, $-SR_{26}$, -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_{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, $-NH_2$, $-SF_5$, $-SR_{27}$, -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; 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;

each R_{24} 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, $-NH_2$, $-SF_5$, $-SR_{28}$, -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;

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;

o is 1 or 2;

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

p is 0, 1, 2, 3 or 4; and

q is 1, 2, or 3.

Embodiment 2: The compound according to embodiment 1, having a Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (Ie), Formula (If), Formula (Ig), or Formula (Ih), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 3: The compound according to any one of embodiment 1 or 2, wherein R_{2a} is H.

Embodiment 4: The compound according to any one of embodiments 1-3, wherein R_{2b} is H.

Embodiment 5: The compound according to any one of embodiments 1-4, wherein R_{2c} is H.

Embodiment 6: The compound according to any one of embodiments 1-5, wherein R_{2d} is H.

Embodiment 7: The compound according to any one of embodiments 1-6, wherein X_1 is CR_3.

Embodiment 8: The compound according to any one of embodiments 1-6, wherein X_1 is N.

Embodiment 9: The compound according to any one of embodiments 1-8, wherein X_2 is N.

Embodiment 10: The compound according to any one of embodiments 1-8, wherein X_2 is $CR_{5'}$.

Embodiment 11: The compound according to any one of embodiments 1-10, wherein R_{7a} is H.

Embodiment 12: The compound according to any one of embodiments 1-11, wherein R_{7b} is H.

Embodiment 13: The compound according to any one of embodiments 1-12, wherein R_{7c} is H.

Embodiment 14: The compound according to any one of embodiments 1-13, wherein R_{7d} is H.

Embodiment 15: The compound according to any one of embodiments 1-14, wherein o is 0.

Embodiment 16: The compound according to any one of embodiments 1-14, wherein o is 1.

Embodiment 17: The compound according to any one of embodiment 1 or 2, having a Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im), Formula (Io), or Formula (Ip), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 18: The compound according to any one of embodiments 1-17, wherein R_1 is H.

Embodiment 19: The compound according to any one of embodiments 1-18, wherein R_3 is H.

Embodiment 20: The compound according to any one of embodiments 1-19, wherein R_6 is H.

Embodiment 21: The compound according to any one of embodiments 1-20, wherein n is 0.

Embodiment 22: The compound according to any one of embodiments 1-21, wherein m is 0.

Embodiment 23: The compound according to any one of embodiments 1-21, wherein m is 1.

Embodiment 24: The compound according to any one of embodiments 1-21, wherein m is 2.

Embodiment 25: The compound according to any one of embodiments 1-24, wherein each R_4 is independently at each occurrence (C_1-C_6)alkyl, halogen, or -NR_9R_{10}.

Embodiment 26: The compound according to any one of embodiments 1-25, wherein $R_{5'}$ is H, (C_1-C_6)alkyl, or halogen.

Embodiment 27: The compound according to any one of embodiments 1-26, wherein each R_{7e} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, halogen, -OH, or (C_3-C_7)carbocyclyl, wherein the alkyl is optionally substituted with one to six R_{19} and the carbocyclyl is optionally substituted with one to three R_{22}; or two R_{7e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl optionally substituted with one to four substituents independently selected from D, (C_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, -$C(O)OR_{13'}$, -$C(O)R_{13}$, and -$C(O)NR_{13'}R_{13'}$.

Embodiment 28: The compound according to any one of embodiments 1-27, wherein R_8 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)alkyl optionally substituted with one to three 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 optionally substituted with one to three R_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to three $R_{15'}$.

Embodiment 29: The compound according to any one of embodiments 1-28, wherein R_8 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)alkyl substituted with one to three 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 three R_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to three $R_{15'}$.

Embodiment 30: The compound according to any one of embodiments 1-29, wherein each R_{19} is independently at each occurrence (C_1-C_6)alkoxy, -$NR_{20}R_{20'}$, or (C_3-C_7)carbocyclyl wherein carbocyclyl is optionally substituted with two to four R_{23}.

Embodiment 31: A compound selected from the group consisting of:

3-(6-(3,3-diethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-2-methyl-6-(1,3,3-triethyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(1,3-diethyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(3-fluoro-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(4-hydroxy-3,3-dipropyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(3-(2,2-difluoroethyl)-3-ethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(4-hydroxy-3-(trifluoromethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(3-benzyl-1-ethyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-ethyl-4-hydroxy-3-isobutylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methyl-1,5-naphthyridin-3-yl)piperidine-2,6-dione;
3-(6-(3-(cyclopropylmethyl)-1-ethyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
1-(6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
3-(6-(4-hydroxy-3-methoxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
1-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1,5-naphthyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
3-(6-(3-benzyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(2-ethyl-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione;
3-(6-(3-(2,2-difluoroethyl)-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(4-hydroxy-3-methyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)piperidine-2,6-dione;

1-(6-(2-ethyl-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(4-chloro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
3-(6-(1-ethyl-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(6-(4-hydroxy-3-(methoxymethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(9-hydroxy-6-(4-(trifluoromethyl)benzyl)-6-azaspiro[3.5]nonan-9-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-2-methyl-1,5-naphthyridin-3-yl)piperidine-2,6-dione;
3-(6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-ethyl-4-hydroxy-3,3-dipropylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
1-(5-fluoro-6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
3-(6-(8-hydroxy-5-(4-(trifluoromethyl)benzyl)-5-azaspiro[2.5]octan-8-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-methylquinolin-3-yl)piperidine-2,6-dione;
3-(6-(3,3-diethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-ethyl-4-hydroxy-3-phenylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(3,3-bis(ethyl-d5)-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methyl-1,5-naphthyridin-3-yl)piperidine-2,6-dione;
3-(6-(3-ethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(4-hydroxy-3-propyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;

3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
1-(5-chloro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione;
3-(6-(3-ethyl-4-hydroxy-3-methyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-ethyl-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(1,3,3-triethyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(3-(cyclopropylmethyl)-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(4-chloro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2,4-dimethylquinolin-3-yl)piperidine-2,6-dione;
1-(5-fluoro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
3-(6-(3,3-diethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(2-ethyl-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(2-chloro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-(4-cyclopropylbenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;

3-(6-(1-(4-(difluoromethoxy)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-(4-cyclopropoxybenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-(4-(1H-pyrazol-1-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-(4-(difluoromethyl)-3-methoxybenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-(4-(2,2-difluoroethoxy)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-1-(3-methoxy-4-(trifluoromethyl)benzyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-1-(4-(isoxazol-3-yl)benzyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(3,3-diethyl-4-hydroxy-1-(4-(isoxazol-3-yl)benzyl)piperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(6-(3,3-diethyl-4-hydroxy-1-(4-(oxetan-3-yl)benzyl)piperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((7-methyl-1H-indol-3-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-((7-chloro-1H-indol-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((7-(trifluoromethyl)-1H-indol-3-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3-(trifluoromethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-2-methyl-1,5-naphthyridin-3-yl)piperidine-2,6-dione;
3-((4-(7-(2,6-dioxopiperidin-3-yl)-6-methyl-1,5-naphthyridin-2-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)-1H-indole-7-carbonitrile;

3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((1-methyl-1H-pyrazol-5-yl)methyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione;
3-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-4-hydroxypiperidin-1-yl)methyl)-1H-indole-7-carbonitrile;
3-(6-(3-(bicyclo[1.1.1]pentan-2-ylmethyl)-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(6-(3-(bicyclo[1.1.1]pentan-2-yl)-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(6-(3,3-diethyl-4-hydroxy-1-((1-methyl-1H-pyrazol-5-yl)methyl)piperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)quinolin-6-yl)-4-hydroxypiperidin-1-yl)methyl)benzonitrile;
1-(6-(4-hydroxy-1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(6-(4-hydroxy-1-(3-methoxy-4-(trifluoromethoxy)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
3-(5-fluoro-6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione;
3-(6-(2-ethyl-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione;
3-(6-(2-ethyl-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(9,9-difluoro-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-ethyl-4-hydroxy-3-(trifluoromethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(3-ethyl-4-hydroxy-3-methoxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-chloro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1,5-naphthyridin-3-yl)piperidine-2,6-dione;
3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1,5-naphthyridin-3-yl)piperidine-2,6-dione;
3-(4-amino-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;

3-(6-(4-hydroxy-3,3-bis(methoxymethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(3-fluoro-4-hydroxy-3-methyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(4-hydroxy-3-(hydroxymethyl)-3-methyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(3,3,3-trifluoropropyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-1,3,3-trimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-(cyclopropylmethyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-1-isopropyl-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-1-isobutyl-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(oxetan-3-ylmethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((tetrahydro-2H-pyran-4-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(3-cyclopropyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(3-((dimethylamino)methyl)-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-benzyl-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(2-amino-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(4-hydroxy-3-(2,2,2-trifluoroethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-((1H-pyrrol-2-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-1-((1-hydroxycyclopropyl)methyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-1-(2-hydroxy-2-methylpropyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-((2-amino-6-(trifluoromethyl)pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;

3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(pyridin-2-ylmethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(pyridin-3-ylmethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(pyridin-4-ylmethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)benzonitrile;
3-(6-(1-((1H-pyrazol-4-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((1-methyl-1H-pyrazol-5-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(9-hydroxy-6-(4-(trifluoromethyl)benzyl)-6-azaspiro[3.5]nonan-9-yl)quinolin-3-yl)piperidine-2,6-dione;
4-((9-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-9-hydroxy-6-azaspiro[3.5]nonan-6-yl)methyl)benzonitrile;
6-amino-5-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)picolinonitrile;
3-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)-1H-indole-7-carbonitrile;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
5-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)picolinonitrile;
3-(6-(3-ethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-ethyl-4-hydroxy-3-(trifluoromethyl)piperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-(4-(difluoromethyl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((6-oxo-1,6-dihydropyridin-2-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;

3-(6-(4-hydroxy-3-isopropyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;

3-(6-(1-ethyl-4-hydroxy-3-isopropylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;

3-(6-(4-hydroxy-3-isobutyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;

3-(6-(1-((4-amino-6-(trifluoromethyl)pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;

3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((6-oxo-5-(trifluoromethyl)-1,6-dihydropyridin-2-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;

3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((4-oxo-5-(trifluoromethyl)-1,4-dihydropyridin-2-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;

3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((4-oxo-1,4-dihydropyridin-2-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;

4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile;

3-(6-(3,3-diethyl-4-hydroxy-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;

3-(6-(3,3-diethyl-4-hydroxy-1-isobutylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;

3-(6-(3,3-diethyl-4-hydroxy-1-((tetrahydro-2H-pyran-4-yl)methyl)piperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;

3-(6-(1-((4,4-difluorocyclohexyl)methyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;

5-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)picolinonitrile;

3-(6-(1-ethyl-4-hydroxy-3,3-dimethylpiperidin-4-yl)-2-methyl-1,5-naphthyridin-3-yl)piperidine-2,6-dione;

4-((4-(7-(2,6-dioxopiperidin-3-yl)-6-methyl-1,5-naphthyridin-2-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)benzonitrile;

3-(6-(4-hydroxy-3,3-dimethyl-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)-2-methyl-1,5-naphthyridin-3-yl)piperidine-2,6-dione;

3-(6-(4-hydroxy-1-isobutyl-3,3-dimethylpiperidin-4-yl)-2-methyl-1,5-naphthyridin-3-yl) piperidine-2,6-dione;

3-(6-(3-cyclopropyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;

3-(6-(3-cyclopropyl-4-hydroxy-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(6-(3-cyclopropyl-4-hydroxy-1-isobutylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
4-((3-cyclopropyl-4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxypiperidin-1-yl)methyl)benzonitrile;
3-(6-(3-ethyl-4-hydroxy-1-isobutylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(6-(3-ethyl-4-hydroxy-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
5-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-3-ethyl-4-hydroxypiperidin-1-yl)methyl)picolinonitrile;
3-(6-(1-ethyl-4-hydroxy-3-(trifluoromethyl)piperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3-(trifluoromethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-1-isobutyl-3-(trifluoromethyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-1-isobutyl-3-(trifluoromethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(9-hydroxy-6-((6-(trifluoromethyl)pyridin-3-yl)methyl)-6-azaspiro[3.5]nonan-9-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-1-isobutyl-3,3-dimethylpiperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((tetrahydro-2H-pyran-4-yl)methyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-((4,4-difluorocyclohexyl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione;
4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)benzonitrile;
3-(6-(1-((1H-pyrrol-2-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione;
4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)-2-methylbenzonitrile;
3-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)benzonitrile;

2-(difluoromethoxy)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)benzonitrile;
3-(5-amino-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
1-(6-(1-benzyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
3-(6-(3-ethoxy-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(2-ethyl-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-propylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-((4,4-difluorocyclohexyl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(6-(1,3,3-triethyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-ethyl-4-hydroxy-3-(2,2,2-trifluoroethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(3-ethyl-3,4-dihydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(2-methylbenzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((4-oxo-6-(trifluoromethyl)-1,4-dihydropyridin-3-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-(4-(2H-1,2,3-triazol-2-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(5-methyl-1,3,4-oxadiazol-2-yl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-(methylamino)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-methoxyquinolin-3-yl)piperidine-2,6-dione;
3-(6-(3-(2,2-difluoroethyl)-4-hydroxy-3-methyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(6-ethyl-9-hydroxy-6-azaspiro[3.5]nonan-9-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(6-(1,3-diethyl-4-hydroxypiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(6-(3-cyclopropyl-1-ethyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;

3-(6-(3-cyclopropyl-1-ethyl-4-hydroxypiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(6-(3-(2,2-difluoroethyl)-1-ethyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-ethyl-4-hydroxy-3-(hydroxymethyl)-3-methylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-1-(2-methoxybenzyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(4-hydroxy-3-phenyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
1-(6-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(6-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-2-methyl-1,5-naphthyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
3-(6-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-2-methyl-1,5-naphthyridin-3-yl)piperidine-2,6-dione;
3-(6-(1-(4-(3,5-dimethylisoxazol-4-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-(4-(1,3-dimethyl-1H-pyrazol-4-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-(3-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-(3-(1H-pyrazol-1-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-(4-(1H-1,2,4-triazol-1-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(4-methylthiazol-5-yl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(pyridazin-3-yl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-(4-(1H-imidazol-1-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(oxazol-2-yl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-(3-(1H-imidazol-1-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(thiazol-4-yl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;

3-(5-fluoro-6-(4-hydroxy-1-(4-(isoxazol-4-yl)benzyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(3-methyl-4-(1,2,4-oxadiazol-3-yl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-(4-(1,2,3-thiadiazol-4-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(oxazol-4-yl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-(4-(1,3,4-oxadiazol-2-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(thiazol-2-yl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(thiazol-5-yl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-((6-(1,2,4-oxadiazol-3-yl)pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-(4-(1H-indazol-1-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(thiazol-2-yloxy)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(thiazol-2-ylamino)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-((3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((1-methyl-3-phenyl-1H-pyrazol-5-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-((1,2,4-oxadiazol-5-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(thiazol-4-ylmethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;

3-(5-fluoro-6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-9-oxa-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-9-oxa-2-azaspiro[5.5]undecan-5-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione;
3-(6-(2-(4-(1,2,4-oxadiazol-3-yl)benzyl)-5-hydroxy-9-oxa-2-azaspiro[5.5]undecan-5-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((1-methyl-1H-1,2,4-triazol-5-yl)methyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-((1H-pyrazol-5-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-1-(isoxazol-5-ylmethyl)-3,3-dimethylpiperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((4-methylthiazol-5-yl)methyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(5-hydroxy-2-((1-methyl-1H-pyrazol-5-yl)methyl)-9-oxa-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(2-(4-(1,2,4-oxadiazol-3-yl)benzyl)-5-hydroxy-9-oxa-2-azaspiro[5.5]undecan-5-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(5-hydroxy-2-((1-methyl-1H-pyrazol-5-yl)methyl)-9-oxa-2-azaspiro[5.5]undecan-5-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-(4-(4-acetylpiperazin-1-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
5-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)picolinamide;
3-(6-(1-(4-(1,2,4-oxadiazol-5-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(3-methyl-1,2,4-oxadiazol-5-yl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(5-methyl-1,2,4-oxadiazol-3-yl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-(1-(4-(1H-benzo[d]imidazol-1-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
1-(5-fluoro-6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-9-oxa-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(5-fluoro-6-(9-hydroxy-6-(4-(trifluoromethyl)benzyl)-6-azaspiro[3.5]nonan-9-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(6-(2-(4-(1,2,4-oxadiazol-3-yl)benzyl)-5-hydroxy-9-oxa-2-azaspiro[5.5]undecan-5-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(6-(1-(4-(1H-benzo[d]imidazol-1-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(6-(1-(4-(1,3,4-oxadiazol-2-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(5-fluoro-6-(4-hydroxy-1-(4-(isoxazol-3-yl)benzyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(oxazol-2-yl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(oxazol-4-yl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(5-fluoro-6-(4-hydroxy-1-(4-(isoxazol-4-yl)benzyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(6-(1-(4-(3,5-dimethylisoxazol-4-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(6-(1-((6-(1,2,4-oxadiazol-3-yl)pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(3-methyl-4-(1,2,4-oxadiazol-3-yl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(thiazol-5-yl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(thiazol-4-yl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(4-methylthiazol-5-yl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(6-(1-(4-(1,3-dimethyl-1H-pyrazol-4-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(pyridazin-3-yl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(thiazol-2-ylamino)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(thiazol-2-yloxy)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(6-(1-(3-(1H-pyrazol-1-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(thiazol-2-yl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(6-(1-(4-cyclopropylbenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(6-(1-(3-(1H-imidazol-1-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(6-(1-(3-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(6-(1-(4-(1H-1,2,4-triazol-1-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
(R)-1-(6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
(S)-1-(6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
3-(6-(3,3-diethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione-3-d;
3-(6-(3,3-diethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)-3-methylpiperidine-2,6-dione;
(R)-3-(6-((R)-8-hydroxy-5-(4-(trifluoromethyl)benzyl)-5-azaspiro[2.5]octan-8-yl)quinolin-3-yl)piperidine-2,6-dione;
(S)-3-(6-((S)-8-hydroxy-5-(4-(trifluoromethyl)benzyl)-5-azaspiro[2.5]octan-8-yl)quinolin-3-yl)piperidine-2,6-dione;
(S)-3-(6-((R)-8-hydroxy-5-(4-(trifluoromethyl)benzyl)-5-azaspiro[2.5]octan-8-yl)quinolin-3-yl)piperidine-2,6-dione;
(R)-3-(6-((S)-8-hydroxy-5-(4-(trifluoromethyl)benzyl)-5-azaspiro[2.5]octan-8-yl)quinolin-3-yl)piperidine-2,6-dione;

1-(6-(1-((6-(1,3,4-oxadiazol-2-yl)pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;
(R)-3-(6-((R)-1-benzyl-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
(R)-3-(6-((S)-1-benzyl-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
(S)-3-(6-((R)-1-benzyl-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
(S)-3-(6-((S)-1-benzyl-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
(S)-3-(6-((S)-4-hydroxy-1-isobutyl-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
(S)-3-(6-((R)-4-hydroxy-1-isobutyl-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
(R)-3-(6-((S)-4-hydroxy-1-isobutyl-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
(R)-3-(6-((R)-4-hydroxy-1-isobutyl-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
(S)-3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethyl-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
(S)-3-(5-fluoro-6-((S)-4-hydroxy-3,3-dimethyl-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
(R)-3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethyl-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
(R)-3-(5-fluoro-6-((S)-4-hydroxy-3,3-dimethyl-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(6-((S)-1-benzyl-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(6-((R)-1-benzyl-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-((S)-4-hydroxy-3,3-dimethyl-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethyl-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione;
(R)-3-(6-((R)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione-3-d;
(R)-3-(6-((S)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione-3-d;
(S)-3-(6-((R)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione-3-d;

3-(6-((R)-1-(4-cyclopropylbenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione-3-d;
(S)-3-(6-((S)-1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione-3-d; and
3-(6-((S)-1-(4-cyclopropylbenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione-3-d;

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 32: A pharmaceutical composition comprising a compound of any one of embodiments 1-31, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier or excipient.

Embodiment 33: The pharmaceutical composition according to embodiment 32, further comprising at least one additional pharmaceutical agent.

Embodiment 34: The pharmaceutical composition according to embodiment 32 or 33 for use in the treatment of a disease or disorder that is affected by the reduction of HIF-1b levels.

Embodiment 35: 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 1-31, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 36: 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 1-31, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 37: 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 1-31, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 38: 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 1-31, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 39: The method according to embodiment 38, 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 40: The method according to embodiments 38 or 39, wherein 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.

Embodiment 41: 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 1-31, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 42: The method according to embodiment 39, wherein the cancer is VHL-deficient cancer.

Embodiment 43: The method according to embodiment 39, 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 44: A method for reducing HIF-1b levels, comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of embodiments 1-31, or a pharmaceutically acceptable salt thereof.

Embodiment 45: 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 1-31, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 46: 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 1-31, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 47: 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 1-31, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Embodiment 48: The method of embodiment 47, wherein the renal cell carcinoma is clear cell renal cell carcinoma (ccRCC).

Embodiment 49: The method according to any one of embodiments 35-48, wherein the administration is oral, parenteral, subcutaneous, by injection, or by infusion.

Embodiment 50: A compound according to any one of embodiments 1-31, 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-1b levels.

Embodiment 51: A compound according to any one of embodiments 1-31, 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-1b levels.

Embodiment 52: Use of a compound according to any one of embodiments 1-31, 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-1b levels.

Embodiment 53: Use of a compound according to any one of embodiments 1-31, 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-1b levels.

Embodiment 54: The compound for use according to embodiment 50 or 51 or the use according to embodiment 52 or 53, 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) 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, fluorine, and, 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-1b protein levels. In one embodiment, the compounds of the present disclosure decrease HIF-1b protein levels. In yet one embodiment, the compounds of the present disclosure reduce HIF-1b protein levels. In another embodiment, the compounds of the present disclosure are degraders of HIF-1b.

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-1b is measured by DC_{50}.

Potency of a compound of the present disclosure towards degradation of HIF-1b 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. As used herein, Dmax is the maximum level of degradation achievable.

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) 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)

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).

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

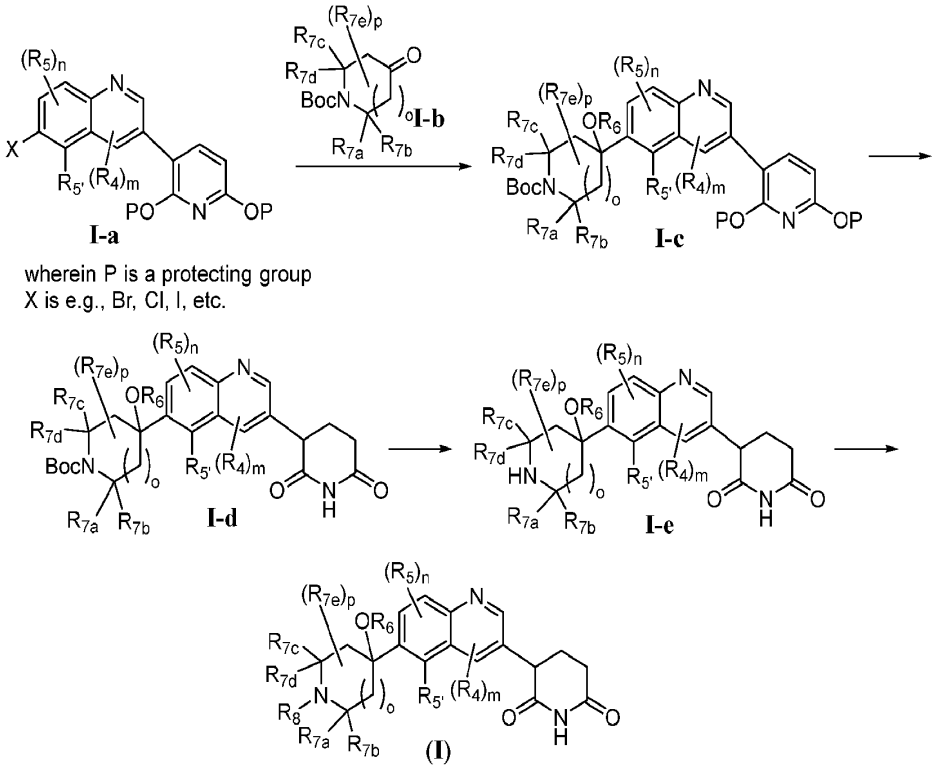
final product, an intermediate, or a starting material may be affected by any suitable method known in the art. See, for example, "Stereochemistry of Organic Compounds" by E.L. Eliel, S.H. Wilen, and L.N. Mander (Wiley-Interscience, 1994).

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, and VI which comprise different sequences of assembling intermediates **I-a**, **I-b**, **I-c**, **I-d**, **I-e**, **II-a**, **II-b**, **II-c**, **II-d**, **II-e**, **III-a**, **III-b, IV-a, V-a, and VI-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:

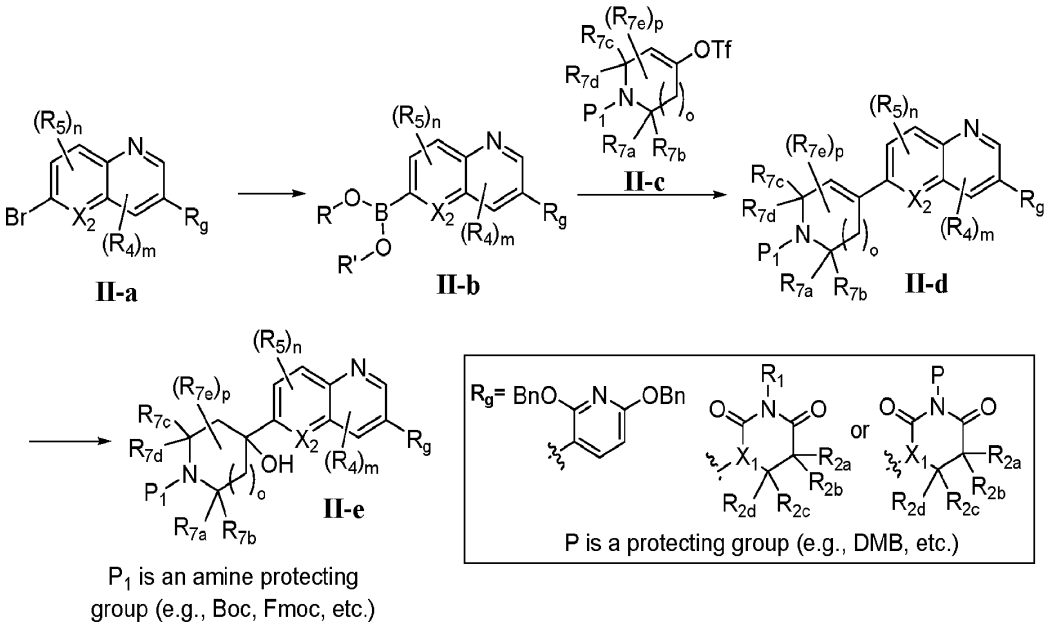


wherein R_4, R_5, $R_{5'}$, R_6, R_{7a}, R_{7b}, R_{7c}, R_{7d}, R_{7e}, m, n, o and p are as defined in Formula (I).

The general way of preparing Compounds of Formula (I), wherein R_8 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)alkyl or (C_1-C_6)alkyl substituted with optionally substituted phenyl, heteroaryl, carbocyclyl, or heterocyclyl by using intermediates **I-a**, **I-b**, **I-c**, **I-d**, and **I-e** is outlined in General Scheme I. Alkylation of **I-a** with **I-b** via an intermediate organometallic species

(e.g., via the corresponding aryl lithium species through treatment with *n*-Butyllithium, etc.) in a solvent (e.g., tetrahydrofuran (THF), diethyl ether, etc.) provides **I-c**. Hydrogenation of **I-c** (when P is e.g., a benzyl group) in the presence of a suitable catalyst (e.g., dihydroxypalladium ($Pd(OH)_2$), palladium on carbon (Pd/C), platinum dioxide (PtO_2), etc.) in a solvent (e.g., N,N-dimethylformamide (DMF), dichloromethane (DCM), ethanol (EtOH), etc. or a combination thereof) and under an atmosphere of hydrogen gas provides **I-d**. Deprotection of **I-d** using an acid such as methanesulfonic acid, trifluoroacetic acid (TFA) or hydrochloric acid (HC1) in a solvent (e.g., THF, 1,2,-dichloroethane, dioxane, DCM, acetonitrile (ACN), etc. or a combination thereof) optionally at elevated temperature provides **I-e**. Reductive animation of **I-e** with an aldehyde or a ketone 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_8 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)alkyl or (C_1-C_6)alkyl substituted with optionally substituted phenyl, heteroaryl, carbocyclyl, or heterocyclyl. Alternatively, treatment of **I-e** and aldehyde or ketone with decaborane in a solvent (e.g., DMF, etc.) optionally at elevated temperatures provides a compound of Formula (**I**) where R_8 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)alkyl or (C_1-C_6)alkyl substituted with optionally substituted phenyl, heteroaryl, carbocyclyl, or heterocyclyl.

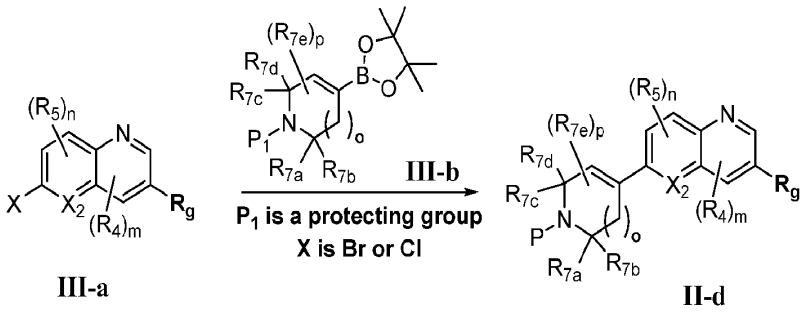
General Scheme II:

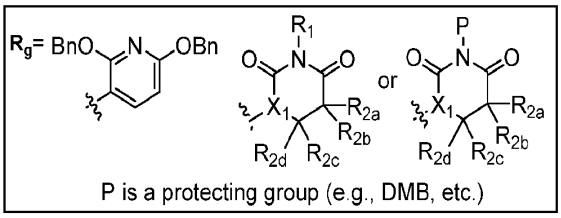


wherein X_1, X_2, R_1, R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_4, R_5, R_{7a}, R_{7b}, R_{7c}, R_{7d}, R_{7e}, m, n, o and p are as defined in Formula (I).

Intermediate **II-e** can be prepared by using intermediates **II-a**, **II-b**, **II-c**, and **II-d** is outlined in General Scheme II. Borylation of bromide **II-a** using a borylation reagent (*e.g.*, tetramethyl-2,2'-bi(1,3,2-dioxaborinane), bis(pinacolato)diboron (B_2Pin_2), or bis(catecholato)diboron (B_2Cat_2), etc.) in the presence of a suitable metal catalyst (e.g., $Pd(dppf)Cl_2$•DCM, $Pd(tBu_3P)_2$, $Pd(OAc)_2$ and *tert*-butyldiphenylphosphane, etc.) and a base (*e.g.*, potassium carbonate (K_2CO_3), cesium carbonate (Cs_2CO_3), potassium acetate (KOAc), K_3PO_4, etc.) in a solvent (*e.g.* DMF, dioxane, water, etc.) and optionally at elevated temperature (*e.g.*, heat, microwave) provides **II-b**. Coupling of boronic ester **II-b** with **II-c** using a suitable 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), KOAc, K_2CO_3, Cs_2CO_3, K_3PO_4, etc.), in a solvent (*e.g.*, DMF, 1,4-dioxane, water, etc. or a combination thereof) optionally at elevated temperature (*e.g.*, heat, microwave) provides **II-d**. Hydration of **II-d** using oxygen, a suitable metal catalyst (*e.g.*, $Mn(dpm)_3$, $Co(acac)_2$, etc.) and an alkyl or aryl silane (*e.g.*, phenylsilane, triethylsilane, etc.) or a borohydride reagent (e.g., $NaBH_4$, etc.) in a solvent (*e.g.*, DCM, isopropanol (IPA), DMF, etc. or a combination thereof) provides Intermediate **II-e**. Intermediate **II-e** 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) wherein R_8 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)alkyl or (C_1-C_6)alkyl substituted with optionally substituted phenyl, heteroaryl, carbocyclyl, or heterocyclyl.

General Scheme III:

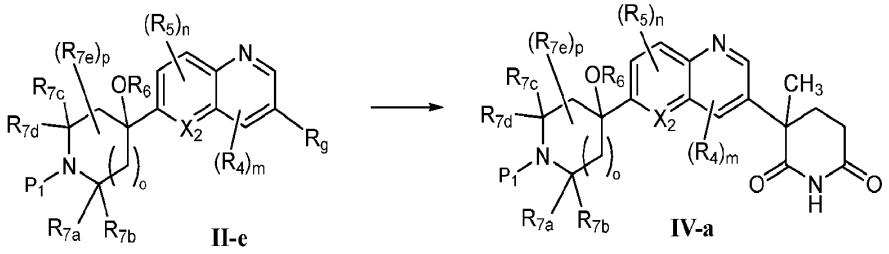




wherein X_1, X_2, R_1, R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_4, R_5, R_{7a}, R_{7b}, R_{7c}, R_{7d}, R_{7e}, m, n, o and p are as defined in Formula (I).

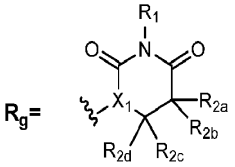
Intermediate **II-d** can also be prepared by using intermediates **III-a** and **III-b** as outlined in General Scheme III. Coupling of boronic ester **III-a** with **III-b** using a suitable metal catalyst (*e.g.*, XPhos Pd G3 and Xphos, bis(*tri-t*-butylphosphine)palladium(0), cataCXium A Pd G_3, $Pd(dppf)Cl_2$•DCM, $Pd(tBu_3P)_2$, etc.) and a base (*e.g.*, DIPEA, triethylamine (Et_3N), KOAc, K_2CO_3, Cs_2CO_3, K_3PO_4, K_2HPO_4, etc.), in a solvent (*e.g.*, DMF, 1,4-dioxane, water, etc. or a combination thereof) optionally at elevated temperature (*e.g.*, heat, microwave) provides **II-d**.

General Scheme IV:



R_6 is H or a protecting group

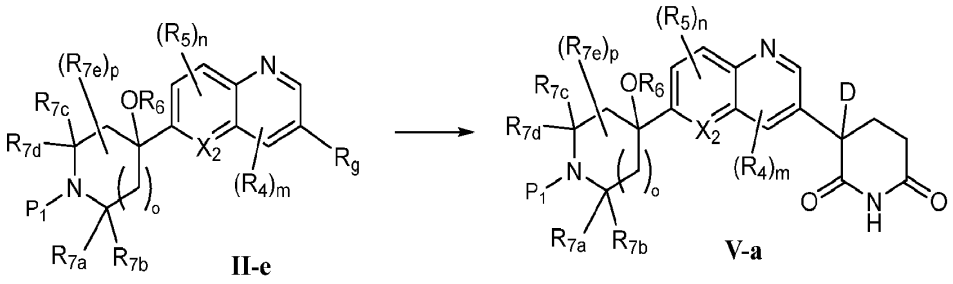
P_1 is an amine protecting group (e.g., Boc, Fmoc, etc.)



wherein X_2, R_4, R_5', R_{7a}, R_{7b}, R_{7c}, R_{7d}, R_{7e}, m, n, o, and p are as defined in Formula (I).

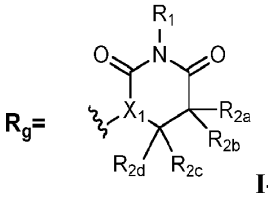
Intermediate **IV-a**, wherein R_1, R_{2a}, R_{2b}, R_{2c}, and R_{2d} are H, X_1 is CR_3, and R_3 is methyl, can be prepared according to the procedures and examples as reported in PCT Application Publication No. WO2017/197046 by using Intermediate **II-e** as outlined in General Scheme IV. Deprotonation of **II-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 **IV-a**. Intermediate **IV-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) wherein R_8 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)alkyl or (C_1-C_6)alkyl substituted with optionally substituted phenyl, heteroaryl, carbocyclyl, or heterocyclyl.

General Scheme V:



R_6 is H or a protecting group

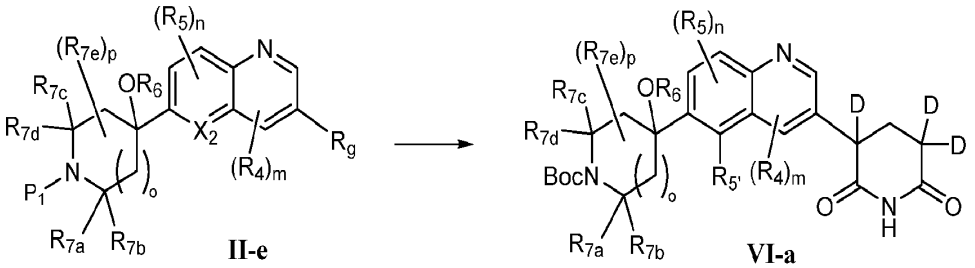
P_1 is an amine protecting group (e.g., Boc, Fmoc, etc.)



wherein X_2, R_4, R_5', R_{7a}, R_{7b}, R_{7c}, R_{7d}, R_{7e}, m, n, o, and p are as defined in Formula (I).

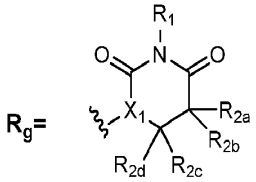
Intermediate **V-a** wherein R_1, R_{2a}, R_{2b}, R_{2c}, and R_{2d} are H, X_1 is CR_3, and R_3 is deuterium, can be prepared according to the procedures and examples as reported in PCT Application Publication No. WO2017/197046 by using Intermediate **II-e** as outlined in General Scheme V. Deprotonation of **II-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 **V-a.** Intermediate **V-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) wherein R_8 is $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$halohydroxyalkyl, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$alkyl substituted with optionally substituted phenyl, heteroaryl, carbocyclyl, or heterocyclyl.

General Scheme VI:



R_6 is H or a protecting group

P_1 is an amine protecting group (e.g., Boc, Fmoc, etc.)



wherein X_2, R_4, $R_{5'}$, R_{7a}, R_{7b}, R_{7c}, R_{7d}, R_{7e}, m, n, o, and p are as defined in Formula (I).

Intermediate **VI-a** wherein R_1, R_{2c}, and R_{2d} are H, X_1 is CR_3, R_3 is deuterium, and R_{2a} and R_{2b} are deuterium, can be prepared according to the procedures and examples as reported in PCT Application Publication No. WO2022/012622 by using Intermediate **II-e** as outlined in General Scheme VI. Treatment of **II-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 **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) wherein R_8 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)alkyl or (C_1-C_6)alkyl substituted with optionally substituted phenyl, 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 X_1, X_2, R_1, R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_4, R_5, $R_{5'}$, R_6, R_{7a}, R_{7a}, R_{7b}, R_{7c}, R_{7d}, R_{7e}, m, n, o and p, and other variables are as defined above, except where otherwise indicated. Furthermore, for synthetic purposes, the compounds of General Schemes I, II, III, IV, V, and VI are merely representative with elected radicals to illustrate the general synthetic methodology of the Compounds of Formula (I) as defined herein.

G. Methods of Using Compounds of Formula (I)

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-1b protein levels. The method comprises administering to a patient in need of a treatment for diseases or disorders associated with modulation of HIF-1b protein levels an effective amount of a Compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), 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-1b 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-1b protein levels. The method comprises administering to a patient in need of a treatment for diseases or disorders affected by the reduction of HIF-1b protein levels an effective amount of a Compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), 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), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a composition comprising a Compound of Formula (I), 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-1b 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 and 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), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a composition comprising a Compound of Formula (I), 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-1b 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), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), 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-1b 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), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), 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-1b 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-1b protein levels. The method involves administering to a patient in need thereof an effective amount of a Compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. In some embodiments, HIF-1b protein levels are modulated, reduced, or decreased through degradation of the HIF-1b protein. In other embodiments, HIF-1b protein levels are modulated, reduced, or decreased through degradation of the HIF-1b protein mediated by an E3 ligase.

Another aspect of the disclosure relates to the use of a Compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a composition comprising a Compound of Formula (I), 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-1b protein levels. In some embodiments, HIF-1b protein levels are modulated, reduced, or decreased through degradation of the HIF-1b protein. In other embodiments, HIF-1b protein levels are modulated, reduced, or decreased through degradation of the HIF-1b protein mediated by an E3 ligase.

In another aspect, the present disclosure relates to a method of treating, preventing, inhibiting, or eliminating an HIF-1b-dependent disease or disorder in a patient in need thereof by modulating HIF-1b protein levels through the degradation of HIF-1b. In some embodiments, HIF-1b protein degradation is mediated by an E3 ligase.

Another aspect of the disclosure relates to the use of a Compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a composition comprising a Compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for treating, preventing, inhibiting, or eliminating an HIF-1b-dependent disease or disorder in a patient in need thereof by modulating HIF-1b protein levels through the degradation of HIF-1b. In some embodiments, I HIF-1b protein degradation is mediated by an E3 ligase.

In another aspect, the present disclosure relates to a Compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a composition comprising a Compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in the treatment, prevention, inhibition or elimination of an HIF-1b-dependent disease or disorder in a patient in need thereof by modulating HIF-1b protein levels through the degradation of HIF-1b. In some embodiments, I HIF-1b 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), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a composition comprising a Compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, that reduces HIF-1b protein levels. In some embodiments, HIF-1b protein levels are reduced through degradation of the HIF-1b protein. In some embodiments, HIF-1b protein levels are reduced through degradation of the HIF-1b protein is mediated by an E3 ligase.

Another aspect of the disclosure relates to a method of degrading HIF-1b. The method comprises administering to a patient in need thereof an effective amount of a Compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. In some embodiments, HIF-1b protein degradation is mediated by an E3 ligase.

In another aspect, the present disclosure relates to a method for treating a HIF-1b-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), or a pharmaceutically acceptable salt, hydrate, solvate,

prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), 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), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a composition comprising a Compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in the treatment of a HIF-1b-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), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for treating a HIF-1b-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), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a composition comprising a Compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in the manufacture of a medicament for treating a HIF-1b-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-1b protein levels. The method comprises administering to the patient in need thereof a Compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), 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-1b protein levels, wherein reduction of HIF-1b protein levels treats or ameliorates the disease or disorder. The method comprises administering to the patient in need thereof a Compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), 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), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), 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), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a composition comprising a Compound of Formula (I), 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), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), 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), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), 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), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a composition comprising a Compound of Formula (I), 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), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), 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), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), 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), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a composition comprising a Compound of Formula (I), 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), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), 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-1b modulator Compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), 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-1b modulator Compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a composition comprising a Compound of Formula (I), 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-1b modulator Compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), 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), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof or a composition comprising a Compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. In some embodiments, the proliferative disorder is a HIF-1□-dependent or HIF-1□-associated proliferative disorder. In one embodiment, the proliferative disorder is a cancer. Representative cancers that compounds of Formula (I), 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), 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 (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 (Iaaa), Formula (Ibbb), Formula (Iccc), Formula (Iddd), Formula (Ieee), Formula (Ifff), Formula (Iggg), Formula (Ihhh), Formula (Iiii), Formula (Ijjj), and/or Formula (Ikkk), a compound according to any one of embodiment No. 1 to No. 54, or any embodiment of 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 (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 (Iaaa), Formula (Ibbb), Formula (Iccc), Formula (Iddd), Formula (Ieee), Formula (Ifff), Formula (Iggg), Formula (Ihhh), Formula (Iiii), Formula (Ijjj), and/or Formula (Ikkk), 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 (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 (Iaaa), Formula (Ibbb), Formula (Iccc), Formula (Iddd), Formula (Ieee), Formula (Ifff), Formula (Iggg), Formula (Ihhh), Formula (Iiii), Formula (Ijjj), and/or Formula (Ikkk), a compound according to any one of embodiment No. 1 to No. 54, or any embodiment of 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 (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 (Iaaa), Formula (Ibbb), Formula (Iccc), Formula (Iddd), Formula (Ieee), Formula (Ifff), Formula (Iggg), Formula (Ihhh), Formula (Iiii), Formula (Ijjj), and/or Formula (Ikkk), 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), 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-1b (e.g., a second HIF-1b 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.

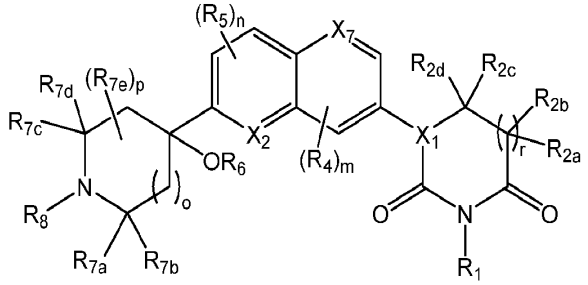
In accordance with the foregoing, the present disclosure also provides a therapeutic combination, *e.g.*, a kit, kit of parts, *e.g.*, for use in any method as defined herein, comprising a Compound of Formula (I), or a pharmaceutically acceptable salt thereof, to be used concomitantly or in sequence 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), 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:

X_1 is N or CR_3;

X_2 is N, N(O), or CR_5;

X_7 is N and N(O);

R_1 is H, D, $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, $-CH_2OP(O)(R_{12})_2$, $-CH_2OC(O)CH_2NHC(O)CH_2NH_2$, $-CH_2OC(O)CH(R_{12'})NHR_{12'}$, $-CH_2OC(O)(CH_2)_q-C(O)OR_{12'}$, 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 optionally substituted with one or more R_{40};

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 optionally substituted with one or more R_{40};

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)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, or $-NR_9R_{10}$; wherein each alkyl, deuteroalkyl, haloalkyl, alkoxy, deuteoalkoxy, haloalkoxy, carbocyclyl, and heterocyclyl is optionally substituted with one or more R_{40};

R_5 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)deuteroalkoxy, (C_1-C_6)haloalkoxy, (C_3-C_7)carbocyclyl, $O(C_3-C_7)$carbocyclyl, (C_3-C_7)carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; halogen, -OH, or $-NR_9R_{10}$, wherein each alkyl, deuteroalkyl, haloalkyl, alkoxy, deuteoalkoxy, haloalkoxy, carbocyclyl, and heterocyclyl is optionally substituted with one or more R_{40};

R_6 is H, D, (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, $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, or $-CH_2OP(O)(R_{12})_2$;

R_{7a}, R_{7b}, R_{7c}, and R_{7d} are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, or (C_1-C_2)haloalkyl; or

two of R_{7a}, R_{7b}, R_{7c}, and R_{7d} are taken together with the carbon atoms to which they are attached form (C_3-C_7)carbocyclyl, (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 carbocyclyl, spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one or more substituents independently selected from D, (C_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, $-C(O)OR_{13'}$, $-C(O)R_{13}$, and $-C(O)NR_{13'}R_{13'}$;

each R_{7e} is independently at each occurrence D, (C_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_{19}, the aryl and heteroaryl are optionally substituted with one or more R_{21}, and the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{22}; or

two R_{7e} together with the carbon atom to which they are attached form a (C_3-C_7)carbocyclyl, (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 carbocyclyl, spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one or more substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$;

one R_{7e} is taken together with any one of R_{7a}, R_{7b}, R_{7c}, and R_{7d} 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_{22};

R_8 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)$NR_{32}R_{33}$, 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 $R_{15'}$;

R_9 and R_{10} are each independently at each occurrence H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, or (C_1-C_6)haloalkyl;

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

$R_{13'}$ is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

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} and $R_{15'}$ 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_{16}, -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 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_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_{29}, $SO_2NR_{30}R_{31}$, -CN, and R_{19}; or

two R_{15}, 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_{17};

two $R_{15'}$, 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_{17}; or

two $R_{15'}$ 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_{17}; or

two $R_{15'}$ when on the same carbon atom form C=(O);

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

R_{17} is independently at each occurrence D, (C_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_{18}, or -CN;

R_{18} is H, (C_1-C_6)alkyl, or (C_1-C_6)haloalkyl;

each R_{19} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{20}R_{20'}$, -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 or more R_{23} and the aryl and heteroaryl are optionally substituted with one or more R_{24}; or

two R_{19} when on the same carbon atom form C=(O); or

two R_{19} 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_{17};

R_{20} and $R_{20'}$ are each independently at each occurrence H or (C_1-C_6)alkyl;

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_{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_{21}, 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_{15};

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_{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_{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_{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; 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;

each R_{24} 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_{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;

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 D, $(C_1$-$C_6)$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_{16}, -CN, -C(O)$NR_{32}R_{33}$, -C(O)OR_{32}, $(C_3$-$C_7)$carbocyclyl, -O$(C_3$-$C_7)$carbocyclyl, phenyl;

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

o is 0, 1 or 2;

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

q is 1, 2, or 3; and

r is 0 or 1.

2. The compound according to embodiment 1, wherein R_1 is H.

3. The compound according to any one of embodiment 1 or 2, wherein R_{2a} is H.

4. The compound according to any one of embodiments 1-3, wherein R_{2b} is H.

5. The compound according to any one of embodiments 1-4, wherein R_{2c} is H.

6. The compound according to any one of embodiments 1-5, wherein R_{2d} is H.

7. The compound according to any of embodiments 1-6, wherein one to four members of R_{2a}, R_{2b}, R_{2c}, and R_{2d} is CH_3.

8. The compound according to any one of embodiments 1-7, wherein X_1 is CR_3.

9. The compound according to any one of embodiments 1-7, wherein X_1 is N.

10. The compound according to any one of embodiments 1-9, wherein X_2 is N.

11. The compound according to any one of embodiments 1-9, wherein X_2 is CR_5.

12. The compound according to any of embodiments 1-11, wherein R_3 is H.

13. The compound according to any of embodiments 1-11, wherein R_3 is D.

14. The compound according to any of embodiments 1-11, wherein R_3 is CH_3.

15. The compound according to any one of embodiments 1-14, wherein R_4 is independently in each instance $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, -OH, -O-$(C_1\text{-}C_6)$alkyl, $-NR_9R_{10}$, or halogen.

16. The compound according to any one of embodiments 1-15, wherein R_4 is independently in each instance $-CH_3$, $-C_2H_5$, $-CF_3$, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, or -Cl.

17. The compound according to any one of embodiments 1-16, wherein R_5 is independently in each instance $(C_1\text{-}C_6)$alkyl or halogen.

18. The compound according to any one of embodiments 1-17, wherein R_5 is independently in each instance $-CH_3$, -F.

19. The compound according to any one of embodiments 1-18, wherein R_5 is independently in each instance $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$carbocyclyl, -OH, -O-$(C_1\text{-}C_6)$alkyl, $-NR_9R_{10}$, or halogen.

20. The compound according to any one of embodiments 1-19, wherein R_5 is independently in each instance $-CH_3$, cyclopropyl, -OH, $-OCH_3$, $-NH_2$, -F, -Cl.

21. The compound according to any one of embodiments 1-20, wherein R_5 is -F and m is 1

22. The compound according to any one of embodiments 1-21, wherein n is 0.

23. The compound according to any one of embodiments 1-21, wherein n is 1.

24. The compound according to any one of embodiments 1-23, wherein m is 0.

25. The compound according to any one of embodiments 1-23, wherein m is 1.

26. The compound according to any one of embodiments 1-23, wherein m is 2.

27. The compound according to any one of embodiments 1-26, wherein R_6 is H.

28. The compound according to any one of embodiments 1-27, wherein R_{7a} is H, or $(C_1\text{-}C_6)$alkyl.

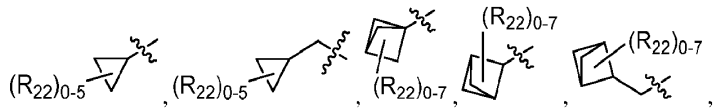
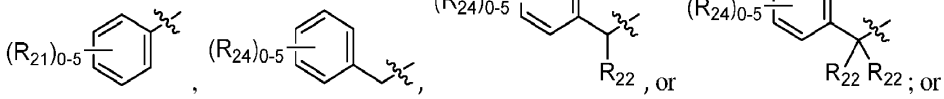
29. The compound according to any one of above embodiments, wherein R_{7a} is -H, $-CH_3$, or $-CH(CH_3)_2$.

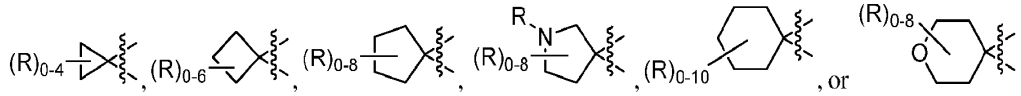
30. The compound according to any one of the above embodiments, wherein R_{7b} is H.

31. The compound according to any one of the above embodiments, wherein R_{7c} is H.

32. The compound according to any one of the above embodiments, wherein R_{7d} is H.

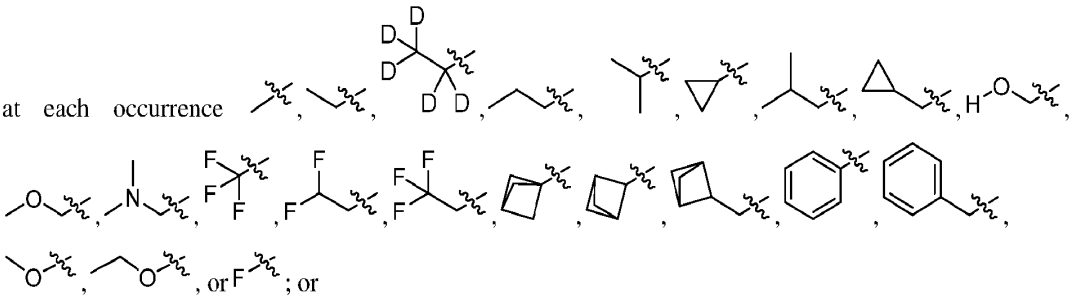
33. The compound according to any one of the above embodiments, wherein each R_{7e} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, halogen, -OH, -O-(C_1-C_6)alkyl, (C_3-C_7)carbocyclyl, or phenyl wherein the alkyl is optionally substituted with one to six R_{19} and the carbocyclyl is optionally substituted with one to five R_{22} and the phenyl is optionally substituted with one to five R_{22}; or two R_{7e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or 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 substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$.

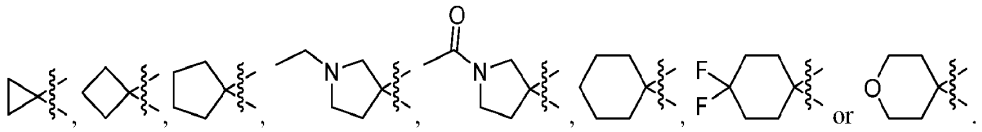
34. The compound according to any one of the above embodiments, wherein each R_{7e} is independently at each occurrence , , or

two R_{7e}, when on the same carbon atom, together with the carbon atom to which they are attached, form , wherein

R in each instance is independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$; and

R_{21}, R_{22}, and R_{24} are defined as in embodiment 1.

35. The compound according to any one of the above embodiments, wherein each R_{7e} is independently at each occurrence 

two R_{7e}, when on the same carbon atom, together with the carbon atom to which they are attached, form .

36. The compound according to any one of embodiments 1-35, wherein o is 2.

37. The compound according to any one of embodiments 1-35, wherein o is 1.

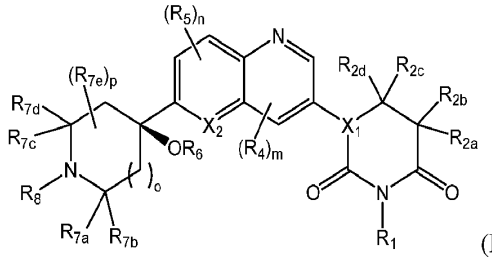
38. The compound according to any of the above embodiments, wherein p is 0.

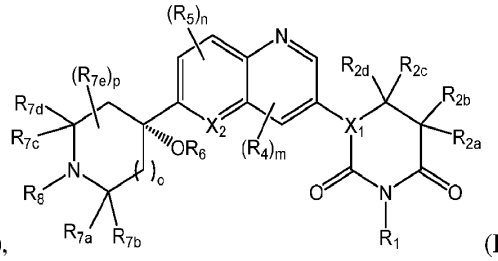
39. The compound according to any of the above embodiments, wherein p is 1.

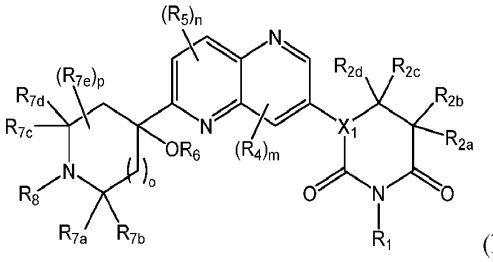
40. The compound according to any of the above embodiments, wherein p is 2.

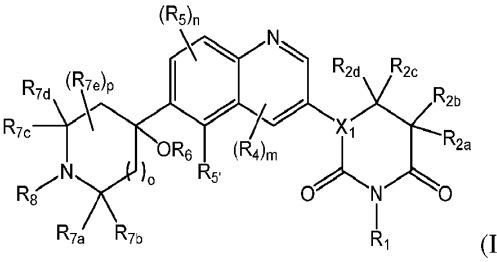
41. The compound according to any of the above embodiments, wherein p is 4.

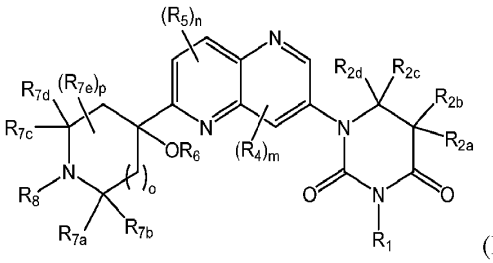
42. The compound according to any of the above embodiments, having a Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), or Formula (Il):

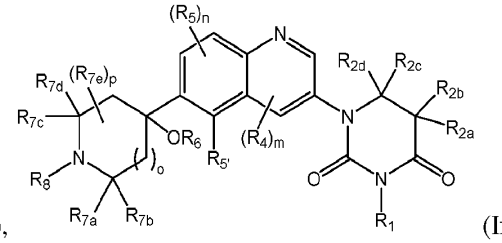

(Ia),

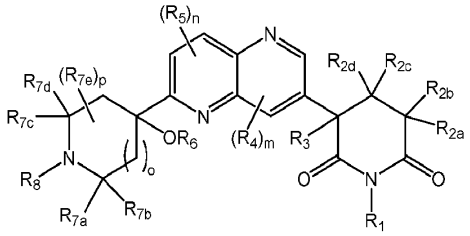
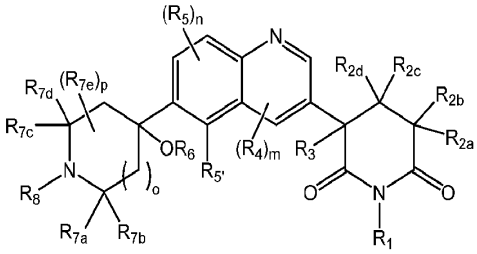
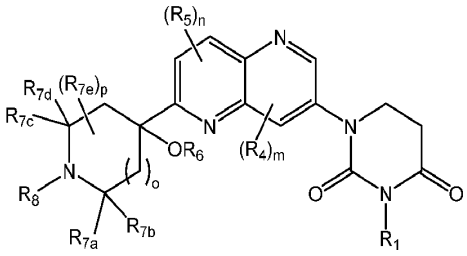
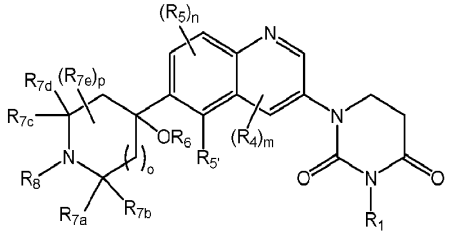
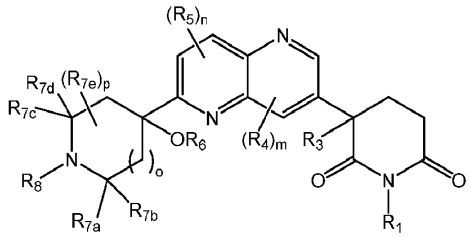
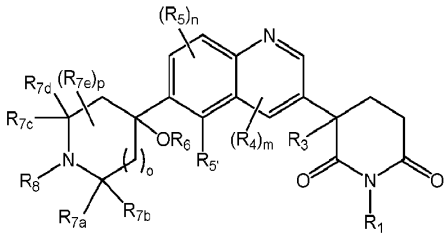

(Ib),


(Ic),


(Id),

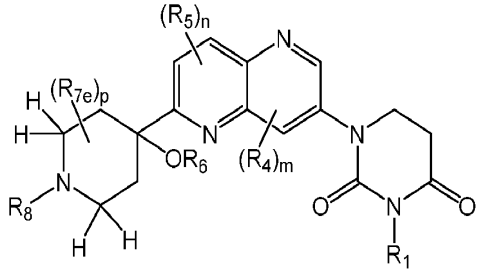
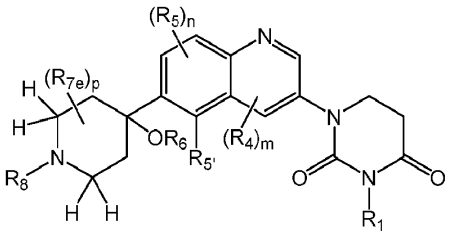
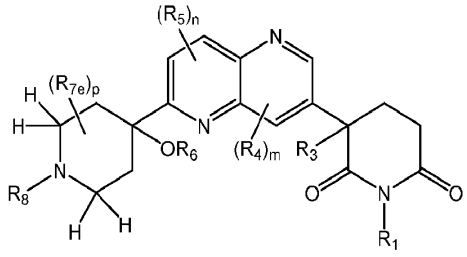
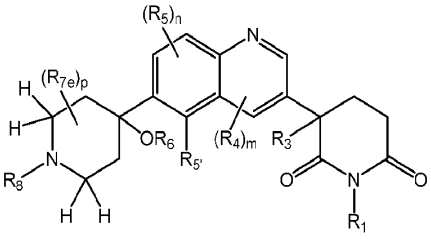

(Ie),

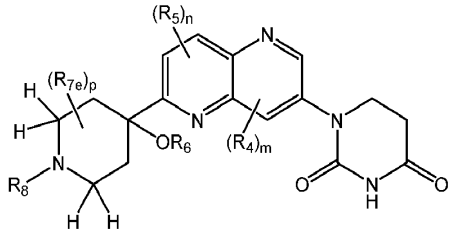
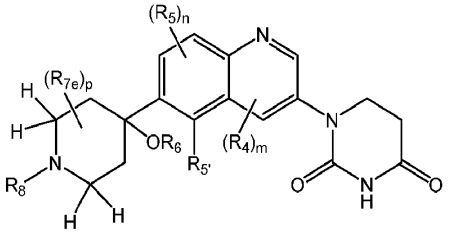
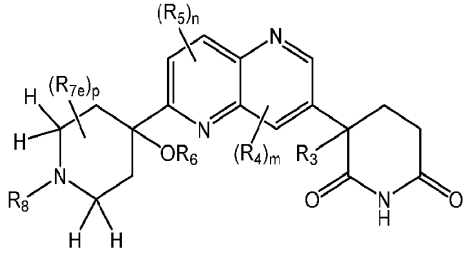
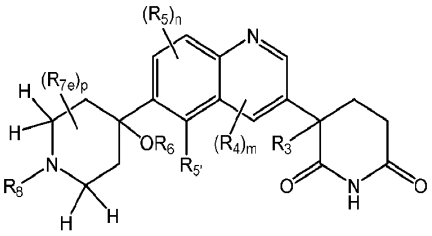
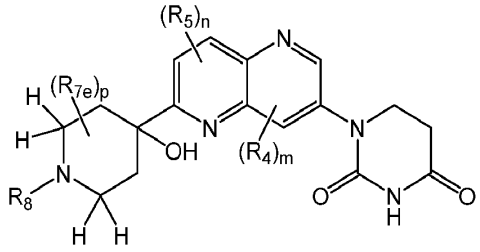
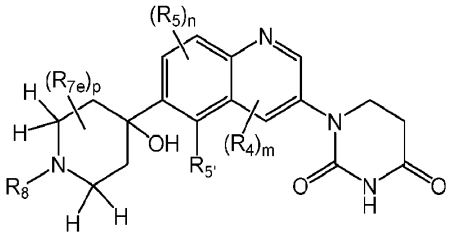
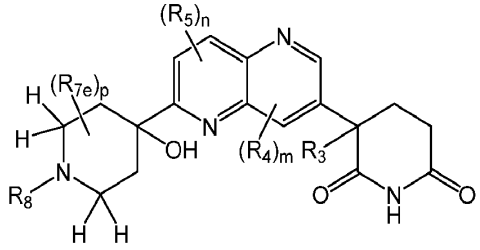
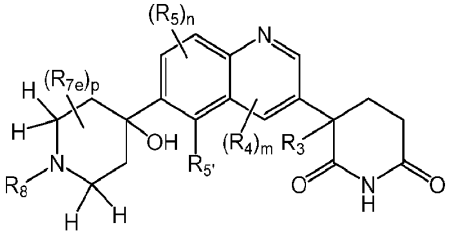
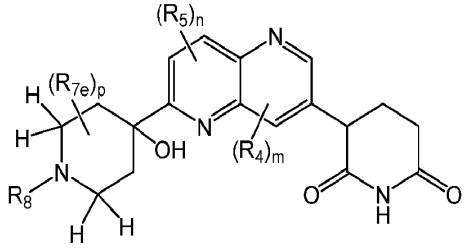
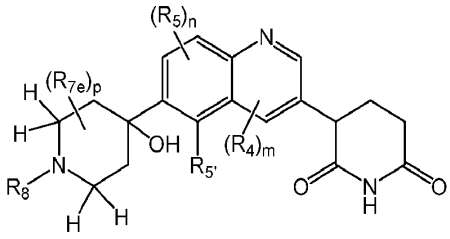

(If),


(Ig),

(Ih),

(Ii),

(Ij),

(Ik), or

(Il),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

43. The compound according to any one of the above embodiments, having a 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), or Formula (Icc):

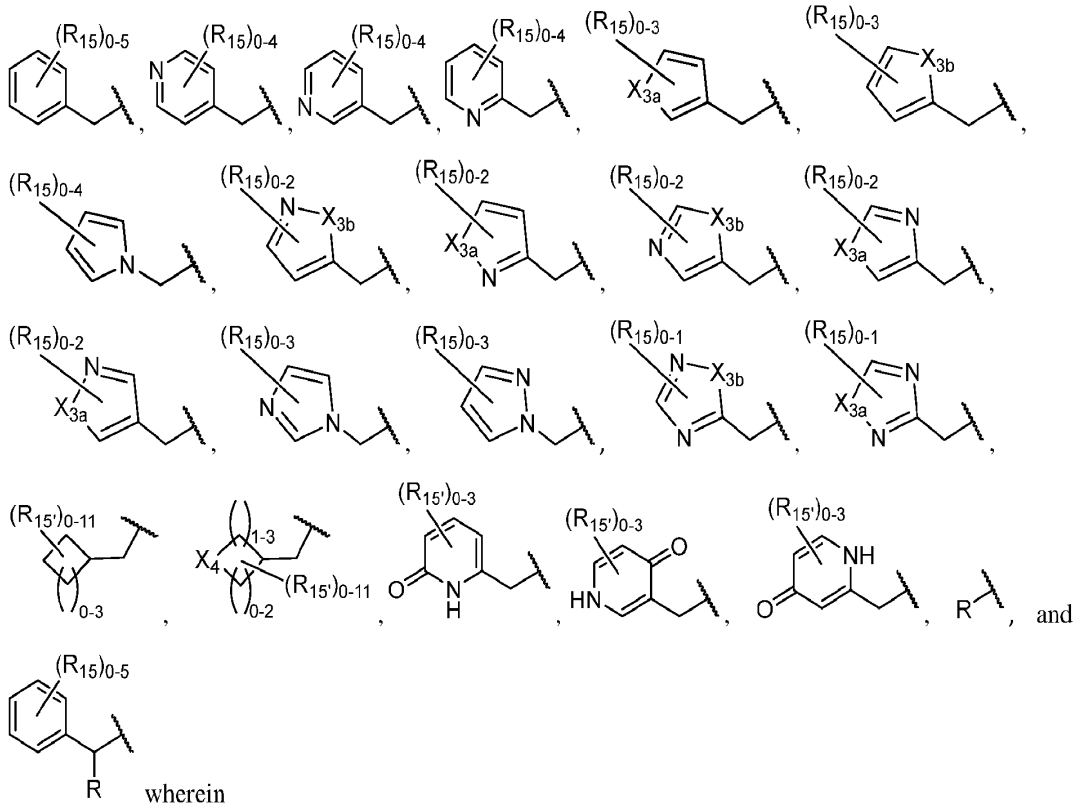

(Im),

(Io),

(Ip),

(Iq),


(Ir),

(Iu),

(Iv),

(Iw),

(Ix),

(Iy),

(Iz),

(Iaa),

(Ibb), or

(Icc),

44. The compound according to any one of the above embodiments, wherein R_8 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)alkyl optionally substituted with one to three 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 optionally

substituted with one to three R_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to three $R_{15'}$.

45. The compound according to any of the above embodiments, wherein R_8 is selected from:



wherein

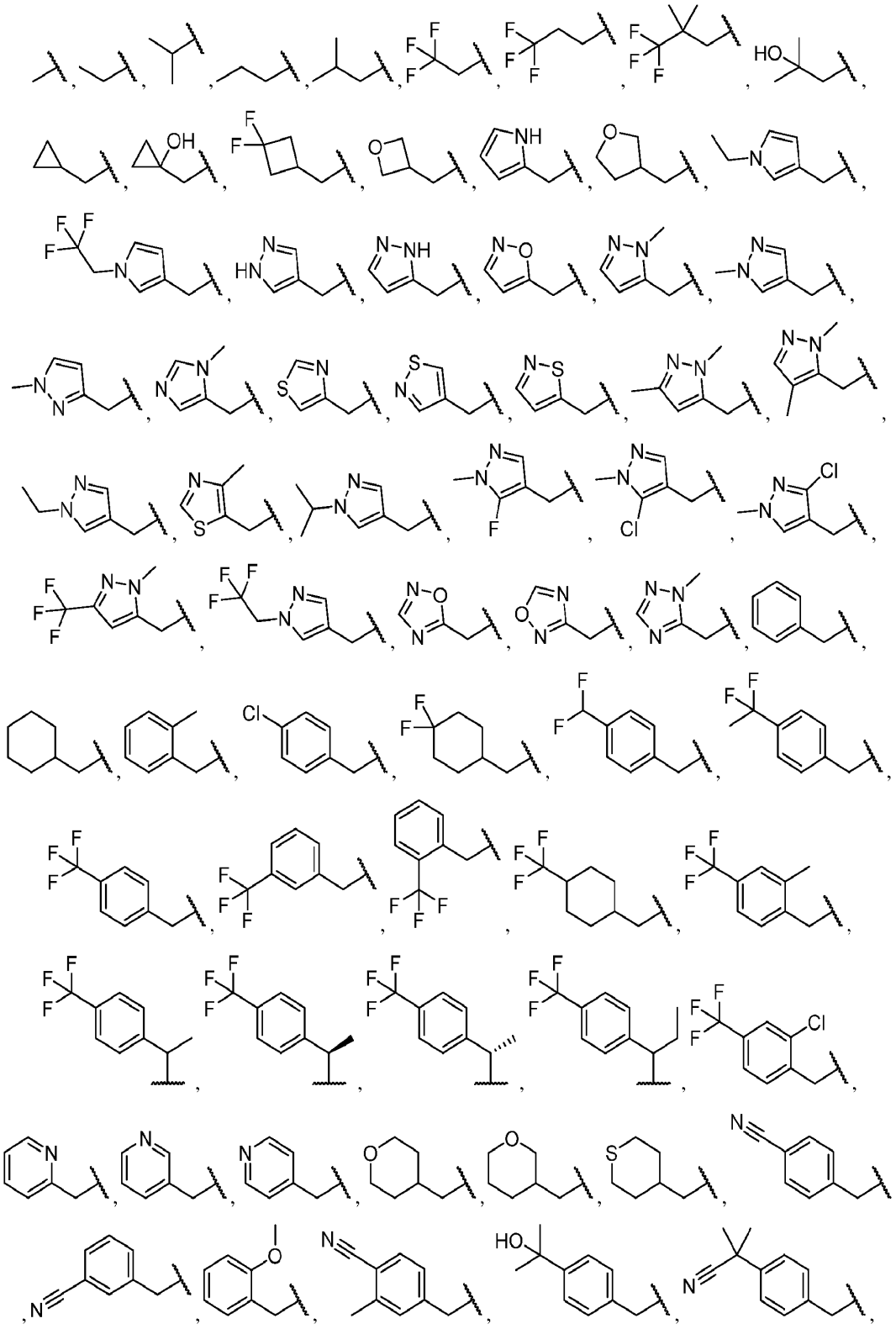
each of X_{3a} and X_{3b} is independently selected from O, S, NH, and NR_{15};

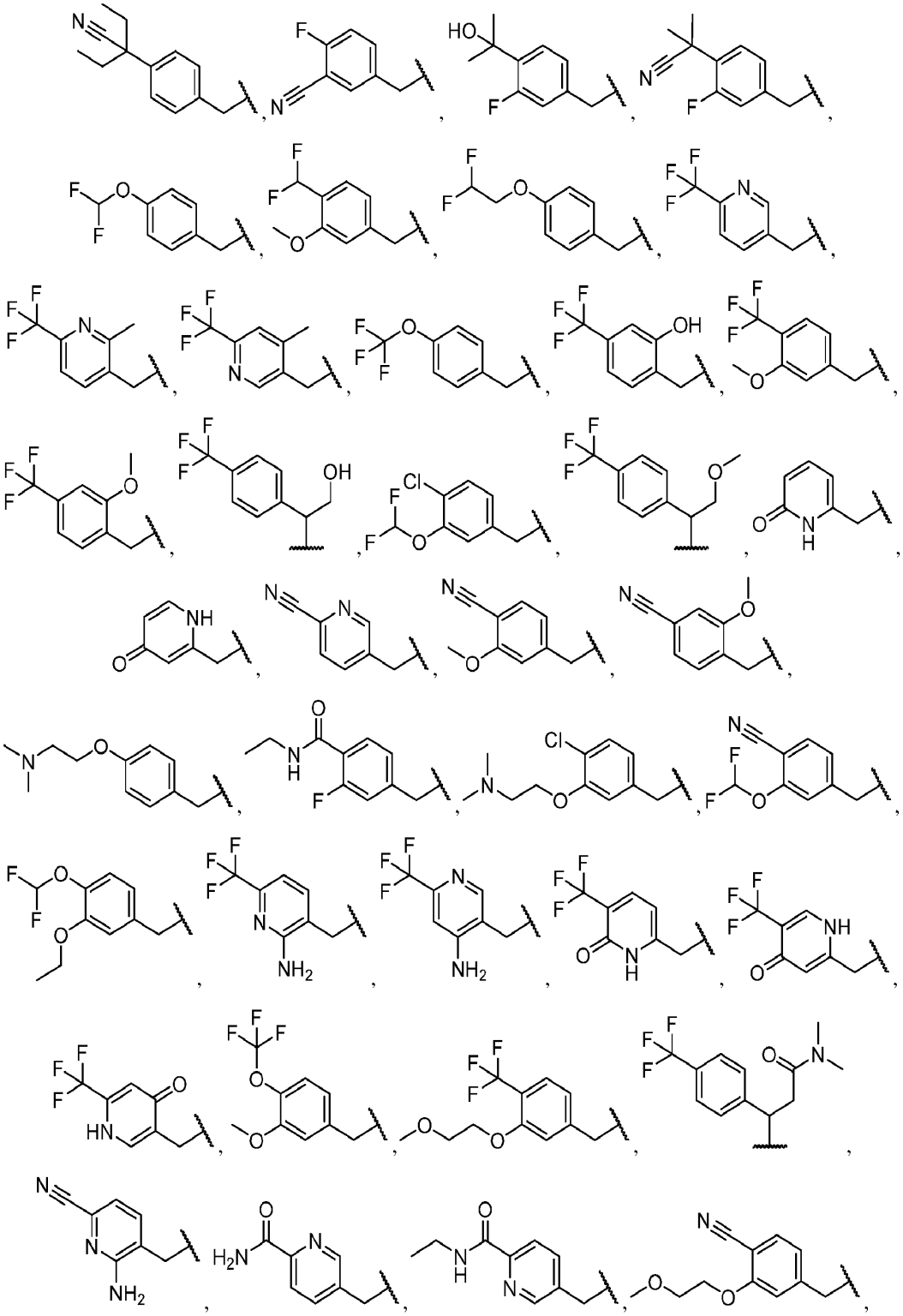
X_4 is O, S, NH, and $NR_{15'}$;

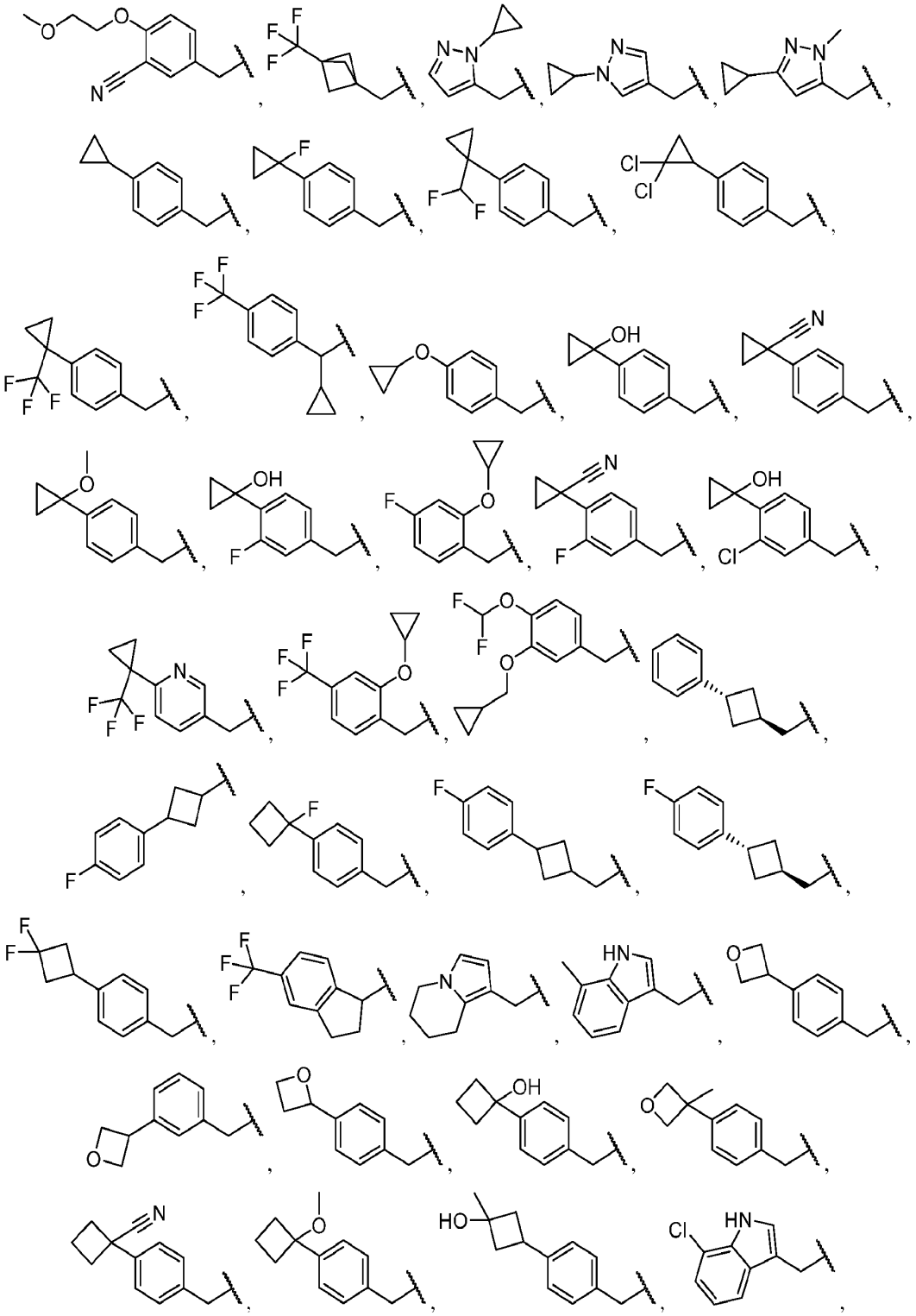
R is selected from (C_1-C_5)alkyl and (C_3-C_7)cycloalkyl, and is optionally substituted with one or more of D, hydroxy, halogen, alkoxy, imidazol-2-yl, and -C(O)$NR_{32}R_{33}$; and

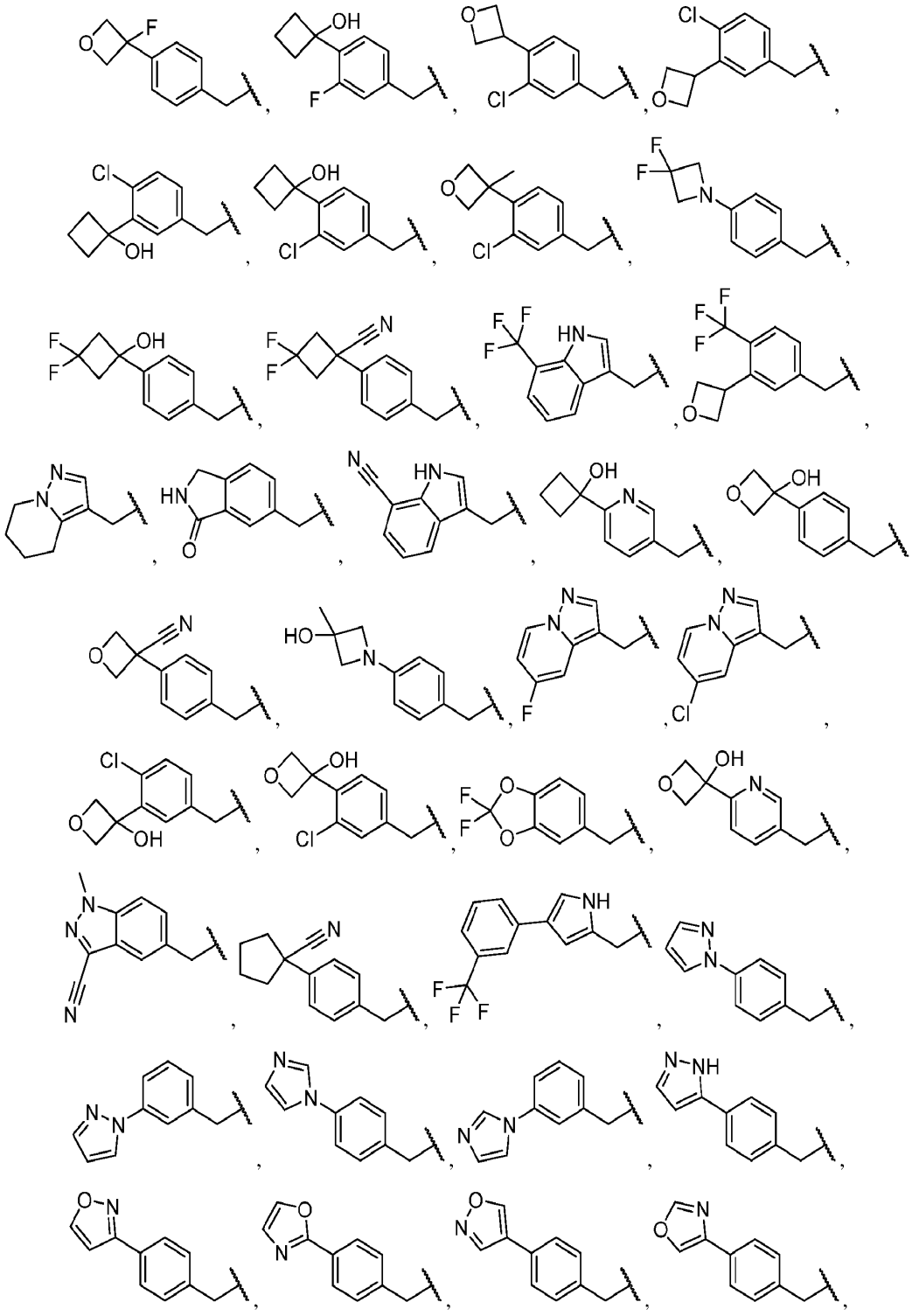
R_{15}, $R_{15'}$, R_{32}, and R_{33} are as defined in embodiment 1.

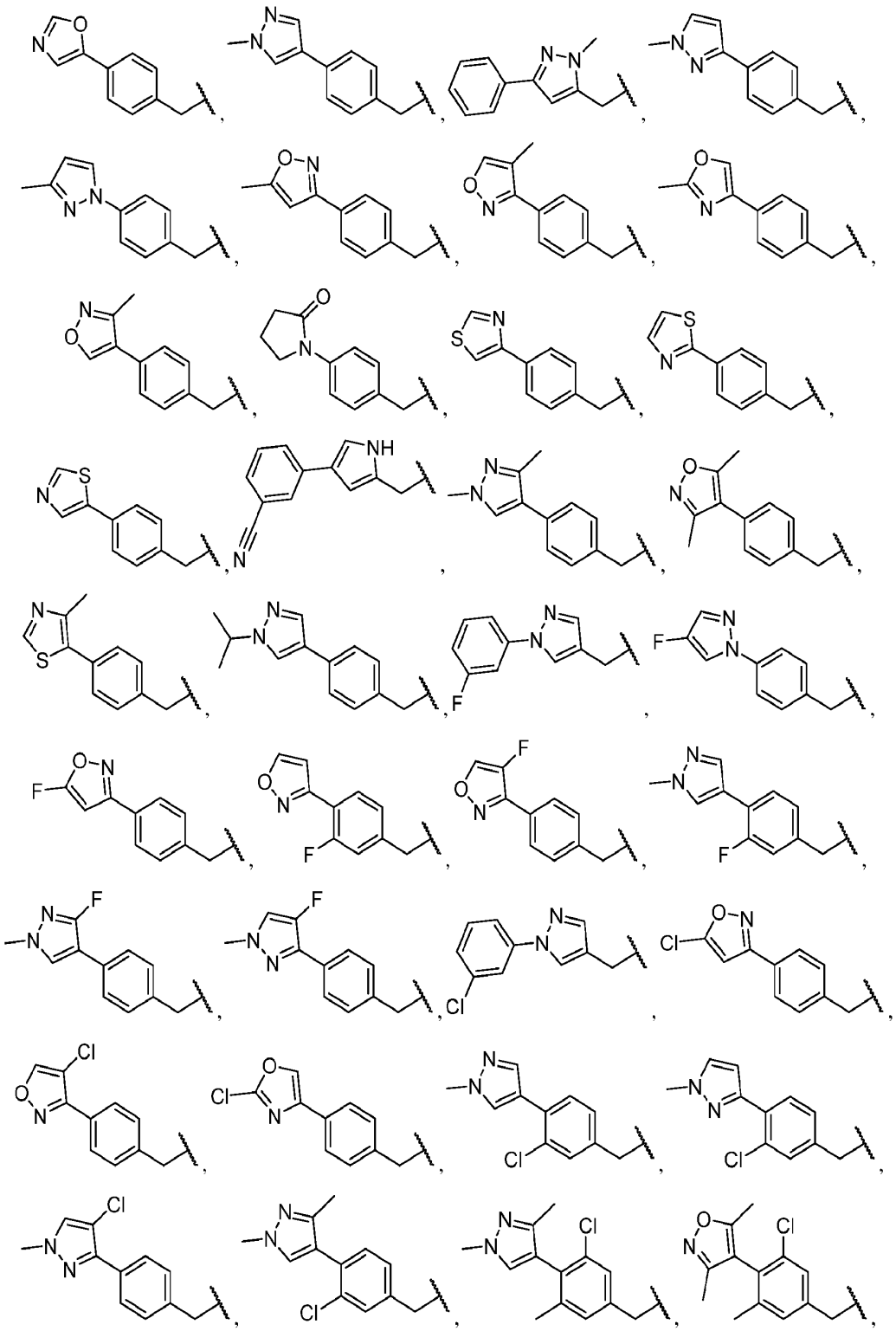
46. The compound according to any of the above embodiments, wherein R_8 is selected from:

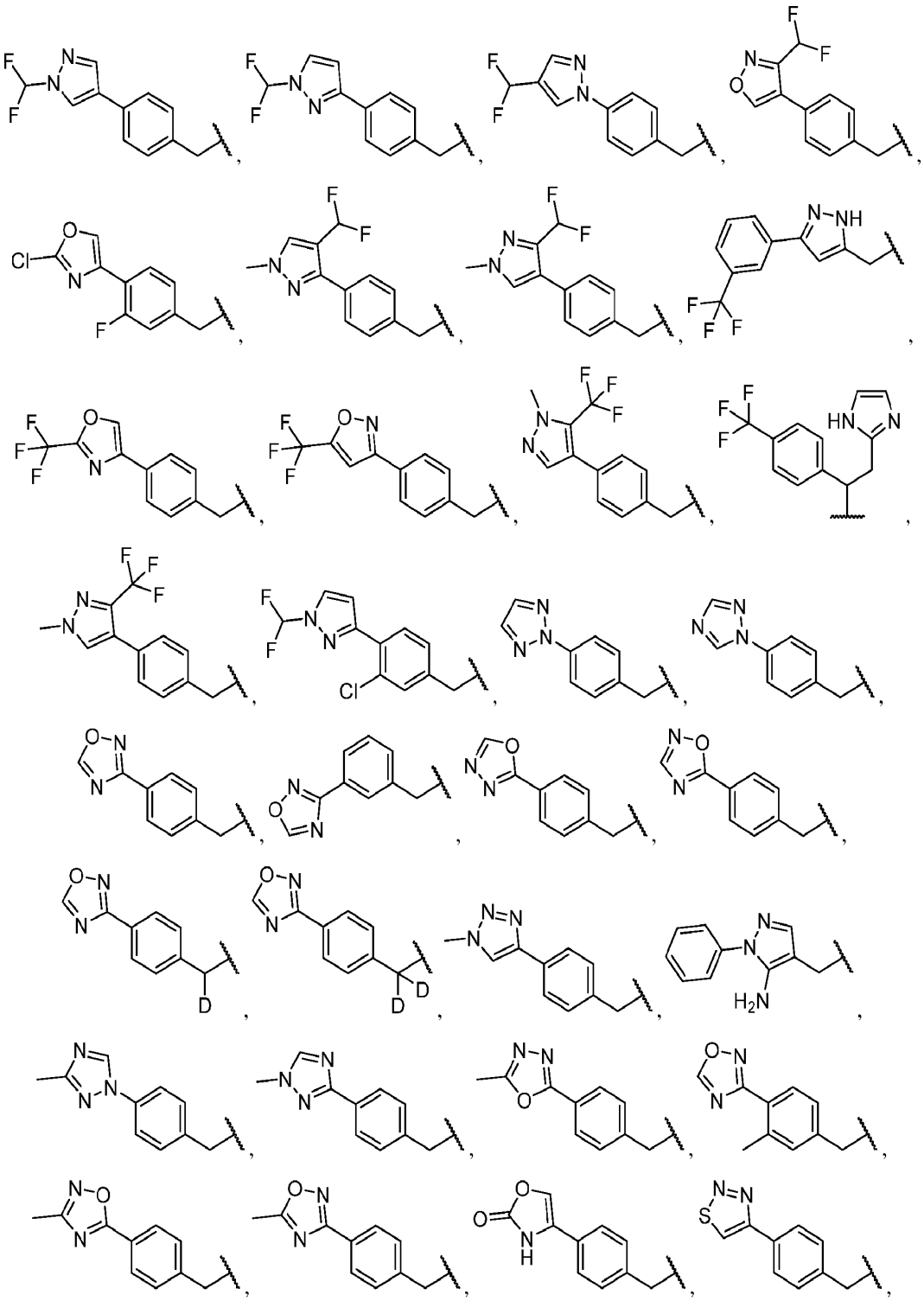


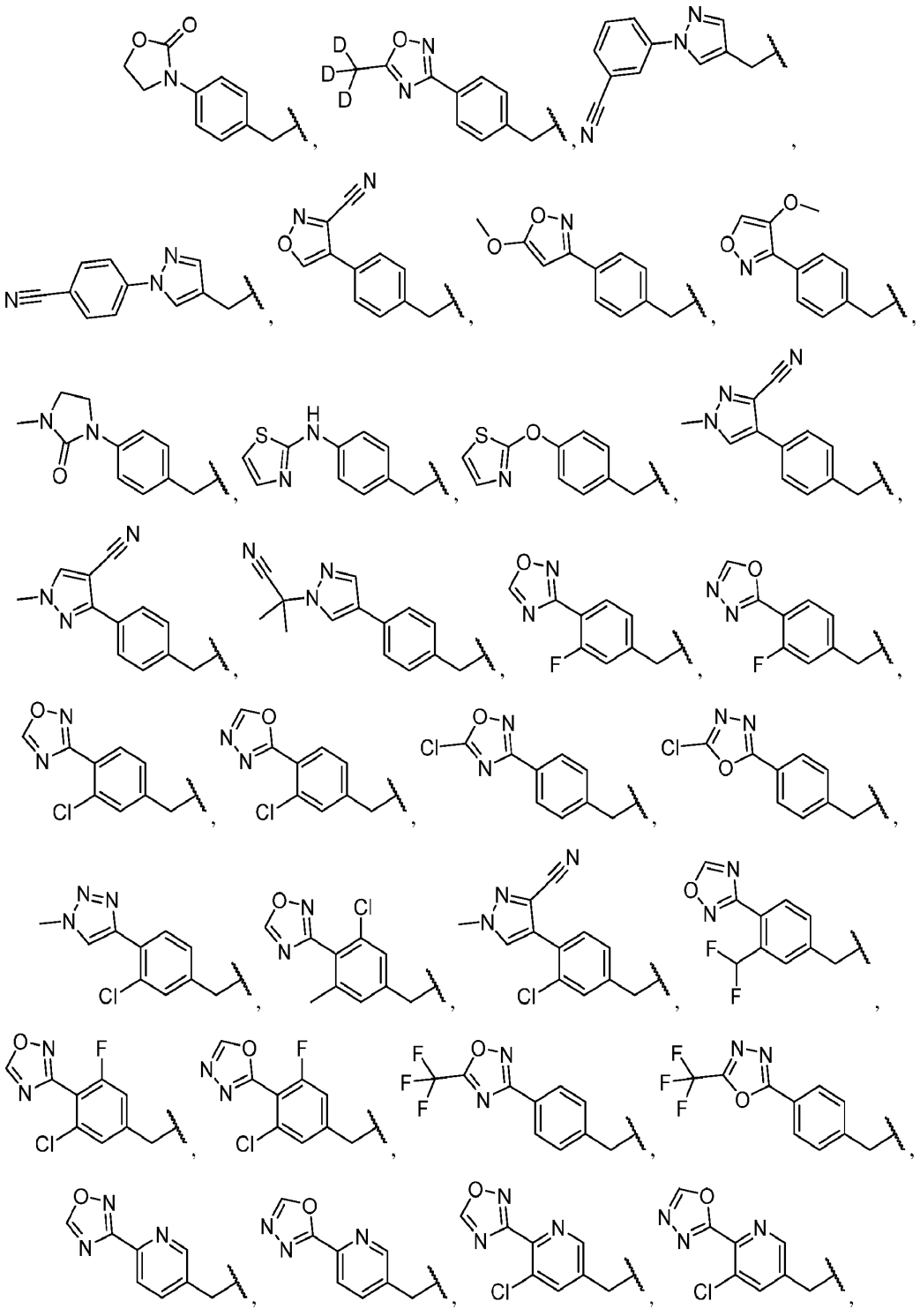


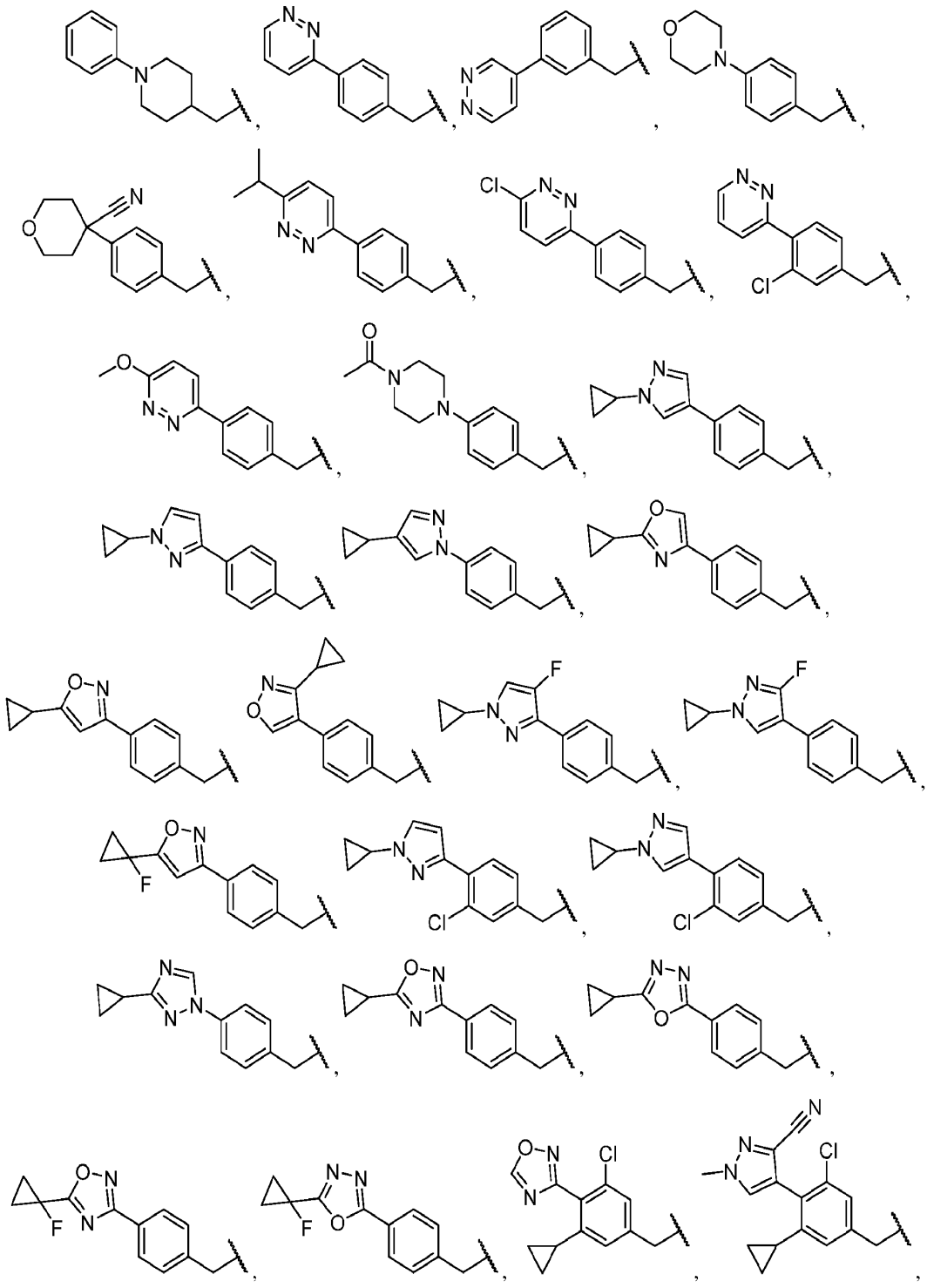


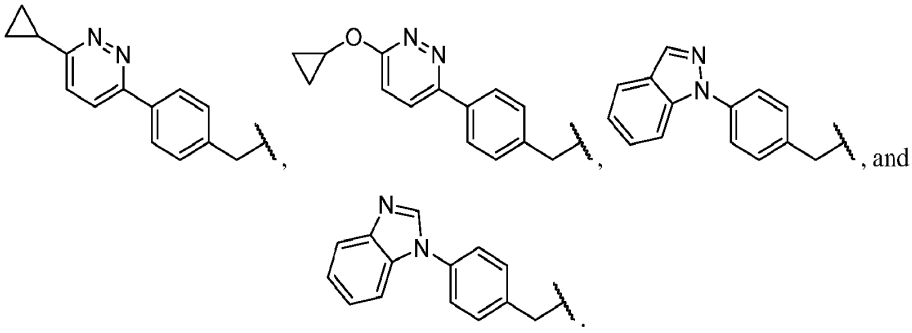












47. The compound according to any one of the above embodiments, wherein each R_{19} is independently at each occurrence (C_1-C_6)alkoxy, -$NR_{20}R_{20'}$, or (C_3-C_7)carbocyclyl wherein carbocyclyl is optionally substituted with two to four R_{23}.

48. The compound according to any one of the above embodiments, wherein the compound is selected from any compound provided in Table 1, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

49. A pharmaceutical composition comprising a compound of any one of the above embodiments, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier or excipient.

50. The pharmaceutical composition according to embodiment 48, further comprising at least one additional pharmaceutical agent.

51. The pharmaceutical composition according to claims 49 or 50 for use in the treatment of a disease or disorder that is affected by the reduction of HIF-1β levels.

52. A method of degrading HIF-1β, comprising administering to a patient in need thereof an effective amount of a compound of any one of the above embodiments, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

53. A method of modulating HIF-1β levels comprising administering to a patient in need thereof an effective amount of a compound of any one of the above embodiments, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

54. An *in vitro* method of reducing the proliferation of a cell, comprising contacting the cell with an effective amount of a compound of any one of the above embodiments, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

55. 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 any one of the above embodiments, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

56. The method according to embodiment 55, 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.

57. The method according to embodiment 55 or 56, 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.

58. A method of treating cancer, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of any one of the above embodiments, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

59. The method according to embodiment 58, wherein the cancer is VHL-deficient cancer.

60. The method according to embodiment 58, 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.

61. A method for reducing HIF-1β levels, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of the above embodiments, or a pharmaceutically acceptable salt thereof.

62. 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 any one of the above embodiments, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

63. A method of treating a neoplastic condition, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of any one of the above embodiments, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

64. A method of treating renal cell carcinoma (RCC), comprising administering to a patient in need thereof a therapeutically effective amount of a compound of any one of the above embodiments, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

65. The method of embodiment 64, wherein the renal cell carcinoma is clear cell renal cell carcinoma (ccRCC).

66. The method according to any one of embodiments 55-65, wherein the administration is oral, parenteral, subcutaneous, by injection, or by infusion.

67. A compound of any one of the above embodiments, 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.

68. A compound of any one of the above embodiments, 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.

69. Use of a compound of any one of the above embodiments, 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.

70. Use of a compound of any one of the above embodiments, 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.

71. The compound for use according to embodiments 69 or 70 or the use according to embodiments 53 or 54, 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 Cl8 1.7µm, 2.1 x 30mm; 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 x 50mm; 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 x 30mm; 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
B_2pin_2	bis(pinacolato)diboron
Boc_2O or Boc anhydride	di-*tert*-butyl dicarbonate
Bn	benzyl
Bu	butyl
br	broad
cataCXium A Pd G_3	Mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′- biphenyl)]palladium(II)
CO	carbon monoxide
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
DAST	N,N-diethylaminosulfur trifluoride
DC_{50}	half maximal degradation concentration
DCE	1,2-dichloroethane
DCM	dichloromethane
DIEA or DIPEA	diisopropylethylamine or N,N-diisopropylethylamine
Dioxane	1,4-dioxane
DMAP	4-dimethylaminopyridine
D_{max}	maximum level of degradation
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMP	Dess-Martin Periodinane, 1,1,1-Tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one
DPPA	diphenylphosphoryl azide

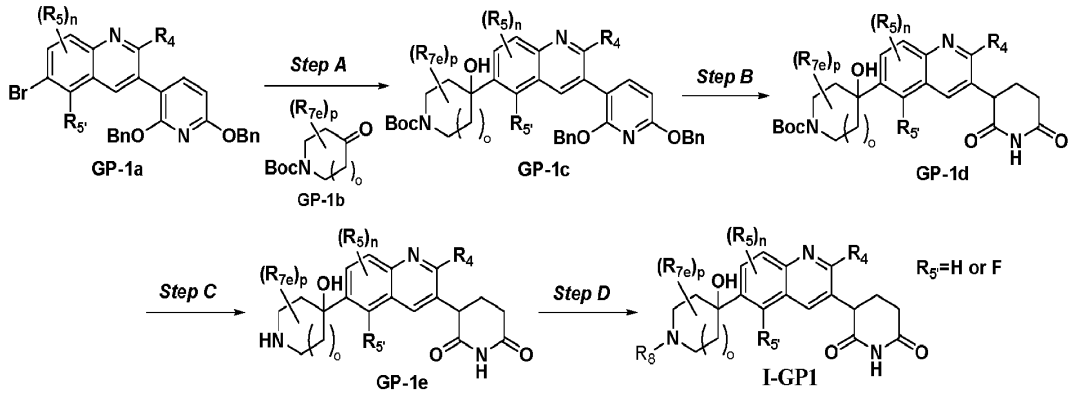
DMSO	dimethylsulfoxide
EC_{50}	half maximal effective concentration
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
eq.	equivalent
ES	electrospray
EtOH	ethanol
Et_2O	diethyl ether
Et_3N	triethylamine
EtOAc	ethyl acetate
FA	formic acid
Grubbs® 2nd gen. catalyst	(1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro-(phenylmethylene)(tricyclohexylphosphine)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 or iPrOH	isopropyl alcohol
$Ir(ppy)_2(dtbbpy)PF_6$	[4,4′-Bis(1,1-dimethylethyl)-2,2′-bipyridine-N1,N1′]bis[2-(2-pyridinyl-N)phenyl-C]iridium(III) hexafluorophosphate
K_2CO_3	potassium carbonate
KI	potassium iodide
KOAc	potassium acetate
KOtBu	potassium tert-butoxide
K_3PO_4	tripotassium phosphate
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
$NaCNBH_3$	sodium cyanoborohydride
NaHMDS	sodium bis(trimethylsilyl)amide
Na_2SO_4	sodium sulfate
NBS	*N*-bromosuccinimide
n-BuLi	n-butyllithium
NMR	nuclear magnetic resonance
$PdCl_2(dppf)$• DCM	1,1'-Bis(diphenylphosphino)ferrocene]-dichloropalladium(II), complex with dichloromethane, $PdCl_2(dppf)$• CH_2Cl_2
$Pd(OAc)_2$	palladium(II) acetate
$PhSO_3H$	benzene sulfonic acid
PTSA	*p*-toluenesulfonic acid
q	quartet
qd	quartet of doublets
quint	quintet
quintd	quintet of doublets
rt	room temperature
Rt	retention time
s	singlet
sat.	saturated
Selectfluor	(1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane

	bis(tetrafluoroborate)
SFC	supercritical fluid chromatography
STAB	sodium triacetoxyborohydride
t	triplet
td	triplet of doublets
tdd	triplet of doublet of doublets
TEA (NEt_3)	triethylamine
tBuOH	*tert*-butyl alcohol
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
TMSOTf	trimethylsilyl triflate
Ts	tosyl or *p*-toluenesulfonyl
tt	triplet of triplets
ttd	triplet of triplet of doublets
TTFA	thallium(III) trifluoroacetate
UPLC	ultra-Performance Liquid Chromatography
wt.	weight

GENERAL PROCEDURES FOR SYNTHESIS OF COMPOUNDS OF FORMULA (I)

General Procedure 1: Synthesis of I-GP1



General Procedure 1, Step A: **Synthesis of Bromoquinoline GP-1c**

To an oven-dried reaction vial equipped with a stir bar and vacuum purged with argon was added **GP-1a** (1 eq.) and THF (0.16 M) and the resulting mixture cooled to -78 °C using a dry ice-acetone bath. *n*-Butyllithium (1.6 M in hexanes,1.5 eq.) was then added and the reaction mixture was stirred at -78 °C for 1 h. Piperidinone **GP-1b** (1.4 eq.) dissolved in THF (1.3 M) was added and stirring was continued at -78 °C for 1 h. The reaction mixture was warmed to ambient temperature and then stirred for an additional 1-3 h at ambient temperature. Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was quenched with water or saturated ammonium chloride solution and extracted with EtOAc (2 times). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified via silica gel column chromatography eluting with EtOAc and heptane. The desired fractions were collected, combined, and concentrated *in vacuo* to provide the desired product, boc-protected piperidine quinoline **GP-1c**.

General Procedure 1, Step B: **Synthesis of Boc-protected piperidine quinoline GP-1d**

Boc-protected piperidine quinoline **GP-1c** (1.0 eq.) and solvent (4:1 DMF:EtOH or DMF, 0.04 M) were added into a reaction vial equipped with a stir bar and under an atmosphere of argon. Dihydroxypalladium (20% wt, 0.2 eq.) or 10% Pd/C (10% wt) was then added and the resulting mixture was sparged continuously for 2-10 h using a balloon of hydrogen gas. Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was worked up and purified via *Workup/Method (a)* or *Workup/Purification Method* (b) below.

Workup/Purification Procedure (a): the reaction mixture was filtered through a pad of celite®, the filter cake was washed with EtOAc, and the filtrate was concentrated *in vacuo*. The crude product was loaded onto a C18 column for purification eluting with MeCN and H_2O. The desired fractions were collected, combined and concentrated *in vacuo* to provide the desired glutarimide product **GP-1d**.

Workup/Purification Procedure (b): The reaction mixture was filtered through a pad of celite®, the filter cake was washed with EtOAc, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash column chromatography using silica gel flash chromatography eluting with ethyl acetate in heptane or hexanes, or on neutral alumina eluting with a linear gradient of 0-20% IPA in EtOAc. The desired fractions were collected, combined and concentrated *in vacuo* to provide the desired glutarimide product **GP-1d**.

General Procedure 1, Step C: **Synthesis of piperidine product GP-1e**

To a stirred solution of glutarimide product **GP-1d** (1.0 eq.) and a 1:1 mixture of DCM and MeCN (0.05 M) in a reaction vial was added methanesulfonic acid (4 eq.), or to a stirred solution of glutarimide product **GP-1d** (1.0 eq.) and DCM was added 4M HCl in 1,4-dioxane (20 eq.) or TFA (to obtain 20% V/V). The resulting mixture was allowed to stir for 30 min. Upon complete consumption of

starting material, as confirmed by LCMS, the reaction mixture was worked up via *Workup Procedure (a)* or *Workup Procedure (b)* below, or in the case of DCM/TFA, by concentration under reduced pressure.

Workup Procedure (a): the reaction mixture was cooled to 0 °C using an ice-water bath and triethylamine (10 eq.) was added. The resulting mixture was then concentrated under reduced pressure and the crude piperidine product **GP-1e** was then carried forward to the next step without further purification (quantitative yield was assumed).

Workup Procedure (b): The reaction mixture was cooled to 0 °C using an ice-water bath and triethylamine (10 eq.) was added. The resulting mixture was triturated using MTBE and pentane and the resulting solid was filtered and dried to afford the desired material, piperidine product **GP-1e**, which was used in the next step without further purification.

General Procedure 1, Step D: **Synthesis of I-GP1**

Method A: To a stirred solution of piperidine product **GP-1e** (1.0 eq.) and an aldehyde (1.1 eq.) in DMF (1 mL) in a reaction vial equipped with a stir bar was added decaborane (0.4 eq.). The resulting mixture was stirred at either room temperature overnight or heated to 70 °C for 30 min. Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was purified via *Purification Method (a)* or *Purification Method* (b) below.

Method B: To a stirred solution of piperidine product **GP-1e** (1.0 eq.) and an aldehyde (1.1 eq.) in DMF (1 mL) in a reaction vial equipped with a stir bar was added sodium triacetoxyborohydride (3 eq.). The resulting mixture was stirred at either room temperature overnight. Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was purified via *Purification Method (a)* or *Purification Method* (b) below.

Purification Method (a): Waters Prep-HPLC [Method info: Phenomenex Luna C18 column 50 x 21.2mm; 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 yield the desired final product **I-GP1**.

Purification Method (b): Shimadzu Prep-HPLC [Method info: Phenomenex Kinetex EVO C18 column 150 x 21.2mm; 5 µm; eluting with 0.1% formic acid in H_2O: 0.1% formic acid in MeCN. Flow rate: 30 mL/min for 15 min]. The desired fractions were collected, combined and concentrated via lyophilization to yield the desired final product **I-GP1**.

The following compounds were made according to General procedure 1.

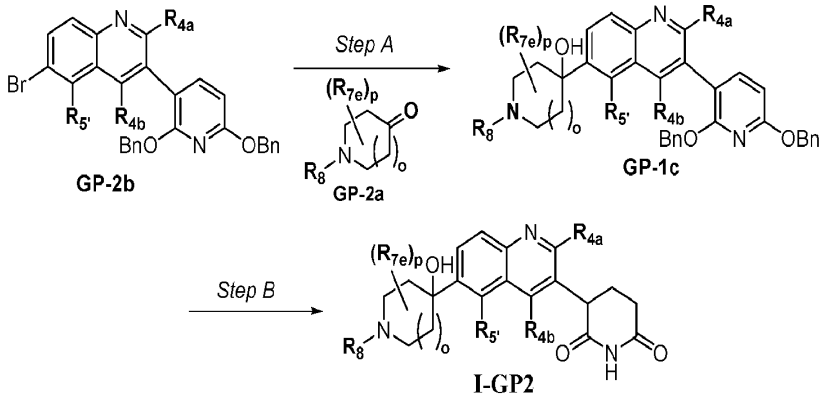
The following compounds in Table 2 were prepared from the appropriate amine and aldehyde starting material for each compound described in Table 2 below according to the reductive amination procedure described in *General Procedure 1, Step D*.

Table 2:

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
INT-15	3-trifluoromethyl benzaldehyde	3-(6-(4-hydroxy-3-methyl-1-(4-(trifluoromethyl) benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-26**)	LCMS: m/z HESI, positive $[M+H]^+$= 512	^{1}H NMR (499 MHz, DMSO-d_6) δ (ppm) = 11.00-10.94 (m, 1H), 8.76-8.72 (m, 1H), 8.40-8.34 (m, 1H), 8.18 (s, 1H), 8.03-7.98 (m, 1H), 7.97-7.93 (m, 1H), 7.87-7.80 (m, 1H), 7.70 (s, 2H), 7.63-7.55 (m, 2H), 5.01-4.84 (m, 1H), 4.18-4.10 (m, 1H), 2.81-2.72 (m, 2H), 2.68-2.61 (m, 2H), 2.61-2.54 (m, 2H), 2.46-2.33 (m, 2H), 2.30-2.22 (m, 1H), 2.18-2.09 (m, 2H), 1.67-1.59 (m, 1H), 1.26-1.18 (m, 1H), 0.48 (d, *J* = 6.3 Hz, 3H).
INT-18	4-(trifluoromethyl)benzaldehyde (**17e**)	3-(6-(3-(cyclopropylmethyl)-4-hydroxy-1-(4-(trifluoromethyl) benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-69**)	LCMS: m/z HESI, positive $[M+H]^+$ = 552	^{1}H NMR (499 MHz, DMSO-d_6) δ (ppm) = 10.99-10.94 (m, 1H), 8.75-8.72 (m, 1H), 8.38-8.33 (m, 1H), 8.19-8.15 (m, 1H), 8.00-7.98 (m, 1H), 7.96-7.92 (m, 1H), 7.88-7.79 (m, 1H), 7.73-7.68 (m, 2H), 7.63-7.55 (m, 2H), 4.96-4.85 (m, 1H), 4.17-4.09 (m, 1H), 3.77-3.70 (m, 1H), 3.64-3.57 (m, 2H), 3.03-2.97 (m, 1H), 2.83-2.72 (m, 2H), 2.65-2.57 (m, 2H), 2.47-2.39 (m, 2H), 2.36-2.26 (m, 1H), 2.26-2.18 (m, 1H), 2.16-2.06 (m, 2H), 1.64-1.56 (m, 1H), 1.05-0.94 (m, 1H), 0.69-0.60 (m, 1H), 0.40-0.33 (m, 1H), 0.23-0.16 (m, 1H), 0.16-0.08 (m, 1H), -0.26--0.33 (m, 1H), -0.45 --0.55 (m, 1H)
INT-18	acetaldehyde	3-(6-(3-(cyclopropylmethyl)-1-ethyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-17**)	LCMS: m/z HESI, positive $[M+H]^+$ = 422	^{1}H NMR (499 MHz, DMSO-d_6) δ (ppm) = 10.96 (s, 1H), 8.73 (d, *J* = 2.2 Hz, 1H), 8.28 (s, 1H), 8.17 (d, *J* = 1.9 Hz, 1H), 7.98 (d, *J* = 1.6 Hz, 1H), 7.94 (d, *J* = 8.8 Hz, 1H), 7.83-7.77 (m, 1H), 4.17-4.10 (m, 1H), 3.06-3.00 (m, 1H), 2.81-2.72 (m, 2H), 2.64-2.57 (m, 1H), 2.46 (br d, *J* = 6.8 Hz, 4H), 2.24-2.17 (m, 2H), 2.16-2.07 (m, 2H), 1.64-1.57 (m, 1H), 1.28-1.19 (m, 1H), 1.08 (s, 4H), 0.69-0.61 (m, 1H), 0.47-0.39 (m, 1H), 0.31-0.24 (m, 1H),

Amine Starting Material	Aldehyde Starting Material	Compound Name (Cmpd No.)	LCMS	^{1}H-NMR
				0.20-0.12 (m, 1H), -0.20--0.27 (m, 1H), -0.44--0.50 (m, 1H).
INT-22	4-(trifluoromethyl)benzaldehyde (**17e**)	3-(6-(8-hydroxy-5-(4-(trifluoromethyl)benzyl)-5-azaspiro[2.5]octan-8-yl)quinolin-3-yl)piperidine-2,6-dione (**I-44**)	LCMS: m/z HESI, positive $[M+H]^+$ = 524	^{1}H NMR (499 MHz, DMSO-d_6) δ (ppm) = 10.99-10.94 (m, 1H), 8.77-8.73 (m, 1H), 8.40-8.37 (m, 1H), 8.23-8.18 (m, 1H), 8.06-8.02 (m, 1H), 7.96-7.88 (m, 2H), 7.71-7.64 (m, 2H), 7.58-7.49 (m, 2H), 5.11-5.02 (m, 1H), 4.18-4.10 (m, 1H), 3.59-3.54 (m, 2H), 2.81-2.69 (m, 3H), 2.66-2.58 (m, 2H), 2.45-2.34 (m, 1H), 2.19-2.09 (m, 1H), 2.06-1.94 (m, 2H), 1.86-1.78 (m, 1H), 1.29-1.19 (m, 2H), 0.37-0.23 (m, 3H).
30c	acetaldehyde	3-(6-(1,3-diethyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-9**)	LCMS: m/z HESI, positive $[M+H]^+$ = 396	^{1}H NMR (499 MHz, DMSO-d_6, 297 K) δ (ppm) = 11.06 (s, 1H), 10.93 (br s, 1H), 9.09 (br s, 1H), 8.75 (br s, 1H), 8.25 (d, J = 8.8 Hz, 1H), 8.20 (s, 1H), 7.98 (br d, J = 8.8 Hz, 1H), 5.78 (br s, 1H), 4.30 (br dd, J = 4.9, 12.6 Hz, 1H), 3.42-3.33 (m, 1H), 3.32-3.11 (m, 4H), 3.07-2.91 (m, 1H), 2.85-2.74 (m, 1H), 2.71-2.61 (m, 2H), 2.55-2.52 (m, 1H), 2.49-2.34 (m, 1H), 2.25-2.13 (m, 1H), 1.86 (br d, J = 14.2 Hz, 1H), 1.34 (t, J = 7.4 Hz, 3H), 1.11-0.92 (m, 2H), 0.66-0.60 (m, 3H).

General Procedure 2: Synthesis of I-GP2



R_8 is alkyl substituted with one or more optionally substituted phenyl

General Procedure 2, Step A: **Synthesis of piperidine quinoline GP-2a**

To an oven-dried reaction vial equipped with a stir bar and vacuum purged with argon was added a 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline GP-2b (1 eq.) and THF (0.16 M). and the resulting mixture cooled to -78 °C using a dry ice-acetone bath. *n*-Butyllithium (1.6 M in hexanes,1.5 eq.) was then added and the reaction mixture was stirred at -78 °C for 1 h. Piperidinone **GP-2a** (1.4 eq.) in THF (1.3 M). was added and stirring was continued at -78 °C for 1 h. The reaction mixture was warmed to ambient temperature and then stirred for an additional 1-3 h at ambient temperature. Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was quenched with water or saturated ammonium chloride solution and extracted with EtOAc (2x). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The material was then loaded onto a silica column for purification with EtOAc and heptanes. The desired fractions were collected, combined, and concentrated *in vacuo* to provide the desired product, piperidine quinoline **GP-2a**.

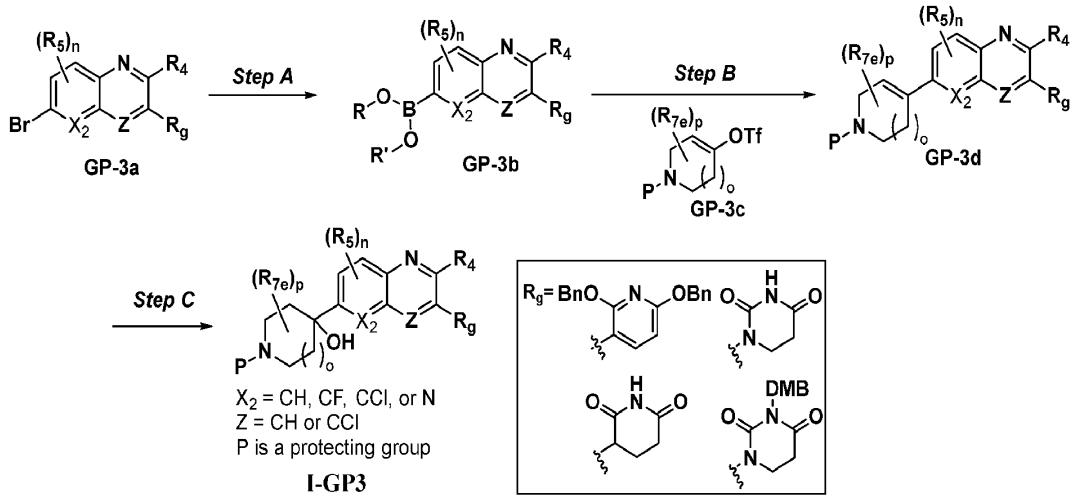
General procedure 2, Step B: **Synthesis of I-GP2**

Piperidine quinoline **GP-1c** (1.0 eq.) and solvent (e.g., 4:1 DMF:EtOH or DMF) were added into a reaction vial equipped with a stir bar and under an atmosphere of argon. Dihydroxypalladium (20% wt, 0.2 eq.) or 10%-50% Pd/C (2 eq.) was then added and the resulting mixture was sparged continuously for 2-10 h using a balloon of hydrogen gas. Upon complete consumption of starting material, as confirmed by LCMS, the reaction was filtered through a pad of celite®, the filter cake was washed with EtOAc, and the filtrate was concentrated *in vacuo*. The crude product was purified via *Purification Method (a)* or *Purification Method* (b) below.

Purification Method (a): Waters Prep-HPLC [Method info: Phenomenex Luna C18 column 50 x 21.2mm; 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 yield the desired final product **I-GP2**.

Purification Method (b): Shimadzu Prep-HPLC [Method info: Regis Evoke C18 column 15 cm x 21 mm; 5 µm; eluting with 0.05% ammonium acetate in H_2O: MeCN, Flow rate: 30 mL/min for 15 min]. The desired fractions were collected, combined and concentrated via lyophilization to yield the desired final product **I-GP2**.

General Procedure 3: Synthesis of I-GP3



General Procedure 3, Step A: **Synthesis of boronic ester GP-3b**

The solution of aromatic bromide **GP-3a** (1 eq.), bis(pinacolato)diboron (1.5 eq.) or 5,5,5',5'-tetramethyl-2,2'-bi(1,3,2-dioxaborinane) (2 eq.) and potassium acetate (3 eq.) in 1, 4-dioxane (0.2M) was sparged with N_2 or argon at 25 °C for 10 min. To this resulting solution was added Pd(dppf)Cl_2 •DCM (10 mol%) or $Pd(OAc)_2$ (10 mol%)/*tert*-butyldiphenylphosphine (20 mol%) in one portion, and the resulting reaction mixture was subjected to microwave irradiation at 100 °C for 1 h, or conventional heating overnight. The reaction mixture was concentrated under reduced pressure. This crude material was purified by silica gel flash column chromatography, eluting with 0-100% EtOAc in hexanes or heptane to afford desired product, boronic and ester **GP-3b**.

General Procedure 3, Step B (Suzuki coupling I): **Synthesis of dihydropiperidine GP-3d**

To the solution of boronic ester **GP-3b** (1 eq.) and enol triflate **GP-3c** (1.2 eq.) in 1,4-dioxane (0.2 M) in a microwave vial under an atmosphere of nitrogen was added a base (e.g., Cs_2CO_3 (1.5 to 2 eq.), K_3PO_4 (1.5 to 2 eq.) or K_2CO_3 (1 to 2 eq.)) dissolved in water (10% v/v) at room temperature. This resulting mixture was sparged with nitrogen for 10 min and Pd(dppf)Cl_2•DCM (10 mol%) was then added in one portion. The reaction mixture was subjected to microwave irradiation at 80 °C for 40 min to 1 h, or conventional heating overnight. The reaction mixture was filtered through a pad of celite® and the filtrate was concentrated under reduced pressure. This crude material was purified via flash column chromatography on silica gel eluting with a linear gradient of 0-100% EtOAc in hexanes or heptane, or C18 column eluting with 0% to 100% MeCN (+0.1% formic acid) in H_2O (+0.1% formic acid) to afford desired product, dihydropiperidine **GP-3d**.

General Procedure 3, Step C (Mukaiyama hydration): **Synthesis of I-GP3**

To a stirred solution of dihydropiperidine **GP-3d** (1 eq.) in DCM and 2-propanol (~1:1 to ~3:1, v/v, 0.025M), or 0.2M DCM with 0.2M 2-propanol with 0.7M DMF were added $Mn(dpm)_3$ (0.5 to 1 eq.)

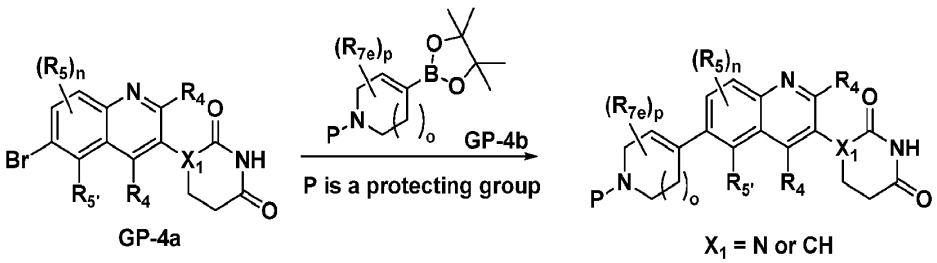
and either phenylsilane (~2.5 eq.) or $NaBH_4$ (~2 eq.) at 0 °C under oxygen atmosphere and the reaction mixture was stirred at 25 °C for 2 to 48h. The reaction mixture was worked up and purified via Workup/purification Procedure (a), Workup/purification Procedure (b) or Workup/purification Procedure (c).

Workup/purification Procedure (a): The reaction mixture was concentrated under reduced pressure and then purified by normal-phase or reverse phase chromatography or preparative HPLC to afford the desired product I-GP3.

Workup/purification Procedure (b): Saturated sodium hypochlorite solution was added and the resulting mixture was stirred for 1 h at room temperature. The crude material was silica gel chromatography or preparative HPLC to afford the desired product I-GP3.

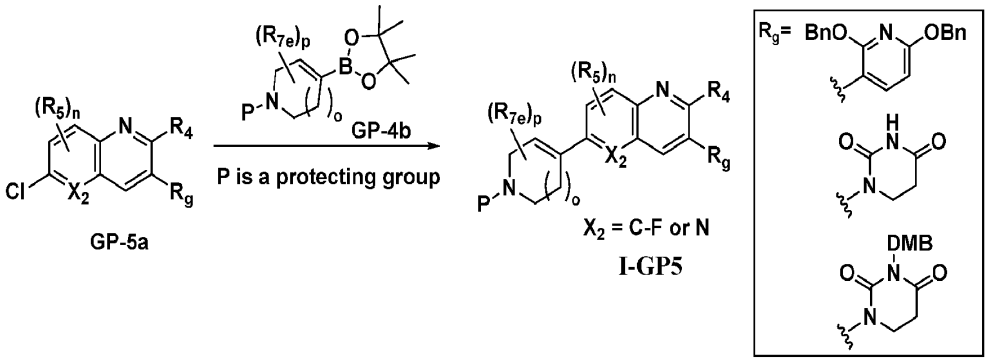
Workup/purification Procedure (c): Saturated sodium thiosulphate was added and the resulting mixture was extracted with DCM. The combined organic phases were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by Biotage Isolera® or preparative HPLC to afford the desired product **I-GP3**.

General Procedure 4: Synthesis of I-GP4



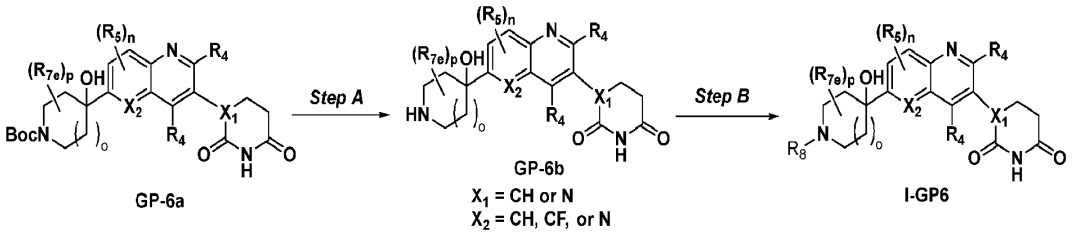
To a stirred solution of substituted or unsubstituted bromoquinolinyl **GP-4a** (1 eq.), and dihydropiperidine boronic ester **GP-4b** (1.5 eq.) in solvent (1,4-dioxane/water (4:1, v/v, ~0.05M) or 100% 1,4-dioxane (0.13M)) under an atmosphere of nitrogen was added a base (DIPEA (2.4 eq.), or K_3PO_4 (2 eq. in 2.5% water v/v), or K_2HPO_4 (1-2 eq.), or K_2CO_3 (1-2 eq.)) followed by palladium catalyst (bis(tri-*tert*-butylphosphine)palladium(0) (10 mol%) or Pd(dppf)Cl_2 •DCM (10 mol%) at room temperature. The reaction mixture was subjected to microwave irradiation at 80 to 100 °C for 1 h and was then filtered through a pad of celite®. The filtrate was concentrated under reduced pressure and the crude compound was purified by column chromatography to provide the desired product **I-GP4**.

General Procedure 5: Synthesis of I-GP5



To a stirred solution of chloroquinolinyl **GP-5a** (1 eq.) and dehydropiperidine boronic ester **GP-4b** (1.2 eq.) in 1,4-dioxane or DMF and water (0.1M, v/v=9:1) was added base (K_2CO_3, DIPEA or Cs_2CO_3, 1-3 eq.) at room temperature. This resulting mixture was sparged with N_2 gas for 10 minutes. To this resulting mixture was added XPhos Pd G3 (5 mol%) followed by Xphos (10 mol%), or bis(*tri-t*-butylphosphine)palladium(0) (10 to 20 mol%) or cataCXium A Pd G_3 (10 to 20 mol%) or $Pd(dppf)Cl_2$•DCM (10 mol%) at room temperature, and the reaction mixture was sparged with N_2 gas for another 10 minutes, and the reaction mixture was stirred at 120 °C with conventional heating overnight or subjected to microwave irradiation at 80 °C or 120 °C for 1 h. The reaction mixture was concentrated under reduced pressure and the crude compound was purified by column chromatography to provide the desired product **I-GP4**.

General Procedure 6: Synthesis of I-GP6



General Procedure 6, Step A: **Synthesis of piperidine quinoline GP-6b**

To a stirred solution of boc-protected piperidine quinoline **GP-6a** (1.0 eq.) in a 1:1 mixture of DCM and MeCN (0.05 M) in a reaction vial was added methanesulfonic acid (4 eq.), or DCM with 4M HCl in 1,4-dioxane (20 eq.). The resulting mixture was allowed to stir for 30 min before monitoring through LCMS. Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was worked up via Workup Procedure (a) or Workup Procedure (b) below.

Workup Procedure (a): the reaction mixture was cooled to 0 °C using an ice-water bath and triethylamine (10 eq.) was added. The resulting mixture was then concentrated under reduced pressure and the crude piperidine product **GP-6b** was then carried forward to the next step without further purification (quantitative yield was assumed).

Workup Procedure (b): The reaction mixture was cooled to 0 °C using an ice-water bath and triethylamine (10 eq.) was added. The resulting mixture was triturated using MTBE and pentane and the resulting solid was filtered and dried to afford the desired material, piperidine quinoline **GP-6b**, which was used in the next step without further purification.

General Procedure 6, Step B: **Synthesis of I-GP6**

Method A: To a stirred solution of piperidine quinoline **GP-6b** (1.0 eq.) and aldehyde or ketone (1.1 eq.) in DMF (1 mL) in a reaction vial equipped with a stir bar was added decaborane (0.4 eq.). The resulting mixture was stirred at either room temperature overnight or heated to 70 °C for 30 min. Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was purified via *Purification Method (a), Purification Method* (b), or *Purification Method* (c) below.

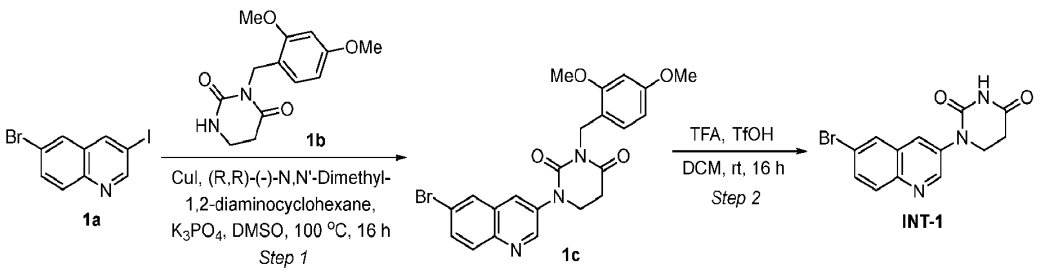
Method B: To a stirred solution of piperidine quinoline **GP-6b** (1.0 eq.) and aldehyde or ketone (1.1 eq.) in DMF (1 mL) in a reaction vial equipped with a stir bar was added sodium triacetoxyborohydride (3 eq.). The resulting mixture was stirred at room temperature overnight. Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was purified via *Purification Method (a), Purification Method* (b), or *Purification Method* (c) below.

Purification Method (a): Waters Prep-HPLC [Method info: Phenomenex Luna C18 column 50 x 21.2mm; 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 yield the desired final product **I-GP6**.

Purification Method (b): Shimadzu Prep-HPLC [Method info: Phenomenex Kinetex EVO C18 column 150 x 21.2mm; 5 µm; eluting with 0.1% formic acid in H_2O: 0.1% formic acid in MeCN. Flow rate: 30 mL/min for 15 min]. The desired fractions were collected, combined, and concentrated via lyophilization to yield the desired final product **I-GP6**.

Purification Method (c): Preparative-HPLC [Method info: (Column: X SELECTC18 (150 x 19 mm) 5 µm, eluting with Mobile phase A: 0.05% HCl in H_2O, Mobile phase B: Acetonitrile, flow rate: 15 mL/min)]. The desired fractions were collected, combined, and concentrated via lyophilization to yield the desired final product **I-GP6**.

Example 1: Synthesis of 5-1-(6-bromoquinolin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione (INT-1)



Step 1: **Synthesis of 1-(6-bromoquinolin-3-yl)-3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (1c)**

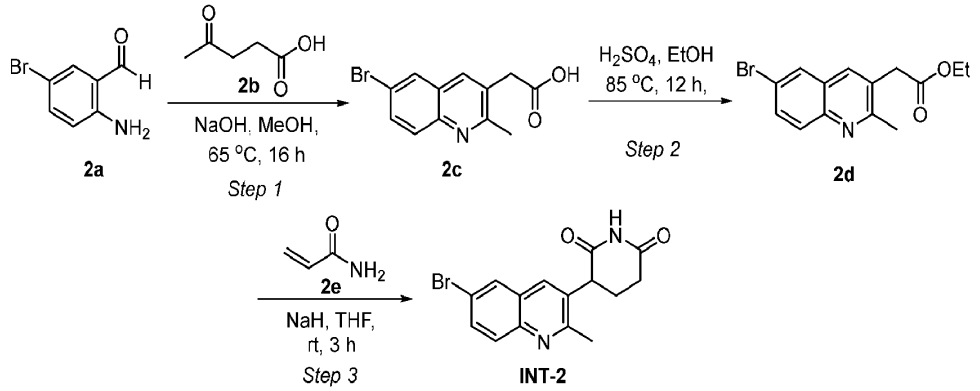
1-(6-bromoquinolin-3-yl)-3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (**1c**) was prepared according to the procedures and examples as reported in PCT Application Publication No. WO2021/188948.

To a stirred solution of 6-bromo-3-iodoquinoline (**1a**, 4.6 g, 13.77 mmol, 1 eq.) and 3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (**1b**, 3.75 g, 14.19 mmol, 1.03 eq.) in DMSO (92 mL, 20 vol.) was added potassium phosphate tribasic (4.12 g, 17.91 mmol, 1.3 eq.), CuI (0.079 g, 0.413 mmol, 0.03 eq.) and (R,R)-(-)-N,N'-dimethyl-1,2-diaminocyclohexane (0.059 g, 0.413 mmol, 0.03 eq.) under continuous nitrogen bubbling for 15 min. The resulting mixture was stirred at 100 °C for 16 h. After complete consumption of starting materials, as confirmed by LCMS, the reaction mixture was cooled to room temperature and poured into ice-cold water (200 mL). The aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic phases were washed with brine solution (150 mL), dried under anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure to provide the crude compound. The crude compound was purified by silica gel flash column chromatography, eluting with 80-85% EtOAc in hexane to afford 1-(6-bromoquinolin-3-yl)-3-(2,4-dimethoxybenzyl)-dihydropyrimidine-2,4(1H,3H)-dione (**1c**, 2.83 g, 4.75 mmol, 36% yield). LCMS: m/z: MM-ES+APCI, positive $[M+2]^+$ 472.3; ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ (ppm): 8.99 (d, J = 2.4 Hz, 1H), 8.36-8.21 (m, 2H), 7.97 (d, J = 8.9 Hz, 1H), 7.86 (dd, J = 2.3, 9.0 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.56 (d, J = 2.4 Hz, 1H), 6.46 (dd, J = 2.4, 8.4 Hz, 1H), 4.82 (s, 2H), 4.08-4.02 (m, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 3.03 (t, J = 6.6 Hz, 2H).

Step 2: **Synthesis of 5-1-(6-bromoquinolin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione (INT-1)**

To a stirred solution of 1-(6-bromoquinolin-3-yl)-3-(2,4-dimethoxybenzyl)-dihydropyrimidine-2,4(1H,3H)-dione (**1c**, 8 g, 17.01 mmol, 1 eq.) in DCM (80 mL, 10 vol.) were added trifluoroacetic acid (20 mL, 2.5 vol.) followed by triflic acid (3.02 mL, 34.0 mmol. 2 eq.) at 0 °C under an atmosphere of nitrogen. The resulting mixture was stirred at room temperature for 16 h. The progress of the reaction was monitored by TLC/LCMS. The reaction mixture was then concentrated under reduced pressure to yield the crude compound. The crude compound was basified with saturated sodium bicarbonate solution (100 mL). The resulting precipitated solid was filtered and washed with water (200 mL) and DCM (2 x 50 mL) and dried under reduced pressure to provide 1-(6-bromoquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**INT-1**, 4.3 g, 13.12 mmol, 77% yield). LCMS: m/z: MM-ES+APCI, positive $[M+2]^+$ 322.2; ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ (ppm): 10.89-10.44 (m, 1H), 8.99 (d, J = 2.4 Hz, 1H), 8.25 (dd, J = 2.1, 18.2 Hz, 2H), 7.96 (d, J = 9.0 Hz, 1H), 7.85 (dd, J = 2.2, 8.9 Hz, 1H), 3.97 (t, J = 6.6 Hz, 2H), 2.80 (t, J = 6.6 Hz, 2H).

Example 2: Synthesis of 3-(6-bromo-2-methylquinolin-3-yl)piperidine-2,6-dione (INT-2)



Step 1: **Synthesis of 2-(6-bromo-2-methylquinolin-3-yl)acetic acid (2c)**

2-(6-bromo-2-methylquinolin-3-yl)acetic acid (**2c**) was prepared according to the procedures and examples as reported in PCT Application Publication No. WO2022/253713.

4-oxopentanoic acid (**2b**, 3.77 g, 32.5 mmol, 1 eq.) and NaOH (19.50 mL, 2M solution, 39.0 mmol, 1.2 eq.) were added to a stirred solution of 2-amino-5-bromobenzaldehyde (**2a**, 6.5 g, 32.5 mmol, 1 eq.) in MeOH (50 mL, 7.69 vol.) at room temperature under an atmosphere of nitrogen. The resulting mixture was stirred at 65 °C for 16 h. The progress of the reaction was monitored by LCMS. After complete consumption of starting materials, as confirmed by LCMS/TLC, the reaction mixture was allowed to cool to room temperature. The solvent was removed under reduced pressure and the resulting crude residue was diluted with water (20 mL). The pH was adjusted pH to ~2-3 with acetic acid. A solid precipitated which was filtered, washed with water, and dried under reduced pressure to afford 2-(6-bromo-2-methylquinolin-3-yl)acetic acid (**2c**, 7.3 g, 26 mmol, 80% yield). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 280.0; ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ (ppm): 13.17-12.26 (m, 1H), 8.18 (d, *J* = 2.1 Hz, 1H), 8.10 (s, 1H), 7.88-7.84 (m, 1H), 7.82-7.77 (m, 1H), 3.85 (s, 2H), 2.60 (s, 3H).

Step 2: **Synthesis of ethyl 2-(6-bromo-2-methylquinolin-3-yl)acetate (2d)**

Ethyl 2-(6-bromo-2-methylquinolin-3-yl)acetate (**2d**) was prepared according to the procedures and examples as reported in EP Application No. EP3848367 A1.

To a stirred solution of 2-(6-bromo-2-methylquinolin-3-yl)acetic acid (**2c**, 13 g, 46.4 mmol, 1 eq.) in ethanol (130 mL, 10 vol.) was added sulfuric acid (3.73 mL, 69.6 mmol, 1.5 eq.) at 25 °C under an atmosphere of nitrogen. The resulting mixture was then stirred at 85 °C for 12 h. After complete consumption of the starting materials, as confirmed by LCMS/TLC, the reaction mixture was cooled to room temperature, and ethanol was removed under reduced pressure. The resulting crude residue was dissolved in EtOAc (200 mL), washed with saturated sodium bicarbonate solution (2 x 50 mL), dried over anhydrous Na_2SO_4 and filtered. The solvent was removed *in vacuo* to afford ethyl 2-(6-bromo-2-

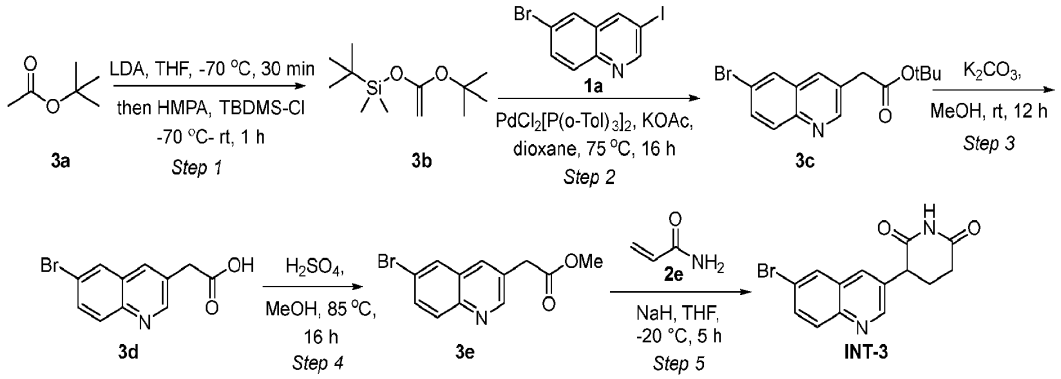
methylquinolin-3-yl)acetate (**2d**, 12 g, 34.7 mmol, 75% yield), LCMS: m/z: MM-ES+APCI, positive $[M+2]^+$ 309.9; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.27 (br s, 2H), 7.90 (br s, 2H), 4.14 (q, J = 7.0 Hz, 2H), 3.99 (s, 2H), 2.65 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H).

Step 3: **Synthesis of 3-(6-bromo-2-methylquinolin-3-yl)piperidine-2,6-dione (INT-2)**

3-(6-Bromo-2-methylquinolin-3-yl)piperidine-2,6-dione (**INT-2**) was prepared according to the procedures and examples as reported in EP Patent Application No. EP3848367 A1.

To a stirred solution of ethyl 2-(6-bromo-2-methylquinolin-3-yl)acetate (**2d**, 4 g, 12.98 mmol, 1 eq.) in THF (40 mL, 10 vol.) was added 60% wt NaH (0.623 g, 15.58 mmol, 1.2 eq.) at -20 °C under an atmosphere of nitrogen. The resulting mixture was stirred at the same temperature for 1 h. Acrylamide (**2e**, 1.015 g, 14.28 mmol, 1.1 eq.) in THF (1 mL) was then added drop-wise at -20 °C, and the reaction mixture was allowed to warm to room temperature and then stirred at room temperature for 2 h. The reaction mixture was quenched with 1.5N HCl in dioxane upon complete consumption of starting materials, as confirmed by LCMS and concentrated under reduced pressure. To the resulting crude residue was added saturated $NaHCO_3$ solution (20 mL) and the resulting mixture was stirred for 30 min. The resulting solid precipitate was filtered, washed the solid with water (2 x 25 mL) and dried under reduced pressure to afford the crude product. The crude product was then triturated in ACN (20 mL), stirred for 30 min, and filtered. The resulting solid was washed with hexane and dried under reduced pressure to afford 3-(6-bromo-2-methylquinolin-3-yl)piperidine-2,6-dione (**INT-2**, 2 g, 5.22 mmol, 40% yield). LCMS: m/z MM+ES+APCI, positive $[M+H]^+$ 333.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.14-10.70 (m, 1H), 8.30-7.99 (m, 2H), 7.91-7.76 (m, 2H), 4.36-4.22 (m, 1H), 2.95-2.71 (m, 1H), 2.66 (s, 4H), 2.43-2.31 (m, 1H), 2.15 (d, J = 3.1 Hz, 1H).

Example 3: Synthesis of 3-(6-bromoquinolin-3-yl)piperidine-2,6-dione (INT-3)



Step 1: **Synthesis of ((1-(*tert*-butoxy)vinyl)oxy)(*tert*-butyl)dimethylsilane (3b)**

((1-(*Tert*-butoxy)vinyl)oxy)(tert-butyl)dimethylsilane (**3b**) was prepared according to the procedures and examples as reported in US Patent Application No. US2005272665A1.

To a stirred solution of *tert*-butyl acetate (**3a**, 50 g, 430 mmol, 1 eq.) in THF (500 mL, 50 vol.) was added 2 M lithium diisopropylamide in THF (237 mL, 473 mmol, 1.1 eq.) drop-wise at -70 °C under an atmosphere of nitrogen and the resulting mixture was stirred at the same temperature for 30 min. Hexamethylphosphoramide (59.9 mL, 344 mmol, 0.8 eq.) and *tert*-butyldimethylsilyl chloride (68.1 g, 452 mmol, 1.05 eq.) dissolved in THF (100 mL) were then added to the pre-stirred reaction mixture at -70 °C. The reaction mixture was warmed to room temperature for 1 h. The progress of the reaction was monitored by TLC. After complete consumption of starting materials, the reaction mixture was concentrated under reduced pressure (below 40 °C, >10 mbar). The resulting crude compound (oily liquid) was dissolved in hexane (1000 mL) and the organic phase was washed with water (1000 mL) and brine solution (500 mL), dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure (below 40 °C, >10 mbar) to afford the crude compound. The crude compound was then further purified via distillation (bp 75 °C-80 °C at 2 mbar) to afford ((1-(*tert*-butoxy)vinyl)oxy)(*tert*-butyl)dimethylsilane (**3b**, 65 g, 282 mmol, 66% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 3.48 (dd, J = 1.3, 9.4 Hz, 2H), 1.37 (s, 9H), 0.96 (s, 9H), 0.23-0.17 (m, 6H).

Step 2: **Synthesis of *tert*-butyl 2-(6-bromoquinolin-3-yl)acetate (3c)**

Tert-butyl 2-(6-bromoquinolin-3-yl)acetate (**3c**) was prepared according to the procedures and examples as reported in PCT Application Publication No. WO2022/253713.

To a stirred solution of 6-bromo-3-iodoquinoline (**1a**, 5 g, 14.97 mmol, 1eq.) in dioxane (100 mL, 20 vol.) was added ((1-(*tert*-butoxy)vinyl)oxy)(*tert*-butyl)dimethylsilane (**3b**,10.35 g, 44.9 mmol, 3 eq.), potassium acetate (2.94 g, 29.9 mmol, 2 eq.) followed by dichlorobis(tri-o-tolylphosphine)palladium(II) (1.765 g, 2.246 mmol, 0.15 eq.) at rt under an atmosphere of argon. The resulting mixture was stirred at 75 °C for 16 h. The progress of the reaction was monitored by TLC/LCMS. Upon complete consumption of starting materials, the reaction mixture was filtered through a celite® pad which was washed with EtOAc (2 x 50 mL). The filtrate was directly concentrated. The resulting crude compound was purified by silica gel flash column chromatography, eluting with 5-10% of EtOAc in hexane to afford *tert*-butyl 2-(6-bromoquinolin-3-yl)acetate (**3c**, 2 g, 4.31 mmol, 29% yield). LCMS: m/z MM+ES+APCI, positive $[M+2]^+$ 324.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.84 (d, J = 2.1 Hz, 1H), 8.27 (d, J = 2.3 Hz, 1H), 8.21 (d, J = 1.5 Hz, 1H), 7.96 (d, J = 8.9 Hz, 1H), 7.86 (dd, J = 2.3, 9.0 Hz, 1H), 3.85 (s, 2H), 1.42 (s, 9H).

Step 3: **Synthesis of 2-(6-bromoquinolin-3-yl)acetic acid (3d)**

To a stirred solution of *tert*-butyl 2-(6-bromoquinolin-3-yl)acetate (**3c**, 8.5 g, 26.4 mmol, 1 eq.) in MeOH (85 mL) added K_2CO_3 (7.29 g, 52.8 mmol, 2 eq.) at rt under an atmosphere of nitrogen and the resulting mixture was stirred at rt for 16 h. The progress of the reaction was monitored by TLC/LCMS. The reaction mixture was then concentrated under reduced pressure. The obtained crude compound was

dissolved in water and the pH of the aqueous mixture was adjusted to ~1-2 with 1.5 N HCl. A solid precipitated which was filtered and washed with water (2 x 60 mL) and followed by hexane (2 x 50 mL). The resultant solid was then triturated with EtOAc (10 mL), stirred for 10 min, filtered, and dried under reduced pressure to afford 2-(6-bromoquinolin-3-yl)acetic acid (**3d**, 7.5 g, 21.03 mmol, 80% yield). LCMS: m/z MM+ES+APCI, positive $[M+2]^+$ 268.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.87-12.46 (m, 1H), 8.85 (d, J = 2.1 Hz, 1H), 8.27 (d, J = 2.1 Hz, 1H), 8.22 (d, J = 1.5 Hz, 1H), 7.96 (d, J = 8.9 Hz, 1H), 7.89-7.80 (m, 1H), 3.86 (s, 2H).

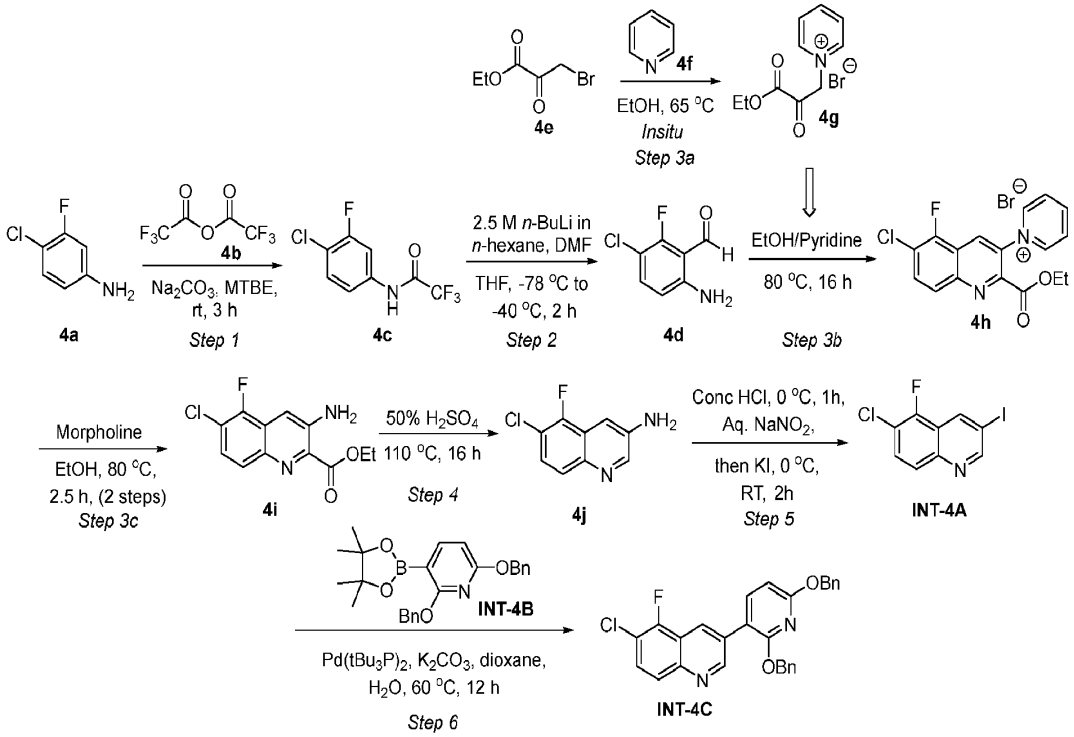
Step 4: **Synthesis of methyl 2-(6-bromoquinolin-3-yl)acetate (3e)**

To a stirred solution of 2-(6-bromoquinolin-3-yl)acetic acid (**3d**, 13 g, 48.9 mmol, 1 eq.) in MeOH (130 mL) was added sulfuric acid (3.91 mL, 73.3 mmol, 1.5 eq.) at room temperature under an atmosphere of nitrogen and the resulting mixture was stirred at 85 °C for 16 h. The reaction mixture was cooled to room temperature (monitored by TLC) and concentrated under reduced pressure. The obtained crude compound was dissolved in water and the aqueous phase was washed with EtOAc (2 x 50 mL). The combined organic phases were washed with saturated sodium bicarbonate solution (2 x 100 mL) and brine solution (1 x 100 mL), dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure. The obtained crude compound was triturated with hexane (2 x 15 mL), and the precipitated solid was filtered and dried under reduced pressure to provide methyl 2-(6-bromoquinolin-3-yl)acetate (**3e**, 7 g, 20.79 mmol, 43% yield). LCMS: m/z MM+ES+APCI, positive $[M+H]^+$ 280.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.89-8.84 (m, 1H), 8.28-8.25 (m, 1H), 8.25-8.22 (m, 1H), 7.99-7.93 (m, 1H), 7.90-7.83 (m, 1H), 3.98 (s, 2H), 3.67 (s, 3H).

Step 5: **Synthesis of 3-(6-bromoquinolin-3-yl)piperidine-2,6-dione (INT-3)**

To a stirred solution of 60% wt NaH (0.493 g, 12.32 mmol, 1.5 eq.) in THF (70 mL) was added methyl 2-(6-bromoquinolin-3-yl)acetate (**3e**, 2.3 g, 8.21 mmol, 1 eq.) and acrylamide (**2e**, 0.584 g, 8.21 mmol, 1 eq.) at -20 °C under an atmosphere of nitrogen and the resulting mixture was stirred at the same temperature for 3 h. The reaction mixture was quenched with saturated ammonium chloride solution (60 mL) at -20 °C. The aqueous mixture was washed with EtOAc (2 x 50 mL). The combined organic phases were dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure. The obtained crude compound was purified by reverse phase column chromatography using a C18 column (330 g snap) eluting with 40% ACN/0.1% of formic acid in water. The pure fractions containing the desired product were concentrated under reduced pressure to provide 3-(6-bromoquinolin-3-yl)piperidine-2,6-dione (**INT-3**, 1.1 g, 3.16 mmol, 39% yield). LCMS: m/z MM+ES+APCI, positive $[M+2]^+$ 320.9, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.00 (s, 1H), 8.86 (d, J = 2.25 Hz, 1H), 8.27 (d, J = 2.25 Hz, 1H), 8.21 (d, J = 2.00 Hz, 1H), 8.00-7.94 (m, 1H), 7.87 (dd, J = 9.01, 2.25 Hz, 1H), 4.18 (dd, J = 12.51, 4.88 Hz, 1H), 2.84-2.72 (m, 1H), 2.70-2.57 (m, 1H), 2.46-2.32 (m, 1H), 2.20-2.10 (m, 1H).

Example 4: Synthesis of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-chloro-5-fluoroquinoline (INT-4C)



Step 1: **Synthesis of N-(4-chloro-3-fluorophenyl)-2,2,2-trifluoroacetamide (4c)**

To a stirred solution of 4-chloro-3-fluoroaniline (**4a**, 25 g, 172 mmol, 1 eq.) in MTBE (500 mL, 20 vol.) was added 2,2,2-trifluoroacetic anhydride (**4b**, 46.9 g, 223 mmol, 1.3 eq.) and sodium carbonate (54.6 g, 515 mmol, 3 eq.) at 10 °C under an atmosphere of nitrogen. The reaction mixture was allowed to warm to room temperature and was stirred for 3 h. The reaction mixture was quenched with water (500 mL) and the aqueous layer was washed with EtOAc (2 x 1000 mL). The combined organic phases were washed with saturated sodium bicarbonate solution (1 x 450 mL) and brine (1 x 450 mL), dried over anhydrous Na_2SO_4 and filtered. The solvent was concentrated under reduced pressure to afford N-(4-chloro-3-fluorophenyl)-2,2,2-trifluoroacetamide (**4c**, 40 g, 1.65 mmol, 96% yield), which was carried onto the next step without further purification. LCMS: m/z MM+ES+APCI, negative $[M-H]^+$ 239.9; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.95 (br s, 1H), 7.66 (dd, J = 10.19, 2.44 Hz, 1H), 7.49-7.40 (m, 1H), 7.27-7.21 (m, 1H).

Step 2: **Synthesis of 6-amino-3-chloro-2-fluorobenzaldehyde (4d)**

n-BuLi (109 mL, 2.5 M in *n*-hexane, 273 mmol, 2.2 eq.) was added drop-wise to a stirred solution of N-(4-chloro-3-fluorophenyl)-2,2,2-trifluoroacetamide (**4c**, 30 g, 124 mmol, 1 eq.) in THF (500 mL, 16 vol.) at -78 °C under an atmosphere of nitrogen and the resulting mixture was stirred at -78 °C for 20 min. N, N-dimethylformamide (27.2 g, 373 mmol, 3 eq.) was then added drop-wise at -50 °C and the reaction

mixture was stirred for 2 h at -40 °C. The reaction mixture was quenched with water (200 mL) at -40 °C and washed with EtOAc (2 x 250 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to provide 6-amino-3-chloro-2-fluorobenzaldehyde (**4d**, 31 g, 100 mmol, 81% yield), which was carried onto the next step without further purification. LCMS: m/z MM+ES+APCI, positive $[M+H]^+$ 173.9; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.15 (s, 1H), 7.61 (br s, 2H), 7.46-7.40 (m, 1H), 6.63 (d, J = 9.13 Hz, 1H).

Step 3: **Synthesis of ethyl 3-amino-6-chloro-5-fluoroquinoline-2-carboxylate (4i)**

Step 3a- Pyridine (**4f**, 13.98 mL, 173 mmol, 1.5 eq.) was added to ethanol (200 mL, 20 vol.) under continuous nitrogen bubbling, followed by ethyl bromopyruvate (**4e**, 20.30 mL, 161 mmol, 1.4 eq.) at room temperature. The resulting mixture was then heated to 65 °C and stirred at 65 °C for 2 h to provide **4g**.

Step 3b- The reaction mixture containing **4g** was cooled to room temperature sparged with nitrogen. 6-amino-3-chloro-2-fluorobenzaldehyde (**4d**, 20 g, 115 mmol, 1 eq.) and pyridine (23.30 mL, 288 mmol, 2.5 eq.) were added at room temperature and the resulting mixture was stirred at 80 °C for 16 h to form **4h**.

Step 3c- Morpholine (28.1 mL, 323 mmol, 2.8 eq.) was added drop-wise at 70 °C to the reaction mixture containing **4h** and the resulting mixture was stirred at 80 °C for 3 h. The reaction mixture was then cooled to room temperature, poured into cold water (500 mL), and stirred for 15 min. A solid precipitated which was filtered and washed with water (200 mL) and dried under reduced pressure to provide ethyl 3-amino-6-chloro-5-fluoroquinoline-2-carboxylate (**4i**, 25 g, 81 mmol, 70% yield). **4i** was carried onto the next step without further purification. LCMS: m/z MM+ES+APCI, positive $[M+H]^+$ 268.9, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.75 (d, J = 9.13 Hz, 1H), 7.61 (s, 1H), 7.46 (dd, J = 9.07, 8.07 Hz, 1H), 6.76 (s, 2H), 4.41 (q, J = 7.13 Hz, 2H), 1.37 (t, J = 7.07 Hz, 3H).

Step 4: **Synthesis of 6-chloro-5-fluoroquinolin-3-amine (4j)**

Ethyl 3-amino-6-chloro-5-fluoroquinoline-2-carboxylate (**4i**, 30 g, 112 mmol) was added portion-wise to sulfuric acid (50%, 150 mL, 112 mmol, 5 vol.)/water (125 mL, 4.2 vol.) at room temperature and the resulting mixture was stirred at 110 °C for 16 h. Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was cooled to room temperature and the pH was adjusted to ~10 with 50% aqueous sodium hydroxide solution to promote precipitation of a solid. The precipitated solid was filtered and washed the solid with water (2 x 10 mL) and dried under reduced pressure to afford 6-chloro-5-fluoroquinolin-3-amine (16 g, 67.5 mmol, 61% yield), which was carried onto the next step without further purification. LCMS: m/z MM+ES+APCI, positive $[M+H]^+$ 197.9; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.59-8.30 (m, 1H), 7.64 (d, J = 9.01 Hz, 1H), 7.37 (t, J = 8.44 Hz, 1H), 7.19 (d, J = 2.38 Hz, 1H), 6.13 (s, 2H).

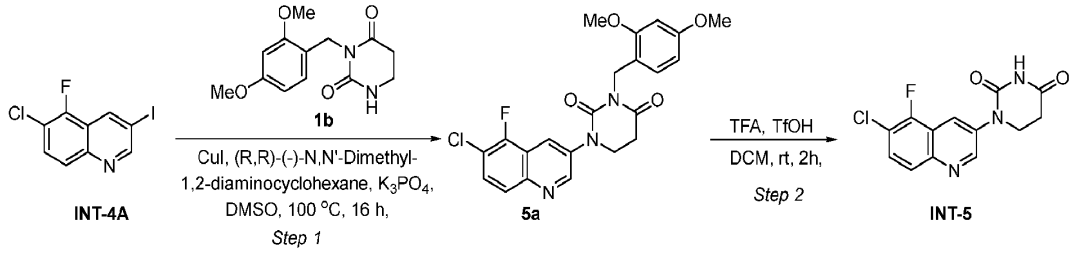
Step 5: **Synthesis of 6-chloro-5-fluoro-3-iodoquinoline (INT-4A)**

Sodium nitrite (6.67 g, 97 mmol, 1.9 eq.) dissolved in water (30 mL, 3 vol.) was added at to a suspension of 6-chloro-5-fluoroquinolin-3-amine (**4j**, 10 g, 50.9 mmol, 1 eq.) in concentrated HCl (60 mL, 6 vol.) at 0 °C and the resulting mixture was stirred at 0 °C for 1 h. KI (21.11 g, 127 mmol, 2.5 eq.) dissolved in water (30 ml, 3 vol.) was then added drop-wise to the pre-stirred reaction mixture at 0 °C and stirring was continued at room temperature for 2 h. The reaction mixture was then poured into a saturated sodium bicarbonate solution (200 mL) and the aqueous layer was washed with EtOAc (2 x 50 mL). The combined organic phases were dried over anhydrous Na_2SO_4 filtered and concentrated under reduced pressure to provide the crude compound (15 g). The crude compound was then purified by Biotage Isolera® using a 330 g silica gel cartridge and eluting with 2-4% EtOAc in hexane to afford 6-chloro-5-fluoro-3-iodoquinoline (**INT-4A**, 6.1 g, 19.42 mmol, 38% yield). LCMS: m/z MM+ES+APCI, positive $[M+2]^+$ 309.8, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.16 (d, J = 2.00 Hz, 1H), 8.91 (d, J = 1.63 Hz, 1H), 8.10-7.61 (m, 2H).

Step 6: **Synthesis of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-chloro-5-fluoroquinoline (INT-4C)**

To a stirred solution of 6-chloro-5-fluoro-3-iodoquinoline (**INT-4A**, 7.5 g, 24.39 mmol, 1 eq.) in dioxane (70 mL, 9 vol.)/water (7.5 mL. 1 vol.) were added 2,6-bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**INT-4B**, 12.21 g, 29.3 mmol, 1.2 eq.) and potassium carbonate (4.05 g, 29.3 mmol, 1.2 eq.), bis(tri-t-butylphosphine)palladium(0) (0.623 g, 1.220 mmol, 0.05 eq.) at 25 °C under continuous bubbling of argon. The resulting mixture was stirred at 60 °C for 12 h. After complete consumption of starting material (confirmed by LCMS), the reaction mixture was filtered through a celite® pad, and the filter cake was washed thoroughly with EtOAc (30 mL). The obtained filtrate was concentrated under reduced pressure to afford the crude compound (13 g). The crude compound was purified by Biotage Isolera ® using a 330 g silica gel cartridge and eluting with 20-30% EtOAc in hexane to afford 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-chloro-5-fluoroquinoline (**INT-4C**, 9.5 g, 18.58 mmol, 76% yield). LCMS: m/z MM+ES+APCI, negative $[M-H]^+$ 469.0; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.23 (d, J = 2.13 Hz, 1H), 8.62 (d, J = 1.88 Hz, 1H), 8.09 (d, J = 8.13 Hz, 1H), 7.94-7.84 (m, 2H), 7.54-7.24 (m, 10H), 6.68 (d, J = 8.13 Hz, 1H), 5.47 (d, J = 6.38 Hz, 4H).

Example 5: Synthesis of 1-(6-chloro-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (INT-5)



Step 1: **Synthesis of 1-(6-chloro-5-fluoroquinolin-3-yl)-3-(2,4-dimethoxybenzyl)dihydro-pyrimidine-2,4(1H,3H)-dione (5a)**

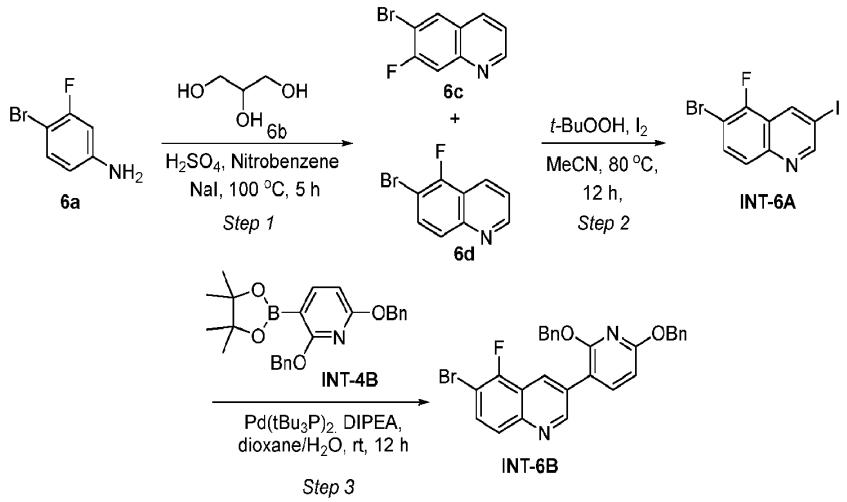
To a stirred solution of 6-chloro-5-fluoro-3-iodoquinoline (**INT-4A**, 2 g, 6.50 mmol, 1 eq.) and 3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (**1b**, 2.063 g, 7.81 mmol, 1.1 eq.) in DMSO (40 mL, 20 vol.) was added potassium phosphate tribasic (2.266 g, 13.0 mmol, 2 eq.) and CuI (0.124 g, 0.650 mmol, 0.1 eq.) and (R,R)-(-)-N,N'-dimethyl-1,2-diamino-cyclohexane (0.093 g, 0.650 mmol, 0.1 eq.) under continuous bubbling of nitrogen at room temperature. The resulting mixture was stirred at 100 °C for 16 h. Upon complete consumption of starting material, the reaction mixture was cooled to room temperature, and then poured into cold water (500 mL). The aqueous mixture was washed with EtOAc (2 x 250 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 filtered, and concentrated *in vacuo*. The crude product was purified by Biotage Isolera® on a silica-gel cartridge (330 g) and eluting with 50-55% of EtOAc/hexane to provide 1-(6-chloro-5-fluoroquinolin-3-yl)-3-(2,4-dimethoxy-benzyl)dihydropyrimidine-2,4(1H,3H)-dione (**5a**, 1g, 2.25 mmol, 34% yield). LCMS: m/z MM+ES+APCI, positive $[M+H]^+$ 444.3; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.05 (d, J = 2.50 Hz, 1H), 8.39 (dd, J = 2.38, 0.63 Hz, 1H), 7.97-7.82 (m, 2H), 6.96 (d, J = 8.38 Hz, 1H), 6.56 (d, J = 2.38 Hz, 1H), 6.49-6.40 (m, 1H), 4.82 (s, 2H), 4.15-4.05 (m, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 3.03 (t, J = 6.57 Hz, 2H).

Step 2: **1-(6-chloro-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (INT-5)**

To a stirred solution of 1-(6-chloro-5-fluoroquinolin-3-yl)-3-(2,4-dimethoxybenzyl)-dihydropyrimidine-2,4(1H,3H)-dione (**5a**, 5 g, 11.26 mmol, 1 eq.) in DCM (100 mL, 20 vol.) was added trifluoroacetic acid (19.93 g, 175 mmol, 15.52 eq.) followed by the drop-wise addition of trifluoromethanesulfonic acid (3.38 g, 22.53 mmol, 2 eq.) at 0 °C under an atmosphere of nitrogen. The resulting mixture was stirred at room temperature for 12 h. The progress of the reaction was monitored by LCMS. Upon complete consumption of starting material, the reaction mixture was concentrated under reduced pressure. The obtained crude residue was dissolved in dichloromethane (50 mL) and the pH ~8 was adjusted with saturated sodium bicarbonate solution (100 mL). The resulting precipitate was filtered. The filtered solid was triturated with MTBE (100 mL), stirred for 10 min, filtered, and dried under reduced pressure to provide 1-(6-chloro-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

(**INT-5**, 2 g, 6.81 mmol, 60% yield), LCMS: m/z MM+ES+APCI, negative $[M-H]^+$ 292.2; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 10.82-10.42 (m, 1H), 9.06 (d, J = 2.38 Hz, 1H), 8.32 (d, J = 2.00 Hz, 1H), 8.02-7.60 (m, 2H), 4.02 (t, J = 6.63 Hz, 2H), 2.79 (t, J = 6.63 Hz, 2H).

Example 6: Synthesis of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-5-fluoroquinoline (INT-6B)



Step 1: **Synthesis of 6-bromo-5-fluoroquinoline (6d)**

To a suspension of 4-bromo-3-fluoroaniline (**6a**, 50 g, 263 mmol, 1 eq.) in sulfuric acid (50 mL, 263 mmol, 1 vol.) was added glycerol (**6b**, 38.5 mL, 526 mmol, 2 eq.), sodium iodide (3.94 g, 26.3 mmol, 0.1 eq.) and nitrobenzene (16.2 mL, 158 mmol, 0.6 eq.) at room temperature under an atmosphere of nitrogen and the resulting mixture was stirred at 100 °C for 5 h. Upon complete consumption of starting material (monitored by LCMS), the reaction mixture was neutralized with aqueous ammonia (300 mL) and washed with EtOAc (2 x 750 mL). The combined organic phases were dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure to afford the crude compound (200 g). The crude compound was purified by flash silica gel column chromatography on 100-200 mesh silica gel eluting with 25-30% of EtOAc/hexane to afford the mixture of regioisomers **6c** & **6d** (140 g). The **6c** and **6d** mixture was refluxed in hexane (600 mL) for 30 min, cooled to room temperature, and filtered. The filtrate was concentrated under reduced pressure to afford the crude compound (100 g), which was further purified by reverse phase chromatography using a C18 column (330 g snap) and eluting with 60% of 0.1% formic acid in H_2O /Acetonitrile, flow rate: 35 mL/min. The pure fractions were concentrated under reduced pressure to afford 6-bromo-5-fluoroquinoline (**6d**, 5.5 g, 24.3 mmol, 9%), LCMS: m/z MM+ES+APCI, positive $[M]^+$ 225.9 & $[M+2]^+$ 227.5; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 9.12-8.94 (m, 1H), 8.52 (d, J = 8.38 Hz, 1H), 8.01 (dd, J = 9.01, 7.63 Hz, 1H), 7.87 (d, J = 9.01 Hz, 1H), 7.71 (dd, J = 8.51, 4.25 Hz, 1H).

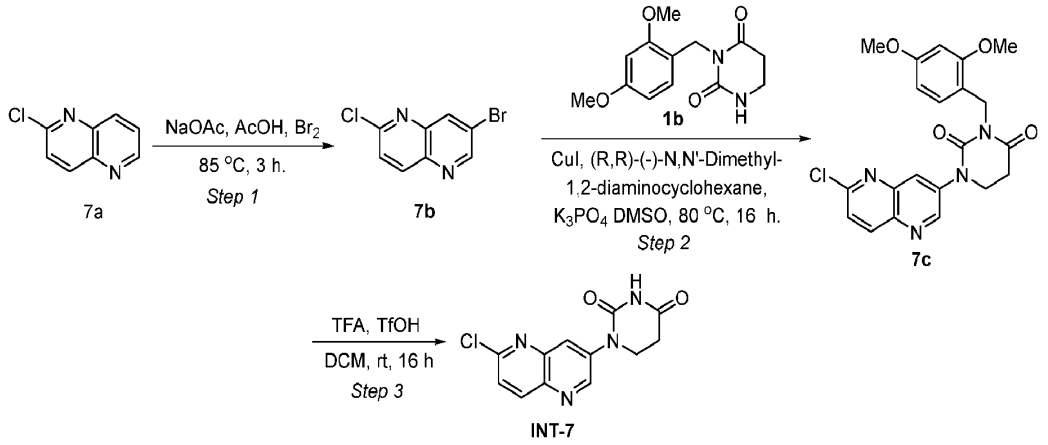
Step 2: **Synthesis of 6-bromo-5-fluoro-3-iodoquinoline (INT-6A)**

To a stirred solution of 6-bromo-5-fluoroquinoline (**6d**, 9 g, 39.8 mmol, 1 eq.) in acetonitrile (180 mL, 20 vol.) was added iodine (12.13 g, 47.8 mmol, 1.2 eq.) and *tert*-butyl hydroperoxide (41.0 g, 319 mmol, 70% wt, 8 eq.) at room temperature under an atmosphere of argon and the resulting mixture was stirred at 80 °C for 16 h. The reaction mixture was then cooled to room temperature, quenched with saturated sodium thiosulfate solution (~100 mL), and concentrated (to remove acetonitrile) under reduced pressure. The aqueous layer was washed with EtOAc (2 x 75 mL) and the combined organic phases were dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*. The obtained crude compound was purified by flash silica gel column chromatography on 100-200 mesh silica gel eluting with 2% EtOAc in hexane to afford 6-bromo-5-fluoro-3-iodoquinoline (**INT-6A**, 8.5 g, 24.15 mmol, 61% yield). LCMS: m/z MM+ES+APCI, positive $[M]^+$ 351.7 & $[M+2]^+$ 353.7; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.17 (d, J = 2.00 Hz, 1H), 8.91 (d, J = 1.38 Hz, 1H), 8.02 (dd, J = 9.01, 7.50 Hz, 1H), 7.83 (d, J = 9.01 Hz, 1H).

Step 3: **Synthesis of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-5-fluoroquinoline (INT-6B)**

In a 250 mL mini clave, to a solution of 6-bromo-5-fluoro-3-iodoquinoline (**INT-6A**, 5 g, 14.2 mmol, 1 eq.) in dioxane (45 mL, 9 vol.)/water (5 mL, 1 vol.) was added 2,6-bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**INT-4B**, 6.52 g, 15.65 mmol, 1.1 eq.) and DIPEA (2.97 mL, 10.23 mmol, 2 eq.) followed by the addition of bis(tri-t-butylphosphine)-palladium(0) (0.365 g, 0.71 mmol, 0.05 eq.) at room temperature under continuous bubbling of argon for 15 min. The resulting mixture was stirred at room temperature for 16 h. Upon complete consumption of starting material (monitored by LCMS), the reaction mixture was filtered through a celite® pad, and the celite® cake was washed with EtOAc (~150 mL). The filtrate was concentrated *in vacuo* to provide the crude compound, which was purified by reverse phase chromatography using a 330 g C18 cartridge and eluting with 90% ACN/0.1% formic acid in water at a 35 mL/min flow rate. The ACN/water mixture was removed under reduced pressure to afford 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-5-fluoroquinoline (**INT-6B**, 3.75 g, 7.18 mmol, 51% yield). LCMS: m/z MM+ES+APCI, positive $[M]^+$ 515.0 & $[M+2]^+$ 516.9; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.35-9.12 (m, 1H), 8.62 (d, J =1.63 Hz, 1H), 8.12-8.05 (m, 1H), 8.02-7.92 (m, 1H), 7.88-7.82 (m, 1H), 7.52-7.31 (m, 10H), 6.72-6.63 (m, 1H), 5.47 (d, J = 6.75 Hz, 4H).

Example 7: Synthesis of 1-(6-chloro-1,5-naphthyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione (INT-7)



Step 1: **Synthesis of 7-bromo-2-chloro-1,5-naphthyridine (7b)**

To a stirred solution of 2-chloro-1,5-naphthyridine (**7a**, 4.5 g, 27.3 mmol, 1 eq.) and sodium acetate (4.5 g, 54.7 mmol, 2.0 eq.) in acetic acid (22 mL, 4.8 vol.) was added bromine (1.831 mL, 35.5 mmol, 1.3 eq.) in acetic acid (4 mL) drop-wise over a period of 15 min at 85 °C under an atmosphere of nitrogen and the resulting mixture was stirred at 85 °C for 3 h. After complete consumption of the starting material, the reaction mixture was cooled to ambient temperature and treated with aq. 6M sodium hydroxide solution (100 mL). The resulting solid was collected by filtration, washed with methanol (20 mL), and dried. The resulting crude compound was purified by Biotage Isolera® on a silica-gel cartridge (120 g) eluting with 13-20% of EtOAc/hexane to obtain 7-bromo-2-chloro-1,5-naphthyridine (**7b**, 3.3 g, 11.93 mmol, 44% yield). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 243.0; ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ (ppm): 9.07-9.19 (m, 1H), 8.76 (d, J = 1.3 Hz, 1H), 8.52 (d, J = 8.8 Hz, 1H), 7.91 (d, J = 8.9 Hz, 1H).

Step 2: **Synthesis of 1-(6-chloro-1,5-naphthyridin-3-yl)-3-(2,4-dimethoxybenzyl) dihydropyrimidine-2,4(1H,3H)-dione (7c)**

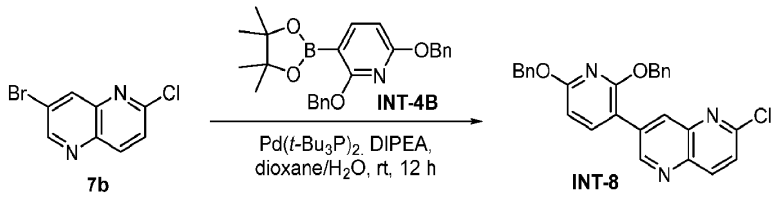
To a stirred solution of 7-bromo-2-chloro-1,5-naphthyridine (**7b**, 2.5 g, 10.27 mmol. 1.0 eq.) and 3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (**1b**, 2.71 g, 10.27 mmol, 1.0 eq.) in DMSO (50 mL, 20 vol.) was added potassium phosphate tribasic (2.83 g, 13.35 mmol, 1.3 eq.), copper(I) iodide (0.098 g, 0.513 mmol, 0.05 eq.) and (R, R)-(-)-N, N'-dimethyl-1,2-diaminocyclohexane (0.073 g, 0.513 mmol, 0.05 eq.) at room temperature under continuous bubbling of argon. The resulting mixture was stirred at 80 °C for 16 h. After complete consumption of the starting material, the reaction mixture was cooled to room temperature, diluted with ice-cold water (100 mL), washed with EtOAc (2 X 300 mL). The combined organic phases were dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure. The crude product was purified by Biotage Isolera® with a 120 g silica-gel cartridge and eluting with 35-40% of EtOAc/hexane to afford 1-(6-chloro-1,5-naphthyridin-3-yl)-3-(2,4-

dimethoxybenzyl) dihydropyrimidine-2,4(1H,3H)-dione (**7c**, 1.6 g, 3.70 mmol, 36% yield). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 427.0; ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ (ppm): 9.12 (d, J = 2.5 Hz, 1H), 8.49 (dd, J = 0.7, 8.8 Hz, 1H), 8.29 (dd, J = 0.8, 2.4 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 6.56 (d, J = 2.4 Hz, 1H), 6.46 (dd, J = 2.4, 8.4 Hz, 1H), 4.82 (s, 2H), 4.20-3.99 (m, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 3.07-3.00 (m, 2H).

Step 3: **Synthesis of 1-(6-chloro-1,5-naphthyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione (INT-7)**

To a stirred solution of 1-(6-chloro-1,5-naphthyridin-3-yl)-3-(2,4-dimethoxybenzyl) dihydropyrimidine-2,4(1H,3H)-dione (**7c**, 1.6 g, 3.75 mmol, 1.0 eq.) in DCM (16 mL, 10 vol.) were added trifluoroacetic acid (4.48 mL, 58.2 mmol, 15.5 eq.) and triflic acid (0.666 mL, 7.50 mmol, 2.0 eq.) at 0 °C under an atmosphere of nitrogen. The resulting mixture was stirred at room temperature for 16 h. Upon complete consumption of the starting material, all volatiles were removed under reduced pressure. The crude compound was treated with saturated sodium bicarbonate solution (50 mL) at 0 °C, and the precipitated solid was collected by filtration, washed with water (3 x 150 mL), and dried to obtain the crude product. The crude product was then triturated with DCM (100 mL), filtered, and dried under reduced pressure to afford 1-(6-chloro-1,5-naphthyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione (**INT-7**, 0.7 g, 2.024 mmol, 54% yield). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 277.0. ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ (ppm): 10.70 (br s, 1H), 9.12 (s, 1H), 8.47 (d, J = 8.5 Hz, 1H), 8.23 (s, 1H), 7.81 (d, J = 8.3 Hz, 1H), 4.03 (s, 2H), 2.80 (s, 2H).

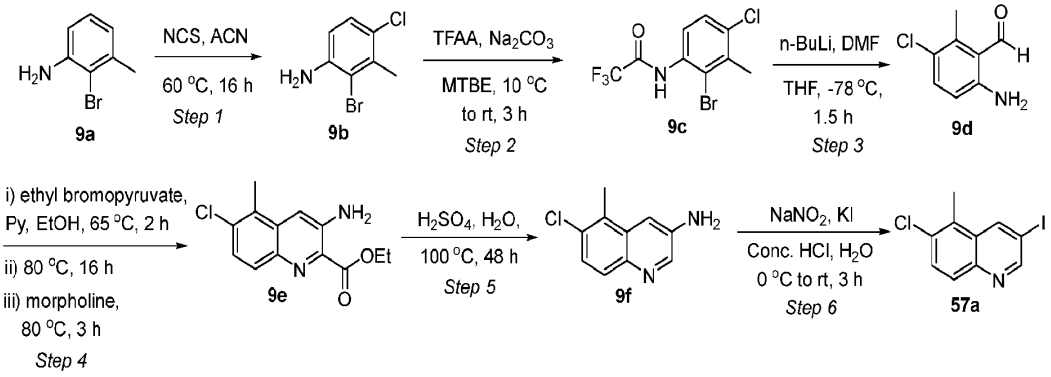
Example 8: Synthesis of 7-(2,6-bis(benzyloxy)pyridin-3-yl)-2-chloro-1,5-naphthyridine (INT-8)



To a stirred solution of 7-bromo-2-chloro-1,5-naphthyridine (**7b**, 3 g, 12.32 mmol, 1.0 eq.) and 2,6-bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**INT-4B**, 5.66 g, 13.55 mmol, 1.1 eq.) in dioxane (27 mL, 9.0 vol.)/water (3.00 mL, 1.0 vol.) was added DIPEA (4.76 g, 6.44 mL, 37.0 mmol, 3.0 eq.) at room temperature under continuous bubbling of argon which was continued for 15 mins. Bis(tri-t-butyl phosphine)palladium(0) (0.630 g, 1.232 mmol, 0.01 eq.) was then added and the resulting mixture was stirred at room temperature for 12 h. After complete consumption of the starting material, the reaction mixture was filtered through a celite® pad and the filter cake was washed thoroughly with EtOAc (100 mL). The filtrate was then washed with water (1 x 50 mL) and brine (1 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get the crude

compound. The crude was purified by Biotage Isolera® with 330 g silica-gel cartridge eluting with 15-20% EtOAc/hexane to afford 7-(2,6-bis(benzyloxy)pyridin-3-yl)-2-chloro-1,5-naphthyridine (**INT-8**, 3.7 g, 8.10 mmol, 66% yield). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 454.2; ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ (ppm): 9.43-9.10 (m, 1H), 8.56-8.38 (m, 2H), 8.07 (d, J = 8.1 Hz, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.56-7.21 (m, 10H), 6.68 (d, J = 8.1 Hz, 1H), 5.49 (s, 2H), 5.44 (s, 2H).

Example 9: Synthesis of 6-chloro-3-iodo-5-methylquinoline (57a)



Step 1: **Synthesis of 2-bromo-4-chloro-3-methylaniline (9b)**

To a solution of 2-bromo-3-methylaniline (**9a**, 50 g, 269 mmol) in ACN (2000 mL) was added N-chlorosuccinimide (37.7 g, 282 mmol) in portions at room temperature and the resulting mixture was stirred at 60 °C for 16 h under an atmosphere of nitrogen. The reaction mixture was cooled and concentrated under reduced pressure. The crude material was partitioned between water (500 mL) and EtOAc (500 mL). The organic phase was dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography using Biotage Isolera® on silica gel (100-200 mesh) eluting with 0 to 2% EtOAc in *n*-hexane to afford 2-bromo-4-chloro-3-methylaniline (**9b**, 44 g, 186 mmol, 69% yield). LCMS: m/z MM- ES+APCI, Positive $[M+H, M+2+H]^+$ 220.0, 222.0. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.12 (d, J = 8.40 Hz, 1H), 6.60 (d, J = 8.40 Hz, 1H), 4.08 (br s, 2H), 2.51 (s, 3H).

Step 2: **Synthesis of N-(2-bromo-4-chloro-3-methylphenyl)-2,2,2-trifluoroacetamide (9c)**

To a stirred solution of 2-bromo-4-chloro-3-methylaniline (**9b**, 3.5 g, 15.87 mmol) in MTBE (20 ml) was added 2,2,2-trifluoroacetic anhydride (2.87 ml, 20.64 mmol) and Na_2CO_3 (5.05 g, 47.6 mmol) at 10 °C and the resulting mixture was stirred at room temperature for 3 h. Ice-cold water (50 mL) was added and the aqueous mixture extracted with EtOAc (2 x 250 mL). The combined organic phases were washed with sat. $NaHCO_3$ (250 mL) and brine (250 mL), dried over anhydrous Na_2SO_4 filtered and concentrated under reduced pressure to afford N-(2-bromo-4-chloro-3-methylphenyl)-2,2,2-trifluoroacetamide (**9c**, 4.8 g, 14.56 mmol, 92% yield). The product was carried onto the next step without

further purification. LCMS: m/z MM- ES+APCI, Positive [M-, M-2]$^+$ 314.0, 316.0. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.54 (br s, 1H), 8.15 (d, *J* = 8.80 Hz, 1H), 7.43 (d, *J* = 8.80 Hz, 1H), 2.60 (s, 3H).

Step 3: **Synthesis of 6-amino-3-chloro-2-methylbenzaldehyde (9d)**

To a stirring solution of N-(2-bromo-4-chloro-3-methylphenyl)-2,2,2-trifluoroacetamide (**9c**, 10 g, 31.6 mmol) in THF (200 ml) was added n-BuLi (27.8 ml, 69.5 mmol) at -78 °C and the resulting mixture was stirred for 30 min. N, N-dimethylformamide (14.11 g, 193 mmol) was then added dropwise at -78 °C and stirring was continued for 1 h at -78 °C. After complete consumption of starting materials, as confirmed by LCMS, the reaction mixture was poured in ice-chilled water (50 mL) and partitioned with EtOAc (2 x 50 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 6-amino-3-chloro-2-methylbenzaldehyde (**9d**, 8 g, 12.26 mmol, 39% yield). The product was carried onto the next step without further purification. LCMS: m/z MM- ES+APCI, Positive [M+H, M+2+H]$^+$ 170.1, 172.1.

Step 4: **Synthesis of ethyl 3-amino-6-chloro-5-methylquinoline-2-carboxylate (9e)**

To a stirring solution of ethanol (100 ml) was added pyridine (7.00 g, 88 mmol) with purging with nitrogen and the resulting mixture was stirred for 10 min. Ethyl bromopyruvate (16.10 g, 83 mmol) was then added dropwise at room temperature, and stirring was continued at 65 °C for 2 h. The reaction mixture was cooled to room temperature and 6-amino-3-chloro-2-methylbenzaldehyde (**9c**, 10 g, 59.0 mmol) was added followed by pyridine (11.66 g, 147 mmol) and the resulting mixture was heated to 80 °C and stirred for 16 h. The mixture was then cooled to 70 °C, and morpholine (14.38 g, 165 mmol) was added slowly at 70 °C. The reaction mixture was heated at 80 °C for 3 h and then cooled to room temperature. Water (500 mL) and stirring was continued for 15 min. The resulting precipitated solid was filtered, washed with water (200 mL) and dried to afford ethyl 3-amino-6-chloro-5-methylquinoline-2-carboxylate (**9e**, 5 g, 17.38 mmol, 30% yield). The product was carried onto the next step without further purification. LCMS: m/z MM- ES+APCI, Positive [M+H, M+2+H]$^+$ 264.9, 266.9. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 9.20 Hz, 1H), 7.68 (s, 1H), 7.38 (d, *J* = 9.20 Hz, 1H), 6.58 (br s, 2H), 4.40 (q, *J* = 7.20 Hz, 2H), 2.56 (s, 3H), 1.37 (q, *J* = 7.20 Hz, 3H).

Step 5: **Synthesis of 6-chloro-5-methylquinolin-3-amine (9f)**

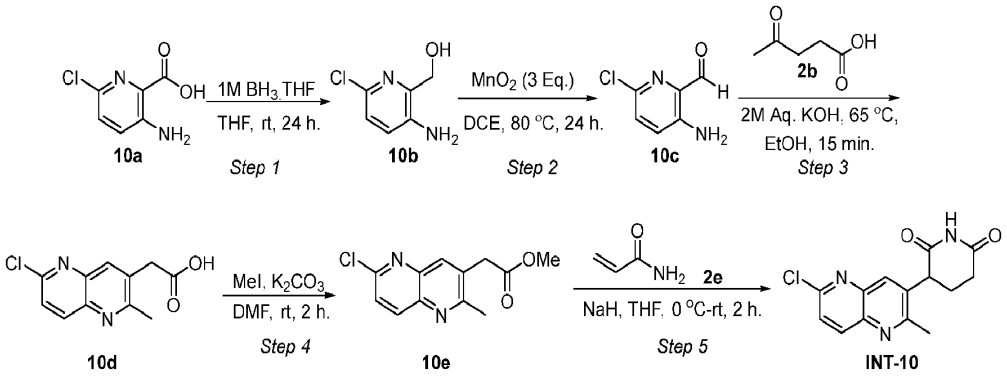
To a stirred solution of H_2SO_4 (8 ml, 15.11 mmol) in water (5 ml) was added ethyl 3-amino-6-chloro-5-methylquinoline-2-carboxylate (**9e**, 4 g, 15.11 mmol) at 0 °C and the resulting mixture was heated at 100 °C and stirred for 48 h. The reaction mixture was cooled to room temperature, and the *p*H was adjusted to ~10 using 50% NaOH solution (with cooling using an ice bath). The aqueous mixture was extracted with EtOAc (2 x 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford 6-chloro-5-methylquinolin-3-amine (**9f**, 2 g,

4.05 mmol, 27% yield). The product was carried onto the next step without further purification. LCMS: m/z MM- ES+APCI, Positive $[M+H, M+2+H]^+$ 192.9, 194.9.

Step 6: **Synthesis of 6-chloro-3-iodo-5-methylquinoline (57a)**

To a stirred solution of 6-chloro-5-methylquinolin-3-amine (**9f**, 2.7 g, 14.02 mmol) in concentrated HCl (16 mL) was added sodium nitrite (1.837 g, 26.6 mmol) dissolved in water (12 mL) at 0 °C, and the resulting mixture was stirred for 1 h at 0 °C. KI (5.82 g, 35.0 mmol) dissolved in water (12 ml) was then added and stirring was continued at room temperature for 2 h. The reaction mixture was poured into 10% $NaHCO_3$ solution (slowly) and extracted with EtOAc (2 x 50 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography using Biotage Isolera® on silica gel (100-200 mesh) eluting with 0 to 2% EtOAc in *n*-hexane to afford 6-chloro-3-iodo-5-methylquinoline (**57a**) 1.7 g, 3.86 mmol, 28% yield). LCMS: m/z MM- ES+APCI, Positive $[M+H, M+2+H]^+$ 304.1, 306.1. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.08 (d, *J* = 2.00 Hz, 1H), 8.96 (d, *J* = 2.00 Hz, 1H), 7.87 (d, *J* = 8.80 Hz, 1H), 7.80 (d, *J* = 8.80 Hz, 1H), 2.70 (s, 3H).

Example 10: Synthesis of 3-(6-chloro-2-methyl-1,5-naphthyridin-3-yl) piperidine-2,6-dione (INT-10)



Step 1: **Synthesis of (3-amino-6-chloropyridin-2-yl) methanol (10b)**

To a stirred solution of 3-amino-6-chloropicolinic acid (**10a**, 10 g, 57.9 mmol, 1.0 eq.) in THF (100 mL, 10 vol.) was added 1M BH_3.THF (500 mL, 500 mmol, 8.0 eq.) at 0 °C under an atmosphere of nitrogen and the resulting mixture was stirred at room temperature for 24 h. After complete consumption of the starting material, MeOH (150 mL) was added, followed by 2M HCl solution (75 mL). The pH of resulting mixture was adjusted to pH ~ 8 with 20% potassium carbonate solution (150 mL) and the aqueous mixture was washed with DCM (3 x 200 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (3-amino-6-chloropyridin-2-yl) methanol (**10b**, 9.5 g, 57.4 mmol, 99% yield). The desired product was carried onto the next step without further purification. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 158.90; ^{1}H NMR (400 MHz,

DMSO-d_6, 298 K) δ (ppm): 7.10-7.03 (m, 2H), 5.35 (s, 2H), 5.20 (t, J = 5.8 Hz, 1H), 4.44 (d, J = 5.8 Hz, 2H).

Step 2: **Synthesis of 3-amino-6-chloropicolinaldehyde (10c)**

To a stirred solution of (3-amino-6-chloropyridin-2-yl) methanol (**10b**, 5 g, 31.5 mmol, 1.0 eq.) in DCE (100 mL, 10 vol.) was added manganese dioxide (8.22 g, 95 mmol, 3.0 eq.) at 0 °C under an atmosphere of nitrogen and the resulting mixture was stirred at 80 °C for 24 h. The reaction mixture was filtered through a bed of celite®, and the filter cake was washed with DCM (2 x 100 mL). The filtrate was concentrated under reduced pressure to afford 3-amino-6-chloropicolinaldehyde (**10c**, 4.5 g, 28.7 mmol, 91% yield), which was carried onto the next step without further purification. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 157.1; ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ (ppm): 9.79 (s, 1H), 7.42-7.31 (m, 4H).

Step 3: **Synthesis of 2-(6-chloro-2-methyl-1,5-naphthyridin-3-yl) acetic acid (10d)**

2M aq. potassium hydroxide solution (2.150 g, 38.3 mmol, 1.99 eq.) was added to a solution of 3-amino-6-chloropicolinaldehyde (**10c**, 3 g, 19.16 mmol, 1.0 eq.) and 4-oxopentanoic acid (**2b**, 2.023 mL, 19.16 mmol, 1.0 eq.) in ethanol (15 mL, 5 vol.) at 0 °C under an atmosphere of nitrogen and the resulting mixture was stirred at 65 °C for 15 min. The reaction mixture was then cooled to ambient temperature, and volatiles were removed under reduced pressure. The crude residue was diluted with water (50 mL) and acidified with acetic acid (pH = ~2). The precipitated solid was collected by filtration and dried under reduced pressure to afford 2-(6-chloro-2-methyl-1,5-naphthyridin-3-yl) acetic acid (**10d**, 1.7 g, 6.71 mmol, 35% yield), which was carried onto the next step without further purification. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 236.9; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.95-12.43 (m, 1H), 8.38 (d, J = 8.76 Hz, 1H), 8.19 (s, 1H), 7.77 (d, J = 8.75 Hz, 1H), 3.95 (s, 2H), 2.65 (s, 3H).

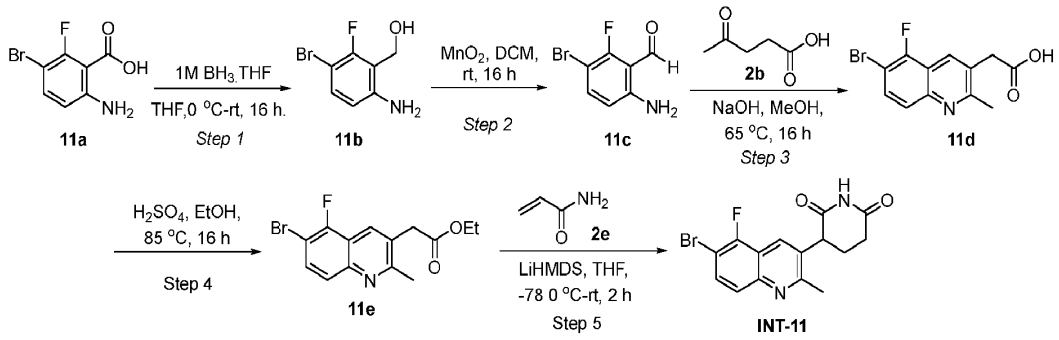
Step 4: **Synthesis of methyl 2-(6-chloro-2-methyl-1,5-naphthyridin-3-yl) acetate (10e)**

To a stirred a solution of 2-(6-chloro-2-methyl-1,5-naphthyridin-3-yl) acetic acid (**10d**, 9.5 g, 40.1 mmol, 1.0 eq.) in DMF (47.5 mL, 5 vol.) was added potassium carbonate (6.66 g, 48.2 mmol, 1.3 eq.) and methyl iodide (2.59 mL, 40.1 mmol, 1.0 eq.) at 0 °C under an atmosphere of nitrogen and the resulting mixture was stirred at room temperature for 2 h. After complete consumption of the starting material, as confirmed by LCMS, ice water (50 mL) was added and the resulting precipitated solid was collected by filtration and dried under reduced pressure to afford methyl 2-(6-chloro-2-methyl-1,5-naphthyridin-3-yl) acetate (**10e**, 6 g, 22.31 mmol, 56% yield). The desired product was carried onto the next step without further purification. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 250.9; ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ (ppm): 8.38 (dd, J = 0.7, 8.8 Hz, 1H), 8.21 (s, 1H), 7.79 (d, J = 8.7 Hz, 1H), 4.06 (s, 2H), 3.68 (s, 3H), 2.63 (s, 3H).

Step 5: **Synthesis of 3-(6-chloro-2-methyl-1,5-naphthyridin-3-yl) piperidine-2,6-dione (INT-10)**

To a stirred solution of methyl 2-(6-chloro-2-methyl-1,5-naphthyridin-3-yl) acetate (**10e**, 3 g, 11.97 mmol, 1.0 eq.) in THF (15 mL, 5 vol.) was added 60% wt NaH (0.345 g, 14.36 mmol, 1.0 eq.) at -20 °C under an atmosphere of nitrogen and stirred at the same temperature for 1 h. Acrylamide (**2e**, 0.851 g, 11.97 mmol, 1.0 eq.) was then added at -20 °C to the pre-stirred reaction mixture and stirring was continued at room temperature for 1 h. After complete consumption of the starting material, aq. ammonium chloride solution (10 mL) was added and the resulting aqueous mixture was washed with EtOAc (3 x 200 mL). The combined organic phases were dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure. The crude compound was purified by reverse phase column chromatography using a 330 g C18 cartridge and eluting with 30-40% ACN in 0.1% ammonium acetate in water. Pure fractions were collected and concentrated under reduced pressure afforded 3-(6-chloro-2-methyl-1,5-naphthyridin-3-yl) piperidine-2,6-dione (**INT-10**, 1.5g, 5.2 mmol, 43% yield). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 289.9, negative $[M-H]^+$ 288.0; ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ (ppm): 11.27-10.61 (m, 1H), 8.39 (d, J = 8.8 Hz, 1H), 8.17 (s, 1H), 7.79 (d, J = 8.8 Hz, 1H), 4.38 (dd, J = 4.6, 12.7 Hz, 1H), 2.91-2.74 (m, 1H), 2.71 (s, 3H), 2.68-2.57 (m, 2H), 2.21-2.02 (m, 1H).

Example 11: Synthesis of 3-(6-bromo-5-fluoro-2-methylquinolin-3-yl) piperidine-2,6-dione (INT-11)



Step 1: **Synthesis of (6-amino-3-bromo-2-fluorophenyl) methanol (11b)**

To a stirred solution of 6-amino-3-bromo-2-fluorobenzoic acid (**11a**, 13 g, 55.5 mmol, 1.0 eq.) in THF (220 mL, 17 vol.) was added 1M BH_3.THF (278 mL, 278 mmol, 5.0 eq.) dropwise at 0 °C under an atmosphere of nitrogen and the resulting mixture was stirred at ambient temperature for 16 h. The reaction mixture was quenched with methanol (50 mL). All volatiles were concentrated under reduced pressure. The crude compound was diluted with water (100 mL) and extracted with EtOAc (3 x 200 mL). The combined organic phases were dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure to afford (6-amino-3-bromo-2-fluorophenyl) methanol (**11b**, 11.5 g, 52.3 mmol, 94% yield). The product was carried onto the next step without further purification. LCMS: m/z: mass was not ionized. ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ (ppm): 7.20 (t, J = 8.4 Hz, 1H), 6.45 (dd, J = 0.9, 8.8 Hz, 1H), 5.48 (s, 2H), 5.05 (t, J = 5.6 Hz, 1H), 4.46 (dd, J = 2.0, 5.6 Hz, 2H).

Step 2: **Synthesis of 6-amino-3-bromo-2-fluorobenzaldehyde (11c)**

To a stirred solution of (6-amino-3-bromo-2-fluorophenyl) methanol (**11b**,11.5 g, 52.3 mmol, 1.0 eq.) in DCM (530 mL, 46 vol.) was added manganese dioxide (27.3 g, 314 mmol, 6.0 eq.) portion wise at room temperature under an atmosphere of nitrogen and the resulting mixture was stirred at room temperature for 16 h. Upon complete consumption of the starting material, the reaction mixture was filtered through a bed of celite® and the filter cake was washed thoroughly with DCM. The filtrate was concentrated under reduced pressure to afford 6-amino-3-bromo-2-fluorobenzaldehyde (**11c**, 10.5 g, 40.2 mmol, 77% yield), which carried onto the next step without further purification. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 218.0; ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ (ppm): 10.14 (s, 1H), 7.63 (br s, 2H), 7.50 (dd, J = 7.9, 9.1 Hz, 1H), 6.59 (d, J = 9.1 Hz, 1H).

Step 3: **Synthesis of 2-(6-bromo-5-fluoro-2-methylquinolin-3-yl) acetic acid (11d)**

To a stirred solution of 6-amino-3-bromo-2-fluorobenzaldehyde (**11c**, 10 g, 45.9 mmol, 1.0 eq.) in methanol (92 mL, 9.2 vol.) was added 4-oxopentanoic acid (**2b**, 5.33 g, 45.9 mmol, 1.0 eq.) and 2M sodium hydroxide solution (2.201 g, 55.0 mmol, 1.2 eq., dissolved in 27.5 mL of water) at room temperature. The resulting mixture was stirred at 65 °C for 16 h. Upon complete consumption of the starting material, all volatiles were concentrated under reduced. The crude compound was diluted with water (50 mL) and acidified with acetic acid. The resulting solid was collected by filtration and dried under reduced pressure to afford 2-(6-bromo-5-fluoro-2-methylquinolin-3-yl) acetic acid (**11d**, 13.5 g, 42.2 mmol, 92% yield), which carried onto the next step without further purification. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 298.0, ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ (ppm): 8.24 (s, 1H), 7.87 (dd, J = 7.6, 9.0 Hz, 1H), 7.75-7.69 (m, 1H), 3.86 (s, 2H), 2.61 (s, 3H).

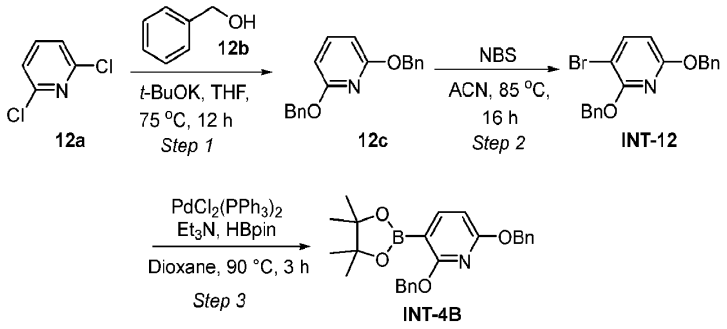
Step 4: **Synthesis of ethyl 2-(6-bromo-5-fluoro-2-methylquinolin-3-yl) acetate (11e)**

To a stirred solution of 2-(6-bromo-5-fluoro-2-methylquinolin-3-yl) acetic acid (**11d**, 17 g, 57.0 mmol, 1.0 eq.) in ethanol (170 mL, 10 vol.) was added sulfuric acid (4.58 mL, 86 mmol, 1.5 eq.) dropwise at 0 °C under an atmosphere of nitrogen and the resulting mixture was stirred at 85 °C for 16 h. Upon complete consumption of the starting material, all volatiles were concentrated under reduced pressure. The crude compound was diluted with water (100 mL) and extracted with EtOAc (3 x 200 mL). The combined organic phases were dried over anhydrous Na_2SO_4 filtered and concentrated under reduced pressure to afford ethyl 2-(6-bromo-5-fluoro-2-methylquinolin-3-yl) acetate (**11e**, 15 g, 28.3 mmol, 50% yield). The product was carried onto the next step without further purification. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 326.0, ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ (ppm): 8.33 (s, 1H), 7.91 (dd, J = 7.7, 8.9 Hz, 1H), 7.75 (d, J = 8.9 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 4.05 (s, 2H), 2.61 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H).

Step 5: **Synthesis of 3-(6-bromo-5-fluoro-2-methylquinolin-3-yl) piperidine-2,6-dione (INT-11)**

To a stirred solution of ethyl 2-(6-bromo-5-fluoro-2-methylquinolin-3-yl) acetate (**11e**, 5 g, 15.33 mmol, 1.0 eq.) in THF (77 mL, 15 vol.) was added 1M LiHMDS in THF (18.40 mL, 18.40 mmol, 1.2 eq.) drop-wise at -78 °C under an atmosphere of nitrogen and the resulting mixture was stirred at -78 °C for 1 h. Acrylamide (**2e**, 1.308 g, 18.40 mmol, 1.2 eq.) was then added to the pre-stirred reaction mixture at -78 °C and stirring was continued at room temperature for 1h. Upon complete consumption of the starting material, the reaction mixture was quenched with saturated ammonium chloride solution (10 mL) and extracted with EtOAc (3 x 200 mL). The combined organic phases were dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure. The crude compound was triturated with acetonitrile (2 x 100 mL), filtered, and dried under reduced pressure to afford 3-(6-bromo-5-fluoro-2-methylquinolin-3-yl) piperidine-2,6-dione (**INT-11**, 2.3 g, 6.50 mmol, 42% yield). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 351.2, ^1H NMR (400 MHz, DMSO-d_6, 298 K) δ (ppm): 11.46-10.56 (m, 1H), 8.26 (s, 1H), 7.92 (dd, J = 7.6, 9.1 Hz, 1H), 7.76 (d, J = 9.1 Hz, 1H), 4.39 (dd, J = 4.6, 12.8 Hz, 1H), 2.91-2.77 (m, 1H), 2.68 (s, 3H), 2.66-2.53 (m, 2H), 2.18-2.05 (m, 1H).

Example 12: Synthesis of 2,6-bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (INT-4B)



Step 1: **Synthesis of 2,6-bis(benzyloxy)pyridine (12c)**

2,6-bis(benzyloxy)pyridine (**12c**) was prepared according to the procedures and examples as reported in PCT Application Publication No. WO2022/261250.

To potassium *tert*-butoxide (284 g, 2534 mmol, 2.5 eq.) in a 5 L three neck RB flask equipped with a condenser and thermal socket, under an atmosphere of nitrogen was added THF (1.5 L, 5.2 vol.). The resulting mixture was cooled to 0 °C, and phenyl methanol (**12b**, 232 mL, 2230 mmol, 2.2 eq.) was added dropwise at 0 °C. The reaction mixture was then stirred at the same temperature for 15 min. A solution of 2,6-dichloropyridine (**12a**, 150 g, 1014 mmol, 1.0 eq.) in THF (1 L, 6 vol.) was added dropwise at 0 °C to the pre-stirred reaction mixture and stirring was continued at 75 °C for 12 h. The reaction mixture was then cooled to room temperature and poured into ice-cold water (2L). The aqueous mixture was extracted with EtOAc (2 x 1L). The combined organic phases were washed with brine (1L), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 2,6-

bis(benzyloxy)pyridine (**12c**, 290 g, 936 mmol, 92% yield), which was carried onto the next step without further purification. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 292.7; ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ (ppm): 7.64 (t, J = 7.9 Hz, 1H), 7.48-7.26 (m, 10H), 6.43 (d, J = 7.9 Hz, 2H), 5.33 (s, 4H).

Step 2: **Synthesis of 2,6-bis(benzyloxy)-3-bromopyridine (INT-12)**

2,6-bis(benzyloxy)-3-bromopyridine (**INT-12**) was prepared according to the procedures and examples as reported in PCT Application Publication No. WO2022/261250.

To 2,6-bis(benzyloxy)pyridine (**12c**, 240 g, 824 mmol, 1 eq.) in a 5 L three neck RB flask equipped with a condenser and thermal socket, under an atmosphere of nitrogen was added acetonitrile (2.5 L, 10.4 vol.) at 25 °C. NBS (148 g, 832 mmol, 1.01 eq.) was then added portion-wise at 25 °C and stirring was continued at 85 °C for 16 h. Upon complete consumption of starting material as monitored by LCMS, the reaction mixture was cooled to room temperature. Three fourths of the volume of the acetonitrile was removed *in vacuo*. The thick mixture was quenched with cold water (1 L), and the aqueous layer was extracted with EtOAc (2 x 2 L). The combined organic phases were washed with brine (1 L), dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure to afford 2,6-bis(benzyloxy)-3-bromopyridine (**INT-12**, 300 g, 810 mmol, 98% yield). The product was carried onto the next step without further purification. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 370.1; ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ (ppm): 7.90 (d, J = 8.3 Hz, 1H), 7.52-7.25 (m, 10H), 6.45 (d, J = 8.4 Hz, 1H), 5.46-5.20 (m, 4H).

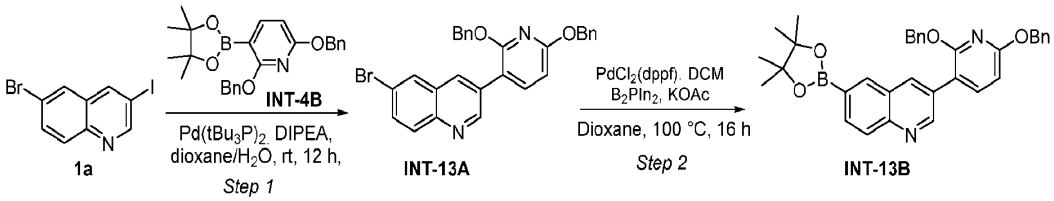
Step 3: **Synthesis of 2,6-bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (INT-4B)**

2,6-bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**INT-4B**) was prepared according to the procedures and examples as reported in Org. Lett., 2014, 16(11), 2916-2919.

To 2,6-bis(benzyloxy)-3-bromopyridine (**INT-12**, 250 g, 675 mmol, 1 eq.) in dioxane (2 L, 8 vol.) was added triethyl amine (281 mL, 2026 mmol, 3 eq.) at room temperature under continuous bubbling of nitrogen. 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (122 mL, 844 mmol, 1.25 eq.) was added drop-wise via cannula at 25 °C under an atmosphere of nitrogen, followed by the addition of bis(triphenylphosphine)palladium(II) dichloride (18.96 g, 27.0 mmol, 0.04 eq.) (18.96 g, 27.0 mmol, 0.04 eq.) at room temperature. The resulting mixture was heated to 90 °C and stirring was continued for 3 h. The reaction mixture was cooled to room temperature, and the dioxane was removed under reduced pressure to provide the crude compound. The crude product was purified by silica gel flash column chromatography eluting with 5-15% of EtOAc in hexane to afford 2,6-bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**INT-4B**, 135 g, 323 mmol, 48% yield). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 418.1 & $[M+H]^+$ 335.6; ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ (ppm): 7.85

(d, *J* = 7.9 Hz, 1H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.47-7.22 (m, 8H), 6.43 (d, *J* = 7.9 Hz, 1H), 5.39 (d, *J* = 6.0 Hz, 4H), 1.29 (s, 12H).

Example 13: Synthesis of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (INT-13A) and 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (INT-13B)



Step 1: **Synthesis of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (INT-13A)**

3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**) was prepared according to the procedures and examples as reported in PCT Application Publication No. WO2017/197046.

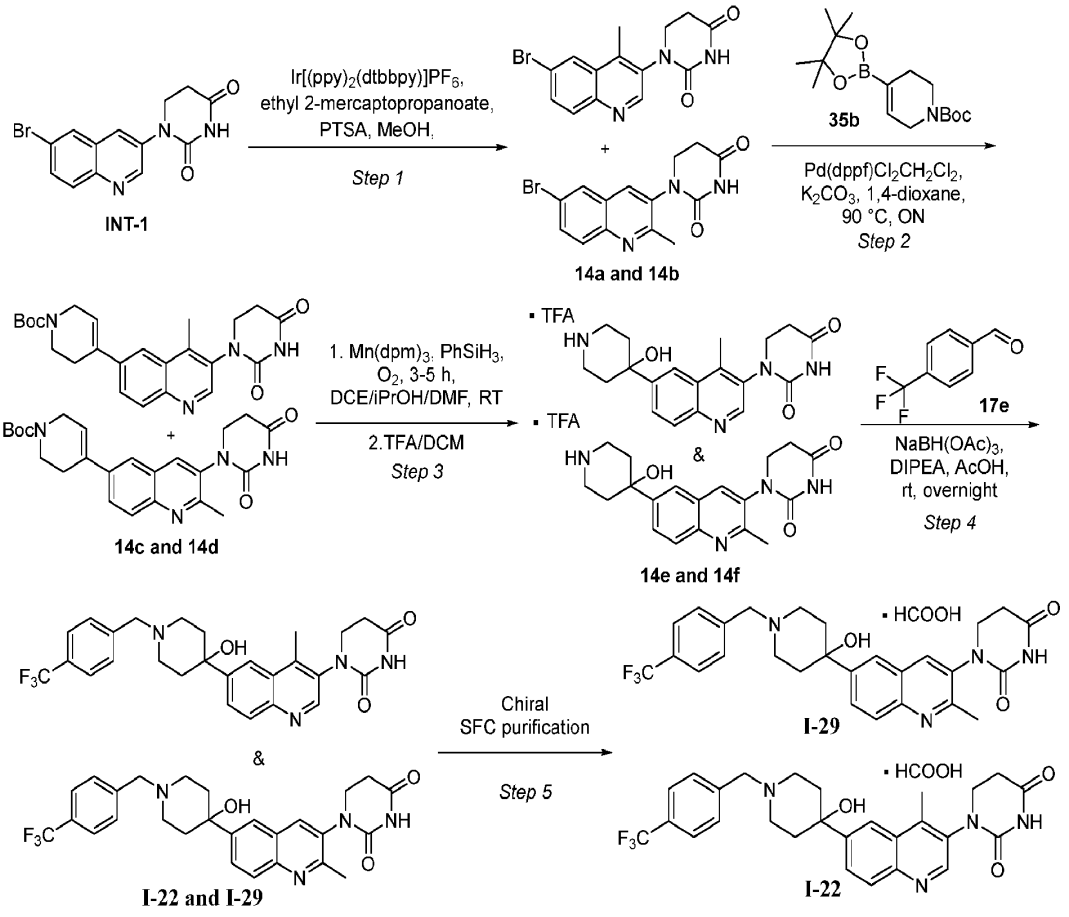
To a pressure-released screw-cap vial containing a stirred solution of 6-bromo-3-iodoquinoline (**1a**, 2 g, 5.99 mmol, 1 eq.) in dioxane (15 mL, 7.5 vol.)/water (1.667 mL, 0.83 vol.) was added 2,6-bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**INT-4B**, 2.75 g, 6.59 mmol, 1.1 eq.) and DIPEA (1.255 mL, 7.19 mmol, 1.2 eq.) followed by the addition of bis(tri-t-butylphosphine)palladium(0) (0.153 g, 0.299 mmol, 0.05 eq.) at ambient temperature under continuous bubbling of nitrogen. Bubbling of nitrogen was continued for 15 min and the resulting mixture was stirred at ambient temperature for 12 h. The reaction mixture was filtered through a bed of celite® and the filter cake was washed with EtOAc (100 mL). The filtrate was washed with water (2 x 30 mL) and brine (30 mL). The organic phase was dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced. The crude product was then purified via Biotage Isolera® on a 120 g silica-gel cartridge eluting with 15-20% EtOAc in hexane to provide 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 1.2 g, 2.407 mmol, 40% yield). LCMS: m/z: MM-ES+APCI, positive $[M+2]^+$ 499.1; ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ (ppm): 9.15 (d, *J* = 2.3 Hz, 1H), 8.48 (d, *J* = 2.1 Hz, 1H), 8.27 (d, *J* = 2.3 Hz, 1H), 8.00-7.92 (m, 2H), 7.87 (dd, *J* = 2.3, 8.9 Hz, 1H), 7.50-7.30 (m, 10H), 6.67 (d, *J* = 8.1 Hz, 1H), 5.45 (d, *J* = 11.3 Hz, 4H).

Step 2: **Synthesis of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (INT-13B)**

To a stirred solution of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 3.5 g, 7.04 mmol. 1 eq.) in dioxane (35 mL, 10 vol.) was added potassium acetate (2.072 g, 21.11 mmol, 3 eq.) and bis(pinacolato)diboron (5.36 g, 21.11 mmol, 3 eq.) followed by $PdCl_2$(dppf).DCM adduct (0.575 g, 0.704 mmol, 0.1 eq.) at 25 °C under continuous bubbling of nitrogen. The resulting mixture was stirred at 100 °C for 16 h. Upon consumption of starting material, the reaction mixture was cooled to room

temperature and filtered through a bed of celite®. The filter cake was washed thoroughly with EtOAc (150 mL). The filtrate was washed with water (50 mL) and brine (50 mL). The organic phase was dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure. The crude was purified via Biotage Isolera® on a 330 g silica-gel cartridge eluting with 25-40% EtOAc in hexane to afford 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (**INT-13B**, 2.375 g, 2.93 mmol, 42% yield). LCMS: m/z: MM-ES+APCI, positive $[M+1]^+$ 545.1 & $[M+1]^+$ 463.1; ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ (ppm): 9.27-9.06 (m, 1H), 8.58 (d, J = 2.0 Hz, 1H), 8.38 (s, 1H), 8.12-7.82 (m, 3H), 7.61-7.29 (m, 10H), 6.67 (d, J = 8.1 Hz, 1H), 5.45 (d, J = 15.0 Hz, 4H), 1.36 (s, 12H).

Example 14: Synthesis of 1-(6-(4-hydroxy-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)-4-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-22) and 1-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-29)



Step 1: **Synthesis of 1-(6-bromo-4-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione and 1-(6-bromo-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (14a) and (14b)**

1-(6-bromo-4-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione and 1-(6-bromo-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (14a) and (14b) were prepared according to the procedures and examples as reported in Nature, 2015, *525*, 87-90.

To a vial with a stir bar was added 1-(6-bromoquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**INT-1**, 0.32 g, 1.0 mmol) and PTSA (0.38 g, 2.0 mmol), MeOH (4 mL) and DMSO (2 mL). (4,4'-Di-t-butyl-2,2'-bipyridine)bis[2-(2-pyridinyl-kN)phenyl-kC]iridium(III) hexafluorophosphate (9 mg, 0.01 mmol) and the resulting mixture was sparged with argon for 5 min. Ethyl 2-mercaptopropanoate (0.033 g, 33µL, 0.25 mmol) was then added and the vial was sealed and subjected to blue light irradiation at 456 nm for 48 h. The obtained crude product mixture containing 1-(6-bromo-4-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione and 1-(6-bromo-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**14a**) and (**14b**) was concentrated and purified directly by reverse phase ISCO chromatography (eluting with 0-100% MeCN in H_2O w/0.1% FA) to afford desired product as a mixture of regioisomers (140 mg, 0.42 mmol, 42%). LCMS: m/z HESI, positive $[M+H]^+$ = 334.17 [calcd for $C_{14}H_{13}BrN_3O_2^+$: 334.02]

Step 2: **Synthesis of *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate and *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methylquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (14c) and (14d)**

The mixture of 1-(6-bromo-4-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione and 1-(6-bromo-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**14a** and **14b**) (140 mg, 0.42 mmol) was dissolved in 1,4-dioxane (3.7 mL) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**35b**, 0.19 g, 0.63 mmol), Pd(dppf)Cl_2•DCM (0.033 g, 0.04 mmol) and K_2CO_3 (0.087 g, 0.63 mmol) in H_2O (370 µL) were added and the resulting mixture was sparged with argon for 4 min (with sonication), sealed, and heated at 90 °C overnight (conventional heating). The reaction mixture was concentrated *in vacuo* and re-dissolved in DMSO for reverse phase purification (eluting with 0% to 100% MeCN in H_2O) to afford desired products as a mixture of regioisomers (0.12 g, 0.28 mmol, 68% yield). LCMS: m/z HESI, positive $[M+H]^+$ = 437.32 [calcd for $C_{24}H_{29}N_4O_4^+$: 437.22]

Step 3: **Synthesis of the trifluoroacetic acid salt of 1-(6-(4-hydroxypiperidin-4-yl)-4-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione and the trifluoroacetic acid salt of 1-(6-(4-hydroxypiperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (14e) and (14f)**

Tert-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate and *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methylquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (14c and 14d, 0.12 g, 0.28 mmol) were dissolved in DCE/iPrOH (1:1) (7 mL) and 10% (v/v) DMF. Oxygen was bubbled through the solution for

10 min. Tris(dipivaloylmethanato)manganese (0.05 g, 0.09 mmol) and phenylsilane (104 µL, 0.84 mmol) were then added and the resulting mixture was stirred for 5 h at rt with bubbling of oxygen through the solution. The crude material was filtered, concentrated, and purified by reverse phase column chromatography (eluting with 0% to 100% MeCN in water) to afford desired product as a mixture of regioisomers (100 mg, 77% yield). LCMS: m/z HESI, positive $[M+H]^+$ = 455.36 [calcd for $C_{24}H_{31}N_4O_5^+$: 455.23]. The product was dissolved in DCM (4 mL) and TFA (2 mL) and the resulting solution was stirred for 3 h and concentrated *in vacuo* to afford the desired product **14e** and **14f** as TFA salt of a mixture of regioisomers, which was used in the next step without further purification. LCMS: m/z HESI, positive $[M+H]^+$ = 355.31 [calcd for $C_{19}H_{23}N_4O_3^+$: 355.18].

Step 4: **Synthesis of 1-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione and 1-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-22) and (I-29)**

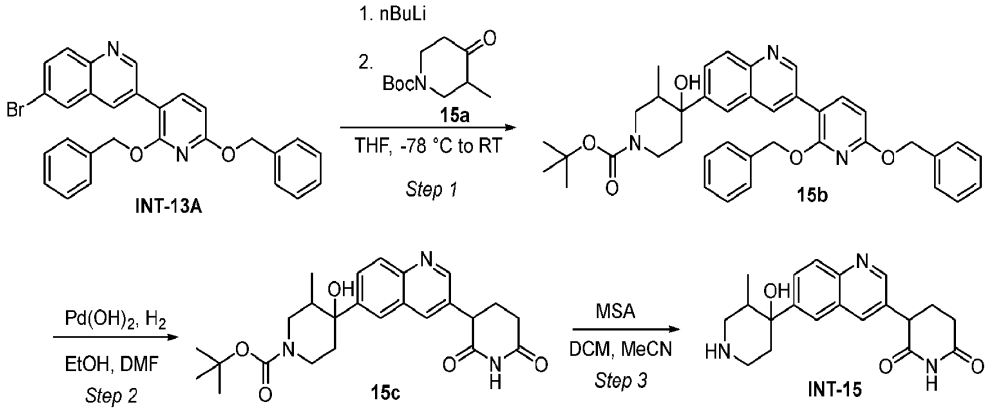
The trifluoroacetic acid salt of 1-(6-(4-hydroxypiperidin-4-yl)-4-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione and the trifluoroacetic acid salt of 1-(6-(4-hydroxy-piperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (0.13 g, 0.36 mmol) was dissolved in DCE/DMF (10:1, 10mL), basified with DIPEA (0.31 µL, 1.8 mmol) at 0 °C. 4-(trifluoromethyl)-benzaldehyde (0.63 g, 3.6 mmol, 10 eq.), sodium triacetoxyborohydride (0.23 g, 1.1 mmol), and a few drops of acetic acid were added and the resulting mixture was stirred at rt overnight. The reaction mixture was concentrated *in vacuo* and purified by reverse phase chromatography (via ISCO, eluting with 0% to 100% MeCN in water) and prep. HPLC (Shimadzu, eluting with MeCN/water with 0.1% formic acid) to afford desired product **I-22** and **I-29** (42 mg, 0.082 mmol, 23%) as a mixture of regioisomers. LCMS: m/z HESI, positive $[M+H]^+$ = 513.36 [calcd for $C_{27}H_{28}F_3N_4O_3^+$: 513.21].

Step 5: **Chiral SFC separation of mixture of (I-22) and (I-29) to provide 1-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-22) and 1-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-29)**

The mixture of 1-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-22**) and 1-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-29**, 40 mg, 0.078 mmol) was separated by chiral SFC using chiral Whelk-(R,R) column eluting with 0.2% FA in IPA as mobile phase A and acetonitrile as mobile phase B. The fractions containing **peak 1** were collected and concentrated under reduced pressure to dryness to afford 1-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-methyl-quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-**

22, 6.7 mg, 0.013 mmol, 3.6%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 513.2. 1H-NMR (400 MHz, DMSO-d_6): δ 10.51 (s, 1H), 8.74 (s, 1H), 8.34 (s, 1H), 8.19 (d, J = 1.60 Hz, 1H), 8.00-7.90 (m, 2H), 7.71 (d, J = 8.00 Hz, 2H), 7.61 (d, J = 8.00 Hz, 2H), 5.13 (s, 1H), 3.92-3.85 (m, 1H), 3.68-3.64 (m, 3H), 3.27-3.23 (m, 1H), 2.93-2.76 (m, 2H), 2.69-2.67 (m, 2H), 2.57 (s, 4H), 2.16-2.10 (m, 2H), 1.69 (d, J = 12.40 Hz, 2H). The fractions containing **peak 3** were collected and concentrated under reduced pressure to dryness to afford 1-(6-(4-hydroxy-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-29**, 15 mg, 0.029 mmol, 8%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 513.2. 1H-NMR (400 MHz, DMSO-d6): δ 10.53 (s, 1H), 8.31 (s, 1H), 8.27 (s, 1H), 7.98 (s, 1H), 7.91 (s, 2H), 7.71 (d, J = 8.00 Hz, 2H), 7.60 (d, J = 8.00 Hz, 2H), 5.06 (s, 1H), 3.98-3.91 (m, 1H), 3.69-3.66 (m, 1H), 3.65 (s, 2H), 2.91-2.65 (m, 5H), 2.56 (s, 4H), 2.08 (t, J = 9.20 Hz, 2H), 1.69 (d, J = 12.40 Hz, 2H).

Example 15: Synthesis of 3-(6-(4-hydroxy-3-methylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (INT-15)



Step 1: **Synthesis of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3-methylpiperidine-1-carboxylate (15b)**

tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3-methyl-piperidine-1-carboxylate (**15b**, 166 mg, 0.26 mmol, 52% yield) was synthesized according to **General Procedure 1, Step A** starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 250 mg, 0.5 mmol) and *tert*-butyl 3-methyl-4-oxopiperidine-1-carboxylate (**15a**, 118 mg, 0.55 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 632.

Step 2: **Synthesis of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3-methylpiperidine-1-carboxylate (15c)**

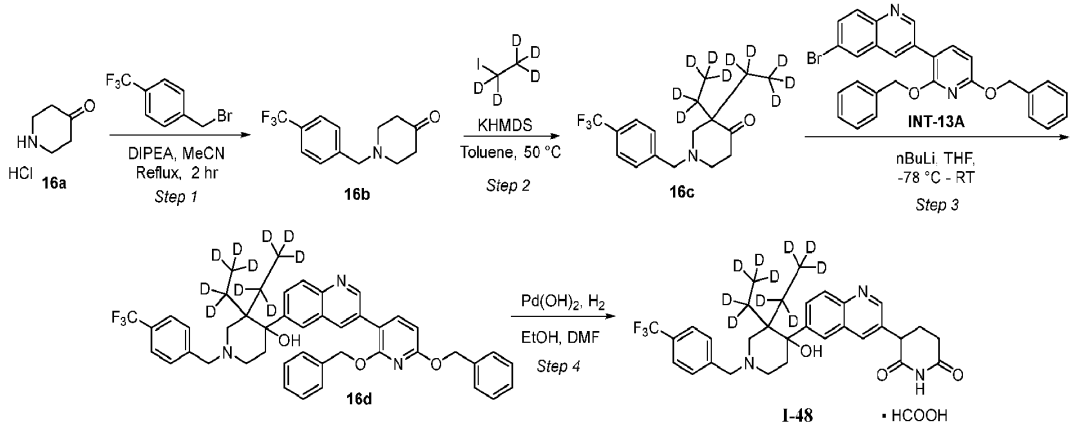
tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3-methylpiperidine-1-carboxylate (**15c**, 36 mg, 0.08 mmol, 30% yield) was synthesized according to **General Procedure 1,**

Step B starting from *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3-methylpiperidine-1-carboxylate (**15b**, 166 mg, 0.26 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 454.

Step 3: **Synthesis of 3-(6-(4-hydroxy-3-methylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (INT-15)**

3-(6-(4-hydroxy-3-methylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**INT-15**, 14 mg, 0.04 mmol, quantitative yield) was synthesized according to **General Procedure 1, Step C** starting from *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3-methyl-piperidine-1-carboxylate (**15c**, 18 mg, 0.04 mmol). LCMS: m/z HESI, positive $[M+H]^+$= 354.

Example 16: Synthesis of 3-(6-(3,3-bis(ethyl-d_5)-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-48)



Step 1: **Synthesis of 1-(4-(trifluoromethyl)benzyl)piperidin-4-one (16b)**

To a stirred solution of piperidin-4-one hydrochloride (**16a**, 4.1 g, 1 eq., 30 mmol) and 1-(bromomethyl)-4-(trifluoromethyl)benzene (**16b**, 5.1 mL, 1.1 eq, 33 mmol) in acetonitrile (76 mL, 0.4 molar, 1 eq., 30 mmol), was added DIPEA (11 mL, 2 eq, 61 mmol) and the resulting mixture was heated to reflux for 2 h. Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was concentrated *in vacuo* and purified via silica gel column chromatography eluting with 0 to 100% EtOAc in heptanes. The desired fractions were collected, combined, and concentrated *in vacuo* to yield 1-(4-(trifluoromethyl)benzyl)piperidin-4-one (**16b**, 6.3 g, 25 mmol, 81% yield). LCMS: m/z HESI, positive $[M+H]^+$ and $[M+H+H_2O]^+$ = 258 and 276.

Step 2: **Synthesis of 3,3-bis(ethyl-d_5)-1-(4-(trifluoromethyl)benzyl)piperidin-4-one (16c)**

To an oven-dried reaction vial equipped with a stir bar was added 1-(4-(trifluoromethyl)benzyl)piperidin-4-one (**16b**, 500 mg, 1 eq., 1.94 mmol) and the resulting mixture was sparged with argon. Toluene (5 mL) was then added and the reaction mixture was cooled to 0 °C. Hexamethyldisilazane potassium salt solution (3.89 mL, 1 molar, 2 eq., 3.89 mmol) was added and the resulting mixture was allowed to stir for 1 h at 0 °C. 1-Iodoethane-1,1,2,2,2-d_5 (311 µL, 2 eq., 3.89 mmol)

was then added and stirring was continued with heating at 50 °C for 3 h. Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was diluted with brine and the aqueous layer was extracted with EtOAc (2x). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material purified via silica gel column chromatography eluting with 0 to 100% EtOAc in heptanes. The desired fractions were collected, combined, and concentrated under reduced pressure to yield 3,3-bis(ethyl-d_5)-1-(4-(trifluoromethyl)benzyl)piperidin-4-one (**16c**, 196 mg, 0.606 mmol, 31% yield). LCMS: m/z HESI, positive $[M+H]^+$ = 324.

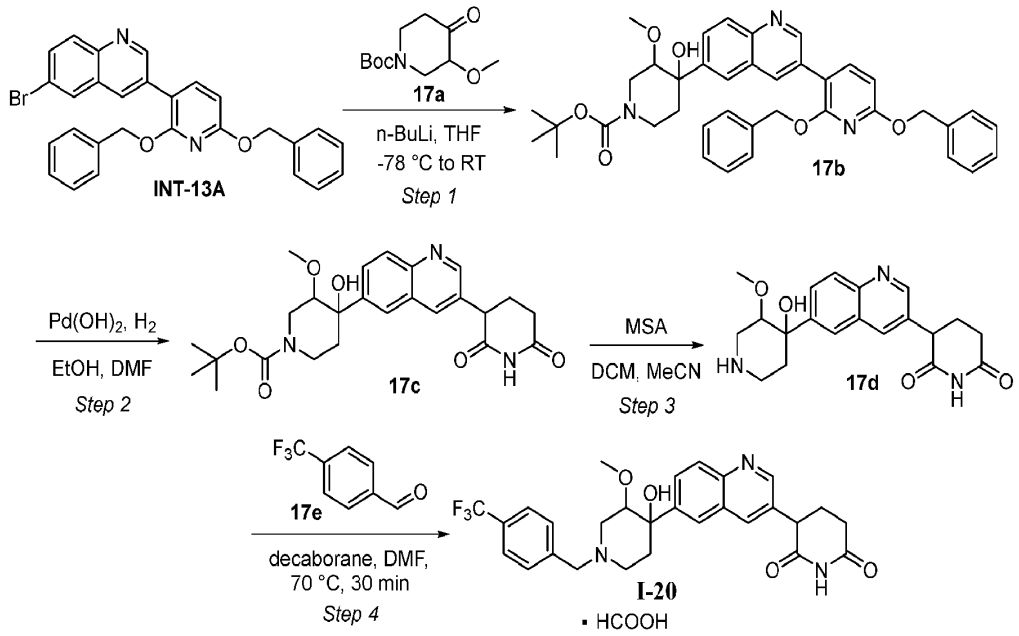
Step 3: **Synthesis of 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3,3-bis(ethyl-d_5)-1-(4-(trifluoromethyl)benzyl)piperidin-4-ol (16d)**

4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3,3-bis(ethyl-d_5)-1-(4-(trifluoromethyl)benzyl)piperidin-4-ol (**16d**, 78.1 mg, 0.11 mmol, 21% yield) was synthesized according to **General Procedure 2, Step A** starting from 3,3-bis(ethyl-d_5)-1-(4-(trifluoromethyl)benzyl)piperidin-4-one (**16c**, 179 mg, 0.55 mmol) and 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 250 mg, 0.5 mmol). LCMS: m/z HESI, positive $[M+H]^+$= 742

Step 4: **Synthesis of 3-(6-(3,3-bis(ethyl-d_5)-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-48)**

3-(6-(3,3-bis(ethyl-d_5)-4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-48**, 2.9 mg, 0.005 mmol, 5% yield) as a mixture of diastereomers was synthesized according to **General Procedure 2, Step B** starting from 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3,3-bis(ethyl-d_5)-1-(4-(trifluoro-methyl)benzyl)piperidin-4-ol (**16d**, 78.1 mg, 0.11 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 564. ^{1}H NMR (499 MHz, DMSO-d_6) δ (ppm) = 10.97-10.94 (m, 1H), 8.74-8.72 (m, 1H), 8.44-8.41 (m, 1H), 8.20-8.17 (m, 1H), 8.03-8.00 (m, 1H), 7.98-7.94 (m, 1H), 7.92-7.88 (m, 1H), 7.73-7.68 (m, 2H), 7.61-7.57 (m, 2H), 4.16-4.08 (m, 1H), 3.58-3.54 (m, 2H), 2.92-2.82 (m, 2H), 2.81-2.72 (m, 1H), 2.69-2.60 (m, 2H), 2.44-2.32 (m, 4H), 2.18-2.09 (m, 1H), 1.50-1.43 (m, 1H).

Example 17: Synthesis of 3-(6-(4-hydroxy-3-methoxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-20)



Step 1: **Synthesis of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3-methoxypiperidine-1-carboxylate (17b)**

tert-Butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3-methoxypiperidine-1-carboxylate (**17b**, 150 mg, 0.23 mmol, 46% yield) was synthesized according to **General procedure 1, Step A** starting from *tert*-butyl 3-methoxy-4-oxopiperidine-1-carboxylate (**17a**, 127 mg 0.55 mmol) and 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 250 mg, 0.5 mmol). LCMS: m/z HESI, positive $[M+H]^+ = 648$.

Step 2: **Synthesis of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3-methoxypiperidine-1-carboxylate (17c)**

tert-Butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3-methoxypiperidine-1-carboxylate (**17c**, 35 mg, 0.07 mmol, 32% yield) was synthesized according to **General procedure 1, Step B** starting from *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3-methoxypiperidine-1-carboxylate (**17b**, 150 mg, 0.23 mmol). LCMS: m/z HESI, positive $[M+H]^+ = 470$.

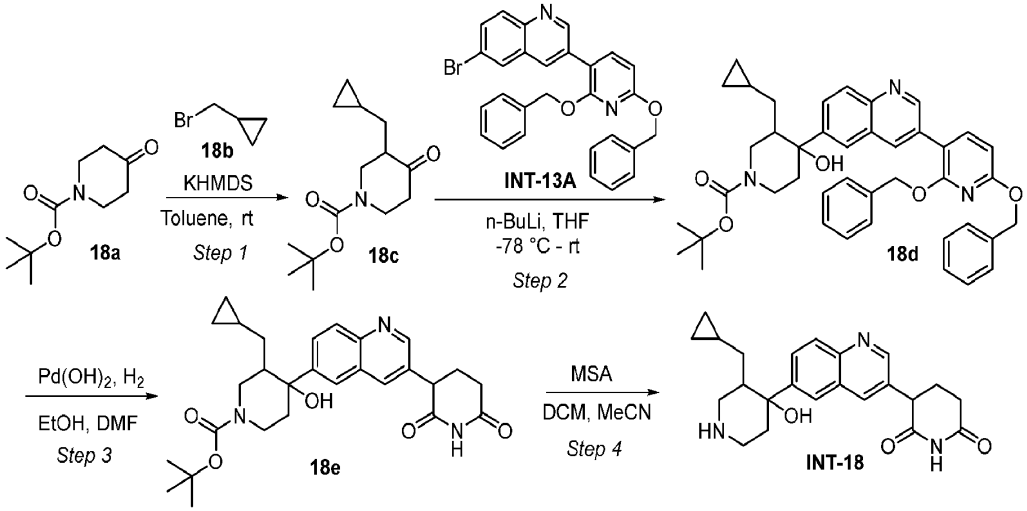
Step 3: **Synthesis of 3-(6-(4-hydroxy-3-methoxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (17d)**

3-(6-(4-Hydroxy-3-methoxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**17d**, 14 mg, 0.04 mmol, quantitative yield) was synthesized according to **General procedure 1, Step** C starting from *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3-methoxypiperidine-1-carboxylate (**17c**, 17.5 mg, 0.04 mmol). LCMS: m/z HESI, positive $[M+H]^+ = 370$.

Step 4: **Synthesis of 3-(6-(4-hydroxy-3-methoxy-1-(4-(trifluoro-methyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-20)**

3-(6-(4-hydroxy-3-methoxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-20**, 5.6 mg, 0.01 mmol, 28% yield) as a mixture of diastereomers was synthesized according to **General procedure 1, Step D** starting from 4-(trifluoromethyl)benzaldehyde (**17e**, 10.2 uL, 0.075 mmol) and 3-(6-(4-hydroxy-3-methoxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**17d**, 14 mg, 0.04 mmol). LCMS: m/z HESI, positive $[M+H]^+ = 528$. ^1H NMR (499 MHz, DMSO-d_6) δ (ppm) = 10.98-10.95 (m, 1H), 8.75-8.73 (m, 1H), 8.42-8.38 (m, 1H), 8.20-8.16 (m, 1H), 7.97-7.90 (m, 3H), 7.74-7.69 (m, 2H), 7.63-7.57 (m, 2H), 4.18-4.10 (m, 1H), 3.82-3.72 (m, 1H), 3.69-3.58 (m, 2H), 2.96 (d, J = 0.8 Hz, 1H), 2.94-2.88 (m, 1H), 2.86 (s, 2H), 2.81-2.72 (m, 1H), 2.70-2.66 (m, 1H), 2.65-2.60 (m, 1H), 2.60-2.55 (m, 2H), 2.47-2.34 (m, 2H), 2.17-2.10 (m, 1H), 2.05-1.94 (m, 1H), 1.73-1.57 (m, 1H)

Example 18: Synthesis of 3-(6-(3-(cyclopropylmethyl)-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (INT-18)



Step 1: **Synthesis of *tert*-butyl 3-(cyclopropylmethyl)-4-oxopiperidine-1-carboxylate (18c)**

To a reaction vial equipped with a stir bar was added *tert*-butyl 4-oxopiperidine-1-carboxylate (**18a**, 1.00 g, 1 eq., 5.02 mmol) and toluene (10 mL) and the resulting mixture was cooled to 0 °C using an ice-water bath. 1M Hexamethyldisilazane potassium salt solution in THF (5.52 mL, 1.1 eq., 5.52 mmol) and the resulting mixture was allowed to stir for 1 h at 0 °C. (Bromomethyl)cyclopropane (**18b**, 813 mg, 584 µL, 1.2 eq., 6.02 mmol) was then added and stirring was continued overnight at rt. Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was diluted with brine and the aqueous layer was extracted with EtOAc (2x). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material purified via silica gel column chromatography eluting with 0 to 100% EtOAc in heptanes. The desired fractions were collected,

combined, and concentrated under reduced pressure to yield *tert*-butyl 3-(cyclopropylmethyl)-4-oxopiperidine-1-carboxylate (**18c**, 178 mg, 0.70 mmol, 14% yield). ^{1}H NMR (499 MHz, DMSO-d_6) δ (ppm) = 4.18-3.97 (m, 1H), 3.94-3.78 (m, 1H), 3.40-3.33 (m, 1H), 3.23-2.96 (m, 1H), 2.46 (br s, 2H), 2.34-2.27 (m, 1H), 1.58-1.49 (m, 1H), 1.43 (s, 9H), 1.19-1.07 (m, 1H), 0.73-0.63 (m, 1H), 0.47-0.33 (m, 2H), 0.09--0.06 (m, 2H).

Step 2: **Synthesis of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-(cyclopropylmethyl)-4-hydroxypiperidine-1-carboxylate (18d)**

tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-(cyclopropylmethyl)-4-hydroxypiperidine-1-carboxylate (**18d**, 142 mg, 0.21 mmol, 42% yield) was synthesized according to **General procedure 1, Step A** starting from *tert*-butyl 3-(cyclopropylmethyl)-4-oxopiperidine-1-carboxylate (**18c,** 140 mg, 0.55 mmol) and 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 250 mg, 0.50 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 672.

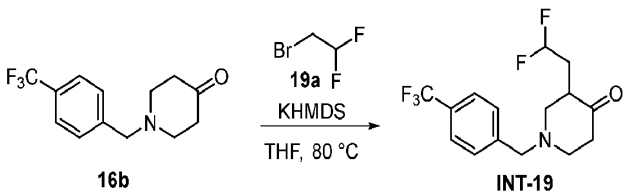
Step 3: **Synthesis of *tert*-butyl 3-(cyclopropylmethyl)-4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (18e)**

tert-butyl 3-(cyclopropylmethyl)-4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (**18e**, 64 mg, 0.13 mmol, 64% yield) was synthesized according to **General procedure 1, Step B** starting from *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-(cyclopropylmethyl)-4-hydroxypiperidine-1-carboxylate (**18d,** 142 mg, 0.21 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 494.

Step 4: **Synthesis of 3-(6-(3-(cyclopropylmethyl)-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (INT-18)**

3-(6-(3-(cyclopropylmethyl)-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**INT-18**, 26 mg, 0.07 mmol quantitative yield) was synthesized according to **General procedure 1, Step C** starting from *tert*-butyl 3-(cyclopropylmethyl)-4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (**18e**, 32 mg, 0.07 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 394.

Example 19: Synthesis of 3-(2,2-difluoroethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-one (INT-19)

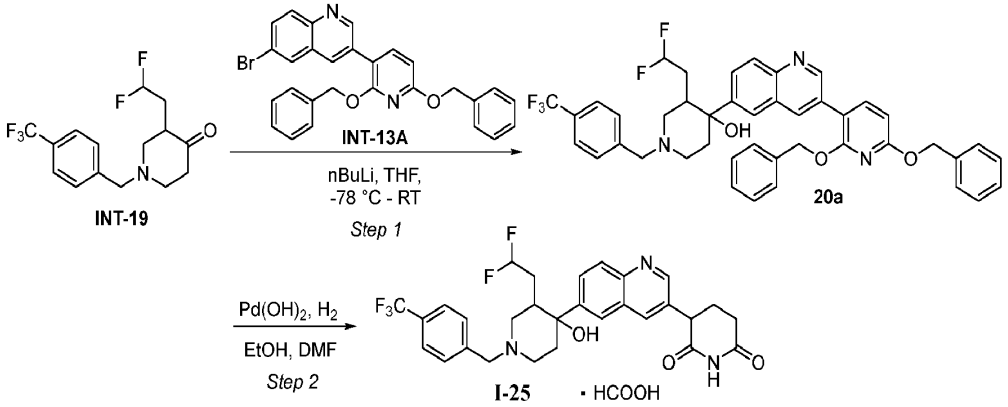


16b INT-19

To a reaction flask equipped with a stir bar was added 1-(4-(trifluoromethyl)benzyl)-piperidin-4-one (**16b**, 4.000 g, 1 eq., 15.55 mmol) and THF (31.10 mL, 0.5M) and the resulting mixture was cooled to

0 °C using an ice-water bath. 1M Hexamethyldisilazane potassium salt in THF solution (17.1 mL, 1.1 eq., 17.10 mmol) and the resulting mixture was allowed to stir for 1 h at 0 °C. 2-Bromo-1,1-difluoroethane (**19a**, 2.479 g, 1.36 mL, 1.1 eq., 17.1 mmol) was then added and the reaction mixture was allowed to want to room temperature and was then stirred for 5 min at room temperature. A condenser was then put onto the reaction flask and the reaction mixture was heated to 80°C overnight. Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was diluted with water and extracted with EtOAc (2x). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material purified via silica gel column chromatography eluting with 0-100% EtOAc in heptane. The desired fractions were collected, combined, and concentrated *in vacuo* to yield 3-(2,2-difluoroethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-one (**INT-19**, 307 mg, 0.96 µmol, 6% yield). LCMS: m/z HESI, positive $[M+H]^+$ = 322.

Example 20: Synthesis of 3-(6-(3-(2,2-difluoroethyl)-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-25)



Step 1: **Synthesis of 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-(2,2-difluoroethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-ol (20a)**

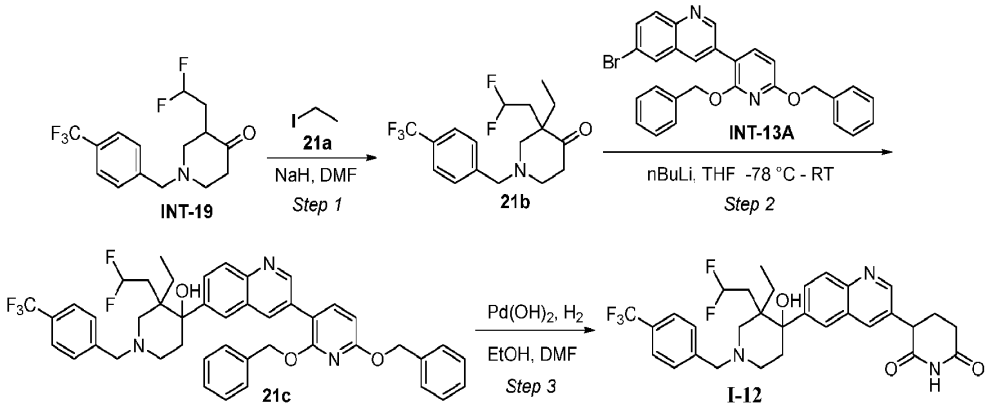
4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-(2,2-difluoroethyl)-1-(4-(trifluoromethyl)-benzyl)piperidin-4-ol (**20a**, 159 mg, 0.22 mmol, 43% yield) was synthesized according to **General Procedure 2, Step A** starting from 3-(2,2-difluoroethyl)-1-(4-(trifluoromethyl)benzyl)-piperidin-4-one (**INT-19**, 178 mg, 0.55 mmol) and 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 250 mg, 0.5 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 740.

Step 2: **Synthesis of 3-(6-(3-(2,2-difluoroethyl)-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-25)**

3-(6-(3-(2,2-difluoroethyl)-4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-25**, 8.7 mg, 0.02 mmol, 7% yield) as a mixture of diastereomers was synthesized according to **General Procedure 2, Step B** starting from 4-(3-(2,6-bis(benzyloxy)pyridin-3-

yl)quinolin-6-yl)-3-(2,2-difluoroethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-ol (**20a**, 159 mg, 0.22 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 562. ^{1}H NMR (499 MHz, DMSO-d_6) δ (ppm) = 11.01-10.92 (m, 1H), 8.79-8.74 (m, 1H), 8.40-8.35 (m, 1H), 8.22-8.17 (m, 1H), 8.05-7.96 (m, 2H), 7.91-7.83 (m, 1H), 7.74-7.68 (m, 2H), 7.65-7.55 (m, 2H), 5.91-5.57 (m, 1H), 4.19-4.11 (m, 1H), 3.75-3.69 (m, 1H), 3.66-3.60 (m, 2H), 2.89-2.70 (m, 3H), 2.67-2.58 (m, 2H), 2.45-2.32 (m, 3H), 2.23-2.04 (m, 2H), 1.85-1.61 (m, 1H), 1.44-1.34 (m, 1H), 1.19-1.03 (m, 1H).

Example 21: Synthesis of 3-(6-(3-(2,2-difluoroethyl)-3-ethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-12)



Step 1: **Synthesis of 3-(2,2-difluoroethyl)-3-ethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-one (21b)**

To a reaction vial equipped with a stir bar was added 3-(2,2-difluoroethyl)-1-(4-(trifluoromethyl)-benzyl)piperidin-4-one (**INT-19**, 250 mg, 1 eq., 0.78 mmol) and DMF (3.9 mL, 0.2 M, 1 eq., 0.8 mmol) and the resulting mixture was cooled to 0 °C using an ice-water bath. Sodium hydride (34 mg, 60% wt, 1.1 eq., 0.86 mmol) was added and the reaction mixture was stirred for 30 min at 0 °C. Iodoethane (**21a**,63 µL, 1 eq., 0.78 mmol) was then added and stirring was continued for 3 h. Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was concentrated *in vacuo* and purified via silica gel column chromatography eluting with 0 to 100% EtOAc in heptanes. The desired fractions were collected, combined, and concentrated *in vacuo* to yield 3-(2,2-difluoroethyl)-3-ethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-one (**21b**, 123 mg, 0.35 mmol, 45% yield). LCMS: m/z HESI, positive $[M+H]^+$ = 350.

Step 2: **Synthesis of 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-(2,2-difluoroethyl)-3-ethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-ol (21c)**

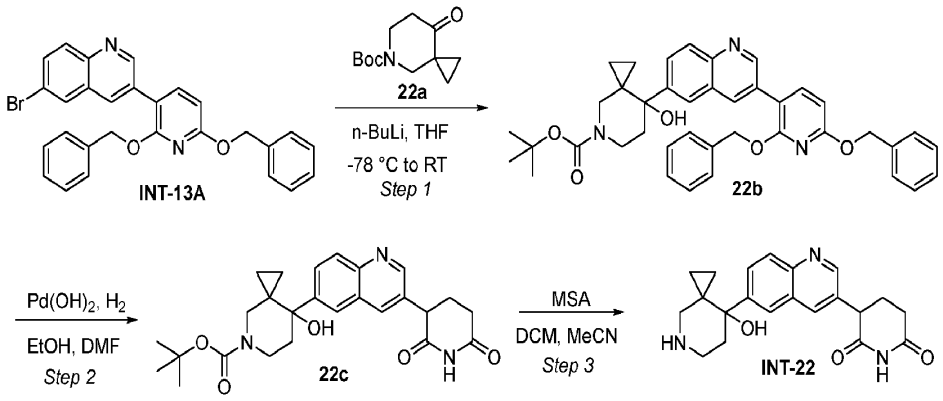
4-(3-(2,6-Bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-(2,2-difluoroethyl)-3-ethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-ol (**21c**, 91 mg, 0.12, mmol, 42% yield) was synthesized according to **General Procedure 2, Step A** starting from 3-(2,2-difluoroethyl)-3-ethyl-1-(4-(trifluoromethyl)benzyl)-

piperidin-4-one (**21b**, 123 mg 0.35 mmol) and 3-(2,6-bis(benzyloxy)-pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 140 mg, 0.28 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 768.

Step 3: **Synthesis of 3-(6-(3-(2,2-difluoroethyl)-3-ethyl-4-hydroxy-1-(4(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-12)**

3-(6-(3-(2,2-difluoroethyl)-3-ethyl-4-hydroxy-1-(4(trifluoromethyl)-benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-12**, 13 mg, 0.12 mmol, 18% yield) as a mixture of diastereomers was synthesized according to **General Procedure 2, Step B** starting from 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-(2,2-difluoroethyl)-3-ethyl-1-(4-(trifluoromethyl)-benzyl)piperidin-4-ol (**21c**, 91 mg, 0.12 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 590. ^{1}H NMR (499 MHz, DMSO-d_6) δ (ppm) = 10.99-10.93 (m, 1H), 8.79-8.74 (m, 1H), 8.45-8.38 (m, 1H), 8.23-8.19 (m, 1H), 8.08-8.04 (m, 1H), 7.95 (s, 2H), 7.72 (s, 2H), 7.62-7.55 (m, 2H), 6.06-5.74 (m, 1H), 5.15-5.09 (m, 1H), 4.19-4.10 (m, 1H), 3.73-3.66 (m, 1H), 3.55-3.48 (m, 1H), 2.90-2.70 (m, 3H), 2.68-2.55 (m, 4H), 2.55-2.52 (m, 1H), 2.45-2.34 (m, 1H), 2.19-2.10 (m, 1H), 1.60-1.37 (m, 4H), 0.61-0.49 (m, 3H).

Example 22: Synthesis of 3-(6-(8-hydroxy-5-azaspiro[2.5]octan-8-yl)quinolin-3-yl)piperidine-2,6-dione (INT-22)



Step 1: **Synthesis of *tert*-butyl 8-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-8-hydroxy-5-azaspiro[2.5]octane-5-carboxylate (22b)**

tert-Butyl 8-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-8-hydroxy-5-azaspiro-[2.5]octane-5-carboxylate (**22b**, 106 mg, 0.16 mmol, 46% yield) was synthesized according to **General procedure 1, Step A** starting from *tert*-butyl 8-oxo-5-azaspiro[2.5]octane-5-carboxylate (**22a**, 82 mg, 0.36 mmol) and 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 180 mg, 0.36 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 644.

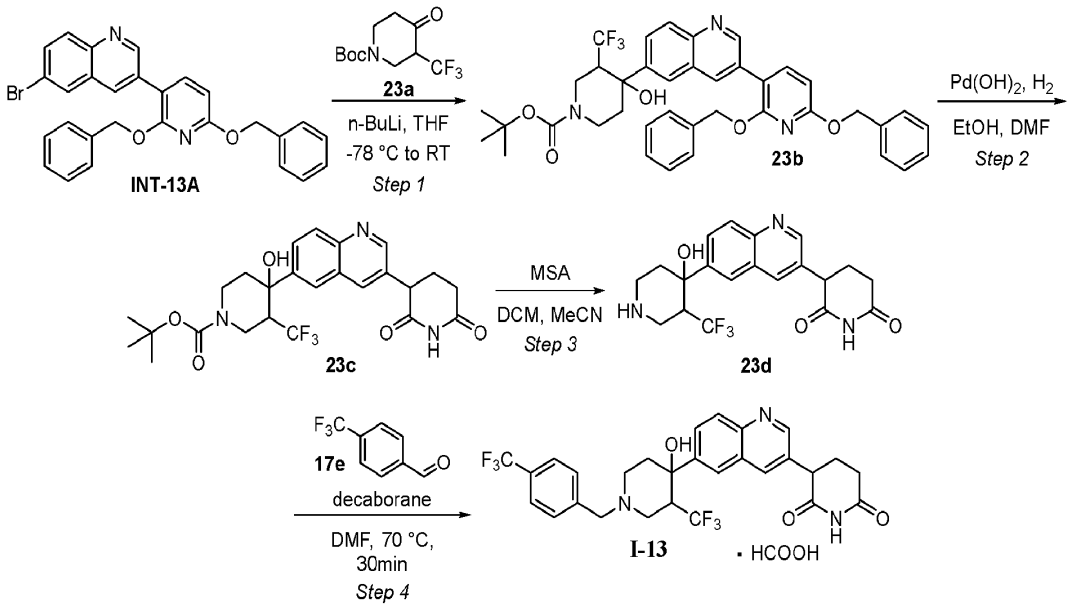
Step 2: **Synthesis of *tert*-butyl 8-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-8-hydroxy-5-azaspiro[2.5]octane-5-carboxylate (22c)**

tert-Butyl 8-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-8-hydroxy-5-azaspiro[2.5]octane-5-carboxylate (**22c**, 48 mg, 0.1 mmol, 80% yield) was synthesized according to **General procedure 1, Step B** starting from *tert*-butyl 8-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-8-hydroxy-5-azaspiro[2.5]-octane-5-carboxylate (**22b**, 106 mg, 0.16 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 466.

Step 3: **Synthesis of 3-(6-(8-hydroxy-5-azaspiro[2.5]octan-8-yl)quinolin-3-yl)piperidine-2,6-dione (INT-22)**

3-(6-(8-Hydroxy-5-azaspiro[2.5]octan-8-yl)quinolin-3-yl)piperidine-2,6-dione (**INT-22**, 38 mg, 0.10 mmol, quantitative yield) was synthesized according to **General procedure 1, Step C** starting from *tert*-butyl 8-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-8-hydroxy-5-azaspiro[2.5]octane-5-carboxylate (**22c**, 48 mg, 0.10 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 366.

Example 23: Synthesis of 3-(6-(4-hydroxy-3-(trifluoromethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-13)



Step 1: **Synthesis of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3-(trifluoromethyl)piperidine-1-carboxylate (23b)**

tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3-(trifluoromethyl)piperidine-1-carboxylate (**23b**, 111 mg, 0.16 mmol, 35% yield) was synthesized according to **General procedure 1, Step A** starting from *tert*-butyl 4-oxo-3-(trifluoromethyl)piperidine-1-carboxylate (**23a**, 148mg, 0.55 mmol) and 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 250 mg, 0.5 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 686.

Step 2: **Synthesis of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3-(trifluoromethyl)piperidine-1-carboxylate (23c)**

tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3-(trifluoromethyl)piperidine-1-carboxylate (**23c**, 32 mg, 0.06 mmol, 39% yield) was synthesized according to **General procedure 1, Step B** starting from *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3-(trifluoromethyl)piperidine-1-carboxylate (**23b**, 111 mg, 0.16 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 508

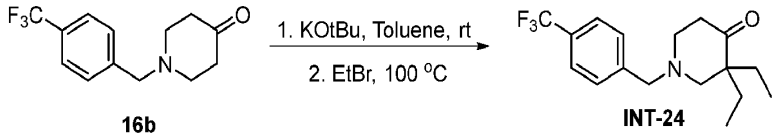
Step 3: Synthesis of **3-(6-(4-hydroxy-3-(trifluoromethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (23d)**

3-(6-(4-hydroxy-3-(trifluoromethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**23d**, 13 mg, 0.03 mmol, quantitative yield) was synthesized according to **General procedure 1, Step C** starting from *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3-(trifluoromethyl)piperidine-1-carboxylate (**23c**, 16 mg, 0.03 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 408

Step 4: **Synthesis of 3-(6-(4-hydroxy-3-(trifluoromethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-13)**

3-(6-(4-hydroxy-3-(trifluoromethyl)-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-13**, 3.7 mg, 0.007 mmol, 21% yield) as a mixture of diastereomers was synthesized according to **General procedure 1, Step D** starting from 4-(trifluoromethyl)benzaldehyde (**17e**, 14 mg, 11 uL, 0.08mmol) and 3-(6-(4-hydroxy-3-(trifluoromethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**23d**,13 mg, 0.03 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 566. ^{1}H NMR (499 MHz, DMSO-d_6) δ (ppm) = 10.99-10.96 (m, 1H), 8.77-8.74 (m, 1H), 8.39-8.35 (m, 1H), 8.20-8.17 (m, 1H), 8.12-8.07 (m, 1H), 7.97-7.92 (m, 2H), 7.76-7.72 (m, 2H), 7.66-7.61 (m, 2H), 5.68-5.63 (m, 1H), 4.18-4.11 (m, 1H), 3.81-3.71 (m, 2H), 2.98-2.91 (m, 1H), 2.82-2.66 (m, 4H), 2.64-2.53 (m, 2H), 2.46-2.37 (m, 1H), 2.20-2.11 (m, 2H), 1.67-1.59 (m, 1H).

Example 24: Synthesis of 3,3-diethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-one (INT-24)

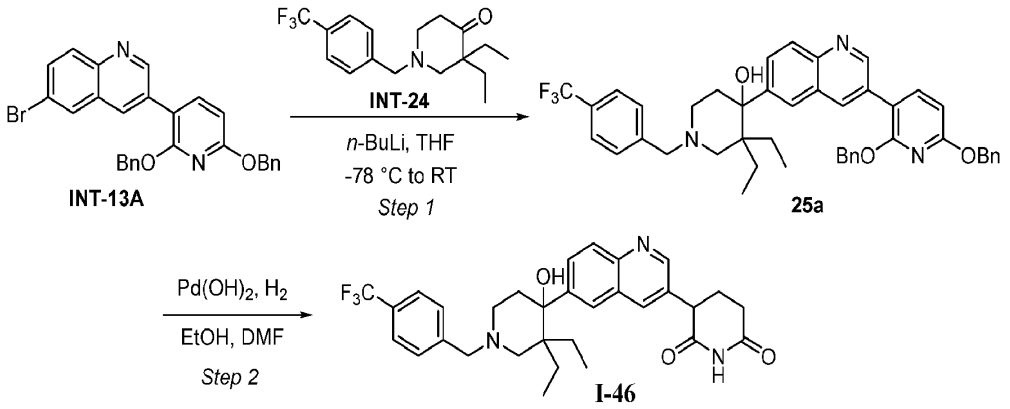


16b **INT-24**

To an oven-dried flask equipped with a stir bar was added 1-(4-(trifluoromethyl)benzyl)-piperidin-4-one (**16b**, 1000 mg, 1 eq., 3.89 mmol) and toluene (0.4M) followed by KO*t*Bu (963.9 mg, 2.21 eq, 8.59 mmol) and the resulting mixture was stirred for 1 h at room temperature. Bromoethane (931.9 mg, 634 µL, 2.2 eq., 8.55 mmol) was then added and the reaction mixture was heated to reflux at 100 °C. After 1 h, LCMS showed complete consumption of starting material. Saturated bicarbonate was added, and the aqueous mixture was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude material was purified via silica gel chromatography on a 40 g silica gel column eluting with 0 to 10% MeOH in DCM

to provide 3,3-diethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-one (**INT-24**, 238 mg, 0.76 mmol, 20% yield). ^{1}H NMR (499 MHz, $CDCl_3$, 302 K) δ (ppm) = 7.60 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H), 3.61 (s, 2H), 2.69 (t, *J* = 6.0 Hz, 2H), 2.49-2.45 (m, 4H), 1.86 (dd, *J* = 7.7, 14.2 Hz, 2H), 1.50 (dd, *J* = 7.4, 14.5 Hz, 2H), 0.72 (t, *J* = 7.7 Hz, 6H).

Example 25: Synthesis of 3-(6-(3,3-diethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-46)



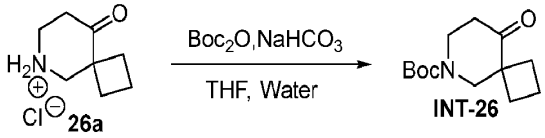
Step 1: **Synthesis of 4-(3-(2,6-Bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3,3-diethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-ol (25a)**

4-(3-(2,6-Bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3,3-diethyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-ol (**25a**, 28.3 mg, 0.39 mmol, 15% yield) was synthesized according to **General Procedure 2, Step A** starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-quinoline (**INT-13A**, 130.0 mg, 1 eq., 0.26 mmol) and 3,3-diethyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-one (**INT-24**, 90.1 mg, 1.1 eq., 0.29 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 732

Step 2: **Synthesis of the 3-(6-(3,3-diethyl-4-hydroxy-1-(4-(trifluoro-methyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-46)**

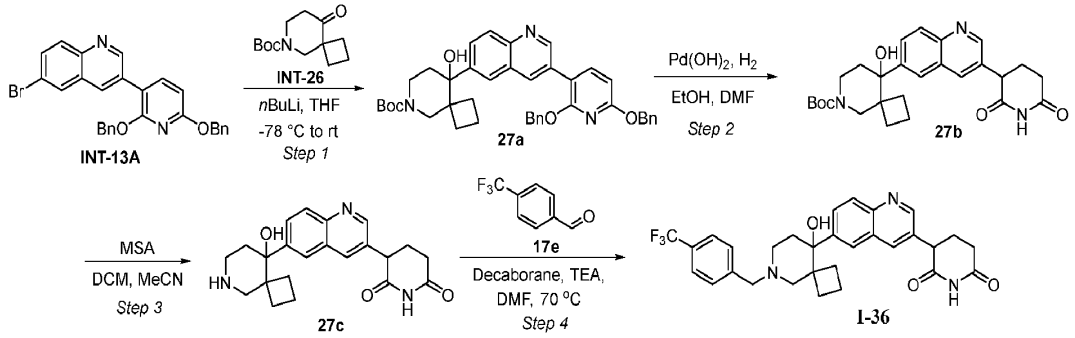
3-(6-(3,3-diethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-46**, 11 mg, 0.02 mmol, 50%, solid) as a mixture of diastereomers was synthesized according to **General Procedure 2, Step B** starting from 1-(3-(2,6-bis(benzyloxy)-pyridin-3-yl)quinolin-6-yl)-2,2-diethyl-4-(4-(trifluoromethyl)-benzyl)cyclohexan-1-ol (**25a**, 28.3 mg, 1 eq., 0.039 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 554; ^{1}H NMR (499 MHz, DMSO-d_6, 298 K) δ (ppm) = 11.02 (s, 1H), 10.36 (br s, 1H), 8.97 (br s, 1H), 8.63 (br s, 1H), 8.14-8.08 (m, 2H), 8.04 (br d, *J* = 8.2 Hz, 3H), 7.89 (d, *J* = 8.2 Hz, 2H), 5.78 (br s, 1H), 4.63-4.52 (m, 1H), 4.46 (br dd, *J* = 6.3, 12.9 Hz, 1H), 4.22 (br dd, *J* = 4.7, 12.9 Hz, 1H), 3.46-3.41 (m, 2H), 3.23 (br t, *J* = 11.8 Hz, 1H), 3.20-3.13 (m, 1H), 2.83-2.72 (m, 2H), 2.68-2.59 (m, 1H), 2.48-2.40 (m, 1H), 2.22-2.09 (m, 2H), 1.79 (br d, *J* = 14.2 Hz, 1H), 1.63-1.50 (m, 1H), 1.19-1.07 (m, 2H), 0.48-0.36 (m, 6H).

Example 26: Synthesis of *tert*-butyl 9-oxo-6-azaspiro[3.5]nonane-6-carboxylate (INT-26)



To a 40 mL vial equipped with a stir bar was added 6-azaspiro[3.5]nonan-9-one HCl (**26a**, 1.00 g, 1 eq., 7.18 mmol) and sodium bicarbonate (1.20 g, 2 eq., 14.37 mmol) and THF (35.9 mL, 0.2 M) and water (8.9 mL, 0.8 M). Di-*tert*-butyl dicarbonate (1.82 mL, 1.1 eq., 7.90 mmol) was then added to the suspension and the resulting solution was stirred for 1 h at rt. The reaction mixture was concentrated *in vacuo* and then diluted with DCM and saturated sodium bicarbonate. The phases were separated, and the aqueous phase was extracted one additional time with DCM. The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified via silica gel chromatography on an 80 g silica gel column eluting with 0 to 100% EtOAc in heptanes. The pure product containing fractions were collected and concentrated to yield a clear viscous solid, which was lyophilized from benzene to yield *tert*-butyl 9-oxo-6-azaspiro[3.5]nonane-6-carboxylate (**INT-26**, 1.27 g, 5.32 mmol, 74% yield). LCMS: m/z HESI, positive $[M+H- tBu]^+ = 184$ and $[M-Boc+H]^+ = 140$.

Example 27: Synthesis of 3-(6-(9-hydroxy-6-(4-(trifluoromethyl)-benzyl)-6-azaspiro[3.5]nonan-9-yl)quinolin-3-yl)piperidine-2,6-dione (I-36)



Step 1: **Synthesis of *tert*-butyl 9-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-9-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (27a)**

tert-Butyl 9-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-9-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (**27a**, 167.4 mg, 0.25 mmol, 51% yield) was synthesized according to **General procedure 1, Step A** starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-quinoline (**INT-13A**, 250 mg, 1 eq., 503 µmol) and *tert*-butyl 9-oxo-6-azaspiro[3.5]nonane-6-carboxylate (**INT-26**, 120 mg, 1 eq., 0.50 mmol). LCMS: m/z HESI, positive $[M+H]^+ = 658$.

Step 2: **Synthesis of *tert*-butyl 9-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-9-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (27b)**

tert-Butyl 9-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-9-hydroxy-6-azaspiro[3.5]-nonane-6-carboxylate (**27b**, 43.2 mg, 0.09 mmol, 47% yield) was synthesized according to **General procedure 1, Step B** starting from *tert*-butyl 9-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-9-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate **27a**, (127 mg, 1 eq., 0.19 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 480.

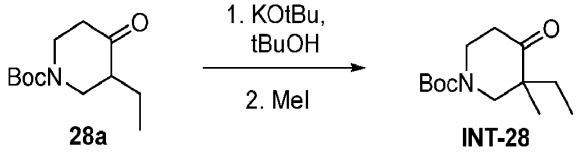
Step 3: **Synthesis of 3-(6-(9-hydroxy-6-azaspiro[3.5]nonan-9-yl)quinolin-3-yl)piperidine-2,6-dione (27c)**

3-(6-(9-hydroxy-6-azaspiro[3.5]nonan-9-yl)quinolin-3-yl)piperidine-2,6-dione (**27c**, 34 mg, 0.09 mmol, quantitative yield) was synthesized according to **General procedure 1, Step C** starting from *tert*-butyl 9-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-9-hydroxy-6-azaspiro[3.5]-nonane-6-carboxylate (**27b**, 43 mg, 1 eq., 0.09 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 380.

Step 4: **Synthesis of 3-(6-(9-hydroxy-6-(4-(trifluoromethyl)benzyl)-6-azaspiro[3.5]nonan-9-yl)quinolin-3-yl)piperidine-2,6-dione (I-36)**

3-(6-(9-hydroxy-6-(4-(trifluoromethyl)benzyl)-6-azaspiro[3.5]-nonan-9-yl)quinolin-3-yl)piperidine-2,6-dione (**I-36**, 48 mg, 0.034 mmol, 38% yield, amorphous solid) as a mixture of diastereomers was synthesized according to **General procedure 1, Step D** starting from 3-(6-(9-hydroxy-6-azaspiro[3.5]nonan-9-yl)quinolin-3-yl)piperidine-2,6-dione (**27c**, 34 mg, 1 eq., 0.090 mmol), 4-(trifluoromethyl)benzaldehyde (**17e**, 17 mg, 13 µL, 1.1 eq., 0.099 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 538. ^{1}H NMR (499 MHz, DMSO-d_6, 297 K) δ (ppm) = 11.05 (s, 1H), 10.73 (br s, 1H), 9.04 (br s, 1H), 8.71 (br s, 1H), 8.26-8.18 (m, 2H), 8.15 (br d, J = 8.8 Hz, 1H), 7.99 (d, J = 7.7 Hz, 2H), 7.89 (d, J = 8.2 Hz, 2H), 4.52 (br d, J = 4.9 Hz, 2H), 4.26 (br dd, J = 4.7, 12.9 Hz, 1H), 3.41-3.25 (m, 5H), 2.93-2.74 (m, 2H), 2.71-2.59 (m, 1H), 2.48-2.35 (m, 1H), 2.28-2.12 (m, 2H), 2.09-1.93 (m, 1H), 1.92-1.74 (m, 2H), 1.50-1.40 (m, 2H), 0.67-0.55 (m, 1H).

Example 28: Synthesis of *tert*-butyl 3-ethyl-3-methyl-4-oxopiperidine-1-carboxylate (INT-28)

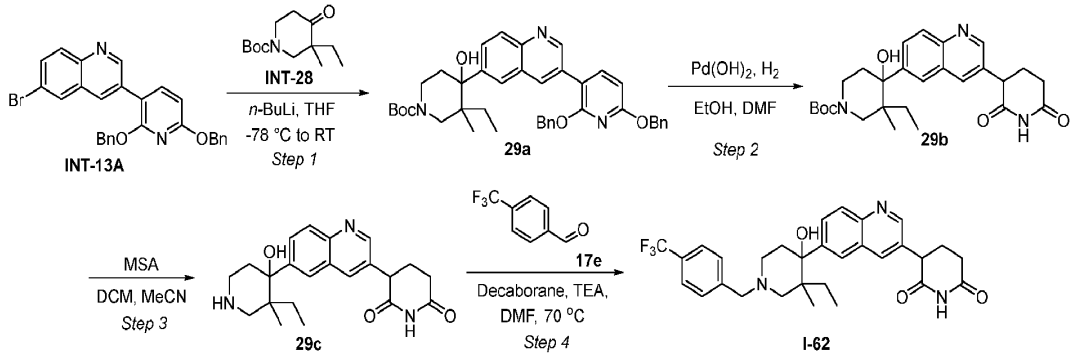


28a **INT-28**

To a 100 mL oven dried round bottomed flask equipped with a stir bar was added tBuOH (5.50 mL, 0.4 molar) and KOtBu (247 mg, 1.0 eq., 2.20 mmol) followed by *tert*-butyl 3-ethyl-4-oxopiperidine-1-carboxylate (**28a**, 500 mg, 1 eq., 2.20 mmol) and the resulting mixture was stirred at 40 °C for 1 h. MeI (151 µL, 1.1 eq., 2.42 mmol) was then added in one portion. Instantly after adding the MeI, precipitate was observed, and the reaction mixture was stirred for an additional 2 h. Once LCMS indicated the formation of the desired product as well as undesired regioisomers, the reaction mixture was diluted with

EtOAc and washed with water. 2 mL of 2 M HCl was added to break the emulsion. The aqueous phase was extracted with EtOAc (3x) and the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was via silica gel chromatography on a 40 g silica gel column eluting with 0 to 25% EtOAc in heptane. The pure product containing fractions were collected and concentrated to provide *tert*-butyl 3-ethyl-3-methyl-4-oxopiperidine-1-carboxylate (**INT-28**, 62.9 mg, 0.26 mmol, 12% yield). LCMS: m/z HESI, positive $[M+H\text{-}Boc]^+ = 142$; ^1H NMR (499 MHz, $CDCl_3$, 297 K) δ (ppm) = 4.21-4.08 (m, 1H), 3.82 (br d, *J* = 13.1 Hz, 1H), 3.40-3.23 (m, 1H), 3.06 (br s, 1H), 2.54 (br s, 1H), 2.35 (td, *J* = 4.6, 14.9 Hz, 1H), 1.70-1.62 (m, 1H), 1.49 (s, 10H), 1.00 (s, 3H), 0.82 (t, *J* = 7.7 Hz, 3H).

Example 29: Synthesis of 3-(6-(3-ethyl-4-hydroxy-3-methyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-62)



Step 1: **Synthesis of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-ethyl-4-hydroxy-3-methylpiperidine-1-carboxylate (29a)**

tert-Butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-ethyl-4-hydroxy-3-methylpiperidine-1-carboxylate (**29a**, 77.5 mg, 0.12 mmol, 29% yield) was synthesized according to **General procedure 1, Step A** starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 200.0 mg, 1 eq., 0.40 mmol), *tert*-butyl 3-ethyl-3-methyl-4-oxopiperidine-1-carboxylate (**INT-28**, 106.7 mg, 1.1 eq., 0.44 mmol). LCMS: m/z HESI, positive $[M+H]^+ = 660$.

Step 2: **Synthesis of the *tert*-Butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3-ethyl-4-hydroxy-3-methylpiperidine-1-carboxylate (29b)**

tert-Butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3-ethyl-4-hydroxy-3-methyl-piperidine-1-carboxylate (**29b**, 31.5 mg, 0.065 mmol, 56% yield) was synthesized according to **General procedure 1, Step B** starting from *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-ethyl-4-hydroxy-3-methylpiperidine-1-carboxylate (**29a**,77.5 mg, 1 eq., 0.12 mmol). LCMS: m/z HESI, positive $[M+H]^+ = 482$.

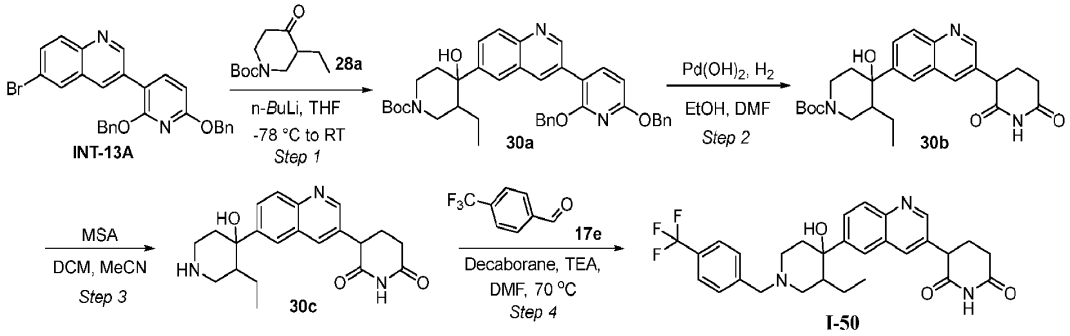
Step 3: **Synthesis of 3-(6-(3-Ethyl-4-hydroxy-3-methylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (29c)**

3-(6-(3-Ethyl-4-hydroxy-3-methylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**29c**, 25 mg, 0.066 mmol, quantitative yield) was synthesized according to **General procedure 1, Step C** starting from *tert*-butyl 4-(3-(2,6.dioxopiperidin-3-yl)quinolin-6-yl)-3-ethyl-4-hydroxy-3-methylpiperidine-1-carboxylate (**29b**, 31.5 mg, 1 eq., 0.65 mmol). LCMS m/z: HESI, positive $[M+H]^+$ = 382.

Step 4: **Synthesis of 3-(6-(3-ethyl-4-hydroxy-3-methyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-62)**

3-(6-(3-ethyl-4-hydroxy-3-methyl-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-62**, 21 mg, 0.039 mmol, 59% yield, amorphous solid) as a mixture of diastereomers was synthesized according to **General procedure 1, Step D** starting from 3-(6-(3-ethyl-4-hydroxy-3-methylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**29c**, 25 mg, 1 eq., 0.066 mmol) and 4-(trifluoromethyl)benzaldehyde (**17e**, 13 mg, 9.8 µL, 1.1 eq., 0.072 µmol). LCMS: m/z HESI, positive $[M+H]^+$ = 540. ^{1}H NMR (499 MHz, DMSO-d_6, 298 K) δ (ppm) = 11.03 (s, 1H), 10.39 (br s, 1H), 9.00 (br s, 1H), 8.65 (br s, 1H), 8.15-8.08 (m, 2H), 8.06-7.96 (m, 3H), 7.89 (d, *J* = 8.2 Hz, 2H), 5.73 (br s, 1H), 4.59-4.47 (m, 2H), 4.23 (dd, *J* = 4.9, 12.6 Hz, 1H), 3.36-3.19 (m, 3H), 3.17-3.02 (m, 2H), 2.85-2.72 (m, 1H), 2.69-2.59 (m, 1H), 2.48-2.40 (m, 1H), 2.21-2.14 (m, 1H), 1.91-1.73 (m, 2H), 1.02 (s, 3H), 0.97-0.84 (m, 1H), 0.56 (t, *J* = 7.7 Hz, 3H).

Example 30: Synthesis of 3-(6-(3-ethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-50)



Step 1: **Synthesis of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-ethyl-4-hydroxypiperidine-1-carboxylate (30a)**

tert-Butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-ethyl-4-hydroxy-piperidine-1-carboxylate (**30a**, 192.3 mg, 0.29 mmol, 37% yield) was synthesized according to **General procedure 1, Step A** starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 400 mg, 1 eq.,

0.80 mmol) and *tert*-butyl 3-ethyl-4-oxopiperidine-1-carboxylate (**28a**, 238 mg, 1.3 eq., 1.05 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 646.

Step 2: **Synthesis of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3-ethyl-4-hydroxypiperidine-1-carboxylate (30b)**

tert-Butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3-ethyl-4-hydroxypiperidine-1-carboxylate (**30b**, 74.0 mg, 0.16 mmol, 53% yield) was synthesized according to **General procedure 1, Step B** starting from *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-ethyl-4-hydroxy-piperidine-1-carboxylate (**30a**, 192 mg, 1 eq., 0.29 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 468.

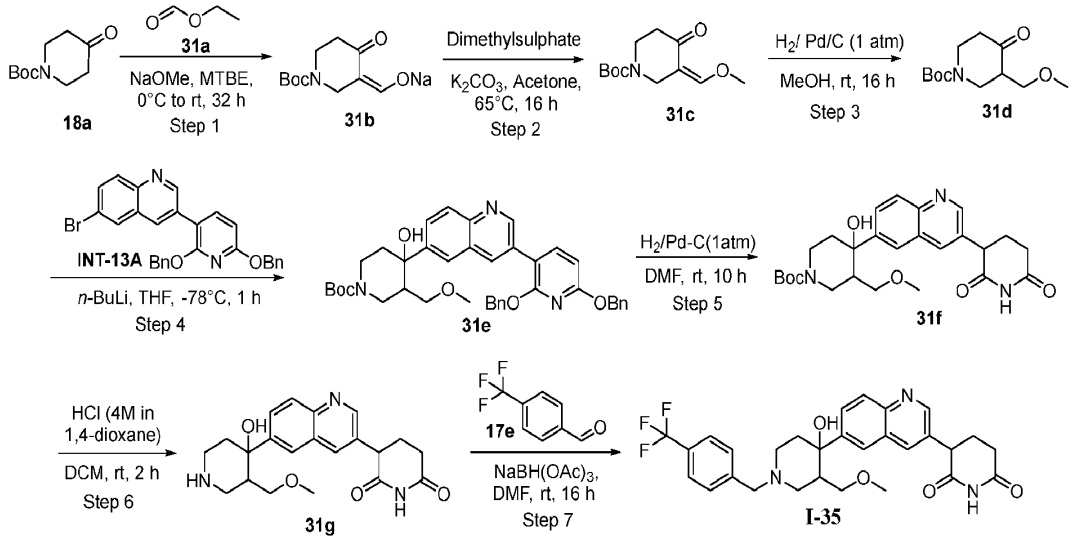
Step 3: **Synthesis of 3-(6-(3-ethyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (30c)**

3-(6-(3-ethyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**30c**, 58 mg, 0.16 mmol, quantitative yield) was synthesized according to **General procedure 1, Step C** starting from *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3-ethyl-4-hydroxypiperidine-1-carboxylate (**30b**,74 mg, 1 eq., 0.16 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 368.

Step 4: **Synthesis of 3-(6-(3-ethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-50)**

3-(6-(3-ethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-50**, 18 mg, 0.034 mmol, 43% yield, amorphous solid) as a mixture of diastereomers was synthesized according to **General procedure 1, Step D** starting from 3-(6-(3-ethyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**30c**, 29 mg, 1 eq., 0.079 mmol) and 4-(trifluoromethyl)benzaldehyde (**17e**, 15 mg, 12 µL, 1.1 eq., 0.087 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 526; ^{1}H NMR (499 MHz, DMSO-d_6, 297 K) δ (ppm) = 11.44 (br s, 1H), 11.04 (s, 1H), 9.00 (br s, 1H), 8.60 (br s, 1H), 8.18 (d, J = 8.8 Hz, 1H), 8.13 (s, 1H), 7.96 (d, J = 7.5 Hz, 2H), 7.93-7.91 (m, 1H), 7.91-7.87 (m, 2H), 4.61 (br dd, J = 4.1, 13.4 Hz, 1H), 4.48 (br dd, J = 5.7, 12.9 Hz, 1H), 4.25 (br dd, J = 4.9, 12.6 Hz, 1H), 3.49 (br d, J = 9.3 Hz, 1H), 3.45-3.33 (m, 2H), 3.30-3.26 (m, 1H), 3.13-3.02 (m, 1H), 2.84-2.73 (m, 1H), 2.70-2.58 (m, 3H), 2.47-2.32 (m, 1H), 2.22-2.11 (m, 1H), 1.82 (br d, J = 13.7 Hz, 1H), 1.10-0.91 (m, 2H), 0.59 (t, J = 7.4 Hz, 3H).

Example 31: Synthesis of 3-(6-(4-hydroxy-3-(methoxymethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-35)



Step 1: **Synthesis of sodium (Z)-(1-(*tert*-butoxycarbonyl)-4-oxopiperidin-3-ylidene)-methanolate (31b)**

To a stirred solution of sodium methoxide (5.42 g, 25.1 mmol) in methanol (5 mL) was added ethyl formate (**31a**, 2.79 g, 37.6 mmol) dropwise at 0 °C and the resulting mixture was warmed to room temperature. *Tert*-butyl 4-oxopiperidine-1-carboxylate (**18a**, 5.0 g, 25.1 mmol) was then added and stirring was continued at room temperature for 32 h. The reaction mixture was concentrated under reduced pressure to provide sodium (Z)-(1-(*tert*-butoxycarbonyl)-4-oxopiperidin-3-ylidene)methanolate (**31b**, 5 g, 18.05 mmol, 72% yield) which was carried onto the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H\text{-Boc-Na}]^+$ 127.9.

Step 2: **Synthesis of *tert*-butyl (Z)-3-(methoxymethylene)-4-oxopiperidine-1-carboxylate (31c)**

To a stirred solution of sodium (Z)-(1-(*tert*-butoxycarbonyl)-4-oxopiperidin-3-ylidene)methanolate (**31b**, 5 g, 20.06 mmol) in acetone (100 mL) were added K_2CO_3 (5.55 g, 40.1 mmol) followed by dimethyl sulfate (1.902 mL, 20.06 mmol) at 25 °C and the resulting mixture was stirred at 65 °C in an autoclave for 16 h. The reaction mixture was then cooled to room temperature, water was added, and the aqueous mixture was extracted with EtOAc (2x). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography on Biotage Isolera® on silica gel (100-200 mesh) eluting with 0 to 60% EtOAc in *n*-hexane to afford *tert*-butyl (Z)-3-(methoxymethylene)-4-oxopiperidine-1-carboxylate (**31c**, 2.5 g, 6.22 mmol, 31% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 242.1, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.34 (s, 1H), 4.29 (s, 2H), 3.92 (s, 3H), 3.57 (t, J = 6.00 Hz, 2H), 2.35 (t, J = 6.00 Hz, 2H), 1.60-1.48 (m, 9H).

Step 3: **Synthesis of *tert*-butyl 3-(methoxymethyl)-4-oxopiperidine-1-carboxylate (31d)**

To a stirred solution of *tert*-butyl (Z)-3-(methoxymethylene)-4-oxopiperidine-1-carboxylate (**31c**, 5 g, 20.72 mmol) in methanol (100 mL) at 25 °C under an atmosphere of nitrogen was added Pd/C (10-50%, 4.4 g, 4.14 mmol) at room temperature and the resulting mixture was stirred under an atmosphere of hydrogen (hydrogen balloon) for 16 h. The reaction mixture was filtered through a pad of celite® and the filter cake was washed with methanol (50 mL). The filtrate was concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography on Biotage Isolera® on silica gel (100-200 mesh) eluting with 0 to 10% EtOAc in *n*-hexane to afford *tert*-butyl 3-(methoxymethyl)-4-oxopiperidine-1-carboxylate (**31d**, 900 mg, 2.52 mmol, 12% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H\text{-}tBu]^+$ 188.1, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 4.01-3.85 (m, 3H), 3.57-3.53 (m, 1H), 3.39-3.32 (m, 2H), 3.25 (s, 3H), 2.75-2.72 (m, 1H), 2.33-2.50 (m, 2H), 1.44-1.15 (m, 9H).

Step 4: **Synthesis of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3-(methoxymethyl)piperidine-1-carboxylate (31e)**

tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3-(methoxy-methyl)piperidine-1-carboxylate (**31e**) was synthesized according to **General procedure 1, Step A** starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 250 mg, 1.0 eq., 0.50 mmol) and *tert*-butyl 3-(methoxymethyl)-4-oxopiperidine-1-carboxylate (**31d**, 183 mg, 1.5 eq., 0.75 mmol). The crude compound was purified by silica gel flash column chromatography, eluting with 0-50% EtOAc in hexanes to afford *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3-(methoxy-methyl)piperidine-1-carboxylate (**31e**, 60 mg, 0.07 mmol, 15% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 662.5, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.08 (d, J = 2.40 Hz, 1H), 8.48 (d, J = 2.00 Hz, 1H), 8.05 (d, J = 1.20 Hz, 1H), 8.00-7.96 (m, 2H), 7.88-7.84 (m, 1H), 7.48-7.31 (m, 11H), 6.66 (d, J = 8.00 Hz, 1H), 5.47 (s, 2H), 5.44 (s, 2H), 4.19-4.12 (br s, 1H), 3.86-3.78 (br s, 1H), 3.28-3.23 (m, 2H), 3.13 (t, J = 9.60 Hz, 1H), 3.00 (s, 3H), 2.87-2.67 (m, 1H), 2.28-1.98 (m, 3H), 1.45 (m, 9H).

Step 5: **Synthesis of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3-(methoxymethyl) piperidine-1-carboxylate (31f)**

tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3-(methoxymethyl)-piperidine-1-carboxylate (**31f**) was synthesized according to **General procedure 1, Step B** starting from *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3-(methoxymethyl)piperidine-1-carboxylate (**31e,** 190 mg, 1.0 eq., 0.29 mmol). The crude compound was purified by silica gel flash column chromatography using Biotage Isolera® (on Neutral alumina) eluting with 0-20% IPA in EtOAc to provide *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3-(methoxymethyl)piperidine-1-carboxylate (**31f**, 80 mg, 0.14 mmol, 47% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 484.4, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.97 (s, 1H), 8.77 (d, J = 2.40

Hz, 1H), 8.21 (s, 1H), 8.03-7.97 (m, 2H), 7.87-7.85 (m, 1H), 5.35 (s, 1H), 4.17-4.13 (m, 2H), 3.97-3.78 (m, 1H), 3.32-3.10 (m, 2H), 3.03 (s, 3H), 2.84-2.59 (m, 4H), 2.42-2.07 (m, 5H), 1.45 (s, 9H).

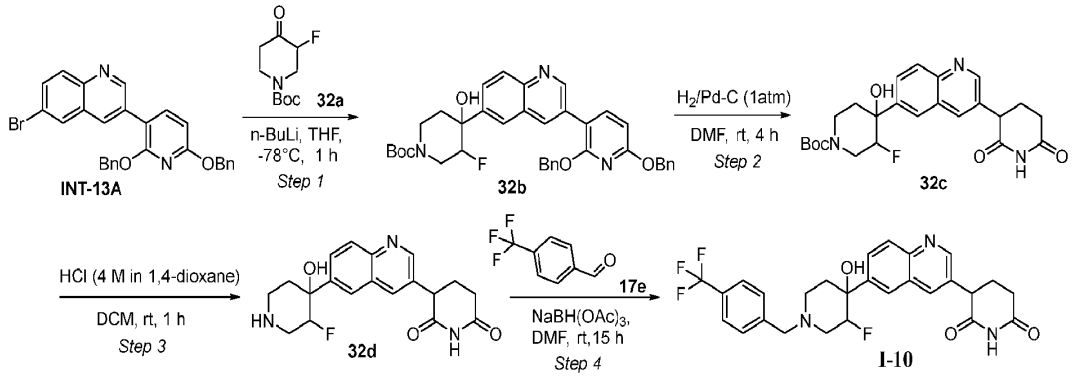
Step 6: **Synthesis of 3-(6-(4-hydroxy-3-(methoxymethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl (31g)**

3-(6-(4-Hydroxy-3-(methoxymethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl (**31g**, 52 mg, 0.11 mmol, 98% yield) was synthesized according to **General procedure 1, Step C** starting from *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3-(methoxymethyl)piperidine-1-carboxylate (**31f**, 75 mg, 1.0 eq., 0.11 mmol). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 384.3, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H), 9.08-8.86 (m, 3H), 8.48 (s, 1H), 8.15 (d, J = 8.80 Hz, 1H), 8.08 (s, 1H), 7.87 (d, J = 8.80 Hz, 1H), 5.58 (s, 1H), 4.25-4.21 (m, 1H), 3.65-3.20 (m, 6H), 3.17 (s, 3H), 2.89-2.62 (m, 4H), 2.46-2.42 (m, 1H), 2.20-2.16 (m, 1H), 1.79 (d, J = 14.00 Hz, 1H).

Step 7: **Synthesis of 3-(6-(4-hydroxy-3-(methoxymethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-35)**

3-(6-(4-hydroxy-3-(methoxymethyl)-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-35**) was synthesized according to **General procedure 1, Step D** starting from 3-(6-(4-hydroxy-3-(methoxymethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl (**31g**, 55 mg, 1.0 eq., 0.13 mmol) and 4-(trifluoro-methyl)benzaldehyde (**17e**, 45 mg, 2.0 eq., 0.26 mmol). The crude compound was purified by preparative-HPLC [(Column: X select C18 (150 x 19 mm) 5 µm, eluting with Mobile phase A: 0.05% HCl in H_2O, Mobile phase B: Acetonitrile, flow rate: 15 mL/min)]. The pure product containing fractions were collected and lyophilized to afford a mixture of diastereomers of 3-(6-(4-hydroxy-3-(methoxymethyl)-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-35**, 22 mg, 0.04 mmol, 28% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 542.6, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.23 (s, 1H), 11.02 (s, 1H), 8.94 (s, 1H), 8.47 (s, 1H), 8.15 (d, J = 8.80 Hz, 1H), 8.08 (s, 1H), 7.96-7.86 (m, 5H), 5.85 (s, 1H), 4.61-4.55 (m, 2H), 4.24-4.21 (m, 1H), 3.52-3.48 (m, 1H), 3.37-3.22 (m, 3H), 3.15 (t, J = 9.20 Hz, 1H), 3.04-2.99 (m, 1H), 2.98 (s, 3H), 2.79-2.76 (m, 2H), 2.68-2.61 (m, 2H), 2.47-2.43 (m, 1H), 2.19-2.14 (m, 1H), 1.86-1.78 (m, 1H).

Example 32: Synthesis of 3-(6-(3-fluoro-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-10)



Step 1: **Synthesis of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-fluoro-4-hydroxypiperidine-1-carboxylate (32b)**

To a stirred solution of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 0.5 g, 1.00 mmol) and *tert*-butyl 3-fluoro-4-oxopiperidine-1-carboxylate (**32a**, 0.328 g, 1.51 mmol) in THF (2 mL) was added *n*-butyllithium (1.6M sol. in THF, 0.754 mL, 1.206 mmol) at -78 °C and the resulting mixture was stirred at -78 °C for 1 h. Saturated ammonium chloride was added and the aqueous mixture was extracted with EtOAc (2x). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography using Biotage Isolera® (on silica gel 100-200 mesh) eluting with 0-20% EtOAc in hexanes to afford *tert*-butyl 4-(3-(2,6-bis(benzyloxy)-pyridin-3-yl)quinolin-6-yl)-3-fluoro-4-hydroxypiperidine-1-carboxylate (**32b**, 210 mg, 0.30 mmol, 30% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+ = 636.4$, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.09 (s, 1H), 8.47 (s, 1H), 8.08 (s, 1H), 7.99-7.94 (m, 3H), 7.49-7.29 (m, 9H), 6.67 (s, 1H), 5.98-5.76 (m, 2H), 5.48-5.44 (m, 4H), 5.05-5.02 (m, 2H), 4.12-3.82 (m, 5H), 1.42 (s, 9H).

Step 2: **Synthesis of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3-fluoro-4-hydroxypiperidine-1-carboxylate (32c)**

tert-Butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3-fluoro-4-hydroxypiperidine-1-carboxylate (**32c**) was synthesized according to **General procedure 1, Step B** starting from *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-fluoro-4-hydroxypiperidine-1-carboxylate (**32b**, 210 mg, 1.0 eq., 0.33 mmol). The crude material was purified by reverse phase column chromatography using a C_{18} cartridge (25 g) and eluting with 50 to 100% MeCN and 0.1% formic acid in water as mobile phase. The pure fractions were collected and lyophilized to afford *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3-fluoro-4-hydroxypiperidine-1-carboxylate (**32c**, 0.1 g, 0.22 mmol, 66% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+ = 458.4$, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.98 (s, 1H), 8.78 (s, 1H), 8.19 (s, 1H), 8.12 (s, 1H), 7.98 (m, 2H), 5.85 (s, 1H), 5.02-4.85 (m, 1H), 4.19-4.14 (m, 2H), 3.84 (s,

1H), 3.21 (m, 1H), 2.77-2.73 (m, 1H), 2.44-2.40 (m, 1H), 2.17-2.13 (m, 1H). 1.82-1.71 (m, 1H), 1.45 (s, 9H), 1.35-1.16 (m, 2H), 0.87-0.84 (m, 1H).

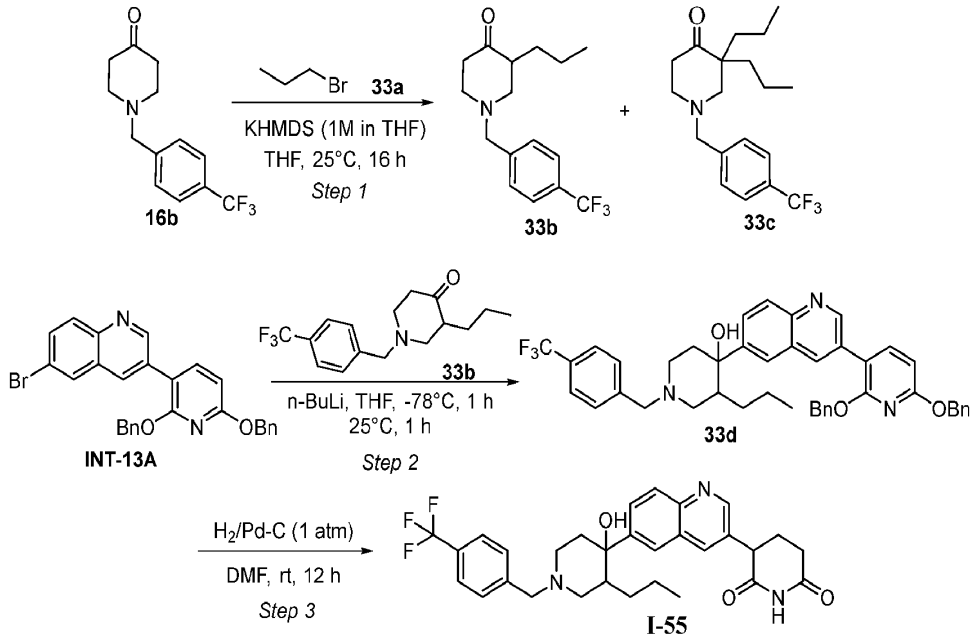
Step 3: **Synthesis of 3-(6-(3-fluoro-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl (32d)**

3-(6-(3-Fluoro-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl (**32d**, 80 mg, 0.2 mmol, 93% yield) was synthesized according to **General procedure 1, Step C** starting from *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3-fluoro-4-hydroxypiperidine-1-carboxylate (**32c**, 100 mg, 1.0 eq., 0.22 mmol). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+ = 358.4$, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 9.27 (br s, 2H), 8.92 (s, 1H), 8.43 (s, 1H), 8.13 (d, J = 6.40 Hz, 2H), 7.93 (d, J = 8.80 Hz, 1H), 6.35-6.2 (br s, 1H), 5.42-5.24 (m, 1H), 4.24-4.20 (m, 1H), 3.57-3.51 (m, 4H), 3.33-3.18 (m, 3H), 2.82-2.70 (m, 1H), 2.25-2.15 (m, 1H), 2.1-1.95 (m, 1H).

Step 4: **Synthesis of 3-(6-(3-fluoro-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-10)**

3-(6-(3-fluoro-4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-10**) was synthesized according to **General procedure 1, Step D** starting from-(6-(3-fluoro-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl (**32d**, 80 mg, 1.0 eq., 0.20 mmol) and 4-(trifluoromethyl)-benzaldehyde (**17e**, 35 mg, 1.0 eq., 0.20 mmol). The crude product was purified by preparative-HPLC [X Select C18 (250*19mm), eluting with Mobile phase A: 0.05% HCl in H_2O, Mobile phase B: Acetonitrile, flow rate: 15 mL/min, Rt:12.0]. The fractions containing pure product were collected and lyophilized to afford 3-(6-(3-fluoro-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-10**, 21.90 mg, 0.04 mmol, 20% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+ = 516.5$, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.62 (s, 1H), 11.01 (s, 1H), 8.91 (s, 1H), 8.42 (s, 1H), 8.13 (d, J = 8.40 Hz, 2H), 7.92-7.89 (m, 5H), 6.38 (s, 1H), 5.55-5.46 (m, 1H), 4.63 (br s, 2H), 4.21 (m, 1H), 3.79-3.48 (m, 2H), 3.32 (m, 3H), 2.83-2.74 (m, 1H), 2.68-2.61 (m, 1H), 2.45-2.40 (m, 1H), 2.22-2.1 (m, 1H), 2.09-1.95 (m, 1H).

Example 33: Synthesis of 3-(6-(4-hydroxy-3-propyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-55)



Step 1: **Synthesis of 3-propyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-one (33b)**

To a stirred solution of 1-(4-(trifluoromethyl)benzyl)piperidin-4-one (**16b**, 6.2 g, 24.1 mmol) in THF (40 mL) was added KHMDS (48.2 mL, 48.2 mmol; 1M solution in THF) dropwise at 25 °C and the resulting mixture was stirred at 25 °C for 1 h. 1-Bromopropane (8.89 g, 72.3 mmol) was then added and stirring was continued at 25 °C for 16 h. Saturated ammonium chloride solution was added and the aqueous mixture was extracted with EtOAc (2x). 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 by silica gel flash column chromatography using Biotage Isolera® on silica gel (100-200 mesh) eluting with 0-5% EtOAc in *n*-hexane to afford as 3-propyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-one (**33b**, 1.5 g, 4.72 mmol, 20% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 300.0, ^{1}H-NMR (400 MHz, $CDCl_3$): 7.62 (d, *J* = 8.00 Hz, 2H), 7.51 (d, *J* = 8.00 Hz, 2H), 3.72 (d, *J* = 13.60 Hz, 1H), 3.63 (d, *J* = 13.60 Hz, 1H), 3.03-3.00 (m, 2H), 2.57-2.50 (m, 3H), 2.45-2.40 (m, 1H), 2.29 (t, *J* = 9.60 Hz, 1H), 1.84-1.79 (m, 1H), 1.32-1.23 (m, 3H), 0.91 (t, *J* = 7.20 Hz, 3H), and 3,3-dipropyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-one (**33c**, 1.0 g, 2.84 mmol, 12% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 342.7, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.62 (d, *J* = 8.00 Hz, 2H), 7.52 (d, *J* = 8.00 Hz, 2H), 3.62 (s, 2H), 2.71 (t, *J* = 6.40 Hz, 2H), 2.49 (s, 2H), 1.83-1.78 (m, 2H), 1.49-1.41 (m, 2H), 1.49-1.41 (m, 2H), 1.39-1.05 (m, 4H), 0.90 (t, *J* = 2.40 Hz, 6H).

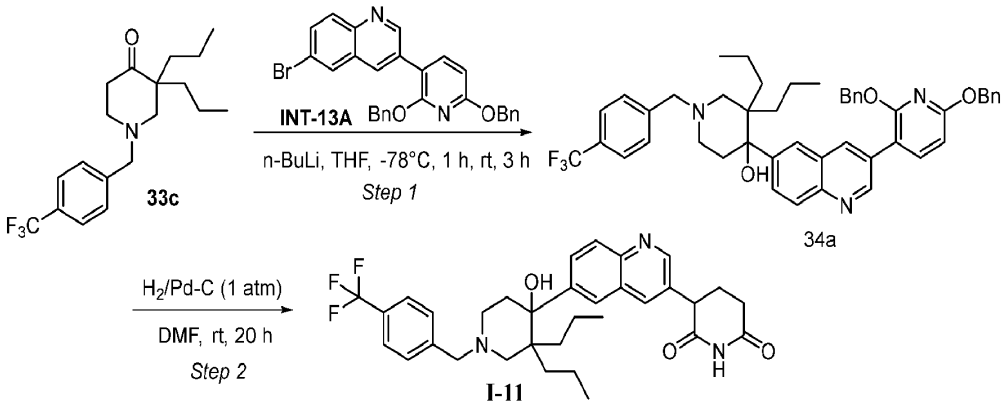
Step 2: **Synthesis of 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-propyl-1-(4-(trifluoromethyl) benzyl) piperidin-4-ol (33d)**

4-(3-(2,6-Bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-propyl-1-(4-(trifluoromethyl)-benzyl)piperidin-4-ol (**33d**) was synthesized according to **General Procedure 2, Step A** starting from 3-propyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-one (**33b**, 226mg, 1.5 eq., 0.75 mmol) and 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 250 mg, 1.0 eq., 0.5 mmol). The crude compound was purified by silica gel flash column chromatography using Biotage Isolera® (on silica gel 100-200 mesh) eluting with 0-50% EtOAc in hexanes to afford 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-propyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-ol (**33d**, 100 mg, 0.139 mmol, 28% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 718.6, ^{1}H-NMR (400 MHz, DMSO-d_6): 9.06 (s, 1H), 8.46 (s, 1H), 8.03 (s, 1H), 7.96 (d, J = 6.40 Hz, 2H), 7.72 (d, J = 8.00 Hz, 2H), 7.62 (d, J = 8.40 Hz, 2H), 7.48-7.28 (m, 11H), 6.66 (d, J = 8.00 Hz, 1H), 5.45 (m, 4H), 4.92 (s, 1H), 3.74-3.57 (m, 2H), 2.81 (m, 1H), 2.78 (m, 1H), 2.51 (m, 1H), 2.34-2.16 (m, 1H), 2.13-1.62 (m, 3H), 1.12-0.92 (m, 4H), 0.58 (t, J = 7.20 Hz, 3H).

Step 3: **Synthesis of 3-(6-(4-hydroxy-3-propyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl) piperidine-2,6-dione (I-55)**

3-(6-(4-Hydroxy-3-propyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)-piperidine-2,6-dione (**I-55**) was synthesized according to **General Procedure 2, Step B** starting from 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-propyl-1-(4-(trifluoromethyl)-benzyl)piperidin-4-ol (**33d**, 150 mg, 1.0 eq., 0.21 mmol). The crude material was purified by prep-HPLC [(Column: X select (150 x 19 mm) 5 µm, eluting with Mobile phase A: 0.1% Acetic acid in H_2O, Mobile phase B: Acetonitrile, flow rate: 15 mL/min)]. The pure product containing fractions were collected and lyophilized to afford 3-(6-(4-hydroxy-3-propyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-55**, 24.7 mg, 0.045 mmol, 22% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 540.4, ^{1}H-NMR (400 MHz, DMSO-d_6):10.97 (s, 1H), 8.75 (2, 1H), 8.20 (s, 1H), 8.02 (s, 1H), 7.99-7.95 (m, 1H), 7.86-7.83 (m, 1H), 7.72 (m, 2H), 7.62 (d, J = 8.00 Hz, 2H), 4.90 (d, J = 1.60 Hz, 1H), 4.14 (m, 1H), 3.72 (d, J = 13.60 Hz, 1H), 3.62 (d, J = 13.60 Hz, 1H), 2.81-2.78 (m, 2H), 2.68-2.60 (m, 3H), 2.51 (m, 2H), δ 2.34-2.16 (m, 1H), 2.13-1.62 (m, 3H), 1.12-0.92 (m, 4H), 0.58 (t, J = 7.20 Hz, 3H).

Example 34: Synthesis of the acetic acid salt of 3-(6-(4-hydroxy-3,3-dipropyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-11)



Step 1: **4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3,3-dipropyl-1-(4-(trifluoromethyl)-benzyl)piperidin-4-ol (34a)**

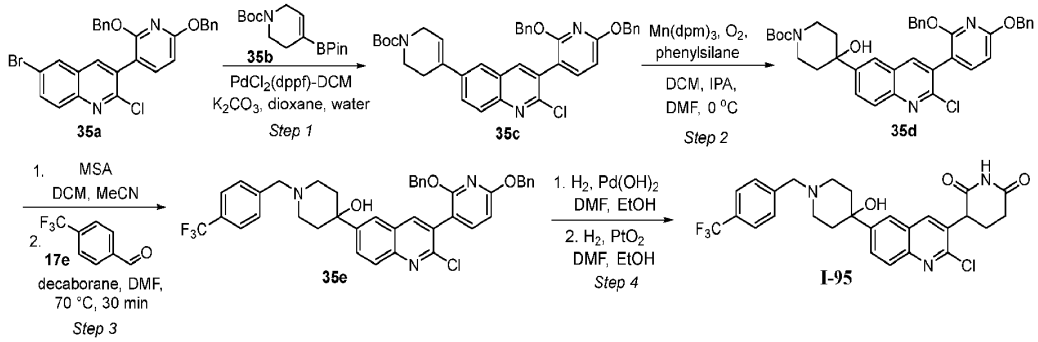
4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3,3-dipropyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-ol (**34a**) was synthesized according to **General Procedure 2, Step A** starting from 3,3-dipropyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-one (**33c**, 412 mg, 1.2 eq., 1.21 mmol) and 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 500 mg, 1.0 eq., 1.0 mmol). The crude material was purified by silica gel flash column chromatography using Biotage Isolera® (on silica gel 100-200 mesh) eluting with 0-50% EtOAc in hexanes to afford 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3,3-dipropyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-ol (**34a**, 0.23 g, 0.30 mmol, 30% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 760.5, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.05 (d, J = 2.00 Hz, 1H), 8.48 (d, J = 2.00 Hz, 1H), 8.04 (s, 1H), 7.98-7.90 (m, 3H), 7.71 (d, J = 8.00 Hz, 2H), 7.60 (t, J = 8.00 Hz, 2H), 7.49-7.38 (m, 10H), 6.66 (d, J = 8.00 Hz, 1H), 5.47 (s, 2H), 5.44 (s, 2H), 3.59-3.54 (m, 2H), 2.91-2.67 (m, 2H), 2.50-2.33 (m, 2H), 2.24-1.91 (m, 2H), 1.51-1.15 (m, 4H), 1.09-0.95 (m, 4H), 0.75-0.63 (m, 6H).

Step 2: **Synthesis of the acetic acid salt of 3-(6-(4-hydroxy-3,3-dipropyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-11)**

The acetic acid salt of 3-(6-(4-hydroxy-3,3-dipropyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-11**) was synthesized according to **General Procedure 2, Step B** starting from 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3,3-dipropyl-1-(4-(trifluoromethyl)-benzyl)piperidin-4-ol (**34a**, 220 mg, 1.0 eq., 0.29 mmol). The crude was purified by prep-HPLC [Method info: column: X select (150 x 19 mm) 5 µm, mobile phase A: 0.05% ammonium acetate in H_2O, mobile phase B: MeCN, Flow rate: 15 mL/min] and the pure fraction containing product was lyophilized to afford the acetic acid salt of 3-(6-(4-hydroxy-3,3-dipropyl-1-(4-(trifluoromethyl)benzyl) piperidin-4-yl)quinolin-3-yl)-piperidine-2,6-dione (**I-11**, 11.2 mg, 0.02 mmol, 7% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 582.39; ^{1}H-NMR (400 MHz, DMSO-d_6): 10.96 (s, 1H), 8.75 (d, J = 2.40 Hz, 1H),

8.21 (d, *J* = 1.60 Hz, 1H), 8.01-7.90 (m, 3H), 7.71 (d, *J* = 8.00 Hz, 2H), 7.58 (d, *J* = 8.00 Hz, 2H), 4.87 (s, 1H), 4.16-4.11 (m, 1H), 3.6-3.5 (m, 2H), 2.81 (m,1H), 2.75-2.7 (m, 1H), 2.68-2.6 (m, 2H), 2.5-2.45 (m, 2H), 2.4-2.3 (m, 1H), 2.2-2.1(m, 1H), 2.0-1.95 (m, 1H), 1.96 (s, 3H), 1.5-1.45 (m, 1H), 1.4-1.3 (m, 1H), 1.35-1.1 (m, 1H), 1.05-0.91 (m, 3H), 0.65-0.2 (m, 9H).

Example 35: Synthesis of 3-(2-chloro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-95)



Step 1: **Synthesis of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-2-chloroquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (35c)**

To a microwave vial equipped with a stir bar was added 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-2-chloroquinoline (**35a**, 338 mg, 0.64 mmol, 1 eq.), $PdCl_2$(dppf)•DCM (77.9 mg, 0.15 eq., 0.95 mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**35b**, 236 mg, 1.2 eq., 0.76 mmol), and 1,4-dioxane (2.54 mL, 0.25M) followed by a solution of 2M potassium carbonate (508 µL, 1.6 eq., 1.02 mmol). The resulting solution was degassed with argon before the vial was sealed and subjected to microwave irradiation for 1 h. At this point LCMS shows conversion to desired product. The solution was diluted with EtOAc and filtered through celite®. The celite® pad was washed with excess EtOAc and the filtrate was concentrated *in vacuo*. The crude material was via silica gel chromatography on a 40 g silica gel column eluting with 0 to 100% EtOAc in heptane. The desired fractions were combined and concentrated *in vacuo* to yield *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-2-chloroquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**35c**, 175 mg, 276 µmol, 43% yield). LCMS: m/z HESI, positive $[M+H]^+$ = 634.

Step 2: **Synthesis of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-2-chloroquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (35d)**

To a vial equipped with a stir bar was added *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-2-chloroquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**35c**, 180 mg, 1 eq., 0.28 mmol), dichloromethane (1.58 mL, 0.18M), propan-2-ol (1.58 mL, 0.18M) and *N,N*-dimethylformamide (526 µL, 0.54M). The resulting solution was sparged with oxygen for 5 minutes at 0 °C before phenylsilane (105

μL, 3 eq., 0.85 mmol) and $Mn(dpm)_3$ (85.8 mg, 0.14 mmol, 0.5 eq.) were added. After 24 h, the desired product was observed by LCMS and the reaction mixture was concentrated *in vacuo*. The crude residue was dissolved in 3 mL of DMSO and filtered to remove insoluble material before being purified on a 40 g C^{18} column eluting with water and 0%-100% MeCN. The desired fractions were combined and concentrated *in vacuo* to yield *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-2-chloroquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (**35d**, 51 mg, 0.078 mmol, 28% yield). LCMS: m/z HESI, positive $[M+H]^+ = 652$.

Step 3: **Synthesis of 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-2-chloroquinolin-6-yl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-ol (35e)**

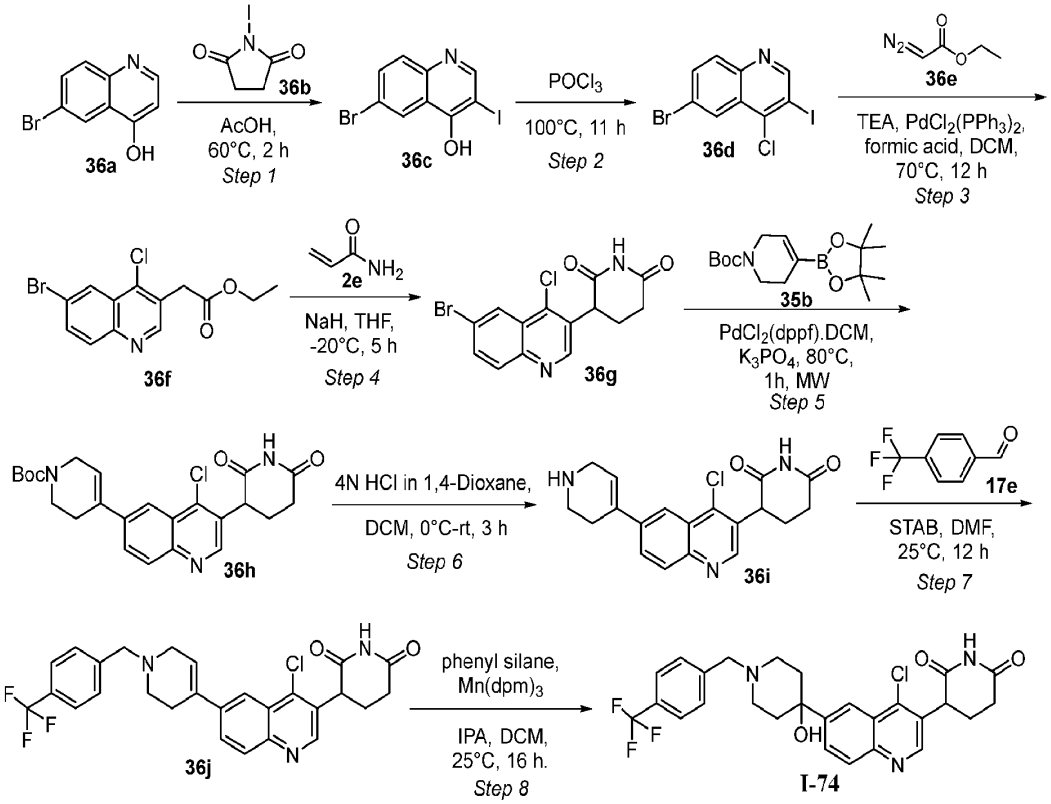
To a vial equipped with a stir bar was added *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-2-chloroquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (**35d**, 95 mg, 1 eq., 0.15 mmol) and DCM (2.4 mL, 0.06 M), followed by methanesulfonic acid (38 μL, 4 eq., 0.58 mmol) and the resulting mixture was stirred for 30 min. Upon complete consumption of starting material, as confirmed by LCMS, triethylamine (80.8 μL, 4 eq., 0.58 mmol) was added and the aqueous mixture was concentrated under reduced pressure (quantitative yield assumed). The crude residue was then suspended in ethanol (580 μL, 0.25M) and acetic acid (8.30 μL, 1 eq., 0.15 mmol) and 4-(trifluoromethyl)benzaldehyde (**17e**, 23.7 μL, 1.2 eq., 0.17 mmol) was added. The resulting mixture was heated at 45 °C for 1 h before sodium cyanoborohydride (18.2 mg, 2 eq., 0.290 μmol) was added in one portion. The reaction was monitored by LCMS. Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was cooled to ambient temperature and loaded directly onto a C^{18} column for purification 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 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-2-chloroquinolin-6-yl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-ol (**35e**, 57.8 mg, 0.084 mmol, 56% yield). LCMS: m/z HESI, positive $[M+H]^+ = 710$.

Step 4: **Synthesis of 3-(2-chloro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-95)**

To a reaction vial equipped with a stir bar was added 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-2-chloroquinolin-6-yl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-ol (**35e**, (50.0 mg, 1 eq., 0.071 μmol) and 4:1 DMF:EtOH (1.75 mL, 0.04M). and the resulting mixture was sparged thoroughly with argon. Dihydroxypalladium (20% wt, 0.2 eq.) was then added and a balloon of hydrogen was placed on the vial. The reaction solution was sparged with hydrogen continuously for 2 h. Upon complete debenzylation, as confirmed by LCMS, the reaction mixture was filtered through a pad of celite® and the filtrate was concentrated *in vacuo*. The crude material was then dissolved in 4:1 DMF:EtOH (0.94 mL, 0.04M) and the resulting mixture was sparged thoroughly with argon. Platinum(IV) Oxide (0.2 eq.) was added and a

balloon of hydrogen was placed on the vial. The reaction solution was sparged with hydrogen continuously. Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was filtered through a pad of celite®, the filter cake was washed with EtOAc, and the filtrate was concentrated *in vacuo*. The crude material was purified on a C^{18} column eluting with water 0.1% formic acid and 0 to 50% MeCN with 0.1% formic acid The desired fractions were collected, combined, and 1M HCl was added and concentrated via lyophilization to yield 3-(2-chloro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-95**, 1.7 mg, 0.003 mmol, 5% yield) was isolated as an amorphous solid. LCMS: m/z HESI, positive $[M+H]^+ = 532$.

Example 36: Synthesis of 3-(4-chloro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-74)



Step 1: **Synthesis of 6-bromo-3-iodoquinolin-4-ol (36c)**

To a stirred solution of 6-bromoquinolin-4-ol (**36a**, 5 g, 22.32 mmol) in acetic acid (120 mL) was added 1-iodopyrrolidine-2,5-dione (**36b**, 5.02 g, 22.32 mmol) at room temperature and the resulting mixture was stirred at 60 °C for 2 h. The reaction mixture was then concentrated under reduced. The crude product was purified by silica gel flash column chromatography using a Biotage Isolera® on a silica gel (100-200 mesh) cartridge (40 g) eluting with EtOAc in *n*-hexane (70%). The pure product containing fractions were collected and concentrated under reduced pressure to afford 6-bromo-3-

iodoquinolin-4-ol (**36c**, 6.5 g, 16.72 mmol, 75% yield). LCMS: m/z MM-ES+APCI, Positive [M+H, M+2+H]$^+$ 349.8, 351.7. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.36 (s, 1H), 8.56 (s, 1H), 8.19 (d, J = 2.40 Hz, 1H), 7.84 (dd, J = 2.40, 8.80 Hz, 1H), 7.57 (d, J = 8.80 Hz, 1H).

Step 2: **Synthesis of 6-bromo-4-chloro-3-iodoquinoline (36d)**

A solution of 6-bromo-3-iodoquinolin-4-ol (**36c**,10 g, 28.6 mmol) in $POCl_3$ (4.38 g, 28.6 mmol) was stirred at 100 °C for 11 h. The reaction mixture was then cooled to room temperature and slowly poured into ice-cooled water. A solid precipitated which was filtered and washed with ice-cold water (2 x 10 mL) followed by hexane (2 x 10 mL) to afford 6-bromo-4-chloro-3-iodoquinoline (**36d**, 9 g, 23.45 mmol, 82% yield). The product was carried onto the next step without further purification. LCMS: m/z MM-ES+APCI, [M+H, M+2+H]$^+$ 369.6, 371.6. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.21 (s, 1H), 8.38 (s, 1H), 8.02 (d, J = 1.20 Hz, 2H).

Step 3: **Synthesis of ethyl 2-(6-bromo-4-chloroquinolin-3-yl)acetate (36f)**

To the stirred solution of triethylamine (2.75 g, 27.10 mmol) in MeCN (30 mL) was added formic acid (0.75 g, 16.29 mmol) followed by ethyl 2-diazoacetate (**36e**, 3.10 g, 27.1 mmol) at room temperature and the resulting mixture was degassed with nitrogen for 10 min. To this solution was added 6-bromo-4-chloro-3-iodoquinoline (**36d**, 4 g, 10.86 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.381 g, 0.54 mmol) at room temperature and the reaction mixture was degassed again with nitrogen for 10 min. The resulting mixture was stirred at 70 °C for 12 h and then was concentrated under reduced pressure. The crude compound was purified by silica gel flash column chromatography using a Biotage Isolera® on a silica gel (100-200 mesh) cartridge (80 g) eluting with EtOAc in *n*-hexane (70%). The pure product containing fractions were collected and concentrated under reduced pressure to afford ethyl 2-(6-bromo-4-chloroquinolin-3-yl)acetate (**36f**, 1.2 g, 2.48 mmol, 23% yield). LCMS: m/z MM-ES+APCI, Positive [M+H, M+2+H]$^+$ 327.9, 329.9, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.80 (s, 1H), 8.44 (d, J = 2.00 Hz, 1H), 8.00 (d, J = 8.80 Hz, 1H), 7.86-7.83 (m, 1H), 4.26-4.09 (m, 2H), 4.01 (s, 2H), 1.33-1.27 (m, 3H).

Step 4: **3-(6-bromo-4-chloroquinolin-3-yl)piperidine-2,6-dione (36g)**

To the stirred solution of sodium hydride (60% in mineral oil) (91 mg, 2.28 mmol) in THF (10 mL) was added ethyl 2-(6-bromo-4-chloroquinolin-3-yl)acetate (**36f**, 500 mg, 1.52 mmol) and acrylamide (**2e**, 108 mg, 1.52 mmol) at -20 °C and the resulting mixture was stirred at -20 °C for 5 h. 1N HCl aqueous solution was added to quench the reaction and the resulting aqueous mixture was extracted with EtOAc (2 x10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude compound was purified by flash column chromatography using Combi-Flash silica gel (100-200 mesh size) eluting with 70-80% of EtOAc in hexane to afford 3-(6-bromo-4-chloroquinolin-3-yl)piperidine-2,6-dione (**36g**, 380 mg, 1.06 mmol, 70% yield). LCMS: m/z

MM-ES+APCI, Positive $[M+H, M+2+H]^+$ 352.9, 354.9. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.06 (s, 1H), 8.91 (s, 1H), 8.40 (d, J = 2.00 Hz, 1H), 8.07-8.01 (m, 2H), 4.57 (dd, J = 5.20, 13.00 Hz, 1H), 2.93-2.84 (m, 1H), 2.68-2.57 (m, 1H), 2.51-2.50 (m, 1H), 2.11-2.08 (m, 1H).

Step 5: **Synthesis of *tert*-butyl 4-(4-chloro-3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (36h)**

tert-Butyl 4-(4-chloro-3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**36h**) was synthesized according to **General procedure 4** starting from 3-(6-bromo-4-chloroquinolin-3-yl)piperidine-2,6-dione (**36g**, 190 mg, 1.0 eq., 0.54 mmol) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**35b**, 166 mg, 1.0 eq., 0.54 mmol). The crude compound was purified by flash column chromatography using Combi-Flash silica gel (100-200 mesh size) eluting with 70-80% of EtOAc in hexane to afford *tert*-butyl 4-(4-chloro-3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**36h**, 350 mg, 0.44 mmol, 83% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 456.2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.06 (s, 1H), 8.80 (s, 1H), 8.13-8.03 (m, 3H), 6.52-6.49 (m, 1H), 4.57-4.52 (m, 1H), 4.09 (s, 2H), 3.63-3.60 (m, 2H), 2.93-2.83 (m, 1H), 2.68-2.60 (m, 3H), 2.51-2.50 (m, 1H), 2.10-2.07 (m, 1H), 1.45 (s, 9H).

Step 6: **Synthesis of 3-(4-chloro-6-(1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)piperidine-2,6-dione (36i)**

To a stirred solution of *tert*-butyl 4-(4-chloro-3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**36h**, 350 mg, 0.77 mmol) in DCM (10 mL) was added 4M HCl in 1,4-dioxane (4 mL, 0.77 mmol) at 0 °C and the resulting mixture was stirred at 25 °C for 3 h. The reaction mixture was then concentrated under reduced pressure at room temperature and the crude material was washed with *n*-hexane and dried to afford 3-(4-chloro-6-(1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**36i**, 150 mg, 0.39 mmol, 50% yield). The product was carried onto the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 356.1, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.07 (s, 1H), 9.20 (br s, 2H), 8.85 (s, 1H), 8.13-8.04 (m, 3H), 6.53 (s, 1H), 4.57 (dd, J = 4.80, 12.80 Hz, 1H), 3.85 (s, 2H), 3.39 (s, 2H), 2.92-2.87 (m, 3H), 2.68-2.60 (m, 2H), 2.11-2.08 (m, 1H).

Step 7: **Synthesis of 3-(4-chloro-6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)piperidine-2,6-dione (36j)**

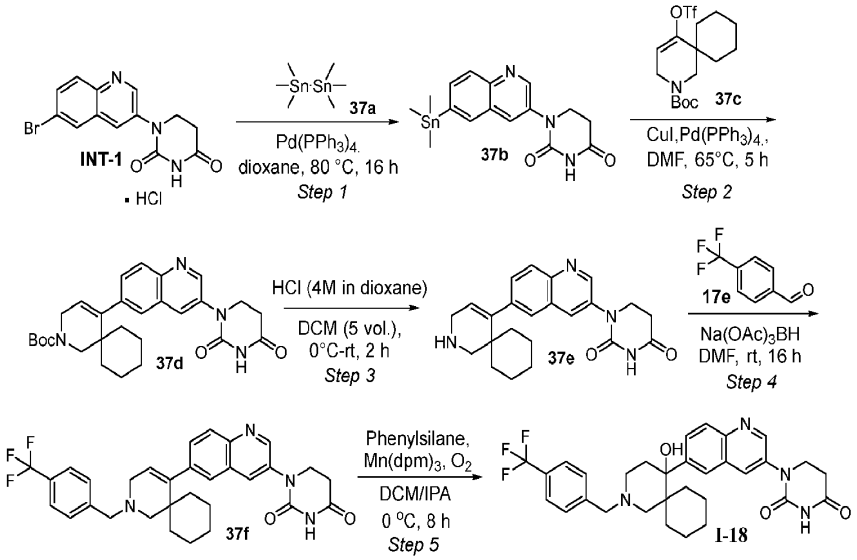
To a stirred solution of 3-(4-chloro-6-(1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**36i**, 120 mg, 0.34 mmol) in DMF (2 mL) was added 4-(trifluoromethyl)benzaldehyde (**17e**, 0.073 mL, 0.51 mmol) at 25 °C and the resulting mixture was stirred for 1 h at 25 °C. Sodium triacetoxyborohydride (179 mg, 0.84 mmol) was then added at 25 °C and stirring was continued at 25 °C for 12 h. The reaction mixture was concentrated under reduced pressure at room temperature. The crude compound was purified by flash column chromatography using Combi-Flash (neutral Alumina) eluting

with 4-7% of IPA/DCM to afford 3-(4-chloro-6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**36j**, 120 mg, 0.22 mmol, 65% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 514.1, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.06 (s, 1H), 8.79 (s, 1H), 8.08-7.96 (m, 3H), 7.72 (d, J = 8.00 Hz, 2H), 7.62 (d, J = 8.00 Hz, 2H), 6.52 (d, J = 12.00 Hz, 1H), 4.54 (dd, J = 5.20, 12.80 Hz, 1H), 3.74 (s, 2H), 3.20-3.19 (m, 2H), 2.90-2.88 (m, 2H), 2.77-2.74 (m, 2H), 2.68-2.50 (m, 3H), 2.10-2.09 (m, 1H).

Step 8: **Synthesis of 3-(4-chloro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-74)**

3-(4-Chloro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-74**) was synthesized according to **General Procedure 3, Step C** starting from 3-(4-chloro-6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**36j**, 110 mg, 1.0 eq., 0.21 mmol). The crude compound was purified by preparative-HPLC [(Column: ZORBAX (150*21) 2.5 µm, eluting with Mobile phase A: 0.1% NH_4OAc in H_2O, Mobile phase B: Acetonitrile, flow rate: 15 mL/min)]. The pure product containing fractions were collected and lyophilized to afford 3-(4-chloro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-74**, 31 mg, 0.06 mmol). To a solution of 3-(4-chloro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (30 mg) in water (0.4 mL) and ACN (0.4 mL) was added 0.5 N aq. HCl (1 mL) solution and this resulting mixture was lyophilized to afford the ide salt of 3-(4-chloro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl (**I-74**, 31 mg, 0.053 mmol, 25% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 532.4. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.05 (s, 1H), 10.27 (s, 1H), 8.85 (d, J = 9.60 Hz, 1H), 8.33 (d, J = 1.60 Hz, 1H), 8.13 (d, J = 8.80 Hz, 1H), 7.95-7.88 (m, 5H), 5.89 (s, 1H), 4.56-4.53 (m, 3H), 3.40-3.35 (m, 4H), 2.91-2.84 (m, 1H), 2.61-2.46 (m, 4H), 2.12-2.07 (m, 1H), 1.93-1.76 (m, 2H).

Example 37: Synthesis of 1-(6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-18)



Step 1: **Synthesis of 1-(6-(trimethylstannyl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (37b)**

A solution of 1-(6-bromoquinolin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione, HCl (**INT-1**, 500 mg, 1.40 mmol) and hexamethyl ditin (**37a**, 92 mg, 0.28 mmol) in 1,4-dioxane (5 mL) was sparged with nitrogen for 10 min. Tetrakis(triphenylphosphine)palladium(0) (162 mg, 0.14 mmol) was then added in one portion, and the resulting mixture was stirred at 80 °C for 16 h. The reaction mixture was cooled to room temperature, water (40 mL) was added and the resulting aqueous mixture was extracted with EtOAc (40 mL x 2). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was triturated with MTBE (10 mL x 2) and the resulting solid was filtered and dried under reduced pressure to afford 1-(6-(trimethylstannyl) quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**37b**, 500 mg, 0.84 mmol, 60% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 405.9. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.58 (s, 1H), 8.92 (d, J = 2.40 Hz, 1H), 8.22 (d, J = 2.00 Hz, 1H), 8.09 (s, 1H), 7.97 (d, J = 8.40 Hz, 1H), 7.86-7.82 (m, 1H), 3.97 (t, J = 6.40 Hz, 2H), 2.80 (t, J = 6.40 Hz, 2H), 0.36 (s, 9H).

Step 2: **Synthesis of *tert*-butyl 5-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl) quinolin-6-yl)-2-azaspiro [5.5]undec-4-ene-2-carboxylate (37d)**

To the stirred solution of 1-(6-(trimethylstannyl) quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**37b**, 500 mg, 1.24 mmol) and *tert*-butyl 5-(((trifluoromethyl)sulfonyl)oxy)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (**37c**, 494 mg, 1.24 mmol) in 1,4-dioxane (10 mL) in a vial under an atmosphere of nitrogen was added copper(I) iodide (47.1 mg, 0.25 mmol) at room temperature. The resulting mixture was sparged with nitrogen for 10 min, tetrakis(triphenylphosphine)palladium(0) (286 mg, 0.25 mmol) was then added and stirring was continued at 65 °C for 5 h. The reaction mixture was cooled to room temperature, filtered through a pad of celite®, and the filtrate was concentrated under reduced pressure.

The crude material was purified by silica gel flash column chromatography using Biotage Isolera® (on silica gel 100-200 mesh) eluting with 50-100% EtOAc in hexanes to afford *tert*-butyl 5-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl) quinolin-6-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (**37d**, 300 mg, 0.33 mmol, 27% yield). LCMS: m/z MM-ES+APCI, Negative $[M-H]^-$ 489.5, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.59 (s, 1H), 8.91 (d, *J* = 2.40 Hz, 1H), 8.25 (d, *J* = 2.00 Hz, 1H), 7.95 (d, *J* = 8.40 Hz, 1H), 7.70 (s, 1H), 7.41 (s, 1H), 5.58-5.53 (m, 1H), 4.06-3.94 (m, 4H), 3.61-3.57 (m, 2H), 2.80 (t, *J* = 6.40 Hz, 2H), 1.60-1.31 (m, 19H).

Step 3: **1-(6-(2-azaspiro [5.5] undec-4-en-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (37e)**

(1-(6-(2-Azaspiro [5.5]undec-4-en-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl (**37e**, 220 mg, 0.29 mmol, 47% yield) was synthesized according to **General Procedure 6, Step A** starting from *tert*-butyl 5-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl) quinolin-6-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (**37d**, 300 mg, 1.0 eq., 0.61 mmol). The product was taken onto the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 391.5; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.64 (s, 1H), 9.29 (s, 1H), 9.02 (d, *J* = 2.40 Hz, 1H), 8.42 (s, 1H), 8.06 (d, *J* = 8.80 Hz, 1H), 7.84-7.73 (m, 2H), 7.54 (d, *J* = 8.80 Hz, 1H), 5.58 (t, *J* = 3.20 Hz 1H), 4.02-3.95 (m, 2H), 3.69 (s, 1H), 3.57 (s, 2H), 3.38 (s, 1H), 2.81 (t, *J* = 6.40 Hz, 2H), 1.83-1.36 (s, 10H).

Step 4: **1-(6-(2-(4-(trifluoromethyl) benzyl)-2-azaspiro [5.5]undec-4-en-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (37f)**

1-(6-(2-(4-(Trifluoromethyl) benzyl)-2-azaspiro [5.5]undec-4-en-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**37f**) was synthesized according to **General Procedure 6, Step B** starting from (1-(6-(2-azaspiro [5.5]undec-4-en-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl (**37e**, 200 mg, 1.0 eq., 0.51 mmol) and 4-(trifluoromethyl)benzaldehyde (**17e**, 107 mg, 1.2 eq., 0.62 mmol). The crude compound was purified by silica gel flash column chromatography using Biotage Isolera® on silica gel (100-200 mesh) eluting with 50-70% EtOAc in *n*-hexane as an eluent to afford 1-(6-(2-(4-(trifluoromethyl) benzyl)-2-azaspiro [5.5]undec-4-en-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**37f**, 120 mg, 0.12 mmol, 24% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 549.6; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.58 (s, 1H), 8.90 (s, 1H), 8.26-8.24 (m, 1H), 8.02-7.93 (m, 1H), 7.77-7.48 (m, 6H), 5.52 (t, *J* = 3.20 Hz, 1H), 4.00-3.94 (m, 2H), 3.74 (s, 2H), 3.11 (d, *J* = 2.80 Hz, 2H), 2.80 (t, *J* = 6.40 Hz, 2H), 2.59 (s, 2H), 1.74 (d, *J* = 12.00 Hz, 2H), 1.56-1.32 (m, 5H), 1.16-1.05 (m, 2H), 0.91-0.79 (m, 1H).

Step 5: **Synthesis of 1-(6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-18)**

The acetic acid salt of 1-(6-(5-hydroxy-2-(4-(trifluoromethyl) benzyl)-2-azaspiro[5.5]-undecan-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-18**) was synthesized according to **General Procedure 3, Step C** starting from 1-(6-(2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**37f**, 120 mg, 1.0 eq., 0.22 mmol). The crude material was purified by preparative-HPLC [(Column: X select (C^{18} 150mm *19) 5 µm, eluting with Mobile phase A: 0.05% acetic acid in H_2O, Mobile phase B: Acetonitrile, flow rate: 15 mL/min for 30 minutes)]. The pure product containing fractions were collected and lyophilized to afford the acetic acid salt of 1-(6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro [5.5]undecan-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-18**, 5.5 mg, 9.68 µmol, 6% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 567.3; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.51 (s, 1H), 8.89 (d, *J* = 2.40 Hz, 1H), 8.27 (d, *J* = 2.40 Hz, 1H), 8.00-7.88 (m, 3H), 7.72 (d, *J* = 8.00 Hz, 2H), 7.61 (d, *J* = 8.00 Hz, 2H), 4.83 (s, 1H), 3.97 (t, *J* = 6.40 Hz, 2H), 3.67 (d, *J* = 14.00 Hz, 1H), 3.59 (d, *J* = 14.00 Hz, 1H), 2.88-2.80 (m, 5H), 2.78-2.62 (m, 1H), 2.51-2.50 (m, 1H), 2.34-2.29 (m, 1H), 1.74 (t, *J* = 12.00 Hz, 1H), 1.51 (t, *J* = 12.00 Hz, 1H), 1.26-1.33 (m, 3H), 1.05-1.24 (m, 2H), 1.02-0.90 (m, 1H), 0.89-0.68 (m, 2H).

Step 6: **Synthesis of tert-butyl 5-oxo-2-azaspiro[5.5]undecane-2-carboxylate (37g)**

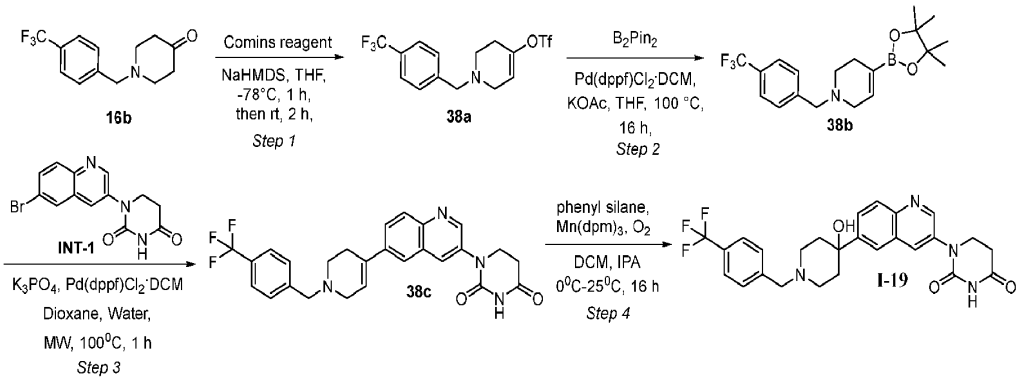
To a stirred solution of tert-butyl 4-oxopiperidine-1-carboxylate (**18a**, 20 g, 100 mmol) in Toluene (200 mL) was added potassium tert-butoxide (22.53 g, 201 mmol) at 25 °C under nitrogen atmosphere and stirred for 1 h. To this resulting mixture was added 1,5-dibromopentane (34.5 g, 151 mmol) at 25 °C, and the reaction mixture was stirred at 100 °C for 12 h. The reaction mixture was cooled, quenched with ice-cold water, and extracted with (3 x 200 mL). The combined organic layer was dried over anhydrous Na_2SO_4 filtered, and evaporated under reduced pressure to get a crude compound. The crude residue was purified by silica gel flash column chromatography, eluting with 0-4% EtOAc in hexanes to afford tert-butyl 5-oxo-2-azaspiro[5.5]undecane-2-carboxylate (11.1 g, 37.4 mmol, 37% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H-56]^+$ 212.1, ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.72 (s, 3H), 3.55 (s, 3H), 2.49 (t, *J*= 6.4 Hz, 2H), 1.78-1.71 (m, 2H), 1.59-1.42 (s, 17H).

Step 7: **Synthesis of tert-butyl 5-(((trifluoromethyl)sulfonyl)oxy)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (37c)**

To a stirred solution of tert-butyl 5-oxo-2-azaspiro[5.5]undecane-2-carboxylate (10 g, 37.4 mmol) in THF (50 mL) was added NaHMDS (1.0 M in THF) (44.9 ml, 44.9 mmol) dropwise at -78 °C and the reaction mixture was stirred at the same temperature for 30 minutes. To this resulting solution was added N-(5-Chloropyridin-2-yl)-N-(methanesulfonyl)-methanesulfonamide (21.99 g, 56.1 mmol) dissolved in THF (40 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 (350 mL x 2). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated to

dryness to obtain the crude. This crude material was purified by silica gel flash column chromatography, eluting with 0-12% EtOAc in hexanes to afford tert-butyl 5-(((trifluoromethyl)sulfonyl)oxy)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (9 g, 22.53 mmol, 60% yield). LCMS: m/z MM-ES+APCI, Negative $[M-H]^-$ 398.1, ^{1}H-NMR (400 MHz, DMSO-d6): δ 5.89-5.85 (m, 1H), 4.05-4.01 (m, 2H), 3.57 (s, 2H), 1.69-1.58 (m, 3H), 1.52-1.42 (m, 15H), 1.12-1.09 (m, 1H).

Example 38: Synthesis of 1-(6-(4-hydroxy-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-19)



Step 1: **Synthesis of 1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (38a)**

To a stirred solution of 1-(4-(trifluoromethyl)benzyl)piperidin-4-one (**16b**, 1 g, 3.89 mmol) in THF (20 ml) was added NaHMDS (1 M in THF) (7.77 ml, 7.77 mmol) at -78 °C under an atmosphere of nitrogen and the resulting mixture was stirred for 1 h. 1,1,1-Trifluoro-N-(pyridin-2-yl)-N-((trifluoromethyl)sulfonyl)methanesulfonamide (2.089 g, 5.83 mmol) dissolved in THF (5 mL) was then added dropwise at -78 °C and stirring was continued at room temperature for 3 h. Saturated ammonium chloride solution was added and the resulting aqueous mixture was extracted with EtOAc (100 mL x 2). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. This crude material was purified by silica gel flash column chromatography using Biotage Isolera® (silica gel 100-200 mesh) eluting with 0-100% EtOAc in hexanes to afford 1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (**38a**, 0.9 g, 2.31 mmol, 60% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 389.9; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.72 (d, J = 8.00 Hz, 2H), 7.55 (d, J = 8.00 Hz, 2H), 5.96 (t, J = 3.00 Hz, 1H), 3.76 (s, 2H), 3.14 (t, J = 3.00 Hz, 2H), 2.74 (t, J = 5.60 Hz, 2H), 2.44 (t, J = 5.60 Hz, 2H).

Step 2: **Synthesis of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(4-(trifluoromethyl)-benzyl)-1,2,3,6-tetrahydropyridine**

A solution of 1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate, (**38a**, 0.2 g, 0.51 mmol), bis(pinacolato)diboron (0.196 g, 0.77 mmol) and

potassium acetate (0.151 g, 1.54 mmol) in 1, 4-dioxane (10 mL) was degassed with nitrogen at 25 °C for 10 min. $Pd(dppf)Cl_2$•DCM (0.021 g, 0.03 mmol) was then added in one portion, and the resulting mixture was stirred at 100 °C for 16 h. The reaction mixture was concentrated under reduced pressure and the crude material was purified by silica gel flash column chromatography using Biotage Isolera® (on silica gel 100-200 mesh) eluting with 0-100% EtOAc in hexanes to afford 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridine (**38b**, 0.1 g, 0.20 mmol, 39% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 368.0; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.68 (d, J = 8.00 Hz, 2H), 7.54 (d, J = 8.00 Hz, 2H), 6.38 (br s, 1H), 3.62 (s, 2H), 2.98-2.94 (m, 2H), 2.49-2.45 (m, 2H), 2.14-2.10 (m, 2H), 1.17 (s, 12H).

Step 3: **Synthesis 1-(6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (38c)**

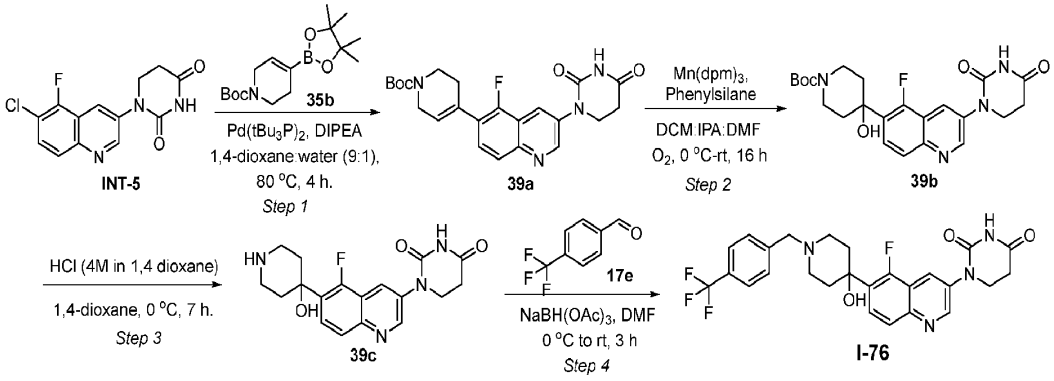
1-(6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**38c**) was synthesized according to **General Procedure 4** starting from 1-(6-bromoquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**INT-1**, 400 mg, 1.0 eq., 1.25 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(4-(trifluoromethyl)-benzyl)-1,2,3,6-tetrahydropyridine (**38b**, 551 mg, 1.2 eq., 1.5 mmol). The crude compound was purified by reverse phase column chromatography eluting with 0-100% MeCN in 0.1% FA in water. The product containing fractions were collected and lyophilized to afford of 1-(6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**38c**, 0.12 g, 0.22 mmol, 18% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 481.7; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.59 (s, 1H), 8.88 (d, J = 2.40 Hz, 1H), 8.21 (t, J = 2.40 Hz, 1H), 7.96-7.92 (m, 3H), 7.72 (d, J = 8.00 Hz, 2H), 7.62 (d, J = 8.00 Hz, 2H), 6.43 (s, 1H), 3.97 (t, J = 13.20 Hz, 2H), 3.74 (s, 2H), 3.18 (s, 2H), 2.80 (t, J = 13.20 Hz, 2H), 2.73 (d, J = 4.80 Hz, 2H), 2.66-2.62 (m, 2H).

Step 4: **Synthesis of 1-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-19)**

1-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-19**) was synthesized according to **General Procedure 3, Step C** starting from 1-(6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**38c,** 200mg, 1.0 eq., 0.42 mmol). The crude material was purified by silica gel flash column chromatography using Biotage Isolera® (on silica gel 100-200 mesh) eluting with 0-10% IPA in DCM followed by preparative-HPLC [(Column: X-SELECT CSH C18 (150 mm, 19 mm, 5µm), eluting with Mobile phase A: 0.05 N HCl in water, Mobile phase B: Acetonitrile, flow rate: 15 mL/min, Rt: 9.65 min)]. The product containing fractions were collected and lyophilized to afford 1-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-19**, 29 mg,

0.05 mmol, 15% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 499.1, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.07 (s, 1H), 10.60 (s, 1H), 8.98 (d, *J* = 2.00 Hz, 1H), 8.37 (s, 1H), 8.10-8.05 (m, 2H), 7.96-7.86 (m, 5H), 5.74 (br s, 1H), 4.53 (d, *J* = 4.80 Hz, 2H), 3.94 (t, *J* = 6.40 Hz, 2H), 3.41-3.37 (m, 4H), 2.80 (t, *J* = 6.40 Hz, 2H), 2.51-2.29 (m, 2H), 1.91 (d, *J* = 13.60 Hz, 2H).

Example 39: Synthesis of 1-(5-fluoro-6-(4-hydroxy-1-(4-(trifluoro-methyl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-76)



Step 1: ***tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (39a)**

tert-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**39a**) was synthesized according to **General Procedure 5** starting from 1-(6-chloro-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**INT-5** 300 mg, 1.0 eq., 1.02 mmol) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**35b**, 316 mg, 1.0 eq., 1.02 mmol). The crude material was purified by silica gel flash column chromatography using Biotage Isolera® on silica gel (100-200 mesh) eluting with 0 to 78% EtOAc in *n*-hexane to afford *tert*-butyl 4-(3-(2,4-dioxotetrahydro-pyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**39a**, 250 mg, 0.53 mmol, 52% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 441.1; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.63 (s, 1H), 8.98 (s, 1H), 8.31 (s, 1H), 7.87-7.85 (m, 1H), 7.76-7.71 (m, 1H), 6.18 (s, 1H), 4.10-3.99 (m, 4H), 3.59 (t, *J* = 5.20 Hz, 2H), 2.81 (t, *J* = 6.60 Hz, 2H), 2.57-2.50 (m, 2H), 1.45 (s, 9H).

Step 2: ***tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (39b)**

tert-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (**39b**) was synthesized according to **General Procedure 3, Step C** starting from *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**39a**, 220 mg, 1.0 eq., 0.5 mmol). The crude material was purified by silica gel flash column chromatography using Biotage Isolera® on silica gel (100-200 mesh) eluting with

0 to 100% EtOAc in *n*-hexane to afford *tert*-butyl 4-(3-(2,4-dioxo-tetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (**39b**, 40 mg, 0.07 mmol, 14% yield). LCMS: m/z MM-ES+APCI, Positive[M+H]$^+$ 459.5.

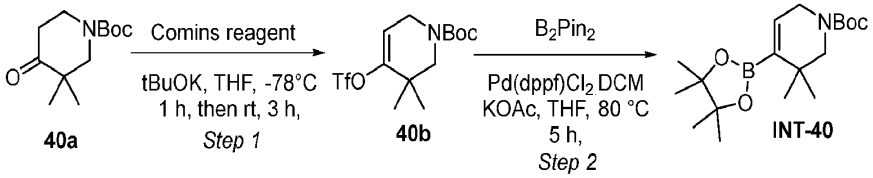
Step 3: **1-(5-fluoro-6-(4-hydroxypiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (39c)**

1-(5-fluoro-6-(4-hydroxypiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**39c**, 20 mg, 0.031 mmol, 36% yield) was synthesized according to **General Procedure 6, Step A** starting from *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (**39b**, 40 mg, 1.0 eq., 0.09 mmol). LCMS: m/z MM-ES+APCI, Positive [M+H]$^+$ = 359.2; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.65 (s, 1H), 8.99 (d, *J* = 6.00 Hz, 1H), 8.34 (s, 1H), 8.05-8.01 (m, 1H), 7.95 (d, *J* = 9.20 Hz, 2H), 4.05-4.01 (m, 4H), 3.39 (m, 3H), 2.82 (t, *J* = 6.40 Hz, 2H), 1.90 (d, *J* = 12.80 Hz, 2H), 1.29 (d, *J* = 12.40 Hz, 2H).

Step 4: **Synthesis of 1-(5-fluoro-6-(4-hydroxy-1-(4-(trifluoro-methyl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-76)**

1-(5-fluoro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-76**) was synthesized according to **General Procedure 6, Step B** starting from 1-(5-fluoro-6-(4-hydroxypiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**39c**, 20 mg, 1.0 eq., 0.056 mmol) and 4-(trifluoromethyl)benzaldehyde (**17e**, 9.72 mg, 1.0 eq., 0.056 mmol). The crude material was purified by preparative-HPLC [X SELECT C18 (19*250MM) eluting with Mobile phase A: 0.5 HCl in water, Mobile phase B: Acetonitrile, flow rate: 15 mL/min), Rt: 10.8]. The product containing fractions were collected and lyophilized to afford 1-(5-fluoro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, (**I-76**, 4.4 mg, 7.91 µmol, 15% yield). LCMS: m/z MM-ES+APCI, Positive [M+H]$^+$ = 517.5; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.63 (s, 1H), 10.38 (w, 1H), 8.99 (d, *J* = 2.4 Hz, 1H), 8.33 (d, *J* = 2.0 Hz, 1H), 8.04-7.89 (m, 6H), 6.12 (br s, 1H), 4.53 (d, *J* = 5.20 Hz, 2H), 4.01 (t, *J* = 6.80 Hz, 2H), 3.44-3.37 (m, 4H), 2.81 (t, *J* = 6.80 Hz, 2H), 2.68-2.63 (m, 2H), 1.96 (d, *J* = 13.20 Hz, 2H).

Example 40: Synthesis of *tert*-butyl 3,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (INT-40)



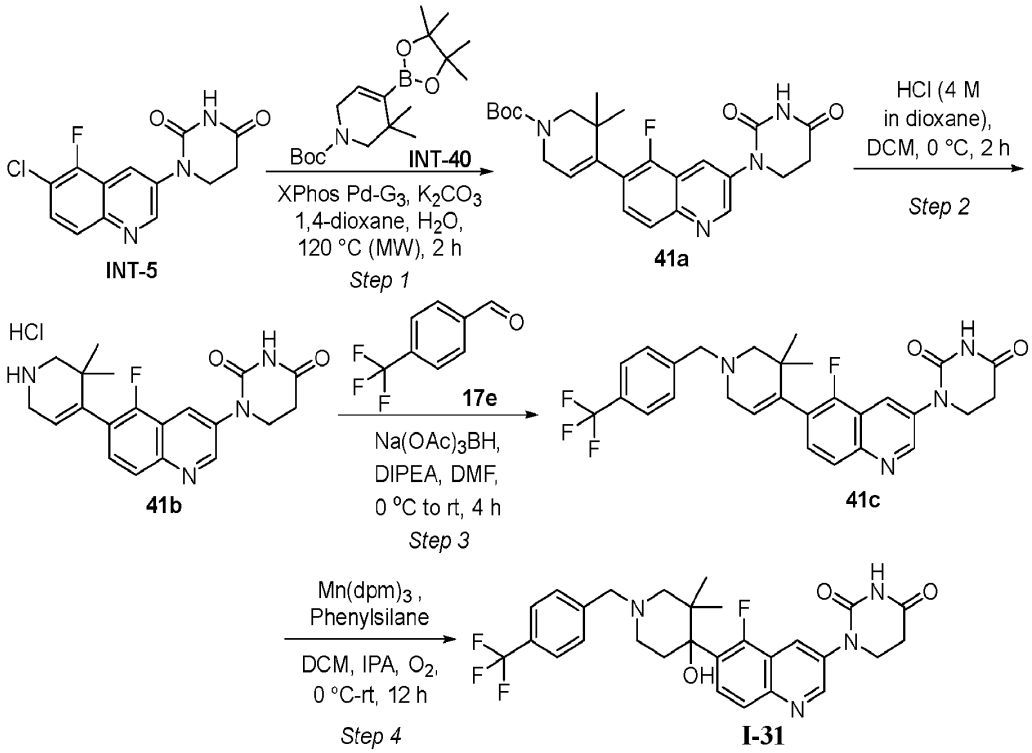
Step 1: **Synthesis of *tert*-butyl 3,3-dimethyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (40b)**

To a stirred solution of *tert*-butyl 3,3-dimethyl-4-oxopiperidine-1-carboxylate (**40a**, 10 g, 44.0 mmol) in THF (120 mL) was added potassium *tert*-butoxide (1M in THF) (52.8 mL, 52.8 mmol) dropwise at -78 °C and the resulting mixture was stirred at same temperature for 1 h. N-(5-chloropyridin-2-yl)-1,1,1-trifluoro-N-((trifluoromethyl)sulfonyl)methanesulfonamide (20.73 g, 52.8 mmol) dissolved in THF (40 mL) was then added drop wise at -78 °C and stirring was continued at room temperature for 3 h. Saturated ammonium chloride solution was added and the resulting aqueous mixture was extracted with EtOAc (350 mL x 2). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness under reduced pressure. This crude material was purified by silica gel flash column chromatography using Biotage Isolera® (on silica gel 100-200 mesh) eluting with 0-2.5% EtOAc in hexanes to afford *tert*-butyl 3,3-dimethyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (**40b**, 10 g, 22.75 mmol, 64% yield). LCMS: m/z MM-ES+APCI, Negative $[M-H]^-$ 358.0, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 5.67 (s, 1H), 4.10 (s, 2H), 3.40 (s, 2H), 1.50 (s, 9H), 1.17 (s, 6H).

Step 2: **Synthesis of *tert*-butyl 3,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (INT-40)**

A solution of *tert*-butyl 3,3-dimethyl-4 ((trifluoromethyl)sulfonyl) oxy)-3,6-dihydropyridine-1(2H)-carboxylate (5 g, 13.91 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (**40b**, 4.24 g, 16.70 mmol) and potassium acetate (2.048 g, 20.87 mmol) in THF (50 mL) was degassed with nitrogen at 25 °C for 10 min. Pd(dppf)Cl_2.DCM (1.136 g, 1.391 mmol) was then in one portion and the resulting mixture was stirred at 80 °C for 5 h. The reaction mixture was concentrated under reduced pressure and the crude material was purified by silica gel flash column chromatography using Biotage Isolera® (on silica gel 100-200 mesh) eluting with 0-10% EtOAc in hexanes to afford *tert*-butyl 3,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**INT-40**, 2 g, 5.93 mmol, 43% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ Not ionized; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.38-6.31 (m, 1H), 3.95 (s, 2H), 3.18 (s, 2H), 1.48(s, 9H), 1.28 (s, 12H), 1.10 (s, 6H).

Example 41: Synthesis of 1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-31)



Step 1: **Synthesis of *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (41a)**

tert-Butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (**41a**) was synthesized according to **General Procedure 5** starting from 1-(6-chloro-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**INT-5**, 100 mg, 1.0 eq., 0.34 mmol) and tert-butyl 3,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**INT-40**, 345 mg, 3.0 eq., 1.02 mmol). The crude material was purified by silica gel flash column chromatography using Biotage Isolera® on silica gel (100-200 mesh) eluting with 0 to 10% isopropanol in DCM to afford *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (**41a**, 110 mg, 0.09 mmol, 28% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 469.3.

Step 2: **Synthesis of 1-(6-(3,3-dimethyl-1,2,3,6-tetrahydropyridin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (41b)**

1-(6-(3,3-dimethyl-1,2,3,6-tetrahydropyridin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**41b**, 80 mg, 0.08 mmol, 33% yield) was synthesized according to **General Procedure 6, Step A** starting from *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (**41a**, 110 mg, 1.0 eq., 0.24 mmol). LCMS: m/z MM-ES+APCI, Negative $[M-H]^-$ 367.1.

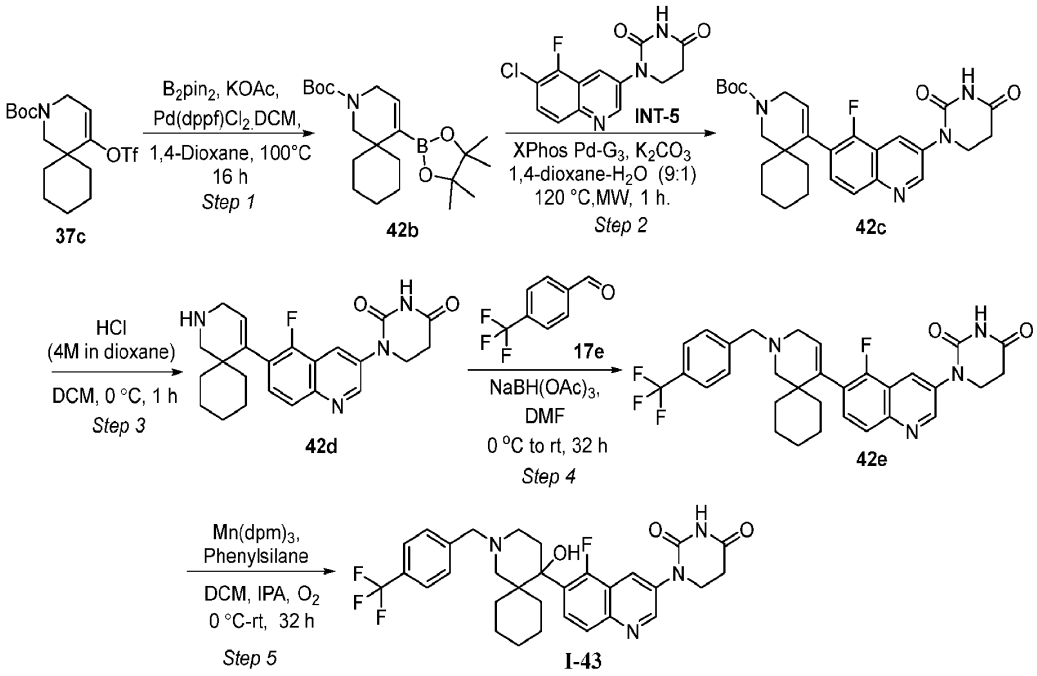
Step 3: **Synthesis of 1-(6-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (41c)**

1-(6-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**41c**) was synthesized according to **General Procedure 6, Step B** starting from 1-(6-(3,3-dimethyl-1,2,3,6-tetrahydropyridin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**41b**, 80 mg, 1.0 eq., 0.22 mmol) and 4-(trifluoromethyl)benzaldehyde (**17e**, 45 mg, 1.2 eq., 0.26 mmol). The crude material was purified by silica gel flash column chromatography using Biotage Isolera® on silica gel (100-200 mesh) eluting with 0 to 15% isopropanol in DCM to afford 1-(6-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**41c**, 90 mg, 0.10 mmol, 46% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 527.2.

Step 4: **Synthesis of 1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-31)**

1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-31**) was synthesized according to **General Procedure 3, Step C** starting from 1-(6-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**41c**, 90 mg, 1.0 eq., 0.17 mmol). The crude material was purified by preparative-HPLC [(Column: X select (150 x 19 mm) 5 µm, eluting with Mobile phase A: 0.1% ammonium acetate in H_2O, Mobile phase B: Acetonitrile, flow rate: 15 mL/min)]. The pure product containing fractions were collected and lyophilized to afford 1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-31**, 2.2 mg, 4.03 µmol, 2% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 545.4; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.61 (s, 1H), 8.96 (d, *J* = 2.40 Hz, 1H), 8.33 (d, *J* = 2.40 Hz, 1H), 8.09 (t, *J* = 8.80 Hz, 1H), 7.85 (d, *J* = 9.20 Hz, 1H), 7.72 (d, *J* = 8.40 Hz, 2H), 7.60 (d, *J* = 8.00 Hz, 2H), 5.16 (s, 1H), 4.00 (t, *J* = 7.20 Hz, 2H), 3.67 (d, *J* = 14.00 Hz, 1H), 3.56 (d, *J* = 14.00 Hz, 1H), 3.16 (t, *J* = Hz, 1H), 2.80 (t, *J* = 6.40 Hz, 2H), 2.68-2.60 (m, 2H), 2.51-2.50 (m, 1H), 2.17 (d, *J* = 10.00 Hz, 1H), 1.72 (d, *J* = 13.20 Hz, 1H), 1.02 (d, *J* = 2.80 Hz, 3H), 0.69 (d, *J* = 11.20 Hz, 3H).

Example 42: Synthesis of 1-(5-fluoro-6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-43)



Step 1: **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 (42b)**

A solution of *tert*-butyl 5-(((trifluoromethyl)sulfonyl)oxy)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (**37c**, 4 g, 10.01 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (3.05 g, 12.02 mmol) and potassium acetate (1.966 g, 20.03 mmol) in 1, 4-dioxane (30 mL) was degassed with nitrogen at room temperature for 10 min. $Pd(dppf)Cl_2$•DCM (0.818 g, 1.00 mmol) was then added in one portion, and the resulting mixture was stirred at 80 °C for 16 h. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure. This crude material was purified by silica gel flash column chromatography using Biotage Isolera® (on silica gel 100-200 mesh) eluting with 0-6% EtOAc in hexanes 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 (**42b**, 1 g, 2.15 mmol, 21% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H-Boc]^+$ 277.6; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 6.3-6.25 (m, 1H), 3.84 (s, 2H), 3.35-3.32 (m, 2H), 1.72-1.64 (m, 3H), 1.45-1.43 (m, 12H), 1.30-1.17 (m, 16H).

Step 2: **Synthesis of *tert*-butyl 5-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (42c)**

tert-Butyl 5-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (**42c**) was synthesized according to **General Procedure 5** starting from 1-(6-chloro-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**INT-5**, 500 mg, 1.0 eq., 1.7 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 (**42b**, 642 mg, 1.0 eq., 1.7 mmol). The crude material was purified by silica gel flash column chromatography using Biotage Isolera® on silica gel (100-200 mesh) eluting with 0 to 90% EtOAc in hexane to afford *tert*-butyl 5-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (**42c**, 0.350 g, 0.25 mmol, 15% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 509.2; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.67 (s, 1H), 9.00 (d, J = 2.40 Hz, 1H), 8.36-8.31 (m, 1H), 7.94-7.83 (m, 1H), 7.51-7.45 (m, 1H), 5.63 (s, 1H), 4.05-3.99 (m, 5H), 3.63 (s, 3H), 2.80 (t, J = 6.40 Hz, 3H), 1.67-1.36 (m, 16H).

Step 3: **Synthesis of 1-(5-fluoro-6-(2-azaspiro[5.5]undec-4-en-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (42d)**

To a stirred solution of tert-butyl 5-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (**42c**, 350 mg, 1.0 eq., 0.69 mmol) in DCM (2 mL) was added HCl in 4M 1, 4-dioxane (2.58 mL, 10.32 mmol) at 0 °C under an atmosphere of nitrogen atmosphere and the resulting mixture was allowed to stir at room temperature for 1 h. The solution was concentrated under reduced pressure and then further concentrated on high-vac to afford 1-(5-fluoro-6-(2-azaspiro[5.5]undec-4-en-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**42d**, 200 mg, 0.26 mmol, 37% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 409.1.

Step 4: **Synthesis of 1-(5-fluoro-6-(2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (42e)**

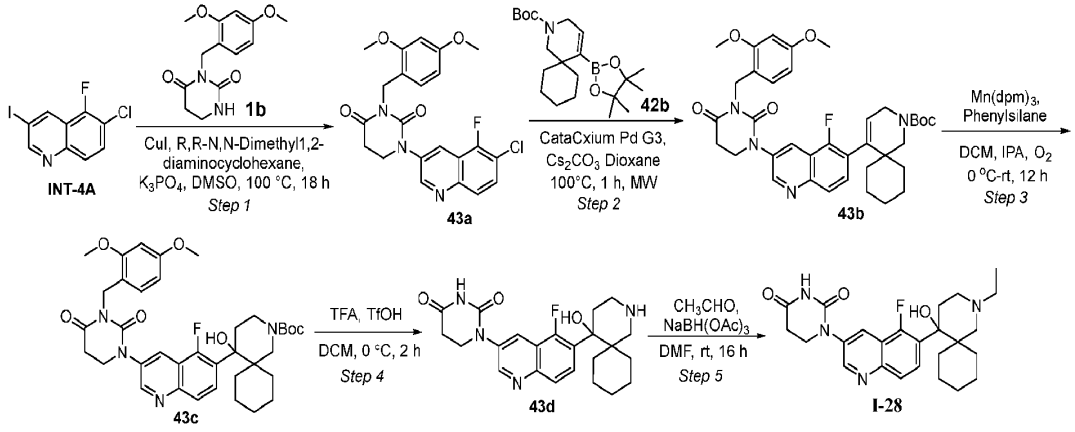
1-(5-fluoro-6-(2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**42e**) was synthesized according to **General Procedure 6, Step B** starting from 1-(5-Fluoro-6-(2-azaspiro[5.5]undec-4-en-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione hydrochloride (**42d**). To a stirred solution of 1-(5-fluoro-6-(2-azaspiro[5.5]undec-4-en-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**42d**, 190 mg, 0.43 mmol) in DMF (2 mL) was added 4-(trifluoromethyl)benzaldehyde (**17e**, 89 mg, 0.51 mmol) at room temperature and the resulting reaction was stirred for 1 h. After 1 h, $NaBH(OAc)_3$ (226 mg, 1.07 mmol) was added, and stirring was continued at room temperature for 32 h. The reaction mixture was concentrated under reduced pressure and the crude material was purified by silica gel flash column chromatography using Biotage Isolera® on silica gel (100-200 mesh) eluting with 0 to 80% EtOAc in hexane to afford 1-(5-fluoro-6-(2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**42e**, 100 mg, 0.08 mmol, 19% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 567.3.

Step 5: **Synthesis of 1-(5-fluoro-6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-43)**

1-(5-fluoro-6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-43**) was synthesized according to **General Procedure 3, Step**

C starting from 1-(5-fluoro-6-(2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**42e**, 100 mg, 1.0 eq., 0.18 mmol). The crude material was purified by preparative-HPLC [X Select C18 (250*19 mm), eluting with Mobile phase A: 0.05% HCl In H_2O, Mobile phase B: Acetonitrile, flow rate: 15 mL/min, Rt: 12.5]. The pure fractions were collected and lyophilized to afford 1-(5-fluoro-6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-43**,14 mg, 0.02 mmol, 11% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 585.2; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.62 (s, 1H), 10.05 (br s, 1H), 9.00 (d, *J* = 2.00 Hz, 1H), 8.35 (d, *J* = 1.60 Hz, 1H), 8.04-7.88 (m, 6H), 5.87 (s, 1H), 4.57 (d, *J* = 3.60 Hz, 2H), 4.01 (t, *J* = 6.40 Hz, 2H), 3.58-3.36 (m, 3H), 3.20-3.14 (m, 1H), 2.80 (t, *J* = 6.40 Hz, 2H), 1.97-1.91 (m, 1H), 1.82 (d, *J* = 12.40 Hz, 1H), 1.42-0.82 (m, 9H).

Example 43: Synthesis of the acetic acid salt of 1-(6-(2-ethyl-5-hydroxy-2-azaspiro[5.5]-undecan-5-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-28)



Step 1: **Synthesis of 1-(6-chloro-5-fluoroquinolin-3-yl)-3-(2,4-dimethoxybenzyl)-dihydropyrimidine-2,4(1H,3H)-dione (43a)**

A solution of 6-chloro-5-fluoro-3-iodoquinoline (**INT-4A**, 0.75 g, 2.44 mmol), 3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (**1b**, 0.774 g, 2.93 mmol) and K_3PO_4 tribasic (1.035 g, 4.88 mmol) in DMSO (2 mL) was degassed with nitrogen for 10 min. Copper(I) iodide (0.046 g, 0.24 mmol) was then added followed by (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (0.035 g, 0.24 mmol) and the resulting mixture was degassed with nitrogen for 10 min. The reaction mixture was stirred at 100 °C for 18 h and then cooled to room temperature. Cold water (50 mL) was added and the resulting aqueous mixture was extracted with EtOAc (2 X 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography, eluting with 0 to 50% EtOAc in hexane to afford 1-(6-chloro-5-fluoroquinolin-3-yl)-3-(2,4-dimethoxy-benzyl)dihydropyrimidine-2,4(1H,3H)-dione (**43a**, 0.8 g, 1.66 mmol, 68% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 444.6.

Step 2: **Synthesis of *tert*-butyl 5-(3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (43b)**

tert-Butyl 5-(3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (**43b**) was synthesized according to **General Procedure 5** starting from *tert*-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (**42b**, 408 mg, 1.2 eq., 1.08 mmol) and 1-(6-chloro-5-fluoroquinolin-3-yl)-3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (**43a**, 400 mg, 1.0 eq., 0.9 mmol). The crude material was purified by silica gel flash column chromatography using Biotage Isolera® on silica gel (100-200 mesh) eluting with 0 to 40% EtOAc in hexane to afford *tert*-butyl 5-(3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (**43b**, 0.3 g, 0.40 mmol, 45% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 659.3; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.98 (d, *J* = 18.40 Hz, 1H), 8.36 (d, *J* = 2.00 Hz, 1H), 7.85 (d, *J* = 8.80 Hz, 1H), 7.48 (t, *J* = 8.40 Hz, 1H), 6.96 (d, *J* = 8.40 Hz, 1H), 6.56 (d, *J* = 2.40 Hz, 1H), 6.46 (d, *J* = 8.40 Hz, 1H), 5.60 (s, 1H), 4.80 (s, 2H), 4.08 (t, *J* = 6.80 Hz, 2H), 4.03 (t, *J* = 7.20 Hz, 2H), 3.93 (s, 3H), 3.81 (s, 3H), 3.74 (s, 3H), 3.63 (s, 2H), 3.03 (t, *J* = 6.40 Hz, 2H), 1.57-1.54 (m, 4H), 1.47 (s, 9H), 1.20-1.16 (m, 3H).

Step 3: **Synthesis of *tert*-butyl 5-(3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-5-hydroxy-2-azaspiro[5.5]undecane-2-carboxylate (43c)**

tert-Butyl 5-(3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-5-hydroxy-2-azaspiro[5.5]undecane-2-carboxylate (**43c**) was synthesized according to **General Procedure 3, Step C** starting from *tert*-butyl 5-(3-(3-(2,4-dimethoxy-benzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (**43b**, 400 mg, 1.0 eq., 0.61 mmol). The crude material was purified by silica gel flash column chromatography using Biotage Isolera® on silica gel (100-200 mesh) eluting with 0 to 50% EtOAc in hexane followed by reverse phase column chromatography using a C^{18} cartridge (25 g) eluting with 5 to 100% MeCN and 0.1% formic acid in water. The pure product containing fractions were collected and lyophilized to obtain *tert*-butyl 5-(3-(3-(2,4-dimethoxy-benzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-5-hydroxy-2-azaspiro[5.5]undecane-2-carboxylate (**43c**, 0.2 g, 0.28 mmol, 46% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 677.5; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.98 (d, *J* = 2.40 Hz, 1H), 8.38 (d, *J* = 2.00 Hz, 1H), 8.07 (t, *J* = 8.80 Hz, 1H), 7.87 (d, *J* = 9.20 Hz, 1H), 6.95 (d, *J* = 8.40 Hz, 1H), 6.56 (d, *J* = 2.40 Hz, 1H), 6.46 (dd, *J* = 2.00, 8.40 Hz, 1H), 5.41 (s, 1H), 4.81 (s, 2H), 4.08 (t, *J* = 7.20 Hz, 4H), 3.81 (s, 3H), 3.74 (s, 3H), 3.03 (t, *J* = 6.40 Hz, 5H), 1.81-1.78 (m, 2H), 1.61-1.51 (m, 2H), 1.44 (s, 9H), 1.38-1.35 (m, 3H), 1.24-1.21 (m, 1H), 0.89-0.80 (m, 2H), 0.65-0.62 (m, 1H).

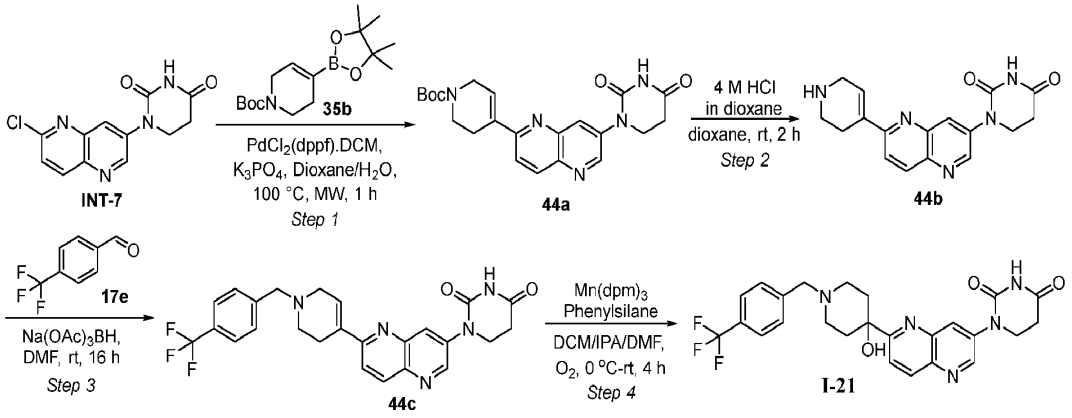
Step 4: **Synthesis of 1-(5-fluoro-6-(5-hydroxy-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (43d)**

To a stirred solution of *tert*-butyl 5-(3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-5-hydroxy-2-azaspiro[5.5]undecane-2-carboxylate (**43c**, 100 mg, 0.15 mmol) in DCM (2 mL) was added trifluoroacetic acid (0.177 mL, 2.29 mmol) followed by trifluoromethanesulfonic acid (0.026 mL, 0.30 mmol) at 0 °C under an atmosphere of nitrogen and the resulting mixture was stirred at 25 °C for 1 h. The reaction mixture was then concentrated under reduced pressure and the crude material was basified with saturated $NaHCO_3$ solution and a solid precipitated. The precipitated solid was filtered and washed with water (2 x 10 mL) and DCM (2 x 80 mL) and dried to afford 1-(5-fluoro-6-(5-hydroxy-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**43d**, 50 mg, 0.07 mmol, 46% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 427.2; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.62 (s, 1H), 8.99 (d, *J* = 2.40 Hz, 1H), 8.34 (d, *J* = 2.00 Hz, 1H), 8.06 (t, *J* = 8.40 Hz, 1H), 7.87 (d, *J* = 9.20 Hz, 1H), 5.50 (s, 1H), 4.01 (t, *J* = 6.80 Hz, 2H), 3.76-3.73 (m, 2H), 3.15-2.94 (m, 4H), 2.80 (t, *J* = 6.40 Hz, 2H), 1.82-1.18 (m, 10H).

Step 5: **Synthesis of the acetic acid salt of 1-(6-(2-ethyl-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-28)**

1-(6-(2-ethyl-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-5-fluoroquinolin-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione (**I-28**) was synthesized according to **General Procedure 6, Step B** starting from 1-(5-fluoro-6-(5-hydroxy-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione (**43d**, 40 mg, 1.0 eq., 0.086 mmol) and acetaldehyde (7.61 mg, 2.0 eq., 0.17 mmol). The crude material was purified by preparative-HPLC [X-select C18,150mm X 19, eluting with Mobile phase A: 10 mM ammonium acetate in H_2O, Mobile phase B: Acetonitrile, flow rate: 15 mL/min, Rt:12.8]. The pure product containing fractions were collected and lyophilized with acetic acid to afford the acetic acid salt of 1-(6-(2-ethyl-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-28**, 10.20 mg, 0.02 mmol, 23% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 455.5; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.61 (s, 1H), 8.97 (d, *J* = 2.40 Hz, 1H), 8.33 (d, *J* = 2.00 Hz, 1H), 8.08 (t, *J* = 8.80 Hz, 1H), 7.84 (d, *J* = 9.20 Hz, 1H), 5.03 (s, 1H), 4.01 (dd, *J* = 5.60, 6.40 Hz, 2H), 3.15 (m, 1H), 2.98 (d, *J* = 11.20 Hz, 1H), 2.80 (t, *J* = 6.40 Hz, 2H), 2.67 (dd, *J* = 2.00, 3.60 Hz, 1H), 2.37 (q, *J* = 6.80 Hz, 3H), 2.14 (d, *J* = 11.20 Hz, 2H), 1.90 (s, 3H), 1.79-1.73 (m, 2H), 1.65-1.62 (m, 1H), 1.45-1.30 (m, 4H), 1.05 (t, *J* = 7.2 Hz, 3H), 0.86 (m, 1H), 0.68 (s, 2H).

Example 44: Synthesis of 1-(6-(4-hydroxy-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)-1,5-naphthyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-21)



Step 1: **Synthesis of *tert*-butyl 4-(7-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1,5-naphthyridin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (44a)**

Tert-butyl 4-(7-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1,5-naphthyridin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**44a**) was synthesized according to **General Procedure 5** starting from 1-(6-chloro-1,5-naphthyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**INT-7**, 300 mg, 1.0 eq., 1.08 mmol) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**35b**, 503 mg, 1.5 eq., 1.63 mmol). The crude material was purified by silica gel flash column chromatography Biotage Isolera® on a silica gel (100-200 mesh) cartridge (25 g) eluting with IPA in DCM (0-20%). The pure product containing fractions were collected and concentrated under reduced pressure to afford *tert*-butyl 4-(7-(2,4-dioxotetra-hydropyrimidin-1(2H)-yl)-1,5-naphthyridin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**44a**, 200 mg, 0.45 mmol, 42% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 424.4. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.65 (s, 1H), 9.00 (d, *J* = 2.40 Hz, 1H), 8.36 (dd, *J* = 8.80, Hz, 1H), 8.21 (d, *J* = 2.00 Hz, 1H), 8.07 (dd, *J* = 9.20 Hz, 1H), 6.94 (br s, 1H), 4.34 (br s, 2H), 4.06-4.01 (m, 3H), 3.61-3.58 (m, 2H), 2.82-2.74 (m, 3H), 1.45 (s, 9H).

Step 2: **Synthesis of 1-(6-(1,2,3,6-tetrahydropyridin-4-yl)-1,5-naphthyridin-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione (44b)**

To a stirred solution of tert-butyl 4-(7-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1,5-naphthyridin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**44a**, 200 mg, 1.0 eq., 0.47 mmol) in DCM (5 mL) was added HCl (4M in 1,4-dioxane) (1.0 mL, 4.00 mmol) at 0 °C and the resulting mixture was stirred for 2 h. After complete consumption of starting material was observed via LCMS, the reaction mixture was concentrated to obtain crude material. The crude material was triturated with MTBE, filtered, and dried under reduced pressure to afford 1-(6-(1,2,3,6-tetrahydropyridin-4-yl)-1,5-naphthyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**44b**, 140 mg, 0.39 mmol, 82% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 324.3. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.60 (s, 1H), 9.42 (br s, 1H), 9.04 (d, *J* = 2.40 Hz, 1H), 8.43 (dd, *J* = 8.80, Hz, 1H), 8.25 (dd, *J* = 2.00, Hz, 1H), 8.13 (dd, *J* = 9.20,

Hz, 1H), 7.58-6.93 (d, *J* = Hz, 1H), 4.05-4.01 (m, 2H), 3.95 (br s, 2H), 3.37-3.36 (m, 2H), 2.97 (br s, 2H), 2.81 (t, *J* = 6.80 Hz, 2H).

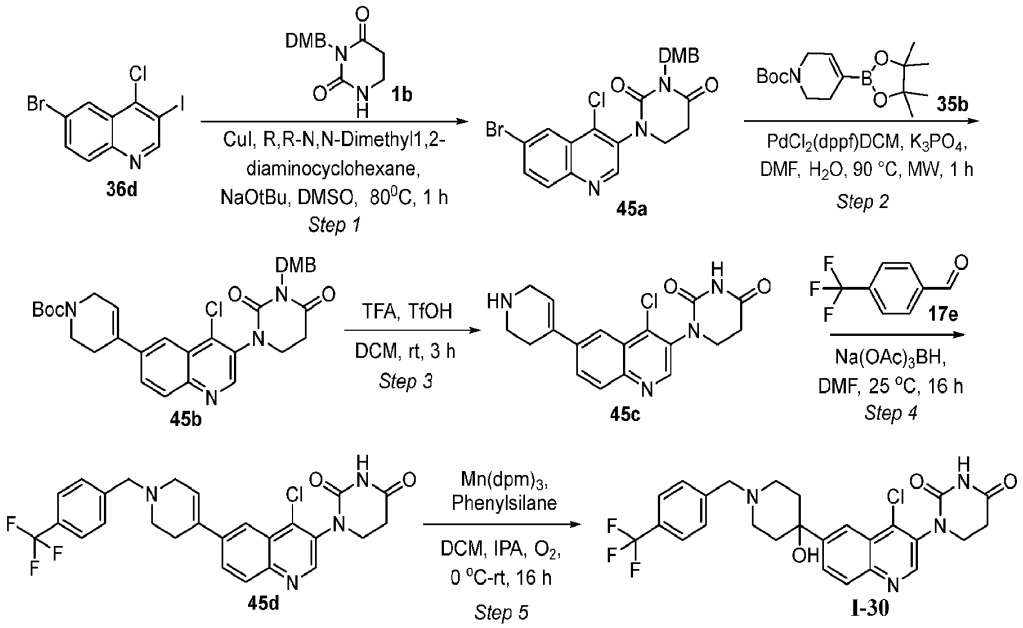
Step 3: **Synthesis of 1-(6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-1,5-naphthyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (44c)**

A solution of 1-(6-(1,2,3,6-tetrahydropyridin-4-yl)-1,5-naphthyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl (**44b**, 150 mg, 1.0 eq., 0.42 mmol) and 4-(trifluoromethyl)benzaldehyde (**17e**, 87 mg, 1.2 eq., 0.5 mmol) in DMF (2 mL) was stirred at 25 °C for 2 h. Sodium triacetoxyborohydride (221 mg, 1.042 mmol) was then added at 25 °C and stirring was continued for 16 h. The reaction mixture was concentrated under reduced pressure to obtain the crude material. The crude material was purified by silica gel flash column chromatography Biotage Isolera® on a silica gel (100-200 mesh) cartridge (25 g) eluting with IPA in DCM (0-20%). The pure product containing fractions were collected and concentrated under reduced pressure to afford 1-(6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-1,5-naphthyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**44c**, 120 mg, 0.21 mmol, 51% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 482.3. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.60 (s, 1H), 8.98 (d, *J* = 2.40 Hz, 1H), 8.29 (dd, *J* = 50.80, Hz, 1H), 8.19 (d, *J* = 0.80 Hz, 1H), 8.05 (dd, *J* = 8.80, Hz, 1H), 7.73-7.71 (m, 2H), 7.63-7.61 (m, 2H), 6.93 (d, *J* = Hz, 1H), 4.05-4.01 (m, 2H), 3.78-3.75 (m, 3H), 3.28 (d, *J* = 35.60 Hz, 2H), 2.82-2.73 (m, 3H), 2.68-2.67 (m, 2H).

Step 4: **Synthesis of 1-(6-(4-hydroxy-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)-1,5-naphthyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-21)**

1-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1,5-naphthyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-21**) was synthesized according to **General Procedure 3, Step C** starting from1-(6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-1,5-naphthyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**44c**, 115 mg, 1 eq., 0.24 mmol). The crude material was purified by preparative-HPLC [(Column: X select (150 x 19 mm) 5 µm, eluting with Mobile phase A: 0.05% HCl in H_2O, Mobile phase B: Acetonitrile, flow rate: 15 mL/min)]. The pure product containing fractions were collected and lyophilized to afford of 1-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-1,5-naphthyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-21**, 37.4 mg, 0.07 mmol, 35% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 500.1. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.71 (br s, 1H), 10.67 (s, 1H), 9.07 (dd, *J* = 2.40, 9.20 Hz, 1H), 8.48 (d, *J* = 8.80 Hz, 1H), 8.19 (d, *J* = 1.60 Hz, 1H), 8.07 (dd, *J* = 3.60, 8.80 Hz, 1H), 7.94-7.86 (m, 4H), 5.97 (s, 1H), 4.53 (d, *J* = 4.80 Hz, 2H), 4.04 (t, *J* = 6.80 Hz, 2H), 3.37 (s, 4H), 2.84-2.79 (m, 2H), 2.68-2.56 (m, 2H), 1.97 (d, *J* = 13.60 Hz, 2H).

Example 45: Synthesis of 1-(4-chloro-6-(4-hydroxy-1-(4-(trifluoro-methyl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-30)



Step 1: **Synthesis of 1-(6-bromo-4-chloroquinolin-3-yl)-3-(2,4-dimethoxybenzyl)-dihydropyrimidine-2,4(1H,3H)-dione (45a)**

To a stirred solution of 6-bromo-4-chloro-3-iodoquinoline (**36d**, 500 mg, 1.36 mmol), 3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (**1b**, 359 mg, 1.36 mmol) in DMSO (10 mL) were added sodium *tert*-butoxide (157 mg, 1.63 mmol) and copper (I) iodide (51.7 mg, 0.27 mmol) and the resulting mixture was degassed with nitrogen for 5 min. Trans-*N,N'*-dimethylcyclohexane-1,2-diamine (38.6 mg, 0.27 mmol) was then added at room temperature, and stirring was continued at 80 °C for 1 h. The reaction mixture was poured into ice-cold water and a solid precipitated. The resulting precipitated solid was filtered and dissolved in EtOAc. The EtOAc phase was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude compound was purified by flash column chromatography using Combi-Flash (on Silica gel, 100-200 mesh) eluting with 22-25% EtOAc in hexane to afford 1-(6-bromo-4-chloroquinolin-3-yl)-3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (**45a**, 550 mg, 0.71 mmol, 52% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ 504.2, 506.2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.03 (s, 1H), 8.27 (d, J = 2.00 Hz, 1H), 8.08 (dd, J = 2.00, 8.80 Hz, 1H), 7.97-7.91 (m, 1H), 6.96 (d, J = 8.40 Hz, 1H), 6.56 (d, J = 2.40 Hz, 1H), 6.49 (d, J = 6.00 Hz, 1H), 4.81 (d, J = 6.40 Hz, 2H), 3.93 (t, J = 6.40 Hz, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 3.09 (s, 1H), 3.01 (d, J = 10.80 Hz, 1H).

Step 2: **Synthesis of *tert*-butyl 4-(4-chloro-3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetra-hydropyrimidin-1(2H)-yl)quinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (45b)**

tert-Butyl 4-(4-chloro-3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)quinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**45b**) was synthesized according to **General Procedure 4** starting from 1-(6-bromo-4-chloroquinolin-3-yl)-3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (**45a**, 780 mg, 1.0 eq., 1.55 mmol) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**35b**, 478 mg, 1.0 eq., 1.55 mmol). The crude compound was purified by flash column chromatography using Combi-Flash (on silica gel, 100-200 mesh) eluting with 80-85% EtOAc in hexane to afford *tert*-butyl 4-(4-chloro-3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)quinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**45b**, 900 mg, 1.16 mmol, 75% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 607.4. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.93 (s, 1H), 8.11 (d, J = 5.20 Hz, 3H), 6.97 (d, J = 8.40 Hz, 1H), 6.56 (d, J = 2.40 Hz, 1H), 6.49 (dd, J = 2.40, 8.40 Hz, 2H), 4.81 (d, J = 8.00 Hz, 2H), 4.10 (s, 1H), 3.94 (t, J = 2.40 Hz, 2H), 3.80 (s, 3H), 3.79-3.75 (m, 1H), 3.74 (s, 3H), 3.62 (t, J = 6.00 Hz, 2H), 3.11 (t, J = 7.20 Hz, 1H), 3.03-3.00 (m, 1H), 2.65 (s, 2H), 1.46 (s, 9H).

Step 3: **Synthesis of 1-(4-chloro-6-(1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione (45c)**

To a stirred solution of *tert*-butyl 4-(4-chloro-3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)quinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**45b**, 800 mg, 1.32 mmol) in DCM (10 mL) was added triflic acid (0.234 mL, 2.64 mmol) and TFA (0.254 mL, 3.29 mmol) at 0 °C and the resulting mixture was stirred at 25 °C for 3 h. The solvent was evaporated under reduced pressure and the resulting crude material was washed with MTBE and dried to afford 1-(4-chloro-6-(1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**45c**, 610 mg, 1.23 mmol, 93% yield), which was carried onto the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 356.9. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.79 (s, 1H), 8.90 (s, 1H), 8.11 (s, 3H), 6.58 (s, 2H), 3.00 (d, J = 5.60 Hz, 2H), 2.92 (d, J = 46.40 Hz, 2H), 1.28-1.25 (m, 4H), 0.88 (s, 2H).

Step 4: **Synthesis of 1-(4-chloro-6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (45d)**

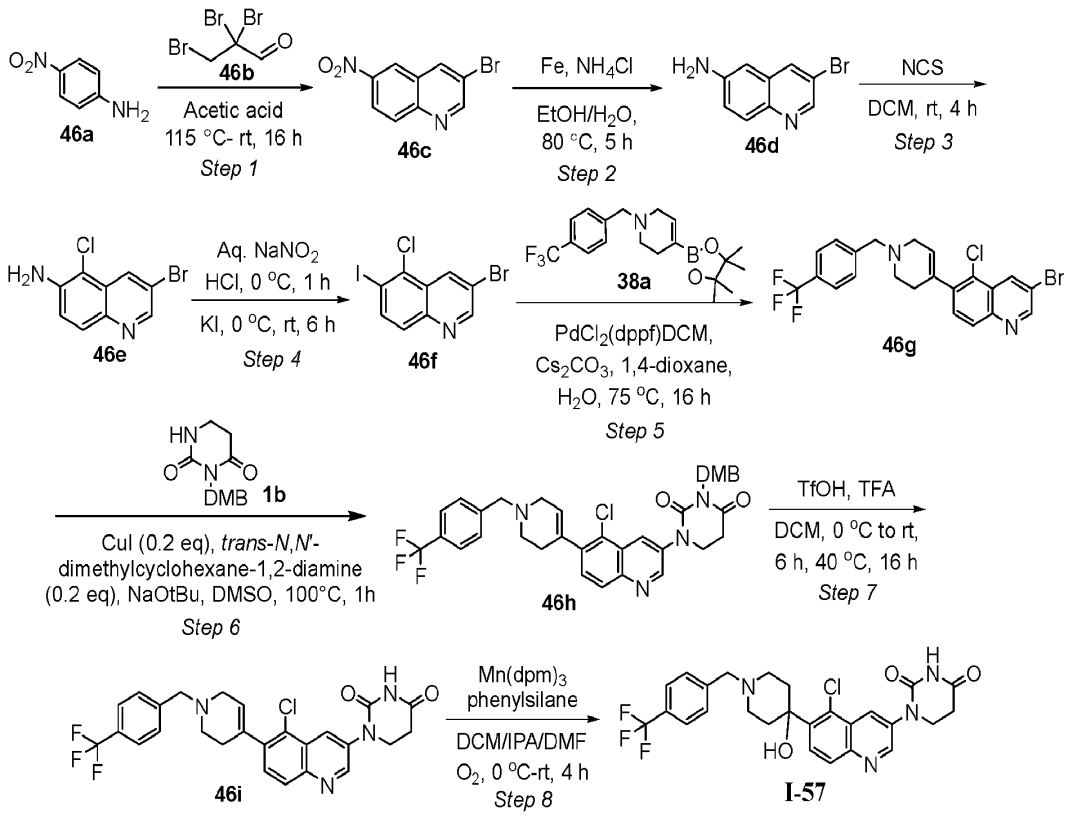
To a stirred solution of 1-(4-chloro-6-(1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**45c**, 320 mg, 1.0 eq., 0.9 mmol) in DMF (7 mL) was added 4-(trifluoromethyl)benzaldehyde (**17e**, 156 mg, 1.0 eq., 0.9 mmol) at room temperature and the resulting mixture was stirred for 1 h. Sodium triacetoxyborohydride (475 mg, 2.24 mmol) was then added and stirring was continued at 25 °C for 16 h. The solvent was removed under reduced pressure to afford crude product. The crude compound was purified by flash column chromatography using Combi-Flash (on Silica gel, 100-200 mesh) and eluting with gradient of 85-90% of EtOAc in hexane to afford 1-(4-chloro-

6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**45d**, 220 mg, 0.31 mmol, 35% yield), which was carried onto the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 515.1. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.67 (s, 1H), 8.90 (s, 1H), 8.11-8.09 (m, 3H), 7.72 (d, J = 8.00 Hz, 2H), 7.62 (d, J = 8.40 Hz, 2H), 6.53 (s, 1H), 3.88-3.82 (m, 6H), 3.20 (s, 2H), 2.84 (t, J = 6.00 Hz, 2H), 2.74 (d, J = 6.00 Hz, 1H), 2.68 (s, 1H).

Step 5: **Synthesis of 1-(4-chloro-6-(4-hydroxy-1-(4-(trifluoro-methyl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-30)**

1-(4-chloro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-30**) was synthesized according to **General Procedure 3, Step C** starting from 1-(4-chloro-6-(1-(4-(trifluoromethyl)-benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**45d**, 130 mg, 1.0 eq., 0.25 mmol). The crude compound was purified by preparative-HPLC [X SELECT C18 (19*150)], eluting with Mobile phase A: 0.05% HCl in H_2O, Mobile phase B: Acetonitrile, flow rate: 15 mL/min)]. The pure product containing fractions were collected and lyophilized to afford 1-(4-chloro-6-(4-hydroxy-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-30**, 28.8 mg, 0.050 mmol, 21% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 533.2. ^{1}H-NMR (400 MHz, DMSO-d_6): 10.98 (s, 1H), 10.67 (s, 1H), 8.95 (s, 1H), 8.35 (d, J = 1.60 Hz, 1H), 8.17 (d, J = 8.80 Hz, 1H), 7.99-7.88 (m, 5H), 5.98 (s, 1H), 4.54 (d, J = 5.20 Hz, 2H), 3.86 (dd, J = 6.00, 7.60 Hz, 2H), 3.38 (d, J = 12.00 Hz, 3H), 2.85 (t, J = 6.40 Hz, 2H), 2.68-2.67 (m, 2H), 1.89 (d, J = 14.00 Hz, 2H).

Example 46: Synthesis of 1-(5-chloro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-57)



Step 1: **Synthesis of 3-bromo-6-nitroquinoline (46c)**

To a stirred solution of 4-nitroaniline (**46a**, 2 g, 14.48 mmol) in AcOH (30 mL) was added 2,2,3-tribromopropanal (**46b**, 6.40 g, 21.72 mmol) at room temperature and the resulting mixture was stirred at room temperature for 1 h and then at 115 °C for 16 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude compound was purified by silica gel flash column chromatography Biotage Isolera® on silica gel (100-200 mesh) eluting with EtOAc in *n*-hexane (20-30%). The pure product containing fractions were collected and concentrated under reduced pressure to afford 3-bromo-6-nitroquinoline (**46c**, 0.34 g, 1.34 mmol, 9% yield). LCMS: Not ionized. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.20 (d, J = 2.40 Hz, 1H), 9.09 (d, J = 2.40 Hz, 1H), 9.06 (d, J = 2.80 Hz, 1H), 8.51 (dd, J = 2.80, 9.20 Hz, 1H), 8.26 (d, J = 9.20 Hz, 1H).

Step 2: **Synthesis of 3-bromoquinolin-6-amine (46d)**

To a stirred solution of 3-bromo-6-nitroquinoline (**46c**, 340 mg, 1.34 mmol) in ethanol (16 mL) and water (4 mL) was added iron (375 mg, 6.72 mmol) and ammonium chloride (719 mg, 13.44 mmol) at room temperature and the resulting mixture was stirred at 80 °C for 5 h. The reaction mixture was cooled, filtered through celite®, and the filter cake was washed with ethanol (30 mL). The filtrate was concentrated under reduced pressure and the crude compound was purified by silica gel flash column

chromatography Biotage Isolera® on silica gel (100-200 mesh) eluting with EtOAc in *n*-hexane (20-30%). The pure fractions were collected and concentrated under reduced pressure to afford 3-bromoquinolin-6-amine (**46d**, 145 mg, 0.55 mmol, 41% yield). LCMS: m/z MM-ES+APCI, [M+H, M+2+H]$^+$ 222.9, 224.9. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.46 (d, J = 2.00 Hz, 1H), 8.25 (d, J = 2.00 Hz, 1H), 7.69 (d, J = 8.80 Hz, 1H), 7.18 (dd, J = 2.40, 8.80 Hz, 1H), 6.74 (d, J = 2.40 Hz, 1H), 5.82 (s, 2H, D_2O exchangeable).

Step 3: **Synthesis of 3-bromo-5-chloroquinolin-6-amine (46e)**

To a stirred solution of 3-bromoquinolin-6-amine (**46d**, 490 mg, 2.20 mmol) in DCM (20 mL) was added 1-chloropyrrolidine-2,5-dione (352 mg, 2.64 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 4 h. Water (50 mL) was added and the resulting aqueous mixture was extracted with EtOAc (2 x 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 flash column chromatography using Combi-Flash (on silica gel, 100-200 mesh) eluting with a gradient of 20-25% of EtOAc in hexane to afford 3-bromo-5-chloroquinolin-6-amine (**46e**, 800 mg, 1.77 mmol, 81% yield). LCMS: m/z MM-ES+APCI, Positive [(M+H, M+2+H]$^+$. 258.9, 260.9. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.61(d, J = 2.40 Hz, 1H), 8.36 (d, J = 2.00 Hz, 1H), 7.75 (d, J = 8.80 Hz, 1H), 7.40 (d, J = 8.80 Hz, 1H), 6.16 (s, 2H, D_2O exchangeable).

Step 4: **Synthesis of 3-bromo-5-chloro-6-iodoquinoline (46f)**

To a stirred solution of 3-bromo-5-chloroquinolin-6-amine (**46e**, 1.1 g, 4.27 mmol) in 10% aq. HCl, (25 mL, 4.27 mmol) was added sodium nitrite (0.589 g, 8.54 mmol) at 0 °C and the resulting mixture was stirred for 1 h. Potassium iodide (1.418 g, 8.54 mmol) was then added and stirring was continued at room temperature for 6 h. The reaction mixture was poured into water (200 mL) and extracted with EtOAc (2 x 300 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude compound was purified by flash column chromatography using Combi-Flash (on silica gel, 100-200 mesh) eluting with gradient of 10% EtOAc in hexane to afford 3-bromo-5-chloro-6-iodoquinoline (**46f**, 1.1 g, 2.23 mmol, 52% yield). LCMS: m/z MM-ES+APCI, Positive [M+H, M+2+H]$^+$ 367.9, 369.9. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.97-8.95 (m, 1H), 8.79-8.77 (m, 1H), 7.97-7.82 (m, 1H), 7.79-7.74 (m, 1H).

Step 5: **Synthesis of 3-bromo-5-chloro-6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinoline (46g)**

To a stirred solution of 3-bromo-5-chloro-6-iodoquinoline (**46f**, 400 mg, 1.09 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridine (**38a**, 399 mg, 1.09 mmol) in 1,4-dioxane (10 mL) and water (1 mL) was added Cs_2CO_3 (708 mg, 2.17 mmol) and the resulting mixture was sparged with N_2 gas for 10 minutes. Pd(dppf)Cl_2•DCM (44.3 mg,

0.05 mmol) was added and stirring was continued at 75 °C for 16 h. The reaction mixture was cooled, poured in water (50 mL) and extracted with EtOAc (2 x 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 flash column chromatography using Combi-Flash (on silica gel, 100-200 mesh) eluting with an isocratic method of 10% EtOAc in hexane to afford 3-bromo-5-chloro-6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinoline (**46g**, 250 mg, 0.52 mmol, 48% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ 481.0, 483.0.

Step 6: **Synthesis of 1-(8-chloro-7-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)naphthalen-2-yl)-3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (46h)**

To a stirred solution of 3-bromo-5-chloro-6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinoline (**46g**, 250 mg, 0.52 mmol) in DMSO (4 mL) under an atmosphere of nitrogen was added copper (I) iodide (29.7 mg, 0.16 mmol), 3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (**1b**, 178 mg, 0.68 mmol) and sodium *tert*-butoxide (100 mg, 1.04 mmol) at 25 °C. The resulting mixture was sparged with N_2 for 10 min. *Trans-N,N'*-dimethylcyclohexane-1,2-diamine (22.15 mg, 0.16 mmol) was then added at 25 °C and the reaction mixture was again sparged with nitrogen for 5 min and stirring was continued at 100 °C for 1 h. The reaction mixture was cooled, water (15 ml) was added and the aqueous mixture was extracted with EtOAc (2 x 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude compound was purified by Grace reverse phase chromatography [(Column: C18, eluting with Mobile phase A: 0.1% FA in H_2O, Mobile phase B: Acetonitrile, flow rate: 20 mL/min)]. The pure product containing fractions were collected and lyophilized to afford 1-(8-chloro-7-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)naphthalen-2-yl)-3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (**46h**, 40 mg, 0.03 mmol, 6% yield) LCMS: m/z MM-ES+APCI, Positive $[M+H]^+ = 665.3$.

Step 7: **Synthesis of 1-(5-chloro-6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (46i)**

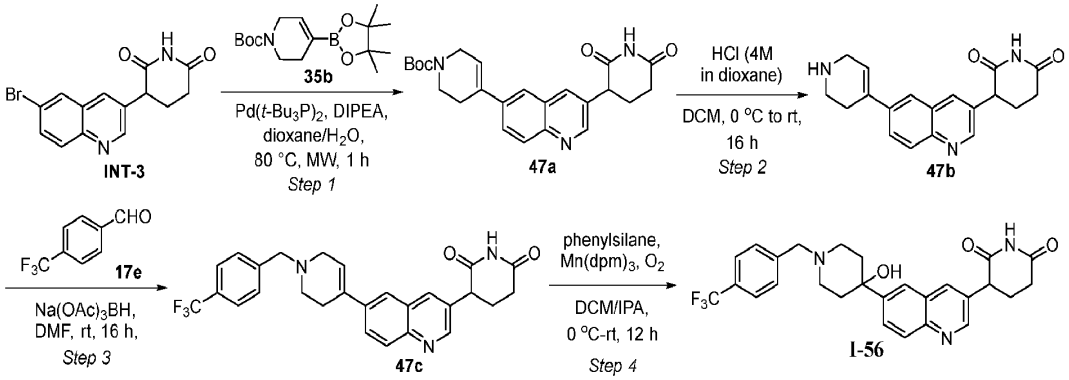
To a stirred solution of 1-(8-chloro-7-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)naphthalen-2-yl)-3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (**46h**, 100 mg, 0.16 mmol) in DCM (2 mL) was added TFA (361 mg, 3.16 mmol) and triflic acid (47.5 mg, 0.32 mmol) at 0 °C the resulting mixture was allowed to stir at room temperature for 6 h. Since starting material was still present as indicated by LCMS, additional TFA (361 mg, 3.16 mmol) and triflic acid (47.5 mg, 0.316 mmol) were added and stirring was continued at 40 °C for 16 h. The reaction mixture was then cooled, and the solvent volume was reduced under reduced pressure. The resulting mixture was basified to pH = 8 using sat. aq. $NaHCO_3$ sol (10 mL) and extracted with DCM (2 x 20 mL). The combined organic phases

were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure to provide 1-(5-chloro-6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**46i**, 20 mg, 0.02 mmol, 15% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 515.3.

Step 8: **Synthesis of 1-(5-chloro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-57)**

1-(5-Chloro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-57**) was synthesized according to **General Procedure 3, Step C** starting from-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione (**46i**, 20 mg, 1.0 eq., 0.04 mmol). The crude compound was purified by preparative-HPLC [(Column: Shimpak C18 (250*21), eluting with Mobile phase A: 0.05% FA in H_2O, Mobile phase B: Acetonitrile, Rt-6.0 min, flow rate: 15 mL/min)]. The pure product containing fractions were collected and lyophilized to afford 1-(5-chloro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione (**I-57**, 2.2 mg, 4.09 µmol, 7% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 533.2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.62 (s, 1H), 8.98 (d, J = 2.40 Hz, 1H), 8.54 (d, J = 2.00 Hz, 1H), 8.27 (d, J = 9.20 Hz, 1H), 8.04 (d, J = 9.20 Hz, 1H), 7.72 (d, J = 8.00 Hz, 2H), 7.64 (d, J = 8.00 Hz, 2H), 6.56 (s, 1H), 5.34 (s, 1H), 4.02 (t, J = 6.80 Hz, 2H), 3.65 (s, 2H), 2.80-2.67 (m, 5H), 2.57-2.50 (m, 2H), 1.63 (d, J = 12.40 Hz, 2H).

Example 47: Synthesis of 3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-56)



Step 1: **Synthesis of *tert*-Butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (47a)**

tert-Butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**47a**) was synthesized according to **General Procedure 4** starting from 3-(6-bromoquinolin-3-yl)piperidine-2,6-dione (**INT-3**, 400 mg, 1.0 eq., 1.26 mmol) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**35b**, 554 mg, 1.5 eq., 1.88 mmol). The crude

material was purified by silica gel flash column chromatography using Biotage Isolera® (on silica gel 100-200 mesh) eluting with 0-70% EtOAc in hexanes to afford *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**47a**, 400 mg, 0.87 mmol, 70% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 422.0. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.98 (s, 1H), 8.76 (s, 1H), 8.18 (s, 1H), 7.99-7.92 (m, 3H), 6.42 (s, 1H), 4.17-4.14 (m, 1H), 4.08-4.03 (m, 2H), 3.61 (t, J = 5.60 Hz, 2H), 2.63-2.61 (m, 4H), 2.46-2.39 (m, 1H), 2.46-2.39 (m, 1H), 1.45 (s, 9H).

Step 2: **Synthesis of 3-(6-(1,2,3,6-Tetrahydropyridin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl (47b)**

To a stirred solution of tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**47a**, 400 mg, 1.0 eq., 0.95 mmol) in DCM (8 mL) was added HCl (4M in dioxane) (1.19 mL, 4.75 mmol) at 0 °C under an atmosphere of nitrogen and the resulting mixture was stirred at room temperature for 16 h. The solution was concentrated under reduced pressure and then further concentrated on high-vac to afford the crude compound. The crude compound was triturated with MTBE and hexane, filtered, and dried under reduced pressure to afford 3-(6-(1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl (**47b**, 350 mg, 0.68 mmol, 71% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 322.2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.06 (s, 1H), 9.34 (s, 2H), 9.04 (s, 1H), 8.62 (s, 1H), 8.21-8.14 (m, 3H), 6.53 (s, 1H), 4.31-4.27 (m, 1H), 3.87-3.83 (m, 2H), 3.41-3.37 (m, 2H), 2.89-2.73 (m, 3H), 2.68-2.63 (m, 1H), 2.47-2.40 (m, 1H), 2.22-2.19 (m, 1H).

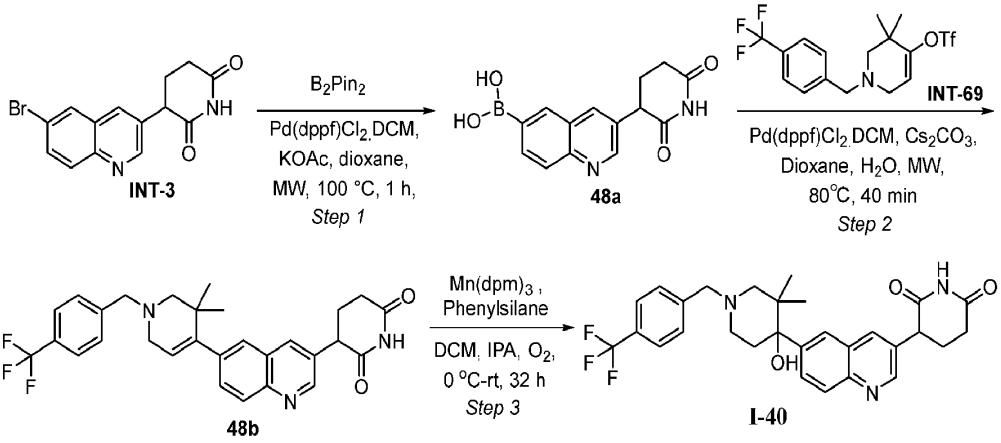
Step 3: **Synthesis of 3-(6-(1-(4-(Trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)piperidine-2,6-dione (47c)**

A solution of 3-(6-(1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl (**47b**, 150 mg, 1.0 eq., 0.42 mmol) and 4-(trifluoromethyl)benzaldehyde (**17e**, 88 mg, 1.2 eq., 0.50mmol) in DMF (8 mL) was stirred at room temperature for 1 h. Sodium triacetoxyborohydride (222 mg, 1.05 mmol) was then added in portions and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure and then further concentrated on high-vac to afford crude product. This crude material was purified by silica gel flash column chromatography using Biotage Isolera® (on silica gel 100-200 mesh) eluting with a linear gradient of 0-100% EtOAc in hexanes to afford 3-(6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**47c**, 170 mg, 0.34 mmol, 81% yield). The product was carried onto the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 480.7. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.98 (s, 1H), 8.75 (s, 1H), 8.17 (d, J = 2.00 Hz, 1H), 7.96-7.91 (m, 3H), 7.72 (d, J = 8.00 Hz, 2H), 7.62 (d, J = 8.00 Hz, 2H), 6.42 (s, 1H), 4.17-4.13 (m, 1H), 3.73 (s, 2H), 3.17 (d, J = 2.80 Hz, 2H), 2.77-2.72 (m, 4H), 2.64-2.62 (m, 2H), 2.47-2.40 (m, 1H), 2.21-2.12 (m, 1H).

Step 4: **Synthesis of 3-(6-(4-Hydroxy-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-56)**

3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione was synthesized according to **General Procedure 3, Step C** starting from 3-(6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**47c**, 170 mg, 1.0 eq., 0.36 mmol). The crude material was purified by preparative-HPLC [(Column: X select (150 x 19 mm) 5 µm, eluting with Mobile phase A: 0.05% HCl in H_2O, Mobile phase B: Acetonitrile, flow rate: 15 mL/min)]. The pure product containing fractions were collected and lyophilized to afford 3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-56**, 84 mg, 0.15 mmol, 47% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 498.5. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.52 (s, 1H), 11.06 (s, 1H), 9.10 (s, 1H), 8.77 (s, 1H), 8.26-8.21 (m, 2H), 8.08 (d, J = 8.40 Hz, 1H), 7.97 (d, J = 8.00 Hz, 2H), 7.87 (d, J = 8.00 Hz, 2H), 5.80 (s, 1H), 4.52 (d, J = 2.80 Hz, 2H), 4.30 (d, J = 10.80 Hz, 1H), 3.35 (s, 4H), 2.83-2.77 (m, 1H), 2.67-2.64 (m, 3H), 2.46-2.43 (m, 1H), 2.15-2.20 (m, 1H), 2.44 (d, J = 12.40 Hz, 2H).

Example 48: Synthesis of 3-(6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-40)



Step 1: **Synthesis of (3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)boronic acid (48a)**

(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)boronic acid (**48a**) was synthesized according to **General Procedure 3, Step A** starting from 3-(6-bromoquinolin-3-yl)piperidine-2,6-dione (**INT-3**, 300 mg, 1.0 eq., 0.94 mmol). This crude material was purified by silica gel flash column chromatography using Biotage Isolera® (on silica gel 100-200 mesh) eluting with 0-100% EtOAc in hexanes to afford (3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)boronic acid (**48a**, 330 mg, 0.51 mmol, 54% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 285.0. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 8.85 (s, 1H),

8.33 (d, *J* = 12.00 Hz, 2H), 8.00-7.93 (m, 2H), 4.18-4.14 (m, 1H), 3.65-3.57 (m, 1H), 2.79-2.51 (m, 1H), 2.46-2.44 (m, 1H), 2.17-2.14 (m, 1H).

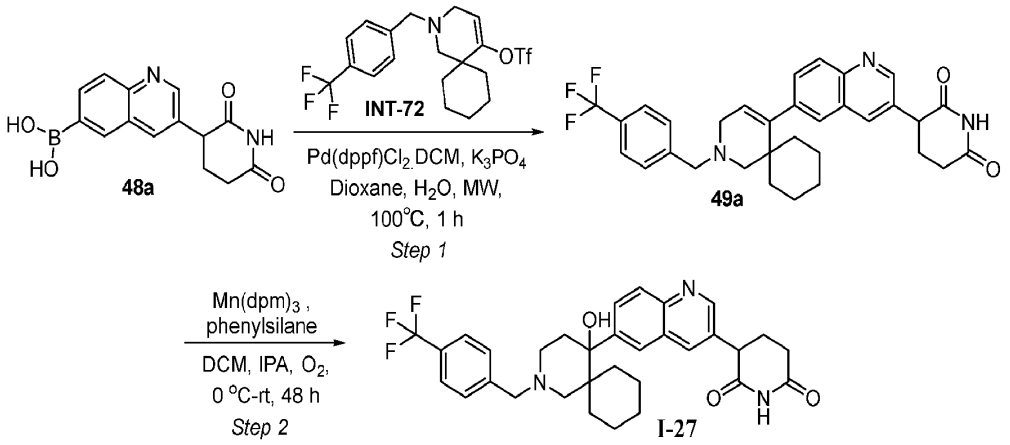
Step 2: **Synthesis of 3-(6-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)piperidine-2,6-dione (48b)**

3-(6-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**48b**) was synthesized according to **General Procedure 3, Step B** starting from (3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)boronic acid (**48a**, 280 mg, 1.0 eq., 1.0mmol) and 3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (**INT-69**, 494 mg, 1.2 eq., 1.18mmol). This crude material was purified by silica gel flash column chromatography using Biotage Isolera® (on silica gel 100-200 mesh) eluting with 0-100% EtOAc in hexanes to afford 3-(6-(3,3-dimethyl-1-(4-(trifluoromethyl)-benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**48b**, 250 mg, 0.44 mmol, 45% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 508.2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.97 (s, 1H), 8.77 (d, *J* = 2.00 Hz, 1H), 8.21 (d, *J* = 1.00 Hz, 1H), 7.95 (d, *J* = 8.80 Hz, 1H), 7.75-7.73 (m, 3H), 7.66-7.57 (m, 4H), 5.58 (t, *J* = 3.20 Hz, 1H), 4.17-4.12 (m, 1H), 3.72 (s, 2H), 3.11 (d, *J* = 2.80 Hz, 1H), 2.78-2.75 (m, 1H), 2.64-2.59 (m, 1H), 2.48-2.44 (m, 3H), 2.17-2.13 (m, 1H), 1.08 (s, 6H).

Step 3: **Synthesis of 3-(6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-40)**

3-(6-(4-Hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-40**) was synthesized according to **General Procedure 3, Step C** starting from 3-(6-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**48b,** 250 mg, 1.0 eq., 0.49 mmol). The crude material was purified by preparative-HPLC [X-SELECT C18 (250*19*5U), eluting with Mobile phase A: 0.1% formic acid in H_2O, Mobile phase B: Acetonitrile, flow rate: 15 mL/min, Rt:11.6]. The pure product containing fractions were collected and lyophilized to afford 3-(6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-40**, 18.10 mg, 0.03 mmol, 7% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 526.2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.96 (s, 1H), 8.76 (d, *J* = 2.00 Hz, 1H), 8.21 (s, 1H), 8.00 (s, 1H), 7.94 (s, 2H), 7.72 (d, *J* = 8.00 Hz, 2H), 7.61 (d, *J* = 8.00 Hz, 2H), 4.85 (s, 1H), 4.16-4.12 (m, 1H), 3.69-3.55 (m, 2H), 2.91-2.88 (m, 3H), 2.67-2.61 (m, 4H), 2.39-2.33 (m, 2H), 1.56 (d, *J* = 13.20 Hz, 1H), 0.93 (s, 3H), 0.69 (s, 3H).

Example 49: Synthesis of 3-(6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]-undecan-5-yl)quinolin-3-yl)piperidine-2,6-dione (I-27)



Step 1: **Synthesis of 3-(6-(2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)quinolin-3-yl)piperidine-2,6-dione (49a)**

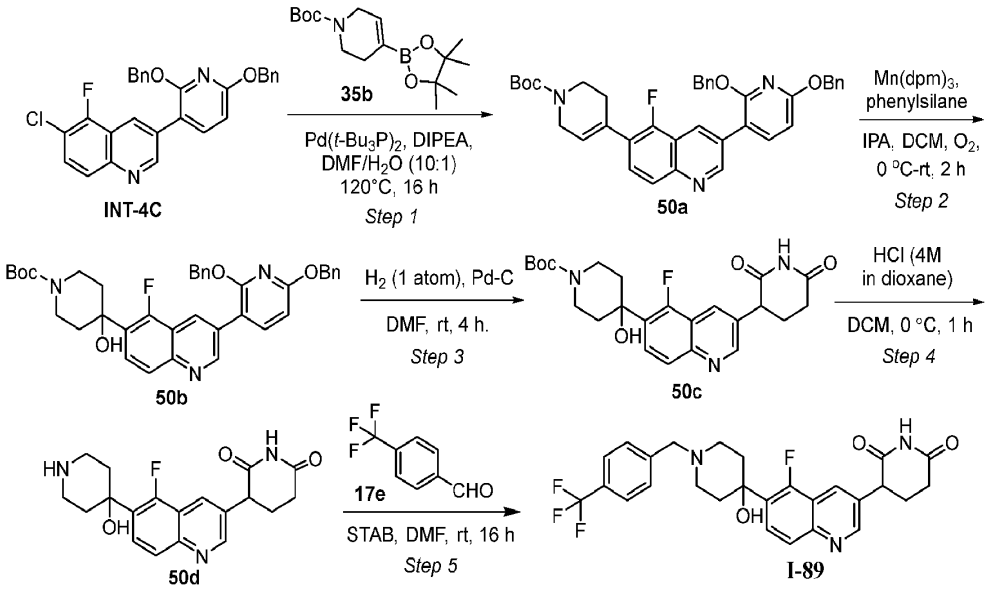
3-(6-(2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)quinolin-3-yl)piperidine-2,6-dione (**49a**) was synthesized according to **General Procedure 3, Step B** starting from (3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)boronic acid (**48a**, 300 mg, 1.0 eq., 1.06 mmol) and 2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl trifluoromethanesulfonate (**INT-72**, 580 mg, 1.2 eq., 1.27 mmol). The crude material was purified by silica gel flash column chromatography using Biotage Isolera® (on silica gel 100-200 mesh) and eluting with 0-80% EtOAc in hexanes to afford 3-(6-(2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)quinolin-3-yl)piperidine-2,6-dione (**49a**, 250 mg, 0.39 mmol, 37% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 548.2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.97 (s, 1H), 8.77 (s, 1H), 8.21 (s, 1H), 7.94 (d, J = 8.80 Hz, 1H), 7.75-7.63 (m, 5H), 7.52-7.49 (m, 1H), 5.51 (s, 1H), 4.17-4.12 (m, 1H), 3.77 (s, 2H), 3.11 (s, 2H), 2.51-2.64 (m, 4H), 2.44-2.33 (m, 2H), 1.89-1.72 (m, 2H), 1.42-1.32 (m, 8H).

Step 2: **Synthesis of 3-(6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)piperidine-2,6-dione (I-27)**

3-(6-(5-Hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)piperidine-2,6-dione (**I-27**) was synthesized according to **General Procedure 3, Step C** starting from 3-(6-(2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)quinolin-3-yl)piperidine-2,6-dione (**49a**, 250 mg, 1.0 eq., 0.46 mmol). The crude compound was purified by preparative-HPLC [(Column: X select (150 x 19 mm) 5 µm, eluting with Mobile phase A: 0.05% acetic acid in H_2O, Mobile phase B: Acetonitrile, flow rate: 15 mL/min)]. The pure product containing fractions were collected and lyophilized to afford 3-(6-(5-hydroxy-2-(4-(trifluoro-methyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)piperidine-2,6-dione (**I-27**, 7.2 mg, 0.01 mmol, 3% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 566.3., ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.97 (s, 1H), 8.76 (s, 1H), 8.22 (s, 1H),

7.98-7.89 (m, 3H), 7.73-7.38 (m, 4H), 4.81 (s, 1H), 4.16-4.12 (m, 1H), 3.69-3.32 (m, 2H), 2.31-2.86 (m, 9H), 1.78-1.73 (m, 2H), 1.52 (m, 1H), 1.49 (m, 3H), 1.29-1.02 (m, 5H).

Example 50: Synthesis of 3-(5-fluoro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-89)



Step 1: **Synthesis of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (50a)**

tert-Butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**50a**) was synthesized according to **General Procedure 5** starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-chloro-5-fluoroquinoline (**INT-4C**, 500 mg, 1.0 eq., 1.06 mmol) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**35b**, 657 mg, 2.0 eq., 2.12 mmol). The crude product was purified by silica gel flash column chromatography using Biotage Isolera® (on neutral alumina) eluting with 0-100% EtOAc in hexanes to afford *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**50a**, 0.3 g, 0.41 mmol, 39% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+ = 618.2$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.15 (s, 1H), 8.60 (d, J = 1.60 Hz, 1H), 8.06 (d, J = 8.40 Hz, 1H), 7.89-7.85 (m, 1H), 7.76-7.49 (m, 1H), 7.48-7.41 (m, 10H), 6.67 (d, J = 8.40 Hz, 1H), 6.17 (s, 1H), 5.47 (d, J = 10.00 Hz, 4H), 4.08-4.03 (m, 2H), 3.91 (s, 2H), 2.52-2.51 (m, 2H), 1.50-1.46 (m, 9H).

Step 2: **Synthesis of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (50b)**

tert-Butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (**50b**) was synthesized according to **General Procedure 3, Step C** starting from *tert*-butyl 4-

(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**50a**, 300 mg, 1.0 eq., 0.49 mmol). The crude product was purified by silica gel flash column chromatography using Biotage Isolera® (on silica gel 100-200 mesh) eluting with 0-100% EtOAc in hexanes to afford *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (**50b**, 0.18 g, 0.22 mmol, 44% yield) as liquid. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 636.4. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.14 (d, *J* = 2.00 Hz, 1H), 8.61 (d, *J* = 1.60 Hz, 1H), 8.03-8.03 (m, 2H), 7.88 (d, *J* = 9.20 Hz, 1H), 7.50-7.43 (m, 10H), 6.66 (s, 1H), 5.62 (s, 1H), 5.49-5.45 (m, 4H), 3.93 (s, 2H), 3.33-3.27 (m, 2H), 2.19-2.16 (m, 2H), 1.70-1.67 (m, 2H), 1.49 (s, 9H).

Step 3: **Synthesis of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (50c)**

Tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (**50c**) was prepared according to the procedures and examples as reported in PCT Application Publication No. WO2023/23255.

tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (**50c**) was synthesized according to **General Procedure 1, Step B** starting from *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (**50b**, 180 mg, 1.0 eq., 0.28 mmol). The crude material was purified by reverse phase chromatography C18 (12 g), eluting with Mobile phase A: 0.1% HCOOH in H_2O: MeCN, Mobile phase B: Acetonitrile, flow rate: 15 mL/min]. The pure product containing fractions were collected and lyophilized to afford *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (**50c**, 0.08 g, 0.14 mmol, 49% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 458.2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.97 (s, 1H), 8.85 (d, *J* = 2.00 Hz, 1H), 8.33 (s, 1H), 8.06 (t, *J* = 8.80 Hz, 1H), 7.89 (d, *J* = 8.80 Hz, 1H), 5.60 (s, 1H), 4.25-4.21 (m, 1H), 3.88-3.52 (m, 3H), 3.31-3.21 (m, 3H), 2.75-2.72 (m, 2H), 2.12-2.00 (m, 4H), 2.00-1.67 (m, 3H), 1.43-1.36 (m, 6H).

Step 4: **Synthesis of 3-(5-fluoro-6-(4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (50d)**

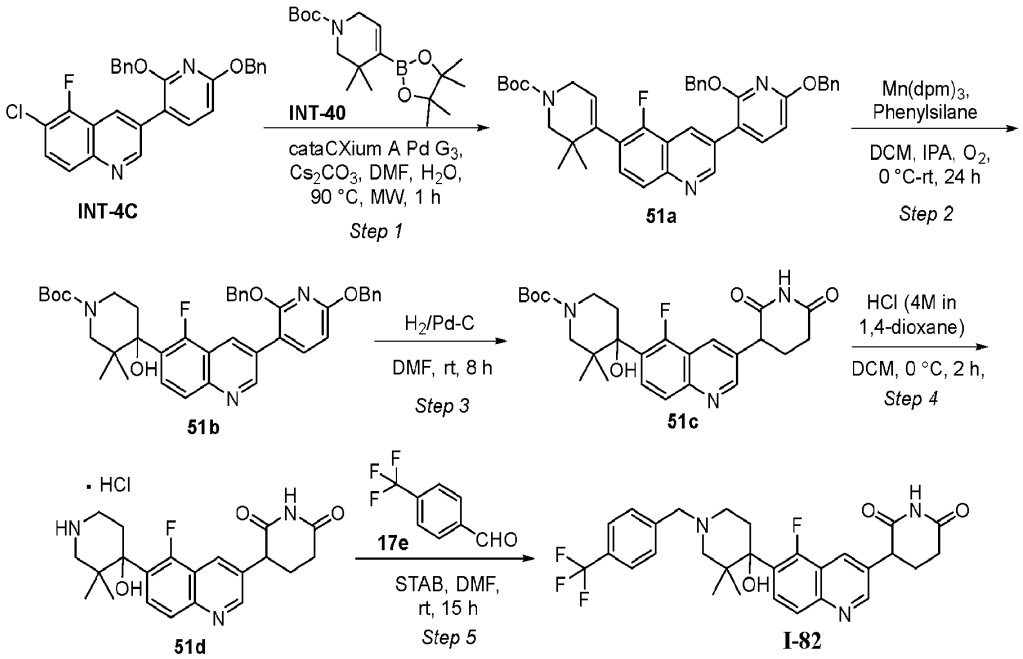
3-(5-fluoro-6-(4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**50d**, 30 mg, 0.07 mmol, 35% yield) was synthesized according to **General Procedure 1, Step C** starting from *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-piperidine-1-carboxylate (**50c**, 80 mg, 1.0 eq., 0.18 mmol). The crude compound was carried onto the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 358.2.

Step 5: **Synthesis of 3-(5-fluoro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-89)**

3-(5-fluoro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-89**) was synthesized according to **General Procedure 1, Step D** starting from 3-(5-fluoro-6-

(4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**50d**, 30 mg, 1.0 eq., 0.066 mmol) and 4-(trifluoromethyl)benzaldehyde (**17e**, 17.7 mg, 1.5 eq., 0.10 mmol). The crude compound was purified by preparative-HPLC [(Column: X Select C^{18} (250*19mm) eluting with Mobile phase A: 0.05% HCl in H_2O: MeCN, Mobile phase B: Acetonitrile, flow rate: 15 mL/min, Rt:12.5 min)]. The pure product containing fractions were collected and lyophilized to afford 3-(5-fluoro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-89**, 3 mg, 5.41 µmol, 9% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 516.3. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 10.40 (s, 1H), 8.92 (s, 1H), 8.36 (s, 1H), 8.04 (t, *J* = 8.80 Hz, 1H), 7.96-7.90 (m, 5H), 6.01 (S, 1H), 4.53 (d, *J* = 5.20 Hz, 2H), 4.26-4.23 (m, 1H), 3.42-3.36 (m, 4H), 2.74-2.67 (m, 1H), 2.64-2.45 (m, 4H), 2.34-2.33 (m, 1H), 2.21-2.14 (m, 2H).

Example 51: Synthesis of 3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-82)



Step 1: **Synthesis of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2*H*)-carboxylate (51a)**

tert-Butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (**51a**) was synthesized according to **General Procedure 5** starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-chloro-5-fluoroquinoline (**INT-4C**, 1.5 g, 1.0 eq., 3.18 mmol) and *tert*-butyl 3,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**INT-40**, 2.15 g, 2.0 eq., 6.37 mmol). The crude material was purified by flash column chromatography using Biotage Isolera® (on silica gel, 100-200 mesh) eluting with 0-60% EtOAc in

hexanes to afford *tert*-butyl 4-(3-(2,6-bis(benzyloxy)-pyridin-3-yl)-5-fluoroquinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2*H*)-carboxylate (**51a**, 1.0g, 1.55mmol, 45% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 646.6. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.17 (s, 1H), 8.59 (s, 1H), 8.06 (d, *J* = 8.00 Hz, 1H), 7.84 (d, *J* = 8.40 Hz, 1H), 7.53-7.51 (m, 3H), 7.49-7.42 (m, 4H), 7.36-7.32 (m, 4H), 6.67 (d, *J* = 8.00 Hz, 1H), 5.61 (s, 1H), 5.46 (d, *J* = 5.20 Hz, 4H), 4.04 (t, *J* = 7.20 Hz, 2H), 3.33 (s, 2H), 1.44 (s, 9H), 1.09 (s, 6H).

Step 2: **Synthesis of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (51b)**

tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (**51b**) was synthesized according to **General Procedure 3, Step C** starting from *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2*H*)-carboxylate (**51a**, 1.0 g, 1.0 eq., 1.55 mmol). The crude material was purified by flash column chromatography using Biotage Isolera® on silica gel (100-200 mesh) eluting with 0 to 70% EtOAc in hexane to afford *tert*-butyl 4-(3-(2,6-bis(benzyloxy)-pyridin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (**51b**, 0.33g, 0.5mmol, 31% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 664.7. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.15 (s, 1H), 8.63 (s, 1H), 8.08 (d, *J* = 8.40 Hz, 2H), 7.85 (d, *J* = 9.20 Hz, 1H), 7.46-7.36 (m, 9H), 6.67 (d, *J* = 8.00 Hz, 2H), 5.46 (s, 4H), 3.98 (d, *J* = 39.20 Hz, 1H), 3.93-2.50 (m, 4H), 1.69-1.66 (m, 2H), 1.70 (s, 9H), 1.26 (s, 3H), 0.79 (s, 3H).

Step 3: **Synthesis of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (51c)**

tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethyl-piperidine-1-carboxylate (**51c**, 550mg, 1.13mmol, 57% yield;) was synthesized according to **General Procedure 1, Step B** starting from *tert*-butyl 4-(3-(2,6-bis(benzyloxy)-pyridin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (**51b**, 1.0 g, 1.0 eq., 1.5 mmol). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 486.8. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.98 (s, 1H), 8.86 (s, 1H), 8.33 (d, *J* = 2.00 Hz, 1H), 8.09 (t, *J* = 4.8 Hz, 1H), 7.87 (d, *J* = 8.80 Hz, 1H), 5.45 (s, 1H), 4.24-4.20 (m, 1H), 4.03 (br s, 2H), 3.49-3.23 (m, 3H), 2.96-2.92 (m, 1H), 2.77-2.72 (m, 1H), 2.68-2.60 (m, 1H), 2.16-2.11 (m, 1H), 1.68 (d, *J* = 13.20 Hz, 1H), 1.41 (s, 9H), 0.86 (s, 3H). 0.68 (s, 3H).

Step 4: **Synthesis of 3-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (51d)**

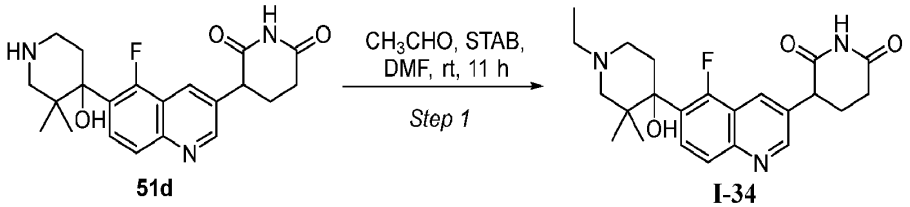
3-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, (**51d**, 500 mg, 1.06 mmol, 93% yield) was synthesized according to **General Procedure 1, Step C** starting from *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-

1-carboxylate (**51c**, 550 mg, 1.0 eq., 1.13 mmol). The product obtained was taken onto the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 386.0. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 9.08 (d, *J* = 11.60 Hz, 1H), 8.90 (s, 1H), 8.38 (s, 2H), 8.08 (t, *J* = 8.40 Hz, 1H), 7.99-7.89 (m, 1H), 5.87 (s, 1H), 4.27-4.22 (m, 1H), 3.23-2.90 (m, 4H), 2.74-2.60 (m, 2H), 2.15-1.91 (m, 2H), 1.30-1.19 (m, 2H), 1.05 (s, 3H), 0.76 (s, 3H).

Step 5: **Synthesis of 3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-82)**

3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-82**) was synthesized according to **General Procedure 1, Step D** starting from 3-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**51d**, 100 mg, 1.0 eq., 0.24mmol) and 4-(trifluoromethyl)benzaldehyde (**17e**, 41 mg, 1.0 eq., 0.24 mmol). The crude compound was purified by preparative-HPLC [(Column: X Select C^{18} (250*19mm) eluting with Mobile phase A: 0.05% HCl in H_2O: MeCN, Mobile phase B: Acetonitrile, flow rate: 15 mL/min]. The pure product containing fractions were collected and lyophilized to afford 3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-82**, 14.99 mg, 0.03 mmol, 12% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 544.3. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 9.98 (s, 1H), 8.89 (d, *J* = 2.00 Hz, 1H), 8.38 (s, 1H), 8.07 (t, *J* = 8.80 Hz, 1H), 7.93-7.95 (m, 5H), 5.93 (s, 1H), 4.56-4.48 (m, 2H), 4.29 (d, *J* = 4.80 Hz, 1H), 3.61-3.33 (m, 4H), 2.82 (t, *J* = 4.40 Hz, 2H), 2.76-2.62 (m, 2H), 2.27-2.25 (m, 1H), 2.02-1.99 (m, 1H), 1.11 (s, 3H), 0.78 (s, 3H).

Example 52: Synthesis of 3-(6-(1-ethyl-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (I-34)

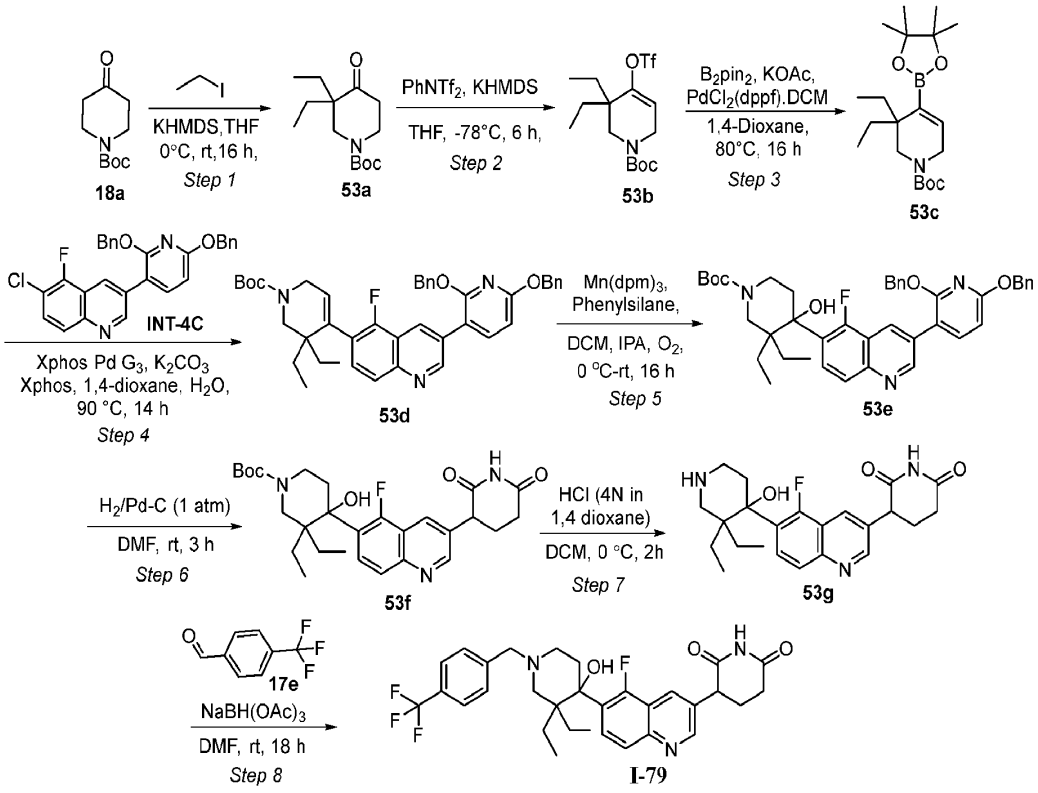


51d **I-34**

3-(6-(1-ethyl-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (**I-34**) was synthesized according to **General Procedure 1, Step D** starting from 3-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**51d**, 250 mg, 1.0 eq., 0.65 mmol) and acetaldehyde (0.073 mL, 2.0 eq., 1.3 mmol). The crude product was purified by reverse phase purification using Column: C18, eluting with Mobile phase A: 0.1% HCOOH in H_2O, Mobile phase B: Acetonitrile, product eluted at 50% MeCN in water (0.1% HCOOH)]. The pure product containing fractions were collected and lyophilized to afford 3-(6-(1-ethyl-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-

fluoroquinolin-3-yl)piperidine-2,6-dione (**I-34**, 21.1 mg, 0.05 mmol, 7% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 414.2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.98 (s, 1H), 8.85 (d, *J* = 2.00 Hz 1H), 8.33 (s, 1H), 8.18 (s, 1H), 8.10 (t, *J* = 8.80 Hz, 1H), 7.84 (d, *J* = 8.80 Hz, 1H), 5.11 (s, 1H), 4.25-4.20 (m, 1H), 3.14-3.07 (m, 1H), 2.68-2.51 (m, 4H), 2.44-2.42 (m, 4H), 2.39-2.37 (m, 1H), 2.32 (t, *J* = 12.80 Hz, 1H), 1.71 (d, *J* = 12.80 Hz, 1H), 1.23 (t, *J* = 7.20 Hz, 3H), 1.07 (s, 3H), 0.82 (s, 3H).

Example 53: Synthesis of 3-(6-(3,3-diethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (I-79)



Step 1: **Synthesis of *tert*-butyl 3,3-diethyl-4-oxopiperidine-1-carboxylate (53a)**

To a solution of *tert*-butyl 4-oxopiperidine-1-carboxylate (**18a**, 40 g, 201 mmol) in THF (480 mL) under an atmosphere of nitrogen was added KHMDS (1 M in THF) (500 mL, 500 mmol) at 0 °C and the resulting mixture was stirred for 1 h. Iodoethane (125 g, 804 mmol) was then added and stirring was continued at 25 °C for 16 h. Water (500 mL) was added and the resulting aqueous mixture was extracted with EtOAc (2 x 500 mL). The combined organic phases were washed with water (50 mL) and brine solution (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. This crude material was purified by flash column chromatography using Biotage Isolera® (on silica gel 100-200 mesh) eluting with 0-10% EtOAc in hexanes to afford *tert*-butyl 3,3-diethyl-4-oxopiperidine-1-carboxylate (**53a**, 7 g, 23.03 mmol, 11% yield). LCMS: m/z MM-ES+APCI, Positive $[M-Boc+H]^+$ 156.0.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.60 (t, J = 6.40 Hz, 2H), 3.40 (s, 2H), 2.39 (t, J = 6.40 Hz, 2H), 1.52-1.37 (m, 13H), 0.72 (t, J = 7.60 Hz, 6H).

Step 2: **Synthesis of *tert*-butyl 3,3-diethyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (53b)**

To a solution of *tert*-butyl 3,3-diethyl-4-oxopiperidine-1-carboxylate (4 g, 15.66 mmol) in THF (40 mL) was added KHMDS (1 M in THF) (31.32 mL, 31.32 mmol) under an atmosphere of nitrogen at -78 °C and the resulting mixture was stirred at -78 °C for 1 h. N-phenylbis(trifluoromethanesulfonimide) (11.18 g, 31.32 mmol) dissolved in THF (10 mL) was then added dropwise at -78 °C and stirring was continued at 25 °C for 6 h. Water (100 mL) was added and the resulting aqueous mixture was extracted with EtOAc (150 mL). The organic phases were washed with water (50 mL) and brine solution (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. This crude material was purified by flash column chromatography using Biotage Isolera® (on silica gel 100-200 mesh) eluting with 0-50% EtOAc in hexanes to afford *tert*-butyl 3,3-diethyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (**53b**, 4.5 g, 11.57 mmol, 74% yield) as gum, LCMS: m/z MM-ES+APCI, Positive $[M\text{-}tBu+H]^+$ 332.2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 5.96 (s, 1H), 4.01 (s, 2H), 3.42 (s, 2H), 1.48-1.37 (m, 13H), 0.85 (t, J = 7.20 Hz, 6H).

Step 3: **Synthesis of *tert*-butyl 3,3-diethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (53c)**

A solution of *tert*-butyl 3,3-diethyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydro-pyridine-1(2H)-carboxylate (**53b**, 5 g, 12.9 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (4.91 g, 19.35 mmol) and potassium acetate (3.8 g, 38.7 mmol) in 1,4-dioxane (10 mL) was degassed with nitrogen at 25 °C for 10 min. $Pd(dppf)Cl_2$•DCM(1.05 g, 1.29 mmol) was then added and the resulting mixture was stirred at 80 °C for 16 h. The reaction mixture was concentrated under reduced pressure and the crude material was purified by flash column chromatography using Biotage Isolera® (on silica gel 100-200 mesh) eluting with 0-7% EtOAc in hexanes to afford *tert*-butyl 3,3-diethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**53c**, 2.5 g, 6.84 mmol, 53% yield). LCMS: m/z MM-ES+APCI, Positive $[M—tBu+H]^+$ 310.32. 1H-NMR (400 MHz, $CDCl_3$): δ 6.55-6.45 (m, 1H), 3.95-3.85 (m, 2H), 3.3-3.25 (m, 2H), 1.48 (br s, 4H), 1.27 (m, 21H), 0.81 (t, J = 7.60 Hz, 6H).

Step 4: **Synthesis of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-3,3-diethyl-3,6-dihydropyridine-1(2H)-carboxylate (53d)**

tert-Butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-3,3-diethyl-3,6-dihydropyridine-1(2H)-carboxylate (**53d**) was synthesized according to **General Procedure 5** starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-chloro-5-fluoroquinoline (**INT-4C**, 500mg, 1.0 eq., 1.06

mmol) and *tert*-butyl 3,3-diethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**53c**, 582 mg, 1.5 eq., 1.59 mmol). The crude material was purified by flash column chromatography Biotage Isolera® on silica gel (100-200 mesh) eluting with 0 to 20% EtOAc in *n*-hexane to afford *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-3,3-diethyl-3,6-dihydropyridine-1(2H)-carboxylate (**53d**, 0.3 g, 0.37 mmol, 34% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 674.4. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.16 (d, *J* = 2.40 Hz, 1H), 8.60 (d, *J* = 1.60 Hz, 1H), 8.07 (d, *J* = 8.00 Hz, 1H), 7.83 (d, *J* = 8.80 Hz, 1H), 7.52-7.37 (m, 11H), 6.67 (d, *J* = 8.40 Hz, 1H), 5.77 (m, 1H), 5.46 (m, 4H), 4.06-4.01 (m, 2H), 3.46 (s, 2H), 1.46 (s, 9H), 1.43-1.41 (m, 4H), 0.80 (s, 6H).

Step 5: **Synthesis of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-3,3-diethyl-4-hydroxypiperidine-1-carboxylate (53e)**

tert-Butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-3,3-diethyl-4-hydroxypiperidine-1-carboxylate (**53e**) was synthesized according to **General Procedure 3, Step C** starting from *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-3,3-diethyl-3,6-dihydropyridine-1(2H)-carboxylate (**53d**, 400 mg, 1 eq., 0.59 mmol). The crude material was purified by flash column chromatography using Biotage Isolera® on silica gel (100-200 mesh) eluting with 0 to 50% EtOAc in hexane to afford *tert*-butyl 4-(3-(2,6-bis(benzyloxy)-pyridin-3-yl)-5-fluoroquinolin-6-yl)-3,3-diethyl-4-hydroxypiperidine-1-carboxylate (**53e**, 140 mg, 0.20 mmol, 34% yield). LCMS: m/z MMES+APCI, Positive $[M+H]^+$ 692.6. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.14 (d, *J* = 2.00 Hz, 1H), 8.63 (s, 1H), 8.19-0.15 (m, 1H), 8.07 (d, *J* = 8.40 Hz, 1H), 7.84 (d, *J* = 9.20 Hz, 1H), 7.44-7.35 (m, 10H), 6.67 (d, *J* = 8.40 Hz, 1H), 5.50-5.42 (m, 5H), 4.06-4.01 (m, 2H), 3.11-3.00 (m, 4H), 1.73-1.59 (m, 4H), 1.45 (s, 9H), 1.24-1.05 (m, 6H).

Step 6: **Synthesis of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-3,3-diethyl-4-hydroxypiperidine-1-carboxylate (53f)**

tert-Butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-3,3-diethyl-4-hydroxy-piperidine-1-carboxylate (**53f**) was synthesized according to **General Procedure 1, Step B** starting from *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-3,3-diethyl-4-hydroxypiperidine-1-carboxylate (**53e**, 200 mg, 1.0 eq., 0.29 mmol). The crude product was purified by reverse phase column chromatography eluting with 5 to 100% MeCN in 0.1% formic acid in water. The pure product containing fractions were collected and lyophilized to afford *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-3,3-diethyl-4-hydroxypiperidine-1-carboxylate (**53f**, 100 mg, 0.18 mmol, 61% yield) as gum. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 514.4. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.98 (s, 1H), 8.85 (d, *J* = 2.40 Hz, 1H), 8.32 (s, 1H), 8.18 (t, *J* = 8.80 Hz, 1H), 7.85 (d, *J* = 9.20 Hz, 1H), 5.47

(s, 1H), 4.25-4.21 (m, 1H), 3.95-3.67 (m, 2H), 3.32-2.98 (m, 3H), 2.76-2.63 (m, 2H), 2.33-2.13 (m, 1H), 1.72 (s, 1H), 1.60 (m, 2H), 1.44 (s, 9H), 1.41 (s, 2H), 1.19 (s, 1H), 0.75-0.72 (m, 4H), 0.52-0.45 (m, 2H).

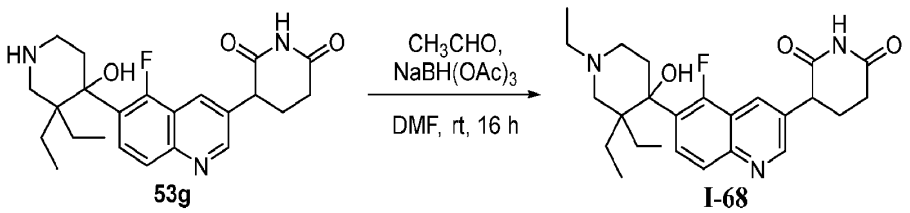
Step 7: **Synthesis of 3-(6-(3,3-diethyl-4-hydroxypiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl (53g)**

3-(6-(3,3-Diethyl-4-hydroxypiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl (**53g**, 80 mg, 0.14 mmol, 89% yield) was synthesized according to **General Procedure 1, Step C** starting from *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-3,3-diethyl-4-hydroxypiperidine-1-carboxylate (**53f**, 80 mg, 1.0 eq., 0.16 mmol). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 414.6. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 9.06 (br s, 1H), 8.90 (d, J = 2.00 Hz, 1H), 8.39 (s, 1H), 8.19-0.15 (m, 1H), 7.92-7.86 (m, 1H), 5.92 (s, 1H), 4.27-4.22 (m, 1H), 3.23-2.96 (m, 5H), 2.77-2.61 (m, 2H), 2.34-2.13 (m, 2H), 1.85-1.83 (m, 1H), 1.64-1.60 (m, 1H), 1.44 (s, 1H), 1.24-1.20 (m, 2H), 0.74-0.52 (m, 3H), 0.49-0.45 (m, 3H).

Step 8: **Synthesis of 3-(6-(3,3-diethyl-4-hydroxy-1-(4-(trifluoro-methyl)benzyl)piperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (I-79)**

3-(6-(3,3-diethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (**I-79**) was synthesized according to **General Procedure 1, Step D** starting from 3-(6-(3,3-diethyl-4-hydroxypiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl (**53g**, 40 mg, 1.0 eq., 0.09 mmol) and 4-(trifluoromethyl)benzaldehyde (**17e**, 19 mg, 1.2 eq., 0.11 mmol). The crude product was purified by preparative-HPLC [X Select C^{18} (250*19mm), eluting with Mobile phase A: 0.05% HCl in H_2O, Mobile phase B: Acetonitrile, flow rate: 15 mL/min, Rt:12.0]. The pure product containing fractions were collected and lyophilized to afford 3-(6-(3,3-diethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (**I-79**, 10.6 mg, 0.02 mmol, 20% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 572.6. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 9.85 (s, 1H), 8.89 (s, 1H), 8.38 (s, 1H), 8.14 (t, J = 8.80 Hz, 1H), 8.00 (m, 2H), 7.89 (d, J = 3.60 Hz, 3H), 5.98 (s, 1H), 4.57-4.52 (m, 2H), 4.29 (m, 2H), 3.25-3.20 (m, 4H), 2.77-2.73 (m, 2H), 2.68-2.64 (m, 1H), 2.13 (m, 2H), 1.93 (m, 1H), 1.63 (m, 1H), 1.18-1.12 (m, 2H), 0.52 (t, J = 7.20 Hz, 3H), 0.45 (t, J = 7.60 Hz, 3H).

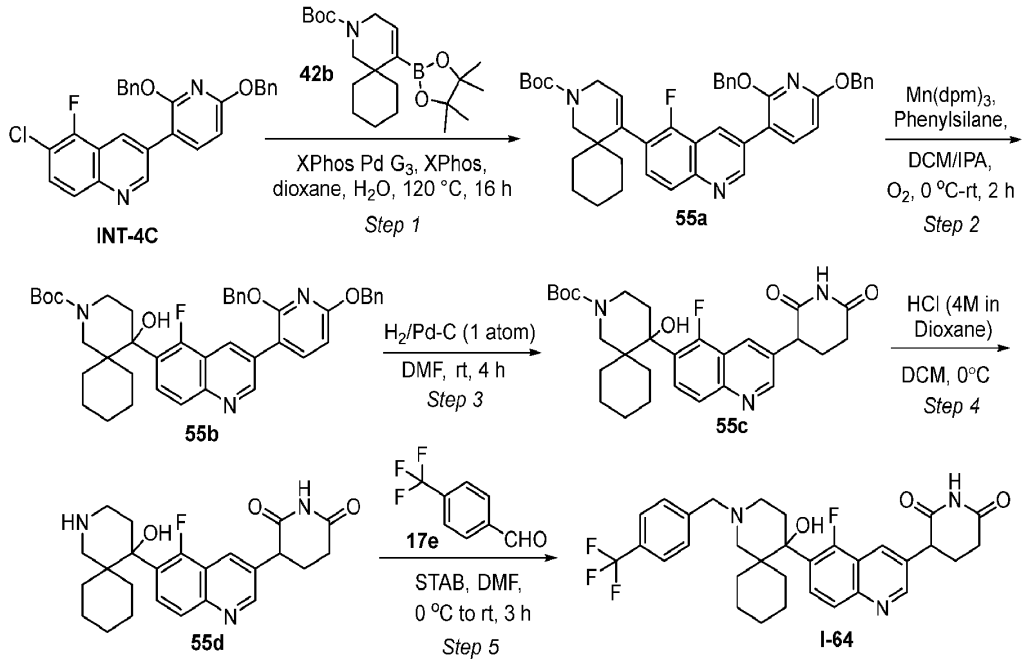
Example 54: Synthesis of 3-(5-fluoro-6-(1,3,3-triethyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-68)



53g **I-68**

3-(5-fluoro-6-(1,3,3-triethyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-68**) was synthesized according to **General Procedure 1, Step D** starting from 3-(6-(3,3-diethyl-4-hydroxypiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl (**53g**, 40 mg, 1.0 eq., 0.09mmol) and acetaldehyde (4.26 mg, 1.1 eq., 0.1mmol).. The crude product was purified by preparative-HPLC [X SELECT C18 (19*250MM), eluting with Mobile phase A: 0.05% HCl in water, Mobile phase B: Acetonitrile, flow rate: 14.0 mL/min) Rt:11.5]. The pure product containing fractions were collected and lyophilized to afford 3-(5-fluoro-6-(1,3,3-triethyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-68**, 9.5 mg, 0.02 mmol, 22% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 442.6.^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 9.42 (s, 1H), 8.91 (d, *J* = 2.00 Hz, 1H), 8.41 (s, 1H), 8.18 (m, 1H), 7.92 (m, 1H), 5.98 (s, 1H), 4.25 (m, 1H), 3.37-3.21 (m, 6H), 3.20-3.11 (m, 2H), 2.68-2.61 (m, 2H), 2.17-2.15 (m, 2H), 1.93 (m, 1H), 1.69-1.67 (m, 1H), 1.33 (t, *J* = 7.20 Hz, 3H), 1.26-1.20 (m, 2H), 0.72 (m, 3H), 0.51 (m, 3H).

Example 55: Synthesis of 3-(5-fluoro-6-(5-hydroxy-2-(4-(trifluoro-methyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)piperidine-2,6-dione (I-64)



Step 1: **Synthesis of *tert*-butyl 5-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (55a)**

tert-butyl 5-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-2-azaspiro[5.5]-undec-4-ene-2-carboxylate (**55a**) was synthesized according to **General Procedure 5** starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-chloro-5-fluoroquinoline (**INT-4C**, 250mg, 1.0 eq., 0.53 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 (**42b**,

240 mg, 1.2 eq., 0.64 mmol). This crude material was purified by flash column chromatography using Biotage Isolera® (on silica gel 100-200 mesh) eluting with 0-100% EtOAc in hexanes to afford *tert*-butyl 5-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-quinolin-6-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (**55a**, 150 mg, 0.19 mmol, 36% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 686.5. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.16 (s, 1H), 8.60 (s, 1H), 8.06 (d, J = 8.40 Hz, 1H), 7.83 (d, J = 8.40 Hz, 1H), 7.41-7.37 (m, 11H), 6.67 (d, J = 8.00 Hz, 1H), 5.65-5.58 (m, 1H), 5.47 (s, 2H), 5.46 (s, 2H), 4.06-4.01 (m, 2H), 3.64 (s, 2H), 1.47-1.16 (m, 19H).

Step 2: **Synthesis of *tert*-butyl 5-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-5-hydroxy-2-azaspiro[5.5]undecane-2-carboxylate (55b)**

tert-Butyl 5-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-5-hydroxy-2-azaspiro[5.5]undecane-2-carboxylate (**55b**) was synthesized according to **General Procedure 3, Step C** starting from *tert*-butyl 5-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (**55a**, 500 mg, 1.0 eq., 0.73 mmol). The crude material was purified by flash column chromatography using Biotage Isolera® on silica gel (100-200 mesh) eluting with 0 to 100% EtOAc in hexane to afford *tert*-butyl 5-(3-(2,6-bis(benzyloxy)-pyridin-3-yl)-5-fluoroquinolin-6-yl)-5-hydroxy-2-azaspiro[5.5]undecane-2-carboxylate (**55b**, 0.2 g, 0.22 mmol, 31% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 704.4, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.15 (s, 1H), 8.62 (s, 1H), 8.08 (d, J = 8.00 Hz, 2H), 7.91-7.83 (m, 1H), 7.43-7.39 (m, 10H), 6.67 (d, J = 8.00 Hz, 1H), 5.42-5.39 (m, 5H), 4.19-4.01 (m, 2H), 3.07-2.96 (m, 2H), 1.82-1.45 (m, 4H), 1.20-1.14 (m, 17H).

Step 3: **Synthesis of *tert*-butyl 5-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-5-hydroxy-2-azaspiro[5.5]undecane-2-carboxylate (55c)**

tert-Butyl 5-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-5-hydroxy-2-azaspiro-[5.5]undecane-2-carboxylate (**55c**, 170 mg, 0.27 mmol, 64% yield) was synthesized according to **General Procedure 1, Step B** starting from *tert*-butyl 5-(3-(2,6-bis(benzyloxy)-pyridin-3-yl)-5-fluoroquinolin-6-yl)-5-hydroxy-2-azaspiro[5.5]undecane-2-carboxylate (**55b**, 300 mg, 1.0 eq., 0.43 mmol). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 526.3.

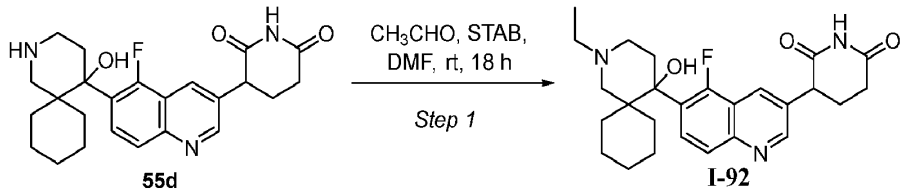
Step 4: **Synthesis of 3-(5-fluoro-6-(5-hydroxy-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)piperidine-2,6-dione (55d)**

3-(5-Fluoro-6-(5-hydroxy-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)piperidine-2,6-dione (**55d**) was synthesized according to **General Procedure 1, Step C** starting from *tert*-butyl 5-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-5-hydroxy-2-azaspiro[5.5]undecane-2-carboxylate (**55c**, 170 mg, 1.0 eq., 0.32 mmol). The crude compound was triturated with hexane 10 mL, filtered, and dried to afford 3-(5-fluoro-6-(5-hydroxy-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)piperidine-2,6-dione (**55d**, 120 mg, 0.21 mmol, 64% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 426.1.

Step 5: **Synthesis of 3-(5-fluoro-6-(5-hydroxy-2-(4-(trifluoro-methyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)piperidine-2,6-dione (I-64)**

3-(5-fluoro-6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)piperidine-2,6-dione (**I-64**) was synthesized according to **General Procedure 1, Step D** starting from 3-(5-fluoro-6-(5-hydroxy-2-azaspiro[5.5]-undecan-5-yl)quinolin-3-yl)piperidine-2,6-dione (**55d,** 60 mg, 1.0 eq., 0.13 mmol) and 4-(trifluoromethyl)benzaldehyde (**17e**, 23 mg, 1.0 eq., 0.13 mmol). The crude compound was purified by preparative-HPLC [(Column: X Select C^{18} (250*19mm) eluting with Mobile phase A: 0.05% HCl in H_2O: MeCN, Mobile phase B: Acetonitrile, flow rate: 15 mL/min]. The pure product containing fractions were collected and lyophilized to afford 3-(5-fluoro-6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)piperidine-2,6-dione (**I-64**, 4.5 mg, 7.23 µmol, 6% yield) as solid. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 584.2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 9.50 (s, 1H), 8.89 (s, 1H), 8.36 (s, 1H), 8.03 (t, *J* = 8.80 Hz, 1H), 7.93-7.89 (m, 5H), 5.88 (s, 1H), 4.60 (s, 2H), 4.26-0.21 (m, 1H), 3.67-3.61 (m, 2H), 3.19-3.17 (m, 2H), 2.77-2.64 (m, 2H), 2.45-2.39 (m, 2H), 2.15-2.12 (m, 1H), 1.97-1.92 (m, 1H), 1.83 (d, *J* = 13.20 Hz, 1H), 1.44-1.24 (m, 4H), 1.08-0.84 (m, 5H).

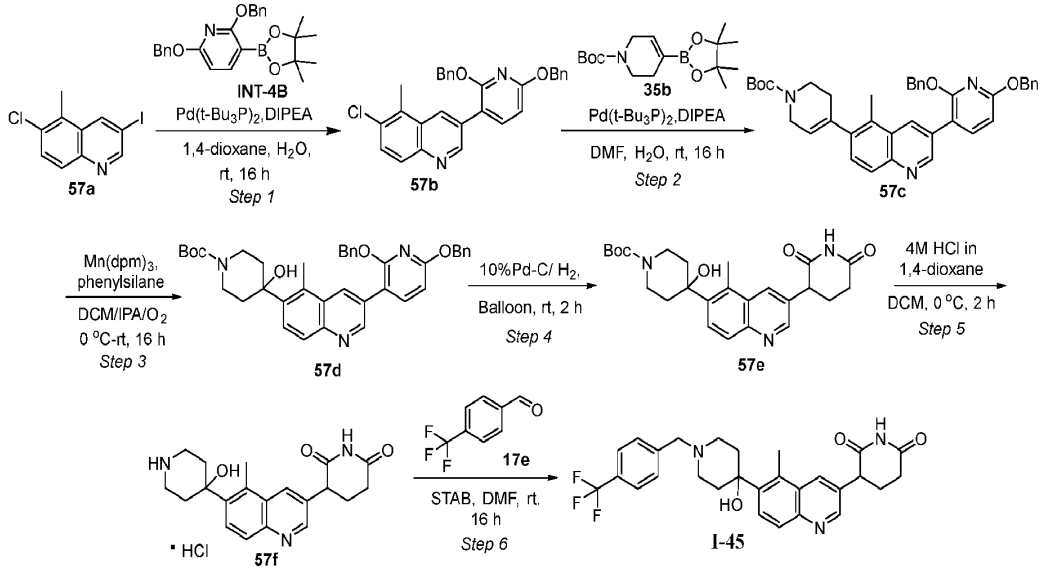
Example 56: Synthesis of 3-(6-(2-ethyl-5-hydroxy-2-azaspiro[5.5]-undecan-5-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (I-92)



3-(6-(2-ethyl-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-5-fluoro-quinolin-3-yl)piperidine-2,6-dione (**I-92**) was synthesized according to **General Procedure 1, Step D** starting from 3-(5-fluoro-6-(5-hydroxy-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)piperidine-2,6-dione (**55d**, 150mg, 1.0 eq., 0.35 mmol) and acetaldehyde (15mg, 1.0 eq., 0.35mmol). The crude compound was purified by prep-HPLC [X SELECT C18 (19*150), eluting with Mobile phase A: 0.1% formic acid, Mobile phase B: Acetonitrile, flow rate: 15 mL/min), Rt: 9.3 min]. The pure product containing fractions were collected and lyophilized to afford 3-(6-(2-ethyl-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (**I-92**, 7.5 mg, 0.02 mmol, 3% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 454.2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.98 (s, 1H), 8.85 (s, 1H), 8.34 (s, 1H), 8.18 (s, 1H), 8.09 (d, *J* = 8.80 Hz, 1H), 7.84 (d, *J* = 8.80 Hz, 1H), 5.06 (s, 1H), 4.24-4.20 (m, 1H), 2.80 (d, *J* = 4.1 Hz, 1H), 2.76 (d, *J* = 4.40 Hz, 1H), 2.64-2.59 (m, 3H), 2.46-2.42 (m, 2H), 2.33 (m, 1H), 2.16 (t, *J* = 5.20 Hz, 3H), 1.77 (d, *J* =

8.80 Hz, 1H), 1.65 (d, *J* = 9.20 Hz, 1H), 1.26-1.30 (m, 6H), 1.07 (t, *J* = 7.20 Hz, 3H), 0.87 (t, *J* = 6.8 Hz, 1H), 0.70 (m, 2H).

Example 57: Synthesis of 3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-methylquinolin-3-yl)piperidine-2,6-dione (I-45)



Step 1: **Synthesis of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-chloro-5-methylquinoline (57b)**

A solution of 6-chloro-3-iodo-5-methylquinoline (**57a**, 180 mg, 0.59 mmol) and 2,6-bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**INT-4B**, 297 mg, 0.71 mmol) in 1,4-dioxane: water (4:1), 5 mL was degassed with nitrogen gas for 10 min. After 10 min, DIPEA (0.259 mL, 1.48 mmol) and $Pd(tBu_3P)_2$ (30.3 mg, 0.06 mmol) were added, and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was filtered through a pad of Celite® and the filtrate was evaporated to dryness. The crude compound was purified by flash column chromatography using Combi-Flash (on silica gel, 100-200 mesh) eluting with 0-10% of EtOAc in hexane to afford 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-chloro-5-methylquinoline (**57b**, 130 mg, 0.23 mmol, 38% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 467.7. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.12 (d, *J* = 2.4 Hz, 1H), 8.64 (d, *J* = Hz, 1H), 8.08 (d, *J* = 8.40 Hz, 1H), 7.88 (d, *J* = 8.80 Hz, 1H), 7.74 (d, *J* = 8.80 Hz, 1H), 7.43-7.37 (m, 10H), 6.69 (d, *J* = 8.00 Hz, 1H), 5.46 (d, *J* = 7.60 Hz, 4H), 2.64 (s, 3H).

Step 2: **Synthesis of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-methylquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (57c)**

tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-methylquinolin-6-yl)-3,6-dihydro-pyridine-1(2H)-carboxylate (**57c**) was synthesized according to **General Procedure 5** starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-chloro-5-methylquinoline (**57b**, 100 mg, 1 eq., 0.21 mmol) and *tert*-butyl

4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (132 mg, 2.0 eq. 0.43 mmol). The crude compound was purified by flash column chromatography using Combi-Flash (on silica gel, 100-200 mesh) eluting with 0-20% of EtOAc in hexane to afford *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-methylquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**57c**, 60 mg, 0.09 mmol, 44% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 614.3. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.07 (d, J = 2.4 Hz 1H), 8.59 (s, 1H), 8.05 (d, J = 8.00 Hz, 1H), 7.82 (d, J = 8.80 Hz, 1H), 7.48-7.37 (m, 11H), 6.68 (d, J = 8.00 Hz, 2H), 5.64 (s, 1H), 5.46 (d, J = 4.40 Hz, 4H), 4.03 (s, 2H), 3.92 (s, 5H), 1.46 (s, 10H).

Step 3: **Synthesis of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-methylquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (57d)**

tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-methylquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (**57d**) was synthesized according to **General Procedure 3, Step C** starting from *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-methylquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**57c**), 80 mg, 1.0 eq., 0.13mmol). The crude compound was purified by flash column chromatography using Combi-Flash (on silica gel, 100-200 mesh) eluting with 0-20% of EtOAc in hexane to afford *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-methylquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (**57d**, 60 mg, 0.06 mmol, 49% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 632.3.

Step 4: **Synthesis of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-methylquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (57e)**

To a stirred solution of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-methyl-quinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (**57d**, 60 mg, 0.10 mmol) in DMF (4 mL) was added Pd/C (505 mg, 0.48 mmol) at room temperature and the resulting mixture was sparged with hydrogen and stirred under an atmosphere of hydrogen using a balloon at room temperature for 2 h. The reaction mixture was filtered through a pad of Celite® and the filtrate was evaporated to dryness to afford *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-methylquinolin-6-yl)-4-hydroxy-piperidine-1-carboxylate (**57e**, 40 mg, 0.04 mmol, 46% yield). The product was carried onto the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 454.4.

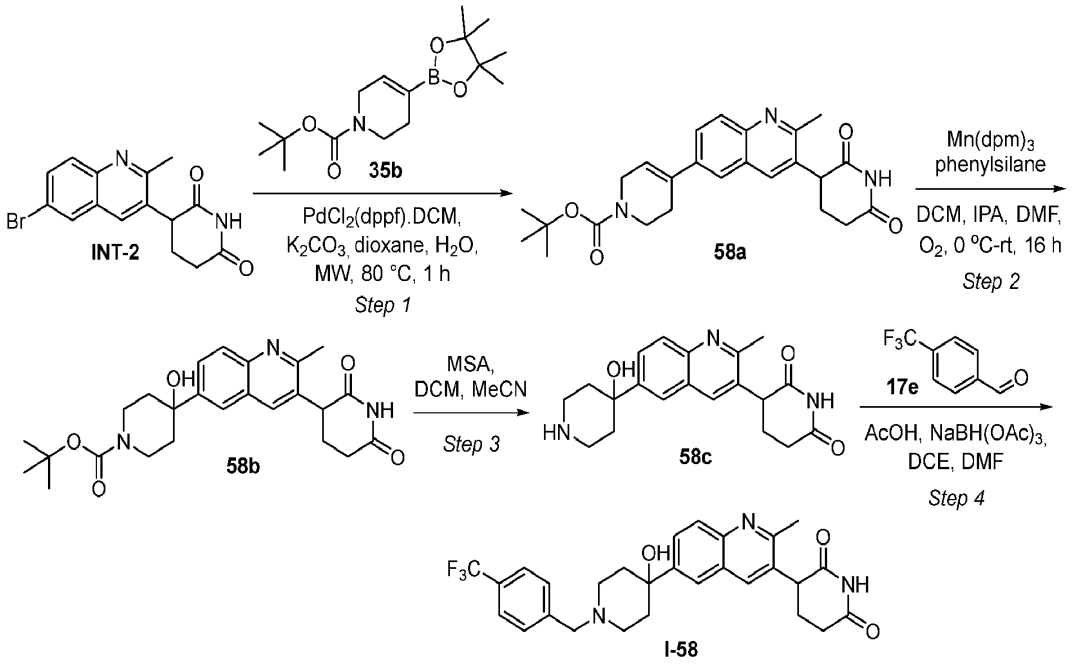
Step 5: **Synthesis of 3-(6-(4-hydroxypiperidin-4-yl)-5-methylquinolin-3-yl)piperidine-2,6-dione (57f)**

3-(6-(4-Hydroxypiperidin-4-yl)-5-methylquinolin-3-yl)piperidine-2,6-dione HCl (**57f**, 30 mg, 0.05 mmol, 64% yield) was synthesized according to **General Procedure 6, Step A** starting from *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-methylquinolin-6-yl)-4-hydroxy-piperidine-1-carboxylate (**57e**, 50 mg, 1 eq., 0.08 mmol). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 354.2.

Step 6: **Synthesis of 3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-methylquinolin-3-yl)piperidine-2,6-dione (I-45)**

3-(6-(4-Hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-methylquinolin-3-yl)piperidine-2,6-dione (**I-45**) was synthesized according to **General Procedure 6, Step B** starting from 3-(6-(4-hydroxypiperidin-4-yl)-5-methylquinolin-3-yl)piperidine-2,6-dione HCl (**57f**, 30 mg, 1.0 eq., 0.085 mmol) and 4-(trifluoromethyl)benzaldehyde (**17e**, 18 mg, 1.2 eq., 0.1 mmol). The crude material was purified by preparative-HPLC [(Column: X select (150 x 19 mm) 5 µm, eluting with Mobile phase A: 0.05% acetic acid in H_2O, Mobile phase B: Acetonitrile, flow rate: 15 mL/min)]. The pure product containing fractions were combined and lyophilized to afford 3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-methylquinolin-3-yl)piperidine-2,6-dione (**I-45**, 1.2 mg, 2.32 mmol, 4% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 512.2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.95 (s, 1H), 8.74 (s, 1H), 8.37 (s, 1H), 7.90 (d, J = 9.20 Hz, 1H), 7.82 (d, J = 8.80 Hz, 1H), 7.71 (d, J = 8.00 Hz, 2H), 7.59 (d, J = 8.00 Hz, 2H), 5.00 (s, 1H), 4.20-4.15 (m, 1H), 3.63 (s, 2H), 2.93 (s, 3H), 2.82-2.76 (m, 2H), 2.65-2.48 (m, 4H), 2.19-2.10 (m, 3H), 1.99-1.88 (m, 3H). ^{19}F-NMR (400 MHz, DMSO-d_6): δ -60.736.

Example 58: Synthesis of 3-(6-(4-hydroxy-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (I-58)



Step 1: **Synthesis of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-2-methylquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (58a)**

tert-Butyl 4-(3-(2,6-dioxopiperidin-3-yl)-2-methylquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**58a**) was synthesized according to **General Procedure 4** starting from 3-(6-bromo-2-methylquinolin-3-yl)piperidine-2,6-dione (**INT-2**, 90 mg, 1 eq., 0.27 mmol) and *tert*-butyl 4-(4,4,5,5-

tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**35b**, 92 mg, 1.1 eq., 0.30 mmol). The reaction mixture was concentrated and loaded onto a silica gel column for purification eluting with heptanes and EtOAc. The compound did not elute with 100% EtOAc and 20% IPA was needed to elute the product. The desired fractions were collected, combined, and concentrated *in vacuo* to yield *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-2-methylquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**58a**, 118 mg, 0.27 mmol, 100% yield). LCMS: m/z HESI, positive $[M+H]^+ = 436$.

Step 2: **Synthesis of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-2-methylquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (58b)**

tert-Butyl 4-(3-(2,6-dioxopiperidin-3-yl)-2-methylquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (**58b**) was synthesized according to **General Procedure 3, Step B** starting from *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-2-methylquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**58a**, 118 mg, 1 eq., 0.27 mmol). Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was concentrated *in vacuo* and purified via C18 column eluting with 0 to 100% MeCN (+0.1% formic acid) in H_2O (+0.1% formic acid). The desired fractions were collected, combined and lyophilized to yield *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-2-methylquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (**58b**, 94 mg, 0.21 mmol, 77% yield). LCMS: m/z HESI, positive $[M+H]^+ = 454$

Step 3: **Synthesis of 3-(6-(4-hydroxypiperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (58c)**

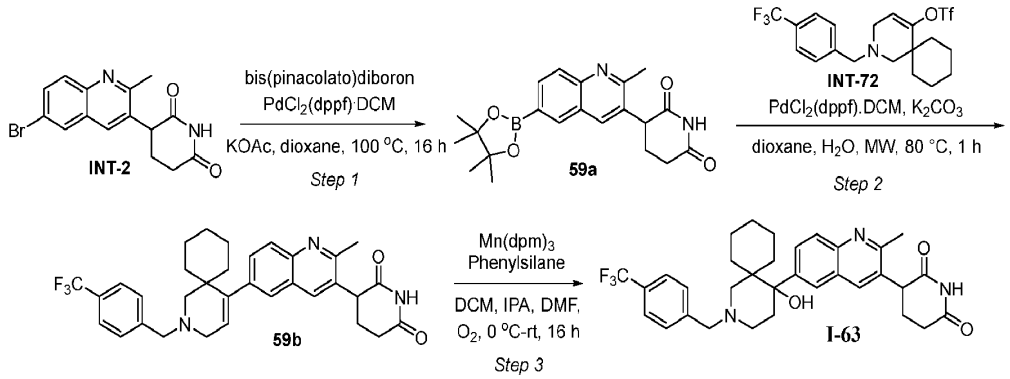
3-(6-(4-Hydroxypiperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (**58c**) was synthesized according to **General Procedure 1, Step C** starting from *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-2-methylquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (**58b**, 94 mg, 1.0 eq., 0.21 mmol). Quantitative yield was assumed for the reaction and 3-(6-(4-hydroxy-piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (**58c**, 73 mg, 0.21 mmol, quantitative yield) was carried onto the next step without further purification. HESI, positive $[M+H]^+ = 354$.

Step 4: **Synthesis of 3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (I-58)**

3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (**I-58**) was synthesized according to **General Procedure 1, Step D** starting from 3-(6-(4-hydroxypiperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (**58c**, 73 mg, 1.0 eq., 0.21 mmol) and 4-(trifluoromethyl)benzaldehyde (**17e**, 34 uL, 1.2 eq., 0.25 mmol). Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was purified via C18 column eluting with 0-100% MeCN (+0.1% formic acid) in H_2O (+0.1% formic acid). The desired fractions were collected, combined and concentrated *in vacuo* to yield 3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (**I-58**, 19.6 mg, 0.04 mmol, 19% yield) as a mixture of

diastereomers. LCMS: m/z HESI, positive $[M+H]^+ = 512$. ^1H NMR (499 MHz, DMSO-d_6) δ (ppm) = 10.96-10.92 (m, 1H), 8.23 (s, 1H), 8.11-8.07 (m, 1H), 7.95-7.92 (m, 1H), 7.85 (s, 2H), 7.72-7.67 (m, 2H), 7.61-7.57 (m, 2H), 5.06-4.96 (m, 1H), 4.31-4.23 (m, 1H), 3.65-3.61 (m, 2H), 2.87-2.77 (m, 1H), 2.67-2.62 (m, 6H), 2.61-2.58 (m, 1H), 2.55-2.51 (m, 1H), 2.46-2.35 (m, 1H), 2.15-2.02 (m, 3H), 1.71-1.64 (m, 2H), 1.24-1.21 (m, 1H).

Example 59: Synthesis of 3-(6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]-undecan-5-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (I-63)



Step 1: **Synthesis of 3-(2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-3-yl)piperidine-2,6-dione (59a)**

3-(2-Methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-3-yl)piperidine-2,6-dione (**59a**, 57 mg, 0.15 mmol, quantitative yield) was synthesized according to **General Procedure 3, Step A** starting from 3-(6-bromo-2-methylquinolin-3-yl)piperidine-2,6-dione (**INT-2**, 50 mg, 1 eq., 0.15 mmol). Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was carried as a solution in dioxane onto to the next step without further purification. Quantitative yield is assumed for the reaction. LCMS: m/z HESI, positive $[M+H]^+ = 381$.

Step 2: **Synthesis of 3-(2-methyl-6-(2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)quinolin-3-yl)piperidine-2,6-dione (59b)**

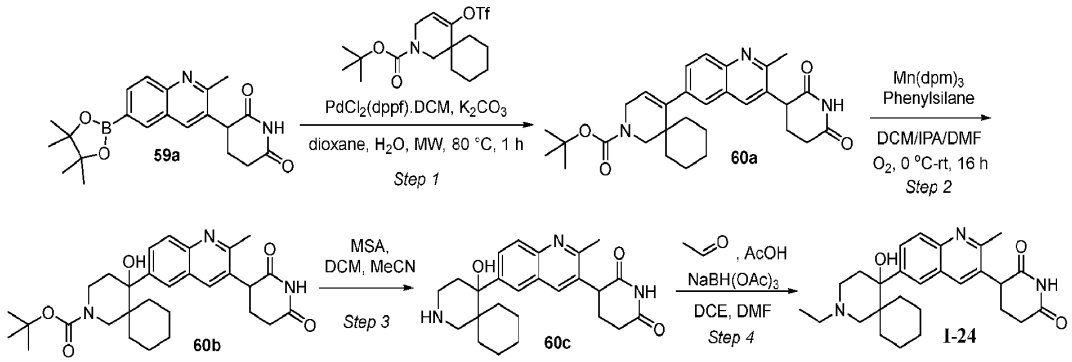
3-(2-Methyl-6-(2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)quinolin-3-yl)piperidine-2,6-dione (**59b**) was synthesized according to **General Procedure 3, Step B** starting from a dioxane solution of 3-(2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-3-yl)piperidine-2,6-dione (**59a**, 57 mg, 1 eq., 0.15 mmol) and 2-(4-(trifluoromethyl)-benzyl)-2-azaspiro[5.5]undec-4-en-5-yl trifluoromethanesulfonate (**INT-72**, 75 mg, 1.1 eq., 0.16 mmol). Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was concentrated *in vacuo* and purified via C18 column eluting with 0 to 100% MeCN (+0.1% formic acid) in H_2O (+0.1% formic acid). The desired fractions were collected, combined and lyophilized to yield 3-(2-methyl-6-(2-(4-(trifluoromethyl)benzyl)-

2-azaspiro[5.5]-undec-4-en-5-yl)quinolin-3-yl)piperidine-2,6-dione (**59b**, 41 mg, 0.07 mmol, 49% yield). LCMS: m/z HESI, positive $[M+H]^+ = 562$.

Step 3: **Synthesis of 3-(6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (I-63)**

3-(6-(5-Hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-2-methyl-quinolin-3-yl)piperidine-2,6-dione (**I-63**) was synthesized according to **General Procedure 3, Step C** starting from 3-(2-methyl-6-(2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)quinolin-3-yl)piperidine-2,6-dione (**59b**, 41 mg, 1 eq., 0.07 mmol). Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was concentrated *in vacuo* and purified via C18 column eluting from 0 to 100% MeCN in H_2O (10 mM NH_4OAc solution). The desired fractions were collected, combined and lyophilized to yield 3-(6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (**I-63**, 1.9 mg, 0.003 mmol, 5% yield) as a mixture of diastereomers. LCMS: m/z HESI, positive $[M+H]^+ = 580$. ^1H NMR (499 MHz, DMSO-d_6) δ (ppm) = 10.98-10.89 (m, 1H), 8.15-8.10 (m, 1H), 7.93-7.87 (m, 1H), 7.86-7.79 (m, 2H), 7.70 (s, 2H), 7.61 (s, 2H), 4.32-4.23 (m, 1H), 3.69-3.64 (m, 1H), 3.61-3.55 (m, 1H), 2.90-2.78 (m, 3H), 2.71-2.67 (m, 1H), 2.66-2.62 (m, 3H), 2.62-2.56 (m, 1H), 2.46-2.41 (m, 1H), 2.32-2.26 (m, 2H), 2.17-2.09 (m, 1H), 2.03-1.94 (m, 1H), 1.75-1.69 (m, 1H), 1.59-1.55 (m, 1H), 1.50-1.44 (m, 1H), 1.26-1.21 (m, 3H), 1.09-0.97 (m, 2H), 0.91-0.82 (m, 1H), 0.71-0.62 (m, 1H), 0.55-0.47 (m, 1H).

Example 60: Synthesis of 3-(6-(2-ethyl-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (I-24)



Step 1: **Synthesis of *tert*-butyl 5-(3-(2,6-dioxopiperidin-3-yl)-2-methylquinolin-6-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (60a)**

tert-Butyl 5-(3-(2,6-dioxopiperidin-3-yl)-2-methylquinolin-6-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (**60a**) was synthesized according to **General Procedure 3, Step B** starting from 3-(2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-3-yl)piperidine-2,6-dione (**59a**, 57 mg, 1 eq., 0.15 mmol) and tert-butyl 5-(((trifluoromethyl)sulfonyl)oxy)-2-azaspiro[5.5]undec-4-ene-2-carboxylate

(**37c**, 66 mg, 1.1 eq., 0.16 mmol). Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was concentrated purified via C18 column eluting 0 to 100% MeCN (+0.1% formic acid) in H_2O (+0.1% formic acid). The desired fractions were collected, combined and concentrated *in vacuo* to yield *tert*-butyl 5-(3-(2,6-dioxopiperidin-3-yl)-2-methylquinolin-6-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (**60a**, 45 mg, 0.09 mmol, 60% yield). LCMS: m/z HESI, positive $[M+H]^+ = 504$.

Step 2: **Synthesis of *tert*-butyl 5-(3-(2,6-dioxopiperidin-3-yl)-2-methylquinolin-6-yl)-5-hydroxy-2-azaspiro[5.5]undecane-2-carboxylate (60b)**

tert-Butyl 5-(3-(2,6-dioxopiperidin-3-yl)-2-methylquinolin-6-yl)-5-hydroxy-2-azaspiro[5.5]undecane-2-carboxylate (**60b**) was synthesized according to **General Procedure 3, Step C** starting from tert-Butyl 5-(3-(2,6-dioxopiperidin-3-yl)-2-methylquinolin-6-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (**60a**, 45 mg, 1 eq., 0.09 mmol). Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was concentrated *in vacuo* and purified via C18 column eluting with 0 to 100% MeCN (+0.1% formic acid) in H_2O (+0.1% formic acid). The desired fractions were collected, combined and lyophilized to yield *tert*-butyl 5-(3-(2,6-dioxopiperidin-3-yl)-2-methylquinolin-6-yl)-5-hydroxy-2-azaspiro[5.5]undecane-2-carboxylate (**60b**, 47 mg, 0.09 mmol, 100% yield). LCMS: m/z HESI, positive $[M+H]^+ = 522$.

Step 3: **Synthesis of 3-(6-(5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (60c)**

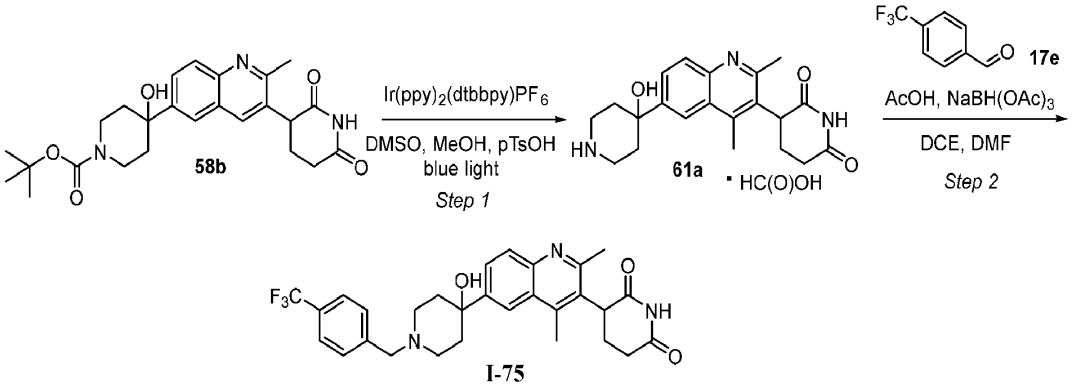
3-(6-(5-Hydroxy-2-azaspiro[5.5]undecan-5-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (**60c**) was synthesized according to **General Procedure 1, Step C** starting from *tert*-butyl 5-(3-(2,6-dioxo-piperidin-3-yl)-2-methylquinolin-6-yl)-5-hydroxy-2-azaspiro[5.5]undecane-2-carboxylate (**60b**, 47 mg, 1 eq., 0.09 mmol). Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was concentrated *in vacuo*. The material was carried onto the next step without step without further purification. 3-(6-(5-hydroxy-2-azaspiro[5.5]-undecan-5-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (**60c**, 38 mg, 0.09 mmol, quantitative yield). LCMS: m/z HESI, positive $[M+H]^+ = 422$.

Step 4: **Synthesis of 3-(6-(2-ethyl-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (I-24)**

3-(6-(2-ethyl-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-2-methyl-quinolin-3-yl)piperidine-2,6-dione **(I-24)** was synthesized according to **General Procedure 1, Step D** starting from 3-(6-(5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (**60c**, 38 mg, 1 eq., 0.09 mmol) and acetaldehyde (10 uL, 2 eq., 0.18 mmol). Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was purified via C18 column eluting with 0 to 100% MeCN (+0.1% formic acid) in H_2O (+0.1% formic acid). The desired fractions were collected, combined and

concentrated via lyophilization to yield 3-(6-(2-ethyl-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (**I-24**, 0.6 mg, 0.001 mmol, 1% yield). LCMS: m/z HESI, positive $[M+H]^+ = 450$.

Example 61: Synthesis of 3-(6-(4-hydroxy-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)-2,4-dimethylquinolin-3-yl)piperidine-2,6-dione (I-75)



Step 1: **Synthesis of 3-(6-(4-hydroxypiperidin-4-yl)-2,4-dimethyl-quinolin-3-yl)piperidine-2,6-dione (61a)**

3-(6-(4-hydroxypiperidin-4-yl)-2,4-dimethylquinolin-3-yl)piperidine-2,6-dione (**61a**) was prepared according to the procedures and examples as reported in Nature, 2015, *525*, 87-90.

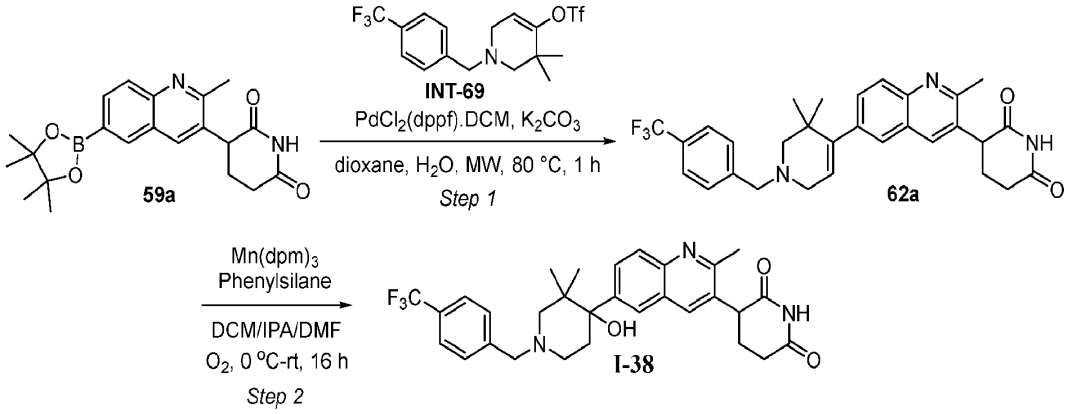
To a reaction vial equipped with a stir bar were added *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-2-methylquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (**58b**, 55.6 mg, 1 eq., 0.12 mmol), 4-methylbenzenesulfonic acid hydrate (47 mg, 2 eq., 0.25 mmol), and $Ir(ppy)_2(dtbbpy)PF_6$ (1.1 mg, 0.01 eq., 0.001 mmol) and DMSO (490 µL, 0.25 molar) and methanol (490 µL, 0.25 molar), followed ethyl 2-mercaptopropanoate (4 µL, 0.25 eq., 0.03 mmol) and the reaction vial was sealed and irradiated under blue light (456 nM) for 48 h. Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was purified via C18 column eluting with 0 to 100% MeCN (+0.1% formic acid) in H_2O (+0.1% formic acid). The desired fractions were collected, combined, and lyophilized to yield 3-(6-(4-hydroxypiperidin-4-yl)-2,4-dimethylquinolin-3-yl)piperidine-2,6-dione (**61a**, 45 mg, 0.12 mmol, quantitative yield). LCMS: m/z HESI, positive $[M+H]^+ = 368$.

Step 2: **Synthesis of 3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-2,4-dimethylquinolin-3-yl)piperidine-2,6-dione (I-75)**

To a reaction vial equipped with a stir bar were added 3-(6-(4-hydroxypiperidin-4-yl)-2,4-dimethylquinolin-3-yl)piperidine-2,6-dione (**61a**, 45 mg, 1 eq., 0.12 mmol), 4-(trifluoro-methyl)benzaldehyde (**17e**, 20 µL, 1.2 eq., 0.15 mmol), DCE (500 uL, 0.25 molar) and DMF (500 uL, 0.25 molar), followed by the addition of sodium triacetoxyborohydride (52 mg, 2 eq., 0.24 mmol) and

acetic acid (14 uL, 2 eq., 0.24 mmol). The resulting mixture was allowed to stir for 2 h. Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was purified via C18 column eluting with 0 to 100% MeCN (+0.1% formic acid) in H_2O (+0.1% formic acid). The desired fractions were collected, combined and lyophilized to yield 3-(6-(4-hydroxy-1-(4-(trifluoromethyl)-benzyl)-piperidin-4-yl)-2,4-dimethyl-quinolin-3-yl)piperidine-2,6-dione (**I-75**, 1.2 mg, 0.002 mmol, 2% yield). LCMS: m/z HESI, positive $[M+H]^+ = 526$.

Example 62: Synthesis of 3-(6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (I-38)



Step 1: **Synthesis of 3-(6-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (62a)**

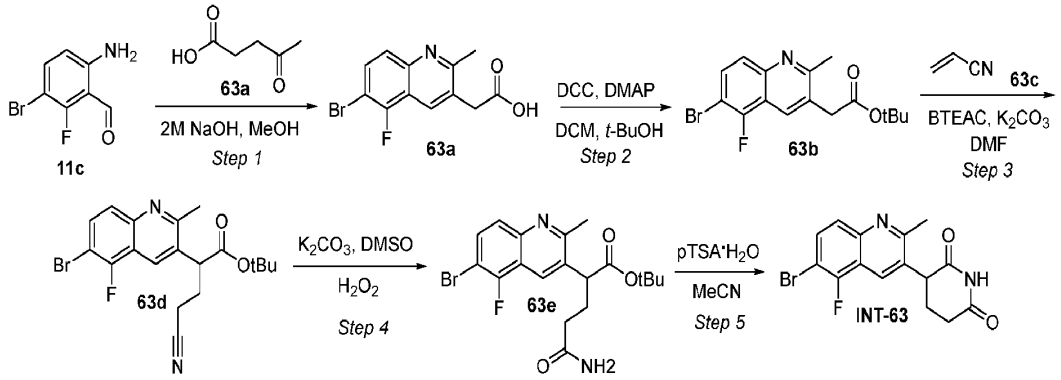
3-(6-(3,3-Dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (**62a**) was synthesized according to **General Procedure 3, Step B** starting from 3-(2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-3-yl)piperidine-2,6-dione (**59a**, 51 mg, 1 eq., 0.13 mmol) and 3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (**INT-69**, 62 mg, 1.1 eq., 0.15 mmol). Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was concentrated in vacuo and purified via C18 column eluting 0 to 100% MeCN (+0.1% formic acid) in H_2O (+0.1% formic acid). The desired fractions were collected, combined, and concentrated *in vacuo* to yield 3-(6-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (**62a**, 0.027 g, 0.05 mmol, 39% yield). LCMS: m/z HESI, positive $[M+H]^+ = 522$.

Step 2: **Synthesis of 3-(6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (I-38)**

3-(6-(4-Hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methyl-quinolin-3-yl)piperidine-2,6-dione (**I-38**) was synthesized according to **General Procedure 3, Step C** starting from 3-(6-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-2-methylquinolin-3-

yl)piperidine-2,6-dione (**62a**, 27 mg, 1 eq., 0.052 mmol). Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was concentrated *in vacuo* and purified via C18 column eluting with 0 to 100% MeCN (+0.1% formic acid) in H_2O (+0.1% formic acid). The desired fractions were collected, combined, and lyophilized to yield 3-(6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (**I-38**, 1.8 mg, 0.003 mmol, 6% yield) as a mixture of diastereomers. LCMS: m/z HESI, positive $[M+H]^+ = 540$. ^1H NMR (499 MHz, DMSO-d_6) δ (ppm) = 10.97-10.92 (m, 1H), 8.14-8.08 (m, 1H), 7.95-7.90 (m, 1H), 7.89-7.80 (m, 2H), 7.73-7.68 (m, 2H), 7.62-7.56 (m, 2H), 4.32-4.23 (m, 1H), 2.90-2.77 (m, 3H), 2.74-2.69 (m, 1H), 2.64 (s, 4H), 2.60-2.55 (m, 2H), 2.46-2.34 (m, 2H), 2.17-2.07 (m, 2H), 1.57-1.50 (m, 1H), 1.28-1.21 (m, 1H), 0.90 (s, 3H), 0.67 (s, 3H).

Example 63: Synthesis of 3-(6-bromo-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (INT-63)



Step 1: **Synthesis of 2-(6-bromo-5-fluoro-2-methylquinolin-3-yl)acetic acid (63a)**

To a reaction vial equipped with a stir bar was added 6-amino-3-bromo-2-fluorobenzaldehyde (**11c**, 1.00 g, 1 eq., 4.59 mmol) and methanol (9.2 mL, 0.5 molar), followed by levulinic acid (**63a**, 533 mg, 1eq., 4.59 mmol) and aqueous solution of NaOH (2.8 mL, 2 molar, 1.2 eq., 5.5 mmol). The resulting mixture was refluxed overnight. Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was concentrated and diluted with H_2O. The aqueous solution was then acidified to pH = 2 with acetic acid, sonicated for 10 min, and filtered. The resulting precipitate was washed with diethyl ether and dried under reduced pressure to yield 2-(6-bromo-5-fluoro-2-methylquinolin-3-yl)acetic acid (**63a**, 1 g, 3 mmol, 70% yield). The product was carried onto to the next step without further purification. LCMS: m/z HESI, positive$[M+H]^+ = 297$.

Step 2: **Synthesis of *tert*-butyl 2-(6-bromo-5-fluoro-2-methylquinolin-3-yl)acetate (63b)**

To a reaction vial equipped with a stir bar was added dicyclohexylcarbodiimide (761.3 mg, 1.1 eq., 3.69 mmol) and DCM (3.7 mL, 0.91 molar) and the resulting mixture was cooled to 0 °C using an ice-water bath. DMAP (328 mg, 0.8 eq., 2.68 mmol), 2-(6-bromo-5-fluoro-2-methylquinolin-3-yl)acetic acid (**63a**, 1.0 g, 1 eq., 3.35 mmol) and *tert*-butyl alcohol (2.55 mL, 8 eq., 26.84 mmol) were then added

and stirring was continued at room temperature overnight. Upon complete consumption of starting material, as confirmed by LCMS, water was added and the aqueous mixture was extracted twice with EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified via silica gel chromatography eluting with 0 to 100% EtOAc in heptanes. The desired fractions were collected, combined, and concentrated *in vacuo* to yield *tert*-butyl 2-(6-bromo-5-fluoro-2-methylquinolin-3-yl)acetate (**63b**, 870 mg, 2.46 mmol, 73% yield). LCMS: m/z HESI, positive $[M+H]^+ = 354$.

Step 3: **Synthesis of *tert*-butyl 2-(6-bromo-5-fluoro-2-methylquinolin-3-yl)-4-cyanobutanoate (63d)**

To a reaction vial equipped with a stir bar was added *tert*-butyl 2-(6-bromo-5-fluoro-2-methylquinolin-3-yl)acetate (**63b**, 870 mg, 1 eq., 2.46 mmol) and DMF (9.8 mL 0.25 molar), followed benzyl(triethyl)ammonium chloride (560 mg, 1 eq., 2.46 mmol), potassium carbonate (340 mg, 1 eq., 2.46 mmol), and acrylonitrile (**63c**, 159 µL, 1 eq., 2.46 mmol) and the resulting mixture was stirred at room temperature overnight Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was diluted with water and the aqueous mixture was extracted twice with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified via silica gel column chromatography eluting with 0 to 100% EtOAc in heptanes. The desired fractions were collected, combined, and concentrated *in vacuo* to yield *tert*-butyl 2-(6-bromo-5-fluoro-2-methylquinolin-3-yl)-4-cyanobutanoate (**63c**, 680 mg, 1.67 mmol, 68% yield). LCMS: m/z HESI, positive $[M+H]^+ = 407$.

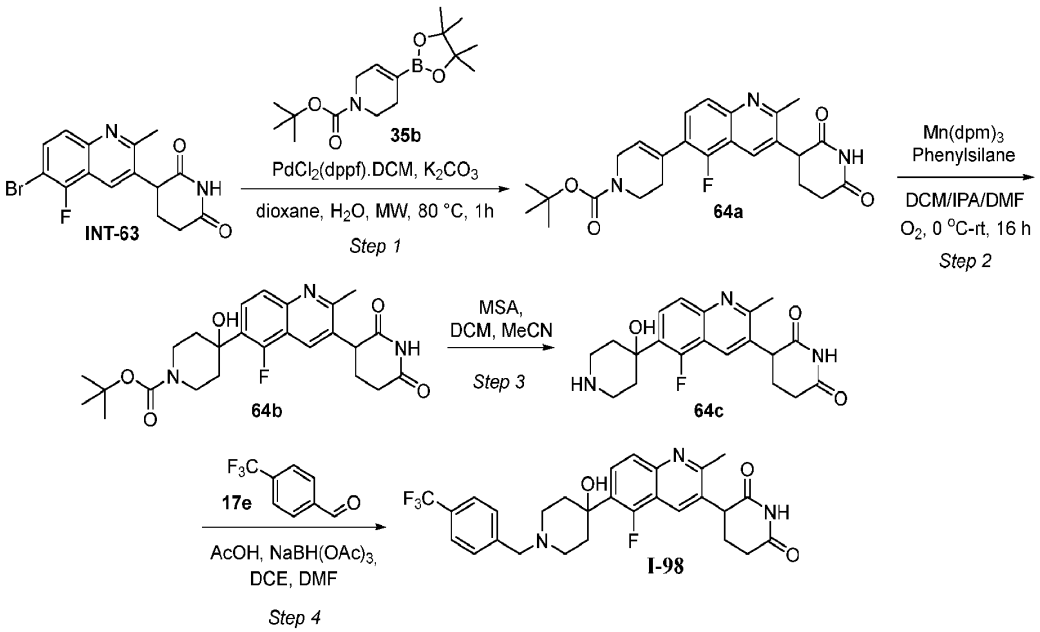
Step 4: **Synthesis of *tert*-butyl 5-amino-2-(6-bromo-5-fluoro-2-methylquinolin-3-yl)-5-oxopentanoate (63e)**

To a reaction vial equipped with a stir bar was added *tert*-butyl 2-(6-bromo-5-fluoro-2-methylquinolin-3-yl)-4-cyanobutanoate (**63d**, 680 mg, 1 eq., 1.67 mmol) and DMSO (5.48 mL, 0.305 molar) and the resulting mixture was cooled to 0 °C using an ice-water bath. Hydrogen peroxide (863 µL, 30% wt, 5 eq., 8.34 mmol) and potassium carbonate (23.1 mg, 0.1 eq., 0.17 mmol) were then added and stirring was continued for 5 h at room temperature. Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was diluted with water and the aqueous phase was extracted twice with EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then loaded onto a silica column for purification eluting with heptanes and EtOAc followed by 20% IPA (desired product will only elute upon the addition of 20% IPA). The desired product fractions were collected, combined, and concentrated *in vacuo* to yield *tert*-butyl 5-amino-2-(6-bromo-5-fluoro-2-methylquinolin-3-yl)-5-oxopentanoate (**63e**, 466 mg, 1.10 mmol, 66% yield). LCMS: m/z HESI, positive $[M+H]^+ = 425$.

Step 5: **Synthesis of 3-(6-bromo-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (INT-63)**

To a reaction vial equipped with a stir bar was added *tert*-butyl 5-amino-2-(6-bromo-5-fluoro-2-methylquinolin-3-yl)-5-oxopentanoate (**63e**, 466 mg, 1 eq., 1.10 mmol) and acetonitrile (3.0 mL, 0.36 molar), followed by *p*-toluenesulfonic acid monohydrate (943 mg, 5 eq., 5.48 mmol) and the resulting mixture was heated to 80 °C overnight. Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was concentrated *in vacuo* and redissolved in DMSO and purified via C18 column eluting with 0 to 100% MeCN (+0.1% formic acid) in H_2O (+0.1% formic acid). The desired fractions were collected, combined, and concentrated via lyophilization to yield 3-(6-bromo-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (**INT-63**, 204 mg, 0.58 mmol, 53% yield). LCMS: m/z HESI, positive $[M+H]^+ = 351$.

Example 64: Synthesis of 3-(5-fluoro-6-(4-hydroxy-1-(4-(trifluoro-methyl)benzyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (I-98)



Step 1: **Synthesis of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (64a)**

tert-Butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-3,6-dihydro-pyridine-1(2H)-carboxylate (**64a**) was synthesized according to **General Procedure 4** starting from 3-(6-bromo-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (**INT-63**, 50mg, 1 eq., 0.14mmol) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**35b**, 48 mg, 1.1 eq., 0.16 mmol). Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was concentrated *in vacuo* and purified via C18 column eluting with 0 to 100% MeCN (+0.1% formic acid) in H_2O (+0.1% formic acid). The desired fractions were collected, combined, and

concentrated *in vacuo* to yield *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**64a**, 41 mg, 0.09 mmol, 63% yield). LCMS: m/z HESI, positive $[M+H]^+ = 454$.

Step 2: **Synthesis of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (64b)**

tert-Butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-4-hydroxy-piperidine-1-carboxylate (**64b**) was synthesized according to **General Procedure 3, Step C** starting from *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**64a**, 41 mg, 1.0 eq., 0.09 mmol). Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was concentrated *in vacuo* and loaded onto a C18 column for purification eluting with 0% to 100% MeCN (+0.1% formic acid) in H_2O (+0.1% formic acid). The desired fractions were collected, combined, and lyophilized to yield *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (**64b**, 43 mg, 0.09 mmol, quantitative yield). LCMS: m/z HESI, positive $[M+H]^+ = 472$.

Step 3: **Synthesis of 3-(5-fluoro-6-(4-hydroxypiperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (64c)**

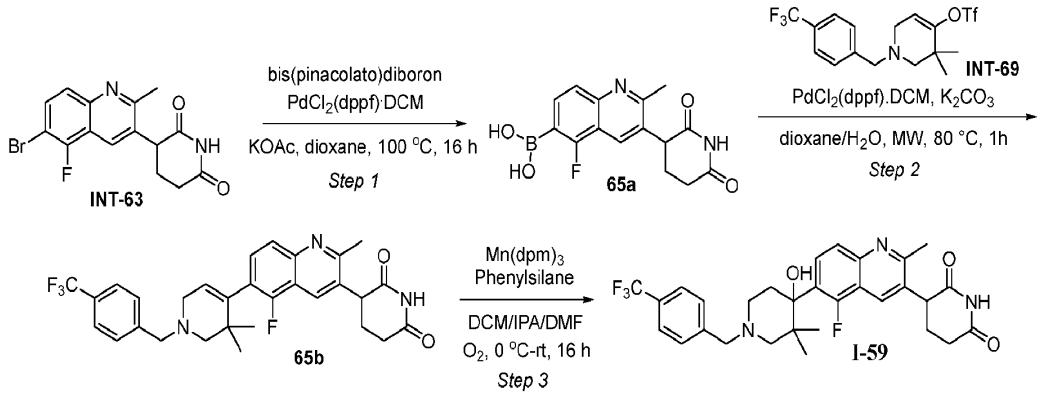
3-(5-Fluoro-6-(4-hydroxypiperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (**64c**) was synthesized according to **General Procedure 1, Step C** starting from *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (**64b**, 43 mg, 1 eq., 0.09 mmol). Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was cooled to 0 °C using an ice-water bath, and triethylamine was then added. The reaction mixture was then concentrated *in vacuo* to provide 3-(5-fluoro-6-(4-hydroxypiperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (**64c**, 34mg, 0.09 mmol, quantitative yield). The product was carried onto the next step without further purification. LCMS: m/z HESI, positive $[M+H]^+ = 372$.

Step 4: **Synthesis of 3-(5-fluoro-6-(4-hydroxy-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (I-98)**

3-(5-fluoro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (**I-98**) was synthesized according to **General Procedure 1, Step D** starting from 3-(5-fluoro-6-(4-hydroxypiperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (**64c**, 34 mg, 1 eq., 0.09 mmol) and 4-(trifluoromethyl)benzaldehyde (**17e**, 15 uL, 1.2 eq., 0.11 mmol). Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was purified via C18 column eluting with 0 to 100% MeCN (+0.1% formic acid) in H_2O (+0.1% Formic acid). The desired fractions were collected, combined, and concentrated via lyophilization to yield 3-(5-fluoro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (**I-98**, 15.5 mg,

0.029 mmol, 32% yield) as a mixture of diastereomers. LCMS: m/z HESI, positive $[M+H]^+$ = 530. ^{1}H-NMR (499 MHz, DMSO-d_6) δ (ppm) = 10.98-10.95 (m, 1H), 8.28-8.23 (m, 1H), 8.22-8.18 (m, 1H), 8.01-7.95 (m, 1H), 7.79-7.74 (m, 1H), 7.73-7.68 (m, 2H), 7.62-7.56 (m, 2H), 5.38-5.16 (m, 1H), 4.38-4.32 (m, 1H), 3.65-3.61 (m, 2H), 2.87-2.77 (m, 1H), 2.66 (s, 3H), 2.65 (br s, 3H), 2.56-2.51 (m, 2H), 2.49-2.45 (m, 1H), 2.38-2.28 (m, 2H), 2.15-2.07 (m, 1H), 1.72-1.63 (m, 2H).

Example 65: Synthesis of 3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (I-59)



Step 1: **Synthesis of (3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)boronic acid (65a)**

(3-(2,6-Dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)boronic acid (**65a**) was synthesized according to **General Procedure 3, Step A** starting from 3-(6-bromo-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (**INT-63**, 40 mg, 1 eq., 0.11 mmol). The reaction mixture was carried onto the next step as a solution in dioxane without further purification and quantitative yield was assumed (3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)boronic acid (**65a**, 36 mg, 0.11 mmol, quantitative yield.) LCMS: m/z HESI, positive $[M+H]^+$ = 317.

Step 2: **Synthesis of 3-(6-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (65b)**

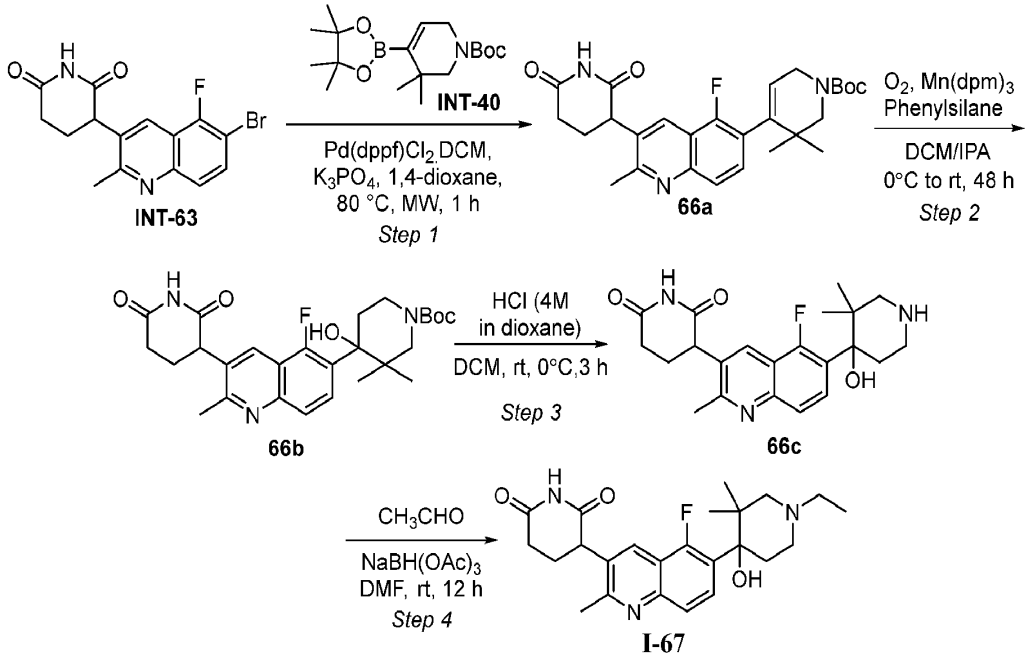
3-(6-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (**65b**) was synthesized according to **General Procedure 3, Step B** starting from a dioxane solution of (3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)boronic acid (**65a**, 36 mg, 1 eq., 0.11 mmol) and 3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (**INT-69**, 52 mg, 1.1 eq., 0.13 mmol). Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was concentrated *in vacuo* and purified via C18 column for purification eluting with 0 to 100% MeCN (+0.1% formic acid) in H_2O (+0.1% formic acid). The desired fractions were collected, combined and concentrated via lyophilization to yield 3-(6-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-fluoro-2-

methylquinolin-3-yl)piperidine-2,6-dione (**65b**, 30 mg, 0.056 mmol, 49% yield). LCMS: m/z HESI, positive $[M+H]^+$ = 540.

Step 3: **Synthesis of 3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (I-59)**

3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (**I-59**) was synthesized according to **General Procedure 3, Step C** starting from 3-(6-(3,3-dimethyl-1-(4-(trifluoro-methyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (**65b**, 30 mg, 1.0 eq., 0.056 mmol). Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was concentrated *in vacuo* and purified via C18 column eluting with 0 to 100% MeCN (+0.1% formic acid) in H_2O (+0.1% formic acid). The desired fractions were collected, combined, and lyophilized to yield 3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (**I-59**, 2.5 mg, 0.005 mmol, 8% yield) as a mixture of diastereomers. LCMS: m/z HESI, positive $[M+H]^+$ = 558. ^{1}H-NMR (499 MHz, DMSO-d_6) δ (ppm) = 11.00-10.92 (m, 1H), 8.24-8.18 (m, 1H), 8.07-7.99 (m, 1H), 7.76-7.67 (m, 3H), 7.62-7.53 (m, 2H), 4.40-4.30 (m, 1H), 3.69-3.62 (m, 2H), 3.57-3.53 (m, 2H), 3.19-3.09 (m, 2H), 2.88-2.79 (m, 1H), 2.66 (s, 3H), 2.64-2.55 (m, 2H), 2.48-2.46 (m, 1H), 2.18-2.14 (m, 1H), 2.13-2.07 (m, 1H), 1.72-1.66 (m, 1H), 1.27-1.21 (m, 1H), 1.02-0.97 (m, 2H), 0.69-0.64 (m, 2H).

Example 66: Synthesis of 3-(6-(1-ethyl-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (I-67)



Step 1: **Synthesis of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (66a)**

tert-Butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (**66a**) was synthesized according to **General Procedure 4** starting from 3-(6-bromo-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (**INT-63**, 250 mg, 1.0 eq., 0.71 mmol) and *tert*-butyl 3,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**INT-40**, 480 mg, 2.0 eq., 1.42 mmol). The crude material was purified by reverse phase purification using Column: C18, eluting with Mobile phase A: 0.1% HCOOH in H_2O, Mobile phase B: Acetonitrile. The product eluted with 50% ACN in water (0.1% HCOOH)]. The pure product containing fractions were collected and lyophilized to afford *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (**66a**, 111 mg, 0.23mmol, 32% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 482.4. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.96 (s, 1H), 8.21 (s, 1H), 7.74 (d, J = 8.40 Hz, 1H), 7.45 (t, J = 8.40 Hz, 1H), 5.59 (s, 1H), 4.37 (d, J = 4.40 Hz, 1H), 4.02 (s, 2H), 3.35 (s, 2H), 2.88-2.79 (m, 1H), 2.68 (s, 3H), 2.64-2.49 (m, 2H), 2.14-2.11 (m, 1H), 1.46-1.28 (m, 9H), 0.99 (s, 6H).

Step 2: **Synthesis of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (66b)**

tert-Butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (**66b**) was synthesized according to **General Procedure 3, Step C** starting from *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (**66a**, 700 mg, 1.0 eq., 1.45 mmol). The crude material was purified by reverse phase column chromatography using C18 cartridge (25 g) eluting with 5 to 100% ACN and 0.1% formic acid in water. The pure product containing fractions were collected and lyophilized to afford *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (**66b**, 310 mg, 0.534 mmol, 37% yield). m/z MM-ES+APCI, Positive $[M+H]^+$ 500.4. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.95 (s, 1H), 8.22 (s, 1H), 8.03 (t, J = 8.80 Hz, 1H), 7.76 (d, J = 8.80 Hz, 1H), 5.76 (s, 1H), 4.37-4.33 (m, 1H), 3.99 (br s, 1H), 3.42-3.08 (m, 4H), 2.88-2.79 (m, 1H), 2.72 (s, 3H), 2.63-2.52 (m, 2H), 2.13-1.09 (m, 2H), 1.43 (s, 9H), 0.83 (s, 3H), 0.72 (s, 3H).

Step 3: **Synthesis of 3-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione, HCl (66c)**

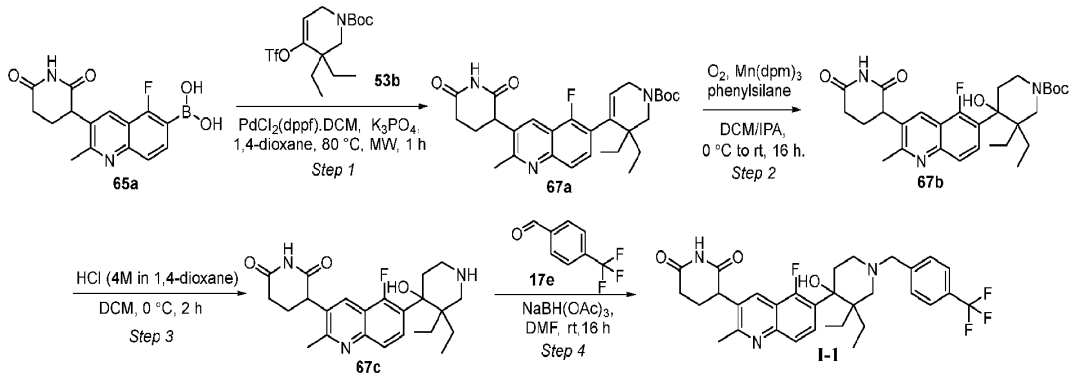
3-(5-Fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione, HCl (**66c**) was synthesized according to **General Procedure 6, Step A** starting from tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (**66b**, 310 mg, 1 eq., 0.64 mmol). The crude material was washed with n-pentane (10 x 2 mL)

and dried under reduced pressure to afford 3-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione, HCl (**66c**, 250 mg, 0.516 mmol, 80% yield). The product was carried onto the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 400.4. ^{1}H-NMR not recorded.

Step 4: **Synthesis of 3-(6-(1-ethyl-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (I-67)**

3-(6-(1-ethyl-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (**I-67**) was synthesized according to **General Procedure 6, Step B** starting from 3-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione, HCl (**66c**, 250 mg, 1.0 eq., 0.63 mmol) and acetaldehyde (55 mg, 2.0 eq., 1.25 mmol). The crude compound was purified by preparative-HPLC [(Column:X select C18 (150mm *19) 5 um, eluting with Mobile phase A: 0.05% FA in H_2O, Mobile phase B: Acetonitrile, flow rate: 15 mL/min)]. The pure product containing fractions were collected and lyophilized to afford 3-(6-(1-ethyl-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (**I-67**, 73.4 mg, 0.155 mmol, 25% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 428.5. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.95 (s, 1H), 8.21 (d, J = 5.20 Hz, 1H), 8.18 (s, 1H), 8.04 (t, J = 8.80 Hz, 1H), 7.74 (d, J = 10.40 Hz, 1H), 5.08 (s, 1H), 4.37-4.32 (m, 1H), 3.09 (t, J = 12.80 Hz, 1H), 2.86-2.74 (m, 2H), 2.67 (s, 3H), 2.66-2.51 (m, 2H), 2.48-2.28 (m, 4H), 2.14-2.08 (m, 1H), 1.69 (d, J = 13.20 Hz, 2H), 1.05 (t, J = 7.60 Hz, 3H), 0.95 (s, 3H), 0.71 (s, 3H).

Example 67: Synthesis of 3-(6-(3,3-diethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (I-1)



Step 1: **Synthesis of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-3,3-diethyl-3,6-dihydropyridine-1(2H)-carboxylate (67a)**

tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-3,3-diethyl-3,6-dihydropyridine-1(2H)-carboxylate (**67a**) was synthesized according to **General Procedure 3, Step B** starting from (3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)boronic acid (**65a**, 408 mg, 1.0 eq., 1.29 mmol) and *tert*-butyl 3,3-diethyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-

carboxylate (**53b**, 500 mg, 1.0 eq., 1.29 mmol). This crude material was purified by flash column chromatography using Biotage Isolera® (on silica gel 100-200 mesh) eluting with 0-80% EtOAc in hexanes to afford *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-3,3-diethyl-3,6-dihydropyridine-1(2H)-carboxylate (**67a**, 320 mg, 0.57 mmol, 44% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 510.8. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.95 (s, 1H), 8.21 (s, 1H), 7.74 (d, J = 8.80 Hz, 1H), 7.48 (d, J = 7.20 Hz, 1H), 5.76 (s, 1H), 4.37-4.10 (m, 1H), 4.05-4.01 (m, 2H), 3.45 (s, 2H), 2.83-2.79 (m, 2H), 2.60-2.51 (m, 4H), 2.13 (s, 1H), 1.45-1.39 (m, 13H), 0.79 (s, 6H).

Step 2: **Synthesis of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-3,3-diethyl-4-hydroxypiperidine-1-carboxylate (67b)**

tert-Butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-3,3-diethyl-4-hydroxypiperidine-1-carboxylate (**67b**) was synthesized according to **General Procedure 3, Step C** starting from 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-3,3-diethyl-3,6-dihydropyridine-1(2H)-carboxylate (**67a**, 320 mg, 1.0 eq., 0.63 mmol). The crude material was purified by reverse phase column chromatography using (C18) cartridge (25 g) eluting with 5 to 100% MeCN and 0.1% formic acid in water. The pure product containing fractions were collected and lyophilized to afford *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-3,3-diethyl-4-hydroxypiperidine-1-carboxylate (**67b**, 220 mg, 0.31 mmol, 50% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 528.6. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.98 (s, 1H), 8.42 (s, 1H), 8.12 (d, J = 7.60 Hz, 1H), 7.76-7.74 (m, 1H), 5.42 (s, 1H), 4.42-4.39 (m, 1H), 4.19-3.93 (m, 3H), 2.83-2.80 (m, 2H), 2.65-2.61 (m, 5H), 2.14-2.11 (m, 1H), 1.59-1.57 (m, 2H), 1.43-1.33 (m, 13H), 0.96-0.80 (t, J = 7.40 Hz, 3H), 0.48-0.46 (t, J = 7.40 Hz, 3H).

Step 3: **Synthesis of 3-(6-(3,3-diethyl-4-hydroxypiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione, HCl (67c)**

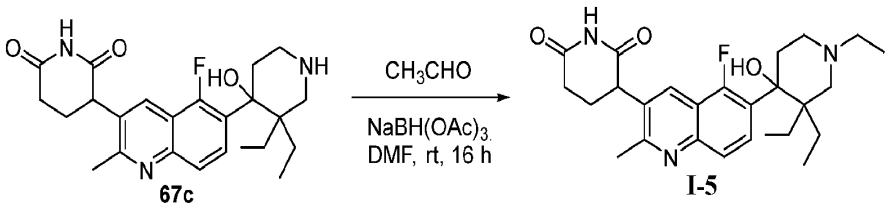
3-(6-(3,3-Diethyl-4-hydroxypiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione, HCl (**67c**, 190 mg, 0.35 mmol, 83% yield) was synthesized according to **General Procedure 1, Step C** was starting from *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-3,3-diethyl-4-hydroxypiperidine-1-carboxylate (**67b**, 220 mg, 1.0 eq., 0.42 mmol). The product was taken onto the next step without further purification. LCMS: m/z MM-ES+APCI, Negative $[M-H]^-$ 426.1.

Step 4: **Synthesis of 3-(6-(3,3-diethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (I-1)**

3-(6-(3,3-Diethyl -4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (**I-1**) was synthesized according to **General Procedure 1, Step D** starting from 3-(6-(3,3-diethyl-4-hydroxypiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione, HCl (**67c**, 100 mg, 1.0 eq., 0.22 mmol) and 4-(trifluoromethyl)benzaldehyde (**17e**, 45 mg, 1.2

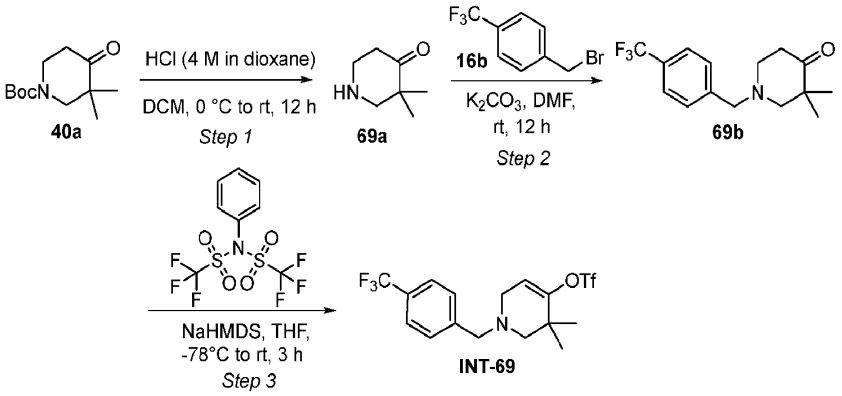
eq., 0.26 mmol). The crude compound was purified by preparative-HPLC [(Column: X select (150 x 19 mm) 5 µm, eluting with Mobile phase A: 0.05% HCOOH in H_2O, Mobile phase B: Acetonitrile, flow rate: 15 mL/min)]. The pure product containing fractions were collected and lyophilized to afford 3-(6-(3,3-diethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (**I-1**, 15.6 mg, 0.03 mmol, 12% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 586.7. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.95 (s, 1H), 8.20 (d, *J* = 3.20 Hz, 1H), 8.12 (t, *J* = 8.80 Hz, 1H), 7.72 (d, *J* = 4.40 Hz, 3H), 7.63 (d, *J* = 8.00 Hz, 2H), 5.11 (s, 1H), 4.37-4.32 (m, 1H), 3.62-3.55 (m, 3H), 3.33-3.17 (m, 1H), 2.83 (m, 2H), 2.66-2.61 (m, 6H), 2.39-2.34 (m, 2H), 2.12 (s, 2H), 1.62-1.49 (m, 1H), 1.11-1.07 (m, 2H), 0.54 (t, *J* = 7.20 Hz, 3H), 0.44 (t, *J* = 7.60 Hz, 3H).

Example 68: Synthesis of 3-(5-fluoro-2-methyl-6-(1,3,3-triethyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-5)



3-(5-fluoro-2-methyl-6-(1,3,3-triethyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-5**) was synthesized according to **General Procedure 1, Step D** starting from 3-(6-(3,3-diethyl-4-hydroxypiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione, HCl (**67c**, 120 mg, 1.0 eq., 0.26 mmol) and acetaldehyde (23 mg, 2.0 eq., 0.52mmol). The crude compound was purified by preparative-HPLC [(Column: X select (150 x 19 mm) 5 µm, eluting with Mobile phase A: 0.05% HCOOH in H_2O, Mobile phase B: Acetonitrile, flow rate: 15 mL/min)]. The pure product containing fractions were collected and lyophilized afford 3-(5-fluoro-2-methyl-6-(1,3,3-triethyl-4-hydroxy-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-5**, 7.8 mg, 0.02 mmol, 6% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 456.5. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.95 (s, 1H), 8.21 (s, 1H), 8.19 (s, 1H), 8.12 (t, *J* = 8.40 Hz, 1H), 7.73 (d, *J* = 8.80 Hz, 1H), 5.06 (s, 1H), 4.37-4.32 (m, 1H), 3.33-3.15 (m, 1H), 2.83-2.66 (m, 1H), 2.52-2.50 (m, 6H), 2.47-2.41 (m, 3H), 2.34-2.33 (m, 1H), 2.23-2.20 (m, 1H), 2.11-2.09 (m, 2H), 1.59-1.53 (m, 2H), 1.18-1.16 (m, 1H), 1.07-1.03 (m, 4H), 0.68 (t, *J* = 7.20 Hz, 3H), 0.50 (t, *J* = 7.60 Hz, 3H).

Example 69: Synthesis of 3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydro-pyridin-4-yl trifluoromethanesulfonate (INT-69)



Step 1: **3,3-dimethylpiperidin-4-one (69a)**

To a stirred solution of *tert*-butyl 3,3-dimethyl-4-oxopiperidine-1-carboxylate (**40a**, 5 g, 22.00 mmol) in DCM (25 mL) was added HCl (4M in dioxane) (11.00 mL, 44.00 mmol) at 0°C under an atmosphere of nitrogen and the resulting mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure and dried under reduced pressure to afford 3,3-dimethylpiperidin-4-one (**69a**, 2.6 g, 20.03 mmol, 91% yield). The product was carried onto the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 128.1.

Step 2: **3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-one (69b)**

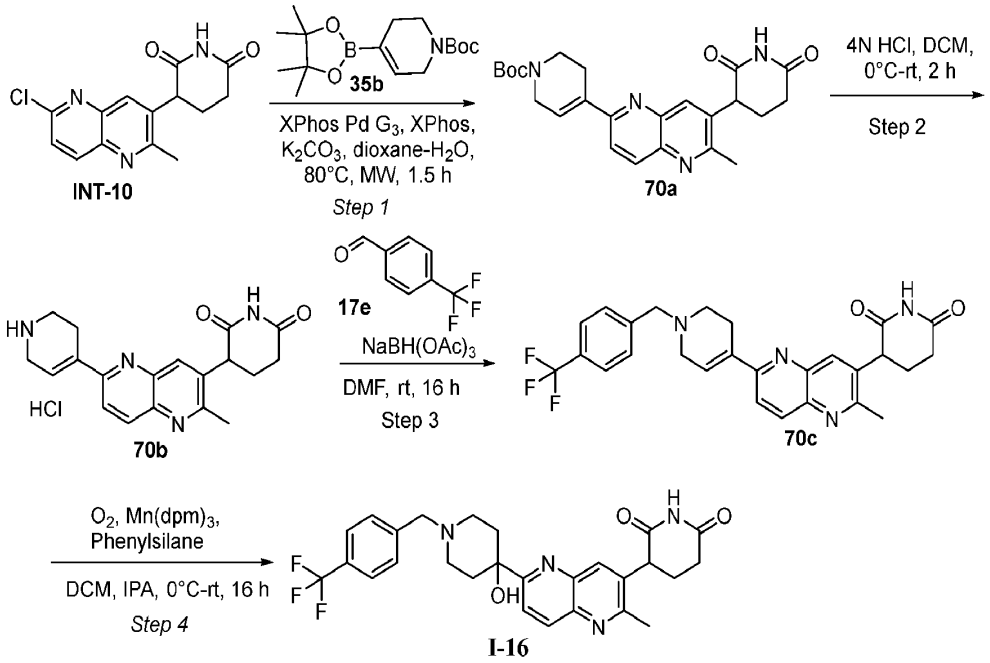
To a stirred solution of 3,3-dimethylpiperidin-4-one (**69a**, 2.6 g, 20.44 mmol) in DMF (25 mL) were added potassium carbonate (5.65 g, 40.90 mmol) and 1-(bromo-methyl)-4-(trifluoromethyl)benzene (**16b**, 5.38 g, 22.49 mmol) at 25 °C and the resulting mixture was stirred at 25 °C for 12 h. Ice-cold water (50 mL) was then added and the aqueous mixture was extracted with EtOAc (2 x 200 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by flash column chromatography using Biotage Isolera® on silica gel (100-200 mesh) eluting with 0-10% EtOAc in *n*-hexane to afford 3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-one (**69b**, 3.6g, 12.61 mmol, 62% yield). 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: **3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (INT-69)**

To a stirred solution of 3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-one (**69b**, 3.3 g, 11.57 mmol) in THF (20 mL) was added NaHMDS (1M in THF) (23.13 mL, 23.13 mmol) at -78 °C and the resulting mixture was stirred at -78 °C for 35 min. 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (5.37 g, 15.04 mmol) dissolved in THF (5 mL) was then added dropwise at -78 °C and stirring was continued at room temperature for 3 h. Aqueous ammonium

chloride solution (50 mL) was added and aqueous mixture extracted with EtOAc (2 x 200 mL). The combined organic phases were dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography using Biotage Isolera® on silica gel (100-200 mesh) eluting with 0-10% EtOAc in *n*-hexane to afford 3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (**INT-69**, 3.2 g, 6.36 mmol, 55% yield). LCMS: m/z 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).

Example 70: Synthesis of 3-(6-(4-hydroxy-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)-2-methyl-1,5-naphthyridin-3-yl)piperidine-2,6-dione (I-16)



Step 1: **Synthesis of *tert*-butyl 4-(7-(2,6-dioxopiperidin-3-yl)-6-methyl-1,5-naphthyridin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (70a)**

tert-Butyl 4-(7-(2,6-dioxopiperidin-3-yl)-6-methyl-1,5-naphthyridin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**70a**) was synthesized according to **General Procedure 5** starting from 3-(6-chloro-2-methyl-1,5-naphthyridin-3-yl)piperidine-2,6-dione (**INT-10**, 200 mg, 1.0 eq., 0.69mmol) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**35b**, 256 mg, 1.2 eq., 0.83mmol). The crude compound was purified by Biotage Isolera® (on a 40g silica gel cartridge) eluting with 95% EtOAc in hexane. The pure product containing fractions were collected and concentrated under reduced pressure to afford *tert*-butyl 4-(7-(2,6-dioxopiperidin-3-yl)-6-methyl-1,5-naphthyridin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**70a**, 325 mg, 0.67 mmol, 97% yield). LCMS:

m/z MM-ES+APCI, Positive $[M+H]^+$ = 437.3. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.96 (s, 1H), 8.27(d, *J* = 8.86 Hz, 1H), 8.10 (s, 1H), 6.89 (s, 1H), 5.76 (s, 1H), 4.36-4.32 (m, 1H), 4.13-4.04 (m, 2H), 3.58 (t, *J* = 5.20 Hz, 2H), 2.87-2.74 (m, 6H), 2.16 (s, 2H), 2.08 (s, 1H), 1.51 (s, 9H).

Step 2: **Synthesis of 3-(2-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)-1,5-naphthyridin-3-yl)piperidine-2,6-dione (70b)**

3-(2-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)-1,5-naphthyridin-3-yl)piperidine-2,6-dione (**70b**) was synthesized according to **General Procedure 6, Step A** starting from *tert*-butyl 4-(7-(2,6-dioxopiperidin-3-yl)-6-methyl-1,5-naphthyridin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**70a**, 350 mg, 1 eq., 0.80 mmol). The crude product was washed by MTBE to afford 3-(2-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)-1,5-naphthyridin-3-yl)piperidine-2,6-dione (**70b**, 250 mg, 0.62 mmol, 78% yield), which was carried onto the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 337. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 8.29 (br s, 2H), 8.46 (d, *J* = 8.80 Hz, 1H), 8.33 (s, 1H), 8.20 (d, *J* = 8.80 Hz, 1H), 6.96 (s, 1H), 4.44-4.42 (m, 1H), 4.39-3.75 (m, 2H), 3.37 (s, 2H), 2.98-2.92 (m, 2H), 2.90-2.81 (m, 1H), 2.81 (s, 3H), 2.68-2.57 (m, 2H), 1.69-1.61 (m, 1H).

Step 3: **Synthesis of 3-(2-methyl-6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-1,5-naphthyridin-3-yl)piperidine-2,6-dione (70c)**

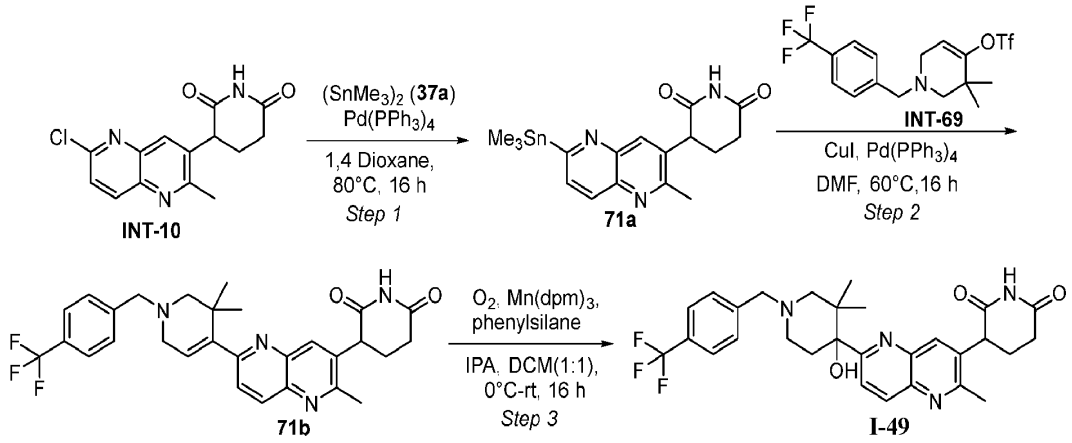
3-(2-Methyl-6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-1,5-naphthyridin-3-yl)piperidine-2,6-dione (**70c**) was synthesized according to **General Procedure 6, Step B** starting from 3-(2-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)-1,5-naphthyridin-3-yl)piperidine-2,6-dione (**70b**, 200 mg, 1.0 eq., 0.60 mmol) and 4-(trifluoromethyl)benzaldehyde (**17e**, 124 mg, 1.2 eq., 0.71mmol). The crude compound was purified by silica gel flash column chromatography, eluting with 65% EtOAc in hexane to afford 3-(2-methyl-6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-1,5-naphthyridin-3-yl)piperidine-2,6-dione (**70c**, 200 mg, 0.35 mmol, 59% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 495.4. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.96 (s, 1H), 8.24 (d, *J* = 8.40 Hz, 1H), 8.08 (s, 1H), 8.01 (d, *J* = 9.20 Hz, 1H), 7.72 (d, *J* = 8.00 Hz, 2H), 7.61 (d, *J* = 8.00 Hz, 2H), 6.87 (s, 1H), 4.35-4.31 (m, 1H), 3.74 (s, 2H), 3.22-3.21 (m, 3H), 2.72-2.63 (m, 4H), 2.52 (s, 3H), 2.51-2.50 (m, 2H), 2.16-2.13 (m, 1H).

Step 4: **Synthesis of 3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-2-methyl-1,5-naphthyridin-3-yl)piperidine-2,6-dione (I-16)**

3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methyl-1,5-naphthyridin-3-yl)piperidine-2,6-dione (**I-16**) was synthesized according to **General Procedure 3, Step C** starting from 3-(2-methyl-6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-1,5-naphthyridin-3-yl)piperidine-2,6-dione (**70c**, 180 mg, 1 eq., 0.36 mmol). The crude compound was purified by preparative-HPLC using X SELECT C18 [19*250MM] column, eluting with Mobile phase A: 0.1%

Ammonium Acetate, Mobile phase B: Acetonitrile, flow rate: 15 ml/min)], RT:12.8. The pure product containing fractions were collected and lyophilized to afford 3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methyl-1,5-naphthyridin-3-yl)piperidine-2,6-dione (**I-16**, 70 mg). This compound was dissolved in acetonitrile, 0.5 M HCl (1.0 eq.) was added and the resulting mixture was lyophilized to afford 3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-2-methyl-1,5-naphthyridin-3-yl)piperidine-2,6-dione, HCl (**I-16**, 56.7 mg, 0.10 mmol, 28% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 513.5. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 10.40 (s, 1H), 8.39 (d, J = 8.80 Hz, 1H), 8.07-8.02 (m, 2H), 7.87 (d, J = 16.80 Hz, 4H), 5.99 (s, 1H), 4.53 (d, J = 4.80 Hz, 2H), 4.39-4.35 (m, 1H), 3.37 (s, 4H), 2.89-2.83 (m, 1H), 2.71 (s, 3H), 2.65-2.59 (m, 4H), 2.16-2.13 (m, 1H), 1.94 (d, J = 14.00 Hz, 2H).

Example 71: 3-(6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methyl-1,5-naphthyridin-3-yl)piperidine-2,6-dione (I-49)



Step 1: **Synthesis of 3-(2-methyl-6-(trimethylstannyl)-1,5-naphthyridin-3-yl)piperidine-2,6-dione (71a)**

To a stirred solution of 3-(6-chloro-2-methyl-1,5-naphthyridin-3-yl)piperidine-2,6-dione (**INT-10**, 200 mg, 0.69 mmol) in 1,4-dioxane (7 mL) under an atmosphere of nitrogen was added hexamethyl ditin (**37a**, 407 mg, 1.24 mmol) at 25 °C and the resulting mixture was sparged with nitrogen for 10 min. Tetrakis(triphenylphosphine)palladium(0) (120 mg, 0.10 mmol) was then added at 25 °C and the reaction mixture was sparged with nitrogen for 10 min and stirring was continued at 80 °C for 2 h. The reaction mixture was filtered through a pad of celite®, and the filtrate was concentrated under reduced pressure to afford 3-(2-methyl-6-(trimethylstannyl)-1,5-naphthyridin-3-yl)piperidine-2,6-dione (**71a**, 300 mg, 0.47 mmol, 68% yield), which was carried onto the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 420.0.

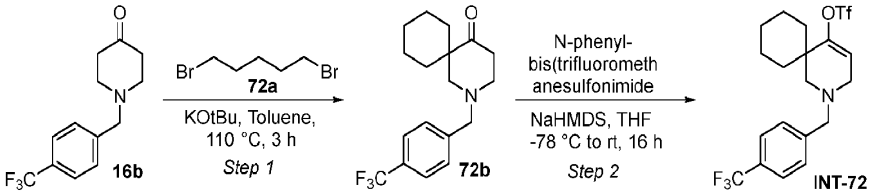
Step 2: **Synthesis of 3-(6-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-2-methyl-1,5-naphthyridin-3-yl)piperidine-2,6-dione (71b)**

To a stirred solution of 3-(2-methyl-6-(trimethylstannyl)-1,5-naphthyridin-3-yl)-piperidine-2,6-dione (**71a**, 200 mg, 0.48 mmol) and 3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yltrifluoromethanesulfonate (**INT-69**, 200 mg, 0.48 mmol) in DMF (5 mL) was added copper(I) iodide (18.22 mg, 0.10 mmol) followed by tetrakis(triphenyl-phosphine)palladium(0) (55.3 mg, 0.05 mmol) at 25 °C under an atmosphere of nitrogen atmosphere and the resulting mixture was stirred at 60 °C for 16 h. The reaction mixture was filtered through a pad of Celite® to remove the inorganic salts. The filtrate was concentrated under reduced pressure and the crude material was purified by flash column chromatography on Biotage Isolera® on silica gel (100-200 mesh) eluting with 0 to 85% EtOAc in *n*-hexane to afford 3-(6-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-2-methyl-1,5 naphthyridin-3-yl)piperidine-2,6-dione (**71b**, 170 mg, 0.27 mmol, 57% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 523.3. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.95 (s, 1H), 8.22 (d, *J* = 8.80 Hz, 1H), 8.11 (s, 1H), 7.91-7.78 (m, 4H), 7.64 (d, *J* = 8.00 Hz, 1H), 6.24 (t, *J* = 3.60 Hz, 1H), 3.74 (d, *J* = 7.60 Hz, 2H), 3.21 (d, *J* = 3.60 Hz, 1H), 2.69 (t, *J* = 4.40 Hz, 4H), 2.51 (t, *J* = 2.00 Hz, 2H), 2.35 (s, 1H), 2.20-2.13 (m, 2H), 1.33 (d, *J* = 10.40 Hz, 5H), 1.11 (s, 3H).

Step 3: **Synthesis of 3-(6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methyl-1,5-naphthyridin-3-yl)piperidine-2,6-dione (I-49)**

3-(6-(4-Hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methyl-1,5-naphthyridin-3-yl)piperidine-2,6-dione (**I-49**) was synthesized according to **General Procedure 3, Step C** starting from afford 3-(6-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-2-methyl-1,5 naphthyridin-3-yl)piperidine-2,6-dione (**71b**, 170 mg, 1 eq., 0.325 mmol). The crude material was purified by preparative-HPLC [(Column: X select C18 [19*250 mm], eluting with Mobile phase A: 0.1% ammonium acetate, Mobile phase B: Acetonitrile, flow rate: 15 mL/min)]. The pure product containing fractions were collected and lyophilized to afford 3-(6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methyl-1,5-naphthyridin-3-yl)piperidine-2,6-dione (**I-49**, 3.7 mg, 6.63 µmol, 22% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 541.5. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.97 (s, 1H), 8.28 (d, *J* = 8.80 Hz, 1H), 8.14 (s, 1H), 8.02 (dd, *J* = 2.00, 9.00 Hz, 1H), 7.71 (d, *J* = 8.00 Hz, 2H), 7.60 (d, *J* = 8.00 Hz, 2H), 5.25 (d, *J* = 10.00 Hz, 1H), 4.35 (dd, *J* = 4.40, 12.20 Hz, 1H), 3.62 (dd, *J* = 14.00, 34.00 Hz, 2H), 3.11 (s, 1H), 2.86-2.81 (m, 4H), 2.77 (t, *J* = 9.60 Hz, 3H), 2.69 (t, *J* = 1.60 Hz, 2H), 2.16 (d, *J* = 10.40 Hz, 2H), 1.53 (d, *J* = 13.60 Hz, 1H), 0.92 (d, *J* = 2.40 Hz, 3H), 0.72 (d, *J* = 3.20 Hz, 3H).

Example 72: Synthesis of 2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl trifluoromethanesulfonate (INT-72)



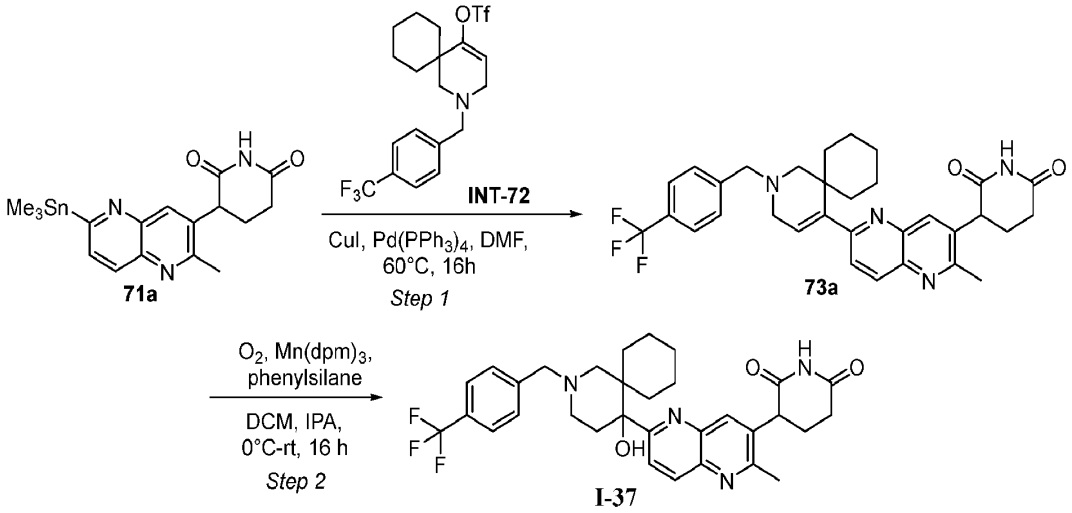
Step 1: **Synthesis of 2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-one (72b)**

To a stirred solution of 1-(4-(trifluoromethyl)benzyl)piperidin-4-one (**16b**, 5 g, 19.44 mmol) in toluene (50 mL) was added potassium *tert*-butoxide (4.80 g, 42.8 mmol) at 25 °C and the resulting mixture was stirred for 1 h. 1,5-dibromopentane (**72a**, 4.47 g, 19.44 mmol) then added dropwise over 5 min at 25 °C. and stirring was continued at 110 °C for 3 h. The reaction mixture was cooled to room temperature, saturated solution of NH_4Cl in water (300 mL) was added, and the aqueous mixture was extracted with EtOAc (3 x 250 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography using Biotage Isolera® on silica gel (100-200 mesh) eluting with 0-15% EtOAc in *n*-hexane to afford 2-(4-(trifluoro-methyl)benzyl)-2-azaspiro[5.5]undecan-5-one (**72b**, 2.5 g, 7.38 mmol, 38% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 326.6. ^{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), 3.82 (s, 2H), 2.69 (t, J = 6.00 Hz, 2H), 2.51-2.45 (m, 2H), 2.43-2.33 (m, 2H), 2.33-2.00 (m, 2H), 1.75 (m, 8H).

Step 2: **Synthesis of 2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl trifluoromethanesulfonate (INT-72)**

To the stirred solution of 2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-one (**72b**, 1 g, 3.07 mmol) in THF (2 mL) was added NaHMDS (1 M in THF) (3.07 mL, 3.07 mmol) at -78 °C under an atmosphere of nitrogen and the resulting mixture stirred for 30 min at -78 °C and at 25 °C for 1 h. This reaction mixture was again cooled to -78 °C and N-phenyl-bis(trifluoromethanesulfonimide) (2.196 g, 6.15 mmol) dissolved in THF (2 mL) was then added dropwise at -78 °C and stirring was continued at room temperature for 16 h. Water (20 mL) was added and the aqueous mixture was extracted with EtOAc (50 mL). The organic phase was washed with water (50 mL) and brine solution (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography (on silica gel 100-200 mesh, Isolera, flow rate of 35 mL/min, eluting with 5-6% EtOAc in pet ether) to afford 2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl trifluoromethanesulfonate (**INT-72**, 1 g, 1.51 mmol, 49% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 458.7. ^{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), 5.83-5.76 (m, 1H), 3.73 (s, 2H), 3.13 (s, 2H), 2.51 (t, J = 1.60 Hz, 2H), 1.63 (d, J = 12.80 Hz, 2H), 1.53-1.40 (m, 6H), 1.10-1.07 (m, 2H).

Example 73: Synthesis of 3-(6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-2-methyl-1,5-naphthyridin-3-yl)piperidine-2,6-dione (I-37)



Step 1: **Synthesis of 3-(2-methyl-6-(2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)-1,5-naphthyridin-3-yl)piperidine-2,6-dione (73a)**

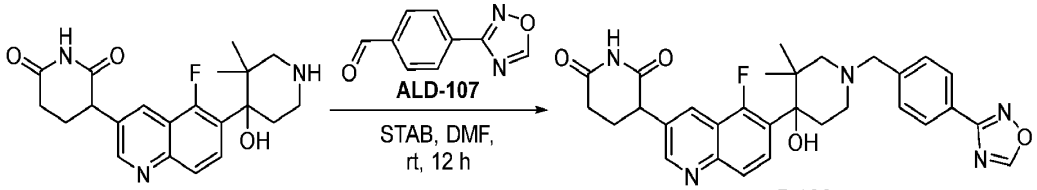
To the stirred solution of 3-(2-methyl-6-(trimethylstannyl)-1,5-naphthyridin-3-yl)piperidine-2,6-dione (**71a**, 200 mg, 0.48 mmol) and 2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl trifluoromethanesulfonate (**INT-72**, 219 mg, 0.48 mmol) in DMF (5 mL) was added tetrakis(triphenylphosphine)palladium(0) (55.3 mg, 0.05 mmol), followed by copper(I) iodide (18.22 mg, 0.10 mmol) at 25 °C under nitrogen atmosphere and the resulting mixture was stirred at 60 °C for 16 h. The reaction mixture was filtered through a pad of celite® to remove the inorganic salts and the filtrate was concentrated under reduced pressure. The crude material was purified by flash column chromatography Biotage Isolera® on silica gel (100-200 mesh) eluting with 0 to 80% EtOAc in *n*-hexane to afford 3-(2-methyl-6-(2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)-1,5-naphthyridin-3-yl)piperidine-2,6-dione (**73a**, 150 mg, 0.21 mmol, 45% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 563.4. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.96 (s, 1H), 8.23 (d, J = 8.80 Hz, 1H), 8.13 (s, 1H), 7.75-7.72 (m, 2H), 7.67-7.65 (m, 2H), 7.63-7.54 (m, 2H), 6.00 (s, 1H), 4.25-4.23 (m, 1H), 3.75 (s, 2H), 3.33 (s, 2H), 2.90 (s, 1H), 2.74 (d, J = 0.40 Hz, 3H), 2.69-2.62 (m, 3H), 2.16-2.15 (m, 2H), 1.39-1.36 (m, 3H), 1.11-1.08 (m, 3H), 0.54-0.55 (m, 3H).

Step 2: **Synthesis of 3-(6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-2-methyl-1,5-naphthyridin-3-yl)piperidine-2,6-dione (I-37)**

3-(6-(5-Hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-2-methyl-1,5-naphthyridin-3-yl)piperidine-2,6-dione (**I-37**) was synthesized according to **General Procedure 3, Step C** starting from 3-(2-methyl-6-(2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undec-4-en-5-yl)-1,5-

naphthyridin-3-yl)piperidine-2,6-dione (**73a**, 140 mg, 1 eq., 0.075 mmol). The crude material was purified by preparative-HPLC [(Column: X select C18 [19*250 mm], eluting with Mobile phase A: 0.1% ammonium acetate, Mobile phase B: Acetonitrile, flow rate: 15 mL/min), Rt 12.8 min]. The pure product containing fractions were collected and lyophilized to afford 3-(6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)-2-methyl-1,5-naphthyridin-3-yl)piperidine-2,6-dione (**I-37**, 4.3 mg, 6.96 µmol, 24% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 581.7. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.97 (s, 1H), 8.27 (d, *J* = 9.20 Hz, 1H), 8.15 (s, 1H), 8.01 (d, *J* = 4.80 Hz, 1H), 7.71 (d, *J* = 8.00 Hz, 2H), 7.61 (d, *J* = 8.00 Hz, 2H), 5.23 (d, *J* = 14.80 Hz, 1H), 4.35-4.33 (m, 1H), 3.65-3.61 (m, 2H), 3.30 (s, 1H), 2.90-2.85 (m, 6H), 2.70-2.65 (m, 3H), 2.34-2.32 (m, 2H), 1.90 (s, 1H), 1.76 (m, 1H), 1.28-1.24 (m, 4H), 1.07-1.04 (m, 2H), 0.68-0.63 (m, 1H), 0.65-0.61 (m, 1H), 0.58-0.53 (m, 1H).

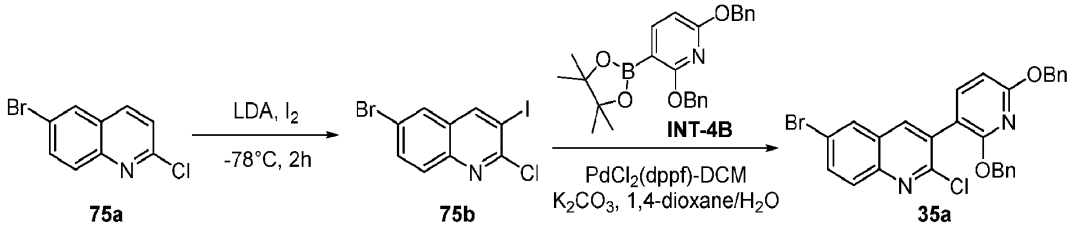
Example 74: Synthesis of 3-(6-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (I-122)



51d **I-122**

To a stirred solution of 3-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl (**51d**, 100 mg, 0.237 mmol) in DMF (3 mL) was added 4-(1,2,4-oxadiazol-3-yl)benzaldehyde (**ALD-107**, 41.3 mg, 0.237 mmol) at room temperature and the resulting mixture was stirred at room temperature for 1 h. Sodium triacetoxyborohydride (151 mg, 0.711 mmol) was then added in portions, and stirring was continued at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure and further on high-vac to obtain the crude material. The crude compound was purified by preparative-HPLC [X-SELECT CSH C18 (250 x19 x5u), eluting with Mobile phase A: 0.05% HCl in H_2O: 100% ACN, Mobile phase B: Acetonitrile, flow rate: 14 ml/min, RT: 12.9]. The pure product containing fractions were collected and lyophilized to afford 3-(6-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (**I-122**, 34.4 mg, 0.059 mmol, 25% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 544.54. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 10.27 (br s, 1H), 9.78 (s, 1H), 8.92 (s, 1H), 8.43 (s, 1H), 8.16 (d, *J* = 8.00 Hz, 2H), 8.08 (t, *J* = 8.40 Hz, 1H), 7.95-7.91 (m, 3H), 5.94 (br s, 1H), 4.52-4.44 (m, 2H), 4.28-4.15 (m, 2H), 3.42 (s, 3H), 3.29 (t, *J* = 11.20 Hz, 1H), 2.90 (d, *J* = 11.60 Hz, 1H), 2.77-2.51 (m, 2H), 2.15-2.01 (m, 2H), 1.10 (s, 3H), 0.77 (s, 3H).

Example 75: Synthesis of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-2-chloroquinoline (35a)



Step 1: **Synthesis of 6-bromo-2-chloro-3-iodoquinoline (75b)**

6-Bromo-2-chloro-3-iodoquinoline (75b) was prepared according to the procedures and examples as reported in PCT Application Publication No. WO2011/090911.

To a dry round bottom flask under an atmosphere of argon at -78 °C (using a dry ice and acetone bath) was added 1M LDA in THF (15mL), followed by the slow addition of a solution of 6-bromo-2-chloroquinoline (**75a**, 3.03 g, 12.5 mmol) in THF (40 mL) and the resulting mixture was stirred at -78°C for 2 h. A solution of I_2 (3.16g, 12.5 mmol) in THF (35 mL) was then added and stirring was continued at -78 °C for 2 h. The reaction mixture was poured onto ice, concentrated to remove most of the THF, and diluted with EtOAc. The organic phase was washed with sat. $Na_2S_2O_3$ solution and sat. $NaHCO_3$ solution. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude material, which was purified by flash column chromatography (on silica gel and eluting with 20% to 60% EtOAc in heptanes). The product containing fractions were collected and the desired product was trituated using hexanes to afford 6-bromo-2-chloro-3-iodoquinoline (**75b**, 340 mg, 0.92 mmol, 7% yield) which was carried onto the next step without further purification. LCMS: m/z HESI, positive $[M+H]^+$ = 368.2; $[M+H+2]^+$=369.9; [calcd for $C_9H5BrClIN^+$ for 367.8].

Step 2: **Synthesis of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-2-chloroquinoline (35a)**

6-bromo-2-chloro-3-iodoquinoline (**75b**, 0.18g, 1.5mmol), 2,6-bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**INT-4B**, 0.25g, 0.6mmol), and $PdCl_2$(dppf)-DCM (0.04g, 0.05 mmol) were weighed into 10mL MW tube and 1,4-dioxane (6 mL) was added, followed by the addition of an aqueous solution of K_2CO_3 (0.097g, 0.7mmol, in 600uL H_2O). The resulting mixture was sparged with argon with sonication for 4 minutes. The MW tube was then sealed and heated at 85 °C under MW irradiation for 2 h. The reaction mixture was then directly loaded onto the silica gel cartridge, and purified by flash column chromatography (eluting with 10% to 100% EtOAc in heptanes) to afford 6-bromo-2-chloro-3-(2,6-dimethoxypyridin-3-yl)quinoline (**35a**, 128mg, 0.24mmol, 40% yield). LC-MS: m/z HESI, positive $[M+H]^+$ = 531.5; $[M+H+2]^+$=533.3 [calcd for $C_{28}H_{21}BrClN_2O_2^+$ for 531.1].

Example 76: General procedure C- Reductive amination

To a stirred solution of the amine or the amine hydrochloride (0.1 mmol, 1.0 eq.) in DMF (1 ml) and the aldehyde (0.12 mmol, 1.2 eq.) at 25 °C is added acetic acid (0.1 mmol, 1.0 eq.) and the resulting mixture is stirred for 0.5 to 1 h. Sodium triacetoxyborohydride (0.3 mmol, 3.0 eq.) 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 x 19) 5 um, eluting with Mobile phase A: 0.05% FA or HCl in H_2O, Mobile phase B: Acetonitrile, 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 hydrochloride salt, or the free amine.

Example 77: General procedure D- Reductive amination

To a stirred solution of the amine or the amine hydrochloride (0.1 mmol, 1.0 eq.) in DMF (1 ml) and the aldehyde (0.12 mmol, 1.2 eq.) at 25 °C was added sodium acetate (0.5 mmol, 5.0 eq.) and acetic acid (0.3 mmol, 3.0 eq.) 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 x 19) 5 um, eluting with Mobile phase A: 0.05% FA or HCl in H_2O, Mobile phase B: Acetonitrile, 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.

Example 78: General procedure E- Reductive amination

To a stirred solution of the amine or the amine hydrochloride (0.1 mmol, 1.0 eq.) in DMF (1 mL) was added acetic acid (0.1 mmol, 0.1 eq.) and triethylamine (0.5 mmol, 5.0 eq.) followed by the aldehyde (0.12 mmol, 1.2 eq.) at 25°C. The resulting mixture was stirred for 4 h. Sodium cyanoborohydride (0.5 mmol, 5.0 eq.) was then added and stirring was continued for 16 h. The reaction mixture was concentrated under reduced pressure to afford crude compound, which was purified by reverse phase chromatography [(Column: X select (150 mm x 19) 5 µm, eluting with Mobile phase A: 0.05% FA or HCl in H_2O, Mobile phase B: Acetonitrile, 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.

Example 79: General procedure F- Reductive amination

To a stirred solution of the amine or the amine hydrochloride (0.1 mmol, 1.0 eq.) in DMF (1 mL) and the aldehyde (0.12 mmol, 1.2 eq.) and DIPEA (0.3 mmol, 3.0 eq.) was added at 25°C, and the reaction mixture was stirred at 25°C for 1 h. To this mixture was added sodium triacetoxyborohydride (0.3 mmol, 3.0 eq.) and the resulting mixture was stirred at 60 °C for 16 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to afford the crude compound, which was purified by reverse phase chromatography [(Column: X select (150 mm x 19) 5 µm, eluting with Mobile phase A: 0.05% FA or HCl in H_2O, Mobile phase B: Acetonitrile, 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.

Example 80: General procedure G- Reductive amination

To a stirred solution of the amine or the amine hydrochloride (0.1 mmol, 1.0 eq.) in IPA (1 mL) was added the aldehyde (0.12 mmol, 1.2 eq.) followed by potassium acetate (0.15 mmol, 1.5 eq.) and sodium cyanoborohydride (0.2 mmol, 2.0 eq.) at 25°C. The resulting mixture was stirred at 80 °C for 2 h. The reaction mixture was concentrated under reduced pressure to afford crude compound, which was purified by reverse phase chromatography [(Column: X select (150 mm x 19) 5 µm, eluting with Mobile phase A: 0.05% FA or HCl in H_2O, Mobile phase B: Acetonitrile, 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.

Example 81: General procedure H- Reductive amination

To a stirred solution of the amine or the amine hydrochloride (0.1 mmol, 1.0 eq.) in DMF (1 mL) were added the aldehyde (0.12 mmol, 1.2 eq.) and TEA (0.2 mmol, 2.0 eq.) at 25°C, and the resulting mixture was stirred at 25 °C for 2 h. To this mixture was added sodium acetate (0.2 mmol, 2.0 eq.) followed by sodium triacetoxyborohydride (0.3 mmol, 3.0 eq.), and the reaction mixture was stirred at room temperature for 16 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 x 19) 5 µm, eluting with Mobile phase A: 0.05% FA or HCl in H_2O, Mobile phase B: Acetonitrile, 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.

Example 82: General procedure I- Reductive amination (with ketones)

To a stirred solution of the amine or the amine hydrochloride (0.1 mmol, 1.0 eq.) and the ketone (0.12 mmol, 1.2 eq.) in DMF (1 mL) was added titanium(IV) isopropoxide (0.5 mmol, 5.0 eq.), followed by DIPEA (0.3 mmol, 3.0 eq.) at 25 °C. The reaction mixture was heated at 80 °C for 16 h. The reaction mixture was cooled to room temperature, sodium cyanoborohydride (0.5 mmol, 5.0 eq.) was added, and the reaction mixture was heated at 80 °C for 3 h. The reaction mixture was cooled, water was added, and the mixture was extracted with EtOAc. The combined organic layers were concentrated under reduced pressure to afford crude compound, which was purified by reverse phase chromatography [(Column: X select (150 mm x 19) 5 µm, eluting with Mobile phase A: 0.05% FA or HCl in H_2O, Mobile phase B: Acetonitrile, 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.

Example 83: General procedure J- Alkylation

To a stirred solution of the amine or the amine hydrochloride (0.1 mmol, 1.0 eq.) in DMF (1 mL) was added the alkyl halide or alkyl sulfonate (0.1 mmol, 0.1 eq.) and triethylamine (0.5 mmol, 5.0 eq.) at 0°C. The resulting mixture was allowed to stir at 25°C for 10 h. The reaction mixture was partitioned between water and EtOAc. The organic layer was concentrated under reduced pressure to afford crude compound, which was purified by reverse phase chromatography [(Column: X select (150 mm x 19) 5 µm, eluting with Mobile phase A: 0.05% FA or HCl in H_2O, Mobile phase B: Acetonitrile, 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.

Example 84: General procedure K- Reductive amination

To a stirred solution of the amine or the amine hydrochloride (0.1 mmol, 1.0 eq.) in DMF (1 mL) and the aldehyde (0.12 mmol, 1.2 eq.) was added MP-cyanoborohydride (0.1 mmol, 1.0 eq.) 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 x 19) 5 µm, eluting with Mobile phase A: 0.05% FA or HCl in H_2O, Mobile phase B: Acetonitrile, 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.

Example 85: General procedure L- Reductive amination

To a stirred solution of the amine or the amine hydrochloride (0.1 mmol, 1.0 eq.) and the aldehyde (0.12 mmol, 1.2 eq.) in DMF (1 mL) was added acetic acid (0.1 mmol, 0.1 eq.) and triethylamine (0.2 mmol, 2.0 eq.) followed by MP cyanoborohydride (0.1 mmol, 1.0 eq.) 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 x 19) 5 µm, eluting with Mobile phase A: 0.05% FA or HCl in H2O, Mobile phase B: Acetonitrile, 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.

Example 86: General procedure M- Reductive amination

To a stirred solution of the amine or the amine hydrochloride (0.1 mmol, 1.0 eq.) in IPA (1 mL) was added the aldehyde (0.12 mmol, 1.2 eq.) followed by potassium acetate (0.3 mmol, 3.0 eq.), and the reaction mixture was stirred at 25°C for 1 h. To this mixture was added sodium cyanoborohydride (0.3 mmol, 3.0 eq.) at 25°C, and the resulting mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated under reduced pressure to afford crude compound, which was purified by reverse phase

chromatography [(Column: X select (150 mm x 19) 5 µm, eluting with Mobile phase A: 0.05% FA or HCl in H2O, Mobile phase B: Acetonitrile, 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.

Example 87: General procedure N- Reductive amination

To a stirred solution of the amine or the amine hydrochloride (0.1 mmol, 1.0 eq.) in DMF (1 mL) and the aldehyde (0.12 mmol, 1.2 eq.) and DIPEA (0.3 mmol, 3.0 eq.) was added sodium triacetoxyborohydride (0.3 mmol, 3.0 eq.) and the resulting mixture was stirred at 60°C for 1 h. The reaction mixture was cooled and filtered; the filtrate was concentrated under reduced pressure to afford the crude compound, which was purified by reverse phase chromatography [(Column: X select (150 mm x 19) 5 µm, eluting with Mobile phase A: 0.05% FA or HCl in H2O, Mobile phase B: Acetonitrile, 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.

Example 88: General procedure O - Reductive amination

Amine (1 Eq) and aldehyde (1.5 Eq) were charged into a reaction vial equipped with a stir bar and dissolved in N,N-dimethylformamide, followed by the addition of decaborane (0.4 Eq). The reaction was allowed to stir for 30mins at 70 – 80 °C before monitoring through LCMS. Upon completion, the reaction mixture was loaded onto a C18 column for purification 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 the desired product.

Example 89: General procedure P- Reductive amination

To a stirred solution of the amine or the amine hydrochloride (0.1 mmol, 1.0 eq.) in DMF (1 ml) and the aldehyde (0.12 mmol, 1.2 eq.) was added sodium triacetoxyborohydride (0.3 mmol, 3.0 eq.) 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 x 19) 5 um, eluting with Mobile phase A: 0.05% FA or HCl in H_2O, Mobile phase B: Acetonitrile, 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.

Example 90: General procedure Q- Reductive amination

To a stirred solution of the amine or the amine hydrochloride (0.1 mmol, 1.0 eq.) in DMF (1 ml) and the aldehyde (0.12 mmol, 1.2 eq.) and DIPEA (0.3 mmol, 3.0 eq.) is added sodium triacetoxyborohydride (0.3 mmol, 3.0 eq.) 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 x 19) 5 um, eluting with Mobile phase A: 0.05% FA or HCl in H_2O, Mobile phase B: Acetonitrile, 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 hydrochloride salt, or the free amine.

Example 91: General procedure R- Reductive amination

To a stirred solution of amine (1.0 eq.) and an aldehyde (1.2 eq.) in DMF (1 mL) in a reaction vial equipped with a stir bar was added sodium triacetoxyborohydride (1.4 eq.). The resulting mixture was stirred at either room temperature overnight or heated to 60 °C for 30 min. Upon complete consumption of starting material, as confirmed by LCMS, the reaction mixture was worked up and purified via the purification method stated in the table entry.

Table 3.

Compound Name (Cmpd No.)	**Amine Starting Material**	**Aldehyde/ Other Starting Material**	**MS observed, MH+**	**1H-NMR**	**Synthesis and Purification Method**
1-(6-(1-benzyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl (**I-306**)	1-(6-(4-hydroxypiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione **INT-S1**	benzaldehyde	431.3	1H-NMR (400 MHz, DMSO-d6): δ 10.60 (s, 1H), 10.55 (s, 1H), 8.95 (d, J = 2.40 Hz, 1H), 8.31 (d, J = 2.00 Hz, 1H), 8.06-8.02 (m, 2H), 7.85 (s, 1H), 7.68-7.66 (m, 2H), 7.51-7.49 (m, 3H), 5.74 (s, 1H), 4.42 (d, J = 5.20 Hz, 2H), 3.98 (t, J = 6.80 Hz, 2H), 3.47-3.34 (m, 4H), 2.81 (t, J = 6.40 Hz, 2H), 2.51-2.50 (m, 2H), 1.93-1.90 (m, 2H).	Q
1-(6-(4-hydroxy-1-(3-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-885**)	1-(6-(4-hydroxypiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione **INT-S1**	3-(trifluoromethyl)benzaldehyde	499.4	1H-NMR (400 MHz, DMSO-d6): δ 10.58 (s, 1H), 8.89 (d, J = 2.80 Hz, 1H), 8.24 (d, J = 2.00 Hz, 1H), 8.04 (d, J = 1.60 Hz, 1H), 7.97 (d, J = 8.80 Hz, 1H), 7.91 (d, J = 2.00 Hz, 1H), 7.68-7.59 (m, 4H), 5.08 (s, 1H), 3.96 (t, J = 6.80 Hz, 2H), 3.66 (s, 2H), 2.80 (t, J	Q

				= 6.80 Hz, 2H), 2.67 (d, J = 6.80 Hz, 1H), 2.51-2.50 (m, 1H), 2.11 (t, J = 8.40 Hz, 2H), 1.70 (d, J = 12.40 Hz, 2H), 1.28-1.24 (m, 2H).	
1-(6-(1-(cyclohexylmethyl)-4-hydroxypiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-919**)	1-(6-(4-hydroxypiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione **INT-S1**	cyclohexanecarbaldehyde	437.5	1H-NMR (400 MHz, DMSO-d6): δ 10.58 (s, 1H), 8.88 (d, J = 2.80 Hz, 1H), 8.24 (d, J = 2.40 Hz, 1H), 8.02 (d, J = 2.00 Hz, 1H), 7.97 (d, J = 8.80 Hz, 1H), 7.90 (d, J = 2.00 Hz, 1H), 5.02 (s, 1H), 3.96 (t, J = 6.80 Hz, 2H), 2.80 (t, J = 6.80 Hz, 2H), 2.68 (d, J = 1.60 Hz, 1H), 2.41-2.36 (m, 2H), 2.15 (d, J = 7.20 Hz, 2H), 2.04 (t, J = 8.80 Hz, 2H), 1.76 (m, 2H), 1.69-1.64 (m, 6H), 1.53 (d, J = Hz, 1H), 1.28-1.19 (m, 3H), 0.86 (q, J = 11.60 Hz, 2H).	Q
4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)quinolin-6-yl)-4-hydroxypiperidin-1-yl)methyl)benzonitrile (**I-167**)	1-(6-(4-hydroxypiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl **INT-S1**	4-formylbenzonitrile	456.4	1H-NMR (400 MHz, DMSO-d6): δ 10.58 (s, 1H), 8.89 (d, J = 2.40 Hz, 1H), 8.24 (d, J = 2.40 Hz, 1H), 8.03 (d, J = 1.60 Hz, 1H), 7.97 (d, J = 8.80 Hz, 1H), 7.91 (d, J = 1.60 Hz, 1H), 7.82 (d, J = 8.00 Hz, 2H), 7.58 (d, J = 8.00 Hz, 2H), 5.09 (s, 1H), 3.97 (t, J = 6.80 Hz, 2H), 3.65 (s, 2H), 2.81 (t, J = 6.80 Hz, 2H), 2.68-2.64 (m, 4H), 2.15-2.12 (m, 2H), 1.70 (d, J = 11.60 Hz, 2H).	P
1-(6-(4-hydroxy-1-(2-(trifluoromethyl)benzyl)piperidin-4-	1-(6-(4-hydroxypiperidin-4-yl)quinolin-3-yl)dihydropyri	2-(trifluoromethyl)benzaldehyde	499.4	1H-NMR (400 MHz, DMSO-d6): δ 10.64 (s, 1H), 9.01 (d, J = 2.40 Hz, 1H), 8.42 (s, 2H), 8.08 (s, 2H),	P

yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl (**I-920**)	midine-2,4(1H,3H)-dione **INT-S1**			7.94-7.91 (m, 3H), 7.71 (t, J = 7.60 Hz, 1H), 4.59 (d, J = 4.80 Hz, 2H), 3.99 (t, J = 6.80 Hz, 3H), 3.48-3.35 (m, 4H), 2.81 (t, J = 6.80 Hz, 2H), 2.75-2.68 (m, 2H), 1.90 (d, J = 13.60 Hz, 2H).	
(**I-916**)	3-(6-(8-hydroxy-5-azaspiro[2.5]octan-8-yl)quinolin-3-yl)piperidine-2,6-dione	acetaldehyde	394.4	1H NMR (499 MHz, DMSO-d6) δ ppm 10.97 (s, 1H) 8.75 (d, J=2.19 Hz, 1H) 8.34 (s, 2H) 8.20 (d, J=2.19 Hz, 1H) 8.02 (s, 1H) 7.84-7.98 (m, 2H) 4.14 (dd, J=12.59, 4.93 Hz, 1H) 2.71-2.81 (m, 1H) 2.55-2.68 (m, 3H) 2.42 (m, 1H) 2.26-2.38 (m, 3H) 2.10-2.18 (m, 1H) 1.95-2.10 (m, 2H) 1.72-1.88 (m, 1H) 1.23 (br s, 2H) 0.99 (t, J=7.12 Hz, 3H) 0.38 (br, 1H) 0.27-0.34 (m, 1H) 0.04-0.13 (m, 1H)	C
(**I-883**)	3-(6-(3,3-bis(cyclopropylmethyl)-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(trifluoromethyl)benzaldehyde	606.5	1H NMR (499 MHz, DMSO-d6) δ = 10.97 (s, 1H), 8.74 (d, J = 2.2 Hz, 1H), 8.15 (d, J = 1.6 Hz, 1H), 8.00-7.91 (m, 3H), 7.77-7.66 (m, 3H), 7.63 (d, J = 7.7 Hz, 2H), 4.50 (br s, 1H), 4.13 (dd, J = 4.9, 12.6 Hz, 1H), 3.71 (s, 2H), 3.01-2.94 (m, 2H), 2.77 (m, 1H), 2.67-2.57 (m, 1H), 2.44 (m, 1H), 2.33-2.07 (m, 5H), 1.05-0.93 (m, 2H), 0.67-0.44 (m, 2H), 0.36-0.25 (m, 2H), 0.20-0.04 (m, 4H), -0.33 (m, 2H), -0.50--0.61 (m, 2H)	O
(**I-886**)	3-(6-(4-hydroxy-3-methylpiperid	acetaldehyde	382.4	1H NMR (499 MHz, DMSO-d6) δ ppm 10.94-10.99 (m, 1H)	O

	in-4-yl)quinolin-3-yl)piperidine-2,6-dione			8.71-8.76 (m, 1H) 8.26-8.31 (m, 1H) 8.15-8.19 (m, 1H) 7.98-8.02 (m, 1H) 7.93-7.97 (m, 1H) 7.80-7.84 (m, 1H) 4.08-4.16 (m, 1H) 2.54-2.84 (m, 5H) 2.08-2.23 (m, 5H) 1.60-1.67 (m, 1H) 1.21-1.26 (m, 1H) 1.03-1.11 (m, 3H) 0.45-0.53 (m, 3H) (peaks overlap with solvent)	
(**I-176**)	3-(6-(5-hydroxy-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)piperidine-2,6-dione	acetaldehyde	436.5	1H NMR (499 MHz, DMSO-d6) δ ppm 10.96 (s, 1H) 8.75 (d, J=2.19 Hz, 1H) 8.19-8.23 (m, 1H) 8.33 (s, 2H) 7.87-7.96 (m, 3H) 4.11-4.17 (m, 1H) 2.94-3.00 (m, 1H) 2.68-2.84 (m, 3H) 2.58-2.65 (m, 1H) 2.31-2.46 (m, 4H) 2.11-2.23 (m, 3H) 1.71-1.78 (m, 1H) 1.38-1.50 (m, 2H) 1.20-1.34 (m, 4H) 1.05 (s, 3H) 0.99 - 0.83 (m, 1H) 0.51-0.67 (m, 2H)	O
3-(6-(1-ethyl-4-hydroxy-3-methoxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-899**)	3-(6-(4-hydroxy-3-methoxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	acetaldehyde	398.3	N/A	O
3-(6-(1-ethyl-4-hydroxy-3-(trifluoromethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-178**)	3-(6-(4-hydroxy-3-(trifluoromethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	acetaldehyde	436.4	1H NMR (499 MHz, DMSO-d6) δ ppm 10.95-10.99 (m, 1H) 8.73-8.76 (m, 1H) 8.21-8.25 (m, 1H) 8.15-8.19 (m, 1H) 8.07-8.11 (m, 1H) 7.91-7.96 (m, 2H) 4.11-4.18 (m, 1H) 3.15-3.21 (m, 1H) 2.92-2.98 (m, 1H)	O

				2.73-2.82 (m, 2H) 2.68-2.72 (m, 1H) 2.52-2.65 (m, 2H) 2.34-2.48 (m, 3H) 2.10-2.19 (m, 2H) 1.60-1.65 (m, 1H) 1.21-1.27 (m, 1H) 1.04-1.10 (m, 3H)	
(I-911)	3-(6-(4-hydroxy-9-azadispiro[2.1.25.33]decan-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(trifluoromethyl)benzaldehyde	550.4	1H NMR (499 MHz, DMSO-d6) δ ppm 10.95-10.98 (m, 1H) 8.80 (d, J = 2.2 Hz, 1H) 8.32-8.36 (m, 1H) 8.24-8.27 (m, 1H) 8.17-8.23 (m, 1H) 7.98-8.03 (m, 1H) 7.60-7.65 (m, 2H) 7.44-7.49 (m, 2H) 4.57-4.63 (m, 1H) 4.09-4.19 (m, 1H) 2.72-2.80 (m, 1H) 2.55-2.65 (m, 3H) 2.40-2.47 (m, 1H) 2.11-2.18 (m, 1H) 1.93-1.99 (m, 2H) 1.13-1.21 (m, 2H) 0.91-1.00 (m, 2H) 0.52-0.61 (m, 3H) 0.25-0.34 (m, 2H)	O
(I-922)	3-(6-(4-hydroxy-9-azadispiro[2.1.25.33]decan-4-yl)quinolin-3-yl)piperidine-2,6-dione	acetaldehyde	420.4	1H NMR (499 MHz, DMSO-d6) δ ppm 10.95-10.97 (m, 1H) 8.75-8.78 (m, 1H) 8.31-8.33 (m, 1H) 8.25-8.27 (m, 1H) 8.18-8.21 (m, 1H) 7.98-8.02 (m, 1H) 2.70-2.82 (m, 2H) 2.57-2.64 (m, 1H) 2.54 (s, 1H) 2.41-2.45 (m, 1H) 2.12-2.23 (m, 6H) 1.15-1.22 (m, 2H) 0.89-0.98 (m, 3H) 0.88 (s, 3H) 0.61-0.68 (m, 2H) 0.32-0.41 (m, 2H)	O
3-(6-(1-ethyl-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-	3-(6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-	acetaldehyde	396.4	1H NMR (499 MHz, DMSO-d6, 298 K) δ (ppm) = 10.98 - 10.95 (m, 1H), 8.77 - 8.73 (m, 1H), 8.24 - 8.19 (m, 2H), 8.00 - 7.96	O

2,6-dione (**I-896**)	yl)piperidine-2,6-dione			(m, 1H), 7.95 - 7.88 (m, 2H), 4.16 - 4.11 (m, 1H), 2.83 - 2.74 (m, 3H), 2.65 - 2.61 (m, 1H), 2.46 - 2.36 (m, 6H), 2.29 - 2.24 (m, 1H), 2.17 - 2.11 (m, 1H), 1.59 - 1.52 (m, 1H), 1.07 - 1.02 (m, 3H), 0.88 - 0.85 (m, 3H), 0.73 - 0.71 (m, 3H)	
(I-250)	3-(6-(3-ethyl-4-hydroxypiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione	4-(trifluoromethyl)benzaldehyde	544.4	1H NMR (499 MHz, DMSO-d6) δ ppm 10.97 - 11.00 (m, 1H) 8.81 - 8.85 (m, 1H) 8.31 - 8.34 (m, 1H) 8.01 - 8.07 (m, 1H) 7.85 - 7.89 (m, 1H) 7.69 - 7.73 (m, 2H) 7.59 - 7.63 (m, 2H) 4.20 - 4.26 (m, 1H) 3.69 - 3.75 (m, 1H) 3.57 - 3.63 (m, 1H) 2.71 - 2.82 (m, 2H) 2.58 - 2.65 (m, 2H) 2.22 - 2.29 (m, 2H) 2.10 - 2.18 (m, 1H) 1.93 - 2.04 (m, 1H) 1.61 - 1.69 (m, 1H) 1.02 - 1.13 (m, 1H) 0.88 - 0.97 (m, 1H) 0.51 - 0.60 (m, 3H) (peaks overlap with solvent)	O
3-{5-fluoro-6-[4-hydroxy-3,3-dimethyl-1-(2,2,2-trifluoroethyl)-4-piperidyl]-3-quinolyl}-2,6-piperidinedione (**I-893**)	3-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	2,2,2-Trifluoroethyl Trifluoromethanesulfonate	468	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 5.20 (s, 1H), 4.23 (q, J = 4.40 Hz, 1H), 3.22-3.09 (m, 3H), 2.95 (t, J = 4.00 Hz, 2H), 2.89 (t, J = 8.00 Hz, 2H), 2.51 (t, J = 1.60 Hz, 1H), 2.34-2.28 (m, 1H), 2.34-2.28 (m, 1H), 2.16-2.12 (m, 1H), 1.70 (d,	J

				J = 3.60 Hz, 1H), 1.00 (s, 3H), 0.95 (s, 3H).	
(**I-259**)	3-(6-(4-hydroxy-3-isopropylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	acetaldehyde	410.4	1H NMR (499 MHz, DMSO-d6, 298 K) δ ppm 10.97 - 10.95 (m, 1H), 8.75 - 8.73 (m, 1H), 8.29 - 8.26 (m, 1H), 8.21 - 8.17 (m, 1H), 8.05 - 8.02 (m, 1H), 7.97 - 7.93 (m, 1H), 7.86 - 7.78 (m, 1H), 4.16 - 4.09 (m, 1H), 2.85 - 2.75 (m, 3H), 2.66 - 2.61 (m, 1H), 2.57 - 2.52 (m, 1H), 2.46 - 2.35 (m, 4H), 2.18 - 2.10 (m, 2H), 2.00 - 1.95 (m, 1H), 1.63 - 1.56 (m, 1H), 1.41 - 1.32 (m, 1H), 1.26 - 1.21 (m, 1H), 1.12 - 1.06 (m, 3H), 0.84 - 0.79 (m, 3H), 0.67 - 0.61 (m, 3H)	O
(**I-260**)	3-(6-(4-hydroxy-3-isobutylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(trifluoromethyl)benzaldehyde	554.4	1H NMR (499 MHz, DMSO-d6, 298 K) δ (ppm) = 10.99 - 10.93 (m, 1H), 8.77 - 8.72 (m, 1H), 8.37 - 8.33 (m, 1H), 8.22 - 8.17 (m, 1H), 8.03 - 8.00 (m, 1H), 7.99 - 7.93 (m, 1H), 7.91 - 7.81 (m, 1H), 7.74 - 7.67 (m, 2H), 7.65 - 7.53 (m, 2H), 4.96 - 4.86 (m, 1H), 4.19 - 4.10 (m, 1H), 3.74 - 3.60 (m, 2H), 3.57 - 3.49 (m, 1H), 2.82 - 2.72 (m, 2H), 2.66 - 2.57 (m, 2H), 2.49 - 2.36 (m, 2H), 2.26 - 2.19 (m, 1H), 2.17 - 2.08 (m, 2H), 1.86 - 1.75 (m, 1H), 1.69 - 1.55 (m, 1H), 1.26 - 1.15 (m, 1H), 1.03 - 0.96 (m, 1H), 0.63 - 0.60	O

				(m, 3H), 0.52 - 0.48 (m, 2H)	
(I-891)	3-(6-(4-hydroxy-3-isobutylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	acetaldehyde	424.5	1H NMR (499 MHz, DMSO-d6) δ = 10.96 (s, 1H), 8.75 (d, J = 1.6 Hz, 1H), 8.37 (s, 2H), 8.20 (d, J = 1.6 Hz, 1H), 7.96 (d, J = 8.8 Hz, 1H), 7.88 (d, J = 9.3 Hz, 1H), 7.85 - 7.80 (m, 1H), 4.17 - 4.10 (m, 1H), 2.82 - 2.72 (m, 2H), 2.66 - 2.57 (m, 2H), 2.47 - 2.28 (m, 4H), 2.19 - 2.11 (m, 1H), 2.04 - 1.95 (m, 1H), 1.84 (m, 1H), 1.77 - 1.71 (m, 1H), 1.57 - 1.48 (m, 1H), 1.36 - 1.27 (m, 3H), 1.27 - 1.19 (m, 3H), 1.02 (t, J = 7.1 Hz, 3H), 0.64 (d, J = 6.6 Hz, 3H), 0.50 (d, J = 6.6 Hz, 3H) (2 extra aliphatic protons)	O
(I-865)	3-(6-(4-hydroxy-3-isobutylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	acetaldehyde	424.4	1H NMR (499 MHz, DMSO-d6, 299 K) δ (ppm) = 10.97 - 10.95 (m, 1H), 8.75 - 8.73 (m, 1H), 8.31 - 8.29 (m, 1H), 8.19 - 8.16 (m, 1H), 8.02 - 8.00 (m, 1H), 7.96 - 7.92 (m, 1H), 7.84 - 7.77 (m, 1H), 4.17 - 4.11 (m, 1H), 2.82 - 2.72 (m, 4H), 2.65 - 2.58 (m, 1H), 2.43 - 2.35 (m, 2H), 2.19 - 2.08 (m, 5H), 1.64 - 1.58 (m, 1H), 1.34 - 1.21 (m, 3H), 1.06 (s, 3H), 1.04 - 0.98 (m, 1H), 0.66 - 0.63 (m, 3H), 0.54 - 0.51 (m, 3H)	O
3-(6-(1-((1H-pyrrol-2-yl)methyl)-4-hydroxy-3,3-dimethylpiperi	3-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-2-	1H-pyrrole-2-carbaldehyde	479	1H NMR (499 MHz, DMSO-d6) δ (ppm) = 11.26 (s, 1H), 11.00 (s, 1H), 10.17 (br s, 1H), 8.55 (br s, 1H), 8.12	O

din-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (**I-299**)	methylquinolin-3-yl)piperidine-2,6-dione, HCl			(br t, J = 8.8 Hz, 1H), 7.96 (br d, J = 9.3 Hz, 1H), 7.00 - 6.85 (m, 1H), 6.31 (br t, J = 3.6 Hz, 1H), 6.10 (q, J = 2.7 Hz, 1H), 5.90 (br s, 1H), 4.43 (br dd, J = 4.4, 12.6 Hz, 2H), 4.32 (br d, J = 4.4 Hz, 2H), 3.36 - 3.27 (m, 2H), 3.23 - 3.16 (m, 2H), 2.87 - 2.81 (m, 2H), 2.80 (s, 2H), 2.68 - 2.55 (m, 2H), 2.15 - 2.09 (m, 1H), 2.05 - 1.92 (m, 1H), 1.09 (s, 3H), 0.76 (s, 3H).	
3-(5-fluoro-6-(4-hydroxy-1-isopropyl-3,3-dimethylpiperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (**I-868**)	3-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione, HCl	acetone	442	1H NMR (499 MHz, DMSO-d6) δ (ppm) = 10.99 (s, 1H), 9.16 (br s, 1H), 8.44 (br d, J = 7.1 Hz, 1H), 8.15 - 8.06 (m, 1H), 7.91 (br d, J = 9.3 Hz, 1H), 5.94 (br s, 1H), 4.44 - 4.38 (m, 1H), 3.55 - 3.48 (m, 1H), 3.37 - 3.31 (m, 3H), 3.21 - 3.15 (m, 2H), 3.07 - 3.00 (m, 1H), 2.88 - 2.80 (m, 1H), 2.76 (s, 3H), 2.66 - 2.60 (m, 1H), 2.16 - 2.08 (m, 1H), 2.07 - 1.96 (m, 1H), 1.42 - 1.26 (m, 6H), 1.11 (s, 3H), 0.84 - 0.79 (m, 3H).	O
(**I-14**)	3-(6-(3-benzyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	acetaldehyde	458.5	1H NMR (499 MHz, DMSO-d6, 298 K) δ (ppm) = 11.00 - 10.95 (m, 1H), 8.79 - 8.72 (m, 1H), 8.26 - 8.22 (m, 2H), 8.15 - 8.12 (m, 1H), 8.07 - 7.99 (m, 1H), 7.98 - 7.92 (m, 1H), 7.22 - 7.14 (m, 2H), 7.13 - 7.07 (m, 1H), 6.95 - 6.86 (m, 2H), 4.19 - 4.10 (m, 1H), 2.79 - 2.72 (m, 2H), 2.66 - 2.58	O

				(m, 1H), 2.47 - 2.40 (m, 3H), 2.38 - 2.32 (m, 3H), 2.27 - 2.11 (m, 5H), 1.72 - 1.65 (m, 1H), 0.93 (s, 3H)	
(I-23)	3-(6-(3-benzyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(trifluoromethyl)benzaldehyde	588.5	1H NMR (499 MHz, DMSO-d6, 297 K) δ (ppm) = 11.01 - 10.95 (m, 1H), 8.79 - 8.74 (m, 1H), 8.38 - 8.35 (m, 1H), 8.25 - 8.22 (m, 1H), 8.15 - 8.13 (m, 1H), 8.07 - 8.00 (m, 1H), 7.98 - 7.95 (m, 1H), 7.71 - 7.61 (m, 2H), 7.60 - 7.47 (m, 2H), 7.16 - 7.03 (m, 2H), 6.99 - 6.87 (m, 2H), 6.75 - 6.62 (m, 1H), 5.18 - 5.15 (m, 1H), 4.18 - 4.12 (m, 1H), 3.64 - 3.60 (m, 1H), 3.52 - 3.48 (m, 1H), 2.82 - 2.73 (m, 1H), 2.67 - 2.61 (m, 1H), 2.61 - 2.56 (m, 1H), 2.48 - 2.42 (m, 2H), 2.37 - 2.32 (m, 1H), 2.28 - 2.19 (m, 2H), 2.19 - 2.11 (m, 2H), 2.01 - 1.77 (m, 1H), 1.69 - 1.64 (m, 1H), 1.26 - 1.22 (m, 1H)	O
I-688	3-(5-fluoro-6-(4-hydroxyazepan-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione	4-(trifluoromethyl)benzaldehyde	544.4	1H NMR (499 MHz, DMSO, 297 K) δ ppm 10.99 - 10.93 (m, 1H), 8.33 - 8.28 (m, 1H), 8.24 - 8.20 (m, 1H), 8.01 - 7.95 (m, 1H), 7.77 - 7.73 (m, 1H), 7.72 - 7.66 (m, 2H), 7.63 - 7.56 (m, 2H), 4.40 - 4.31 (m, 1H), 3.84 - 3.73 (m, 2H), 3.00 - 2.94 (m, 1H), 2.87 - 2.80 (m, 1H), 2.75 - 2.71 (m, 2H), 2.66 (s, 3H), 2.65 - 2.62 (m, 1H), 2.62 - 2.53 (m, 2H), 2.42 -	O

				2.35 (m, 2H), 2.15 - 2.00 (m, 2H), 1.83 - 1.71 (m, 2H), 1.68 - 1.59 (m, 1H) (peak overlap with solvent)	
I-872	3-(5-fluoro-6-(4-hydroxyazepan-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione	acetaldehyde	414.3	1H NMR (499 MHz, DMSO, 300 K) δ ppm 10.99 - 10.90 (m, 1H), 8.29 (s, 1H), 8.21 - 8.18 (m, 1H), 8.00 - 7.94 (m, 1H), 7.77 - 7.73 (m, 1H), 4.38 - 4.31 (m, 1H), 3.12 - 3.06 (m, 1H), 2.93 - 2.87 (m, 1H), 2.87 - 2.78 (m, 2H), 2.77 - 2.71 (m, 1H), 2.70 - 2.68 (m, 1H), 2.66 (s, 3H), 2.64 - 2.58 (m, 1H), 2.48 - 2.40 (m, 2H), 2.30 - 2.23 (m, 1H), 2.15 - 2.08 (m, 1H), 2.06 - 1.97 (m, 1H), 1.85 - 1.77 (m, 2H), 1.72 - 1.62 (m, 1H), 1.08 (s, 3H) (peak overlap with solvent)	O
I-255	3-(5-fluoro-6-(4-hydroxy-3-(trifluoromethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	acetaldehyde	454.4	1H NMR (499 MHz, DMSO, 297 K) δ ppm 11.02 - 10.94 (m, 1H), 8.88 - 8.83 (m, 1H), 8.33 (s, 2H), 8.10 - 8.02 (m, 1H), 7.94 - 7.89 (m, 1H), 6.00 - 5.90 (m, 1H), 4.27 - 4.20 (m, 1H), 2.98 - 2.92 (m, 1H), 2.81 - 2.72 (m, 2H), 2.65 - 2.54 (m, 2H), 2.48 - 2.30 (m, 4H), 2.17 - 2.11 (m, 1H), 2.05 - 1.94 (m, 1H), 1.76 - 1.69 (m, 1H), 1.35 - 1.22 (m, 1H), 1.07 (s, 3H)	O
I-853	3-(6-(4-hydroxyazepan-4-yl)quinolin-3-	4-(trifluoromethyl)benzaldehyde	512.3	1H NMR (499 MHz, DMSO-d6, 297 K) δ ppm 10.98 - 10.95 (m, 1H), 8.74 (d, J = 2.2 Hz, 1H), 8.31 - 8.27	O

	yl)piperidine-2,6-dione			(m, 1H), 8.21 - 8.18 (m, 1H), 7.94 (s, 2H), 7.91 - 7.87 (m, 1H), 7.69 (s, 2H), 7.63 - 7.56 (m, 2H), 4.17 - 4.10 (m, 1H), 3.78 - 3.73 (m, 2H), 2.96 - 2.89 (m, 1H), 2.81 - 2.70 (m, 3H), 2.64 - 2.61 (m, 1H), 2.60 - 2.53 (m, 1H), 2.46 - 2.35 (m, 1H), 2.25 - 2.18 (m, 2H), 2.17 - 2.09 (m, 1H), 2.06 - 1.95 (m, 1H), 1.88 - 1.77 (m, 2H), 1.68 - 1.58 (m, 1H)	
I-910	3-(6-(4-hydroxyazepan-4-yl)quinolin-3-yl)piperidine-2,6-dione	acetaldehyde	382.4	1H NMR (499 MHz, DMSO-d6, 297 K) δ ppm11.00 - 10.94 (m, 1H), 8.74 (d, J = 2.2 Hz, 1H), 8.31 (s, 1H), 8.20 - 8.16 (m, 1H), 8.00 - 7.94 (m, 2H), 7.92 - 7.86 (m, 1H), 4.16 - 4.11 (m, 1H), 3.21 - 3.13 (m, 1H), 2.99 - 2.90 (m, 2H), 2.84 - 2.75 (m, 4H), 2.64 - 2.57 (m, 1H), 2.47 - 2.30 (m, 3H), 2.16 - 1.97 (m, 3H), 1.86 - 1.79 (m, 2H), 1.71 - 1.62 (m, 1H), 1.12 (s, 3H)	O
3-(6-(1-((4,4-difluorocyclohexyl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (**I-297**)	3-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione, HCl	4,4-difluorocyclohexane-1-carbaldehyde	532	No NMR recorded	O
3-(5-fluoro-6-(4-hydroxy-1-isobutyl-3,3-dimethylpiperi	3-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiper	isobutyraldehyde	456	1H NMR (499 MHz, DMSO-d6) δ (ppm) = 10.94 (s, 1H), 8.20 (s, 1H), 8.03 (t, J = 8.8	O

din-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (**I-293**)	idin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione, HCl			Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 5.01 (br s, 1H), 4.34 (dd, J = 4.7, 12.9 Hz, 1H), 3.14 - 3.01 (m, 1H), 2.89 - 2.73 (m, 1H), 2.66 (s, 3H), 2.65 - 2.59 (m, 2H), 2.54 - 2.51 (m, 1H), 2.48 - 2.40 (m, 1H), 2.35 (d, J = 10.4 Hz, 1H), 2.18 (d, J = 10.4 Hz, 1H), 2.14 - 1.99 (m, 3H), 1.84 - 1.73 (m, 1H), 1.72 - 1.59 (m, 1H), 0.96 (d, J = 3.3 Hz, 3H), 0.88 (dd, J = 2.7, 6.6 Hz, 6H), 0.69 (s, 3H). (no signals for salt observed)	
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((4-oxo-6-(trifluoromethyl)-1,4-dihydropyridin-3-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl (**I-318**)	3-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	4-hydroxy-6-(trifluoromethyl)nicotinaldehyde	561.4	1H-NMR (400 MHz, DMSO-d6): δ 12.56 (bs, 1H), 10.99 (s, 1H), 9.42 (s, 1H), 8.89 (d, J = 2.00 Hz, 1H), 8.74 (s, 1H), 8.37 (s, 1H), 8.06 (t, J = 8.40 Hz, 1H), 7.90 (d, J = 8.80 Hz, 1H), 7.37 (s, 1H), 5.92 (s, 1H), 4.43 (s, 2H), 4.24 (dd, J = 4.80, 12.80 Hz, 1H), 3.49-3.34 (m, 5H), 3.13 (d, J = 12.00 Hz, 1H), 2.73-2.64 (m, 2H), 2.14-2.12 (m, 1H), 2.00 (d, J = 13.60 Hz, 1H), 1.08 (s, 3H), 0.81 (s, 3H).	P
I-291	3-(5-fluoro-6-(4-hydroxy-3-(trifluoromethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	isobutyraldehyde	482.5	1H NMR (499 MHz, DMSO-d6, 297 K) δ ppm 11.01 - 10.96 (m, 1H), 8.87 - 8.83 (m, 1H), 8.41 - 8.37 (m, 1H), 8.34 - 8.31 (m, 1H), 8.09 - 8.03 (m, 1H), 7.93 - 7.88 (m, 1H), 4.25 - 4.18 (m, 1H), 2.92 - 2.85 (m, 1H), 2.80 - 2.68 (m, 2H), 2.67 - 2.56 (m,	O

				2H), 2.46 - 2.30 (m, 3H), 2.22 - 2.17 (m, 2H), 2.17 - 2.11 (m, 1H), 2.03 - 1.94 (m, 1H), 1.87 - 1.76 (m, 1H), 1.74 - 1.67 (m, 1H), 1.26 - 1.21 (m, 1H), 0.92 - 0.88 (m, 5H), 0.89 - 0.86 (m, 1H)	
3-(6-(1-ethyl-4-hydroxy-3-(2,2,2-trifluoroethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl (**I-313**)	3-(6-(4-hydroxy-3-(2,2,2-trifluoroethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	acetaldehyde	450.4	1H-NMR (400 MHz, DMSO-d6): δ 11.01 (s, 1H), 10.64 (s, 1H), 8.92 (d, J = 1.60 Hz, 1H), 8.43 (s, 1H), 8.13 (t, J = 7.20 Hz, 1H), 7.84 (s, 1H), 6.11 (s, 1H), 4.25-4.20 (m, 1H), 3.31-3.27 (m, 6H), 3.01 (t, J = 5.60 Hz, 1H), 2.75-2.67 (m, 4H), 2.50-2.46 (m, 1H), 2.19-2.16 (m, 2H), 1.95-1.91 (m, 2H), 1.33 (t, J = 7.60 Hz, 3H).	P
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((1-methyl-1H-pyrazol-5-yl)methyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione (**I-158**)	3-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione, HCl	1-methyl-1H-pyrazole-5-carbaldehyde	494	1H NMR (499 MHz, DMSO-d6) δ (ppm) = 10.96 (s, 1H), 9.99 (br d, J = 4.4 Hz, 1H), 8.31 (br d, J = 8.8 Hz, 1H), 8.03 (br t, J = 8.5 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.53 (d, J = 1.6 Hz, 1H), 6.67 (s, 1H), 5.90 (br s, 1H), 4.54 (br d, J = 3.8 Hz, 2H), 4.42 - 4.34 (m, 1H), 3.96 (s, 3H), 3.32 - 3.24 (m, 3H), 3.05 - 2.98 (m, 1H), 2.90 - 2.76 (m, 2H), 2.70 (s, 3H), 2.65 - 2.52 (m, 2H), 2.15 - 2.05 (m, 1H), 2.05 - 1.96 (m, 1H), 1.07 (s, 3H), 0.79 (s, 3H).	O
3-(6-(1-ethyl-4-hydroxy-3-(2,2,2-trifluoroethyl)p	3-(6-(4-hydroxy-3-(2,2,2-trifluoroethyl)	acetaldehyde	450.4	1H-NMR (400 MHz, DMSO-d6): δ 11.01 (s, 1H), 10.09 (s, 1H), 8.90 (s, 1H), 8.39 (s,	P

iperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl (**I-314**)	piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione			1H), 8.11 (d, J = 8.80 Hz, 1H), 8.01-7.97 (m, 2H), 6.09 (s, 1H), 4.21 (dd, J = 4.80, 12.40 Hz, 1H), 3.66-3.63 (m, 2H), 3.29-3.19 (m, 6H), 2.79-2.75 (m, 1H), 2.68-2.61 (m, 2H), 2.46-2.41 (m, 1H), 2.34-2.15 (m, 2H), 1.50 (m, 1H), 1.33 (t, J = 7.20 Hz, 3H).	
I-680	3-(6-(3-benzyl-4-hydroxypiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione	4-(trifluoromethyl)benzaldehyde	606.3	1H NMR (499 MHz, DMSO-d6, 298 K) δ ppm 11.02 - 10.98 (m, 1H), 8.88 - 8.83 (m, 1H), 8.50 - 8.47 (m, 1H), 8.37 - 8.32 (m, 1H), 8.14 - 8.09 (m, 1H), 7.94 - 7.89 (m, 1H), 7.66 - 7.61 (m, 2H), 7.52 - 7.48 (m, 2H), 7.12 - 7.07 (m, 2H), 7.03 - 6.97 (m, 1H), 6.88 - 6.83 (m, 2H), 4.28 - 4.22 (m, 1H), 3.66 - 3.60 (m, 1H), 3.52 - 3.47 (m, 1H), 2.71 - 2.57 (m, 3H), 2.42 - 2.30 (m, 4H), 2.24 - 2.12 (m, 3H), 2.02 - 1.95 (m, 1H), 1.74 - 1.67 (m, 1H), 1.29 - 1.20 (m, 3H) (one extra aliphatic proton)	O
(**I-780**)	3-(6-(3-benzyl-4-hydroxypiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione	isobutyraldehyde	504.4	1H NMR (499 MHz, DMSO-d6, 298 K) δ ppm 11.04 - 10.97 (m, 1H), 8.85 (s, 1H), 8.32 (s, 2H), 8.16 - 8.07 (m, 1H), 7.91 (s, 1H), 7.13 (s, 2H), 7.08 - 7.00 (m, 1H), 6.87 (d, J = 7.1 Hz, 2H), 4.28 - 4.21 (m, 1H), 2.82 - 2.73 (m, 1H), 2.68 - 2.59 (m, 3H), 2.47 - 2.34 (m, 4H), 2.34 - 2.28 (m, 1H), 2.23 - 2.13	O

				(m, 3H), 2.08 - 2.02 (m, 1H), 2.02 - 1.95 (m, 1H), 1.75 - 1.60 (m, 2H), 1.27 - 1.20 (m, 1H), 0.83 - 0.73 (m, 6H)	
3-(5-fluoro-6-(9-hydroxy-6-(4-(trifluoromethyl)benzyl)-6-azaspiro[3.5]nonan-9-yl)quinolin-3-yl)piperidine-2,6-dione (**I-238**)	3-(5-fluoro-6-(9-hydroxy-6-azaspiro[3.5]nonan-9-yl)quinolin-3-yl)piperidine-2,6-dione **INT-S4**	4-(trifluoromethyl)benzaldehyde	556	1H NMR (499 MHz, DMSO-d6) δ (ppm) = 11.01 (s, 1H), 10.54 - 10.38 (m, 1H), 8.94 (d, J = 1.6 Hz, 1H), 8.46 (s, 1H), 8.17 (t, J = 8.8 Hz, 1H), 8.01 - 7.93 (m, 3H), 7.92 - 7.88 (m, 2H), 6.07 - 5.77 (m, 1H), 4.58 - 4.49 (m, 2H), 4.27 (dd, J = 4.9, 12.6 Hz, 1H), 3.56 (d, J = 12.0 Hz, 1H), 3.38 - 3.37 (m, 1H), 3.34 - 3.24 (m, 2H), 3.22 - 3.10 (m, 1H), 2.81 - 2.74 (m, 1H), 2.78 - 2.74 (m, 1H), 2.67 - 2.59 (m, 1H), 2.30 - 2.26 (m, 1H), 2.18 - 2.10 (m, 1H), 2.01 - 1.92 (m, 2H), 1.89 - 1.81 (m, 1H), 1.60 - 1.50 (m, 1H), 1.50 - 1.43 (m, 1H), 0.99 - 0.83 (m, 1H).	R
I-651	3-(6-(3-benzyl-4-hydroxypiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione	1-methyl-1H-pyrazole-5-carbaldehyde	542.3	1H NMR (499 MHz, DMSO-d6, 298 K) δ ppm 11.02 - 10.98 (m, 1H), 8.87 - 8.83 (m, 1H), 8.36 (s, 2H), 8.13 - 8.08 (m, 1H), 7.92 - 7.88 (m, 1H), 7.26 - 7.24 (m, 1H), 7.13 - 7.08 (m, 2H), 7.05 - 6.99 (m, 1H), 6.87 - 6.83 (m, 2H), 6.07 (d, J = 1.6 Hz, 1H), 5.51 - 5.37 (m, 1H), 4.27 - 4.20 (m, 1H), 3.75 (s, 3H), 3.56 - 3.51 (m, 2H), 2.81 - 2.73 (m, 1H), 2.66 - 2.57 (m, 3H), 2.43 - 2.28 (m, 4H), 2.24 - 2.10 (m,	O

				3H), 1.74 - 1.68 (m, 1H), 1.29 - 1.16 (m, 1H).	
3-[5-fluoro-6-(4-hydroxy-1-isopropyl-3,3-dimethyl-4-piperidyl)-3-quinolyl]-2,6-piperidinedione (**I-202**)	3-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	Propan-2-one	428.6	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 9.11 (bs, 1H), 8.91 (d, J = 1.60 Hz, 1H), 8.41 (s, 1H), 8.11-8.06 (m, 1H), 7.92 (d, J = 9.20 Hz, 1H), 5.93 (bs, 1H), 4.32-4.28 (m, 1H), 3.54-3.40 (m, 1H), 3.38-3.22 (m, 3H), 3.20 (t, J = 10.2 Hz, 1H), 3.05 (d, J = 11.2 Hz, 1H), 2.76-2.50 (m, 3H), 2.16-2.01 (m, 2H), 1.36 (t, J = 2.00 Hz, 6H), 1.12 (s, 3H), 0.84 (s, 3H).	P
3-[5-fluoro-6-(4-hydroxy-1-{[p-(1H-indazol-1-yl)phenyl]methyl}-3,3-dimethyl-4-piperidyl)-3-quinolyl]-2,6-piperidinedione (**I-409**)	3-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	4-(1H-indazol-1-yl)benzaldehyde	592.5	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 9.82 (s, 1H), 8.90 (s, 1H), 8.45-8.39 (m, 2H), 8.08-7.89 (m, 8H), 7.57-7.53 (m, 1H), 7.32 (t, J = 7.60 Hz, 1H), 5.95 (s, 1H), 4.52 (t, J = 5.20 Hz, 2H), 4.27-4.23 (m, 1H), 3.66-3.34 (m, 4H), 3.01 (d, J = 12.00 Hz, 1H), 2.68-2.51 (m, 3H), 2.15-2.05 (m, 2H), 1.11 (s, 3H), 0.81 (s, 3H).	P
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((1-methyl-1H-1,2,4-triazol-5-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-918**)	3-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	1-methyl-1H-1,2,4-triazole-5-carbaldehyde	481.5	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.31 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 8.00 Hz, 2H), 5.17 (s, 1H), 4.22 (dd, J = 4.80, 12.80 Hz, 1H), 3.94 (s, 3H), 3.69 (s, 2H), 3.08 (t, J = 2.40 Hz, 1H), 2.78-2.72 (m, 1H), 2.67-2.57 (m, 5H), 2.13 (d, J = 4.00	P

				Hz, 2H), 1.70 (d, J = 13.20 Hz, 1H), 0.95 (s, 3H), 0.69 (s, 3H).	
(**I-428**)	3-(5-fluoro-6-(5-hydroxy-9-oxa-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)piperidine-2,6-dione	4-(1,2,4-oxadiazol-3-yl)benzaldehyde **ALD-107**	586.4	N/A	O
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((1-methyl-1H-1,2,4-triazol-5-yl)methyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione, Formic Acid (**I-431**)	3-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione, HCl	1-methyl-1H-1,2,4-triazole-5-carbaldehyde	495.5	1H-NMR (400 MHz, DMSO-d6): δ 10.95 (s, 1H), 8.20 (d, J = 4.80 Hz, 1H), 8.14 (s, 1H), 8.03 (t, J = 8.80 Hz, 1H), 7.83 (s, 1H), 7.74 (d, J = 8.80 Hz, 1H), 5.13 (s, 1H), 4.37-4.33 (m, 1H), 3.93 (s, 3H), 3.69 (s, 2H), 3.07 (m, 1H), 2.84-2.82 (m, 1H), 2.68 (s, 3H), 2.67-2.52 (m, 5H), 2.14-2.12 (m, 2H), 1.70-1.67 (m, 1H), 0.94 (s, 3H), 0.68 (s, 3H).	P
3-(6-(1-((1,2,4-oxadiazol-5-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (**I-422**)	3-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	5-(chloromethyl)-1,2,4-oxadiazole	468.4	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 9.00 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.34 (s, 1H), 8.08 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 5.15 (s, 1H), 4.25-4.23 (m, 1H), 3.98 (s, 2H), 3.14 (t, J = 11.60 Hz, 1H), 2.80-2.64 (m, 4H), 2.48-2.45 (m, 2H), 2.25 (d, J = 10.40 Hz, 1H), 2.15-2.12 (m, 1H), 1.71 (d, J = 12.40 Hz, 1H), 0.98 (s, 3H), 0.70 (s, 3H).	J
3-(6-(1-((1,2,4-oxadiazol-5-yl)methyl)-4-hydroxy-3,3-	3-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiper	5-(chloromethyl)-1,2,4-oxadiazole	482.2	1H-NMR (400 MHz, DMSO-d6): δ 10.94 (s, 1H), 8.99 (s, 1H), 8.21 (s, 1H), 8.02 (t, J	J

dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (**I-892**)	idin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione, HCl			= 8.80 Hz, 1H), 7.74 (s, 1H), 5.11 (s, 1H), 4.37-4.33 (m, 1H), 3.98 (s, 2H), 3.33-3.11 (m, 1H), 2.82-2.59 (m, 8H), 2.24 (d, J = 10.40 Hz, 1H), 2.12-2.10 (m, 1H), 1.89 (s, 1H), 1.69 (d, J = 12.80 Hz, 1H), 0.97 (s, 3H), 0.68 (s, 3H).	
(R)-1-(6-(1-((5-chloro-6-(1,2,4-oxadiazol-3-yl)pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-890**)	(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl **INT-(R)-S2**	5-chloro-6-(1,2,4-oxadiazol-3-yl)nicotinaldehyde	580.3	1H-NMR (400 MHz, DMSO-d6): δ 10.59 (s, 1H), 9.86 (s, 1H), 8.97 (d, J = 2.40 Hz, 1H), 8.73 (d, J = 1.60 Hz, 1H), 8.33 (d, J = 2.00 Hz, 1H), 8.15 (d, J = 1.20 Hz, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.85 (d, J = 9.20 Hz, 1H), 5.19 (s, 1H), 4.01 (t, J = 6.40 Hz, 2H), 3.78-3.62 (m, 2H), 3.19 (m, 1H), 2.80 (t, J = 6.80 Hz, 2H), 2.68-2.67 (m, 2H), 2.21 (d, J = 10.40 Hz, 1H), 1.91 (s, 1H), 1.76-1.73 (m, 1H), 1.02 (s, 3H), 0.70 (s, 3H).	M
(R)-1-(5-fluoro-6-(1-((5-fluoro-1-methyl-1H-pyrazol-4-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-913**)	(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione **INT-(R)-S2**	5-fluoro-1-methyl-1H-pyrazole-4-carbaldehyde	499.2	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.96 (d, J = 2.40 Hz, 1H), 8.32 (d, J = 2.00 Hz, 1H), 8.07 (t, J = 8.80 Hz, 1H), 7.83 (d, J = 9.20 Hz, 1H), 7.38 (d, J = 2.40 Hz, 1H), 5.93-5.91 (m, 1H), 5.11 (s, 1H), (s, 2H), 4.00 (t, J = 6.40 Hz, 2H), 3.57 (s, 3H), 2.88 (t, J = 6.40 Hz, 1H), 2.76 (m, 2H), 2.71-2.66 (m, 2H), 2.12 (d, J = 10.40 Hz, 1H), 1.67 (d, J = 13.60 Hz, 1H), 0.85 (s, 3H), 0.67 (s, 3H).	G

(R)-1-(6-(1-(3-chloro-5-fluoro-4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl (**I-889**)	(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl **INT-(R)-S2**	3-chloro-5-fluoro-4-(1,2,4-oxadiazol-3-yl)benzaldehyde	597.3	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.98 (s, 1H), 9.68 (bs, 1H), 9.01 (d, J = 2.40 Hz, 1H), 8.36 (d, J = 2.00 Hz, 1H), 8.07 (t, J = 8.80 Hz, 1H), 7.96-7.87 (m, 3H), 5.98 (s, 1H), 4.53 (d, J = 4.80 Hz, 2H), 4.01 (t, J = 6.40 Hz, 2H), 3.36-3.34 (m, 4H), 3.10 (d, J = 11.20 Hz, 1H), 2.81 (t, J = 6.40 Hz, 2H), 2.03 (d, J = 14.00 Hz, 1H), 1.10 (s, 3H), 0.83 (s, 3H).	G
1-{5-fluoro-6-[(R)-4-hydroxy-3,3-dimethyl-1-[(S)-1-[p-(trifluoromethyl)phenyl]ethyl]-4-piperidyl]-3-quinolyl}hexahydro-2,4-pyrimidinedione (**I-825**)	(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl **INT-(R)-S2**	1-(4-(trifluoromethyl)phenyl)ethan-1-one	559.3	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 10.12 (s, 1H), 9.00 (d, J = 2.40 Hz, 1H), 8.36 (d, J = 2.00 Hz, 1H), 8.00-7.87 (m, 6H), 5.82 (s, 1H), 4.74 (s, 1H), 4.01 (t, J = 6.40 Hz, 2H), 3.56-3.48 (m, 2H), 3.11-3.03 (m, 2H), 2.81 (t, J = 6.80 Hz, 3H), 2.04 (d, J = 13.60 Hz, 1H), 1.80 (d, J = 6.80 Hz, 3H), 1.11 (d, J = 2.40 Hz, 3H), 0.73 (s, 3H).	I
1-{5-fluoro-6-[(R)-4-hydroxy-3,3-dimethyl-1-[(R)-1-[p-(trifluoromethyl)phenyl]ethyl]-4-piperidyl]-3-quinolyl}hexahydro-2,4-pyrimidinedione (**I-829**)	(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl **INT-(R)-S2**	1-(4-(trifluoromethyl)phenyl)ethan-1-one	559.3	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.68 (s, 1H), 9.00 (d, J = 2.40 Hz, 1H), 8.34 (d, J = 2.00 Hz, 1H), 8.04-7.99 (m, 3H), 7.92-7.88 (m, 3H), 5.85 (s, 1H), 4.78 (t, J = 6.00 Hz, 1H), 4.00 (t, J = 6.40 Hz, 2H), 3.41-3.32 (m, 2H), 3.21-3.15 (m, 3H), 2.82-2.68 (m, 2H), 1.96 (d, J = 14.40 Hz, 1H), 1.80 (m, 3H), 1.15 (s, 3H), 0.83 (s, 3H).	I

1-(5-fluoro-6-(9-hydroxy-6-(4-(trifluoromethyl)benzyl)-6-azaspiro[3.5]nonan-9-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-459**)	1-(5-fluoro-6-(9-hydroxy-6-azaspiro[3.5]nonan-9-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione **INT-S8**	4-(trifluoromethyl)benzaldehyde	557	1H NMR (499 MHz, DMSO-d6) δ (ppm) = 10.63 (s, 1H), 10.04 (br d, J = 1.6 Hz, 1H), 9.02 (d, J = 2.2 Hz, 1H), 8.37 (d, J = 2.2 Hz, 1H), 8.14 (t, J = 8.8 Hz, 1H), 8.00 - 7.85 (m, 5H), 5.92 (br s, 1H), 4.61 - 4.48 (m, 2H), 4.06 - 3.96 (m, 2H), 3.62 - 3.57 (m, 2H), 3.40 - 3.21 (m, 1H), 3.15 - 3.05 (m, 1H), 2.80 (t, J = 6.8 Hz, 2H), 2.26 - 2.18 (m, 1H), 2.03 - 1.93 (m, 2H), 1.91 - 1.81 (m, 1H), 1.80 - 1.72 (m, 1H), 1.63 - 1.43 (m, 2H), 1.26 - 1.20 (m, 1H), 0.96 - 0.84 (m, 1H).	R
1-{5-fluoro-6-[(R)-1-[3-(p-fluorophenyl)cyclobutyl]-4-hydroxy-3,3-dimethyl-4-piperidyl]-3-quinolyl}hexahydro-2,4-pyrimidinedione (**I-894**)	(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl **INT-(R)-S2**	3-(4-fluorophenyl)cyclobutan-1-one	535.3	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.67 (d, J = 8.00 Hz, 1H), 9.01 (d, J = 2.40 Hz, 1H), 8.36 (d, J = 1.60 Hz, 1H), 7.93-7.91 (m, 2H), 7.46 (t, J = 5.60 Hz, 2H), 7.22-7.18 (m, 2H), 5.97 (s, 1H), 4.12-4.00 (m, 2H), 3.86-3.80 (m, 1H), 3.27-3.15 (m, 7H), 2.81 (t, J = 6.80 Hz, 2H), 2.68 (t, J = 2.00 Hz, 1H), 2.51-2.34 (m, 2H), 2.05 (d, J = 13.60 Hz, 1H), 1.14 (s, 3H), 0.84 (s, 3H).	I
(R)-1-(6-(1-(2-chloro-4-(trifluoromethyl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-	(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-	2-chloro-4-(trifluoromethyl)benzaldehyde	579.2	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.64 (s, 1H), 9.00 (d, J = 2.40 Hz, 1H), 8.35 (d, J = 1.60 Hz, 1H), 8.17 (d, J = 8.40 Hz, 1H), 8.10 (s, 1H), 8.05 (t, J = 8.80 Hz, 1H), 7.96-7.90 (m,	G

yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl (**I-882**)	dione **INT-(R)-S2**			2H), 5.97 (s, 1H), 4.66 (s, 2H), 4.01 (t, J = 6.80 Hz, 2H), 3.42-3.39 (m, 3H), 3.16 (d, J = 11.60 Hz, 1H), 2.80 (t, J = 6.40 Hz, 2H), 2.08 (s, 1H), 2.04-2.00 (m, 1H), 1.10 (s, 3H), 0.82 (s, 3H).	
1-(6-(6-(4-(1,2,4-oxadiazol-3-yl)benzyl)-9-hydroxy-6-azaspiro[3.5]nonan-9-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-781**)	1-(5-fluoro-6-(9-hydroxy-6-azaspiro[3.5]nonan-9-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione **INT-S8**	4-(1,2,4-oxadiazol-3-yl)benzaldehyde	557	1H NMR (499 MHz, DMSO-d6) δ (ppm) = 10.62 (s, 1H), 9.70 (s, 1H), 8.99 (d, J = 2.2 Hz, 1H), 8.35 (d, J = 2.2 Hz, 1H), 8.27 (s, 1H), 8.15 (t, J = 8.8 Hz, 1H), 8.04 (d, J = 8.8 Hz, 2H), 7.90 (d, J = 8.8 Hz, 1H), 7.60 (d, J = 8.2 Hz, 2H), 5.15 (br s, 1H), 4.05 - 3.97 (m, 2H), 3.73 - 3.65 (m, 1H), 3.64 - 3.59 (m, 1H), 2.80 (t, J = 6.6 Hz, 2H), 2.79 - 2.75 (m, 1H), 2.64 - 2.56 (m, 3H), 1.99 - 1.91 (m, 1H), 1.91 - 1.82 (m, 2H), 1.74 - 1.66 (m, 1H), 1.57 - 1.43 (m, 1H), 1.31 (br s, 1H), 1.27 - 1.20 (m, 1H), 1.04 - 0.93 (m, 1H).	R
1-{6-[(R)-1-[(1,7a-diaza-4,5,6,7-tetrahydro-3-indenyl)methyl]-4-hydroxy-3,3-dimethyl-4-piperidyl]-5-fluoro-3-quinolyl}hexahydro-2,4-pyrimidinedione (**I-888**)	(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione **INT-(R)-S2**	4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-3-carbaldehyde	521	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 10.21 (s, 1H), 9.02 (d, J = 2.40 Hz, 1H), 8.39 (d, J = 2.00 Hz, 1H), 8.05 (t, J = 8.40 Hz, 1H), 8.03 (d, J = 8.40 Hz, 1H), 7.70 (s, 1H), 5.90 (s, 1H), 4.17-4.07 (m, 4H), 4.03-4.01 (m, 2H), 3.41-3.33 (m, 3H), 3.12 (q, J = 11.60 Hz, 1H), 2.96 (t, J = 12.00 Hz, 1H), 2.94-2.78 (m, 4H), 1.99 (t, J = 5.60	G

				Hz, 3H), 1.82 (d, J = 5.60 Hz, 2H), 1.11 (d, J = 2.40 Hz, 3H), 0.79 (s, 3H).	
(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((4-methyl-6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl (**I-897**)	(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl **INT-(R)-S2**	4-methyl-6-(trifluoromethyl)nicotinaldehyde	558.5	1H-NMR (400 MHz, DMSO-d6): δ 10.62 (s, 1H), 9.27 (s, 1H), 9.00 (d, J = 2.40 Hz, 1H), 8.34 (d, J = 2.00 Hz, 1H), 8.07 (t, J = 8.80 Hz, 1H), 7.95-7.93 (m, 2H), 5.98 (s, 1H), 4.63 (s, 2H), 4.01 (t, J = 7.60 Hz, 2H), 3.57-3.51 (m, 3H), 3.19 (d, J = 13.20 Hz, 1H), 2.80 (t, J = 6.40 Hz, 2H), 2.60 (s, 3H), 2.53-2.52 (m, 2H), 2.02 (d, J = 14.00 Hz, 1H), 1.09 (s, 3H), 0.86 (s, 3H).	G
1-{5-fluoro-6-[(R)-4-hydroxy-3,3-dimethyl-1-[(5,6,7,8-tetrahydro-1-indolizinyl)methyl]-4-piperidyl]-3-quinolyl}hexahydro-2,4-pyrimidinedione (**I-881**)	(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione **INT-(R)-S2**	5,6,7,8-tetrahydroindolizine-1-carbaldehyde	520.5	1H-NMR (400 MHz, DMSO-d6): δ 10.60 (s, 1H), 8.96 (d, J = 2.40 Hz, 1H), 8.32 (d, J = 2.00 Hz, 1H), 8.26 (s, 1H), 8.08 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 6.49 (d, J = 2.40 Hz, 1H), 5.92 (d, J = 2.80 Hz, 1H), 5.05 (s, 1H), 4.00 (t, J = 6.80 Hz, 2H), 3.87 (t, J = 6.40 Hz, 2H), 3.36 (s, 2H), 3.29-3.21 (m, 1H), 2.80 (t, J = 6.80 Hz, 2H), 2.69-2.66 (m, 3H), 2.53-2.50 (m, 2H), 2.33 (t, J = 1.60 Hz, 1H), 1.86 (t, J = 4.80 Hz, 2H), 1.75 (t, J = 5.20 Hz, 2H), 1.68 (d, J = 13.60 Hz, 1H), 0.95 (d, J = 3.20 Hz, 3H), 0.68 (s, 3H).	G
3-{5-fluoro-6-[(R)-4-hydroxy-3,3-dimethyl-1-	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiper	4-(oxazol-5-yl)benzaldehyde	543.2	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (s, 1H), 8.47 (s, 1H), 8.36 (s,	L

{[p-(1,3-oxazol-5-yl)phenyl]methyl}-4-piperidyl]-3-quinolyl}-2,6-piperidinedione (**I-613**)	idin-4-yl)quinolin-3-yl)piperidine-2,6-dione			1H), 8.14-8.07 (m, 1H), 7.85 (d, J = 8.80 Hz, 1H), 7.74-7.68 (m, 3H), 7.51-7.49 (m, 2H), 5.16 (s, 1H), 4.16-4.06 (m, 1H), 3.64-3.42 (m, 2H), 3.15-3.05 (m, 1H), 2.86-2.53 (m, 6H), 2.45-2.21 (m, 2H), 1.92 (s, 1H), 1.02 (s, 3H), 0.69 (s, 3H).	
3-{5-fluoro-6-[(R)-1-{[3-fluoro-4-(1,2,4-oxadiazol-3-yl)phenyl]methyl}-4-hydroxy-3,3-dimethyl-4-piperidyl]-3-quinolyl}-2,6-piperidinedione (**I-643**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	3-fluoro-4-(1,2,4-oxadiazol-3-yl)benzaldehyde	562.4	1H-NMR (400 MHz, DMSO-d6): δ 11.01 (s, 1H), 10.60 (s, 1H), 9.83 (s, 1H), 8.96 (m, 1H), 8.54-8.49 (m, 1H), 8.18-8.13 (m, 2H), 8.11-7.95 (m, 2H), 7.82 (t, J = 7.20 Hz, 1H), 5.98 (s, 1H), 4.56-4.28 (m, 2H), 4.28-3.44 (m, 1H), 3.81-3.72 (m, 4H), 3.17 (t, J = 10.80 Hz, 1H), 2.88-2.57 (m, 3H), 2.35-2.01 (m, 2H), 1.12 (s, 3H), 0.77 (s, 3H).	L
3-{5-fluoro-6-[(R)-4-hydroxy-1-{[p-(3-isoxazolyl)phenyl]methyl}-3,3-dimethyl-4-piperidyl]-3-quinolyl}-2,6-piperidinedione (**I-133**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	4-(isoxazol-3-yl)benzaldehyde	543.1	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 9.00 (s, 1H), 8.85 (s, 1H), 8.34 (s, 1H), 8.22 (s, 1H), 8.12-8.08 (m, 1H), 7.89-7.83 (m, 3H), 7.52 (d, J = 8.40 Hz, 2H), 7.15 (s, 1H), 5.14 (s, 1H), 4.26-4.21 (m, 1H), 3.65 (d, J = 14.00 Hz, 1H), 3.52 (s, 1H), 3.18-3.16 (m, 2H), 2.64-2.63 (m, 2H), 2.61-2.59 (m, 2H), 2.34-2.33 (m, 3H), 1.73-1.71 (m, 1H), 1.02 (s, 3H), 0.68 (s, 3H).	L
3-{6-[(R)-1-{[3-chloro-4-(1,2,4-	3-(5-fluoro-6-((R)-4-hydroxy-3,3-	3-chloro-4-(1,2,4-oxadiazol-3-	578.3	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 9.79 (s, 1H),	L

oxadiazol-3-yl)phenyl]methyl}-4-hydroxy-3,3-dimethyl-4-piperidyl]-5-fluoro-3-quinolyl}-2,6-piperidinedione (**I-631**)	dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	yl)benzaldehyde		8.85 (s, 1H), 8.34 (s, 1H), 8.13-8.08 (m, 1H), 7.92 (d, J = 7.60 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.69 (s, 1H), 7.55 (d, J = 7.20 Hz, 1H), 5.16 (s, 1H), 4.23 (d, J = 4.80 Hz, 1H), 3.69 (d, J = 14.40 Hz, 1H), 3.57 (d, J = 14.40 Hz, 1H), 3.32 (s, 1H), 2.74-2.67 (m, 2H), 2.64-2.60 (m, 3H), 2.34-2.33 (m, 2H), 2.20 (s, 1H), 1.82-1.80 (m, 1H), 1.40 (s, 3H), 0.69 (s, 3H).	
3-(p-{[(R)-4-[3-(2,6-dioxo-3-piperidyl)-5-fluoro-6-quinolyl]-4-hydroxy-3,3-dimethyl-1-piperidyl]methyl}phenyl)-3-oxetanecarbonitrile (**I-928**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	3-(4-formylphenyl)oxetane-3-carbonitrile	557.5	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.81 (d, J = 2.40 Hz, 1H), 8.34 (s, 1H), 8.20 (s, 1H), 8.07 (t, J = 8.80 Hz, 1H), 7.83 (d, J = 9.20 Hz, 1H), 7.56 (d, J = 8.40 Hz, 2H), 7.49 (d, J = 8.40 Hz, 2H), 5.19-5.12 (m, 3H), 4.90 (d, J = 6.80 Hz, 2H), 4.24 (t, J = 8.00 Hz, 1H), 3.63-3.49 (m, 3H), 3.23-3.16 (m, 2H), 2.64-2.51 (m, 4H),2.34-2.20 (m, 2H), 1.71 (d, J = 12.40 Hz, 1H), 1.02 (s, 3H), 0.68 (s, 3H).	L
3-{6-[(R)-1-{[p-(2,2-dichlorocyclopropyl)phenyl]methyl}-4-hydroxy-3,3-dimethyl-4-piperidyl]-5-fluoro-3-quinolyl}-2,6-piperidinedione (**I-1196**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(2,2-dichlorocyclopropyl)benzaldehyde	582.5	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.84 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.26 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.35 (d, J = 8.00 Hz, 2H), 7.28 (d, J = 8.00 Hz, 2H), 5.11 (s, 1H), 4.23 (dd, J = 4.40, 12.60 Hz, 1H), 3.59-3.44 (m, 2H),	L

				3.17-3.09 (m, 4H), 2.81-2.77 (m, 1H), 2.73-2.67 (m, 3H), 2.34-2.16 (m, 4H), 1.70 (d, J = 13.20 Hz, 1H), 1.24 (s, 3H), 0.65 (s, 3H).	
3-{6-[(R)-1-{[p-(6-chloro-3-pyridazinyl)phenyl]methyl}-4-hydroxy-3,3-dimethyl-4-piperidyl]-5-fluoro-3-quinolyl}-2,6-piperidinedione **(I-931)**	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(6-chloropyridazin-3-yl)benzaldehyde	588.3	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (d, J= 1.60 Hz, 1H), 8.37-8.33 (m, 2H), 8.15-8.08 (m, 3H), 8.01 (d, J = 8.80 Hz, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.57 (d, J = 8.00 Hz, 2H), 5.14 (s, 1H), 4.24 (d, J = 7.60 Hz, 1H), 3.68 (d, J = 14.4 Hz, 1H), 3.56 (d, J = 13.6 Hz, 1H), 2.72-2.64 (m, 3H), 2.22-2.13 (m, 4H), 1.76-1.71 (m, 4H), 1.03 (s, 3H), 0.69 (s, 3H).	L
3-{5-fluoro-6-[(R)-4-hydroxy-3,3-dimethyl-1-{[p-(1,3,4-oxadiazol-2-yl)phenyl]methyl}-4-piperidyl]-3-quinolyl}-2,6-piperidinedione **(I-389)**	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(1,3,4-oxadiazol-2-yl)benzaldehyde	544.	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 9.33 (s, 1H), 8.84 (d, J= 2.0 Hz, 1H), 8.33 (s, 1H), 8.19 (s, 1H), 8.12-8.10 (m, 1H), 8.10-8.08 (m, 2H), 7.84 (d, J = 9.2 Hz, 1H), 8.02 (d, J = 8.00 Hz, 2H), 7.61 (d, J = 8.00 Hz, 2H), 5.15 (s, 1H), 4.23 (dd, J = 12.60, 4.40 Hz, 1H), 3.67 (d, J = 14.00 Hz, 1H), 3.17 (s, 2H), 2.90-2.80 (m, 3H), 2.73 (d, J = 4.40 Hz, 2H), 2.44-2.20 (m, 2H), 1.72 (d, J = 12.80 Hz, 1H), 1.23 (s, 1H), 1.02 (s, 1H), 0.68 (s, 3H).	K
3-{6-[(R)-1-{[p-(5-cyclopropyl-1,2,4-	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiper	4-(5-cyclopropyl-1,2,4-oxadiazol-3-	584.4	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 9.87 (s, 1H), 8.89 (s, 1H), 8.37 (s,	L

oxadiazol-3-yl)phenyl]methyl}-4-hydroxy-3,3-dimethyl-4-piperidyl]-5-fluoro-3-quinolyl}-2,6-piperidinedione (**I-1200**)	idin-4-yl)quinolin-3-yl)piperidine-2,6-dione	yl)benzaldehyde		1H), 8.11-8.06 (m, 3H), 7.91-7.82 (m, 3H), 5.92 (s, 1H), 4.50 (s, 2H), 4.37-4.29 (m, 1H), 3.45-3.22 (m, 2H), 2.96-2.92 (m, 1H), 2.77-2.52 (m, 4H), 2.50-2.40 (m, 2H), 2.11-2.02 (m, 2H), 1.32-0.94 (m, 4H), 1.20 (s, 3H), 0.78 (s, 3H).	
3-{5-fluoro-6-[(R)-4-hydroxy-3,3-dimethyl-1-{[p-(1-methyl-3-pyrazolyl)phenyl]methyl}-4-piperidyl]-3-quinolyl}-2,6-piperidinedione (**I-938**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	4-(1-methyl-1H-pyrazol-3-yl)benzaldehyde	556.2	1H-NMR (400 MHz, DMSO-d6): δ 0.98 (s, 1H), 8.84 (s, 1H), 8.33 (s, 1H), 8.19 (s, 1H), 8.12-8.08 (m, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.74-7.72 (m, 3H), 7.37 (d, J = 8.00 Hz, 2H), 6.67 (s, 1H), 5.11 (s, 1H), 4.25-4.21 (m, 1H), 3.88 (s, 3H), 3.59 (d, J = 13.60 Hz, 1H), 3.46 (s, 2H), 3.19-3.13 (m, 2H), 2.73-2.72 (m, 2H), 2.69-2.67 (m, 2H), 2.19-2.08 (m, 2H), 1.72-1.70 (m, 1H), 1.01 (s, 3H), 0.68 (s, 3H).	L
3-{5-fluoro-6-[(R)-4-hydroxy-3,3-dimethyl-1-({p-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl}methyl)-4-piperidyl]-3-quinolyl}-2,6-piperidinedione (**I-1190**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzaldehyde	612.3	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 9.79 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.34 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.92 (d, J = 7.60 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.69 (s, 1H), 7.55 (d, J = 7.20 Hz, 1H), 5.16 (s, 1H), 4.26-4.21 (m, 1H), 3.69 (d, J = 14.40 Hz, 1H), 3.57 (d, J = 14.40 Hz, 1H), 3.32 (s, 1H), 2.74-2.68 (m, 5H), 2.33-2.18 (m, 2H), 1.86 (s, 1H), 1.76 (d, J	L

				= Hz, 1H), 1.04 (s, 3H), 0.69 (s, 3H).	
3-{5-fluoro-6-[(R)-4-hydroxy-1-{[p-(6-methoxy-3-pyridazinyl)phenyl]methyl}-3,3-dimethyl-4-piperidyl]-3-quinolyl}-2,6-piperidinedione (**I-941**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(6-methoxypyridazin-3-yl)benzaldehyde	584.3	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (d, J = 4.40 Hz, 2H), 8.19-8.11 (m, 5H), 7.84 (d, J = 9.20 Hz, 1H), 7.53-7.46 (m, 3H), 7.33-7.29 (m, 1H), 5.14 (s, 1H), 4.23 (dd, J = 4.80, 12.80 Hz, 1H), 4.10-4.07 (m, 4H), 3.66 (d, J = 14.00 Hz, 1H), 3.54 (d, J = 14.00 Hz, 1H), 3.21-3.15 (m, 1H), 2.77-2.68 (m, 2H), 2.64-2.49 (m, 2H), 2.24-2.13 (m, 1H), 1.78-1.71 (m, 1H), 1.03 (s, 3H), 0.69 (s, 3H).	K
3-{6-[(R)-1-{[p-(1-cyclopropyl-4-pyrazolyl)phenyl]methyl}-4-hydroxy-3,3-dimethyl-4-piperidyl]-5-fluoro-3-quinolyl}-2,6-piperidinedione (**I-944**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(1-cyclopropyl-1H-pyrazol-4-yl)benzaldehyde	582.4	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.22 (d, J = 14.00 Hz, 1H), 8.24 (s, 1H), 8.21 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.84 (t, J = 8.80 Hz, 2H), 7.54 (d, J = 8.40 Hz, 2H), 7.33 (d, J = 8.00 Hz, 2H), 5.11 (d, J = Hz, 1H), 4.23 (dd, J = 4.80, 12.60 Hz, 1H), 3.76-3.72 (m, 2H), 3.45-3.15 (m, 2H), 2.72-2.63 (m, 2H), 2.47-2.33 (m, 2H), 2.21-2.15 (m, 2H), 1.69 (d, J = 12.40 Hz, 1H), 1.09-1.05 (m, 2H), 0.99-0.97 (m, 5H), 0.67 (s, 3H).	K
3-{5-fluoro-6-[(R)-4-hydroxy-1-{[p-(1-isopropyl-4-pyrazolyl)phen	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-	4-(1-isopropyl-1H-pyrazol-4-yl)benzaldehyde	584.3	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (s, 1H), 8.33 (s, 1H), 8.22-8.19 (m, 2H), 8.10 (t, J =	L

yl]methyl}-3,3-dimethyl-4-piperidyl]-3-quinolyl}-2,6-piperidinedione **(I-947)**	yl)quinolin-3-yl)piperidine-2,6-dione			8.80 Hz, 2H), 7.83 (d, J = 6.40 Hz, 2H), 7.55 (d, J = 8.00 Hz, 2H), 7.33 (d, J = 8.00 Hz, 1H), 5.11 (s, 1H), 4.53-4.48 (m, 2H), 4.25-4.21 (m, 2H), 3.59-3.55 (m, 2H), 3.24-3.17 (m, 3H), 2.68-2.64 (m, 3H), 2.34-2.17 (m, 2H), 1.45 (d, J = 6.40 Hz, 6H), 1.00 (s, 3H), 0.67 (s, 3H).	
3-{5-fluoro-6-[(R)-1-{[p-(1-fluorocyclopropyl)phenyl]methyl}-4-hydroxy-3,3-dimethyl-4-piperidyl]-3-quinolyl}-2,6-piperidinedione **(I-950)**	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	4-(1-fluorocyclopropyl)benzaldehyde	534.3	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.84 (s, 1H), 8.41 (s, 2H), 8.09 (t, J = 8.80 Hz, 1H), 7.83 (d, J = 9.20 Hz, 1H), 7.37 (d, J = 8.00 Hz, 2H), 7.26 (d, J = 8.40 Hz, 2H), 5.11 (s, 1H), 4.25-4.21 (m, 1H), 3.59-3.48 (m, 2H), 3.17-3.11 (m, 3H), 2.76-2.67 (m, 1H), 2.68-2.63 (m, 2H), 2.19-2.12 (m, 3H), 1.70 (d, J = 12.80 Hz, 1H), 1.47-1.43 (m, 2H), 1.14 (d, J = 7.20 Hz, 2H), 1.00 (s, 3H), 0.67 (s, 3H).	K
3-{5-fluoro-6-[(R)-4-hydroxy-1-{[p-(1-hydroxycyclopropyl)phenyl]methyl}-3,3-dimethyl-4-piperidyl]-3-quinolyl}-2,6-piperidinedione **(I-953)**	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(1-hydroxycyclopropyl)benzaldehyde	532.2	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (s, 1H), 8.33 (s, 1H), 8.23 (s, 1H)8.12-8.07 (m, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.27 (d, J = 8.40 Hz, 2H), 7.21 (d, J = 8.00 Hz, 2H), 5.87 (s, 1H), 5.10 (s, 1H), 4.23 (d, J = 4.80 Hz, 1H), 3.54 (d, J = 13.20 Hz, 2H), 3.17-3.13 (m, 2H), 2.68-2.67 (m, 1H), 2.64 (m, 3H), 2.16-2.13 (m, 3H), 0.72-0.70 (m, 1H),	K

				1.10-1.07 (m, 2H), 0.95-0.92 (m, 5H), 0.67 (s, 3H).	
3-{6-[(R)-1-{[3-chloro-4-(1-methyl-4-pyrazolyl)phenyl]methyl}-4-hydroxy-3,3-dimethyl-4-piperidyl]-5-fluoro-3-quinolyl}-2,6-piperidinedione (**I-956**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	3-chloro-4-(1-methyl-1H-pyrazol-4-yl)benzaldehyde	590.6	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 9.75 (s, 1H), 8.89 (s, 1H), 8.38 (s, 1H), 8.26 (s, 1H), 8.07 (t, J = 8.40 Hz, 1H), 7.93-7.92 (m, 3H), 7.74 (d, J = 8.00 Hz, 1H), 7.66 (d, J = 8.00 Hz, 1H), 5.93 (s, 1H), 4.42 (s, 2H), 4.24 (dd, J = 4.80, 12.80 Hz, 1H), 3.92 (s, 3H), 3.38-3.27 (m, 5H), 2.99 (d, J = 11.20 Hz, 1H), 2.77 (m, 1H), 2.68-2.63 (m, 1H), 2.33-2.14 (m, 1H), 2.03-2.00 (m, 1H), 1.09 (s, 3H), 0.80 (s, 3H).	K
3-{6-[(R)-1-{[p-(5-chloro-3-isoxazolyl)phenyl]methyl}-4-hydroxy-3,3-dimethyl-4-piperidyl]-5-fluoro-3-quinolyl}-2,6-piperidinedione (**I-1197**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(5-chloroisoxazol-3-yl)benzaldehyde	577.2	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.34 (s, 1H), 8.14-8.08 (m, 1H), 7.84 (t, J = 3.20 Hz, 3H), 7.54 (d, J = 7.60 Hz, 2H), 7.35 (s, 1H), 5.14 (s, 1H), 4.23 (dd, J = 4.40, 12.60 Hz, 1H), 3.64-3.55 (m, 2H), 3.32-3.12 (m, 2H), 2.79-2.57 (m, 5H), 2.18-2.13 (m, 2H), 1.92-1.71 (m, 1H), 0.93 (s, 3H), 0.68 (s, 3H).	L
3-{5-fluoro-6-[(R)-1-({p-[5-(1-fluorocyclopropyl)-1,2,4-oxadiazol-3-yl]phenyl}methyl)-4-hydroxy-3,3-dimethyl-4-piperidyl]-3-	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(5-(1-fluorocyclopropyl)-1,2,4-oxadiazol-3-yl)benzaldehyde	602.1	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (d, J = 2.40 Hz, 1H), 8.34 (d, J = 2.40 Hz, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.99 (d, J = 8.40 Hz, 2H), 7.84 (d, J = 9.20 Hz, 1H), 7.58 (d, J = 8.40 Hz, 2H), 5.14 (s,	L

quinolyl}-2,6-piperidinedione (**I-959**)				1H), 4.23 (dd, J = 4.40, 12.60 Hz, 1H), 3.67 (d, J = 14.00 Hz, 1H), 3.55 (d, J = 14.00 Hz, 1H), 3.33 (m, 1H), 2.73-2.68 (m, 2H), 2.67-2.49 (m, 3H), 2.20-2.18 (m, 2H), 1.90-1.85 (m, 3H), 1.74-1.71 (m, 1H), 1.63-1.60 (m, 2H), 1.02 (s, 3H), 0.68 (s, 3H).	
3-{6-[(R)-1-({p-[1-(difluoromethyl)-4-pyrazolyl]phenyl}methyl)-4-hydroxy-3,3-dimethyl-4-piperidyl]-5-fluoro-3-quinolyl}-2,6-piperidinedione (**I-962**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(1-(difluoromethyl)-1H-pyrazol-4-yl)benzaldehyde	592.1	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (s, 1H), 8.70 (s, 1H), 8.33 (s, 1H), 8.27 (s, 1H), 8.18-7.84 (m, 4H), 7.68 (d, J = 8.40 Hz, 2H), 7.40 (d, J = 8.00 Hz, 2H), 5.12 (s, 1H), 4.23 (dd, J = 4.80, 12.60 Hz, 1H), 3.60 (d, J = 13.60 Hz, 1H), 3.47 (d, J = 13.60 Hz, 1H), 3.20-3.13 (m, 1H), 2.77-2.70 (m, 3H), 2.51-2.51 (m, 2H), 2.46-2.41 (m, 1H), 2.19-2.13 (m, 2H), 1.72 (d, J = 13.60 Hz, 1H), 1.01 (s, 3H), 0.68 (s, 3H).	K
3-{5-fluoro-6-[(R)-4-hydroxy-3,3-dimethyl-1-({p-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]phenyl}methyl)-4-piperidyl]-3-quinolyl}-2,6-piperidinedione (**I-1193**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	4-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)benzaldehyde	612.3	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (s, 1H), 8.34 (s, 1H), 8.17-8.10 (m, 4H), 7.85 (d, J = 9.20 Hz, 1H), 7.66 (d, J = 8.00 Hz, 2H), 5.16 (s, 1H), 4.23 (t, J = 4.80 Hz, 1H), 3.71 (d, J = 14.00 Hz, 1H), 3.58 (d, J = 14.00 Hz, 1H), 3.18 (s, 1H), 2.74-2.68 (m, 5H), 2.19 (s, 1H), 1.73 (d, J = 12.80 Hz, 1H), 1.02 (s, 3H), 0.68 (s, 3H); 2	L

				protons merged with solvent.	
3-{5-fluoro-6-[(R)-1-{[3-fluoro-4-(1-methyl-4-pyrazolyl)phenyl]methyl}-4-hydroxy-3,3-dimethyl-4-piperidyl]-3-quinolyl}-2,6-piperidinedione (**I-965**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	3-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzaldehyde	574.6	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (d, J = 1.60 Hz, 1H), 8.33 (s, 1H), 8.14-8.08 (m, 2H), 7.85 (t, J = 8.80 Hz, 2H), 7.69-7.65 (m, 1H), 7.25-7.20 (m, 2H), 5.14 (s, 1H), 4.23 (dd, J = 4.80, 12.80 Hz, 1H), 3.90 (s, 3H), 3.62-3.42 (m, 2H), 3.26-3.09 (m, 2H), 2.72-2.51 (m, 5H), 2.25-2.08 (m, 2H), 1.72 (d, J = 13.20 Hz, 1H), 1.02 (s, 3H), 0.69 (s, 3H).	K
3-{5-fluoro-6-[(R)-4-hydroxy-3,3-dimethyl-1-{[p-(1-methyl-1H-1,2,3-triazol-4-yl)phenyl]methyl}-4-piperidyl]-3-quinolyl}-2,6-piperidinedione (**I-968**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	4-(1-methyl-1H-1,2,3-triazol-4-yl)benzaldehyde	557.2	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.49 (s, 1H), 8.33 (s, 1H), 8.19 (s, 1H), 8.12 (s, 1H), 8.09 (d, J = 8.80 Hz, 1H), 7.85-7.77 (m, 3H), 7.45-7.41 (m, 2H), 5.12 (s, 1H), 4.52 (s, 1H), 4.25-4.21 (m, 1H), 4.09 (d, J = 2.80 Hz, 2H), 3.60 (d, J = 13.20 Hz, 2H), 2.77-0.70 (m, 2H), 2.60-2.51 (m, 2H), 2.16 (d, J = 2.40 Hz, 4H), 1.71 (d, J = 12.80 Hz, 1H), 1.01 (s, 3H), 0.68 (s, 3H).	L
3-{5-fluoro-6-[(R)-4-hydroxy-1-{[p-(1-methoxycyclopropyl)phenyl]methyl}-3,3-dimethyl-4-piperidyl]-3-quinolyl}-2,6-	3-(5-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione	4-(1-methoxycyclopropyl)benzaldehyde	546.1	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.10 (t, J = 9.20 Hz, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.33 (d, J = 8.00 Hz, 2H), 7.24 (d, J = 8.00 Hz, 2H), 5.11 (s, 1H), 4.25-4.21 (m, 1H), 3.56-3.43 (m,	K

piperidinedione **(I-975)**				3H), 3.19 (s, 3H), 2.51-2.51 (m, 2H), 2.23-2.13 (m, 3H), 1.70 (d, J = 11.60 Hz, 1H), 1.45 (d, J = 12.00 Hz, 2H), 1.15-1.12 (m, 2H), 1.00 (s, 3H), 0.96 (t, J = 2.00 Hz, 2H), 0.84 (s, 1H), 0.68 (s, 3H).	
3-{5-fluoro-6-[(R)-4-hydroxy-3,3-dimethyl-1-{[p-(2-oxo-1-pyrrolidinyl)phenyl]methyl}-4-piperidyl]-3-quinolyl}-2,6-piperidinedione **(I-978)**	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(2-oxopyrrolidin-1-yl)benzaldehyde	559.3	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (s, 1H), 8.33 (s, 1H), 8.14-8.07 (m, 1H), 7.85 (d, J = 8.80 Hz, 1H), 7.64 (s, 2H), 7.37 (s, 2H), 5.30 (s, 1H), 4.25-4.20 (m, 1H), 3.85 (t, J = 6.80 Hz, 2H), 3.61-3.39 (m, 4H), 3.27-3.16 (m, 3H), 2.93-2.77 (m, 2H), 2.76-2.68 (m, 2H), 2.15-2.09 (m, 4H), 1.81-1.24 (m, 1H), 0.99 (s, 3H), 0.68 (s, 3H).	L
3-{5-fluoro-6-[(R)-4-hydroxy-3,3-dimethyl-1-{[p-(2-oxo-1,3-oxazolidin-3-yl)phenyl]methyl}-4-piperidyl]-3-quinolyl}-2,6-piperidinedione **(I-981)**	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(2-oxooxazolidin-3-yl)benzaldehyde	561.3	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.84 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.15 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.83 (d, J = 9.20 Hz, 1H), 7.54 (d, J = 8.40 Hz, 2H), 7.37 (d, J = 8.40 Hz, 2H), 5.11 (s, 1H), 4.44 (t, J = 8.00 Hz, 2H), 4.25-4.21 (m, 1H), 4.07 (t, J = 7.60 Hz, 2H), 3.57 (d, J = 13.20 Hz, 1H), 3.43 (d, J = 13.20 Hz, 1H), 3.14 (s, 1H), 2.76-2.70 (m, 2H), 2.68-2.64 (m, 2H), 2.63-2.56 (m, 2H), 2.43-2.33 (m, 2H), 1.81-1.69 (m, 1H), 0.99 (s, 3H), 0.67 (s, 3H).	L

3-{5-fluoro-6-[(R)-4-hydroxy-3,3-dimethyl-1-{[p-(3-methyl-2-oxo-1-imidazolidinyl)phenyl]methyl}-4-piperidyl]-3-quinolyl}-2,6-piperidinedione (**I-984**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(3-methyl-2-oxoimidazolidin-1-yl)benzaldehyde	574.6	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.84 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.16 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.83 (d, J = 9.20 Hz, 1H), 7.53 (d, J = 8.40 Hz, 2H), 7.29 (d, J = 8.80 Hz, 2H), 5.11 (s, 1H), 4.23 (dd, J = 4.80, 12.80 Hz, 1H), 3.80-3.61 (m, 4H), 3.18-3.10 (m, 2H), 2.81-2.72 (m, 5H), 2.68-2.59 (m, 2H), 2.49-2.38 (s, 2H), 2.19-2.12 (m, 2H), 1.70 (d, J = 13.20 Hz, 1H), 1.05 (s, 3H), 1.04 (s, 3H).	K
3-{5-fluoro-6-[(R)-4-hydroxy-3,3-dimethyl-1-({p-[2-(trifluoromethyl)-1,3-oxazol-4-yl]phenyl}methyl)-4-piperidyl]-3-quinolyl}-2,6-piperidinedione (**I-1050**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(2-(trifluoromethyl)oxazol-4-yl)benzaldehyde	611.2	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 9.01 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.12-8.05 (m, 1H), 7.89-7.78 (m, 3H), 7.49 (d, J = 8.40 Hz, 2H), 5.13 (m, 1H), 4.23 (q, J = 4.80 Hz, 1H), 3.63 (d, J = 13.60 Hz, 1H), 3.50 (d, J = 13.60 Hz, 1H), 3.17 (t, J = 13.20 Hz, 1H), 2.80-2.76 (m, 2H), 2.74-2.49 (m, 4H), 2.20-2.12 (m, 2H), 1.91 (s, 3H), 1.73 (t, J = 12.40 Hz, 1H), 1.01 (s, 3H), 0.67 (s, 3H).	L
1-(6-{1-[(5-amino-1-phenyl-4-pyrazolyl)methyl]-4-hydroxy-3,3-dimethyl-4-piperidyl}-5-fluoro-2-methyl-3-quinolyl)hexah	1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-	5-amino-1-phenyl-1H-pyrazole-4-carbaldehyde	572.4	1H-NMR (400 MHz, DMSO-d6): δ 10.55 (s, 1H), 8.42 (s, 1H), 8.15 (s, 1H), 8.08 (t, J = 9.20 Hz, 1H), 7.80 (d, J = 9.20 Hz, 1H), 7.64-7.62 (m, 2H), 7.50 (t, J = 8.40 Hz, 2H), 7.36-7.32 (m, 2H), 5.37 (s, 2H),	K

ydro-2,4-pyrimidinedione (**I-985**)	2,4(1H,3H)-dione **INT-S6**			4.00-3.96 (m, 1H), 3.86-3.79 (m, 3H), 3.15 (t, J = 13.60 Hz, 1H), 2.94-2.56 (m, 6H), 2.51 (s, 3H), 1.80 (d, J = 12.40 Hz, 1H), 0.98 (m, 3H), 0.77 (m, 3H).	
3-{5-fluoro-6-[(R)-4-hydroxy-1-{[p-(5-methoxy-3-isoxazolyl)phenyl]methyl}-3,3-dimethyl-4-piperidyl]-3-quinolyl}-2,6-piperidinedione (**I-986**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(5-methoxyisoxazol-3-yl)benzaldehyde	573.4	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.83 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.10 (t, J = 8.40 Hz, 1H), 7.85-7.77 (m, 3H), 7.50 (d, J = 8.00 Hz, 2H), 6.18 (s, 1H), 5.13 (s, 1H), 4.23 (dd, J = 4.80, 12.80 Hz, 1H), 4.05 (s, 3H), 3.64 (d, J = 14.00 Hz, 1H), 3.51 (d, J = 13.60 Hz, 1H), 3.21-3.14 (m, 2H), 2.77-2.68 (m, 5H), 2.21-2.15 (m, 3H), 1.72 (d, J = 12.80 Hz, 1H), 1.02 (s, 3H), 0.68 (s, 3H).	L
3-[6-(4-hydroxy-3,3-dimethyl-1-{[p-(1,2,4-oxadiazol-3-yl)phenyl]methyl}-4-piperidyl)-3-quinolyl]-2,6-piperidinedione (**I-992**)	3-(6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione **INT-S20**	4-(1,2,4-oxadiazol-3-yl)benzaldehyde	526.3	1H-NMR (400 MHz, DMSO-d6): δ 10.96 (s, 1H), 9.70 (s, 1H), 8.76 (s, 1H), 8.21 (s, 1H), 8.14 (s, 1H), 8.04-8.01 (m, 3H), 7.94 (s, 2H), 7.59 (d, J = 8.40 Hz, 2H), 4.86 (s, 1H), 4.16-4.12 (m, 1H), 3.69-3.65 (m, 1H), 3.58-3.55 (m, 1H), 2.89 (m, 1H), 2.78-2.75 (m, 2H), 2.64-2.51 (m, 3H), 2.45-2.42 (m, 1H), 2.21-2.16 (m, 2H), 1.57 (s, 1H), 0.93 (s, 3H), 0.69 (s, 3H).	K
3-{5-fluoro-6-[(R)-4-hydroxy-3,3-dimethyl-1-{[p-(1,2,4-oxadiazol-5-	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-	4-(1,2,4-oxadiazol-5-yl)benzaldehyde	544.1	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 9.05 (s, 1H), 8.88 (d, J = 1.20 Hz, 2H), 8.36 (s, 1H), 8.04 (q, J = 8.40 Hz, 2H),	K

yl)phenyl]methyl}-4-piperidyl]-3-quinolyl}-2,6-piperidinedione (**I-446**)	yl)piperidine-2,6-dione			7.89 (d, J = 8.80 Hz, 1H), 7.55 (d, J = 8.00 Hz, 2H), 5.90 (s, 1H), 4.44 (m, 2H), 4.23 (dd, J = 4.80, 12.80 Hz, 1H), 3.56-3.32 (m, 4H), 3.01 (d, J = 12.00 Hz, 1H), 2.79-2.67 (m, 2H), 2.13 (d, J = 5.60 Hz, 1H), 2.13 (d, J = 5.60 Hz, 1H), 1.24 (s, 1H), 1.03 (s, 3H), 0.79 (s, 3H).	
3-[6-(1-{[3-fluoro-4-(1,2,4-oxadiazol-3-yl)phenyl]methyl}-4-hydroxy-3,3-dimethyl-4-piperidyl)-3-quinolyl]-2,6-piperidinedione (**I-995**)	3-(6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl **INT-S20**	3-fluoro-4-(1,2,4-oxadiazol-3-yl)benzaldehyde	544.2	1H-NMR (400 MHz, DMSO-d6): δ 11.95 (s, 1H), 10.97 (s, 1H), 9.77 (s, 1H), 8.76 (d, J = 2.00 Hz, 1H), 8.22 (m, 1H), 8.14-8.01 (m, 2H), 7.94-7.90 (m, 2H), 7.55-7.32 (m, 2H), 4.87 (s, 1H), 4.17-4.12 (m, 1H), 3.69 (d, J = 14.40 Hz, 1H), 3.58 (d, J = 14.80 Hz, 1H), 2.91 (m, 1H), 2.81 (m, 1H), 2.75-2.60 (m, 4H), 2.33-2.15 (m, 2H), 1.91 (s, 3H), 1.59-1.56 (m, 1H), 0.95 (s, 3H), 0.70 (s, 3H).	K
3-{6-[(R)-1-{[p-(2-cyclopropyl-1,3-oxazol-4-yl)phenyl]methyl}-4-hydroxy-3,3-dimethyl-4-piperidyl]-5-fluoro-3-quinolyl}-2,6-piperidinedione (**I-1047**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	4-(2-cyclopropyloxazol-4-yl)benzaldehyde	583.6	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.84 (d, J = 2.00 Hz, 1H), 8.38 (s, 1H), 8.33 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.69 (d, J = 8.40 Hz, 2H), 7.39 (d, J = 8.00 Hz, 2H), 5.11 (s, 1H), 4.23 (q, J = 4.80 Hz, 1H), 3.60 (d, J = 13.20 Hz, 1H), 3.45 (d, J = 13.20 Hz, 1H), 3.33-3.18 (m, 2H), 2.78-2.31 (m, 5H), 2.19-2.13 (m, 3H), 1.71 (d, J = 14.40 Hz,	K

				1H), 1.08-1.00 (m, 7H), 0.67 (s, 3H).	
3-(6-(1-(3-chloro-4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-996**)	3-(6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione **INT-S20**	3-chloro-4-(1,2,4-oxadiazol-3-yl)benzaldehyde	560.3	1H-NMR (400 MHz, DMSO-d6): δ 10.97 (s, 1H), 9.79 (s, 1H), 8.76 (s, 1H), 8.23 (s, 1H), 8.02 (s, 1H), 7.96-7.91 (m, 3H), 7.70 (s, 1H), 7.55 (d, J = 1.20 Hz, 1H), 4.88 (s, 1H), 4.17-4.12 (m, 1H), 3.70-3.67 (m, 1H), 3.60-3.56 (m, 1H), 2.97-2.83 (m, 1H), 2.78-2.75 (m, 2H), 2.68-2.57 (m, 2H), 2.45-2.33 (m, 2H), 2.21-2.15 (m, 2H), 1.59-1.56 (m, 1H), 1.58 (s, 3H), 0.70 (s, 3H).	K
3-(6-(1-benzyl-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-997**)	3-(6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione **INT-S20**	benzaldehyde	458.1	1H-NMR (400 MHz, DMSO-d6): δ 10.97 (s, 1H), 8.75 (s, 1H), 8.21 (s, 1H), 8.00 (s, 1H), 7.93 (s, 2H), 7.39-7.33 (m, 4H), 7.26 (t, J = 6.40 Hz, 1H), 4.86 (s, 1H), 4.16-4.12 (m, 1H), 3.60-3.52 (m, 2H), 2.87-2.73 (m, 3H), 2.68-2.58 (m, 2H), 2.45-2.41 (m, 2H), 2.22-2.13 (m, 2H), 1.58-1.55 (m, 1H), 0.91 (s, 3H), 0.69 (s, 3H).	L
3-{6-[(R)-1-{[p-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)phenyl]methyl}-4-hydroxy-3,3-dimethyl-4-piperidyl]-5-fluoro-3-quinolyl}-2,6-piperidinedione (**I-1019**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	4-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)benzaldehyde	584.4	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (s, 1H), 8.34 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.94 (d, J = 8.00 Hz, 2H), 7.84 (d, J = 9.20 Hz, 1H), 7.56 (d, J = 10.00 Hz, 2H), 5.14 (s, 1H), 4.23 (d, J = 4.80 Hz, 1H), 3.65-3.52 (m, 1H), 2.72-2.68 (m, 1H), 2.59-2.41 (m,	L

				2H), 2.19-2.14 (m, 3H), 1.43 (s, 1H), 1.24 (s, 2H), 1.19 (s, 1H), 1.19-1.16 (m, 5H), 1.11 (s, 3H), 1.02 (m, 1H), 0.68 (s, 3H).	
3-[6-(4-hydroxy-3,3-dimethyl-1-{[6-(trifluoromethyl)-3-pyridyl]methyl}-4-piperidyl)-3-quinolyl]-2,6-piperidinedione	3-(6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione **INT-S20**	6-(trifluoromethyl)nicotinaldehyde	527.2	1H-NMR (400 MHz, DMSO-d6): δ 10.97 (s, 1H), 8.76 (d, J = 2.00 Hz, 2H), 8.21 (s, 1H), 8.07 (d, J = 8.80 Hz, 1H), 8.00 (s, 1H), 7.94-7.89 (m, 3H), 4.88 (s, 1H), 4.15-4.12 (m, 1H), 3.73 (s, 1H), 3.63 (m, 1H), 2.78-2.73 (m, 3H), 2.64-2.55 (m, 4H), 2.33 (d, J = 2.00 Hz, 2H), 2.70-2.50 (m, 1H), 0.92 (s, 3H), 0.69 (s, 3H).	K
3-(6-(1-(4-(2,2-dichlorocyclopropyl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-999**)	3-(6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl **INT-S20**	4-(2,2-dichlorocyclopropyl)benzaldehyde	566.2	1H-NMR (400 MHz, DMSO-d6): δ 10.97 (s, 1H), 8.75 (d, J = 2.00 Hz, 1H), 8.21 (s, 1H), 8.00 (s, 1H), 7.93 (s, 2H), 7.35 (dd, J = 8.40 Hz, 2H), 7.28 (dd, J = 8.00 Hz, 2H), 4.83 (s, 1H), 4.16-4.12 (m, 1H), 3.55 (d, J = 2.40 Hz, 1H), 3.49 (d, J = 2.40 Hz, 1H), 3.12-3.09 (m, 1H), 2.78-2.67 (m, 3H), 2.68-2.57 (m, 2H), 2.45-2.44 (m, 2H), 2.17-2.08 (m, 4H), 1.57 (m, 1H), 0.91 (s, 3H), 0.68 (s, 3H).	L
3-{6-[(R)-1-{[3-chloro-4-(1-methyl-3-pyrazolyl)phenyl]methyl}-4-hydroxy-3,3-dimethyl-4-piperidyl]-5-fluoro-3-quinolyl}-2,6-	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	3-chloro-4-(1-methyl-1H-pyrazol-3-yl)benzaldehyde	590.2	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.34 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.78-7.73 (m, 2H), 7.50 (s, 1H), 7.38-7.35 (m, 1H), 6.70 (d, J = 2.40	L

piperidinedione (**I-1142**)				Hz, 1H), 5.14 (s, 1H), 4.25-4.21 (m, 1H), 3.91 (s, 3H), 3.62 (d, J = 13.60 Hz, 1H), 3.49 (d, J = 13.60 Hz, 1H), 3.20-3.14 (m, 1H), 2.78-2.71 (m, 3H), 2.68-2.62 (m, 3H), 2.34-2.21 (m, 2H), 1.81-1.71 (m, 1H), 1.02 (s, 3H), 0.69 (s, 3H).	
3-{6-[(R)-1-{[p-(3-cyclopropyl-1H-1,2,4-triazol-1-yl)phenyl]methyl}-4-hydroxy-3,3-dimethyl-4-piperidyl]-5-fluoro-3-quinolyl}-2,6-piperidinedione (**I-1074**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(3-cyclopropyl-1H-1,2,4-triazol-1-yl)benzaldehyde	583.5	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 9.06 (s, 1H), 8.85 (s, 1H), 8.33 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.77 (d, J = 8.40 Hz, 2H), 7.51 (d, J = 8.40 Hz, 2H), 5.14 (s, 1H), 4.25-4.21 (m, 1H), 3.63 (d, J = 13.60 Hz, 1H), 3.51 (d, J = 13.60 Hz, 1H), 3.49-3.33 (m, 2H), 2.77-2.70 (m, 2H), 2.68-2.60 (m, 2H), 2.21-2.11 (m, 4H), 1.72 (d, J = 12.40 Hz, 1H), 0.99-0.90 (m, 5H), 0.89-0.86 (m, 2H), 0.68 (s, 3H).	L
3-{6-[(R)-1-{[p-(5-chloro-1,3,4-oxadiazol-2-yl)phenyl]methyl}-4-hydroxy-3,3-dimethyl-4-piperidyl]-5-fluoro-3-quinolyl}-2,6-piperidinedione (**I-1034**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(5-chloro-1,3,4-oxadiazol-2-yl)benzaldehyde	578.2	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (s, 1H), 8.33 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.97 (d, J = 8.40 Hz, 2H), 7.84 (d, J = 9.20 Hz, 1H), 7.77-7.49 (m, 2H), 5.14 (s, 1H), 4.25-4.21 (m, 1H), 3.68 (d, J = 14.00 Hz, 1H), 3.56 (d, J = 14.40 Hz, 1H), 3.22-3.16 (m, 1H), 2.70-2.53 (m, 6H), 2.19-2.12 (m, 2H), 1.72 (d, J = 12.80 Hz, 1H), 1.02 (s, 3H), 0.68 (s, 3H).	K

1-[p-({4-[3-(2,6-dioxo-3-piperidyl)-6-quinolyl]-4-hydroxy-3,3-dimethyl-1-piperidyl}methyl)phenyl]cyclopropanecarbonitrile (**I-1002**)	3-(6-((S)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	1-(4-formylphenyl)cyclopropane-1-carbonitrile	523.3	1H-NMR (400 MHz, DMSO-d6): δ 10.96 (s, 1H), 8.75 (d, J = 2.00 Hz, 1H), 8.19 (d, J = 10.40 Hz, 2H), 7.99 (s, 1H), 7.93 (s, 2H), 7.38 (d, J = 8.40 Hz, 2H), 7.30 (d, J = 8.00 Hz, 2H), 4.83 (s, 1H), 4.16-4.12 (m, 1H), 2.86-2.82 (m, 4H), 2.78-2.64 (m, 2H), 2.47-2.41 (m, 3H), 2.18-2.15 (m, 2H), 1.76-1.73 (m, 2H), 1.56-1.49 (m, 3H), 0.90 (s, 3H), 0.68 (s, 3H).	K
3-(6-(4-hydroxy-1-(4-(isoxazol-3-yl)benzyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-1006**)	3-(6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl **INT-S20**	4-(isoxazol-3-yl)benzaldehyde	525.3	1H-NMR (400 MHz, DMSO-d6): δ 10.97 (s, 1H), 9.00 (s, 1H), 8.75 (s, 1H), 8.21 (s, 1H), 8.01 (s, 1H), 7.94 (s, 2H), 7.88 (d, J = 8.00 Hz, 2H), 7.52 (d, J = 8.00 Hz, 2H), 7.15 (s, 1H), 4.85 (s, 1H), 4.16-4.12 (m, 1H), 3.67-3.63 (m, 1H), 3.55-3.51 (m, 1H), 2.89-2.73 (m, 3H), 2.68-2.58 (m, 2H), 2.45-2.41 (m, 1H), 2.21-2.13 (m, 2H), 1.58-1.55 (m, 2H), 0.93 (s, 3H), 0.69 (s, 3H).	L
3-[6-(4-hydroxy-3,3-dimethyl-1-{[p-(1,3,4-oxadiazol-2-yl)phenyl]methyl}-4-piperidyl)-3-quinolyl]-2,6-piperidinedione (**I-1009**)	3-(6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione **INT-S20**	4-(1,3,4-oxadiazol-2-yl)benzaldehyde	526.2	1H-NMR (400 MHz, DMSO-d6): δ 10.97 (s, 1H), 9.34 (s, 1H), 8.76 (d, J = 2.40 Hz, 1H), 8.22 (s, 1H), 8.17 (s, 1H), 8.03-8.01 (m, 3H), 7.94 (m, 2H), 7.62 (d, J = 8.40 Hz, 2H), 4.87 (s, 1H), 4.17-4.12 (m, 1H), 3.68 (d, J = 14.00 Hz, 1H), 3.58 (d, J = 14.40 Hz, 1H), 2.90-2.89 (m, 1H), 2.89-2.74 (m,	K

				2H), 2.89-2.74 (m, 2H), 2.48-2.42 (m, 2H), 2.21-2.14 (m, 2H), 1.57 (d, J = 13.60 Hz, 1H), 0.93 (s, 3H), 0.69 (s, 3H).	
3-{6-[4-hydroxy-3,3-dimethyl-1-({p-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]phenyl}methyl)-4-piperidyl]-3-quinolyl}-2,6-piperidinedione (**I-1010**)	3-(6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl **INT-S20**	4-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)benzaldehyde	594.3	1H-NMR (400 MHz, DMSO-d6): δ 10.97 (s, 1H), 8.76 (d, J = 2.00 Hz, 1H), 8.22 (s, 1H), 8.07 (d, J = 8.00 Hz, 2H), 8.01 (s, 1H), 7.94 (s, 2H), 7.66 (d, J = 8.40 Hz, 2H), 4.87 (s, 1H), 4.14 (t, J = 4.40 Hz, 1H), 3.71 (d, J = 14.00 Hz, 1H), 3.59 (d, J = 14.40 Hz, 1H), 2.78-2.67 (m, 6H), 2.52-4.00 (m, 1H), 2.19-2.17 (m, 2H), 1.57-1.59 (m, 1H), 0.93 (s, 3H), 0.69 (s, 3H).	L
3-[6-(4-hydroxy-3,3-dimethyl-1-{[p-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]methyl}-4-piperidyl)-3-quinolyl]-2,6-piperidinedione (**I-1011**)	3-(6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione **INT-S20**	4-(5-methyl-1,3,4-oxadiazol-2-yl)benzaldehyde	540.3	1H-NMR (400 MHz, DMSO-d6): δ 10.97 (s, 1H), 8.76 (d, J = 2.40 Hz, 1H), 8.20 (m, 2H), 8.01-7.94 (m, 5H), 7.59 (d, J = 8.40 Hz, 2H), 4.86 (s, 1H), 4.17-4.12 (m, 1H), 3.67 (d, J = 14.00 Hz, 1H), 3.56 (d, J = 14.00 Hz, 1H), 2.92-2.86 (m, 1H), 2.81-2.75 (m, 2H), 2.64-2.59 (m, 5H), 2.45-2.41 (m, 1H), 2.20-2.15 (m, 2H), 2.18 (d, J = 8.40 Hz, 1H), 0.93 (s, 3H), 0.69 (s, 3H).	K
3-(6-(4-hydroxy-1-isobutyl-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione,	3-(6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione **INT-S20**	isobutyraldehyde	424.2	1H-NMR (400 MHz, DMSO-d6): δ 10.96 (s, 1H), 8.75 (s, 1H), 8.21 (s, 1H), 8.18 (s, 1H), 7.99 (s, 1H), 7.93 (s, 2H), 4.78 (s, 1H), 4.16-4.12 (m, 1H), 2.84-2.75 (m, 2H), 2.68-2.59 (m, 1H),	K

Formic Acid (**I-1012**)				2.50-2.33 (m, 4H), 2.20-2.05 (m, 4H), 1.80 (m, 1H), 1.55-1.51 (m, 1H), 0.91-0.89 (m, 9H), 0.71 (s, 3H).	
3-(6-{4-hydroxy-3,3-dimethyl-1-[(1-methyl-5-pyrazolyl)methyl]-4-piperidyl}-3-quinolyl)-2,6-piperidinedione (**I-1013**)	3-(6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione **INT-S20**	1-methyl-1H-pyrazole-5-carbaldehyde	462.2	1H-NMR (400 MHz, DMSO-d6): δ 10.97 (s, 1H), 8.75 (d, J = 2.00 Hz, 1H), 8.20 (s, 1H), 7.99 (s, 1H), 7.93 (s, 2H), 7.32 (d, J = 1.60 Hz, 1H), 6.16 (d, J = 2.00 Hz, 1H), 4.87 (s, 1H), 4.16-4.12 (m, 1H), 3.87 (s, 3H), 3.54 (s, 2H), 2.82-2.71 (m, 2H), 2.68-2.55 (m, 2H), 2.45-2.40 (m, 2H), 2.16-2.13 (m, 2H), 1.91 (s, 1H), 1.54 (d, J = 8.6 Hz, 1H), 0.87 (s, 3H), 0.70 (s, 3H).	K
3-(6-((S)-4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-42**)	3-(6-((S)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	4-(trifluoromethyl)benzaldehyde	526.1	1H-NMR (400 MHz, DMSO-d6): δ 10.97 (s, 1H), 8.76 (d, J = 2.00 Hz, 1H), 8.21 (s, 1H), 8.00 (s, 1H), 7.93 (s, 2H), 7.72 (d, J = 8.00 Hz, 2H), 7.61 (d, J = 8.00 Hz, 2H), 4.86 (s, 1H), 4.17-4.12 (m, 1H), 3.67 (d, J = 14.40 Hz, 1H), 3.57 (d, J = 14.00 Hz, 1H), 2.89-2.88 (m, 1H), 2.75-2.73 (m, 2H), 2.68-2.63 (m, 1H), 2.45-2.42 (m, 1H), 2.16 (d, J = 10.40 Hz, 2H), 1.58-1.55 (m, 2H), 1.24 (s, 1H), 0.93 (s, 3H), 0.69 (s, 3H).	K
3-[6-(4-hydroxy-3,3-dimethyl-1-{[6-(1,2,4-oxadiazol-3-yl)-3-pyridyl]methyl	3-(6-((S)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-	6-(1,2,4-oxadiazol-3-yl)nicotinaldehyde	527.3	1H-NMR (400 MHz, DMSO-d6): δ 11.03 (s, 1H), 10.40 (s, 1H), 9.08 (s, 1H), 9.08 (s, 1H), 9.00 (s, 1H), 8.66 (s, 1H), 8.45 (d, J = 8.00 Hz, 1H), 8.24 (d,	K

}-4-piperidyl)-3-quinolyl]-2,6-piperidinedione (**I-1016**)	2,6-dione, HCl			J = 8.00 Hz, 1H), 8.13 (d, J = 9.60 Hz, 2H), 8.01 (d, J = 9.20 Hz, 1H), 5.80 (s, 1H), 4.59-4.55 (m, 2H), 4.26-4.22 (m, 1H), 3.47-3.32 (m, 3H), 3.06-2.94 (m, 2H), 2.78-2.47 (m, 3H), 2.19 (d, J = 5.60 Hz, 1H), 1.90 (d, J = 14.40 Hz, 1H), 1.00 (s, 3H), 0.80 (s, 3H).	
3-{6-[(R)-1-{[p-(5-cyclopropyl-3-isoxazolyl)phenyl]methyl}-4-hydroxy-3,3-dimethyl-4-piperidyl]-5-fluoro-3-quinolyl}-2,6-piperidinedione (**I-1055**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(5-cyclopropylisoxazol-3-yl)benzaldehyde	583.3	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.12 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.77 (d, J = 7.60 Hz, 2H), 7.51 (d, J = 8.00 Hz, 2H), 6.75 (d, J = 2.80 Hz, 1H), 5.13 (m, 1H), 4.22 (t, J = 4.80 Hz, 1H), 3.63 (d, J = 13.60 Hz, 1H), 3.51-3.32 (m, 2H), 2.68 (d, J = 2.00 Hz, 2H), 2.55 (q, J = 2.00 Hz, 2H), 2.33 (t, J = 1.60 Hz, 2H), 2.18 (d, J = 10.80 Hz, 2H), 2.04 (d, J = 5.20 Hz, 2H), 1.07-1.01 (m, 5H), 0.83 (d, J = 2.00 Hz, 2H), 0.68 (s, 3H).	K
3-(6-((R)-1-(4-(4-chloroisoxazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, Formic Acid (**I-1056**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	4-(4-chloroisoxazol-3-yl)benzaldehyde	577.4	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 9.44 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.14 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.86-7.81 (m, 3H), 7.59 (d, J = 8.00 Hz, 2H), 5.16 (s, 1H), 4.25-4.21 (m, 1H), 3.67-3.60 (m, 2H), 3.32-3.15 (m, 1H), 2.81-2.74 (m, 3H), 2.68-2.47 (m, 3H), 2.34-2.24 (m,	L

				1H), 2.16-2.12 (m, 1H), 1.75-1.72 (m, 1H), 1.03 (s, 3H), 0.70 (s, 3H).	
3-{5-fluoro-6-[(R)-4-hydroxy-3,3-dimethyl-1-({p-[5-(trifluoromethyl)-3-isoxazolyl]phenyl}methyl)-4-piperidyl]-3-quinolyl}-2,6-piperidinedione (**I-1059**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(5-(trifluoromethyl)isoxazol-3-yl)benzaldehyde	611.3	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.10 (t, J = 8.00 Hz, 2H), 7.95 (d, J = 8.40 Hz, 2H), 7.84 (d, J = 9.20 Hz, 1H), 7.56 (d, J = 8.00 Hz, 2H), 5.14 (m, 1H), 4.23 (dd, J = 4.80, 12.80 Hz, 1H), 3.67 (d, J = 14.00 Hz, 1H), 3.54 (d, J = 14.00 Hz, 1H), 3.19-3.16 (m, 1H), 2.77-2.71 (m, 2H), 2.68-2.59 (m, 2H), 2.34-2.21 (m, 2H), 1.72 (d, J = 12.00 Hz, 1H), 1.02 (s, 3H), 0.68 (s, 3H); 2 protons missing, merged with solvent.	K
3-{6-[(R)-1-{[3-chloro-4-(3-pyridazinyl)phenyl]methyl}-4-hydroxy-3,3-dimethyl-4-piperidyl]-5-fluoro-3-quinolyl}-2,6-piperidinedione (**I-1065**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	3-chloro-4-(pyridazin-3-yl)benzaldehyde	588.5	1H-NMR (400 MHz, DMSO-d6): δ 11.01 (s, 1H), 10.28 (s, 1H), 9.34-9.32 (m, 1H), 8.93 (s, 1H), 8.45 (s, 1H), 8.10 (t, J = 6.00 Hz, 2H), 8.05 (d, J = 1.60 Hz, 1H), 8.03 (d, J = 1.60 Hz, 1H), 7.89-7.81 (m, 2H), 7.79 (d, J = Hz, 1H), 5.98 (s, 1H), 4.55-4.28 (m, 2H), 3.43-2.98 (m, 4H), 2.76 (d, J = 12.80 Hz, 1H), 2.73-2.68 (m, 1H), 2.65-2.61 (m, 1H), 2.51-2.50 (m, 2H), 2.34-2.31 (m, 2H), 1.12 (s, 3H), 0.81 (s, 3H).	L
3-(5-fluoro-6-((R)-1-(4-(3-fluoro-1-methyl-1H-	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiper	4-(3-fluoro-1-methyl-1H-pyrazol-4-	574.4	1H NMR (499 MHz, DMSO-d6) δ ppm 10.98 (s, 1H) 8.84 (d, J=2.19 Hz, 1H) 8.32	C

pyrazol-4-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione **(I-1068)**	idin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	yl)benzaldehyde **ALD-114**		(t, J=2.46 Hz, 1H) 8.06 - 8.12 (m, 2H) 7.83 (d, J=9.31 Hz, 1H) 7.48 (d, J=8.21 Hz, 2H) 7.38 (d, J=8.21 Hz, 2H) 5.10 (s, 1H) 4.22 (dd, J=13.14, 4.93 Hz, 1H) 3.76 (s, 3H) 3.50 - 3.62 (m, 1H) 3.45 (br d, J=13.69 Hz, 1H) 3.14 (br, 1H) 2.67 - 2.80 (m, 2H) 2.53 - 2.65 (m, 2H) 2.46 (br d, J=10.40 Hz, 2H) 2.10 - 2.21 (m, 2H) 1.70 (br d, J=12.05 Hz, 1H) 1.00 (br s, 3H) 0.67 (s, 3H)	
3-(5-fluoro-6-((R)-1-(4-(4-fluoro-1-methyl-1H-pyrazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione **(I-1071)**	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	4-(4-fluoro-1-methyl-1H-pyrazol-3-yl)benzaldehyde **ALD-113**	574.3	1H NMR (499 MHz, DMSO-d6) δ ppm 10.97 (s, 1H) 8.84 (d, J=1.64 Hz, 1H) 8.33 (t, J=2.74 Hz, 1H) 8.09 (t, J=8.76 Hz, 1H) 7.94 (d, J=4.93 Hz, 1H) 7.83 (d, J=9.31 Hz, 1H) 7.70 (d, J=7.67 Hz, 2H) 7.43 (d, J=8.21 Hz, 2H) 5.11 (d, J=1.64 Hz, 1H) 4.22 (dd, J=12.87, 4.65 Hz, 1H) 3.82 (s, 3H) 3.59 (d, J=13.69 Hz, 1H) 3.48 (d, J=13.69 Hz, 1H) 3.15 (m, 1H) 2.67 - 2.79 (m, 2H) 2.52 - 2.66 (m, 2H) 2.43 - 2.49 (m, 2H) 2.07 - 2.24 (m, 2H) 1.71 (br d, J=11.50 Hz, 1H) 1.00 (s, 3H) 0.68 (s, 3H)	C
3-{6-[(R)-1-{[p-(6-cyclopropoxy-3-pyridazinyl)phenyl]methyl}-4-hydroxy-3,3-	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-	4-(6-cyclopropoxypyridazin-3-yl)benzaldehyde	610.6	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.34 (s, 1H), 8.19 (t, J = 9.20 Hz, 1H), 8.12-8.06 (m, 3H), 7.84 (d, J = 9.20	K

dimethyl-4-piperidyl]-5-fluoro-3-quinolyl}-2,6-piperidinedione (**I-1183**)	2,6-dione, HCl			Hz, 2H), 7.34 (d, J = 9.60 Hz, 1H), 5.14 (s, 1H), 4.46 (t, J = 2.80 Hz, 1H), 4.24-4.21 (m, 1H), 3.66 (d, J = 14.00 Hz, 1H), 3.55 (d, J = 14.00 Hz, 1H), 3.22-3.13 (m, 1H), 2.74-2.57 (m, 5H), 2.48-2.33 (m, 2H), 2.27-2.13 (m, 1H), 1.68 (d, J = 8.00 Hz, 1H), 1.03 (s, 3H), 0.86 (t, J = 6.00 Hz, 2H), 0.79 (dd, J = 6.40, 7.60 Hz, 2H), 0.69 (s, 3H).	
3-{6-[(R)-1-{[4-(2-chloro-1,3-oxazol-4-yl)-3-fluorophenyl]methyl}-4-hydroxy-3,3-dimethyl-4-piperidyl]-5-fluoro-3-quinolyl}-2,6-piperidinedione (**I-1062**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	4-(2-chlorooxazol-4-yl)-3-fluorobenzaldehyde	595.1	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.56 (d, J = 4.00 Hz, 1H), 8.33 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.90-7.83 (m, 2H), 7.35-7.32 (m, 2H), 5.14 (s, 1H), 4.23 (dd, J = 4.80, 12.80 Hz, 1H), 3.64 (d, J = 14.40 Hz, 1H), 3.51 (d, J = 14.00 Hz, 1H), 3.21-3.17 (m, 1H), 3.14-2.80 (m, 2H), 2.77-2.73 (m, 3H), 2.22-2.01 (m, 3H), 1.76-1.62 (m, 1H), 1.24 (s, 3H), 0.68 (s, 3H).	K
3-{6-[(R)-1-{[p-(2-chloro-1,3-oxazol-4-yl)phenyl]methyl}-4-hydroxy-3,3-dimethyl-4-piperidyl]-5-fluoro-3-quinolyl}-2,6-piperidinedione (**I-1082**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	4-(2-chlorooxazol-4-yl)benzaldehyde	577.3	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.74 (s, 1H), 8.33 (s, 1H), 8.08 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.72 (d, J = 8.40 Hz, 2H), 7.45 (d, J = 8.40 Hz, 2H), 5.12 (s, 1H), 4.28-4.17 (m, 1H), 3.58-3.46 (m, 2H), 3.26-3.08 (m, 2H), 2.68-2.56 (m, 5H), 2.29-2.05 (m,	K

				2H), 1.81-1.62 (m, 1H), 1.01 (s, 3H), 0.68 (s, 3H).	
3-{5-fluoro-6-[(R)-4-hydroxy-3,3-dimethyl-1-{[p-(2-methyl-1,3-oxazol-4-yl)phenyl]methyl}-4-piperidyl]-3-quinolyl}-2,6-piperidinedione (**I-1085**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(2-methyloxazol-4-yl)benzaldehyde	557.4	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (d, J = 2.0 Hz, 1H), 8.44 (s, 1H), 8.33 (s, 1H), 8.17 (s, 1H), 8.10 (q, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.72 (d, J = 8.40 Hz, 2H), 7.40 (d, J = 8.00 Hz, 2H), 5.11 (s, 1H), 4.23 (dd, J =12.8, 4.80 Hz, 1H), 3.60 (d, J = 13.60 Hz, 1H), 3.47 (d, J = 13.60 Hz, 1H), 3.32-3.16 (m, 1H), 2.77-2.69 (m, 2H), 2.68-2.63 (m, 2H), 2.58-2.51 (m, 5H), 2.18-2.13 (m, 2H), 1.71 (d, J = 12.40 Hz, 1H), 1.01 (s, 3H), 0.68 (m, 3H).	L
3-{6-[4-hydroxy-3,3-dimethyl-1-({p-[1-(trifluoromethyl)cyclopropyl]phenyl}methyl)-4-piperidyl]-3-quinolyl}-2,6-piperidinedione (**I-1042**)	3-(6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione **INT-S20**	4-(1-(trifluoromethyl)cyclopropyl)benzaldehyde	566.3	1H-NMR (400 MHz, DMSO-d6): δ 10.97 (s, 1H), 8.76 (s, 1H), 8.21 (s, 1H), 8.00 (s, 1H), 7.93 (s, 2H), 7.45-7.36 (m, 4H), 4.84,s, 1H), 4.17-4.12 (m, 1H), 3.57-3.48 (m, 2H), 2.85-2.52 (m, 5H), 2.51-2.45 (m, 2H), 2.22-2.15 (m, 2H), 1.55 (d, J = 13.20 Hz, 1H), 1.35-1.31 (m, 2H), 1.13 (s, 2H), 0.92 (s, 3H), 0.69 (s, 3H).	L
3-{5-fluoro-6-[(R)-4-hydroxy-3,3-dimethyl-1-{[p-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl]methyl}-4-piperidyl]-3-	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	4-(1-methyl-1H-1,2,4-triazol-3-yl)benzaldehyde	557.4	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.51 (s, 1H), 8.34 (s, 1H), 8.10 (s, 1H), 7.96 (d, J = 8.00 Hz, 2H), 7.84 (d, J = 9.20 Hz, 1H), 7.45 (d, J = 8.40 Hz, 2H), 5.13 (s, 1H), 4.23 (dd,	L

quinolyl}-2,6-piperidinedione (**I-1173**)				J = 4.80, 12.60 Hz, 1H), 3.92 (s, 3H), 3.61 (d, J = 13.60 Hz, 1H), 3.50 (d, J = 13.60 Hz, 1H), 3.20-3.16 (m, 1H), 3.16-2.70 (m, 3H), 2.69-2.60 (m, 3H), 2.16 (dd, J = 4.80, 9.00 Hz, 2H), 1.72 (d, J = 12.00 Hz, 1H), 1.02 (s, 3H), 0.68 (s, 3H).	
3-(6-((R)-1-(4-(4-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (**I-1210**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	4-(4-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)benzaldehyde **ALD-115**	606.4	1H NMR (499 MHz, DMSO-d6) δ ppm 10.98 (s, 1H) 8.84 (d, J=2.19 Hz, 1H) 8.33 (t, J=2.74 Hz, 1H) 8.08 - 8.15 (m, 2H) 7.84 (d, J=9.31 Hz, 1H) 7.63 (d, J=8.21 Hz, 2H) 7.44 (d, J=8.21 Hz, 2H) 6.95 - 7.36 (t, J = 55Hz, 1H) 5.14 (br s, 1H) 4.23 (dd, J=12.59, 4.93 Hz, 1H) 3.91 (s, 3H) 3.58 - 3.68 (m, 1H) 3.52 (br, 1H) 3.09 - 3.21 (m, 1H) 2.68 - 2.82 (m, 2H) 2.55 - 2.67 (m, 2H) 2.20 - 2.28 (m, 1H) 2.08 - 2.18 (m, 1H) 1.72 (br d, J=11.50 Hz, 1H) 1.02 (s, 3H) 0.68 (s, 3H) (two protons partially overlapped with DMSO solvent)	C
3-{5-fluoro-6-[(R)-4-hydroxy-1-{2-methoxy-1-[p-(trifluoromethyl)phenyl]ethyl}-3,3-dimethyl-4-piperidyl]-3-quinolyl}-2,6-piperidinedione (**I-1093**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	2-methoxy-1-(4-(trifluoromethyl)phenyl)ethan-1-one	588.2	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.84 (s, 1H), 8.32 (s, 1H), 8.05 (t, J = 8.40 Hz, 1H), 7.82 (d, J = 9.20 Hz, 1H), 7.72 (t, J = 4.00 Hz, 2H), 7.60 (d, J = 5.20 Hz, 2H), 5.01 (m, 1H), 4.23 (d, J = 13.60 Hz, 1H), 3.76 (t, J = 9.20 Hz, 3H), 3.25 (d, J = 8.40 Hz, 3H), 3.14-	I

				3.15 (m, 2H), 2.95-2.73 (m, 4H), 2.51-2.34 (m, 1H), 2.15-2.05 (m, 2H), 1.72-1.61 (m, 1H), 1.01-0.95 (m, 3H), 0.68-0.61 (m, 3H).	
3-(6-((R)-1-(3-chloro-4-(1-(difluoromethyl)-1H-pyrazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione **(I-1149)**	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	3-chloro-4-(1-(difluoromethyl)-1H-pyrazol-3-yl)benzaldehyde	626.3	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (s, 1H), 8.35 (d, J = 2.80 Hz, 2H), 8.13 (d, J = 8.80 Hz, 1H), 7.89-7.73 (m, 3H), 7.45 (s, 1H), 7.43 (d, J = 1.20 Hz, 1H), 6.97 (s, 1H), 6.53 (s, 1H), 5.15 (s, 1H), 4.26-4.21 (m, 1H), 3.65 (d, J = 14.00 Hz, 1H), 3.53 (d, J = 14.00 Hz, 1H), 3.18 (t, J = 12.40 Hz, 1H), 2.81-2.77 (m, 2H), 2.68-2.63 (m, 3H), 2.19-2.13 (m, 2H), 1.73 (d, J = 13.20 Hz, 1H), 1.03 (s, 3H), 0.69 (s, 3H).	L
3-(6-((R)-1-(3-chloro-4-(1-methyl-1H-1,2,3-triazol-4-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione **(I-1128)**	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	3-chloro-4-(1-methyl-1H-1,2,3-triazol-4-yl)benzaldehyde	591.3	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.60 (s, 1H), 8.34 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 8.03 (d, J = 8.00 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.56 (s, 1H), 7.45 (d, J = 8.00 Hz, 1H), 5.15 (s, 1H), 4.26-4.21 (m, 1H), 4.15 (s, 3H), 3.63 (d, J = 14.00 Hz, 1H), 3.51 (d, J = 14.00 Hz, 1H), 3.18 (t, J = 15.20 Hz, 2H), 2.72-2.68 (m, 2H), 2.63-2.60 (m, 2H), 2.19-2.18 (m, 2H), 1.86 (s, 1H), 1.75 (d, J = 6.80 Hz, 1H), 1.03 (s, 3H), 0.69 (s, 3H).	K

3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethyl-1-((1-methyl-1H-pyrazol-5-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, Formic Acid (**I-1029**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	1-methyl-1H-pyrazole-5-carbaldehyde	480.2	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.84 (d, J = 2.00 Hz, 1H), 8.32 (t, J = 2.40 Hz, 1H), 8.19 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.31 (d, J = 2.00 Hz, 1H), 6.16 (d, J =2.00 Hz, 1H), 5.15 (s, 1H), 4.25-4.20 (m, 1H), 3.86 (s, 3H), 3.53 (s, 2H), 3.17-3.09 (m, 1H), 2.76-2.72 (m, 1H), 2.68-2.58 (m, 3H), 2.51-2.47 (m, 2H), 2.18-2.12 (m, 2H), 1.70 (d, J = 12.80 Hz, 1H), 0.96 (s, 3H), 0.69 (s, 3H).	K
3-(6-((R)-1-(3-(difluoromethyl)-4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (**I-1234**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	3-(difluoromethyl)-4-(1,2,4-oxadiazol-3-yl)benzaldehyde	594.3	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 9.82 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.35 (s, 1H), 8.13-8.05 (m, 2H), 7.93 (s, 1H), 7.85 (d, J = 8.80 Hz, 1H), 7.75 (d, J = 8.00 Hz, 1H), 7.55 (m, 1H), 5.17 (s, 1H), 4.26-4.21 (m, 2H), 3.73 (m, 1H), 3.58 (d, J = 12.80 Hz, 1H), 3.33-3.24 (m, 1H), 2.82-2.74 (m, 3H), 2.68-2.60 (m, 2H), 2.20-2.14 (m, 2H), 1.75 (d, J = 13.60 Hz, 1H), 1.04 (s, 3H), 0.68 (s, 3H).	K
3-(5-fluoro-6-((R)-4-hydroxy-1-isobutyl-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione,	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	isobutyraldehyde	442.3	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.19 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 8.80 Hz, 1H), 5.07 (s, 1H), 4.25-4.21 (m, 1H), 3.36-3.12 (m, 1H),	K

Formic Acid (**I-1026**)				2.77-2.68 (m, 1H), 2.67-2.55 (m, 3H), 2.53-2.48 (m, 2H), 2.38 (t, J = 9.20 Hz, 1H), 2.21-2.07 (m, 3H), 1.80-1.70 (m, 1H), 1.67 (m, 1H), 0.99 (s, 3H), 0.90 (s, 6H), 0.71 (s, 3H).	
3-(5-fluoro-6-((4R)-4-hydroxy-3,3-dimethyl-1-(5-(trifluoromethyl)-2,3-dihydro-1H-inden-1-yl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-1105**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	1-bromo-5-(trifluoromethyl)-2,3-dihydro-1H-indene	570.4	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (s, 1H), 8.34 (d, J = 8.40 Hz, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.59-7.50 (m, 1H), 5.11 (d, J = 14.40 Hz, 1H), 4.42 (d, J = 26.80 Hz, 1H), 4.23 (t, J = 4.00 Hz, 1H), 3.22-2.96 (m, 4H), 2.89-2.74 (m, 3H), 2.68-2.60 (m, 2H), 2.24-2.13 (m, 3H), 1.79-1.76 (m, 2H), 1.04 (m, 3H), 0.68 (m, 3H).	J
3-(5-fluoro-6-((4R)-4-hydroxy-3,3-dimethyl-1-(1-(4-(trifluoromethyl)phenyl)propyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, Formic Acid (**I-1111**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	1-(4-(trifluoromethyl)phenyl)propan-1-one	572.1	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.84 (d, J = 2.00 Hz, 1H), 8.32 (d, J = 2.40 Hz, 2H), 8.04 (t, J = 8.40 Hz, 1H), 7.81 (d, J = 9.20 Hz, 1H), 7.74-7.71 (m, 2H), 7.52-7.48 (m, 2H), 4.94 (d, J = 5.60 Hz, 1H), 4.25-4.20 (m, 1H), 3.47-3.41 (m, 1H), 3.14-3.01 (m, 1H), 2.68-2.61 (m, 3H), 2.48-2.41 (m, 2H), 2.22-2.14 (m, 3H), 1.98-1.94 (m, 1H), 1.79-1.55 (m, 2H), 1.03-0.94 (m, 3H), 0.83-0.74 (m, 3H), 0.66-0.61 (m, 3H).	I
3-(5-fluoro-6-((R)-4-	3-(5-fluoro-6-((R)-4-	4-(5-methylisoxaz	557.5	1H-NMR (400 MHz, DMSO-d6): δ 10.99	K

hydroxy-3,3-dimethyl-1-(4-(5-methylisoxazol-3-yl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione **(I-1037)**	hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	ol-3-yl)benzaldehyde		(s, 1H), 8.87 (d, J = 12.80 Hz, 1H), 8.36 (s, 1H), 8.08-7.76 (m, 5H), 6.84-6.76 (m, 1H), 6.53 (s, 1H), 5.92 (s, 1H), 5.13 (s, 1H), 4.50 (s, 1H), 4.26-4.23 (m, 1H), 3.69-3.501 (m, 3H), 3.39-2.99 (m, 4H), 2.61-2.52 (m, 3H), 2.33-2.04 (m, 3H), 1.04 (s, 3H), 0.68 (s, 3H).	
3-(6-((R)-1-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione **(I-1121)**	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	4-(1-(difluoromethyl)-1H-pyrazol-3-yl)benzaldehyde	592.4	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.84 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.29 (s, 1H), 8.13 (t, J = 8.80 Hz, 1H), 7.86-7.84 (m, 3H), 7.45 (d, J = 8.00 Hz, 2H), 7.03 (d, J = 2.40 Hz, 1H), 5.13 (s, 1H), 4.25-4.22 (m, 1H), 3.64-3.61 (m, 2H), 3.20 (m, 2H), 2.77-2.71 (m, 2H), 2.68-2.63 (m, 2H), 2.57-2.50 (m, 2H), 2.21-2.18 (m, 2H), 1.71 (d, J = 12.80 Hz, 1H), 1.02 (s, 3H), 0.67 (s, 3H).	K
3-(6-((R)-1-(4-(1-cyclopropyl-1H-pyrazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione **(I-1156)**	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	4-(1-cyclopropyl-1H-pyrazol-3-yl)benzaldehyde	582.6	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.84 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.80 (d, J = 2.40 Hz, 1H), 7.74 (d, J = 8.40 Hz, 2H), 7.37 (d, J = 8.00 Hz, 2H), 6.66 (d, J = 2.40 Hz, 1H), 5.11 (s, 1H), 4.25-4.21 (m, 1H), 3.76-3.75 (m, 1H), 3.59 (d, J = 13.60 Hz, 1H), 3.46 (d, J = 13.20 Hz, 1H), 3.35 (t, J = 19.60 Hz, 1H), 2.67-	K

				2.51 (m, 4H), 2.21-2.18 (m, 3H), 1.61 (d, J = 34.80 Hz, 1H), 1.09-1.07 (m, 8H), 0.67 (s, 3H).	
3-(5-fluoro-6-((R)-1-(4-(4-fluoro-1H-pyrazol-1-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-1213**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(4-fluoro-1H-pyrazol-1-yl)benzaldehyde	560.3	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.68 (d, J = 4.40 Hz, 1H), 8.33 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.83 (t, J = 4.00 Hz, 2H), 7.76 (d, J = 8.80 Hz, 2H), 7.48 (d, J = 8.80 Hz, 2H), 5.12 (d, J = 0.80 Hz, 1H), 4.23 (dd, J = 4.80, 12.40 Hz, 1H), 3.62 (d, J = 13.60 Hz, 1H), 3.49 (d, J = 13.60 Hz, 1H), 3.18 (d, J = 13.20 Hz, 1H), 2.74 (t, J = 4.40 Hz, 2H), 2.70-2.67 (m, 3H), 2.33 (t, J = 2.00 Hz, 3H), 1.72 (d, J = 12.80 Hz, 1H), 1.01 (s, 3H), 0.68 (s, 3H).	L
3-(6-((R)-1-(3-chloro-4-(1-cyclopropyl-1H-pyrazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (**I-1135**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	3-chloro-4-(1-cyclopropyl-1H-pyrazol-3-yl)benzaldehyde	616.2	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (s, 1H), 8.34 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.87-7.83 (m, 2H), 7.74 (d, J = 8.00 Hz, 1H), 7.49 (s, 1H), 7.37 (d, J = 6.80 Hz, 1H), 6.69 (s, 1H), 5.14 (s, 1H), 4.23 (dd, J = 4.80, Hz, 1H), 3.80-3.78 (m, 1H), 3.62 (d, J = 14.00 Hz, 1H), 3.49 (d, J = 13.60 Hz, 1H), 3.33 (m, 1H), 2.74-2.71 (m, 2H), 2.68-2.67 (m, 3H), 2.34-2.33 (m, 2H), 1.86(s, 1H), 1.71 (m, 1H), 1.11 (s, 3H), 1.09-1.01 (m, 5H), 0.99 (s, 3H).	K

3-{6-[(R)-1-{[3-chloro-4-(1-cyclopropyl-4-pyrazolyl)phenyl]methyl}-4-hydroxy-3,3-dimethyl-4-piperidyl]-5-fluoro-3-quinolyl}-2,6-piperidinedione (**I-1163**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	3-chloro-4-(1-cyclopropyl-1H-pyrazol-4-yl)benzaldehyde	616.2	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (s, 1H), 8.43 (s, 1H), 8.34 (s, 1H), 8.12-8.07 (m, 1H), 7.87-7.83 (m, 2H), 7.57 (d, J = 8.00 Hz, 1H), 7.48 (s, 1H), 7.34-7.32 (m, 1H), 5.13 (m, 1H), 4.31-4.25 (m, 1H), 3.82-3.72 (m, 1H), 3.60-3.32 (m, 2H), 3.20-3.11 (s, 1H), 2.92-2.48 (m, 6H), 2.22-2.12 (m, 2H), 1.76-1.65 (m, 1H), 1.11-0.98 (m, 7H), 0.69 (s, 3H).	K
3-(6-((R)-1-(4-(4-chloro-1-methyl-1H-pyrazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (**I-1166**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	4-(4-chloro-1-methyl-1H-pyrazol-3-yl)benzaldehyde	590.3	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.34 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 8.04 (s, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.79 (d, J = 8.40 Hz, 2H), 7.44 (d, J = 8.00 Hz, 2H), 5.13 (s, 1H), 4.26-4.21 (m, 1H), 3.87 (s, 3H), 3.61 (d, J = 13.60 Hz, 1H), 3.50 (d, J = 13.60 Hz, 1H), 3.17 (t, J = 4.00 Hz, 1H), 2.63-2.52 (m, 5H), 2.18 (d, J = 14.80 Hz, 1H), 2.15-2.13 (m, 1H), 1.84 (s, 1H), 1.72 (d, J = 12.80 Hz, 1H), 1.02 (s, 3H), 0.69 (s, 3H).	K
3-{5-fluoro-6-[(R)-4-hydroxy-3,3-dimethyl-1-{[p-(3-methyl-1-pyrazolyl)phenyl]methyl}-4-piperidyl]-3-quinolyl}-2,6-	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(3-methyl-1H-pyrazol-1-yl)benzaldehyde	556.3	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.84 (s, 1H), 8.34 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.75 (d, J = 8.40 Hz, 2H), 7.44 (d, J = 8.00 Hz, 2H), 6.32 (d, J = 2.00 Hz, 1H), 5.12 (s, 1H), 4.23 (dd, J =	K

piperidinedione (**I-1180**)				4.80, 12.80 Hz, 1H), 3.60 (d, J = 13.60 Hz, 1H), 3.48 (d, J = 13.60 Hz, 1H), 3.18-3.13 (m, 1H), 2.81-2.72 (m, 4H), 2.33-2.18 (m, 6H), 1.91 (s, 3H), 1.76-1.24 (m, 1H), 1.01 (s, 3H), 0.68 (s, 3H).	
3-(6-((R)-1-(4-(4-cyclopropyl-1H-pyrazol-1-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (**I-1227**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	4-(4-cyclopropyl-1H-pyrazol-1-yl)benzaldehyde	582.3	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.29 (s, 1H), 8.24 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.74 (d, J = 8.40 Hz, 2H), 7.55 (s, 1H), 7.44 (d, J = 8.40 Hz, 2H), 5.12 (s, 1H), 4.30-4.20 (m, 1H), 3.60 (d, J = 10.80 Hz, 1H), 3.48 (d, J = 13.60 Hz, 1H), 3.18-3.12 m, 1H), 2.69-2.53 (m, 3H), 2.20-2.18 (m, 3H), 1.89 (s, 1H), 1.77-1.76 (m, 3H), 1.01 (s, 3H), 0.89-0.85 (m, 2H), 0.68 (s, 3H), 0.62-0.58 (m, 2H).	K
2-(4-(((4R)-4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)phenyl)-2-ethylbutanenitrile (**I-1279**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	2-ethyl-2-(4-formylphenyl)butanenitrile	571.3	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.21 (s, 1H), 8.09 (d, J = 8.80 Hz, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.43-7.38 (m, 5H), 5.12 (s, 1H), 4.25-4.21 (m, 1H), 3.58 (d, J = 10.00 Hz, 1H), 3.53 (d, J = 19.20 Hz, 1H), 3.32 (s, 1H), 2.68-2.67 (m, 1H), 2.67-2.63 (m, 2H), 2.05-2.02 (m, 7H), 1.69 (s, 1H), 1.00 (s, 3H), 0.80 (t, J = 7.20 Hz, 6H), 0.68 (s, 3H).	L

1-(4-(((4R)-4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)phenyl)cyclopentane-1-carbonitrile, Formic Acid (**I-1286**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	1-(4-formylphenyl)cyclopentane-1-carbonitrile	569.3	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.29 (s, 1H), 8.14 (s, 1H), 8.16 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.48 (d, J = 8.40 Hz, 2H), 7.41 (d, J = 8.40 Hz, 2H), 5.12 (s, 1H), 4.21-4.24 (m, 1H), 3.51-3.59 (m, 1H), 3.33-3.47 (m, 2H), 2.68-2.69 (m, 1H), 2.64-2.67 (m, 2H), 2.47-2.51 (m, 4H), 2.10-2.21 (m, 4H), 1.90-1.92 (m, 4H), 1.88-1.89 (m, 1H), 1.01 (s, 3H), 0.68 (s, 3H).	K
3-(6-((R)-1-(4-(4-(difluoromethyl)-1H-pyrazol-1-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (**I-1220**)	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	4-(4-(difluoromethyl)-1H-pyrazol-1-yl)benzaldehyde	592.4	1H-NMR (400 MHz, DMSO-d6): 10.99 (s, 1H), 8.85 (s, 2H), 8.33 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.99 (s, 1H), 7.84 (d, J = 8.40 Hz, 3H), 7.51 (d, J = 8.80 Hz, 2H), 7.27-6.99 (m, 1H), 5.13 (s, 1H), 4.25-4.21 (m, 1H), 3.65-3.57 (m, 2H), 3.20-3.17 (m, 1H), 2.77-2.71 (m, 2H), 2.60-2.51 (m, 3H), 2.19-2.12 (m, 3H), 1.72 (d, J = 12.80 Hz, 1H), 1.02 (s, 3H), 0.69 (s, 3H).	K
3-(4-(((4R)-4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)phenyl)-1-methyl-	3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	3-(4-formylphenyl)-1-methyl-1H-pyrazole-4-carbonitrile	581.4	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (s, 1H), 8.62 (s, 1H), 8.34 (s, 1H), 8.13 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 8.40 Hz, 3H), 7.51 (d, J = 8.40 Hz, 2H), 5.13 (s, 1H), 4.23 (q, J = 4.80 Hz, 1H), 3.95 (s, 3H), 3.63 (d, J = 14.00	K

1H-pyrazole-4-carbonitrile **(I-1203)**				Hz, 1H), 3.52 (d, J = 13.60 Hz, 1H), 3.23 (t, J = 13.20 Hz, 1H), 2.77-2.71 (m, 2H), 2.68-2.63 (m, 4H), 2.22 (m, 2H), 1.72 (d, J = 13.20 Hz, 1H), 1.02 (s, 3H), 0.69 (s, 3H).	

Table 4.

Compound Name (Cmpd No.)	**Cmpd No.**	**Amine Starting Material**	**Aldehyde/ Other Starting Material**	**MS observed, MH+**	**1H-NMR**	**Synthesis and Purification Method**
1-(6-(4-hydroxy-1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	**I-168**	**INT-S1**	4-(trifluoromethoxy)benzaldehyde	515.3	1H-NMR (400 MHz, DMSO-d6): δ 10.58 (s, 1H), 8.88 (s, 1H), 8.24 (s, 1H), 8.03 (s, 1H), 7.97 (d, J = 8.80 Hz, 1H), 7.90 (d, J = 1.60 Hz, 1H), 7.49 (d, J = 8.40 Hz, 1H), 7.33 (d, J = 8.00 Hz, 1H), 5.07 (s, 1H), 3.96 (t, J = 6.80 Hz, 2H), 3.58 (s, 2H), 3.32 (s, 1H), 2.80 (t, J = 6.80 Hz, 2H), 2.66 (d, J = 11.60 Hz, 2H), 2.14-2.05 (m, 2H), 1.91 (s, 1H), 1.71 (t, J = 12.40 Hz, 2H).	Q
1-(6-(4-hydroxy-1-(3-methoxy-4-(trifluoromethoxy)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	**I-169**	**INT-S1**	3-methoxy-4-(trifluoromethoxy)benzaldehyde	545.4	Tha	C

3-(6-(3,3-diethyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione	**I-1**	**67c**	4-(trifluoromethyl)benzaldehyde	586.7	1H-NMR (400 MHz, DMSO-d6): δ 10.95 (s, 1H), 8.41 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.74-7.71 (m, 3H), 7.60 (d, J = 8.00 Hz, 2H), 5.11 (s, 1H), 4.36-4.32 (m, 1H), 3.57 (q, J = 13.20 Hz, 2H), 3.32 (m, 1H), 2.83 (m, 1H), 2.64-2.52 (m, 6H), 2.39-2.33 (m, 3H), 2.15-2.12 (m, 2H), 1.60 (d, J = 13.60 Hz, 1H), 1.52-1.49 (m, 1H), 1.13-1.09 (m, 2H), 0.55 (t, J = 7.20 Hz, 3H), 0.44 (t, J = 7.60 Hz, 3H).	P
3-(5-fluoro-2-methyl-6-(1,3,3-triethyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, Formic Acid	**I-5**	**67c**	acetaldehyde	456.5	1H-NMR (400 MHz, DMSO-d6): δ 10.95 (s, 1H), 8.22-8.20 (m, 2H), 8.12 (t, J = 8.80 Hz, 1H), 7.73 (d, J = 8.80 Hz, 1H), 5.06 (s, 1H), 4.34 (dd, J = 4.40, 12.60 Hz, 1H), 3.27-3.21 (m, 1H), 2.83 (m, 1H), 2.68-2.61 (m, 5H), 2.53-2.50 (m, 2H), 2.47-2.41 (m, 3H), 2.39-2.33 (m, 1H), 2.21 (d, J = 11.20 Hz, 1H), 2.10 (d, J = 2.40 Hz, 2H), 1.62-1.51 (m, 2H), 1.18-1.16 (m, 1H), 1.06-1.01 (m, 4H), 0.68 (t, J = 7.20 Hz, 3H), 0.50 (t, J = 7.60 Hz, 3H).	P
3-(5-fluoro-2-methyl-6-(1,3,3-triethyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidin	**I-8**	**67c**	acetaldehyde	456.6	1H-NMR (400 MHz, DMSO-d6): δ 10.94 (s, 1H), 8.22-8.20 (m, 2H), 8.11 (t, J = 8.80 Hz, 1H), 7.73 (d, J = 9.20 Hz, 1H), 5.06 (s, 1H), 4.34 (dd, J = 4.80, 12.80 Hz, 1H), 3.27-3.21 (m, 1H),	P

e-2,6-dione, Formic Acid					2.83 (m, 1H), 2.68-2.59 (m, 5H), 2.53-2.50 (m, 2H), 2.46-2.41 (m, 3H), 2.21 (d, J = 11.20 Hz, 1H), 2.13-2.10 (m, 2H), 1.61-1.53 (m, 2H), 1.18-1.16 (m, 1H), 1.06-1.01 (m, 4H), 0.67 (t, J = 7.20 Hz, 3H), 0.49 (t, J = 7.60 Hz, 3H).	
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(3,3,3-trifluoropropyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	**I-199**	**51d**	3,3,3-trifluoropropanal	482.4	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (s, 1H), 8.33 (s, 1H), 8.12-8.07 (m, 1H), 7.84 (d, J = 9.20 Hz, 1H), 5.12 (s, 1H), 4.25-4.20 (m, 1H), 3.09-3.07 (m, 1H), 2.76-2.72 (m, 2H), 2.68-2.51 (m, 5H), 2.51-2.44 (m, 3H), 2.28-2.25 (m, 1H), 2.16-2.12 (m, 1H), 1.76-1.68 (m, 1H), 0.96 (s, 3H), 0.71 (s, 3H),	P
4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)benzonitrile	**I-231**	**51d**	4-formylbenzonitrile	501.12	1H-NMR (400 MHz, DMSO-d6): δ 8.85 (s, 1H), 8.22 (s, 1H), 8.08 (t, J = 8.80 Hz, 1H), 7.85-7.81 (m, 3H), 7.58 (d, J = 8.00 Hz, 2H), 5.15 (s, 1H), 4.25-4.21 (m, 1H), 3.68-3.65 (m, 1H), 3.57-3.54 (m, 1H), 3.19-3.13 (m, 1H), 2.77 (m, 1H), 2.69-2.66 (m, 1H), 2.67-2.64 (m, 2H), 2.50-2.49 (m, 2H), 2.38-2.36 (m, 2H), 1.91 (s, 1H), 1.75-1.74 (m, 1H), 0.96 (s, 3H), 0.66 (s, 3H).	P
3-(5-fluoro-6-(4-hydroxy-3,3-	**I-207**	**51d**	tetrahydro-2H-pyran-4-carbaldehyde	484.1	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.84 (s, 1H), 8.32 (s, 1H), 8.09 (t, J	P

dimethyl-1-((tetrahydro-2H-pyran-4-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione					= 8.80 Hz, 1H), 7.83 (d, J = 9.20 Hz, 1H), 5.07 (s, 1H), 4.25-4.24 (m, 1H), 3.86-3.84 (m, 2H), 3.32-3.25 (m, 2H), 3.14-3.06 (m, 1H), 2.68-2.68 (m, 1H), 2.65-2.62 (m, 2H), 2.35-2.32 (m, 2H), 2.20-2.12 (m, 4H), 1.89 (s, 3H), 1.76 (s, 2H), 1.17-1.13 (m, 2H), 0.97 (s, 3H), 0.70 (s, 3H).	
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(oxetan-3-ylmethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, AcOH	**I-206**	**51d**	oxetane-3-carbaldehyde	456.5	1H-NMR (400 MHz, DMSO-d6): δ10.98 (s, 1H), 8.84 (s, 1H), 8.31 (s, 1H), 8.08 (t, J = 8.80 Hz, 1H), 7.83 (d, J = 8.80 Hz, 1H), 5.09 (s, 1H), 4.69-4.65 (m, 2H), 4.32-4.20 (m, 3H), 3.33-3.19 (m, 3H), 2.68-2.61 (m, 5H), 2.59-2.50 (m, 2H), 2.11-2.09 (m, 2H), 1.86 (s, 3H), 1.67 (d, J = 13.2 Hz, 1H), 0.93 (s, 3H), 0.69 (s, 3H).	P
3-(6-(1-((4,4-difluorocyclohexyl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione	**I-311**	**51d**	4,4-difluorocyclohexane-1-carbaldehyde	518.5	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.84 (s, 1H), 8.32 (s, 1H), 8.10-8.08 (m, 1H), 7.85-7.83 (m, 1H), 5.07 (s, 1H), 4.25-4.21 (m, 1H), 3.32 (m, 1H), 2.68-2.67 (m, 1H), 2.60-2.50 (m, 2H), 2.344-2.37 (m, 1H), 2.22-2.12 (m, 4H), 2.02-1.78 (m, 2H), 1.70-1.55 (m, 8H), 1.16-1.11 (m, 2H), 0.98 (s, 3H), 0.71 (s, 3H).	P

3-(5-fluoro-6-(4-hydroxy-1-isobutyl-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	**I-203**	**51d**	isobutyraldehyde	442.2	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (s, 1H), 8.59 (s, 1H), 8.10-8.08 (m, 1H), 7.84 (d, J = 9.20 Hz, 1H), 4.25-4.21 (m, 1H), 3.13 (m, 1H), 2.80-2.77 (m, 1H), 2.76-2.74 (m, 1H), 2.74-2.72 (m, 2H), 2.37 (s, 2H), 2.16-2.08 (m, 5H), 1.80-1.79 (m, 1H), 1.70-1.69 (m, 1H), 1.00 (s, 3H), 0.85 (s, 6H), 0.71 (s, 3H).	P
3-(6-(1-(cyclopropylmethyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, AcOH	**I-201**	**51d**	cyclopropanecarbaldehyde	440.1	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.84 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 5.06 (s, 1H), 4.25-4.21 (m, 1H), 3.33-3.29 (m, 1H), 2.68-2.63 (m, 2H), 2.56-2.50 (m, 1H), 2.47-2.44 (m, 3H), 2.34-2.32 (m, 4H), 1.86 (s, 3H), 1.69 (d, J = 14.00 Hz, 1H), 0.98-0.95 (m, 3H), 0.86-0.84 (m, 1H), 0.71 (s, 3H), 0.47 (d, J = 1.20 Hz, 2H), 0.10 (d, 2H).	P
3-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)-1H-indole-7-	**I-243**	**51d**	3-formyl-1H-indole-7-carbonitrile	540.3	1H-NMR (400 MHz, DMSO-d6): δ 12.47 (d, J = 2.00 Hz, 1H), 10.99 (s, 1H), 8.88 (s, 1H), 8.36 (s, 1H), 8.29 (d, J = 8.00 Hz, 1H), 8.03 (t, J = 8.80 Hz, 1H), 7.90 (d, J = 2.80 Hz, 2H), 7.73 (d, J = 7.20 Hz, 1H), 7.33 (t, J = 7.60 Hz, 1H), 5.81 (s, 1H), 4.61 (d, J = 3.20 Hz, 2H), 4.26-4.21 (m,	P

carbonitrile, HCl					1H), 3.39-3.36 (m, 1H), 3.28-3.23 (m, 4H), 3.18-3.08 (m, 1H), 2.77-2.67 (m, 1H), 2.64-2.60 (m, 1H), 2.34-2.33 (m, 1H), 2.00-1.98 (m, 1H), 1.07 (s, 3H), 0.76 (s, 3H).	
3-(6-(1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-228**	**51d**	4-chlorobenzaldehyde	510.1	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 8.89 (s, 1H), 8.38 (s, 1H), 8.06 (t, J = 8.80 Hz, 1H), 7.90 (d, J = 8.80 Hz, 1H), 7.71 (d, J = 8.00 Hz, 2H), 7.59 (d, J = 8.40 Hz, 2H), 5.92 (s, 1H), 4.42 (t, J = 7.60 Hz, 1H), 4.26-4.22 (m, 1H), 3.46-3.36 (m, 4H), 3.29-3.23 (m, 1H), 2.92-2.89 (m, 1H), 2.77-2.68 (m, 1H), 2.68-2.64 (m, 1H), 2.63-2.60 (m, 1H), 2.51 (s, 1H), 2.50-2.34 (m, 1H), 2.33-2.33 (m, 1H), 1.06 (s, 3H), 0.78 (s, 3H).	P
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((1-methyl-1H-pyrazol-5-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	**I-235**	**51d**	1-methyl-1H-pyrazole-5-carbaldehyde	480.4	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 9.86 (s, 1H), 8.90 (s, 1H), 8.39 (s, 1H), 8.08 (t, J = 8.80 Hz, 1H), 7.91 (d, J = 9.20 Hz, 1H), 7.55 (s, 1H), 6.67 (s, 1H), 5.94 (s, 1H), 4.56 (d, J = 3.60 Hz, 2H), 4.27-4.23 (m, 1H), 3.97 (s, 3H), 3.61-3.41 (m, 2H), 3.37-3.31 (m, 2H), 3.06-3.03 (m, 1H), 2.77-2.74 (m, 1H), 2.22-2.12 (m, 1H), 2.11-2.01 (m, 1H), 1.11 (s, 3H), 0.81 (s, 3H).	P

3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(2-methylbenzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	**I-317**	**51d**	2-methylbenzaldehyde	490.6	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 9.45 (s, 1H), 8.91 (d, J = 1.60 Hz, 1H), 8.40 (s, 1H), 8.08 (t, J = 8.80 Hz, 1H), 7.92-7.90 (m, 1H), 7.72-7.70 (m, 1H), 7.41-7.32 (m, 3H), 5.94 (s, 1H), 4.46-4.45 (m, 2H), 4.27-4.23 (m, 1H), 3.50-3.31 (m, 3H), 3.01-2.98 (m, 1H), 2.78-2.73 (m, 1H), 2.68-2.60 (m, 1H), 2.54-2.50 (m, 2H), 2.49 (s, 3H), 2.15-2.13 (m, 1H), 2.12-2.00 (m, 1H), 1.10 (s, 3H), 0.78 (s, 3H).	P
3-(5-fluoro-6-(4-hydroxy-1,3,3-trimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	**I-200**	**51d**	paraformaldehyde	400.4	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 9.57 (s, 1H), 8.90 (d, J = 2.00 Hz, 1H), 8.38 (s, 1H), 8.11-8.07 (m, 1H), 7.92-7.90 (m, 1H), 5.94 (s, 1H), 4.27-4.23 (m, 1H), 3.42-3.26 (m, 3H), 3.13-3.11 (m, 1H), 2.84-2.75 (m, 4H), 2.67-2.60 (m, 1H), 2.51-2.48 (m, 2H), 2.16-2.13 (m, 1H), 2.12-2.00 (m, 1H), 1.08 (s, 3H), 0.80 (s, 3H).	P
3-(6-(1-((2-amino-6-(trifluoromethyl)pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-	**I-218**	**51d**	2-amino-6-(trifluoromethyl)nicotinaldehyde	560	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 8.90 (d, J = 2.00 Hz, 1H), 8.39 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 8.03-8.01 (m, 1H), 7.93-7.90 (m, 1H), 7.08 (d, J = 8.00 Hz, 1H), 5.96 (s, 1H), 4.37-4.26 (m, 2H), 4.24-4.23 (m, 1H), 3.46-3.38 (m, 4H), 3.08-3.05 (m,	P

yl)piperidine-2,6-dione					1H), 2.68-2.67 (m, 1H), 2.64-2.60 (m, 1H), 2.14-2.13 (m, 1H), 2.02 (m, 1H), 1.09 (s, 3H), 0.81 (s, 3H).	
3-(6-(1-(4-cyclopropylbenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-101**	**51d**	4-cyclopropylbenzaldehyde	516.5	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 8.90 (s, 1H), 8.39 (s, 1H), 8.04 (t, J = 8.40 Hz, 1H), 7.90 (d, J = 8.80 Hz, 1H), 7.53 (d, J = 8.00 Hz, 2H), 7.19 (d, J = 8.00 Hz, 2H), 5.89 (s, 1H), 4.35-4.22 (m, 3H), 3.66 (s, 3H), 3.37-3.22 (m, 1H), 2.89 (d, J = 8.00 Hz, 1H), 2.71-2.60 (m, 2H), 2.56-2.50 (m, 1H), 2.45-2.33 (m, 1H), 2.31-2.25 (m, 1H), 1.99-1.94 (m, 2H), 1.06 (s, 3H), 1.04 - 0.99 (m, 2H), 0.76(s, 3H), 0.74-0.71 (m, 2H).	P
3-(6-(1-(4-(difluoromethoxy)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione	**I-104**	**51d**	4-(difluoromethoxy)benzaldehyde	542.8	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.09-8.07 (m, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.41 (d, J = 3.20 Hz, 2H), 7.40-7.04 (m, 3H), 5.12 (s, 1H), 4.25-4.21 (m, 1H), 3.58-3.44 (m, 3H), 3.33-3.29 (m, 1H), 2.68-2.67 (m, 2H), 2.64-2.63 (m, 1H), 2.51-2.45 (m, 2H), 2.18-2.16 (m, 2H), 1.72-1.69 (m, 1H), 0.99 (s, 3H), 0.67 (s, 3H).	P
3-(6-(1-benzyl-4-hydroxy-3,3-	**I-210**	**51d**	benzaldehyde	476.2	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (s, 1H), 8.33 (s, 1H), 8.15-	P

dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione					8.12 (m, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.38-7.33 (m, 4H), 7.26 (t, J = 6.40 Hz, 1H), 5.12 (s, 1H), 4.25-4.21 (m, 1H), 3.57-3.49 (m, 1H), 3.45-3.33 (m, 1H), 3.15 (s, 1H), 2.79-2.74 (m, 5H), 2.68-2.64 (m, 1H), 2.18-2.13 (m, 2H), 1.72-1.69 (m, 1H), 1.00 (s, 3H), 0.67 (s, 3H).	
3-(6-(1-(4-cyclopropoxybenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-107**	**51d**	4-cyclopropoxybenzaldehyde	532.5	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 8.90 (s, 1H), 8.38 (s, 1H), 8.06 (t, J = 8.80 Hz, 1H), 7.90 (d, J = 9.20 Hz, 1H), 7.60 (d, J = 8.40 Hz, 2H), 7.16 (d, J = 8.80 Hz, 2H), 5.89 (s, 1H), 4.36-4.32 (m, 3H), 4.27-4.22 (m, 1H), 3.42 (s, 3H), 3.07 (s, 1H), 2.89-2.77 (m, 1H), 2.68-2.64 (m, 1H), 2.51-2.47 (m, 2H), 2.16-2.05 (m, 1H), 2.02-1.99 (m, 1H), 1.07 (s, 3H), 0.82 (s, 2H), 0.77 (s, 3H), 0.68 (s, 3H).	P
3-(6-(1-(4-(difluoromethyl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-256**	**51d**	4-(difluoromethyl)benzaldehyde	526.6	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.89 (s, 1H), 8.37 (s, 1H), 8.06 (t, J = 8.80 Hz, 1H), 7.90 (d, J = 8.80 Hz, 1H), 7.81 (d, J = 8.00 Hz, 2H), 7.75 (d, J = 8.00 Hz, 2H), 7.25-6.98 (m, 1H), 5.92 (s, 1H), 4.49 (s, 2H), 4.26-4.22 (m, 1H), 3.40-3.26 (m, 4H), 2.97-2.93 (m, 1H), 2.77-60 (s, 2H), 2.53-50 (s, 2H), 2.14-2.03 (m, 1H), 2.00-1.92 (m,	P

					1H), 1.06 (s, 3H), 0.78 (s, 3H).	
3-(6-(1-(4-(2H-1,2,3-triazol-2-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-319**	**51d**	4-(2H-1,2,3-triazol-2-yl)benzaldehyde	543.8	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.89 (s, 1H), 8.38 (s, 1H), 8.17 (d, J = 8.40 Hz, 4H), 8.09-8.04 (m, 1H), 7.91-7.86 (m, 3H), 5.93 (s, 1H), 4.51 (t, J = 5.20 Hz, 2H), 4.26-4.22 (m, 1H), 3.40-3.30 (m, 2H), 2.98-2.95 (m, 1H), 2.77-2.73 (m, 1H), 2.64-2.60 (m, 2H), 2.46-2.41 (m, 2H), 2.14-2.10 (m, 1H), 2.04-1.92 (m, 1H), 1.07 (s, 3H), 0.79 (s, 3H). (salt resonance not observed)	P
3-(6-(1-(4-(1H-pyrazol-1-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-110**	**51d**	4-(1H-pyrazol-1-yl)benzaldehyde	542.8	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 8.92 (s, 1H), 8.59 (s, 1H), 8.42 (s, 1H), 8.08 (t, J = 8.80 Hz, 1H), 7.99-7.90 (m, 3H), 7.84-7.80 (m, 3H), 6.60 (s, 1H), 5.91 (s, 1H), 4.47-4.41 (m, 2H), 4.28-4.23 (m, 1H), 3.41 (s, 3H), 3.27-3.24 (m, 1H), 2.92-2.89 (m, 1H), 2.68-2.64 (m, 1H), 2.52-2.51 (m, 1H), 2.48-2.44 (m, 1H), 2.15-2.12 (m, 1H), 2.05-1.98 (m, 1H), 1.09 (s, 3H), 0.78 (s, 3H).	P
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((6-(trifluorome	**I-244**	**51d**	6-(trifluoromethyl)nicotinaldehyde	545	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 10.32 (s, 1H), 9.08 (s, 1H), 8.91-8.90 (m, 1H), 8.50 (d, J = 8.00 Hz, 1H), 8.40 (m, 1H), 8.10-	P

thyl)pyridin-3-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl					8.06 (m, 2H), 7.91 (d, J = 9.20 Hz, 2H), 5.97 (s, 1H), 4.58-4.57 (m, 2H), 4.27-4.23 (m, 1H), 3.51-3.31 (m, 4H), 3.00-2.97 (m, 1H), 2.77-2.67 (m, 1H), 2.64-2.60 (m, 1H), 2.15-2.12 (m, 1H), 2.11-2.00 (m, 1H), 1.10 (s, 3H), 0.89 (s, 3H).	
3-(5-fluoro-6-(4-hydroxy-1-(2-methoxybenzyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	**I-335**	**51d**	2-methoxybenzaldehyde	506.5	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 9.73 (s, 1H), 8.93 (d, J = 1.60 Hz, 1H), 8.43 (s, 1H), 8.08-8.04 (m, 1H), 7.93-7.90 (m, 1H), 7.64-7.62 (m, 1H), 7.53-7.48 (m, 1H), 7.19-7.17 (m, 1H), 7.10-7.06 (m, 1H), 5.98 (s, 1H), 4.37-4.24 (m, 3H), 3.94-3.78 (m, 3H), 3.42-3.20 (m, 4H), 2.97-2.95 (m, 1H), 2.81-2.73 (m, 1H), 2.68-2.60 (m, 1H), 2.68-2.60 (m, 1H), 2.53-2.49 (2H), 2.15-1.97 (m, 2H), 1.10 (s, 3H), 0.77 (s, 3H).	P
3-(6-(1-((1H-pyrazol-4-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-234**	**51d**	1H-pyrazole-4-carbaldehyde	466.1	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 9.81 (s, 1H), 8.92 (d, J = 1.20 Hz, 1H), 8.42-8.42 (m, 1H), 8.09-8.05 (m, 1H), 7.92-7.88 (m, 3H), 5.87 (s, 1H), 4.28-4.17 (m, 3H), 3.38-3.14 (m, 4H), 2.95-2.92 (m, 1H), 2.82-2.81 (m, 1H), 2.79-2.73 (m, 1H), 2.52-2.47 (m, 2H), 2.16-2.14 (m, 1H), 2.12-1.98 (m, 1H),	P

					1.08 (s, 3H), 0.79 (s, 3H).	
3-(5-fluoro-6-(4-hydroxy-1-isobutyl-3,3-dimethylpiperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione, 0.78Formic Acid	**I-293**	**66c**	isobutyraldehyde	454.52 (Negative)	1H-NMR (400 MHz, DMSO-d6): δ 10.95 (s, 1H), 8.36 (s, 1H), 8.21 (d, J = 4.80 Hz, 1H), 8.04 (t, J = 8.40 Hz, 1H), 7.73 (d, J = 8.80 Hz, 1H), 5.02 (s, 1H), 4.35 (dd, J = 4.80, 12.60 Hz, 1H), 3.21 (t, J = 12.80 Hz, 1H), 2.87-2.77 (m, 1H), 2.67-2.59 (m, 5H), 2.60-2.44 (m, 3H), 2.19-2.03 (m, 4H), 1.81-1.77 (m, 1H), 1.66 (d, J = 13.20 Hz, 1H), 0.97-0.88 (m, 9H), 0.69 (s, 3H).	P
3-(6-(1-(4-(difluoromethyl)-3-methoxybenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-113**	**51d**	4-(difluoromethyl)-3-methoxybenzaldehyde	556.6	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 9.96 (s, 1H), 8.90 (d, J = 2.00 Hz, 1H), 8.38 (s, 1H), 8.07 (t, J = 8.80 Hz, 1H), 7.92-7.89 (m, 1H), 7.64-7.61 (m, 2H), 7.35-7.34 (m, 1H), 7.12 (m, 1H), 5.93 (s, 1H), 4.48-4.36 (m, 2H), 4.27-4.22 (m, 1H), 3.81 (s, 3H), 3.45-3.27 (m, 4H), 2.91-2.72 (m, 2H), 2.74-2.51 (m, 2H), 2.14-2.12 (m, 1H), 2.02-1.99 (m, 1H), 1.05 (s, 3H), 0.77 (s, 3H).	P
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(pyridin-3-ylmethyl)piperidin-4-	**I-222**	**51d**	nicotinaldehyde	477.4	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 10.80 (s, 1H), 9.12 (t, J = Hz, 1H), 8.93-8.87,(m, 2H), 8.63 (s, 1H), 8.44 (d, J = Hz, 1H), 8.10 (t, J = 8.80 Hz, 1H),	P

yl)quinolin-3-yl)piperidine-2,6-dione, HCl					7.94-7.88 (m, 2H), 6.01 (s, 1H), 4.59 (s, 2H), 4.28-4.24 (m, 2H), 3.41-3.30 (m, 4H), 2.95 (d, J = 11.60 Hz, 1H), 2.78-2.74 (m, 1H), 2.68-2.64 (m, 1H), 2.15 (d, J = 5.20 Hz, 1H), 2.01 (d, J = 9.20 Hz, 1H), 1.11 (s, 3H), 0.78 (s, 3H).	
3-(6-(1-(4-(2,2-difluoroethoxy)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-116**	**51d**	4-(2,2-difluoroethoxy)benzaldehyde	556.6	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 9.53 (s, 1H), 8.89 (d, J = 1.60 Hz, 1H), 8.37 (m, 1H), 8.05 (t, J = 8.80 Hz, 1H), 7.91-7.89 (m, 1H), 7.62-7.60 (m, 2H), 7.62-7.60 (m, 2H), 6.43-6.41 (m, 1H), 5.89 (s, 1H), 4.36-4.33 (m, 4H), 4.26-4.22 (m, 1H), 3.35 (m, 3H), 3.25-3.19 (m, 1H), 2.91-2.88 (m, 1H), 2.81-2.73 (m, 1H), 2.68-2.48 (m, 2H), 2.14-2.12 (m, 1H), 2.02-1.99 (m, 1H), 1.05 (s, 3H), 0.77 (s, 3H).	P
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	**I-119**	**51d**	4-(trifluoromethoxy)benzaldehyde	560.6	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 10.03 (s, 1H), 8.91 (d, J = 1.20 Hz, 1H), 8.40 (s, 1H), 8.07 (t, J = 8.80 Hz, 1H), 7.92-7.85 (m, 3H), 7.52-7.50 (m, 2H), 5.93 (s, 1H), 4.48-4.42 (m, 2H), 4.27-4.23 (m, 1H), 3.38-3.25 (m, 4H), 2.92-2.89 (m, 1H), 2.78-2.73 (m, 1H), 2.68-2.50 (m, 2H), 2.15-2.12 (m, 1H), 2.11-2.00 (m, 1H),	P

					1.09 (s, 3H), 0.78 (s, 3H).	
5-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)picolinonitrile	**I-247**	**51d**	5-formylpicolinonitrile	502.4	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.75 (s, 1H), 8.33 (s, 1H), 8.12-8.01 (m, 3H), 7.84 (d, J = 8.80 Hz, 1H), 5.17 (s, 1H), 4.23 (dd, J = 4.80, 12.40 Hz, 1H), 3.72 (d, J = 14.40 Hz, 1H), 3.61 (d, J = 14.40 Hz, 1H), 3.16 (t, J = 12.40 Hz, 1H), 2.76-2.63 (m, 5H), 2.15 (d, J = 10.40 Hz, 2H), 1.90 (s, 1H), 1.76-1.70 (m, 1H), 1.00 (s, 3H), 0.68 (s, 3H).	P
6-amino-5-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)picolinonitrile	**I-242**	**51d**	6-amino-5-formylpicolinonitrile	517	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.32 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.85 (d, J = 9.20 Hz, 1H), 7.56-7.54 (m, 1H), 7.13-7.12 (m, 1H), 6.84 (s, 2H), 5.22 (s, 1H), 4.25-4.21 (m, 1H), 3.51-3.43 (m, 2H), 3.17-3.13 (m, 1H), 2.81-2.73 (m, 1H), 2.64-2.60 (m, 2H), 2.52-2.50 (m, 2H), 2.18-2.12 (m, 2H), 1.89-1.71 (m, 1H), 0.97 (s, 3H), 0.70 (s, 3H).	P
3-(6-(1-((1H-pyrrol-2-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-	**I-213**	**51d**	1H-pyrrole-2-carbaldehyde	465.2	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 10.59 (s, 1H), 8.84 (s, 1H), 8.32 (s, 1H), 8.17 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.83 (d, J = 8.80 Hz, 1H), 6.64 (t, J =	P

5-fluoroquinolin-3-yl)piperidine-2,6-dione, 0.68Formic Acid					2.40 Hz, 1H), 5.94 (dd, J = 2.40, 5.40 Hz, 2H), 5.06 (s, 1H), 4.22 (dd, J = 4.80, 12.80 Hz, 1H), 3.46-3.42 (m, 3H), 3.06-3.02 (m, 1H), 2.68-2.64 (m, 3H), 2.42 (d, J = 10.80 Hz, 2H), 2.34-2.33 (m, 2H), 1.68 (d, J = 12.40 Hz, 1H), 0.97 (s, 3H), 0.68 (s, 3H).	
3-(5-fluoro-6-(4-hydroxy-1-(3-methoxy-4-(trifluoromethyl)benzyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	**I-129**	**51d**	3-methoxy-4-(trifluoromethyl)benzaldehyde	574.4	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 10.30 (s, 1H), 8.92 (s, 1H), 8.42 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.82-7.78 (m, 1H), 7.72 (s, 1H), 7.40 (d, J = 8.00 Hz, 1H), 7.40 (d, J = 8.00 Hz, 1H), 5.95 (s, 1H), 4.50 (d, J = 3.20 Hz, 1H), 4.44 (d, J = 6.00 Hz, 1H), 4.27-4.25 (m, 1H), 3.96 (s, 3H), 3.47-3.44 (m, 3H), 3.31-3.28 (m, 1H), 2.86-2.83 (m, 2H), 2.78-2.60 (m, 2H), 2.15 (d, J = 2.80 Hz, 1H), 2.02 (d, J = 12.40 Hz, 1H), 1.11 (s, 3H), 0.78 (s, 3H).	P
3-(5-fluoro-6-(4-hydroxy-1-(4-(isoxazol-3-yl)benzyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	**I-132**	**51d**	Synthesied using 3-(4-(bromomethyl)phenyl)isoxazole using alkylation	543.49	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 9.91 (s, 1H), 9.07 (d, J = 1.60 Hz, 1H), 8.90 (d, J = 1.60 Hz, 1H), 8.40 (s, 1H), 8.09-8.02 (m, 3H), 7.92-7.83 (m, 3H), 7.23 (d, J = 1.60 Hz, 1H), 5.93 (s, 1H), 4.50-4.46 (m, 2H), 4.25 (dd, J = 4.40, 12.60 Hz, 1H), 3.41 (s, 3H), 3.05 (t, J = 11.60 Hz, 1H), 2.93 (d, J = 11.60 Hz, 1H),	J

					2.77-2.68 (m, 1H), 2.67-2.49 (m, 2H), 2.34-2.03 (m, 2H), 1.08 (s, 3H), 0.78 (s, 3H).	
5-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)picolinamide	**I-441**	**51d**	5-formylpicolinonitrile	520.4	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 10.01 (s, 1H), 8.91 (d, J = 10.00 Hz, 2H), 8.38-8.36 (m, 1H), 8.32 (d, J = 6.40 Hz, 1H), 8.30-8.26 (dm, 1H), 8.15 (d, J = 8.00 Hz, 1H), 8.07 (t, J = 8.40 Hz, 1H), 7.90 (d, J = 9.20 Hz, 1H), 7.76 (s, 1H), 5.95 (s, 1H), 4.55 (s, 2H), 4.24 (dd, J = 4.80, 12.80 Hz, 1H), 3.49-3.37 (m, 3H), 2.98 (d, J = 11.60 Hz, 1H), 2.77-2.68 (m, 1H), 2.68-2.64 (m, 1H), 2.60 (s, 1H), 2.33-2.14 (m, 1H), 2.02 (d, J = 12.00 Hz, 1H), 1.08 (s, 3H), 0.79 (s, 3H).	P
5-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)picolinonitrile	**I-274**	**53g**	5-formylpicolinonitrile	530.4	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.83 (d, J = 2.00 Hz, 1H), 8.76 (s, 1H), 8.32 (s, 2H), 8.18 (t, J = 8.80 Hz, 1H), 8.06-8.02 (m, 1H), 7.83 (d, J = 8.80 Hz, 1H), 5.18 (s, 1H), 4.24-4.20 (m, 2H), 3.68-3.57 (m, 2H), 3.33-3.31 (m, 1H), 2.68-2.63 (m, 4H), 2.42-2.33 (m, 2H), 2.16-2.12 (m, 2H), 1.65-1.45 (m, 2H), 1.14-1.11 (m, 2H), 0.53 (t, J = 7.20 Hz, 3H), 0.45 (t, J = 7.60 Hz, 3H).	P

3-(6-(3,3-diethyl-4-hydroxy-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione	**I-268**	**53g**	6-(trifluoromethyl)nicotinaldehyde	573.49	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.83 (d, J = 2.00 Hz, 1H), 8.76 (s, 1H), 8.32 (s, 2H), 8.17 (t, J = 8.80 Hz, 1H), 8.07 (d, J = 8.00 Hz, 1H), 7.91 (d, J = 8.00 Hz, 1H), 7.83 (d, J = 8.80 Hz, 1H), 5.18 (s, 1H), 4.24-4.20 (m, 1H), 3.69-3.58 (m, 2H), 3.34-3.31 (m, 1H), 2.68-2.63 (m, 4H), 2.42-2.33 (m, 2H), 2.16-2.12 (m, 2H), 1.65-1.45 (m, 2H), 1.14-1.11 (m, 2H), 0.53 (t, J = 7.20 Hz, 3H), 0.45 (t, J = 7.60 Hz, 3H).	P
3-(6-(3,3-diethyl-4-hydroxy-1-(4-(isoxazol-3-yl)benzyl)piperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-139**	**53g**	Synthesied using 3-(4-(bromomethyl)phenyl)isoxazole using alkylation	570.8	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 9.81 (s, 1H), 9.07 (d, J = 1.60 Hz, 1H), 8.89 (d, J = 2.40 Hz, 1H), 8.39 (s, 1H), 8.14 (t, J = 8.80 Hz, 1H), 8.04 (d, J = 8.40 Hz, 2H), 7.91 (d, J = 4.80 Hz, 1H), 7.88 (d, J = 3.60 Hz, 2H), 7.24 (d, J = 2.00 Hz, 1H), 5.98 (d, J = Hz, 1H), 4.56-4.21 (m, 3H), 2.96 (t, J = 12.40 Hz, 2H), 2.77-2.64 (m, 3H), 2.23-2.12 (m, 3H), 1.97-1.93 (m, 2H), 1.63-1.60 (m, 2H), 1.17-1.10 (m, 2H), 0.51 (t, J = 7.20 Hz, 3H), 0.43 (t, J = 7.60 Hz, 3H).	J
3-(6-(3,3-diethyl-4-hydroxy-1-((tetrahydro-2H-pyran-	**I-272**	**53g**	tetrahydro-2H-pyran-4-carbaldehyde	512.3	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H) D2O Exachange, 8.90 (s, 1H) D2O Exchange,	P

4-yl)methyl)piperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl					8.90 (s, 1H), 8.39 (s, 1H), 8.17 (t, J = 8.80 Hz, 1H), 7.91 (d, J = 9.20 Hz, 1H), 5.98 (s, 1H) D2O Exchange, 4.27-4.22 (m, 1H), 3.88 (d, J = 11.60 Hz, 2H), 3.68-3.34 (m, 5H), 3.18-3.15 (m, 3H), 3.14-3.05 (m, 1H), 2.78-2.61 (m, 1H), 2.52-2.50 (m, 1H), 2.21-2.13 (m, 3H), 1.91 (d, J = 13.20 Hz, 1H), 1.74-1.65 (m, 3H), 1.34-1.23 (m, 5H), 0.70 (t, J = 7.20 Hz, 3H), 0.53 (t, J = 7.20 Hz, 3H).	
4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-3,3-diethyl-4-hydroxypiperidin-1-yl)methyl)benzonitrile, HCl	**I-265**	**53g**	4-formylbenzonitrile	529.53	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H) D2O Exachange, 10.28 (s, 1H) D2O Exchange, 8.91 (d, J = 1.60 Hz, 1H), 8.42 (s, 1H), 8.16 (t, J = 8.80 Hz, 1H), 8.03-7.90 (m, 5H), 6.00 (s, 1H) D2O Exchange, 4.58-4.43 (m, 2H), 4.27-4.23 (m, 1H), 3.52-3.94 (m, 4H), 3.23-3.17 (m, 1H), 2.75-2.50 (m, 3H), 2.34-2.13 (m, 3H), 1.63-1.59 (m, 1H), 1.17-1.09 (m, 2H), 0.50 (t, J = 7.20 Hz, 3H), 0.42 (t, J = 7.60 Hz, 3H).	G
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((7-(trifluoromethyl)-1H-indol-3-	**I-149**	**51d**	7-(trifluoromethyl)-1H-indole-3-carbaldehyde	583.45	1H-NMR (400 MHz, DMSO-d6): δ 11.93 (d, J = 2.00 Hz, 1H), 10.99 (s, 1H), 9.84 (s, 1H), 8.90 (d, J = 1.60 Hz, 1H), 8.39 (s, 1H), 8.24 (d, J = 8.40 Hz, 1H), 8.03 (t, J = 8.40 Hz, 1H), 7.89 (d, J =	G

yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl					9.20 Hz, 2H), 7.56 (d, J = 7.60 Hz, 1H), 7.33 (t, J = 7.60 Hz, 1H), 5.81 (s, 1H), 4.61 (d, J = 2.80 Hz, 2H), 4.24 (q, J = 4.80 Hz, 1H), 3.60-3.34 (s, 4H), 3.26 (t, J = 11.20 Hz, 1H), 3.09 (d, J = 8.00 Hz, 1H), 2.75 (d, J = 12.80 Hz, 1H), 2.62 (t, J = 14.40 Hz, 1H), 2.13 (q, J = 4.80 Hz, 1H), 1.99 (d, J = 10.40 Hz, 1H), 1.10 (s, 3H), 0.76 (s, 3H).	
3-(6-(1-(4-(1H-1,2,4-triazol-1-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione	**I-354**	**51d**	4-(1H-1,2,4-triazol-1-yl)benzaldehyde	543.52	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 9.28 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.23 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (m, 3H), 7.55 (d, J = 8.40 Hz, 2H), 5.14 (s, 1H), 4.23 (q, J = 4.80 Hz, 1H), 3.65 (d, J = 13.60 Hz, 1H), 3.52 (d, J = 13.60 Hz, 1H), 3.17 (s, 2H), 2.77-2.68 (m, 2H), 2.64 (d, J = 3.20 Hz, 1H), 2.20 (d, J = 10.40 Hz, 2H), 1.74 (q, J = 12.80 Hz, 3H), 1.02 (s, 3H), 0.68 (s, 3H).	Q
3-(6-(3,3-diethyl-4-hydroxy-1-((1-methyl-1H-pyrazol-5-yl)methyl)piperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-164**	**53g**	1-methyl-1H-pyrazole-5-carbaldehyde	508.54	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H) D2O exchanged, 8.90 (s, 1H) D2O exchanged, 8.897 (s, 1H), 8.34 (s, 1H), 8.16 (t, J = 8.80 Hz, 1H), 7.91 (d, J = 9.20 Hz, 1H), 7.55 (d, J = 1.60 Hz, 1H), 6.72 (s, 1H), 5.99 (s, 1H) D2O exchanged, 4.59 (d, J = 4.80 Hz, 2H), 4.27-4.22 (m,	P

					1H), 3.97 (s, 3H), 3.54-3.45 (m, 3H), 3.33-3.25 (m, 1H), 2.95-2.92 (m, 1H), 2.68-2.60 (m, 1H), 2.52-2.40 (m, 2H), 2.20-1.94 (m, 3H), 1.68-1.60 (m, 1H), 1.23-1.17 (m, 2H), 0.57 (t, J = 7.20 Hz, 3H), 0.48 (t, J = 7.60 Hz, 3H).	
3-(6-(1-((7-chloro-1H-indol-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-146**	**51d**	7-chloro-1H-indole-3-carbaldehyde	549.46	1H-NMR (400 MHz, DMSO-d6): δ 11.94 (d, J = 2.00 Hz, 1H), 10.99 (s, 1H), 9.70 (s, 1H), 8.89 (d, J = 1.60 Hz, 1H), 8.37 (s, 1H), 8.02 (t, J = 8.80 Hz, 1H), 7.89-7.83 (m, 3H), 7.29 (d, J = 7.60 Hz, 1H), 7.16 (t, J = 8.00 Hz, 1H), 5.79 (s, 1H), 4.59 (d, J = 12.00 Hz, 2H), 4.26-3.42 (m, 1H), 3.27-3.21 (m, 6H), 3.10-3.07 (m, 2H), 2.14-1.91 (m, 2H), 1.08 (s, 3H), 0.75 (s, 3H).	Q
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((6-oxo-5-(trifluoromethyl)-1,6-dihydropyridin-2-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	**I-262**	**51d**	6-oxo-5-(trifluoromethyl)-1,6-dihydropyridine-2-carbaldehyde	561.4	1H-NMR (400 MHz, DMSO-d6): δ 12.07 (s, 1H), 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.92-7.83 (m, 2H), 6.37 (d, J = 7.20 Hz, 1H), 5.18 (s, 1H), 4.26-4.21 (m, 1H), 3.51-3.38 (m, 2H), 3.21-3.18 (m, 1H), 2.68-2.51 (m, 5H), 2.21-2.12 (m, 2H), 1.79-1.76 (m, 2H), 1.74 (s, 3H), 0.69 (s, 3H).	Q
3-(6-(3,3-diethyl-4-hydroxy-1-isobutylpipe	**I-271**	**53g**	isobutyraldehyde	470.52	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H) D2O Exchange, 8.89 (d, J	P

ridin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl					= 2.00 Hz, 1H), 8.634 (br s, 1H) D2O Exchange, 8.37 (s, 1H), 8.17 (t, J = 8.80 Hz, 1H), 7.91 (d, J = 9.20 Hz, 1H), 5.97 (s, 1H) D2O Exchange, 4.24 (d, J = 7.20 Hz, 1H), 3.43-3.35 (m, 3H), 3.17-3.14 (m, 3H), 3.00-2.90 (m, 1H), 2.83-2.72 (m, 1H), 2.68-2.61 (m, 1H), 2.55-2.33 (m, 3H), 2.16 (d, J = 3.20 Hz, 1H), 1.75-1.62 (m, 1H), 1.28-1.25 (m, 3H), 1.04-0.99 (m, 6H), 0.72 (t, J = 7.20 Hz, 3H), 0.52 (t, J = 7.60 Hz, 3H).	
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((7-methyl-1H-indol-3-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, AcOH	**I-145**	**51d**	7-methyl-1H-indole-3-carbaldehyde	529.5	1H-NMR (400 MHz, DMSO-d6): δ 10.84 (s, 2H), 8.83 (s, 1H), 8.32 (s, 1H), 8.08 (t, J = 8.80 Hz, 1H), 7.82 (d, J = 8.80 Hz, 1H), 7.55 (d, J = 7.60 Hz, 1H), 7.22 (d, J = 2.00 Hz, 1H), 6.93-6.86 (m, 2H), 5.03 (s, 1H), 4.22 (q, J = 4.80 Hz, 1H), 3.66 (s, 2H), 3.09 (s, 2H), 2.72 (d, J = 5.60 Hz, 3H), 2.68-2.62 (m, 1H), 2.58 (d, J = 2.80 Hz, 1H), 2.46 (s, 1H), 2.34 (s, 3H), 2.34-2.27 (m, 1H), 1.72 (d, J = 32.40 Hz, 1H), 0.97 (s, 3H), 0.67 (s, 3H).	Q
3-(6-(1-((4,4-difluorocyclohexyl)methyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-	**I-273**	**53g**	4,4-difluorocyclohexane-1-carbaldehyde	546.3	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.84 (s, 1H), 8.31 (s, 1H), 8.18 (t, J = 8.80 Hz, 1H), 7.83 (d, J = 8.80 Hz, 1H), 5.10 (s, 1H), 4.22 (dd, J = 4.40, 12.60	P

5-fluoroquinolin-3-yl)piperidine-2,6-dione					Hz, 1H), 3.17 (s, 1H), 2.75 (d, J = 14.40 Hz, 1H), 2.68-2.64 (m, 1H), 2.60-2.50 (m, 2H), 2.40-2.33 (m, 1H), 2.15 (t, J = 3.60 Hz, 4H), 2.01 (s, 2H), 1.69-1.53 (m, 8H), 1.20-1.12 (m, 5H), 0.67 (t, J = 7.20 Hz, 3H), 0.49 (t, J = 7.60 Hz, 3H).	
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, AcOH	**I-400**	**51d**	4-(1-methyl-1H-pyrazol-4-yl)benzaldehyde	556.5	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.84 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.10 (t, J = 10.80 Hz, 2H), 7.84 (t, J = 4.80 Hz, 2H), 7.52 (d, J = 8.00 Hz, 2H), 7.33 (d, J = 8.00 Hz, 2H), 5.10 (s, 1H), 4.23 (d, J = 4.80 Hz, 1H), 3.87 (s, 3H), 3.58-3.32 (m, 2H), 3.20-3.11 (m, 1H), 2.72-2.60 (m, 4H), 2.44-2.41 (m, 2H), 2.18-2.13 (m, 2H), 1.86 (s, 3H), 1.70 (d, J = 13.60 Hz, 1H), 1.24 (s, 3H), 0.68 (s, 3H).	Q
3-(6-(3,3-diethyl-4-hydroxy-1-(4-(oxetan-3-yl)benzyl)piperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione	**I-142**	**53g**	4-(oxetan-3-yl)benzaldehyde	560.7	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.83 (s, 1H), 8.17 (t, J = -9.20 Hz, H), 7.83 (d, J = 8.80 Hz, 1H), 7.39-7.34 (m, 4H), 5.12 (s, 1H), 4.96-4.92 (m, 2H), 4.65-4.60 (m, 2H), 4.27-4.20 (m, 2H), 3.52-3.41 (m, 2H), 3.42-3.33 (m, 1H), 2.68-2.63 (m, 3H), 2.51-2.50 (m, 2H), 2.38-2.30 (m, 2H), 2.16-2.14 (m, 2H), 1.86 (s, 1H), 1.76-1.24 (m, 2H), 1.13-	H

					1.09 (m, 2H), 0.56 (t, J = 7.20 Hz, 3H), 0.44 (t, J = 7.60 Hz, 3H).	
3-(5-fluoro-6-((S)-4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	**I-83**	**(S)-51d**	4-(trifluoromethyl)benzaldehyde	544.54	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.72 (d, J = 8.00 Hz, 2H), 7.60 (d, J = 8.00 Hz, 2H), 5.14 (s, 1H), 4.23 (dd, J = 4.40, 12.80 Hz, 1H), 3.69-3.55 (m, 2H), 3.33-3.13 (m, 1H), 2.80-2.68 (m, 3H), 2.64-2.51 (m, 3H), 2.19-2.16 (m, 2H), 1.73-1.70 (m, 1H), 1.02 (s, 3H), 0.68 (s, 3H).	P
3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	**I-84**	**(R)-51d**	4-(trifluoromethyl)benzaldehyde	544.54	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.72 (d, J = 8.00 Hz, 2H), 7.60 (d, J = 8.00 Hz, 2H), 5.15 (s, 1H), 4.23 (q, J = 4.80 Hz, 1H), 3.69-3.55 (m, 2H), 3.17 (t, J = 12.00 Hz, 1H), 2.76-2.51 (m, 6H), 2.34-2.16 (m, 2H), 1.72 (d, J = 12.80 Hz, 1H), 1.02 (s, 3H), 0.68 (s, 3H).	P
3-(6-(1-(4-(1H-imidazol-1-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-	**I-365**	**51d**	4-(1H-imidazol-1-yl)benzaldehyde	542.53	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 10.69 (s, 1H), 9.76 (s, 1H), 8.90 (s, 1H), 8.38 (t, J = 12.40 Hz, 2H), 8.09-8.04 (m, 3H), 7.97-7.89 (m, 4H), 5.95 (s, 1H), 4.55-4.42 (m,	P

fluoroquinolin-3-yl)piperidine-2,6-dione, HCl					2H), 4.26-4.22 (m, 1H), 3.28-2.73 (m, 3H), 2.83-2.64 (m, 5H), 2.50-2.13 (m, 2H), 1.10 (s, 3H), 0.77 (s, 3H).	
3-(6-(1-(4-(1H-imidazol-1-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-364**	**51d**	4-(1H-imidazol-1-yl)benzaldehyde	542.53	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 10.32 (s, 1H), 9.54 (s, 1H), 8.89 (d, J = 1.60 Hz, 1H), 8.37 (s, 1H), 8.28 (s, 1H), 8.08-8.00 (m, 7H), 5.93 (s, 1H), 4.55-4.46 (m, 2H), 4.26-4.22 (m, 1H), 3.42-2.88 (m, 2H), 2.88-2.85 (m, 1H), 2.77-2.74 (m, 1H), 2.68-2.68 (m, 1H), 2.60-2.51 (m, 3H), 2.14-2.02 (m, 2H), 1.10 (s, 3H), 0.77 (s, 3H).	P
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(oxazol-2-yl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	**I-366**	**51d**	4-(oxazol-2-yl)benzaldehyde	543.55	1H-NMR (400 MHz, DMSO-d6): δ 11.01 (s, 1H), 10.21 (s, 1H), 8.94 (s, 1H), 8.45 (s, 1H), 8.29 (d, J = 0.40 Hz, 1H), 8.09 (m, 3H), 7.94-7.87 (m, 3H), 7.44 (d, J = 0.80 Hz, 1H), 5.95 (s, 1H), 4.54-4.23 (m, 3H), 3.31-3.25 (m, 4H), 2.90-2.73 (m, 2H), 2.66-2.43 (m, 2H), 2.25-2.00 (m, 2H), 1.10 (s, 3H), 0.77 (s, 3H).	P
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(thiazol-2-yl)benzyl)piperidin-4-yl)quinolin-3-	**I-394**	**51d**	4-(thiazol-2-yl)benzaldehyde	559.53	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 10.12 (s, 1H), 8.93 (s, 1H), 8.44 (s, 1H), 8.09 (t, J = 8.00 Hz, 3H), 7.99 (d, J = 3.20 Hz, 1H), 7.92 (d, J = 8.80 Hz, 1H), 7.87-7.83 (m, 3H), 5.94 (s, 1H), 4.53-4.49 (m, 3H), 3.42	P

yl)piperidine-2,6-dione, HCl					(m, 3H), 3.32-3.26 (m, 1H), 2.93-2.74 (m, 2H), 2.68-2.49 (m, 2H), 2.15-2.01 (m, 2H), 1.10 (s, 3H), 0.78 (s, 3H).	
3-(6-(1-(3-(1H-pyrazol-1-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-351**	**51d**	3-(1H-pyrazol-1-yl)benzaldehyde ALD-16	542.56	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 9.87 (s, 1H), 8.89 (d, J = 1.60 Hz, 1H), 8.55 (d, J = 2.40 Hz, 1H), 8.38 (s, 1H), 8.29 (s, 1H), 8.07 (t, J = 8.80 Hz, 1H), 7.97-7.89 (m, 2H), 7.81 (d, J = 1.60 Hz, 1H), 7.81 (t, J = 1.60 Hz, 2H), 6.61 (t, J = 2.00 Hz, 1H), 5.92 (s, 1H), 4.50-4.46 (m, 2H), 4.27-4.22 (m, 1H), 3.41-3.29 (m, 4H), 2.98-2.72 (m, 2H), 2.65-2.49 (m, 2H), 2.14-2.01 (m, 2H), 1.09 (s, 3H), 0.79 (s, 3H).	P
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(4-methylthiazol-5-yl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	**I-357**	**51d**	4-(4-methylthiazol-5-yl)benzaldehyde	573.52	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 9.00 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.48-7.45 (m, 4H), 5.14 (s, 1H), 4.23 (dd, J = 4.40, 12.60 Hz, 1H), 3.63-3.51 (m, 2H), 3.06 (m, 1H), 2.80-2.74 (m, 4H), 2.52 (s, 3H), 2.23 (d, J = 10.40 Hz, 2H), 2.16-2.14 (m, 1H), 1.89 (s, 2H), 1.03 (s, 3H), 0.69 (s, 3H).	P
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-	**I-403**	**51d**	4-(thiazol-5-yl)benzaldehyde	559.53	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 10.08 (s, 1H), 9.15 (s, 1H), 8.91 (d, J = 1.60 Hz, 1H),	P

(4-(thiazol-5-yl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl					8.42 (d, J = 10.00 Hz, 2H), 8.07 (t, J = 8.80 Hz, 1H), 7.91 (d, J = 9.20 Hz, 1H), 7.85-7.77 (m, 4H), 5.92 (s, 1H), 4.49-4.42 (m, 2H), 4.27-4.23 (m, 1H), 3.46-3.30 (m, 5H), 2.90 (d, J = 12.00 Hz, 1H), 2.77-2.73 (m, 1H), 2.68-2.64 (m, 1H), 2.15-2.12 (m, 1H), 2.02 (d, J = 11.60 Hz, 1H), 1.09 (s, 3H), 0.78 (s, 3H).	
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(pyridazin-3-yl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	**I-360**	**51d**	4-(pyridazin-3-yl)benzaldehyde	554.54	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 9.21 (d, J = 1.60 Hz, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.34 (s, 1H), 8.26 (d, J = 1.20 Hz, 1H), 8.14-8.08 (m, 3H), 7.86-7.77 (m, 2H), 7.57 (d, J = 8.00 Hz, 2H), 5.16 (s, 1H), 4.26-4.21 (m, 1H), 3.68-3.33 (m, 2H), 3.22-3.16 (m, 2H), 2.81-2.60 (m, 7H), 2.33-2.12 (m, 2H), 1.76-1.24 (m, 1H), 1.04 (s, 1H), 0.70 (s, 3H).	P
3-(6-(1-(4-(1,3,4-oxadiazol-2-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione	**I-387**	**51d**	4-(1,3,4-oxadiazol-2-yl)benzaldehyde	544.54	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 9.34 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.34 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 8.02 (d, J = 8.40 Hz, 2H), 7.84 (d, J = 8.80 Hz, 1H), 7.61 (d, J = 8.40 Hz, 2H), 5.15 (s, 1H), 4.26-4.21 (m, 1H), 3.70-3.55 (m, 2H), 3.21-3.18 (m, 1H), 2.73-2.63 (m, 4H), 2.51-2.50 (m, 2H), 2.34-	P

					2.18 (m, 2H), 1.84-1.71 (m, 1H), 1.026 (s, 3H), 0.683 (s, 3H).	
3-(5-fluoro-6-(4-hydroxy-1-(isoxazol-5-ylmethyl)-3,3-dimethylpiperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione	**I-433**	**66c**	isoxazole-5-carbaldehyde	481.5	1H-NMR (400 MHz, DMSO-d6): δ 10.94 (s, 1H), 8.52 (s, 1H), 8.21 (d, J = 6.00 Hz, 1H), 8.02 (t, J = 8.80 Hz, 1H), 7.74 (d, J = 9.20 Hz, 1H), 6.41 (s, 1H), 5.08 (d, J = 3.60 Hz, 1H), 4.35 (dd, J = 4.80, 12.60 Hz, 1H), 3.75 (d, J = 1.60 Hz, 2H), 3.22 (m, 1H), 2.85-2.82 (m, 1H), 2.75-2.62 (m, 5H), 2.60-2.49 (m, 3H), 2.19-2.11 (m, 2H), 1.75-1.71 (m, 1H), 0.97 (s, 3H), 0.68 s, 3H).	P
3-(6-(1-(4-(1H-benzo[d]imidazol-1-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-455**	**51d**	4-(1H-benzo[d]imidazol-1-yl)benzaldehyde ALD-13	592.59	1H-NMR (400 MHz, DMSO-d6): δ 11.01 (s, 1H), 10.54 (s, 1H), 9.39 (s, 1H), 8.93 (s, 1H), 8.44 (d, J = 2.40 Hz, 1H), 8.09 (t, J = 8.40 Hz, 3H), 7.94-7.90 (m, 4H), 7.80 (d, J = 2.80 Hz, 1H), 7.55-7.53 (m, 2H), 6.01 (s, 1H), 4.60-4.47 (m, 2H), 4.28-4.24 (m, 2H), 3.52-3.31 (m, 4H), 2.91-2.65 (m, 3H), 2.16-2.03 (m, 2H), 1.24 (s, 3H), 0.80 (s, 3H).	P
3-(6-(1-(4-(3,5-dimethylisoxazol-4-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinol	**I-342**	**51d**	4-(3,5-dimethylisoxazol-4-yl)benzaldehyde	569.56	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.11 (t, J = 9.20 Hz, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.47 (d, J = 8.00 Hz, 2H), 7.37 (d, J = 8.00 Hz, 2H), 5.14 (s, 1H), 4.25-4.21 (m, 1H),	P

in-3-yl)piperidine-2,6-dione					3.62-3.33 (m, 2H), 3.20-3.17 (m, 1H), 2.76-2.54 (m, 7H), 2.42 (s, 3H), 2.35-2.32 (m, 4H), 1.72 (d, J = 14.40 Hz, 1H), 1.03 (s, 3H), 0.70 (s, 3H).	
3-(6-(1-(3-(1H-imidazol-1-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione	**I-369**	**51d**	3-(1H-imidazol-1-yl)benzaldehyde ALD-17	542.56	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.25 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.74 (s, 1H), 7.62 (s, 1H), 7.54-7.48 (m, 2H), 7.39 (d, J = 7.20 Hz, 1H), 7.12 (s, 1H), 5.15 (s, 1H), 4.25-4.21 (m, 1H), 3.70-3.57 (m, 2H), 3.21-3.15 (m, 1H), 2.80-2.60 (m, 4H), 2.51-2.47 (m, 2H), 2.24-2.12 (m, 2H), 1.75-1.71 (m, 1H), 1.02 (s, 3H), 0.68 (s, 3H).	P
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(thiazol-4-yl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	**I-372**	**51d**	4-(thiazol-4-yl)benzaldehyde	559.8	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 9.90 (s, 1H), 9.25 (d, J = 2.00 Hz, 1H), 8.90 (d, J = 1.60 Hz, 1H), 8.40 (s, 1H), 8.29 (d, J = 2.00 Hz, 1H), 8.13-8.04 (m, 3H), 7.90 (d, J = 8.80 Hz, 1H), 7.76 (d, J = 8.40 Hz, 2H), 5.92 (s, 1H), 4.44-4.36 (m, 2H), 4.27-4.22 (m, 1H), 3.41-3.25 (m, 4H), 2.93 (d, J = 8.00 Hz, 1H), 2.80-2.48(m, 3H), 2.15-2.00 (m, 2H), 1.09 (s, 3H), 0.78 (s, 3H).	P

3-(6-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-3,3-diethyl-4-hydroxypiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-535**	**53g**	4-(1,2,4-oxadiazol-3-yl)benzaldehyde	570.62	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 10.05 (s, 1H), 9.78 (s, 1H), 8.91 (s, 1H), 8.41 (s, 1H), 8.18-8.13 (m, 3H), 8.01-7.97 (m, 2H), 7.92-7.90 (m, 1H), 5.99 (s, 1H), 4.59-4.45 (m, 2H), 4.27-4.22 (m, 1H), 3.49-3.42 (m, 3H), 3.25-3.19 (m, 1H), 2.84-2.77 (m, 2H), 2.68-2.48 (m, 2H), 2.16-2.12 (m, 2H), 1.97-1.93 (m, 1H), 1.64-1.61 (m, 1H), 1.18-1.11 (m, 2H), 0.52-0.40 (m, 6H).	P
3-(6-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione, HCl	**I-526**	**51d**	4-(1,2,4-oxadiazol-3-yl)benzaldehyde	558.4	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 10.32 (s, 1H), 9.78 (d, J = Hz, 1H), 8.52 (d, J = 4.80 Hz, 1H), 8.17-8.10 (m, 3H), 7.93 (d, J = 7.60 Hz, 3H), 5.97 (s, 1H), 4.55-4.40 (m, 3H), 3.42 (s, sH), 3.32-3.25 (m, 1H), 2.90-2.83 (m, 3H), 2.79 (s, 3H), 2.68-2.49 (m, 2H), 2.14-2.00 (m, 2H), 1.09 (s, 3H), 0.76 (s, 3H).	P
3-(6-(1-((1,4-dimethyl-1H-pyrazol-5-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidin	**I-799**	**51d**	1,4-dimethyl-1H-pyrazole-5-carbaldehyde	508.6	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 9.78 (s, 1H), 8.44 (d, J = 5.20 Hz, 1H), 8.10 (t, J = 8.40 Hz, 1H), 7.91 (d, J = 9.20 Hz, 1H), 7.41 (s, 1H), 5.94 (s, 1H), 4.56-4.39 (m, 3H), 3.89 (s, 3H), 3.38-3.20 (m, 5H), 2.84-2.54 (m, 6H), 2.05-1.98 (m, 5H), 1.10 (s, 3H), 0.81 (s, 3H).	P

e-2,6-dione, HCl						
3-(6-(1-(4-(1,3-dimethyl-1H-pyrazol-4-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-345**	**51d**	4-(1,3-dimethyl-1H-pyrazol-4-yl)benzaldehyde ALD-55	570.58	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.10 (t, J = 8.40 Hz, 1H), 7.87-7.83 (m, 2H), 7.38 (q, J = 8.40 Hz, 4H), 5.12 (s, 1H), 4.25-4.21 (m, 1H), 3.79 (s, 3H), 3.79-3.33 (m, 2H), 3.18-3.15 (m, 1H), 2.68 (s, 3H), 2.50-2.47 (m, 2H), 2.34 (s, 3H), 2.23-2.21 (m, 2H), 1.84 (m, 2H), 1.02 (s, 3H), 0.35 (s, 3H). (resonance for salt not observed)	P
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)methyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione, HCl	**I-820**	**66c**	1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carbaldehyde	560.58	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 10.15 (s, 1H), 8.36 (d, J = 6.40 Hz, 1H), 8.07 (t, J = 8.40 Hz, 1H), 7.86 (d, J = 9.20 Hz, 1H), 7.19 (s, 1H), 5.94 (s, 1H), 4.61 (d, J = 4.00 Hz, 2H), 4.39 (dd, J = 4.80, 13.00 Hz, 1H), 4.37 (s, 3H), 3.46 (s, 2H), 3.37 (t, J = 11.20 Hz, 2H), 3.12 (d, J = 11.60 Hz, 1H), 2.83 (t, J = 8.00 Hz, 1H), 2.68 (s, 3H), 2.58-2.51 (m, 2H), 2.12 (d, J = 7.60 Hz, 1H), 2.10 (s, 1H), 1.10 (s, 3H), 1.09 (s, 3H).	P
3-(6-(1-((1H-pyrazol-5-yl)methyl)-4-hydroxy-3,3-	**I-432**	**66c**	1H-pyrazole-5-carbaldehyde	480.7	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 9.98 (s, 1H), 8.47 (d, J = 6.00 Hz, 1H), 8.09 (t, J = 8.40 Hz, 1H), 7.93-7.85	P

dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione, HCl					(m, 2H), 6.57 (d, J = 2.00 Hz, 1H), 5.88 (s, 1H), 4.43-4.38 (m, 4H), 3.91 (s, 3H), 3.30 (t, J = 12.00 Hz, 1H), 3.00 (d, J = 12.4 Hz, 1H), 2.85-2.77 (m, 4H), 2.67-2.60 (m, 2H), 2.14-2.11 (m, 1H), 1.99 (d, J = 9.60 Hz, 1H), 1.07 (s, 3H), 0.76 (s, 3H).	
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione, HCl	**I-777**	**66c**	1-methyl-1H-pyrazole-3-carbaldehyde	494.5	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 9.93 (s, 1H), 8.41-8.39 (m, 1H), 8.06 (t, J = 8.40 Hz, 1H), 7.89-7.81 (m, 2H), 6.55 (s, 1H), 5.86 (s, 1H), 4.40 (dd, J = 4.80, 12.60 Hz, 1H), 4.33-4.31 (m, 2H), 3.90 (s, 3H), 3.36 (s, 3H), 3.24 (t, J = 11.60 Hz, 1H), 3.01-2.98 (m, 1H), 2.84-2.80 (m, 1H), 2.74 (s, 3H), 2.68-2.58 (m, 2H), 2.13-2.00 (m, 2H), 1.07 (s, 3H), 0.76 (s, 3H).	P
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione, HCl	**I-155**	**66c**	6-(trifluoromethyl)nicotinaldehyde	557.55 (Negative)	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 9.07 (s, 1H), 8.50 (d, J = 8.00 Hz, 1H), 8.43 (d, J = Hz, 1H), 8.12-8.07 (m, 2H), 7.89 (d, J = 8.80 Hz, 1H), 5.97 (s, 1H), 4.57 (d, J = 3.60 Hz, 2H), 4.41 (q, J = 8.40 Hz, 1H), 3.55-3.31 (m, 4H), 2.99 (d, J = 10.80 Hz, 1H), 2.85-2.75 (m, 4H), 2.68-2.61 (m, 2H), 2.13-2.10 (m, 1H), 2.08-2.04 (m, 1H), 1.08 (s, 3H), 0.79 (s, 1H).	P

3-(6-(1-((1,3-dimethyl-1H-pyrazol-5-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione, HCl	**I-632**	**66c**	1,3-dimethyl-1H-pyrazole-5-carbaldehyde	508.54	1H-NMR (400 MHz, DMSO-d6): δ 11.02 (s, 1H), 10.38 (s, 1H), 8.61 (d, J = 6.40 Hz, 1H), 8.17 (t, J = 8.40 Hz, 1H), 8.01 (d, J = 8.80 Hz, 1H), 6.47 (s, 1H), 5.99 (s, 1H), 4.55-4.43 (m, 3H), 4.05 (s, 3H), 3.42 (s, 3H), 3.27 (t, J = 11.20 Hz, 1H), 3.00 (d, J = 11.60 Hz, 1H), 2.88-2.76 (m, 4H), 2.62-2.56 (m, 2H), 2.14-2.01 (m, 5H), 1.11 (s, 3H), 0.79 (s, 3H).	P
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((1-methyl-1H-pyrazol-4-yl)methyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione, HCl	**I-697**	**66c**	1-methyl-1H-pyrazole-4-carbaldehyde	494.6	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 9.82 (s, 1H), 8.45 (d, J = 6.40 Hz, 1H), 8.09 (t, J = 8.40 Hz, 1H), 7.96-7.90 (m, 2H), 7.66 (s, 1H), 5.89 (s, 1H), 4.43 (d, J = 3.60 Hz, 1H), 4.23-3.85 (m, 5H), 3.26-3.14 (m, 4H), 2.68-2.61 (m, 7H), 2.13-1.97 (m, 2H), 1.00 (s, 3H), 0.78 (s, 3H),	P
3-(6-(1-((3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione, HCl	**I-749**	**66c**	3-cyclopropyl-1-methyl-1H-pyrazole-5-carbaldehyde **ALD-44**	534.58	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 10.10 (s, 1H), 8.48 (s, 1H), 8.06 (t, J = 8.40 Hz, 1H), 7.93 (d, J = 8.80 Hz, 1H), 6.38 (s, 1H), 5.95 (s, 1H), 4.45-4.40 (m, 2H), 3.93 (s, 3H), 3.37-3.40 (m, 3H), 3.08-3.04 (m, 1H), 2.78-2.68 (m, 1H), 2.68-2.66 (m, 4H), 2.65-2.51 (m, 3H), 2.15-1.86 (m, 3H), 1.09 (s, 3H), 0.89-0.85 (m, 2H), 0.80 (s,	P

					3H), 0.67-0.63 (m, 2H).	
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(pyridin-2-ylmethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	**I-221**	**51d**	picolinaldehyde	477.52	1H-NMR (400 MHz, DMSO-d6): δ 11.02 (s, 1H), 10.23 (s, 1H), 9.00 (t, J = 2.00 Hz, 1H), 8.74 (t, J = 4.00 Hz, 1H), 8.54 (s, 1H), 8.14 (t, J = 8.80 Hz, 1H), 8.02-7.96 (m, 2H), 7.74 (d, J = 8.00 Hz, 1H), 7.56-7.41 (m, 1H), 6.03 (s, 1H), 4.57 (s, 2H), 4.53-4.42 (m, 2H), 3.51-3.34 (m, 3H), 2.99 (d, J = 12.00 Hz, 1H), 2.79-2.75 (m, 1H), 2.66-2.61 (m, 1H), 2.17-2.16 (m, 1H), 2.15-2.03 (m, 1H), 1.13 (s, 3H), 0.76 (s, 3H).	P
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(pyridin-4-ylmethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	**I-225**	**51d**	isonicotinaldehyde	477.49	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 10.85 (s, 1H), 8.92-8.80 (m, 3H), 8.42 (s, 1H), 8.11-8.09 (m, 3H), 7.92 (d, J = 8.80 Hz, 1H), 5.99 (s, 1H), 4.62-4.55 (m, 2H), 4.28-4.25 (m, 2H), 3.46-3.40 (m, 3H), 3.32 (t, J = 11.20 Hz, 1H), 2.84-2.75 (m, 2H), 2.74-2.65 (m, 1H), 2.34-2.33 (m, 1H), 2.15-2.01 (m, 1H), 1.12 (s, 3H), 0.76 (s, 3H).	P
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((1-methyl-1H-imidazol-5-	**I-793**	**66c**	1-methyl-1H-imidazole-5-carbaldehyde	494.6	1H-NMR (400 MHz, DMSO-d6): δ 11.14 (s, 1H), 11.00 (s, 1H), 9.23 (s, 1H), 8.52 (s, 1H), 8.15-8.11 (m, 2H), 7.96 (s, 1H), 6.02 (s, 1H), 4.56 (s, 2H), 4.45-4.42 (m,	P

yl)methyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione, HCl					1H), 3.84 (s, 3H), 3.58 (s, 3H), 3.47-3.34 (m, 1H), 3.12 (d, J = 11.60 Hz, 1H), 2.93-2.80 (m, 4H), 2.68-2.51 (m, 2H), 2.14-2.11 (m, 1H), 2.03-2.01 (m, 1H), 1.24 (s, 3H), 0.80 (s, 3H).	
3-(6-(1-((1,4-dimethyl-1H-pyrazol-5-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-858**	**51d**	1,4-dimethyl-1H-pyrazole-5-carbaldehyde	494.55	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 9.64 (s, 1H), 8.91 (s, 1H), 8.39 (s, 1H), 8.07 (t, J = 8.80 Hz, 1H), 7.91 (d, J = 9.20 Hz, 1H), 7.41 (s, 1H), 5.93 (s, 1H), 4.54 (q, J = 4.80 Hz, 2H), 4.25 (d, J = 4.80 Hz, 1H), 3.95 (s, 3H), 3.39-3.21 (m, 5H), 2.77-2.73 (m, 1H), 2.65 (t, J = 2.00 Hz, 1H), 2.51-2.48 (m, 1H), 2.14-2.11 (m, 4H), 2.04-2.02 (m, 1H), 1.12 (s, 3H), 0.83 (s, 3H).	P
3-(6-(1-(3-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-348**	**51d**	3-(1,2,4-oxadiazol-3-yl)benzaldehyde ALD-43	544.54	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 9.80 (s, 2H), 8.92 (d, J = 1.60 Hz, 1H), 8.39 (s, 2H), 8.17 (d, J = 8.00 Hz, 1H), 8.07 (d, J = 8.80 Hz, 1H), 7.95-7.90 (m, 2H), 7.73 (t, J = 7.60 Hz, 1H), 5.94 (s, 1H), 4.56 (d, J = 4.00 Hz, 2H), 4.27-4.22 (m, 1H), 3.72-3.40 (m, 4H), 3.01-2.98 (m, 1H), 2.78-2.51 (m, 3H), 2.14-2.00 (m, 2H), 1.08 (s, 3H), 0.79 (s, 3H).	P
1-(6-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-	**I-337**	**INT-S2**	4-(1,2,4-oxadiazol-3-yl)benzalde	545.53	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 9.71 (s, 1H), 8.97 (s, 1H), 8.33 (s,	P

4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione			hyde ALD-107		1H), 8.09 (t, J = 8.80 Hz, 1H), 8.03 (d, J = 8.00 Hz, 2H), 7.85 (d, J = 8.80 Hz, 1H), 7.58 (d, J = 8.00 Hz, 2H), 5.16 (s, 1H), 4.01 (t, J = 7.20 Hz, 2H), 3.67 (d, J = 14.00 Hz, 1H), 3.55 (d, J = 14.00 Hz, 1H), 3.32 (s, 1H), 2.80 (t, J = 6.80 Hz, 2H), 2.71-2.67 (m, 1H), 2.62-2.59 (m, 2H), 2.20 (d, J = 10.40 Hz, 1H), 1.74 (d, J = 13.60 Hz, 1H), 1.03 (s, 3H), 0.69 (s, 3H).	
3-(6-(1-((1,3-dimethyl-1H-pyrazol-5-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione	**I-796**	**51d**	1,3-dimethyl-1H-pyrazole-5-carbaldehyde	492.53	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (s, 1H), 8.32 (s, 1H), 8.11-8.07 (m, 1H), 7.84 (d, J = 8.80 Hz, 1H), 5.93 (s, 1H), 5.14 (s, 1H), 4.23 (q, J = 4.80 Hz, 1H), 3.77 (s, 3H), 3.46 (s, 2H), 3.12-3.05 (m, 1H), 2.80-2.59 (m, 4H), 2.51-2.47 (m, 2H), 2.20-1.96 (m, 5H), 1.69 (d, J = 13.60 Hz, 1H), 0.96 (s, 3H), 0.70 (s, 3H).	P
3-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)-1H-indole-7-carbonitrile	**I-538**	**66c**	3-formyl-1H-indole-7-carbonitrile	554.4	1H-NMR (400 MHz, DMSO-d6): δ 11.49 (s, 1H), 10.94 (s, 1H), 8.23 (t, J = 5.60 Hz, 2H), 8.03 (t, J = 8.80 Hz, 1H), 7.73 (d, J = 9.20 Hz, 1H), 7.53 (d, J = 8.40 Hz, 1H), 7.46-7.42 (m, 2H), 5.02 (d, J = 4.40 Hz, 1H), 4.34 (dd, J = 4.40, 12.40 Hz, 1H), 3.70 (s, 2H), 3.13 (s, 1H), 2.84 (d, J = 13.20 Hz, 2H), 2.75 (t, J = 9.60 Hz, 5H),	M

					2.25 (d, J = 10.40 Hz, 1H), 2.10 (d, J = 14.80 Hz, 1H), 1.86 (s, 2H), 1.76 (s, 1H), 0.95 (d, J = 3.20 Hz, 3H), 0.66 (s, 3H).	
3-(6-(1-(4-(4-acetylpiperazin-1-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione	**I-438**	**51d**	4-(4-acetylpiperazin-1-yl)benzaldehyde	602.63	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.86 (s, 1H), 8.34 (s, 1H), 8.07 (t, J = 8.40 Hz, 1H), 7.86 (d, J = 8.80 Hz, 1H), 7.40-7.29 (m, 2H), 6.98-6.95 (m, 2H), 5.08 (s, 1H), 4.23 (q, J = 4.80 Hz, 1H), 3.68-3.58 (m, 4H), 3.37-3.32 (m, 2H), 3.19-3.13 (m, 6H), 2.78-2.59 (m, 5H), 2.48-2.33 (m, 2H), 2.15-2.12 (m, 1H), 2.05 (s, 3H), 1.00 (s, 3H), 0.71 (s, 3H).	P
3-(5-fluoro-6-(4-hydroxy-1-(isoxazol-5-ylmethyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	**I-832**	**51d**	isoxazole-5-carbaldehyde	467.3	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.53 (d, J = 1.20 Hz, 1H), 8.33 (s, 1H), 8.08 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 6.42 (d, J = 1.60 Hz, 1H), 5.13 (s, 1H), 4.23 (q, J = 4.80 Hz, 1H), 3.76 (s, 2H), 3.33-3.13 (m, 1H), 2.78-2.59 (m, 6H), 2.46-2.20 (m, 2H), 1.72-1.24 (m, 1H), 0.98 (s, 3H), 0.69 (s, 3H).	P
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((1-methyl-1H-imidazol-5-yl)methyl)pi	**I-847**	**51d**	1-methyl-1H-imidazole-5-carbaldehyde	480.52	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (s, 1H), 8.31 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.93 (s, 1H), 7.85 (d, J = 9.20 Hz, 1H), 7.01 (s, 1H), 5.22 (s, 1H), 4.25-4.20 (m, 1H),	P

peridin-4-yl)quinolin-3-yl)piperidine-2,6-dione					3.75 (s, 3H), 3.57-3.33 (s, 4H), 3.12-3.06 (m, 1H), 2.80-2.72 (m, 2H), 2.64-2.47 (m, 2H), 2.34-2.11 (m, 2H), 1.75-1.71 (m, 1H), 0.95 (s, 3H), 0.71 (s, 3H).	
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((1-methyl-3-phenyl-1H-pyrazol-5-yl)methyl)piperidin-4-yl)-2-methylquinolin-3-yl)piperidine-2,6-dione	**I-635**	**66c**	1-methyl-3-phenyl-1H-pyrazole-5-carbaldehyde	570.68	1H-NMR (400 MHz, DMSO-d6): δ 10.95 (s, 1H), 8.20 (d, J = 4.00 Hz, 1H), 8.04 (t, J = 8.80 Hz, 1H), 7.79-7.73 (m, 3H), 7.39 (t, J = 7.60 Hz, 2H), 7.27 (t, J = 7.20 Hz, 1H), 6.63 (s, 1H), 5.12 (s, 1H), 4.37-4.33 (m, 1H), 3.92 (s, 3H), 3.57 (s, 2H), 3.10 (s, 1H), 2.82 (d, J = 4.40 Hz, 1H), 2.65 (d, J = 12.40 Hz, 5H), 2.65 (s, 2H), 2.34 (t, J = 1.60 Hz, 1H), 2.11 (t, J = 4.80 Hz, 1H), 1.70 (d, J = 13.20 Hz, 1H), 1.02 (s, 4H), 0.70 (s, 3H).	P
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(thiazol-2-ylamino)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, 0.61AcOH	**I-415**	**51d**	4-(thiazol-2-ylamino)benzaldehyde	574.51	1H-NMR (400 MHz, DMSO-d6): δ 12.00 (bs, 1H), 10.98 (s, 1H), 10.13 (s, 1H), 8.84 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.59 (d, J = 8.40 Hz, 2H), 7.26-7.24 (m, 3H), 6.89-6.88 (m, 1H), 5.09 (s, 1H), 4.25-4.21 (m, 1H), 3.53-3.137 (m, 2H), 3.19 (t, J = 12.40 Hz, 1H), 2.76-2.59 (m, 3H), 2.49-2.33 (m, 2H), 2.20-2.12 (m, 2H), 1.91 (s, 3H), 1.72 (t, J = 12.40 Hz, 1H), 0.99 (s, 3H), 0.67 (s, 3H).	P

3-(6-(1-((3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-418**	**51d**	3-cyclopropyl-1-methyl-1H-pyrazole-5-carbaldehyde ALD-44	520.55	1H-NMR (400 MHz, DMSO-d6): δ 11.02 (s, 1H), 10.44 (s, 1H), 8.98 (s, 1H), 8.52 (s, 1H), 8.13 (t, J = 8.80 Hz, 1H), 7.96 (d, J = 9.20 Hz, 1H), 6.41 (s, 1H), 5.96 (s, 1H), 4.76 (s, 2H), 4.44-4.27 (m, 1H), 3.86 (s, 1H), 3.41 (s, 3H), 3.27-3.24 (m, 1H), 3.00 (d, J = 11.60 Hz, 1H), 2.78-2.60 (m, 5H), 2.16 (t, J = 5.20 Hz, 1H), 2.02 (d, J = 12.00 Hz, 1H), 1.89-1.85 (m, 1H), 1.12 (s, 3H), 0.90-0.85 (m, 2H), 0.80 (s, 3H), 0.67-0.63 (m, 2H).	P
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(thiazol-2-yloxy)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	**I-412**	**51d**	4-(thiazol-2-yloxy)benzaldehyde	575.53	1H-NMR (400 MHz, DMSO-d6): δ 11.93 (s, 1H), 10.98 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.46 (d, J = 8.40 Hz, 2H), 7.33-7.30 (m, 3H), 7.23 (d, J = 3.60 Hz, 1H), 5.13 (s, 1H), 4.23 (dd, J = 4.80, 12.80 Hz, 1H), 3.61-3.48 (m, 2H), 3.36-3.16 (m, 1H), 2.76-2.48 (m, 5H), 2.21-2.12 (m, 2H), 1.92 (s, 3H), 1.76-1.72 (m, 1H), 1.01 (s, 3H), 0.69 (s, 3H).	P
3-(6-(1-((1H-pyrazol-5-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-	**I-822**	**51d**	1H-pyrazole-5-carbaldehyde	466.5	1H-NMR (400 MHz, DMSO-d6): δ 12.60 (s, 1H), 10.98 (s, 1H), 8.84 (d, J = 2.00 Hz, 1H), 8.33 (t, J = 2.40 Hz, 1H), 8.15 (s, 1H), 8.08 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.56 (s, 1H),	P

fluoroquinolin-3-yl)piperidine-2,6-dione, 0.79Formic Acid					6.19 (s, 1H), 5.12 (s, 1H), 4.23 (d, J = 4.80 Hz, 1H), 3.59 (s, 2H), 3.16-3.10 (m, 1H), 2.81-2.72 (m, 2H), 2.58 (d, J = 3.60 Hz, 2H), 2.47-2.43 (m, 2H), 2.26-2.20 (m, 1H), 2.15-2.08 (m, 1H), 1.72-1.69 (m, 1H), 0.97 (s, 3H), 0.68 (s, 3H).	
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(oxazol-4-yl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, 0.7AcOH	**I-384**	**51d**	4-(oxazol-4-yl)benzaldehyde	543.55	1H-NMR (400 MHz, DMSO-d6): δ 11.01 (s, 1H), 8.85 (s, 1H), 8.61 (s, 1H), 8.46 (s, 1H), 8.33 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.77 (d, J = 8.40 Hz, 2H), 7.43 (d, J = 8.40 Hz, 2H), 5.12 (s, 1H), 4.23 (d, J = 4.80 Hz, 1H), 3.63-3.59 (m, 1H), 3.49-3.46 (m, 1H), 3.16 (m, 1H), 2.77-2.70 (m, 2H), 2.69-2.60 (m, 2H), 2.46 (m, 2H), 2.21-2.14 (m, 2H), 1.73-1.70 (m, 1H), 1.01 (s, 3H), 0.68 (s, 3H).	P
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	**I-851**	**51d**	1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carbaldehyde	548.57	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 10.07 (s, 1H), 8.90 (d, J = 2.00 Hz, 1H), 8.39 (s, 1H), 8.08 (t, J = 8.40 Hz, 1H), 7.91 (d, J = 9.20 Hz, 1H), 7.18 (s, 1H), 5.96 (s, 1H), 4.62 (s, 2H), 4.27-4.23 (m, 1H), 4.07 (s, 3H), 3.50-3.35 (m, 4H), 3.15-3.12 (m, 1H), 2.77-2.67 (m, 2H), 2.52-2.49 (m, 1H), 2.15-2.05 (m, 2H), 1.10 (s, 3H), 1.10 (s, 3H).	P

3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	**I-839**	**51d**	1-methyl-1H-pyrazole-3-carbaldehyde	480.52	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 9.87 (s, 1H), 8.91 (s, 1H), 8.41 (s, 1H), 8.06 (t, J = 8.40 Hz, 1H), 7.91 (d, J = 9.20 Hz, 1H), 7.82 (d, J = 2.00 Hz, 1H), 6.55 (d, J = 2.00 Hz, 1H), 5.87 (s, 1H), 4.34-4.41 (m, 3H), 3.91 (s, 3H), 3.37 (s, 3H), 3.24 (t, J = 11.60 Hz, 1H), 3.02-2.99 (m, 1H), 2.76-2.67 (m, 2H), 2.51-2.48 (m, 1H), 2.16-2.14 (m, 1H), 2.08-1.99 (m, 1H), 1.16 (m, 3H), 0.78 (s, 3H).	Q
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((1-methyl-1H-pyrazol-4-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, 0.75AcOH	**I-752**	**51d**	1-methyl-1H-pyrazole-4-carbaldehyde	480.5	1H-NMR (400 MHz, DMSO-d6): δ 11.98 (s, 1H), 11.00 (s, 1H), 8.85 (s, 1H), 8.33 (s, 1H), 8.08 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.60 (s, 1H), 7.34 (s, 1H), 5.09 (s, 1H), 4.23 (d, J = 4.80 Hz, 1H), 3.82 (s, 3H), 3.49-3.34 (m, 2H), 3.12 (s, 1H), 2.76 (t, J = 4.80 Hz, 1H), 2.63 (d, J = 2.80 Hz, 1H), 2.59-2.45 (m, 3H), 2.25-2.11 (m, 2H), 1.92 (s, 3H), 1.72 (s, 1H), 0.97 (s, 3H), 0.70 (s, 3H).	P
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((1-methyl-3-phenyl-1H-pyrazol-5-yl)methyl)piperidin-4-	**I-419**	**51d**	1-methyl-3-phenyl-1H-pyrazole-5-carbaldehyde	556.5	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 10.19 (s, 1H), 8.92 (s, 1H), 8.42 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.92 (d, J = 8.80 Hz, 1H), 7.81 (d, J = 1.20 Hz, 2H), 7.44 (t, J = 7.60 Hz, 2H), 7.33 (t, J = 7.20 Hz, 1H), 7.13 (s, 1H),	P

yl)quinolin-3-yl)piperidine-2,6-dione, HCl					5.96 (s, 1H), 4.59 (s, 2H), 4.26 (d, J = 4.40 Hz, 1H), 4.03 (s, 3H), 3.49-3.34 (m, 4H), 3.16-3.13 (m, 1H), 2.76 (t, J = 4.40 Hz, 1H), 2.63 (d, J = 3.20 Hz, 1H), 2.51-2.49 (m, 1H), 2.16-2.12 (m, 1H), 2.06-2.02 (m, 1H), 1.13 (s, 3H), 0.83 (s, 3H).	
3-(5-fluoro-6-(4-hydroxy-1-(4-(isoxazol-4-yl)benzyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, AcOH	**I-375**	**51d**	4-(isoxazol-4-yl)benzaldehyde	543.2	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 9.43 (s, 1H), 9.16 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.68 (d, J = 8.00 Hz, 2H), 7.43 (d, J = 8.00 Hz, 2H), 5.12 (s, 1H), 4.25-4.24 (m, 1H), 3.62 (d, J = 13.60 Hz, 1H), 3.51-3.46 (m, 2H), 3.33-3.26 (m, 1H), 2.80-2.45 (m, 4H), 2.20-2.15 (m, 3H), 1.87 (s, 3H), 1.74-1.69 (m, 1H), 1.01 (s, 3H), 0.68 (s, 3H).	P
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	**I-397**	**51d**	4-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)benzaldehyde	624.2	1H-NMR (400 MHz, DMSO-d6): δ 10.97 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.16 (s, 1H), 8.10 (t, J = 8.40 Hz, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.40 (q, J = 8.00 Hz, 4H), 5.13 (s, 1H), 4.25-4.21 (m, 1H), 3.96 (s, 3H), 3.61-3.49 (m, 2H), 3.19-3.16 (m, 1H), 2.74-2.63 (m, 4H), 2.34-2.16 (m, 2H), 1.76-1.69 (m, 3H), 1.02 (s, 3H), 0.69 (s, 3H).	P

3-(6-((R)-1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-124**	**(R)-51d**	4-(1,2,4-oxadiazol-3-yl)benzaldehyde ALD-107	544.54	1H-NMR (400 MHz, DMSO-d6): 11.00 (s, 1H), 10.16 (s, 1H), 9.78 (s, 1H), 8.91 (s, 1H), 8.42 (s, 1H), 8.16 (d, J = 8.00 Hz, 2H), 8.08 (t, J = 8.80 Hz, 1H), 7.92 (m, 3H), 5.94 (s, 1H), 4.52 (m, 2H), 4.26 (d, J = 8.00 Hz, 1H), 3.42 (s, 3H), 3.30 (t, J = 12.00 Hz, 1H), 2.91 (d, J = 12.00 Hz, 1H), 2.82-2.70 (m, 1H), 2.68-2.52 (m, 1H), 2.50-2.40 (m, 1H), 2.18-2.13 (m, 1H), 2.02 (m, 1H), 1.10 (s, 3H), 0.78 (s, 3H).	Q
3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(3-methyl-4-(1,2,4-oxadiazol-3-yl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, 0.7Formic Acid	**I-378**	**51d**	3-methyl-4-(1,2,4-oxadiazol-3-yl)benzaldehyde	556.5	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 9.70 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.34 (s, 1H), 8.17 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.93 (d, J = 8.00 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.40 (d, J = 7.60 Hz, 2H), 5.14 (s, 1H), 4.25-4.21 (m, 1H), 3.64 (d, J = 14.00 Hz, 1H), 3.51 (d, J = 14.00 Hz, 1H), 3.33-3.15 (m, 1H), 2.80-2.71 (m, 2H), 2.68-2.48 (m, 7H), 2.22-2.12 (m, 2H), 1.72 (d, J = 8.00 Hz, 1H), 1.03 (s, 3H), 0.68 (s, 3H).	P
3-(6-(1-((6-(1,2,4-oxadiazol-3-yl)pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpip	**I-406**	**51d**	6-(1,2,4-oxadiazol-3-yl)nicotinaldehyde	545.53	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 9.78 (s, 1H), 8.80 (m, 1H), 8.75 (s, 1H), 8.34 (s, 1H), 8.13-8.08 (m, 2H), 8.02-8.00 (m, 1H), 7.84 (d, J = 9.20 Hz, 1H), 5.18 (s, 1H),	P

eridin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione					4.25-4.21 (m, 1H), 3.72 (d, J = 14.00 Hz, 1H), 3.60 (d, J = 14.00 Hz, 1H), 3.29-3.17 (m, 1H), 2.77-2.64 (m, 2H), 2.63-2.48 (m, 4H), 2.20-2.10 (m, 2H), 1.76-1.71 (m, 1H), 1.01 (s, 3H), 0.68 (s, 3H).	
3-(6-(1-(4-(1,2,3-thiadiazol-4-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, AcOH	**I-381**	**51d**	4-(1,2,3-thiadiazol-4-yl)benzaldehyde ALD-69	560.9	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 9.61 (s, 1H), 8.85 (d, J = 2.40 Hz, 1H), 8.34 (s, 1H), 8.11 (m, 3H), 7.84 (d, J = 9.20 Hz, 1H), 7.55 (d, J = 8.00 Hz, 2H), 5.14 (s, 1H), 4.26-4.21 (m, 1H), 3.69-3.65 (m, 1H), 3.56-3.52 (m, 1H), 3.32-3.18 (m, 1H), 2.76-2.64 (m, 4H), 2.34-2.16 (m, 2H), 1.90 (s, 2H), 1.74 (s, 2H), 1.03 (s, 3H), 0.69 (s, 3H).	P
(R)-1-(6-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-339**	**INT-(R)-S2**	4-(1,2,4-oxadiazol-3-yl)benzaldehyde ALD-107	545.5	1H-NMR (400 MHz, DMSO-d6): δ 10.62 (s, 1H), 10.04 (s, 1H), 9.77 (s, 1H), 9.00 (d, J = 2.40 Hz, 1H), 8.35 (s, 1H), 8.15 (d, J = 5.60 Hz, 2H), 8.04 (t, J = 8.80 Hz, 1H), 7.92-7.88 (m, 3H), 5.93 (s, 1H), 4.55-4.48 (m, 2H), 4.00 (t, J = 6.40 Hz, 2H), 3.41 (s, 3H), 3.30 (t, J = 11.60 Hz, 1H), 2.92 (d, J = 11.60 Hz, 1H), 2.79 (t, J = 6.80 Hz, 2H), 2.02 (d, J = 9.60 Hz, 1H), 1.08 (s, 3H), 0.77 (s, 3H).	M

(S)-1-(6-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	**I-338**	**INT-(S)-S2**	4-(1,2,4-oxadiazol-3-yl)benzaldehyde ALD-107	545.5	1H-NMR (400 MHz, DMSO-d6): δ 10.62 (s, 1H), 9.77 (s, 1H), 9.00 (d, J = 2.40 Hz, 1H), 8.35 (s, 1H), 8.09 (t, J = 8.80 Hz, 2H), 8.03 (d, J = 8.00 Hz, 1H), 7.85 (d, J = 9.20 Hz, 1H), 7.58 (d, J = 8.40 Hz, 2H), 5.16 (s, 1H), 4.01 (t, J = 6.80 Hz, 2H), 3.67 (d, J = 14.00 Hz, 1H), 3.55 (d, J = 14.00 Hz, 1H), 3.20-3.14 (m, 1H), 2.79 (t, J = 22.00 Hz, 2H), 2.52-2.50 (m, 3H), 2.20 (d, J = 10.80 Hz, 1H), 1.76 (d, J = 11.20 Hz, 1H), 1.01 (s, 3H), 0.68 (s, 3H).	M
3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	**I-454**	**(R)-51d**	4-(5-methyl-1,2,4-oxadiazol-3-yl)benzaldehyde	558.54	1H-NMR (400 MHz, DMSO-d6): 10.99 (s, 1H), 9.62 (s, 1H), 8.89 (d, J = 2.00 Hz, 1H), 8.37 (s, 1H), 8.14-8.04 (m, 3H), 7.91-7.84 (m, 3H), 5.93 (s, 1H), 4.51 (s, 2H), 4.24 (dd, J = 4.40, 12.60 Hz, 1H), 3.42-3.29 (m, 2H), 2.98 (d, J = 11.60 Hz, 1H), 2.77-2.68 (m, 5H), 2.60-2.50 (m, 3H), 2.14-2.00 (m, 2H), 1.07 (s, 3H), 0.79 (s, 3H).	P
3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethyl-1-(4-(5-methyl-1,3,4-oxadiazol-2-yl)benzyl)piperidin-4-yl)quinolin-	**I-324**	**(R)-51d**	4-(5-methyl-1,3,4-oxadiazol-2-yl)benzaldehyde	558.54	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (s, 1H), 8.33 (s, 1H), 8.15-8.07 (m, 2H), 7.96 (d, J = 8.40 Hz, 2H), 7.84 (d, J = 8.40 Hz, 1H), 7.59 (d, J = 8.40 Hz, 2H), 5.15 (s, 1H), 4.21-4.26 (m, 1H), 3.65-3.69 (m, 1H), 3.57-3.54 (m, 1H),	P

3-yl)piperidine-2,6-dione, 0.518Formic Acid					3.19-3.16 (m, 1H), 2.77-2.74 (m, 3H), 2.73-2.50 (m, 6H), 2.20-2.11 (m, 2H), 1.78-1.75 (m, 1H), 1.02 (s, 3H), 0.69 (s, 3H).	
(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(oxazol-4-yl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-465**	**INT-(R)-S2**	4-(oxazol-4-yl)benzaldehyde	544.48	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.83 (s, 1H), 9.00 (d, J = 2.40 Hz, 1H), 8.73 (s, 1H), 8.53 (s, 1H), 8.35 (d, J = 2.00 Hz, 1H), 8.04 (t, J = 8.40 Hz, 1H), 7.93-7.89 (m, 3H), 7.75 (d, J = 8.40 Hz, 2H), 5.91 (s, 1H), 4.48-4.38 (m, 2H), 4.00 (t, J = 6.40 Hz, 2H), 3.40 (s, 4H), 3.27 (t, J = 11.20 Hz, 1H), 2.93 (d, J = 11.20 Hz, 1H), 2.80 (t, J = 6.40 Hz, 1H), 2.04 (t, J = 10.00 Hz, 1H), 1.08 (d, J = 2.80 Hz, 3H), 0.78 (s, 3H).	G
(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(5-methyl-1,3,4-oxadiazol-2-yl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	**I-766**	**INT-(R)-S2**	4-(5-methyl-1,3,4-oxadiazol-2-yl)benzaldehyde	559.46	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.97 (d, J = 2.40 Hz, 1H), 8.33 (d, J = 2.00 Hz, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.96 (d, J = 8.40 Hz, 2H), 7.85 (d, J = 9.20 Hz, 1H), 7.59 (d, J = 8.00 Hz, 2H), 5.16 (s, 1H), 4.01 (t, J = 6.80 Hz, 2H), 3.67 (d, J = 14.00 Hz, 1H), 3.55 (d, J = 14.00 Hz, 1H), 3.20-3.17 (m, 2H), 2.80 (t, J = 6.40 Hz, 2H), 2.73-2.62 (m, 1H), 2.59 (s, 4H), 2.19 (d, J = 10.40 Hz, 1H), 1.73 (d, J = 13.20 Hz, 1H), 1.02 (m, 3H), 0.68 (s, 3H)	M

4-(4-(((4R)-4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)phenyl)-1-methyl-1H-pyrazole-3-carbonitrile	**I-584**	**(R)-51d**	4-(4-formylphenyl)-1-methyl-1H-pyrazole-3-carbonitrile	581.51	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (s, 1H), 8.40 (s, 1H), 8.33 (s, 1H), 8.12-8.08 (m, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.62 (d, J = 8.00 Hz, 2H), 7.48 (d, J = 8.00 Hz, 2H), 5.13 (s, 1H), 4.25-4.21 (m, 1H), 3.99 (s, 3H), 3.63-3.59 (m, 1H), 3.52-3.49 (m, 1H), 3.20-3.16 (m, 1H), 2.77-2.60 (m, 4H), 4.52-2.48 (m, 2H), 2.19-2.15 (m, 2H), 1.73-1.70 (m, 1H), 1.02 (s, 3H), 0.68 (s, 3H)	P
(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(5-methyl-1,2,4-oxadiazol-3-yl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-705**	**INT-(R)-S2**	4-(5-methyl-1,2,4-oxadiazol-3-yl)benzaldehyde	559.4	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.87 (s, 1H), 9.00 (d, J = 2.40 Hz, 1H), 8.35 (d, J = 2.00 Hz, 1H), 8.12 (d, J = 8.00 Hz, 2H), 8.05 (t, J = 8.80 Hz, 1H), 7.91-7.86 (m, 3H), 5.94 (s, 1H), 4.54-4.46 (m, 2H), 4.00 (t, J = 6.80 Hz, 2H), 3.41 (s, 3H), 3.31 (t, J = 11.20 Hz, 1H), 2.96 (d, J = 11.60 Hz, 1H), 2.80 (t, J = 6.80 Hz, 2H), 2.70-2.67 (m, 3H), 2.02 (d, J = 10.80 Hz, 1H), 1.08 (d, J = 2.80 Hz, 3H), 0.79 (s, 3H).	G
(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(3-methyl-4-(1,2,4-oxadiazol-3-yl)benzyl)piperidin-4-	**I-475**	**INT-(R)-S2**	3-methyl-4-(1,2,4-oxadiazol-3-yl)benzaldehyde	559.46	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.78 (s, 1H), 9.41 (s, 1H), 9.00 (s, 1H), 8.35 (d, J = 2.40 Hz, 1H), 8.08-8.03 (m, 2H), 7.91 (d, J = 9.20 Hz, 1H), 7.70-7.66 (m, 2H), 5.94 (s, 1H), 4.49 (d, J = 4.00	M

yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl					Hz, 2H), 4.02-3.98 (m, 2H), 3.40-3.30 (m, 4H), 3.03 (d, J = 12.00 Hz, 1H), 2.82-2.79 (m, 2H), 2.63 (s, 3H), 2.05 (d, J = 13.60 Hz, 1H), 1.07 (s, 3H), 0.80 (s, 3H).	
(R)-1-(6-(1-((6-(1,2,4-oxadiazol-3-yl)pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-473**	**INT-(R)-S2**	6-(1,2,4-oxadiazol-3-yl)nicotinaldehyde	546.2	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 10.54 (s, 1H), 9.84 (s, 1H), 9.09 (s, 1H), 9.01 (d, J = 2.40 Hz, 1H), 8.45 (dd, J = 2.00, 8.20 Hz, 1H), 8.37 (d, J = 1.60 Hz, 1H), 8.24 (d, J = 8.40 Hz, 1H), 8.06 (t, J = 8.80 Hz, 1H), 7.91 (d, J = 9.20 Hz, 1H), 5.97 (s, 1H), 4.57 (q, J = 6.00 Hz, 2H), 4.01 (t, J = 6.80 Hz, 2H), 3.43-3.31 (m, 4H), 2.96 (d, J = 11.60 Hz, 1H), 2.80 (t, J = 6.40 Hz, 2H), 2.03 (d, J = 9.20 Hz, 1H), 1.11 (s, 3H), 0.79 (s, 3H).	G
(R)-1-(6-(1-(4-(1H-pyrazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-734**	**INT-(R)-S2**	4-(1H-pyrazol-3-yl)benzaldehyde ALD-80	543.46	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.59 (s, 1H), 9.00 (s, 1H), 8.35 (s, 1H), 8.06-8.04 (m, 1H), 7.95-7.89 (m, 3H), 7.78 (s, 1H), 7.70-7.68 (m, 2H), 6.80 (s, 1H), 5.92 (s, 1H), 4.44-4.38 (m, 2H), 4.02-3.99 (m, 3H), 3.28-3.25 (m, 4H), 2.96 (d, J = 11.60 Hz, 1H), 2.80 (t, J = 6.80 Hz, 2H), 2.04-2.01 (m, 1H), 1.07 (s, 3H), 0.79 (s, 3H).	M

(R)-1-(6-(1-(4-(3,5-dimethylisoxazol-4-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-471**	**INT-(R)-S2**	4-(3,5-dimethylisoxazol-4-yl)benzaldehyde	572.5	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.86 (s, 1H), 9.00 (d, J = 2.40 Hz, 1H), 8.35 (d, J = 2.00 Hz, 1H), 8.05 (t, J = 8.40 Hz, 1H), 7.90 (d, J = 9.20 Hz, 1H), 7.78 (d, J = 8.40 Hz, 2H), 7.53 (d, J = 8.40 Hz, 2H), 5.95 (s, 1H), 4.45 (s, 2H), 4.00 (t, J = 6.80 Hz, 2H), 3.81 (s, 3H), 3.31 (t, J = 11.20 Hz, 1H), 2.97 (d, J = 11.60 Hz, 1H), 2.80 (t, J = 6.40 Hz, 2H), 2.45 (s, 3H), 2.28 (s, 3H), 2.03 (d, J = 9.60 Hz, 1H), 1.10 (s, 3H), 0.80 (s, 3H).	M
(R)-1-(6-(1-(4-(1,3-dimethyl-1H-pyrazol-4-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-708**	**INT-(R)-S2**	4-(1,3-dimethyl-1H-pyrazol-4-yl)benzaldehyde ALD-55	571.5	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.9 (bs, s), 9.01 (s, 1H), 8.36 (s, 1H), 8.06-8.00 (m, 2H), 7.95 (d, J = 16.00 Hz, 1H), 7.68 (m, 2H), 7.55 (d, J = 7.20 Hz, 2H), 5.92 (s, 1H), 4.44-4.38 (m, 2H), 4.02-3.99 (m, 2H), 3.89-3.81 (m, 3H), 3.39 (s, 3H), 3.27 (s, 1H), 2.95 (s, 1H), 2.80 (t, J = 6.80 Hz, 2H), 2.47 (s, 4H), 2.03 (d, J = 11.20 Hz, 1H), 1.09 (s, 3H), 0.79 (s, 3H).	G
(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(4-methylthiazol-5-yl)benzyl)piperidin-4-	**I-479**	**INT-(R)-S2**	4-(4-methylthiazol-5-yl)benzaldehyde	574.44	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 10.09 (s, 1H), 9.03 (s, 2H), 8.37 (s, 1H), 8.05 (t, J = 8.80 Hz, 1H), 7.90 (d, J = 9.20 Hz, 1H), 7.81 (d, J = 8.40 Hz, 2H), 7.64 (d, J = 8.00 Hz, 2H), 5.94 (s, 1H),	M

yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl					4.47-4.43 (m,2H), 4.01 (t, J = 6.40 Hz, 2H), 3.41-3.27 (m, 4H), 2.94 (d, J = 11.20 Hz, 1H), 2.80 (t, J = 6.80 Hz, 2H), 2.50 (s, 3H), 2.03 (d, J = 11.20 Hz, 1H), 1.11 (s, 3H), 0.79 (s, 3H).	
(R)-4-(4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)phenyl)-1-methyl-1H-pyrazole-3-carbonitrile, HCl	**I-731**	**INT-(R)-S2**	4-(4-formylphenyl)-1-methyl-1H-pyrazole-3-carbonitrile	582.46	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.96 (s, 1H), 8.84 (s, 1H), 8.32 (d, J = 2.00 Hz, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 8.40 Hz, 1H), 7.61 (d, J = 8.40 Hz, 2H), 7.47 (d, J = 8.00 Hz, 2H), 5.14 (s, 1H), 4.16-3.99 (m, 5H), 3.62 (d, J = 13.40 Hz, 1H), 3.51 (d, J = 13.40 Hz, 1H), 3.16 (t, J = 12.00 Hz, 1H), 2.80 (t, J = 6.80 Hz, 2H), 2.78-2.67 (m, 1H), 2.61-2.49 (m, 2H), 2.01 (d, J = 11.20 Hz, 1H), 1.72 (d, J = 13.20 Hz, 1H), 1.02 (s, 3H), 0.68 (s, 3H).	M
(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-819**	**INT-(R)-S2**	6-(trifluoromethyl)nicotinaldehyde	546.43	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 10.27 (s, 1H), 9.08-9.00 (m, 2H), 8.50 (d, J = 8.00 Hz, 1H), 8.35 (d, J = 2.00 Hz, 1H), 8.10-8.04 (m, 2H), 8.09 (d, J = 8.00 Hz, 1H), 5.97 (s, 1H), 4.59 (s, 2H), 4.02-3.97 (m, 3H), 3.40-3.32 (m, 4H), 3.00 (d, J = 11.60 Hz, 1H), 2.80 (t, J = 6.80 Hz, 2H), 1.09 (d, J = 2.80 Hz, 3H), 0.80 (s, 3H).	M

3-(6-((R)-1-((6-(1,2,4-oxadiazol-3-yl)pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-408**	**(R)-51d**	6-(1,2,4-oxadiazol-3-yl)nicotinaldehyde	543.4 (Negative)	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 9.84 (s, 2H), 9.04 (s, 1H), 8.90 (s, 1H), 8.38 (d, J = 6.40 Hz, 2H), 8.10-7.92 (m, 3H), 5.96 (s, 1H), 4.24 (d, J = 8.40 Hz, 2H), 3.96-3.92 (m, 1H), 3.39-3.05 (m, 5H), 2.92-2.88 (m, 1H), 2.67-2.60 (m, 2H), 2.04-2.01 (m, 2H), 1.08 (s, 3H), 0.80 (s, 3H).	Q
3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethyl-1-(4-(5-(methyl-d3)-1,2,4-oxadiazol-3-yl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	**I-674**	**(R)-51d**	Synthesized using alkylation method	561.47	1H-NMR (400 MHz, DMSO-d6; 10.99 (s, 1H), 9.41 (s, 1H), 8.88 (d, J = 2.00 Hz, 1H), 8.36 (s, 1H), 8.13 (d, J = 8.00 Hz, 2H), 8.06 (t, J = 8.80 Hz, 1H), 7.90 (d, J = 9.20 Hz, 1H), 7.83 (d, J = 8.00 Hz, 2H), 5.93 (s, 1H), 4.52 (d, J = 4.40 Hz, 2H), 4.24 (dd, J = 4.40, 12.60 Hz, 1H), 3.01 (d, J = 12.00 Hz, 1H), 2.51-2.77 (m, 3H), 2.01-2.14 (m, 2H), 1.06 (s, 3H), 0.0779(s, 3H), (Note: two aliphatic proton overlapped with deutorated solvent).	J
(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((1-methyl-1H-pyrazol-4-yl)methyl)piperidin-4-yl)quinolin-3-yl)dihydrop	**I-856**	**INT-(R)-S2**	1-methyl-1H-pyrazole-4-carbaldehyde	481.45	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.91 (s, 1H), 9.01 (d, J = 2.40 Hz, 1H), 8.36 (d, J = 1.60 Hz, 1H), 8.04 (t, J = 8.80 Hz, 1H), 7.95 (s, 1H), 7.90 (d, J = 8.80 Hz, 1H), 7.66 (d, J = Hz, 1H), 5.88 (s, 1H), 4.24 (s, 2H), 4.03 (t, J = 6.40 Hz, 2H), 3.89 (s, 3H), 3.34-3.26 (m,	M

yrimidine-2,4(1H,3H)-dione, HCl					4H), 2.94 (d, J = 11.60 Hz, 1H), 2.80 (t, J = 6.40 Hz, 2H), 2.00 (d, J = 13.20 Hz, 1H), 1.08 (s, 3H), 0.79 (s, 3H).	
3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethyl-1-((4-(3-(trifluoromethyl)phenyl)-1H-pyrrol-2-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	**I-572**	**(R)-51d**	4-(3-(trifluoromethyl)phenyl)-1H-pyrrole-2-carbaldehyde	609.52	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 2H), 8.84 (d, J = 1.60 Hz, 1H), 8.32 (s, 1H), 8.15 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.85-7.81 (m, 3H), 7.51 (t, J = 7.60 Hz, 1H), 7.41 (d, J = 7.60 Hz, 1H), 7.33 (t, J = 2.00 Hz, 1H), 6.43 (s, 1H), 5.10 (s, 1H), 4.22 (dd, J = 4.40, 12.60 Hz, 1H), 3.51-3.47 (m, 2H), 3.12 (t, J = 12.40 Hz, 1H), 2.76-2.67 (m, 3H), 2.64-2.58 (m, 3H), 2.25 (d, J = 10.80 Hz, 1H), 2.15-2.08 (m, 1H), 1.71 (d, J = 12.00 Hz, 1H), 0.99 (s, 3H), 0.70 (s, 3H).	G
(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((3-(3-(trifluoromethyl)phenyl)-1H-pyrazol-5-yl)methyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-884**	**INT-(R)-S2**	3-(3-(trifluoromethyl)phenyl)-1H-pyrazole-5-carbaldehyde	611.5	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 10.20 (s, 1H), 9.01 (d, J = 2.40 Hz, 1H), 8.36 (d, J = 2.00 Hz, 1H), 8.18-8.13 (m, 3H), 8.04 (t, J = 8.80 Hz, 1H), 7.90 (d, J = 8.80 Hz, 1H), 7.73 (t, J = 8.00 Hz, 2H), 7.18 (s, 1H), 5.89 (s, 1H), 4.45 (d, J = 2.40 Hz, 2H), 4.01 (t, J = 6.40 Hz, 2H), 3.40-3.31 (m, 4H), 3.10 (d, J = 11.60 Hz, 1H), 2.68 (t, J = 1.60 Hz, 2H), 2.02 (d, J = 9.60 Hz, 1H), 1.13 (s, 3H), 0.81 (s, 3H).	M

(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-484**	**INT-(R)-S2**	4-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)benzaldehyde	625.46	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.63 (s, 1H), 9.00 (s, 1H), 8.35 (s, 1H), 8.05 (t, J = 8.80 Hz, 1H), 7.90 (d, J = 9.20 Hz, 1H), 7.81 (s, 1H), 7.73 (d, J = 8.00 Hz, 2H), 7.51 (d, J = 8.00 Hz, 2H), 5.94 (s, 1H), 4.46 (s, 2H), 4.06 (s, 3H), 4.00 (t, J = 6.80 Hz, 2H), 3.39-3.31 (m, 4H), 3.00 (d, J = 12.00 Hz, 1H), 2.80 (t, J = 6.40 Hz, 2H), 2.04 (s, 1H), 1.08 (s, 3H), 0.80 (s, 3H).	M
(R)-5-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)picolinonitrile	**I-841**	**INT-(R)-S2**	5-formylpicolinonitrile	503.43	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 8.97 (d, J = 2.40 Hz, 1H), 8.75 (d, J = Hz, 1H), 8.33 (d, J = 2.00 Hz, 1H), 8.10-8.01 (m, 3H), 7.85 (d, J = 9.20 Hz, 1H), 5.18 (s, 1H), 4.01 (t, J = 6.40 Hz, 2H), 3.72 (d, J = 14.40 Hz, 1H), 3.61 (d, J = 14.40 Hz, 1H), 3.16 (s, 1H), 2.80 (t, J = 6.40 Hz, 2H), 2.68 (t, J = 1.60 Hz, 1H), 2.34 (t, J = 1.60 Hz, 2H), 2.15 (d, J = 10.40 Hz, 1H), 1.74 (t, J = 13.20 Hz, 1H), 1.08 (s, 3H), 0.68 (s, 3H).	M
(R)-1-(6-(1-((1,3-dimethyl-1H-pyrazol-5-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-	**I-855**	**INT-(R)-S2**	1,3-dimethyl-1H-pyrazole-5-carbaldehyde	495.47	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 10.12 (s, 1H), 9.01 (d, J = 2.40 Hz, 1H), 8.36 (d, J = 2.00 Hz, 1H), 8.05 (t, J = 8.40 Hz, 1H), 7.91 (d, J = 9.20 Hz, 1H), 6.45 (s, 1H), 5.93 (s, 1H), 4.48 (d, J = 4.00	M

5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl					Hz, 2H), 4.08-3.99 (m, 2H), 3.87 (s, 3H), 3.42 (s, 3H), 3.28 (t, J = 11.20 Hz, 1H), 3.02 (d, J = 11.60 Hz, 1H), 2.80 (t, J = 6.80 Hz, 2H), 2.03 (s, 3H), 2.01 (d, J = 5.20 Hz, 1H), 1.10 (s, 3H), 0.80 (s, 3H).	
(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((4-(3-(trifluoromethyl)phenyl)-1H-pyrrol-2-yl)methyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-569**	**INT-(R)-S2**	4-(3-(trifluoromethyl)phenyl)-1H-pyrrole-2-carbaldehyde	610.4	1H-NMR (400 MHz, DMSO-d6): δ 11.55 (s, 1H), 10.63 (s, 1H), 9.91 (s, 1H), 9.00 (d, J = 2.40 Hz, 1H), 8.35 (d, J = 2.00 Hz, 1H), 8.28 (t, J = 83.20 Hz, 1H), 8.03 (t, J = 8.40 Hz, 3H), 7.90 (d, J = 4.40 Hz, 2H), 7.88 (d, J = 4.00 Hz, 1H), 6.84 (d, J = 14.00 Hz, 1H), 5.88 (s, 1H), 4.37 (d, J = 3.20 Hz, 2H), 4.00 (t, J = 6.80 Hz, 2H), 3.25-3.02 (m, 5H), 3.00 (d, J = 12.00 Hz, 1H), 2.79 (t, J = 6.80 Hz, 2H), 1.11 (s, 3H), 0.77 (t, J = 30.40 Hz, 3H).	G
(R)-1-(6-(1-((1-cyclopropyl-1H-pyrazol-5-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-870**	**INT-(R)-S2**	1-cyclopropyl-1H-pyrazole-5-carbaldehyde ALD-78	507.48	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 10.06 (s, 1H), 9.01 (d, J = 2.40 Hz, 1H), 8.36 (d, J = 2.00 Hz, 1H), 8.07-8.03 (m, 1H), 7.91 (d, J = 8.80 Hz, 1H), 7.51 (d, J = 1.60 Hz, 1H), 6.71 (d, J = 1.60 Hz, 1H), 5.95 (s, 1H), 4.68-4.65 (m, 2H), 4.02-3.99 (m, 2H), 3.96-3.91 (m, 1H), 3.48-3.31 (m, 4H), 3.06-3.03 (m, 1H), 2.81 (t, J = 6.40 Hz, 2H), 2.04 (d, J = 13.60 Hz, 1H), 1.20-	Q

					1.09 (m, 7H), 0.81 (s, 3H).	
3-(5-(((4R)-4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)-1H-pyrrol-3-yl)benzonitrile	**I-559**	**(R)-51d**	3-(5-formyl-1H-pyrrol-3-yl)benzonitrile ALD-103	566.49	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 2H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.11 (t, J = 9.20 Hz, 1H), 7.99 (s, 1H), 7.87-7.83 (m, 3H), 7.50-7.45 (m, 2H), 7.35 (s, 1H), 6.45 (s, 1H), 5.12 (s, 1H), 4.24-4.00 (m, 1H), 3.53 (s, 2H), 3.17-3.11 (m, 1H), 2.67-2.50 (m, 5H), 2.34-2.14 (m, 2H), 1.82-1.77 (m, 1H), 0.99 (s, 3H), 0.70 (s, 3H).	G
3-(6-((R)-1-((1-cyclopropyl-1H-pyrazol-5-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-835**	**(R)-51d**	1-cyclopropyl-1H-pyrazole-5-carbaldehyde ALD-78	506.46	1H-NMR (400 MHz, DMSO-d6): δ 11.01 (s, 1H), 10.45 (s, 1H), 8.96 (s, 1H), 8.48 (s, 1H), 8.11 (t, J = 8.40 Hz, 1H), 7.94 (d, J = 9.20 Hz, 1H), 7.50 (d, J = 1.60 Hz, 1H), 6.74 (d, J = 1.20 Hz, 1H), 5.90 (s, 1H), 4.64 (s, 2H), 4.27 (d, J = 4.80 Hz, 1H), 3.99-3.95 (m, 2H), 3.47 (m, 3H), 3.32 (t, J = 7.20 Hz, 1H), 3.01 (d, J = 5.60 Hz, 1H), 2.78-2.74 (m, 1H), 2.63 (t, J = 7.20 Hz, 1H), 2.15 (d, J = 5.20 Hz, 1H), 2.04 (d, J = 9.60 Hz, 1H), 1.18-1.07 (m, 7H), 0.80 (s, 3H).	G
(S)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-	**I-689**	**INT-(R)-S2**	3-(5-formyl-1H-pyrrol-3-yl)benzonitrile	567.48	1H-NMR (400 MHz, DMSO-d6): δ 11.48 (s, 1H), 10.63 (s, 1H), 9.45 (s, 1H), 9.00 (d, J = 2.40 Hz, 1H), 8.34 (d, J = 2.40 Hz, 1H), 8.07-8.00 (m,	N

3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl					2H), 7.94-7.89 (m, 2H), 7.52-7.63 (m, 3H), 6.80 (s, 1H), 5.88 (s, 1H), 4.37 (d, J = 2.00 Hz, 2H), 4.00 (t, J = 6.80 Hz, 2H), 3.52-3.34 (m, 3H), 3.04 (d, J = 11.60 Hz, 1H), 2.80 (t, J = 6.40 Hz, 2H), 2.19 (d, J = 10.40 Hz, 1H), 2.00 (d, J = 13.20 Hz, 1H), 1.08 (s, 3H), 0.82 (s, 3H).	
3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethyl-1-((3-(3-(trifluoromethyl)phenyl)-1H-pyrazol-5-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl	**I-852**	**(R)-51d**	3-(3-(trifluoromethyl)phenyl)-1H-pyrazole-5-carbaldehyde	610.48	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 9.67 (s, 1H), 8.89 (s, 1H), 8.37 (s, 1H), 8.19-8.12 (m, 3H), 8.04 (d, J = 8.40 Hz, 1H), 7.85 (t, J = 52.40 Hz, 2H), 7.14 (s, 1H), 5.89 (s, 1H), 4.47 (s, 2H), 4.26-4.22 (m, 2H), 3.15 (d, J = 11.60 Hz, 1H), 2.77-2.73 (m, 3H), 2.52-2.50 (m, 2H), 2.15 (s, 1H), 2.11 (m, 2H), 2.02 (d, J = 14.00 Hz, 1H), 1.27-1.09 (m, 3H), 0.81 (m, 3H).	G
3-(6-((R)-1-(4-(1H-pyrazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione	**I-603**	**(R)-51d**	4-(1H-pyrazol-3-yl)benzaldehyde ALD-80	542.5	1H-NMR (400 MHz, DMSO-d6): δ 12.80 (s, 1H), 11.00 (s, 1H), 9.66 (s, 1H), 8.90 (s, 1H), 8.39 (s, 1H), 8.06 (t, J = 8.80 Hz, 1H), 7.92-7.89 (m, 3H), 7.78 (d, J = 1.60 Hz, 1H), 7.69 (d, J = 8.00 Hz, 2H), 6.80 (d, J = 2.00 Hz, 1H), 5.91 (s, 1H), 4.44-4.38 (m, 2H), 4.25 (dd, J = 4.80, 12.80 Hz, 1H), 3.39-3.35 (m, 3H), 3.30-3.25 (m, 1H), 2.96-2.93 (m, 1H), 2.77-2.73	Q

					(m, 1H), 2.68-2.60 (m, 1H), 2.40-2.34 (m, 1H), 2.14-2.13 (m, 1H), 2.02 (d, J = 9.20 Hz, 1H), 1.07 (s, 3H), 0.78 (s, 3H).	
(R)-1-(6-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-543**	**INT-(R)-S6**	4-(1,2,4-oxadiazol-3-yl)benzaldehyde	559.49	1H-NMR (400 MHz, DMSO-d6): δ 10.56 (s, 1H), 9.78 (s, 1H), 9.70 (s, 1H), 8.47 (s, 1H), 8.19-8.17 (m, 2H), 8.05 (d, J = 8.80 Hz, 1H), 7.89-7.83 (m, 3H), 5.94-5.92 (m, 1H), 4.52 (s, 2H), 3.99 (m, 1H), 3.70-3.67 (m, 1H), 3.33-3.25 (m, 1H), 2.97-2.87 (m, 2H), 2.79-2.75 (m, 1H), 2.60 (s, 3H), 2.50-2.47 (m, 2H)2.03-2.00 (m, 1H), 1.07-1.06 (m, 3H), 0.78 (s, 3H).	G
(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-546**	**INT-(R)-S6**	4-(trifluoromethyl)benzaldehyde	557.48 (Negative)	1H-NMR (400 MHz, DMSO-d6): δ 10.57 (s, 1H), 9.99 (s, 1H), 8.48 (s, 1H), 8.05 (t, J = 8.80 Hz, 1H), 7.95-7.83 (m, 5H), 5.93 (s, 1H), 4.54 (s, 2H), 3.99 (s, 1H), 3.70-3.68 (m, 1H), 3.49-3.27 (m, 4H), 2.95-2.76 (m, 3H), 2.68 (s, 3H), 2.01 (d, J = 10.40 Hz, 1H), 1.07 (s, 3H), 0.77 (s, 3H).	G
(S)-1-(6-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-	**I-542**	**INT-(S)-S6**	4-(1,2,4-oxadiazol-3-yl)benzaldehyde	557.5 (Negative)	1H-NMR (400 MHz, DMSO-d6): δ 10.56 (s, 1H), 9.78 (s, 1H), 9.68 (s, 1H), 8.46 (s, 1H), 8.17 (d, J = 8.40 Hz, 2H), 8.04 (t, J = 8.80 Hz, 1H), 7.89-7.83 (m, 3H), 5.93 (d, J = 7.20 Hz, 1H), 4.52 (s, 2H), 3.99-3.96 (m, 1H), 3.70-	G

yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl					3.67 (m, 1H), 3.34-3.28 (m, 4H), 2.97-2.79 (m, 3H), 2.60 (s, 3H), 2.01 (d, J = 12.40 Hz, 1H), 1.06 (s, 3H), 0.78 (s, 3H).	
(S)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-545**	**INT-(S)-S6**	4-(trifluoromethyl)benzaldehyde	557.42 (Negative)	1H-NMR (400 MHz, DMSO-d6): δ 10.56 (s, 1H), 9.68 (s, 1H), 8.46 (s, 1H), 8.05 (t, J = 8.40 Hz, 1H), 7.91 (s, 4H), 7.84 (d, J = 8.80 Hz, 1H), 5.93 (d, J = 8.00 Hz, 1H), 4.54 (s, 2H), 3.98-3.97 (m, 1H), 3.70-3.67 (m, 1H), 3.34-3.28 (m, 4H), 2.96-2.87 (m, 3H), 2.60 (s, 3H), 2.01 (d, J = 12.40 Hz, 1H), 1.06 (s, 3H), 0.78 (s, 3H).	G
(R)-1-(6-(1-(3-chloro-4-(1,3-dimethyl-1H-pyrazol-4-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-616**	**INT-(R)-S2**	3-chloro-4-(1,3-dimethyl-1H-pyrazol-4-yl)benzaldehyde ALD-85	[M+H, M+2+H]+ 605.3, 607.3.	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.71 (s, 1H), 9.01 (d, J = 2.40 Hz, 1H), 8.35 (d, J = 2.40 Hz, 1H), 8.06 (t, J = 8.80 Hz, 1H), 7.92-7.90 (m, 2H), 7.84 (s, 1H), 7.57 (m, 1H), 7.27-7.02 (m, 1H), 5.95 (s, 1H), 4.44 (d, J = 4.00 Hz, 2H), 4.01 (t, J = 6.80 Hz, 2H), 3.83 (m, 4H), 3.32-3.29 (m, 2H), 3.03 (d, J = 11.60 Hz, 1H), 2.80 (t, J = 6.40 Hz, 2H), 2.14-2.02 (m, 5H), 1.10 (s, 3H), 0.81 (s, 3H).	M
(R)-1-(6-(1-((2,2-difluorobenzo[d][1,3]dioxol-5-yl)methyl)-4-hydroxy-3,3-dimethylpip	**I-790**	**INT-(R)-S2**	2,2-difluorobenzo[d][1,3]dioxole-5-carbaldehyde	557.3	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.55 (s, 1H), 9.00 (d, J = 2.40 Hz, 1H), 8.35 (d, J = 2.00 Hz, 1H), 8.05 (t, J = 8.40 Hz, 1H), 7.91 (d, J = 8.80 Hz, 1H), 7.79 (s, 1H), 7.58-	G

eridin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl					7.51 (m, 2H), 5.93 (s, 1H), 4.44 (s, 2H), 4.00 (t, J = 6.80 Hz, 2H), 3.48-3.36 (s, 2H), 2.95 (d, J = 12.00 Hz, 1H), 2.80 (t, J = 6.80 Hz, 2H), 2.60-2.55 (m, 1H), 2.03 (s, 1H), 1.06 (s, 3H), 0.79 (s, 3H).	
1-(6-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-541**	**INT-S6**	4-(1,2,4-oxadiazol-3-yl)benzaldehyde	557.2 (Negative)	1H-NMR (400 MHz, DMSO-d6): δ 10.57 (s, 1H), 9.78 (s, 1H), 9.65 (s, 1H), 8.47 (s, 1H), 8.18 (d, J = 8.40 Hz, 2H), 8.07-8.03 (m, 1H), 7.88-7.83 (m, 3H), 5.93 (d, J = 7.20 Hz, 1H), 4.53 (s, 2H), 3.98 (s, 1H), 3.70-3.67 (m, 1H), 3.53-3.29 (m, 4H), 3.01-2.72 (m, 3H), 2.60 (s, 3H), 2.02 (d, J = 13.20 Hz, 1H), 1.06 (s, J = 2.80 Hz, 3H), 0.78 (s, 3H).	G
(R)-4-(2-chloro-4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)phenyl)-1-methyl-1H-pyrazole-3-carbonitrile, HCl	**I-675**	**INT-(R)-S2**	4-(2-chloro-4-formylphenyl)-1-methyl-1H-pyrazole-3-carbonitrile ALD-86	[M+H, M+2+H]+ 616.46, 618.44.	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.63 (s, 1H), 9.01 (d, J = 2.40 Hz, 1H), 8.36 (d, J = 2.00 Hz, 2H), 8.06 (t, J = 8.40 Hz, 1H), 8.01 (d, J = 1.20 Hz, 1H), 7.91 (d, J = 8.80 Hz, 1H), 7.76 (dd, J = 1.20, 8.00 Hz, 1H), 7.67 (d, J = 8.00 Hz, 1H), 5.96 (s, 1H), 4.48 (d, J = 4.00 Hz, 2H), 4.04-3.99 (m, 5H), 3.40-3.32 (m, 4H), 3.07 (d, J = 11.60 Hz, 1H), 2.80 (t, J = 6.80 Hz, 2H), 2.03 (d, J = 12.80 Hz, 1H), 1.10 (s, 3H), 0.82 (s, 3H).	M

(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(3-(pyridazin-4-yl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-792**	**INT-(R)-S2**	3-(pyridazin-4-yl)benzaldehyde **ALD-87**	555.47	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 10.05 (s, 1H), 9.74 (d, J = 1.20 Hz, 1H), 9.38 (dd, J = 1.20, 5.40 Hz, 1H), 9.00 (d, J = 2.40 Hz, 1H), 8.38-8.35 (m, 2H), 8.13-8.03 (m, 3H), 7.91-7.84 (m, 2H), 7.72 (t, J = 7.60 Hz, 1H), 5.93 (s, 1H), 4.56-4.46 (m, 2H), 4.00 (t, J = 6.80 Hz, 2H), 3.43 (s, 3H), 3.33 (t, J = 11.60 Hz, 1H), 2.96 (d, J = 11.60 Hz, 1H), 2.80 (t, J = 6.40 Hz, 2H), 2.13 (d, J = 9.60 Hz, 1H), 1.10 (s, 3H), 0.79 (s, 3H).	G
(R)-4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)-2-methoxybenzonitrile, HCl	**I-713**	**INT-(R)-S2**	4-formyl-2-methoxybenzonitrile	532.2	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 10.34 (s, 1H), 9.01 (d, J = 2.40 Hz, 1H), 8.36 (d, J = 2.00 Hz, 1H), 8.05 (t, J = 8.80 Hz, 1H), 7.91-7.83 (m, 3H), 7.41 (d, J = 8.00 Hz, 1H), 5.95 (s, 1H), 4.51-4.42 (m, 2H), 4.02-3.96 (m, 5H), 3.45 (d, J = 11.60 Hz, 3H), 3.29 (t, J = 11.20 Hz, 1H), 2.84-2.79 (m, 3H), 2.02 (d, J = 12.80 Hz, 1H), 1.10 (s, 3H), 0.77 (s, 3H).	G
(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((3-oxoisoindolin-5-yl)methyl)piperidin-4-yl)quinolin-	**I-880**	**INT-(R)-S2**	3-oxoisoindoline-5-carbaldehyde **ALD-88**	532	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.57 (s, 1H), 9.00 (d, J = 2.40 Hz, 1H), 8.72 (s, 1H), 8.35 (d, J = 1.60 Hz, 1H), 8.06-8.01 (m, 2H), 7.97-7.87 (m, 2H), 7.73 (d, J = 8.00 Hz, 1H), 5.92 (s, 1H), 4.54 (d, J = 4.00 Hz,	G

3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl					2H), 4.45 (s, 2H), 4.00 (t, J = 6.80 Hz, 2H), 3.37-3.26 (m, 4H), 2.98 (d, J = 11.60 Hz, 1H), 2.80 (t, J = 6.80 Hz, 2H), 2.01 (d, J = 12.40 Hz, 1H), 1.06 (s, 3H), 0.79 (s, 3H).	
(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(oxetan-3-yl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	**I-662**	**INT-(R)-S2**	4-(oxetan-3-yl)benzaldehyde	533.4	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.97 (s, 1H), 8.33 (s, 1H), 8.08 (t, J = 8.80 Hz, 1H), 7.85 (d, J = 9.20 Hz, 1H), 7.40-7.35 (m, 4H), 5.14 (s, 1H), 4.94 (q, J = 6.00 Hz, 2H), 4.63 (t, J = 6.40 Hz, 2H), 4.25 (t, J = 7.60 Hz, 1H), 4.01 (t, J = 6.80 Hz, 2H), 3.53 (m, 2H), 3.14 (t, J = 12.00 Hz, 1H), 2.80 (t, J = 6.80 Hz, 2H), 2.56-2.50 (m, 2H), 2.68-2.68 (m, 1H), 2.21 (d, J = 10.00 Hz, 1H), 1.71 (d, J = 13.20 Hz, 1H), 1.00 (s, 3H), 0.68 (s, 3H).	G
(R)-5-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)-1-methyl-1H-indazole-3-carbonitrile	**I-824**	**INT-(R)-S2**	5-formyl-1-methyl-1H-indazole-3-carbonitrile	556.46	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.97 (d, J = 2.40 Hz, 1H), 8.33 (d, J = 2.40 Hz, 1H), 8.14-8.07 (m, 1H), 7.90-7.81 (m, 3H), 7.65 (d, J = 8.80 Hz, 1H), 5.15 (s, 1H), 4.20 (s, 3H), 4.01 (t, J = 6.40 Hz, 2H), 3.78-3.61 (m, 2H), 3.17 (t, J = 11.60 Hz, 1H), 2.90-2.80 (m, 1H), 2.80 (t, J = 6.40 Hz, 2H), 2.53-2.49 (m, 2H), 2.19 (d, J = 8.80 Hz, 1H), 1.73 (d, J = 12.80 Hz, 1H), 1.01 (s, 3H), 0.67 (s, 3H).	G

(R)-1-(5-fluoro-6-(1-(3-fluoro-4-(1,3,4-oxadiazol-2-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	**I-787**	**INT-(R)-S2**	3-fluoro-4-(1,3,4-oxadiazol-2-yl)benzaldehyde **ALD-76**	563.2	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 9.41 (s, 1H), 8.97 (d, J = 2.40 Hz, 1H), 8.33 (s, 1H), 8.11-8.02 (m, 2H), 7.85 (d, J = 9.20 Hz, 1H), 7.47 (t, J = 7.20 Hz, 2H), 5.18 (s, 1H), 4.01 (t, J = 6.40 Hz, 2H), 3.99-3.56 (m, 2H), 2.80 (t, J = 6.80 Hz, 2H), 1.74 (d, J = 16.00 Hz, 4H), 1.24 (s, 2H), 1.03 (s, 3H), 0.69 (s, 3H).	G
(R)-1-(5-fluoro-6-(4-hydroxy-1-(2-methoxy-4-(trifluoromethyl)benzyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-795**	**INT-(R)-S2**	2-methoxy-4-(trifluoromethyl)benzaldehyde	575.3	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.44 (s, 1H), 9.00 (s, 1H), 8.35 (d, J = 2.00 Hz, 1H), 8.03 (t, J = 8.80 Hz, 1H), 7.91-7.83 (m, 2H), 7.48-7.47 (m, 2H), 5.92 (s, 1H), 4.45 (d, J = 4.00 Hz, 2H), 4.02-3.99 (m, 5H), 3.40 (s, 3H), 3.38-3.27 (m, 1H), 3.02 (d, J = 12.00 Hz, 1H), 2.80 (t, J = 6.80 Hz, 2H), 1.99 (d, J = 10.80 Hz, 1H), 1.09 (s, 3H), 0.79 (s, 3H).	G
(R)-2-(difluoromethoxy)-4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)benzonitrile	**I-732**	**INT-(R)-S2**	2-(difluoromethoxy)-4-formylbenzonitrile **ALD-97**	568.2	1H-NMR (400 MHz, DMSO-d6): δ 10.62 (s, 1H), 8.98 (s, 1H), 8.34 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.92-7.84 (m, 2H), 7.51 (s, 1H), 7.45-7.41 (m, 1H), 5.19 (s, 1H), 4.01 (t, J = 6.80 Hz, 2H), 3.73 (d, J = 15.20 Hz, 1H), 3.55 (d, J = 14.80 Hz, 1H), 3.19 (t, J = 13.20 Hz, 1H), 2.82-2.79 (m, 2H), 2.70-2.47 (m, 4H), 2.14 (d, J = 10.40 Hz, 1H), 1.74	G

					(d, J = 13.20 Hz, 1H), 1.03 (s, 3H), 0.68 (s, 3H).	
(R)-1-(5-fluoro-6-(1-(3-fluoro-4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-723**	**INT-(R)-S2**	3-fluoro-4-(1,2,4-oxadiazol-3-yl)benzaldehyde **ALD-94**	563.45	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 10.23 (s, 1H), 9.84 (s, 1H), 9.01 (s, 1H), 8.36 (s, 1H), 8.36-8.16 (m, 1H), 8.08-8.03 (m, 1H), 7.95-7.89 (m, 2H), 7.77-7.75 (m, 1H), 5.96 (s, 1H), 4.57-4.48 (m, 2H), 4.02-3.99 (m, 2H), 3.35-3.29 (m, 5H), 2.94 (d, J = 11.60 Hz, 1H), 2.82-2.79 (m, 2H), 2.03 (d, J = 9.60 Hz, 1H), 1.10 (m, 3H), 0.79 (s, 3H).	G
(R)-1-(6-(1-(4-chloro-3-(difluoromethoxy)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-748**	**INT-(R)-S2**	4-chloro-3-(difluoromethoxy)benzaldehyde	[M+H,M+2+H] + 577.5, 579.4	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.83 (s, 1H), 9.00 (s, 1H), 8.35 (s, 1H), 8.05 (t, J = 8.80 Hz, 1H), 7.90 (d, J = 8.80 Hz, 1H), 7.78-7.75 (m, 2H), 7.61 (dd, J = 8.00 Hz, 1.60 Hz, 1H), 7.31 (t, J = 72.8 Hz, 1H), 5.95 (s, 1H), 4.46-4.44 (m, 2H), 4.00 (t, J = 6.40 Hz, 2H), 3.38 (m, 2H), 3.32-3.26 (m, 1H), 2.91 (d, J = 12.00 Hz, 1H), 2.80 (t, J = 6.40 Hz, 2H), 2.68-2.67 (m, 2H), 2.02 (d, J = 10.40 Hz, 1H), 1.07 (s, 3H), 0.79 (s, 3H).	G
(R)-1-(6-(1-(4-(difluoromethoxy)-3-ethoxybenzyl)-4-hydroxy-	**I-597**	**INT-(R)-S2**	4-(difluoromethoxy)-3-ethoxybenzaldehyde	587.51	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 10.33 (s, 1H), 9.01 (d, J = 2.40 Hz, 1H), 8.36 (d, J = 2.00 Hz, 1H), 8.05 (t, J = 8.80 Hz, 1H), 7.90 (d,	G

3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl					J = 9.20 Hz, 1H), 7.73 (s, 1H), 7.33-6.96 (m, 3H), 5.90 (s, 1H), 4.33-4.28 (m, 2H), 4.15 (q, J = 6.80 Hz, 2H), 4.01 (t, J = 6.80 Hz, 2H), 3.49-3.35 (m, 3H), 3.26 (t, J = 11.60 Hz, 1H), 2.80 (t, J = 6.80 Hz, 3H), 2.01 (d, J = 14.00 Hz, 1H), 1.38 (t, J = 7.20 Hz, 3H), 1.10 (s, 3H), 0.77 (s, 3H).	
(R)-1-(6-(1-(3-chloro-4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-712**	**INT-(R)-S2**	3-chloro-4-(1,2,4-oxadiazol-3-yl)benzaldehyde **ALD-96**	579.43	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 10.03 (s, 1H), 9.86 (s, 1H), 9.01 (s, 1H), 8.36 (s, 1H), 8.12-8.04 (m, 3H), 7.92-7.87 (m, 2H), 5.96 (s, 1H), 4.51 (s, 2H), 4.02-3.99 (m, 2H), 3.36-3.31 (m, 4H), 3.00 (d, J = 12.00 Hz, 1H), 2.82-2.79 (m, 2H), 2.03 (d, J = 10.40 Hz, 1H), 1.10 (s, 3H), 0.80 (s, 3H).	M
(R)-4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)-3-methoxybenzonitrile, HCl	**I-791**	**INT-(R)-S2**	4-formyl-3-methoxybenzonitrile	532.47	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.40 (s, 1H), 9.00 (d, J = 2.40 Hz, 1H), 8.34 (d, J = 2.00 Hz, 1H), 8.03 (t, J = 8.80 Hz, 1H), 7.90 (d, J = 9.20 Hz, 1H), 7.81-7.58 (m, 4H), 5.92 (s, 1H), 4.44 (d, J = 4.00 Hz, 1H), 4.02-3.96 (m, 5H), 3.65 (s, 3H), 3.26 (t, J = 11.20 Hz, 1H), 2.99 (d, J = 11.60 Hz, 1H), 2.80 (t, J = 6.40 Hz, 2H), 2.65-2.55 (m, 2H), 1.99 (d, J = 10.40 Hz, 1H), 1.07 (s, 3H), 0.78 (s, 3H).	M

(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(1-(trifluoromethyl)cyclopropyl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-578**	**INT-(R)-S2**	4-(1-(trifluoromethyl)cyclopropyl)benzaldehyde **ALD-29**	585.3	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.44 (s, 1H), 9.00 (d, J = 2.00 Hz, 1H), 8.34 (d, J = 1.60 Hz, 1H), 8.04 (t, J = 8.80 Hz, 1H), 7.90 (d, J = 8.80 Hz, 1H), 7.64 (dd, J = 8.00, 27.20 Hz, 4H), 5.93 (s, 1H), 4.43 (d, J = 4.00 Hz, 2H), 4.00 (t, J = 6.80 Hz, 2H), 3.30-3.27 (m, 3H), 3.01 (d, J = 12.00 Hz, 1H), 2.80 (t, J = 6.80 Hz, 2H), 2.02 (d, J = 12.00 Hz, 1H), 1.41-1.37 (m, 2H), 1.24-1.18 (m, 3H), 1.06 (s, 3H), 0.79 (s, 3H).	G
(R)-1-(6-(1-(3-chloro-4-(1,3,4-oxadiazol-2-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione,HCl	**I-776**	**INT-(R)-S2**	3-chloro-4-(1,3,4-oxadiazol-2-yl)benzaldehyde **ALD-77**	[M+H,M+2+H] + 579.3,581.2	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.53 (s, 1H), 9.14 (s,1H), 9.00 (d, J = 2.00 Hz, 1H), 8.34 (d, J = 2.00 Hz, 1H), 8.16-8.03 (m, 3H), 7.85 (d, J = 9.20 Hz, 1H), 7.81 (d, J = 9.20 Hz, 1H), 5.98 (s, 1H), 4.01 (t, J = 6.80 Hz, 2H), 3.52-3.41 (m, 2H), 3.33-3.09 (m, 3H), 2.80 (t, J = 6.80 Hz, 2H), 2.53-2.48 (m, 2H), 2.06-2.02 (m, 1H), 1.07 (s, 3H), 0.83 (s, 3H).	G
(R)-1-(6-(1-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-	**I-619**	**INT-(R)-S2**	3-(cyclopropylmethoxy)-4-(difluoromethoxy)benzaldehyde	613.4	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H),9.72 (s, 1H), 8.97 (s, 1H), 8.33 (s, 1H), 8.14-8.06 (m, 1H), 7.85 (d, J = 9.20 Hz, 1H), 7.56 (s, 1H), 7.34-7.05 (m, 2H), 5.15 (s, 1H), 4.01 (t, J = 6.80 Hz, 2H), 3.93 (d, J = 6.80 Hz, 2H), 3.60-3.57 (m, 1H),	G

5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl					3.42 (m, 1H), 3.16 (t, J = 12.00 Hz, 1H), 2.80 (t, J = 6.80 Hz, 2H), 2.69-2.67 (m, 1H), 2.56-2.33 (m, 2H), 2.19 (m, 1H), 1.73 (d, J = 12.00 Hz, 1H), 1.27-1.23 (m, 1H), 1.01 (m, 3H), 0.68 (s, 3H), 0.57 (q, J = 4.00 Hz, 2H), 0.36 (q, J = 4.00 Hz, 2H).	
(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-33**	**INT-(R)-S2**	4-(trifluoromethyl)benzaldehyde	545.5	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 10.51 (s, 1H), 9.01 (d, J = 2.00 Hz, 1H), 8.37 (s, 1H), 8.07-7.98 (m, 3H), 7.89 (m, 3H), 5.95 (s, 1H), 4.57-4.46 (m, 2H), 4.01 (t, J = 6.40 Hz, 2H), 3.46-3.41 (m, 3H), 3.28 (t, J = 11.20 Hz, 1H), 2.87-2.79 (m, 3H), 2.01 (d, J = 12.80 Hz, 1H), 1.10 (s, 3H), 0.77 (s, 3H).	G
(R)-1-(6-(1-(3-chloro-5-methyl-4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-876**	**INT-(R)-S2**	3-chloro-5-methyl-4-(1,2,4-oxadiazol-3-yl)benzaldehyde **ALD-89**	593.3	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.93 (s, 1H), 9.59 (s, 1H), 9.01 (d, J = 2.40 Hz, 1H), 8.35 (d, J = 2.00 Hz, 1H), 8.06 (t, J = 8.40 Hz, 1H), 7.92-7.89 (m, 2H), 7.69 (s, 1H), 5.96 (s, 1H), 4.47 (d, J = 4.40 Hz, 2H), 4.00 (t, J = 6.40 Hz, 2H), 3.38-3.33 (m, 4H), 3.08 (d, J = 12.00 Hz, 1H), 2.80 (t, J = 6.40 Hz, 2H), 2.21 (s, 3H), 2.03 (d, J = 13.20 Hz, 1H), 1.10 (d, J = 2.80 Hz, 3H), 0.83 (s, 3H).	G

(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)methyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-843**	**INT-(R)-S2**	1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carbaldehyde	549.2	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 10.09 (s, 1H), 9.01 (d, J = 2.40 Hz, 1H), 8.36 (d, J = 2.00 Hz, 1H), 8.15 (s, 1H), 8.04 (t, J = 8.80 Hz, 1H), 7.91-7.71 (m, 2H), 5.90 (s, 1H), 5.24 (q, J = 9.20 Hz, 2H), 4.36-4.24 (m, 2H), 4.00 (t, J = 6.80 Hz, 2H), 3.35-3.16 (m, 3H), 2.92 (d, J = 12.00 Hz, 2H), 2.80 (t, J = 6.40 Hz, 2H), 2.00 (d, J = 13.60 Hz, 1H), 1.08 (d, J = 2.40 Hz, 3H), 0.79 (s, 3H).	G
(R)-1-(5-fluoro-6-(4-hydroxy-1-((1-isopropyl-1H-pyrazol-4-yl)methyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-864**	**INT-(R)-S2**	1-isopropyl-1H-pyrazole-4-carbaldehyde	509.56	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.60 (s, 1H), 9.00 (d, J = 2.40 Hz, 1H), 8.35 (d, J = 2.00 Hz, 1H), 8.07-8.01 (m, 2H), 8.03 (d, J = 3.60 Hz, 1H), 7.67 (s, 1H), 5.89 (s, 1H), 4.59-4.52 (m, 1H), 4.25 (d, J = 4.00 Hz, 2H), 4.00 (t, J = 6.80 Hz, 2H), 3.31-3.17 (m, 5H), 2.80 (t, J = 6.80 Hz, 2H), 2.02-1.99 (m, 1H), 1.44 (d, J = 6.80 Hz, 6H), 1.07 (d, J = 2.80 Hz, 3H), 0.80 (s, 3H).	G
(R)-1-(6-(1-((1-cyclopropyl-1H-pyrazol-4-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-	**I-866**	**INT-(R)-S2**	1-cyclopropyl-1H-pyrazole-4-carbaldehyde	507.5	1H-NMR (400 MHz, DMSO-d6): δ 10.64 (s, 1H), 10.08 (s, 1H), 9.02 (d, J = 2.40 Hz, 1H), 8.37 (d, J = 2.00 Hz, 1H), 8.07-8.02 (m, 2H), 7.90 (d, J = 9.20 Hz, 1H), 7.66 (s, 1H), 5.90 (s, 1H), 4.21 (s, 1H), 4.20-4.03 (m, 2H), 3.99-3.79 (m, 2H), 3.83-3.77 (m, 1H), 3.36-	G

yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl					3.14 (m, 3H), 2.95-2.82 (m, 1H), 2.81 (t, J = 6.80 Hz, 2H), 2.01-1.98 (m, 1H), 1.10-1.05 (m, 3H), 1.04 (d, J = 4.40 Hz, 2H), 1.02-0.99 (m, 2H), 0.79 (s, 3H).	
(R)-1-(6-(1-((5-chloro-1-methyl-1H-pyrazol-4-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-867**	**INT-(R)-S2**	5-chloro-1-methyl-1H-pyrazole-4-carbaldehyde	515.47	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.87 (s, 1H), 9.01 (d, J = 2.40 Hz, 1H), 8.35 (d, J = 2.00 Hz, 1H), 8.03 (t, J = 8.80 Hz, 1H), 7.90 (d, J = 9.20 Hz, 2H), 5.89 (s, 1H), 4.25-4.19 (m, 2H), 4.00 (t, J = 6.40 Hz, 2H), 3.87 (s, 3H), 3.34 (t, J = 10.00 Hz, 3H), 3.22 (m, 1H), 3.05 (d, J = 12.00 Hz, 1H), 2.82-2.67 (m, 2H), 2.01 (d, J = 10.00 Hz, 1H), 1.09 (d, J = 2.80 Hz, 3H), 0.8 (s, 3H).	G
(R)-3-(4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)-1H-pyrazol-1-yl)benzonitrile, 0.64Formic Acid	**I-842**	**INT-(R)-S2**	3-(4-formyl-1H-pyrazol-1-yl)benzonitrile **ALD-103**	568.47	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.96 (d, J = 2.40 Hz, 1H), 8.58 (s, 1H), 8.33 (t, J = 2.00 Hz, 2H), 8.23 (t, J = 6.00 Hz, 2H), 8.15-8.06 (m, 1H), 7.85 (d, J = 8.80 Hz, 1H), 7.84-7.73 (m, 3H), 5.13 (s, 1H), 4.02-3.99 (m, 2H), 3.56-3.48 (m, 2H), 3.33-3.11 (m, 2H), 2.82-2.68 (m, 3H), 2.60-2.55 (m, 1H), 2.31 (d, J = 10.40 Hz, 1H), 1.73 (d, J = 13.60 Hz, 1H), 0.99 (d, J = 2.80 Hz, 3H), 0.71 (s, 3H).	G
(R)-1-(5-fluoro-6-(4-hydroxy-3,3-	**I-755**	**INT-(R)-S2**	4-morpholinobenzaldehyde	562.2	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.96 (d, J = 2.40 Hz, 1H), 8.32 (d,	G

dimethyl-1-(4-morpholinobenzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, 0.85Formic Acid					J = 2.00 Hz, 1H), 8.15 (m, 1H), 8.07 (d, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.20 (d, J = 8.40 Hz, 2H), 6.91 (d, J = 8.80 Hz, 2H), 5.10 (s, 1H), 4.00 (t, J = 6.80 Hz, 2H), 3.75-3.73 (m, 4H), 3.49-3.38 (m, 3H), 3.15-3.08 (m, 5H), 2.82-2.78 (m, 2H), 2.69-2.67 (m, 1H), 2.50-2.16 (m, 2H), 1.69 (d, J = 13.20 Hz, 1H), 0.98 (d, J = 2.80 Hz, 3H), 0.98 (s, 3H).	
(R)-1-(6-(1-((1-ethyl-1H-pyrazol-4-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-862**	**INT-(R)-S2**	1-ethyl-1H-pyrazole-4-carbaldehyde **ALD-101**	495.6	1H-NMR (400 MHz, DMSO-d6): δ 10.64 (s, 1H), 10.06 (s, 1H), 9.02 (d, J = 2.40 Hz, 1H), 8.38 (s, 1H), 8.03 (dd, J = 7.60, 17.00 Hz, 2H), 7.90 (d, J = 9.20 Hz, 1H), 7.69 (s, 1H), 5.90 (s, 1H), 4.24-4.18 (m, 4H), 4.15-3.99 (m, 2H), 3.36-3.17 (m, 4H), 2.93 (d, J = 12.00 Hz, 1H), 2.82-2.51 (m, 2H), 2.34-1.98 (m, 1H), 1.39 (t, J = 7.20 Hz, 3H), 1.09 (s, 3H), 0.79 (s, 3H).	G
(R)-1-(6-(1-((3-chloro-1-methyl-1H-pyrazol-4-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydrop	**I-871**	**INT-(R)-S2**	3-chloro-1-methyl-1H-pyrazole-4-carbaldehyde **ALD-102**	515	1H-NMR (400 MHz, DMSO-d6): δ 10.64 (s, 1H), 10.41 (s, 1H), 9.02 (d, J = 2.40 Hz, 1H), 8.37 (d, J = 2.00 Hz, 1H), 8.17 (s, 1H), 8.04 (t, J = 8.80 Hz, 1H), 7.90 (d, J = 9.20 Hz, 1H), 5.90 (s, 1H), 4.24-4.17 (m, 2H), 4.05-3.99 (m, 3H), 3.89 (s, 2H), 3.41-3.16 (m, 4H), 3.01 (d, J = 11.60 Hz, 1H),	M

yrimidine-2,4(1H,3H)-dione, HCl					2.80 (t, J = 6.80 Hz, 2H), 2.05 (d, J = 23.20 Hz, 1H), 1.12 (d, J = 2.40 Hz, 3H), 0.80 (s, 3H).	
1-(6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, 0.86HCl	**I-816**	**INT-S7**	4-(trifluoromethyl)benzaldehyde	527.45	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (d, J = 7.20 Hz, 1H), 9.43 (s, 1H), 8.93 (s, 1H), 8.34 (s, 1H), 8.02-7.83 (m, 7H), 5.68 (s, 1H), 4.55 (s, 2H), 3.97 (t, J = 6.80 Hz, 2H), 3.00-2.97 (m, 2H), 2.80 (t, J = 6.40 Hz, 2H), 1.84 (m, 2H), 1.24 (s, 3H), 0.87 (s, 3H).	G
(R)-1-(5-fluoro-6-(1-((1-(3-fluorophenyl)-1H-pyrazol-4-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-838**	**INT-(R)-S2**	1-(3-fluorophenyl)-1H-pyrazole-4-carbaldehyde **ALD-58**	561.2	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.75 (s, 1H), 9.00 (d, J = 2.40 Hz, 1H), 8.80 (s, 1H), 8.35 (d, J = 2.00 Hz, 1H), 8.07-8.03 (m, 2H), 7.90 (dd, J = 9.20, Hz, 1H), 7.78-7.73 (m, 2H), 7.63-7.58 (m, 1H), 7.25-7.20 (m, 1H), 5.91 (s, 1H), 4.36 (s, 2H), 4.00 (t, J = 6.40 Hz, 2H), 3.41-3.31 (m, 5H), 3.26 (d, J = 11.60 Hz, 1H), 3.08 (t, J = 12.00 Hz, 2H), 2.02 (d, J = 10.00 Hz, 1H), 1.09 (s, 3H), 0.83 (s, 3H).	G
(R)-4-(4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-	**I-849**	**INT-(R)-S2**	4-(4-formyl-1H-pyrazol-1-yl)benzonitrile	568.5	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 10.04 (s, 1H), 9.01 (d, J = 2.40 Hz, 1H), 8.92 (s, 1H), 8.36 (d, J = 2.00 Hz, 1H), 8.10-8.02 (m, 6H), 7.96-7.89 (m, 1H), 5.91 (s, 1H), 4.36 (s, 2H), 4.01 (t, J	G

dimethylpiperidin-1-yl)methyl)-1H-pyrazol-1-yl)benzonitrile					= 6.80 Hz, 2H), 3.39-3.30 (m, 4H), 3.25 (d, J = 11.60 Hz, 1H), 3.07 (t, J = 11.60 Hz, 2H), 2.02 (d, J = 10.00 Hz, 1H), 1.11 (s, 3H), 0.82 (s, 3H).	
(R)-4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)-2-(2-methoxyethoxy)benzonitrile, AcOH	**I-717**	**INT-(R)-S2**	4-formyl-2-(2-methoxyethoxy)benzonitrile	576.2	1H-NMR (400 MHz, DMSO-d6): δ 11.96 (s, 1H), 10.62 (s, 1H), 8.97 (s, 1H), 8.33 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.85 (t, J = 9.20 Hz, 1H), 7.70 (s, 1H), 7.27 (s, 1H), 7.11 (d, J = 7.60 Hz, 1H), 5.17 (s, 1H), 4.33-4.23 (m, 2H), 4.01 (t, J = 6.80 Hz, 2H), 3.74-3.70 (m, 3H), 3.66 (d, J = Hz, 1H), 3.37-3.33 (m, 2H), 3.22-3.17 (m, 3H), 2.82-2.67 (m, 3H), 2.50-2.35 (m, 1H), 2.17-2.16 (m, 1H),1.92-1.85 (s, 3H), 1.80-1.70 (m, 1H), 1.03 (s, 3H), 0.68 (s, 3H).	G
(R)-1-(6-(1-((1-(3-chlorophenyl)-1H-pyrazol-4-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-844**	**INT-(R)-S2**	1-(3-chlorophenyl)-1H-pyrazole-4-carbaldehyde **ALD-59**	577.4	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.99 (s, 1H), 9.01 (s, 1H), 8.84 (s, 1H), 8.36 (s, 1H), 8.05 (t, J = 9.20 Hz, 2H), 7.97 (s, 1H), 7.92-7.85 (m, 2H), 7.59 (t, J = 8.00 Hz, 1H), 7.45 (d, J = 8.00 Hz, 1H), 5.91 (s, 1H), 4.35 (s, 2H), 4.00 (t, J = 6.80 Hz, 2H), 3.41-3.34 (m, 4H), 3.26 (d, J = 11.20 Hz, 1H), 3.06 (t, J = 12.00 Hz, 1H), 2.81-2.80 (m, 1H), 2.02 (d, J = 11.20 Hz, 1H), 1.10 (s, 3H), 0.82 (s, 3H).	M

(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((1-(2,2,2-trifluoroethyl)-1H-pyrrol-3-yl)methyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-833**	**INT-(R)-S2**	1-(2,2,2-trifluoroethyl)-1H-pyrrole-3-carbaldehyde **ALD-61**	548.4	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.36 (s, 1H), 9.01 (s, 1H), 8.35 (s, 1H), 8.03 (t, J = 8.80 Hz, 1H), 7.90 (d, J = 8.80 Hz, 1H), 7.13 (s, 1H), 6.95 (s, 1H), 5.86 (s, 1H), 5.01-4.94 (m, 2H), 4.22 (s, 2H), 4.00 (t, J = 6.80 Hz, 3H), 3.32 (s, 3H), 3.19 (t, J = 11.60 Hz, 1H), 2.93 (d, J = 12.00 Hz, 1H), 2.80 (t, J = 6.40 Hz, 2H), 2.00 (d, J = 10.00 Hz, 1H), 1.05 (s, 3H), 0.78 (s, 3H).	G
(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((6-(1-(trifluoromethyl)cyclopropyl)pyridin-3-yl)methyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-784**	**INT-(R)-S2**	6-(1-(trifluoromethyl)cyclopropyl)nicotinaldehyde	586.52	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 9.43 (bs, 1H), 8.97 (s, 1H), 8.51 (s, 1H), 8.33 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.86-7.83 (m, 1H), 7.81-7.78 (m, 1H), 7.54 (d, J = 8.00 Hz, 1H), 5.15 (s, 1H), 4.02-3.99 (m, 2H), 3.61-3.50 (m, 2H), 3.13 (t, J = 13.60 Hz, 1H), 2.82-2.79 (m, 2H), 2.68 (s, 1H), 2.17 (d, J = 6.40 Hz, 1H), 1.92 (s, 1H), 1.73 (t, J = 12.80 Hz, 2H), 1.40 (d, J = 18.80 Hz, 4H), 0.99 (s, 3H), 0.68 (s, 3H).	G
(R)-1-(4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpip	**I-622**	**INT-(R)-S2**	1-(4-formylphenyl)cyclopropane-1-carbonitrile **ALD-99**	542.2	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.96 (d, J = 2.40 Hz, 1H), 8.32 (d, J = 2.00 Hz, 1H), 8.08 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.38 (d, J = 8.00 Hz, 2H), 7.31 (d, J = 8.00 Hz, 2H), 5.13 (s, 1H), 4.04-	G

eridin-1-yl)methyl)phenyl)cyclopropane-1-carbonitrile					3.99 (m, 2H), 3.57 (d, J = 13.60 Hz, 1H), 3.46 (d, J = 13.60 Hz, 1H), 3.12-3.08 (m, 1H), 2.80 (t, J = 6.80 Hz, 2H), 2.68-2.51 (m, 1H), 2.47-2.34 (m, 2H), 2.17 (d, J = 10.40 Hz, 1H), 1.76-1.73 (m, 3H), 1.51 (t, J = 2.80 Hz, 2H), 1.00 (s, 3H), 0.67 (s, 3H).	
(R)-5-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)-2-(2-methoxyethoxy)benzonitrile	**I-821**	**INT-(R)-S2**	5-formyl-2-(2-methoxyethoxy)benzonitrile	576.5	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.96 (d, J = 2.40 Hz, 1H), 8.32 (d, J = 2.00 Hz, 1H), 8.10-8.06 (m, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.65-7.61 (m, 2H), 7.26 (d, J = 8.40 Hz, 1H), 5.14 (s, 1H), 4.27 (t, J = 4.40 Hz, 2H), 4.00 (t, J = 6.80 Hz, 2H), 3.71 (t, J = 4.40 Hz, 2H), 3.60-3.41 (m, 3H), 3.34 (d, J = 7.60 Hz, 3H), 3.17-3.10 (m, 1H), 2.80 (t, J = 6.40 Hz, 2H), 2.68 (t, J = 1.60 Hz, 1H), 2.34 (m, 1H), 2.14 (d, J = 10.80 Hz, 1H), 1.75-1.69 (m, 1H), 0.99 (s, 3H), 0.68 (s, 3H).	G
(R)-1-(5-fluoro-6-(4-hydroxy-1-(3-(2-methoxyethoxy)-4-(trifluoromethyl)benzyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydrop	**I-771**	**INT-(R)-S2**	3-(2-methoxyethoxy)-4-(trifluoromethyl)benzaldehyde **(ALD-93)**	619.3	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.42 (s, 1H), 9.01 (d, J = 2.40 Hz, 1H), 8.35 (d, J = 2.00 Hz, 1H), 8.05 (t, J = 8.80 Hz, 1H), 7.91 (d, J = 9.20 Hz, 1H), 7.77 (d, J = 8.00 Hz, 1H), 7.63 (s, 1H), 7.35 (d, J= 7.60 Hz, 1H), 5.96 (s, 1H), 4.47 (d, J = 5.60 Hz, 2H), 4.30 (d, J = 3.20	G

yrimidine-2,4(1H,3H)-dione, HCl					Hz, 2H), 4.00 (t, J = 6.40 Hz, 2H), 3.74 (t, J = 4.40 Hz, 2H), 3.60-3.29 (m, 7H), 2.97 (d, J = 11.20 Hz, 1H), 2.80 (t, J = 6.80 Hz, 2H), 2.09-2.02 (m, 1H), 1.06 (d, J = 2.80 Hz, 3H), 0.80 (s, 3H).	
(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(3-methyloxetan-3-yl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, 0.65AcOH	**I-737**	**INT-(R)-S2**	4-(3-methyloxetan-3-yl)benzaldehyde	547.48	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.96 (d, J = 2.40 Hz, 1H), 8.32 (t, J = 2.00 Hz, 1H), 8.10-8.06 (m, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.34 (d, J = 8.00 Hz, 2H), 7.22 (d, J = 8.40 Hz, 2H), 5.13 (s, 1H), 4.81 (d, J = 5.20 Hz, 2H), 4.54 (d, J = 5.60 Hz, 2H), 4.01 (t, J = 6.80 Hz, 2H), 3.55 (d, J = 13.60 Hz, 1H), 3.46 (d, J = 13.60 Hz, 1H), 3.14 (t, J = 12.00 Hz, 1H), 2.80 (d, J = 13.60 Hz, 2H), 2.52-2.50 (m, 1H), 2.21 (t, J = 10.80 Hz, 1H), 1.72-1.69 (m, 6H), 1.24 (s, 3H), 0.70 (s, 3H).	G
1-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethyl-1-((S)-1-(4-(trifluoromethyl)phenyl)ethyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	**I-825**	**INT-(R)-S2**	1-(4-(trifluoromethyl)phenyl)ethan-1-one	559.3	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 10.21 (s, 1H), 9.00 (d, J = 2.40 Hz, 1H), 8.36 (d, J = 2.00 Hz, 1H), 8.00-7.87 (m, 6H), 5.85 (s, 1H), 4.74 (s, 1H), 4.01 (t, J = 6.40 Hz, 2H), 3.68-3.51 (m, 2H), 3.31-3.13 (m, 2H), 2.82-2.79 (m, 3H), 2.01 (m, 1H), 1.79 (m, 3H), 1.11 (m, 3H), 0.73 (s, 3H).	I

1-(5-fluoro-6-((4S)-4-hydroxy-3,3-dimethyl-1-(1-(4-(trifluoromethyl)phenyl)ethyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-829**	**INT-(R)-S2**	1-(4-(trifluoromethyl)phenyl)ethan-1-one	559.3	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.68 (s, 1H), 9.00 (d, J = 2.40 Hz, 1H), 8.34 (d, J = 2.00 Hz, 1H), 8.02 (t, J = 8.80 Hz, 3H), 7.92-7.88 (m, 3H), 5.85 (s, 1H), 4.78 (t, J = 6.00 Hz, 1H), 4.00 (t, J = 6.40 Hz, 2H), 3.41-3.32 (m, 2H), 3.21-3.15 (m, 3H), 2.80 (t, J = 6.80 Hz, 2H), 1.96 (d, J = 14.40 Hz, 1H), 1.82 (d, J = 6.80 Hz, 3H), 1.17 (s, 3H), 0.88 (s, 3H).	I
(R)-5-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)-N-ethylpicolinamide, HCl	**I-800**	**INT-(R)-S2**	N-ethyl-5-formylpicolinamide	549.3	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 10.38 (s, 1H), 9.01-8.91 (m, 3H), 8.36 (m, 2H), 8.13 (d, J = 8.00 Hz, 1H), 8.05 (t, J = 8.80 Hz, 1H), 7.90 (d, J = 9.20 Hz, 1H), 6.03 (s, 1H), 4.58-4.52 (m, 2H), 4.01 (t, J = 6.80 Hz, 2H), 3.41 (m, 3H),-3.31 (m, 6H), 2.93-2.82 (m, 1H), 2.80-2.67 (m, 2H), 2.35-2.33 (m, 1H), 1.16-1.09 (m, 6H), 0.78 (s, 3H),	G
(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(2-methyl-4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-	**I-798**	**INT-(R)-S2**	2-methyl-4-(trifluoromethyl)benzaldehyde	559.5	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.78 (s, 1H), 9.01 (d, J = 2.40 Hz, 1H), 8.36 (d, J = 2.00 Hz, 1H), 8.08-8.04 (m, 2H), 8.01 (d, J = 8.40 Hz, 1H), 7.72 (t, J = 8.40 Hz, 2H), 5.97 (s, 1H), 4.54 (s, 2H), 4.01 (t, J = 6.80 Hz, 2H), 3.57-3.43 (m, 4H), 3.02 (d, J = 11.60 Hz, 1H), 2.80 (t, J = 6.40 Hz, 2H),	G

2,4(1H,3H)-dione, HCl					2.68 (t, J = 1.60 Hz, 3H), 2.03 (d, J = 14.00 Hz, 1H), 1.12 (s, 3H), 0.80 (s, 3H),	
(R)-1-(6-(1-(4-(2-(dimethylamino)ethoxy)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, 2Formic Acid	**I-818**	**INT-(R)-S2**	4-(2-(dimethylamino)ethoxy) benzaldehyde **ALD-66**	564.3	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.96 (d, J = 2.40 Hz, 1H), 8.32 (d, J = 2.00 Hz, 1H), 8.18 (s, 2H), 8.08 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.26 (d, J = 8.40 Hz, 2H), 6.91 (d, J = 8.80 Hz, 2H), 5.13 (s, 1H), 4.06 (t, J = 5.60 Hz, 2H), 4.00 (t, J = 7.20 Hz, 2H), 3.52 (d, J = 12.80 Hz, 1H), 3.41 (d, J = 13.20 Hz, 1H), 3.24 (m, 1H), 2.80 (t, J = 6.80 Hz, 2H), 2.73-2.68 (m, 3H), 2.50-2.43 (m, 2H), 2.29 (s, 6H), 2.26-2.20 (m, 1H), 1.71 (d, J = 13.20 Hz, 1H), 0.98 (m, 3H), 0.67 (s, 3H),	G
(R)-1-(6-(1-((5-chloropyrazolo[1,5-a]pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-857**	**INT-(R)-S2**	5-chloropyrazolo[1,5-a]pyridine-3-carbaldehyde	551.3	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.41 (s, 1H), 9.00 (d, J = 2.40 Hz, 1H), 8.84 (d, J = 7.60 Hz, 1H), 8.34 (t, J = 2.40 Hz, 3H), 8.04 (t, J = 8.80 Hz, 1H), 7.90 (dd, J = 9.20, Hz, 1H), 7.09 (dd, J = 2.40, 7.60 Hz, 1H), 5.89 (s, 1H), 4.61 (s, 2H), 4.00 (t, J = 7.20 Hz, 2H), 3.95 -3.54 (m, 1H), 3.33-3.28 (m, 3H), 2.81 (dd, J = 6.40, Hz, 1H), 2.79 (t, J = 6.80 Hz, 2H), 2.08-2.00 (m, 1H),	G

					1.06 (s, 3H), 0.80 (s, 3H).	
(R)-1-(5-fluoro-6-(1-(4-(3-fluorooxetan-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	**I-591**	**INT-(R)-S2**	4-(3-fluorooxetan-3-yl)benzaldehyde	551.5	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 8.97 (d, J = 2.40 Hz, 1H), 8.33 (q, J = 0.40 Hz, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.85 (d, J = 8.80 Hz, 1H), 7.53 (d, J = 7.60 Hz, 2H), 7.47 (d, J = 8.40 Hz, 2H), 5.15 (s, 1H), 4.99-4.96 (m, 2H), 4.94-4.90 (m, 3H), 4.01 (t, J = 6.80 Hz, 2H), 3.61 (d, J = 13.60 Hz, 1H), 3.51 (d, J = 13.60 Hz, 1H), 3.34 (s, 1H), 2.80 (t, J = 6.80 Hz, 2H), 2.68 (q, J = 1.60 Hz, 1H), 2.56-2.51 (m, 1H), 2.19 (dd, J = 10.40, Hz, 1H), 1.78-1.70 (m, 1H), 1.01 (d, J = 3.60 Hz, 3H), 0.68 (s, 3H).	G
(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((3-phenylcyclobutyl)methyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	**I-875**	**INT-(R)-S2**	3-phenylcyclobutane-1-carbaldehyde **ALD-35**	531.3	1H-NMR (400 MHz, DMSO-d6): δ 10.60 (s, 1H), 8.96 (d, J = 2.40 Hz, 1H), 8.31 (s, 1H), 8.21 (s, 1H), 8.08 (s, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.31-7.19 (m, 5H), 5.13 (s, 1H), 3.99 (t, J = 6.40 Hz, 2H), 3.29 (s, 2H), 3.12 (q, J = 13.20 Hz, 2H), 2.80 (t, J = 6.40 Hz, 2H), 2.69 (d, J = 11.60 Hz, 1H), 2.47 (t, J = 5.60 Hz, 2H), 2.34 (s, 3H), 2.22 (t, J = 13.60 Hz, 3H), 1.75-1.67 (m, 2H), 0.97 (s, 3H), 0.71 (s, 3H).	G

(R)-1-(5-fluoro-6-(4-hydroxy-1-(isothiazol-5-ylmethyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-794**	**INT-(R)-S2**	isothiazole-5-carbaldehyde	484.4	1H-NMR (400 MHz, DMSO-d6): δ 10.72 (s, 1H), 10.63 (s, 1H), 9.01 (d, J = 2.40 Hz, 1H), 8.67 (s, 1H), 8.37 (d, J = 2.40 Hz, 1H), 8.05 (t, J = 8.80 Hz, 1H), 7.90 (d, J = 8.80 Hz, 1H), 7.78 (s, 1H), 5.96 (s, 1H), 4.83 (q, J = 5.20 Hz, 2H), 4.03-3.99 (m, 2H), 3.41-3.28 (m, 4H), 2.91 (d, J = 11.60 Hz, 1H), 2.81 (t, J = 6.40 Hz, 2H), 2.03 (d, J = 9.20 Hz, 1H), 1.10 (d, J = 2.40 Hz, 3H), 0.79 (s, 3H).	M
(R)-1-(5-fluoro-6-(4-hydroxy-1-(4-(3-hydroxyoxetan-3-yl)benzyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, Formic Acid	**I-709**	**INT-(R)-S2**	4-(3-hydroxyoxetan-3-yl)benzaldehyde	549.6	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.96 (d, J = 2.40 Hz, 1H), 8.33 (d, J = 2.00 Hz, 1H), 8.20 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.57 (d, J = 8.40 Hz, 2H), 7.38 (d, J = 8.00 Hz, 2H), 6.29 (s, 1H), 5.12 (s, 1H), 4.77 (d, J = 6.40 Hz, 2H), 4.70 (q, J = 2.40 Hz, 2H), 4.01 (t, J = 1.60 Hz, 2H), 3.57 (d, J = 2.00 Hz, 1H), 3.48 (d, J = 13.60 Hz, 2H), 3.33 (s, 2H), 2.80 (t, J = 6.80 Hz, 2H), 2.48 (t, J = 11.20 Hz, 2H), 2.20 (d, J = 10.80 Hz, 1H), 1.71 (d, J = 13.60 Hz, 1H), 1.01 (d, J = 3.20 Hz, 3H), 0.68 (s, 3H).	M
(R)-1-(6-(1-(2-cyclopropoxy-4-(trifluoromethyl)benzyl)	**I-845**	**INT-(R)-S2**	2-cyclopropoxy-4-(trifluoromethyl)benzald	601.2	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.97 (d, J = 2.40 Hz, 1H), 8.33 (d, J = 2.00 Hz, 1H), 8.08 (t, J = 8.80 Hz,	G

-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione			ehyde **ALD-37**		1H), 7.85 (d, J = 9.20 Hz, 1H), 7.64 (d, J = 7.60 Hz, 1H), 7.53 (s, 1H), 7.36 (d, J = 7.60 Hz, 1H), 5.13 (s, 1H), 4.05-3.99 (m, 3H), 3.50 (m, 1H), 3.18-3.15 (m, 1H), 2.79-2.60 (m, 6H), 2.19 (d, J = 10.40 Hz, 1H), 1.92-1.69 (m, 1H), 1.02 (m, 3H), 0.88-0.83 (m, 7H).	
3-(6-(1-((4-(1,2,4-oxadiazol-3-yl)phenyl)methyl-d)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-561**	**51d**	No	545.3	1H-NMR (400 MHz, DMSO-d6 10.99 (s, 1H), 9.84 (s, 1H), 9.78 (s, 1H), 8.89 (d, J = 2.00 Hz, 1H), 8.38 (s, 1H), 8.17 (d, J = 8.40 Hz, 2H), 8.07 (t, J = 8.80 Hz, 1H), 7.91-7.88 (m, 3H), 5.93 (s, 1H), 4.50 (dd, J = 5.20, 16.20 Hz, 1H), 4.24 (dd, J = 4.80, 12.80 Hz, 1H), 3.56-3.40 (m, 4H), 3.31-3.28 (s, 1H), 2.67-2.98 (m, 3H), 2.08-2.03 (m, 2H), 1.08 (s, 3H), 0.078 (s, 3H).	J
(R)-1-(5-fluoro-6-(4-hydroxy-1-(2-hydroxy-4-(trifluoromethyl)benzyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	**I-861**	**INT-(R)-S2**	2-cyclopropoxy-4-(trifluoromethyl)benzaldehyde	561.2	1H-NMR (400 MHz, DMSO-d6): δ 10.62 (s, 1H), 8.98 (d, J = 2.40 Hz, 1H), 8.34 (d, J = 2.40 Hz, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.86 (d, J = 9.20 Hz, 1H), 7.39 (d, J = 7.60 Hz, 1H), 7.12 (d, J = 8.40 Hz, 1H), 7.04 (s, 1H), 5.34 (s, 1H), 4.01 (t, J = 6.40 Hz, 2H), 3.78 (d, J = 7.20 Hz, 2H), 3.33 (s, 4H), 2.81 (t, J = 6.40 Hz, 3H), 1.79 (d, J = 8.00 Hz, 2H), 1.01 (d, J = 3.20 Hz, 3H), 0.73 (s, 3H).	G

(R)-1-(5-fluoro-6-(4-hydroxy-1-(isothiazol-4-ylmethyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-733**	**INT-(R)-S2**	isothiazole-4-carbaldehyde	484.4	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 10.40 (s, 1H), 9.42 (s, 1H), 9.01 (s, 1H), 8.86 (s, 1H), 8.36 (s, 1H), 8.05 (m, 1H), 7.90 (d, J = 8.80 Hz, 1H), 5.92 (s, 1H), 4.50 (m, 2H), 4.01 (m, 2H), 3.45 (m, 2H), 3.40-3.20 (m, 2H), 2.92 (m, 1H), 2.81 (m, 2H), 1.98 m, 1H),1.10 (s, 3H), 0.79 (s, 3H).	G
(R)-1-(5-fluoro-6-(4-hydroxy-1-(4-(1-hydroxycyclobutyl)benzyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, 0.88Formic Acid-	**I-656**	**INT-(R)-S2**	4-(1-hydroxycyclobutyl)benzaldehyde **ALD-38**	547	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.96 (d, J = 2.40 Hz, 1H), 8.32 (d, J = 2.00 Hz, 1H), 8.21 (s, 1H), 8.11-8.07 (m, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.45 (d, J = 8.40 Hz, 2H), 7.32 (d, J = 8.00 Hz, 2H), 5.12 (s, 1H), 4.00 (t, J = 7.60 Hz, 2H), 3.56 (d, J = 13.60 Hz, 1H), 3.45 (d, J = 13.60 Hz, 2H), 3.14 (s, 2H), 2.80 (t, J = 6.80 Hz, 2H), 2.68 (d, J = 1.60 Hz, 1H), 2.67 (d, J = 1.60 Hz, 1H), 2.52-2.47 (m, 2H), 2.44-2.37 (m, 2H), 2.29-2.19 (m, 3H), 1.92 (m, 1H), 1.72-1.65 (m, 2H), 1.00 (d, J = 3.20 Hz, 3H), 0.68 (s, 3H).	G
(R)-1-(6-(1-(3-chloro-4-(3-hydroxyoxetan-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-	**I-785**	**INT-(R)-S2**	3-chloro-4-(3-hydroxyoxetan-3-yl)benzaldehyde **ALD-20**	583.2	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (br s, 1H), 8.97 (d, J = 3.00 Hz, 1H), 8.33 (d, J = 2.00 Hz, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.85 (d, J = 8.80 Hz, 1H), 7.44-7.32 (m, 3H), 6.24 (s, 1H), 5.15 (s, 1H), 5.08 (d,	G

5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione					J = 7.20 Hz, 2H), 4.70 (d, J = 7.20 Hz, 2H) 4.00 (t, J = 8.80 Hz, 2H), 3.62-3.47 (m, 2H), 3.18-3.12 (m, 1H), 2.81-2.67 (m, 4H), 2.52-2.49 (m, 1H), 2.18 (d, J = 10.8 Hz, 1H), 1.72 (d, J = 10.8 Hz, 1H), 1.02 (d, J = 3.20 Hz, 3H), 0.69 (s, 3H).	
3-(6-((R)-1-((4-(1,2,4-oxadiazol-3-yl)phenyl)methyl-d2)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-581**	**(R)-51d**	alkylation	546.2	1H-NMR (400 MHz, DMSO-d6 11.00 (s, 1H), 10.06 (s, 1H), 9.78 (s, 1H), 8.91 (d, J = 1.60 Hz, 1H), 8.41 (s, 1H), 8.17 (m, 2H), 8.08 (t, J = 8.80 Hz, 1H), 7.93-7.90 (m, 3H), 5.94 (s, 1H), 4.25 (dd, J = 4.40, 12.60 Hz, 1H), 3.42-3.27 (m, 4H), 2.91-2.65 (m, 3H), 2.15-1.96 (m, 2H), 1.09 (s, 3H), 0.78 (s, 3H), (Note: one aliphatic proton overlapped with deuterated solvent).	J
3-(6-(1-((4-(1,2,4-oxadiazol-3-yl)phenyl)methyl-d2)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, HCl	**I-579**	**51d**	alkylation	546.3	1H-NMR (400 MHz, DMSO-d6 11.00 (s, 1H), 10.26 (s, 1H), 9.78 (s, 1H), 8.92 (d, J = 1.20 Hz, 1H), 8.43 (s, 1H), 8.16 (m, 2H), 8.08-8.06 (m, 1H), 7.92-7.90 (m, 3H), 5.94 (s, 1H), 4.26 (dd, J = 4.80, 12.80 Hz, 1H), 3.42-3.27(m, 4H), 2.88-2.64 (m, 3H), 2.16-2.01 (m, 2H), 1.10 (s, 3H), 0.77 (s, 3H). (Note: one aliphatic proton overlapped with deuterated solvent).	J

1-(4-(((4R)-4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)phenyl)cyclopropane-1-carbonitrile	**I-549**	**(R)-51d**	1-(4-formylphenyl)cyclopropane-1-carbonitrile **ALD-99**	541.3	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.84 (s, 1H), 8.33 (s, 1H), 8.11-8.07 (m, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.38 (d, J = 8.40 Hz, 2H), 7.30 (d, J = 6.40 Hz, 2H), 5.11 (s, 1H), 4.23 (dd, J = 4.80, 14.20 Hz, 1H), 3.58-3.43 (m, 2H), 3.33-3.14 (m, 1H), 2.78-2.76 (m, 1H), 2.68-2.51 (m, 2H), 2.50-2.44 (m, 2H), 2.34-2.14 (m, 2H), 1.76-1.72 (m, 3H), 1.51 (t, J = 4.80 Hz, 2H), 1.00 (s, 3H), 0.67 (s, 3H).	G
(R)-1-(6-(1-(3-chloro-4-(oxetan-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, 0.629AcOH	**I-758**	**INT-(R)-S2**	3-chloro-4-(oxetan-3-yl)benzaldehyde **ALD-50**	567.1	1H-NMR (400 MHz, DMSO-d6): δ 10.67 (br s, 1H), 8.97 (d, J = 2.4 Hz, 1H), 8.32 (2, J = 2.00 Hz, 1H), 8.08 (t, J 8.80 Hz, 1H), 7.84 (d, J = 9.2 Hz, 1H), 7.51 (d, J = 6.6 Hz, 1H), 7.39 (s, 1H), 7.37 (d, J = 1.6 Hz, 1H), 5.15 (s, 1H), 4.96-4.92 (m, 2H), 4.74-4.70 (m, 2H), 4.57-4.51 (m, 1H), 4.00 (t, j = 7.2 Hz, 2H), 3.60-3.33 (m, 2H), 2.82-2.67 (m, 2H), 2.53-2.51 (m, 1H), 2.18 (d, J = 10.8 Hz, 1H), 1.83 (s, 3H), 1.76 (s, 1H), 1.01 (s, 3H), 0.68 (s, 3H).	G
(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((2-methyl-6-(trifluorome	**I-830**	**INT-(R)-S2**	2-methyl-6-(trifluoromethyl)nicotinaldehyde	560.2	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.96 (s, 1H), 9.01 (d, J = 2.40 Hz, 1H), 8.51 (d, J = 8.00 Hz, 1H), 8.36 (d, J = 2.00 Hz, 1H), 8.06 (d, J = 8.80 Hz, 1H),	G

thyl)pyridin-3-yl)methyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl					7.91 (d, J = 8.40 Hz, 2H), 5.98 (s, 1H), 4.61 (s, 2H), 4.60-4.02 (m, 2H), 3.60-3.42 (m, 4H),3.07 - 3.10 (m, 1H), 2.81-2.70 (m, 5H), 2.04-2.01(m, 1H), 1.00 (s, 3H), 0.67 (s, 3H).	
3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethyl-1-(4-(oxetan-3-yl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	**I-575**	**(R)-51d**	4-(oxetan-3-yl)benzaldehyde	532.3	1H NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.84 (s, 1H), 8.32 (s, 1H), 8.11-8.07 (m, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.39-7.34 (m, 4H), 5.10 (s, 1H), 4.95-4.92 (m, 2H), 4.64-4.61 (m, 2H), 4.26-4.20 (m, 2H), 3.57-3.54 (m, 1H), 3.51-3.47 (m, 1H), 3.46-3.44 (m, 1H), 3.18-3.13 (m, 2H), 2.76-2.63 (m, 1H), 2.47-2.44 (m, 2H), 2.19-2.15 (m, 2H), 1.71-1.68 (m, 2H), 0.99 (s, 3H), 0.67 (s, 3H).	G
3-(6-((R)-1-(3-chloro-4-(oxetan-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione	**I-625**	**(R)-51d**	3-chloro-4-(oxetan-3-yl)benzaldehyde **ALD-50**	566.4	1H NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.84 (d, J = 8.0 Hz, 1H), 8.33 (s, 1H), 8.09 (s, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.43 (s, 1H), 7.38 (d, J = 8.0 Hz, 1H), 5.12 (s, 1H), 4.96-4.92 (m, 2H), 4.73-4.70 (m, 2H), 3.60-3.56 (m, 1H), 3.53-3.49 (m, 1H), 2.68-2.66 (m, 1H), 2.56-2.52 (m, 2H), 2.49-2.47 (m, 1H), 2.38-2.34 (m, 2H), 2.18-2.16 (m, 2H), 2.12-2.08 (m, 2H), 2.01-1.98 (s, 1H),	G

					1.90-1.86 (m, 1H), 1.00 (s, 3H), 0.68 (s, 3H).	
(R)-1-(5-fluoro-6-(4-hydroxy-1-((6-(3-hydroxyoxetan-3-yl)pyridin-3-yl)methyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, 1.33AcO-	**I-778**	**INT-(R)-S2**	6-(3-hydroxyoxetan-3-yl)nicotinaldehyde	550.3	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.97 (d, J = 2.80 Hz, 1H), 8.59 (d, J = 1.20 Hz, 1H), 8.33 (d, J = 2.00 Hz, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.86-7.78 (m, 2H), 7.59 (d, J = 8.00 Hz, 1H), 5.16 (s, 1H), 4.93 (t, J = 5.20 Hz, 2H), 4.66 (d, J = 6.00 Hz, 2H), 4.02-3.99 (m, 2H), 3.65-3.51 (m, 2H), 3.18-3.15 (m, 2H), 2.80 (t, J = 6.80 Hz, 2H), 2.68-2.53 (m, 2H), 2.35-2.33 (m, 1H), 1.76-1.70 (m, 5H), 1.00 (s, 3H), 0.68 (s, 3H).	G
(R)-1-(5-fluoro-6-(1-((3-(4-fluorophenyl)cyclobutyl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl	**I-874**	**INT-(R)-S2**	(1r,3r)-3-(4-fluorophenyl)cyclobutane-1-carbaldehyde **ALD-34**	549.5	1H-NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 9.27 (s, 1H), 9.01 (d, J = 2.00 Hz, 1H), 8.36 (d, J = 2.40 Hz, 1H), 8.07 (t, J = 8.80 Hz, 1H), 7.91 (d, J = 8.80 Hz, 1H), 7.35-7.26 (m, 2H), 7.19-7.13 (m, 2H), 5.95 (s, 1H), 4.03-3.99 (m, 2H), 3.45-3.07 (m, 7H), 2.83-2.60 (m, 5H), 2.51-2.50 (m, 1H), 1.99-1.91 (m, 2H), 1.11 (s, 3H), 0.88 (s, 3H).	G
(R)-1-(6-(1-(4-chloro-3-(2-(dimethylamino)ethoxy)benzyl)-4-hydroxy-3,3-	**I-770**	**INT-(R)-S2**	4-chloro-3-(2-(dimethylamino)ethoxy)benzaldehyde	599.2	1H-NMR (400 MHz, DMSO-d6): δ 10.60 (s, 1H), 8.97 (d, J = 2.40 Hz, 1H), 8.33 (d, J = 2.00 Hz, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.85 (d, J = 9.20 Hz, 1H), 7.36 (t, J =	G

dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione					4.00 Hz, 1H), 7.17 (s, 1H), 6.94 (d, J = 9.20 Hz, 1H), 5.15 (s, 1H), 4.16-3.99 (m, 4H), 3.59-3.43 (m, 1H), 2.80-2.59 (m, 5H), 2.50-2.25 (m, 9H), 1.76-1.72 (m, 2H), 1.02 (s, 3H), 0.67 (s, 3H).	
(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(3-(oxetan-3-yl)-4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	**I-628**	**INT-(R)-S2**	3-(oxetan-3-yl)-4-(trifluoromethyl)benzaldehyde **ALD-33**	601.3	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.97 (d, J = 2.40 Hz, 1H), 8.34 (d, J = 2.00 Hz, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.98 (s, 1H), 7.85 (d, J = 8.80 Hz, 1H), 7.69 (d, J = 8.40 Hz, 1H), 7.48 (d, J = 8.40 Hz, 1H), 5.18 (s, 1H), 4.99-4.94 (m, 2H), 4.72-4.66 (m, 3H), 4.01 (t, J = 6.80 Hz, 2H), 3.79-3.57 (m, 2H), 3.33-3.21 (m, 2H), 2.80-2.67 (m, 3H), 2.50-2.50 (m, 1H), 1.80-1.76 (m, 2H), 1.05 (s, 3H), 0.68 (s, 3H).	G
(R)-1-(6-(1-(4-chloro-3-(1-hydroxycyclobutyl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, 0.77AcOH	**I-665**	**INT-(R)-S2**	4-chloro-3-(1-hydroxycyclobutyl)benzaldehyde	581.5	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.97 (d, J = 2.40 Hz, 1H), 8.34 (d, J = 2.00 Hz, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.85 (d, J = 9.20 Hz, 1H), 7.44 (d, J = 1.60 Hz, 1H), 7.34 (d, J = 8.00 Hz, 1H), 7.25 (d, J = 1.60 Hz, 1H), 7.23 (d, J = 2.00 Hz, 1H), 5.36 (s, 1H), 5.15 (s, 1H), 4.01 (t, J = 6.40 Hz, 2H), 3.61 (d, J = 14.00 Hz, 1H), 3.44 (d, J = 14.00 Hz, 1H), 3.33-3.17 (m, 1H), 2.80 (t, J = 6.80 Hz, 2H), 2.79-2.67	E

					(m, 1H), 2.67-2.49 (m, 3H), 2.36-2.29 (m, 2H), 2.20-2.18 (m, 1H), 2.17-2.05 (m, 1H), 1.81 (s, 3H), 1.76-1.71 (m, 1H), 1.60-1.58 (m, 1H), 1.03 (m, 3H), 0.68 (s, 3H).	
(R)-1-(6-(1-(4-chloro-3-(oxetan-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	**I-659**	**INT-(R)-S2**	4-chloro-3-(oxetan-3-yl)benzaldehyde	567.5	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.97 (d, J = 2.40 Hz, 1H), 8.34-8.31 (m, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.85 (d, J = 9.20 Hz, 1H), 7.55 (d, J = Hz, 1H), 7.42 (d, J = 8.00 Hz, 1H), 7.29 (t, J = 1.60 Hz, 1H), 5.15 (s, 1H), 4.99-4.96 (m, 2H), 4.74-4.68 (m, 2H), 4.58-4.56 (m, 1H), 4.01 (t, J = 6.80 Hz, 2H), 3.67-3.46 (m, 2H), 3.33-3.17 (m, 2H), 2.82-2.60 (m, 4H), 2.33-2.19 (m, 1H), 1.75-1.72 (m, 1H), 1.03 (s, 3H), 0.68 (s, 3H).	G
(R)-1-(5-fluoro-6-(1-(3-fluoro-4-(1-hydroxycyclobutyl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	**I-668**	**INT-(R)-S2**	3-fluoro-4-(1-hydroxycyclobutyl)benzaldehyde	565.5	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.97 (d, J = 2.80 Hz, 1H), 8.33 (d, J = 1.60 Hz, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.85 (d, J = 8.80 Hz, 1H), 7.37 (t, J = 8.00 Hz, 1H), 7.15-7.10 (m, 2H), 5.45 (s, 1H), 5.14 (s, 1H), 4.01 (t, J = 6.80 Hz, 2H), 3.58 (d, J = 13.60 Hz, 1H), 3.46 (d, J = 13.60 Hz, 1H), 3.33-3.15 (m, 1H), 2.81 (t, J = 6.40 Hz, 2H), 2.59-2.52 (m, 2H), 2.28-2.21 (m, 4H), 2.05-1.95 (m,	G

					1H), 1.72-1.58 (m, 2H), 1.01 (d, J = 3.20 Hz, 3H), 0.68 (s, 3H)	
(R)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(3-(oxetan-3-yl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, 0.519Formic Acid	**I-775**	**INT-(R)-S2**	3-(oxetan-3-yl)benzaldehyde **ALD-19**	533.3	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.97 (d, J = 2.40 Hz, 1H), 8.33 (d, J = 1.60 Hz, 1H), 8.15 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.44 (s, 1H), 7.28-7.25 (m, 3H), 5.13 (s, 1H), 4.98-4.94 (m, 2H), 4.63-4.60 (m, 2H), 4.27-4.25 (m, 1H), 4.00 (t, J = 6.40 Hz, 1H), 3.63 (d, J = 13.60 Hz, 1H), 3.46 (d, J = 13.60 Hz, 1H), 3.18-3.15 (m, 1H), 2.80 (t, J = 6.80 Hz, 2H), 2.68-2.68 (m, 1H), 2.68-2.68 (m, 1H), 2.50-2.47 (m, 1H), 2.19 (d, J = 10.80 Hz, 1H), 1.72 (d, J = 13.60 Hz, 1H), 1.01 (m, 3H), 0.67(d, J = Hz, 3H).	G
(R)-1-(6-(1-(4-chloro-3-(3-hydroxyoxetan-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, Formic Acid	**I-747**	**INT-(R)-S2**	4-chloro-3-(3-hydroxyoxetan-3-yl)benzaldehyde	583.5	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.97 (d, J = 2.40 Hz, 1H), 8.33 (d, J = 2.00 Hz, 1H), 8.26 (s, 1H), 8.09 (t, J = 8.40 Hz, 1H), 7.85 (d, J = 8.80 Hz, 1H), 7.42 (d, J = 8.00 Hz, 1H), 7.35 (t, J = 8.40 Hz, 2H), 6.27 (s, 1H), 5.16 (s, 1H), 5.07 (d, J = 6.80 Hz, 2H), 4.73-4.71 (m, 2H), 4.01 (t, J = 6.80 Hz, 2H), 3.61 (d, J = 14.00 Hz, 1H), 3.46 (d, J = 14.00 Hz, 1H), 3.17-3.14 (m, 1H), 2.80 (t, J = 6.80 Hz,	G

					2H), 2.68-2.67 (m, 1H), 2.51-2.51 (m, 1H), 2.33-2.17 (m, 1H), 1.74-1.71 (m, 1H), 1.24-1.02 (m, 1H), 1.01 (s, 3H), 0.68 (s, 3H).	
3-(5-fluoro-6-((R)-4-hydroxy-1-(4-(1-hydroxycyclobutyl)benzyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	**I-556**	**(R)-51d**	4-(1-hydroxycyclobutyl)benzaldehyde **ALD-38**	546.4	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.84 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.45 (d, J = 8.40 Hz, 2H), 7.32 (d, J = 8.00 Hz, 2H), 5.42 (s, 1H), 5.10 (s, 1H), 4.23 (dd, J = 4.80, 12.60 Hz, 1H), 3.56 (d, J = 13.20 Hz, 1H), 3.46 (d, J = 13.20 Hz, 1H), 3.14 (t, J = 1.60 Hz, 1H), 2.78-2.75 (m, 1H), 2.72-2.60 (m, 3H), 2.48-2.45 (m, 2H), 2.40-2.35 (m, 2H), 2.30-2.10 (m, 4H), 1.99-1.85 (m, 1H), 1.72-1.85 (m, 2H), 1.00 (s, 3H), 0.68 (s, 3H).	G
(R)-1-(5-fluoro-6-(4-hydroxy-1-((6-(1-hydroxycyclobutyl)pyridin-3-yl)methyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	**I-698**	**INT-(R)-S2**	6-(1-hydroxycyclobutyl)nicotinaldehyde	548.3	1H-NMR (400 MHz, DMSO-d6): δ 10.59 (s, 1H) 8.96 (d, J = 2.40 Hz, 1H), 8.49 (d, J = 1.60 Hz, 1H), 8.32 (d, J = 2.00 Hz, 1H), 8.08 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.74-7.71 (m, 1H), 7.55 (d, J = 8.00 Hz, 1H), 5.68 (s, 1H), 5.14 (s, 1H), 4.00 (t, J = 6.80 Hz, 2H), 3.61-3.48 (m, 2H), 3.17-3.11 (m, 1H), 2.80 (t, J = 6.80 Hz, 2H), 2.67-2.50 (m, 4H), 2.24-2.17 (m, 3H), 1.91-	G

					1.76 (m, 4H), 0.99 (d, J = 3.20 Hz, 3H), 0.68 (s, 3H).	
(R)-1-(6-(1-(3-chloro-4-(1-hydroxycyclobutyl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, 0.72Formic Acid	**I-759**	**INT-(R)-S2**	3-chloro-4-(1-hydroxycyclobutyl)benzaldehyde **ALD-20**	581.5	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.97 (d, J = 2.40 Hz, 1H), 8.33 (d, J = 2.00 Hz, 1H), 8.18 (s, 1H), 8.08 (t, J = 8.80 Hz, 1H), 7.85 (d, J = 8.80 Hz, 1H), 7.39-7.37 (m, 2H), 7.29-7.26 (m, 1H), 5.33 (s, 1H), 5.14 (s, 1H), 4.01 (t, J = 7.20 Hz, 2H), 3.57 (d, J = 13.60 Hz, 1H), 3.46 (d, J = 14.00 Hz, 1H), 3.44-3.33 (m, 1H), 2.80 (t, J = 6.80 Hz, 2H), 2.68-2.60 (m, 1H), 2.68-2.60 (m, 3H), 2.50-2.46 (m, 1H), 2.34-2.19 (m, 2H), 2.18 (d, J = 10.40 Hz, 1H), 1.73-1.70 (m, 1H), 1.01 (m, 3H), 0.68 (s, 3H)	G
1-(6-(1-((1H-pyrrol-2-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	**I-598**	**INT-S6**	1H-pyrrole-2-carbaldehyde	480.2	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 10.54 (s, 1H), 8.42 (d, J = 2.40 Hz, 1H), 8.16 (s, 1H), 8.06 (d, J = 8.80 Hz, 1H), 7.78 (d, J = 9.20 Hz, 1H), 6.66 (dd, J = 2.80, 4.20 Hz, 1H), 5.96-5.91 (m, 2H), 5.09 (d, J = 8.40 Hz, 1H), 4.05-3.95 (m, 1H), 3.70-3.65 (m, 1H), 3.49-3.45 (m, 1H), 3.10-3.10 (m, 1H), 2.86-2.68 (m, 2H), 2.67 (s, 3H), 2.47-2.44 (m, 2H), 2.24-2.22 (m, 2H), 0.96 (d, J = 3.20 Hz, 3H), 0.68 (s, 3H),	G

1-(6-(1-(cyclohexylmethyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	**I-859**	**INT-S6**	cyclohexanecarbaldehyde	497.3	1H-NMR (400 MHz, DMSO-d6): δ 10.54 (s, 1H), 8.41 (s, 1H), 8.21 (s, 1H), 8.08 (t, J = 8.80 Hz, 1H), 7.78 (d, J = 9.20 Hz, 1H), 5.06 (d, J = 8.00 Hz, 1H), 4.05-3.95 (m, 1H), 3.71-3.67 (m, 1H), 3.10-3.09 (m, 2H), 2.86-2.68 (m, 3H), 2.67 (s, 3H), 2.46-2.33 (m, 2H), 2.20-2.08 (m, 3H), 1.83-1.75 (m, 6H), 1.23-1.17 (m, 4H), 0.97 (d, J = 3.20 Hz, 3H), 0.88-0.85 (m, 2H), 0.70 (s, 1H).	G
1-(6-(1-((4,4-difluorocyclohexyl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	**I-837**	**INT-S6**	4,4-difluorocyclohexane-1-carbaldehyde	533.2	1H-NMR (400 MHz, DMSO-d6): δ 10.57 (s, 1H), 9.01-8.95 (m, 1H), 8.49 (d, J = 3.20 Hz, 1H), 8.07 (d, J = 8.80 Hz, 1H), 7.86 (d, J = 8.80 Hz, 1H), 5.99 (s, 1H), 4.05-3.95 (m, 1H), 3.72-3.68 (m, 4H), 3.22-3.20 (m, 3H), 3.18-3.16 (m, 1H), 2.88-2.68 (m, 2H), 2.67 (s, 2H), 2.08-2.00 (m, 4H), 1.97-1.85 (m, 4H), 1.32-1.24 (m, 2H), 1.12 (d, J = 2.40 Hz, 3H), 0.83 (s, 3H).	G
1-(6-(1-((3,3-difluorocyclobutyl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)dihydropyrimidine-	**I-860**	**INT-S6**	3,3-difluorocyclobutane-1-carbaldehyde	505.2	1H-NMR (400 MHz, DMSO-d6): δ 10.57 (s, 1H), 8.47 (s, 1H), 8.07 (t, J = 8.40 Hz, 1H), 7.85 (d, J = 9.20 Hz, 1H), 5.92 (s 1H), 3.99-3.71 (m, 1H), 3.71-3.68 (m, 1H), 3.68-3.34 (m, 6H), 3.32-3.24 (m, 1H), 3.21-3.09 (m, 1H), 2.84-2.75 (m, 4H), 2.60-2.51 (m, 3H), 2.50-2.40 (m, 1H),	G

2,4(1H,3H)-dione					2.00-1.98 (m, 1H), 1.09 (s, 3H), 0.81 (s, 3H),	
1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((tetrahydro-2H-thiopyran-4-yl)methyl)piperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	**I-831**	**INT-S6**	tetrahydro-2H-thiopyran-4-carbaldehyde	515.2	1H-NMR (400 MHz, DMSO-d6): δ 10.57 (s, 1H), 8.85 (s, 1H), 8.49 (s, 1H), 8.08 (d, J = 8.80 Hz, 1H),7.86 (d, J = 9.20 Hz, 1H), 5.93 (s, 1H), 3.99-4.11 (m, 1H), 3.71-3.68 (m, 1H), 3.40-3.38 (m, 3H), 3.24-3.02 (m, 4H), 2.89-2.68 (m, 8H), 2.07-0.00 (m, 5H), 1.32-1.41 (m, 2H), 1.10 (s, 3H), 0.81 (s, 3H)	G
1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(3,3,3-trifluoropropyl)piperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	**I-854**	**INT-S6**	3,3,3-trifluoropropanal	497.4	1H-NMR (400 MHz, DMSO-d6): δ 10.54 (s, 1H), 8.42 (d, J = 2.80 Hz, 1H), 8.08 (t, J = 8.80 Hz, 1H), 7.78 (d, J = 8.80 Hz, 1H), 5.12 (d, J = 9.60 Hz, 1H), 4.00-3.96 (m, 1H), 3.75-3.64 (m, 1H), 3.09-3.06 (m, 1H), 2.85-2.68 (m, 3H), 2.67-2.64 (m, 5H), 2.57-2.52 (m, 4H), 2.50-2.44 (m, 1H), 2.34 (d, J = 2.00 Hz, 1H), 1.70 (d, J = 13.20 Hz, 3H), 0.71 (s, 3H).	G
1-(6-(1-(cyclopropylmethyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)dihydropyrimidine-	**I-850**	**INT-S6**	cyclopropanecarbaldehyde	455.2	1H-NMR (400 MHz, DMSO-d6): δ 10.55 (s, 1H), 8.44 (d, J = 2.40 Hz, 1H), 8.24 (s, 1H), 8.08 (t, J = 8.80 Hz, 1H), 7.80 (d, J = 8.80 Hz, 1H), 5.50 (s, 1H), 4.00-3.98 (m, 1H), 3.18-3.17 (m, 1H), 3.04-3.01 (m, 1H), 2.68-2.86 (m, 5H), 2.43-2.54 (m,	G

2,4(1H,3H)-dione, Formic Acid-					5H), 1.78 (d, J = 13.60 Hz, 1H), 1.01-0.94 (m, 4H), 0.74 (s, 3H), 0.53 (dd, J = 1.60, 7.80 Hz, 2H), 0.19 (d, J = 2.40 Hz, 2H)	
1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((tetrahydro-2H-pyran-3-yl)methyl)piperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, Formic Acid-	**I-869**	**INT-S6**	tetrahydro-2H-pyran-3-carbaldehyde	499.3	1H-NMR (400 MHz, DMSO-d6): δ 10.54 (s, 1H), 8.41 (s, 1H), 8.17 (s, 1H), 8.08 (t, J = 8.80 Hz, 1H), 7.78 (d, J = 8.80 Hz, 1H), 5.00 (s, 1H), 3.87-3.76 (m, 1H), 3.74-3.72 (m, 1H), 3.71-3.69 (m, 2H), 3.38-3.32 (m, 1H), 3.28-3.25 (m, 1H), 3.26-3.24 (m, 1H), 3.22-3.21 (m, 1H), 2.79 (s, 3H), 2.51-2.51 (m, 1H), 2.50-2.13 (m, 3H), 1.82-1.79 (m, 3H), 1.55-1.51 (m, 4H), 1.20-1.1 (m, 1H), 0.96 (d, J = 2.80 Hz, 3H), 0.70 (d, J = 4.00 Hz, 3H),	G
1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((1-phenylpiperidin-4-yl)methyl)piperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, Formic Acid-	**I-815**	**INT-S6**	1-phenylpiperidine-4-carbaldehyde	574.6	1H-NMR (400 MHz, DMSO-d6): δ 10.55 (s, 1H), 8.41 (s, 1H), 8.18 (s, 1H), 8.14 (s, 1H), 7.79-7.77 (m, 1H), 7.19 (t, J = 7.60 Hz, 2H), 6.93 (d, J = 8.00 Hz, 2H), 6.92-6.72 (m, 1H), 5.10 (s, 1H), 4.01-3.95 (m, 1H), 3.70-3.68 (m, 3H), 3.33-3.11 (m, 2H), 2.80-2.70 (m, 2H), 2.68-2.67 (m, 3H), 2.64 (s, 3H), 2.41-2.17 (m, 3H), 1.84-1.83 (m, 2H), 1.71-1.67 (m, 2H), 1.24-1.22 (m, 2H), 0.99 (d, J = 2.80 Hz, 3H), 0.70 (s, 3H).	G

1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((tetrahydrofuran-3-yl)methyl)piperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, Formic Acid-	**I-840**	**INT-S6**	tetrahydrofuran-3-carbaldehyde	485.3	1H-NMR (400 MHz, DMSO-d6): δ 10.54 (s, 1H), 8.41 (s, 1H), 8.15 (s, 1H), 8.08 (t, J = 8.40 Hz, 1H), 7.78 (d, J = 8.80 Hz, 1H), 5.12 (d, J = Hz, 1H), 4.00 (m, 1H), 3.78-3.71 (m, 6H), 3.46-3.44 (m, 1H), 3.10 (t, J = Hz, 1H), 2.90 (m, 1H), 2.79-2.78 (m, 2H), 2.68 (s, 3H), 2.40-2.31 (m, 3H), 1.96 (m, 1H), 1.71-1.68 (m, 2H), 0.96 (q, J = 3.60 Hz, 3H), 0.70 (s, 3H).	G
1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(oxetan-3-ylmethyl)piperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, Formic Acid-	**I-873**	**INT-S6**	oxetane-3-carbaldehyde	471.2	1H-NMR (400 MHz, DMSO-d6): δ 10.54 (s, 1H), 8.41 (s, 1H), 8.18 (s, 1H), 8.07 (t, J = 8.80 Hz, 1H), 7.78 (d, J = 9.20 Hz, 1H), 5.50-5.00 (m, 1H), 4.69-4.65 (m, 2H), 4.65-4.29 (m, 2H), 4.29 (s, 1H), 4.00-3.96 (m, 1H), 3.70-3.67 (m, 1H), 3.24-3.21 (m, 1H), 3.06 (s, 1H), 2.86-2.78 (m, 7H), 2.70-2.61 (m, 1H), 2.14 (d, J = 10.40 Hz, 1H), 1.68 (d, J = 13.20 Hz, 1H), 0.93 (s, 3H), 0.69 (s, 3H).	G
1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-propylpiperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione,	**I-836**	**INT-S6**	propionaldehyde	443.2	1H-NMR (400 MHz, DMSO-d6): δ 10.54 (s, 1H), 8.42 (s, 1H), 8.31 (d, J = Hz, 1H), 8.09-8.08 (m, 1H), 7.79-3.71 (m, 1H), 5.05 (s, 1H), 4.05-3.95 (m, 1H), 3.72-3.65 (m, 1H), 3.72-3.68 (m, 1H), 3.18-3.16 (m, 1H), 2.88-2.68 (m, 2H), 2.67 (s, 3H), 2.08-2.00 (m,	G

1.4Formic Acid-					2H), 1.97-1.85 (m, 4H), 1.69-1.66 (m, 2H), 1.48-1.44 (m, 2H), 0.89- 0.88 (m, 3H) 0.70 (s, 3H).	
(R)-1-(6-(1-((1H-pyrrol-2-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	**I-600**	**INT-S6**	1H-pyrrole-2-carbaldehyde	480.3	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H),10.53 (s, 1H), 8.41 (s, 1H), 8.07 (t, J = 8.40 Hz, 1H), 7.78 (d, J = 9.20 Hz, 1H), 6.74 (s, 1H),5.95-5.91 (m, 2H), 5.09 (d, J = 8.00 Hz, 1H), 4.01-3.96 (m, 1H), 3.71-3.68 (m, 1H), 3.49 (s, 2H), 3.18-3.09 (m, 1H), 2.99-2.91 (m, 1H), 2.64 (s, 3H), 2.51-2.48 (m, 4H), 2.23 (d, J = 10.40 Hz, 1H), 1.76-1.71 (m, 1H), 0.97 (s, 3H), 0.68 (s, 3H).	G
(S)-1-(6-(1-((1H-pyrrol-2-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	**I-599**	**INT-S6**	1H-pyrrole-2-carbaldehyde	480.3	1H-NMR (400 MHz, DMSO-d6): δ 10.58 (s, 1H),10.54 (s, 1H), 8.41 (s, 1H), 8.08 (t, J = 8.40 Hz, 1H), 7.77 (d, J = 9.20 Hz, 1H), 6.64 (s, 1H), 5.94-5.88 (m, 2H), 5.04 (d, J = 8.00 Hz, 1H), 3.98 (s, 1H), 3.69 (s, 1H), 3.49 (s, 2H), 3.18-3.09 (m, 1H), 2.99-2.91 (m, 1H), 2.63 (s, 3H), 2.52-2.48 (m, 3H), 2.18 (d, J = 10.40 Hz, 1H), 1.69-1.65 (m, 1H), 0.95 (s, 3H), 0.67 (s, 3H).	
1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((tetrahydro-2H-pyran-4-	**I-823**	**INT-S6**	tetrahydro-2H-pyran-4-carbaldehyde	499.4	1H-NMR (400 MHz, DMSO-d6): δ 8.41 (s, 1H), 8.25 (s, 1H), 8.33 (t, J = 13.60 Hz, 1H), 7.79 (d, J = 2.00 Hz, 1H), 5.09 (d, J = 3.60 Hz, 1H), 4.05-3.94 (m, 1H), 3.90-	G

yl)methyl)piperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione					3.85 (m, 2H), 3.70-3.63 (m, 1H), 3.19-3.11 (m, 1H), 2.92-2.81 (m, 2H), 2.59 (s, 3H), 2.51 (t, J = 1.60 Hz, 1H), 2.29-2.09 (m, 3H), 1.70-1.59 (m, 4H), 1.20-1.11 (m, 4H), 0.96 (d, J = 2.80 Hz, 3H), 0.70 (s, 3H).	
1-(5-fluoro-6-(4-hydroxy-1-isobutyl-3,3-dimethylpiperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, Formic Acid-	**I-783**	**INT-S6**	Isobutyraldehyde	457.3	1H-NMR (400 MHz, DMSO-d6): δ 10.54 (s, 1H), 8.42 (s, 1H), 8.15 (s, 1H), 8.08 (t, J = 8.80 Hz, 1H), 7.78 (d, J = 8.80 Hz, 1H), 5.09 (s, 1H), 4.02-3.96 (m, 1H), 3.72-3.67 (m, 1H), 3.21-3.15 (m, 1H), 2.94-2.64 (m, 3H), 2.58 (s, 3H), 2.51-2.33 (m, 2H), 2.25-2.09 (m, 3H), 1.82-1.68 (m, 2H), 1.13 (d, J = 8.00 Hz, 3H), 0.98 (d, J = 4.00 Hz, 6H), 0.80 (s, 3H).	G
(R)-1-(5-fluoro-6-(4-hydroxy-1-(4-(2-hydroxypropan-2-yl)benzyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	**I-760**	**INT-(R)-S2**	4-(2-hydroxypropan-2-yl)benzaldehyde **ALD-46**	535.4	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.96 (d, J = 2.40 Hz, 1H), 8.33 (d, J = 2.00 Hz, 1H), 8.07 (d, J = 8.80 Hz, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.43 (d, J = 8.40 Hz, 2H), 7.27 (d, J = 8.40 Hz, 2H), 5.12 (s, 1H), 4.95 (s, 1H), 4.01 (t, J = 6.80 Hz, 2H), 3.56-3.43 (m, 2H), 3.43-3.33 (m, 1H), 2.80 (t, J = 6.40 Hz, 2H), 2.68-2.67 (m, 2H), 2.51-2.51 (m, 1H), 2.21-2.19 (m, 1H). 1.72-1.69 (m, 1H), 1.43 (s, 6H), 1.01 (s, 3H), 0.68 (s, 3H).	G

(R)-2-(4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)phenyl)-2-methylpropanenitrile	**I-720**	**INT-(R)-S2**	2-(4-formylphenyl)-2-methylpropanenitrile **ALD-45**	544.4	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.97 (d, J = 2.40 Hz, 1H), 8.11 (s, 1H), 8.08 (d, J = 8.80 Hz, 1H), 7.85 (d, J = 8.80 Hz, 1H), 7.50 (d, J = 8.40 Hz, 2H), 7.42 (d, J = 8.40 Hz, 2H), 5.14 (s, 1H), 4.01-3.99 (m, 2H), 3.59-3.47 (m, 2H), 3.33-3.15 (m, 1H), 2.82-2.79 (m, 2H), 2.68-2.67 (m, 3H), 2.21-2.18 (m, 1H), 1.71 (s, 7H), 1.02 (s, 3H), 0.68 (s, 3H).	G
(R)-5-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)-2-fluorobenzonitrile, Formic Acid	**I-817**	**INT-(R)-S2**	2-fluoro-5-formylbenzonitrile	520.2	1H-NMR (400 MHz, DMSO-d6): δ 10.6 (s, 1H), 8.92 (d, J = 2.40 Hz, 1H), 8.33 (d, J = 1.60 Hz, 2H), 8.05 (t, J = 8.40 Hz, 1H), 7.83-7.74 (m, 3H), 7.48-7.44 (m, 1H), 5.04 (s, 1H), 4.00 (t, J = 6.80 Hz, 2H), 3.36-3.22 (m, 3H), 2.82-2.79 (m, 2H), 2.68-2.60 (m, 3H), 2.34-2.33 (m, 1H), 1.98-1.95 (m, 1H), 1.01 (s, 3H), 0.64 (s, 3H).	G
(R)-1-(5-fluoro-6-(4-hydroxy-1-(4-(1-methoxycyclobutyl)benzyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	**I-640**	**INT-(R)-S2**	4-(1-methoxycyclobutyl)benzaldehyde **ALD-39**	561.2	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.96 (d, J = 2.40 Hz, 1H), 8.32 (d, J = 2.00 Hz, 1H), 8.08 (d, J = 8.80 Hz, 1H), 7.86-7.83 (m, 1H), 7.38 (s, 4H), 5.13 (s, 1H), 4.02-3.99 (m, 2H), 3.58-3.47 (m, 3H), 3.47-3.32 (m, 2H), 2.83 (s, 3H), 2.82-2.80 (m, 2H), 2.79 (s, 3H), 2.51-2.50 (m, 3H), 2.35-2.34 (m, 1H),	G

					2.33-2.30 (m, 1H), 2.28-2.27 (m, 1H), 1.02 (s, 3H), 0.69 (s, 3H).	
(R)-1-(5-fluoro-6-(4-hydroxy-1-(4-(3-hydroxy-3-methylazetidin-1-yl)benzyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, Acetic acid	**I-789**	**INT-(R)-S2**	4-(3-hydroxy-3-methylazetidin-1-yl)benzaldehyde	562.4	1H-NMR (400 MHz, DMSO-d6): δ 10.60 (s, 1H), 8.96 (d, J = 2.40 Hz, 1H), 8.32 (d, J = 2.00 Hz, 1H), 8.08 (t, J = 8.40 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.11 (dd, J = 4.80, 16.20 Hz, 2H), 6.41 (d, J = 8.40 Hz, 2H), 5.46 (s, 1H), 5.08 (s, 1H), 4.00 (t, J = 6.80 Hz, 2H), 3.72 (t, J = 6.00 Hz, 2H), 3.58 (d, J = 7.20 Hz, 2H), 3.57-3.47 (m, 1H), 3.33-2.82 (m, 1H), 2.82-2.79 (m, 2H), 2.55-2.51 (m, 1H), 2.50-2.38 (m, 1H), 2.34-2.33 (m, 1H), 1.91 (s, 3H), 1.76 (s, 1H), 1.71 (s, 1H), 1.46 (s, 3H), 0.97 (s, 3H), 0.67 (s, 3H).	G
3-(6-((R)-1-(4-(3,3-difluoroazetidin-1-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, Formic Acid	**I-740**	**(R)-51d**	4-(3,3-difluoroazetidin-1-yl)benzaldehyde	567.3	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.84 (s, 1H), 8.33 (s, 1H), 8.25 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.83 (d, J = 9.20 Hz, 1H), 7.21 (d, J = 8.40 Hz, 2H), 6.55 (d, J = 8.40 Hz, 2H), 5.08 (s, 1H), 4.25 (t, J = 8.00 Hz, 5H), 2.77-2.74 (m, 1H), 2.68-2.64 (m, 2H), 2.50-2.47 (m, 1H), 2.34-2.18 (m, 2H), 1.70-1.67 (m, 1H), 0.97 (s, 3H), 0.67 (s, 3H). (Note: 4 protons overlapped with solvent peak).	L

1-(4-(((4R)-4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)-2-fluorophenyl)cyclopropane-1-carbonitrile	**I-692**	**(R)-51d**	1-(2-fluoro-4-formylphenyl)cyclopropane-1-carbonitrile **ALD-106**	559.2	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (s, 1H), 8.34 (s, 1H), 8.09 (t, J = 9.60 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.43 (t, J = 7.60 Hz, 1H), 7.28-7.21 (m, 2H), 5.14 (s, 1H), 4.26-4.21 (m, 1H), 3.61-3.57 (m, 2H), 3.47-3.39 (m, 1H), 3.18-3.17 (m, 2H), 2.77-2.73 (m, 2H), 2.68-2.64 (m, 2H), 2.35-2.34 (m, 2H), 1.69 (m, 3H), 1.46 (m, 2H), 1.02 (s, 3H), 0.68 (s, 3H).	L
4-(((4R)-4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)-N-ethyl-2-fluorobenzamide	**I-769**	**(R)-51d**	N-ethyl-2-fluoro-4-formylbenzamide	565.4	1H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 9.98 (s, 1H), 8.90 (s, 1H), 8.41 (d, J = 6.00 Hz, 2H), 8.07 (t, J = 8.80 Hz, 1H), 7.91 (d, J = 8.80 Hz, 1H), 7.71 (t, J = 7.60 Hz, 2H), 7.57 (d, J = 7.60 Hz, 1H), 4.48-4.44 (m, 2H), 4.25 (dd, J = 4.80, 12.80 Hz, 1H), 3.68 (s, 3H), 3.33-3.26 (m, 3H), 2.90 (d, J = 11.20 Hz, 1H), 2.77-2.74 (m, 1H), 2.66 (d, J = 13.60 Hz, 1H), 2.13 (d, J = 5.20 Hz, 1H), 2.02 (d, J = 11.20 Hz, 2H), 1.15-1.09 (m, 6H), 0.78 (s, 3H).	K
2-(4-(((4R)-4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpip	**I-678**	**(R)-51d**	2-(4-formylphenyl)-2-methylpropanenitrile **ALD-45**	543.4	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.22 (s, 1H), 8.25 (s, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.50 (d, J = 8.40 Hz, 2H), 7.42 (d, J = 8.00	D

eridin-1-yl)methyl)phenyl)-2-methylpropanenitrile, 0.55Formic Acid					Hz, 2H), 5.12 (s, 1H), 4.23 (dd, J = 4.80, 12.40 Hz, 1H), 3.57 (d, J = 13.60 Hz, 1H), 3.49 (m, 2H), 3.33-3.12 (m, 2H), 2.77-2.68 (m, 1H), 2.25-2.16 (m, 2H), 1.70 (s, 8H), 1.01 (s, 3H), 0.68 (s, 3H), two protons overlapped with solvent peak	
3-(5-fluoro-6-((R)-4-hydroxy-1-((6-(1-hydroxycyclobutyl)pyridin-3-yl)methyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, Formic Acid	**I-746**	**(R)-51d**	6-(1-hydroxycyclobutyl)nicotinaldehyde	547.6	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.84 (d, J = 2.00 Hz, 1H), 8.49 (d, J = 1.60 Hz, 1H), 8.33 (s, 1H), 8.21 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.73 (dd, J = 8.0, 2.00 Hz, 1H), 7.55 (d, J = 8.00 Hz, 1H), 5.12 (s, 1H), 4.25-4.21 (m, 1H), 3.17-3.14 (m, 2H), 2.76-2.63 (m, 4H), 2.59-2.50 (m, 3H), 2.48-2.12 (m, 6H), 1.94-1.90 (m, 2H), 1.89-1.69 (m, 2H), 0.99 (s, 3H), 0.68 (s, 3H).	K
3-(5-fluoro-6-((R)-1-(4-(1-fluorocyclobutyl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	**I-687**	**(R)-51d**	4-(1-fluorocyclobutyl)benzaldehyde	548.3	1H-NMR (400 MHz, DMSO-d6): 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.34 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.85 (d, J = 9.20 Hz, 1H), 7.47-7.42 (m, 4H), 5.16 (s, 1H), 4.26-4.21 (m, 1H), 3.52 (m, 2H), 3.33-3.17 (m, 1H), 2.77-2.73 (m, 2H), 2.69-2.60 (m, 5H), 2.15-2.03 (m, 3H), 2.03-2.01 (m, 2H), 1.74-1.68 (m, 2H), 1.02 (s, 3H), 0.69 (s, 3H).	K

5-(((4R)-4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)-2-fluorobenzonitrile, 0.562Formic Acid	**I-786**	**(R)-51d**	2-fluoro-5-formylbenzonitrile	519.5	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (d, J = 2.40 Hz, 1H), 8.33 (s, 1H), 8.15-8.07 (m, 2H), 7.81-7.77 (m, 2H), 7.53 (t, J = 9.20 Hz, 1H), 5.14 (d, J = 1.20 Hz, 1H), 4.23 (dd, J = 4.80, 12.80 Hz, 1H), 3.60 (d, J = 14.00 Hz, 1H), 3.18-3.12 (m, 1H), 2.78-2.76 (m, 1H), 2.68-2.63 (m, 3H), 2.16-2.13 (m, 2H), 1.71 (d, J = 13.60 Hz, 1H), 1.97-1.94 (m, 2H), 1.00 (s, 3H), 0.68 (s, 3H).	L
3-(6-((R)-1-(4-(1,1-difluoroethyl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione	**I-650**	**(R)-51d**	4-(1,1-difluoroethyl)benzaldehyde	540.2	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (s, 1H), 8.33 (s, 1H), 8.10 (t, J = 9.20 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.55 (d, J = 8.00 Hz, 2H), 7.48 (d, J = 8.40 Hz, 2H), 5.13 (d, J = 1.20 Hz, 1H), 4.23 (dd, J = 4.80, 12.60 Hz, 1H), 3.62 (d, J = 14.00 Hz, 1H), 3.52 (d, J = 14.00 Hz, 1H), 3.16 (t, J = 8.00 Hz, 2H), 2.80-2.70 (m, 5H), 2.21-2.10 (m, 2H), 1.99-1.97 (m, 3H), 1.73-1.63 (m, 1H), 1.01 (s, 3H), 0.68 (s, 3H).	F
3-(5-fluoro-6-((R)-4-hydroxy-1-(4-(2-hydroxypropan-2-yl)benzyl)-3,3-dimethylpiperidin-4-	**I-726**	**(R)-51d**	4-(2-hydroxypropan-2-yl)benzaldehyde **ALD-46**	534.6	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.84 (d, J = 2.00 Hz, 1H), 8.32 (d, J = 7.60 Hz, 2H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.43 (d, J = 8.00 Hz, 2H), 7.27 (d, J = 8.00 Hz, 2H),	K

yl)quinolin-3-yl)piperidine-2,6-dione, Formic Acid					5.10 (s, 1H), 4.97 (s, 1H), 4.25-4.21 (m, 1H), 2.68-2.60 (m, 4H), 2.34-2.09 (m, 4H), 1.70 (d, J = 12.40 Hz, 1H), 1.42 (d, J = 6.80 Hz, 6H), 1.24 (s, 1H), 1.24 (s, 3H), 0.68 (s, 3H)	
1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((4-(trifluoromethyl)cyclohexyl)methyl)piperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, 0.55Acetic acid	**I-834**	**INT-S6**	4-(trifluoromethyl)cyclohexane-1-carbaldehyde	565.6	1H-NMR (400 MHz, DMSO-d6): δ 10.55 (s, 1H), 8.41 (s, 1H), 8.17 (s, 1H), 8.09 (t, J = 8.40 Hz, 1H), 7.78 (d, J = 9.20 Hz, 1H), 5.07 (d, J = 8.00 Hz, 1H), 4.15-3.91 (m, 1H), 3.80-3.60 (m, 1H), 3.35-3.10 (m, 1H), 2.95-2.81 (m, 3H), 2.80-2.52 (m, 3H), 2.49-2.41 (m, 1H), 2.31-2.13 (m, 4H), 1.91-1.85 (m, 2H), 1.71-1.63 (m, 7H), 1.32-1.26 (m, 1H), 0.95-0.92 (m, 4H), 0.70 (s, 3H).	G
3-(6-((R)-1-(4-(3,3-difluorocyclobutyl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione	**I-716**	**(R)-51d**	4-(3,3-difluorocyclobutyl)benzaldehyde	566.4	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.84 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.34-7.27 (m, 4H), 5.10 (s, 1H), 4.25-4.21 (m, 1H), 3.57-3.40 (m, 4H), 3.01-2.98 (m, 3H), 2.72-2.68 (m, 5H), 2.52-2.50 (m, 2H), 2.22-2.11 (m, 2H), 1.70-1.68 (m, 1H), 0.99 (s, 3H), 0.67 (s, 3H).	D
1-(4-(((4R)-4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-	**I-701**	**(R)-51d**	1-(4-formylphenyl)cyclobutane-1-carbonitrile **ALD-23**	555.6	1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.85 (d, J = 2.40 Hz, 1H), 8.33 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (d, J =	D

hydroxy-3,3-dimethylpiperidin-1-yl)methyl)phenyl)cyclobutane-1-carbonitrile					9.20 Hz, 1H), 7.44 (s, 4H), 5.12 (s, 1H), 4.22 (d, J = 4.80 Hz, 1H), 3.57-3.51 (m, 1H), 3.51-3.49 (m, 1H), 3.35-3.31 (m, 1H), 2.77-2.63 (m, 7H), 2.34-2.04 (m, 7H), 1.92-1.76 (m, 1H), 1.01 (s, 3H), 0.68 (s, 3H).	
3-(5-fluoro-6-((R)-4-hydroxy-1-(4-(1-methoxycyclobutyl)benzyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, 0.61Formic Acid	**I-594**	**(R)-51d**	4-(1-methoxycyclobutyl)benzaldehyde **ALD-39**	560.6	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.84 (d, J = 2.00 Hz, 1H), 8.34 (d, J = 10.00 Hz, 2H), 8.11 (t, J = 8.40 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.48-7.38 (m, 4H), 5.12 (s, 1H), 4.23 (q, J = 4.80 Hz, 1H), 2.83 (s, 3H), 2.41-2.20 (m, 7H), 1.90-1.85 (m, 2H), 1.30 (s, 1H), 1.01 (s, 3H), 0.70 (s, 3H). (Note: 7 protons overlapped with solvent peak).	D
3-(5-fluoro-6-((R)-1-(3-fluoro-4-(1-hydroxycyclobutyl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	**I-743**	**(R)-51d**	3-fluoro-4-(1-hydroxycyclobutyl)benzaldehyde	564.6	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.45 (s, 1H), 8.33 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.37 (t, J = 7.60 Hz, 1H), 7.14-7.09 (m, 1H), 5.45 (s, 1H), 5.12 (s, 1H), 4.25-4.21 (m, 1H), 3.59-3.44 (m, 2H), 2.37 (s, 2H), 2.34-2.33 (m, 7H), 2.14-2.01 (m, 3H), 1.69-1.63 (m, 3H), 1.24 (s, 1H), 1.01 (s, 3H), 0.68 (s, 3H).	G

3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethyl-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione	**I-519**	**(R)-51d**	6-(trifluoromethyl)nicotinaldehyde	545.2	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (s, 1H), 8.75 (s, 1H), 8.33 (s, 1H), 8.12-8.06 (m, 2H), 7.91 (d, J = 8.00 Hz, 1H), 7.84 (d, J = 8.80 Hz, 1H), 5.17 (s, 1H), 4.25-4.21 (m, 1H), 3.73 (d, J = 14.00 Hz, 1H), 3.63 (d, J = 14.00 Hz, 1H), 3.17 (t, J = Hz, 1H), 2.69-2.67 (m, 5H), 2.18-2.13 (m, 2H), 1.87 (s, 1H), 1.76-1.71 (m, 1H), 1.01 (s, 3H), 0.69 (m, 3H).	E
(R)-1-(4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)phenyl)cyclobutane-1-carbonitrile	**I-679**	**INT-(R)-S2**	1-(4-formylphenyl)cyclobutane-1-carbonitrile **ALD-23**	556.2	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.91 (s, 1H), 8.33 (t, J = 0.80 Hz, 1H), 8.09 (t, J = 8.40 Hz, 1H), 7.85 (d, J = 9.20 Hz, 1H), 7.47-7.42 (m, 4H), 5.17 (s, 1H), 4.01 (t, J = 7.20 Hz, 2H), 3.63 (m, 2H), 3.33 (t, J = Hz, 1H), 2.79-0.75 (m, 5H), 2.68-2.65 (m, 3H), 2.33-2.30 (m, 3H), 2.04-2.01 (m, 1H), 1.76-1.71 (m, 1H), 1.01 (s, 3H), 0.69 (m, 3H).	K
3-(5-fluoro-6-((R)-4-hydroxy-3,3-dimethyl-1-(4-(1-(trifluoromethyl)cyclopropyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidin	**I-606**	**(R)-51d**	4-(1-(trifluoromethyl)cyclopropyl)benzaldehyde **ALD-29**	584.2	1H-NMR (400 MHz, DMSO-d6): δ 10.97 (s, 1H), 8.84 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.09 (s, 1H), 7.84 (t, J = 9.20 Hz, 1H), 7.45-7.36 (m, 4H), 5.10 (s, 1H), 4.25-4.21 (m, 1H), 3.57-3.47 (m, 2H), 3.18-0.11 (m, 2H), 2.77-2.72 (m, 2H), 2.66 (d, J = 12.00 Hz, 3H), 2.20 (d, J = 10.40 Hz, 2H), 1.89	E

e-2,6-dione, 0.8AcO-					(s, 3H), 1.74 (d, J = 18.40 Hz, 1H), 1.33 (t, J = 5.20 Hz, 2H), 1.13 (s, 2H), 1.01 (s, 3H), 0.68 (s, 3H).	
(R)-1-(4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidin-1-yl)methyl)-2-fluorophenyl)cyclopropane-1-carbonitrile	**I-774**	**INT-(R)-S2**	1-(2-fluoro-4-formylphenyl)cyclopropane-1-carbonitrile **ALD-106**	560.2	1H-NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.97 (d, J = 2.40 Hz, 1H), 8.33 (d, J = 2.00 Hz, 1H), 8.08 (t, J = 8.80 Hz, 1H), 7.85 (d, J = 8.80 Hz, 1H), 7.43 (t, J = 7.60 Hz, 1H), 7.28-7.21 (m, 2H), 5.15 (s, 1H), 4.01 (t, J = 6.80 Hz, 2H), 3.59 (d, J = 14.00 Hz, 1H), 3.49 (d, J = 14.00 Hz, 1H), 3.15 (t, J = 12.40 Hz, 1H), 2.82-2.68 (m, 2H), 2.68-2.67 (m, 2H), 2.18 (d, J = 10.80 Hz, 1H), 1.73-1.68 (m, 3H), 1.47-1.43 (m, 2H), 1.24 (s, 1H), 1.01 (s, 3H), 0.68 (s, 3H).	G
3-(5-fluoro-6-((R)-1-(3-fluoro-4-(1-hydroxycyclopropyl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, 0.465Formic Acid	**I-729**	**(R)-51d**	3-fluoro-4-(1-hydroxycyclopropyl)benzaldehyde **ALD-68**	550.2	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.85 (d, J = Hz, 1H), 7.46 (t, J = 8.00 Hz, 1H), 7.14-7.09 (m, 2H), 5.87 (s, 1H), 5.12 (s, 1H), 4.25-4.21 (m, 1H), 3.58-3.52 (m, 3H), 3.18-3.12 (m, 2H), 2.77-2.72 (m, 1H), 2.68-2.60 (m, 1H), 2.18-2.08 (m, 2H), 1.70 (d, J = 14.40 Hz, 1H), 1.24 (s, 3H), 1.01-0.86 (m, 6H), 0.68 (s, 3H).	K

3-(5-fluoro-6-((R)-1-(3-fluoro-4-(2-hydroxypropan-2-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, 0.837Formic Acid	**I-763**	**(R)-51d**	3-fluoro-4-(2-hydroxypropan-2-yl)benzaldehyde **ALD-92**	552.3	1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.23 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.58 (t, J = 8.40 Hz, 1H), 7.15-7.06 (m, 2H), 5.21 (s, 1H), 5.12 (s, 1H), 4.26-4.21 (m, 1H), 3.57-3.44 (m, 6H), 2.74-2.68 (m, 2H), 2.20-2.14 (m, 2H), 1.71 (d, J = 12.80 Hz, 1H), 1.49 (s, 6H), 1.01 (s, 3H), 0.68 (m, 3H).	E

Table 5. Characterization data of Exemplary compounds

Compound Name (Cmpd No.)	**MS observed, MH+**	**LCMS**	**1H-NMR**
(I-170)	300	LCMS: m/z MM-ES+APCI, Positive [M+H] + 300.0 (half mass)	1H NMR (499 MHz, DMSO-d6, 297 K) δ (ppm) = 11.07 - 10.85 (m, 1H), 8.24 - 8.15 (m, 1H), 8.05 - 7.96 (m, 1H), 7.75 - 7.68 (m, 3H), 7.63 - 7.58 (m, 2H), 4.42 – 4.30 (m, 1H) 3.72 - 3.52 (m, 3H), 3.19 - 3.07 (m, 1H), 2.90 - 2.76 (m, 2H), 2.66 (s, 4H), 2.44 - 2.33 (m, 1H), 2.30 - 2.23 (m, 1H), 2.18 - 1.91 (m, 2H), 1.76 - 1.59 (m, 2H), 1.36 - 1.21 (m, 4H), 1.18 - 0.96 (m, 2H), 0.89 - 0.52 (m, 3H)
3-(6-(6-ethyl-9-hydroxy-6-azaspiro[3.5]nonan-9-yl)quinolin-3-yl)piperidine-2,6-dione (**I-908**)	408	LCMS: m/z HESI, positive [M+H]+= 408	1H NMR (500 MHz, DMSO-d6) δ (ppm) = 11.08 (s, 1H), 10.13 (br s, 1H), 9.15 (br s, 1H), 8.89 (br s, 1H), 8.34 (br s, 1H), 8.32 - 8.28 (m, 1H), 8.28 - 8.25 (m, 1H), 4.34 - 4.28 (m, 2H), 3.64 - 3.57 (m, 1H), 3.40 - 3.38 (m, 1H), 3.32 - 3.12 (m, 4H), 2.86 - 2.75 (m, 2H), 2.71 - 2.62 (m, 1H), 2.49 - 2.40 (m, 1H), 2.28 - 2.16 (m, 2H), 2.07 - 1.94 (m, 1H), 1.90 - 1.82 (m, 1H), 1.82 - 1.73 (m, 1H), 1.61 - 1.46 (m, 2H), 1.35 (t, J = 7.1 Hz, 3H), 0.71 - 0.61 (m, 1H).
(I-915)	626.4	LCMS: m/z MM-ES+APCI, Positive [M+H] + 626.4	1H NMR (499 MHz, DMSO-d6) δ ppm 10.96 - 10.99 (m, 1H) 8.78 - 8.80 (m, 1H) 8.46 (s, 1H) 8.20 - 8.25 (m, 1H) 7.98 - 8.09 (m, 2H) 7.71 (s, 2H) 7.73 (s, 1H) 7.59 - 7.64 (m, 2H) 5.61 - 5.89 (m, 2H) 4.12 - 4.18 (m, 1H) 2.83 - 2.88 (m, 2H) 2.73 - 2.82 (m, 1H)

			2.58 - 2.65 (m, 1H) 2.34 - 2.45 (m, 4H) 2.08 - 2.19 (m, 1H) 1.92 - 2.03 (m, 1H) 1.46 - 1.68 (m, 3H) 1.21 - 1.37 (m, 4H)
(**I-895**)	582.5	LCMS: m/z MM-ES+APCI, Positive [M+H] + 582.5	1H NMR (499 MHz, DMSO-d6) δ = 10.99 (s, 1H), 8.90 - 8.77 (m, 1H), 8.33 (d, J = 2.2 Hz, 1H), 8.02 (br t, J = 8.8 Hz, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.77 - 7.66 (m, 2H), 7.60 (br d, J = 8.2 Hz, 2H), 4.22 (br dd, J = 4.9, 12.6 Hz, 1H), 3.69 (s 2H) 2.76 (m 1H), 2.65 - 2.63 (m 1H), 2.36 (m 1H), 2.32 - 2.27 (m, 1H), 2.25 - 2.19 (m, 1H), 2.18 - 2.11 (m, 1H), 2.04 - 1.96 (m, 1H), 1.48 - 1.40 (m, 1H), 0.88 - 0.84 (m, 1H) (some peaks overlap with solvent)
3-(6-(3-ethoxy-4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-308**)	542	LCMS: m/z HESI, positive [M+H]+= 542	1H NMR (500 MHz, DMSO-d6) δ (ppm) = 11.03 (s, 1H), 9.79 (br s, 1H), 9.09 - 8.88 (m, 1H), 8.57 (br s, 1H), 8.21 - 8.08 (m, 2H), 8.06 - 8.00 (m, 1H), 7.98 - 7.94 (m, 1H), 7.91 (s, 2H), 7.90 - 7.87 (m, 1H), 6.21 - 6.01 (m, 1H), 4.65 - 4.42 (m, 3H), 4.28 - 4.22 (m, 1H), 4.03 (q, J = 7.1 Hz, 1H), 3.64 (br s, 1H), 3.47 - 3.41 (m, 1H), 3.37 - 3.31 (m, 1H), 3.31 - 3.19 (m, 2H), 2.91 - 2.74 (m, 2H), 2.69 - 2.60 (m, 1H), 2.24 - 2.11 (m, 1H), 2.05 - 1.98 (m, 1H), 0.79 - 0.65 (m, 3H).
3-(6-((3S,5R)-4-hydroxy-3,5-dimethyl-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)-5-methylquinolin-3-yl)piperidine-2,6-dione (**I-921**)	540	LCMS: m/z HESI, positive [M+H]+= 540	1H NMR (500 MHz, DMSO-d6) δ (ppm) = 11.46 (br d, J = 6.0 Hz, 1H), 11.04 (s, 1H), 9.10 - 8.92 (m, 1H), 8.83 (br s, 1H), 8.27 (br d, J = 8.8 Hz, 1H), 8.02 (br d, J = 9.3 Hz, 1H), 8.00 - 7.93 (m, 2H), 7.91 - 7.85 (m, 2H), 5.46 (br s, 1H), 4.49 (br d, J = 4.4 Hz, 2H), 4.34 - 4.23 (m, 1H), 3.21 - 3.03 (m, 6H), 3.01 (s, 1H), 2.90 (s, 3H), 2.84 - 2.72 (m, 1H), 2.69 - 2.61 (m, 1H), 2.21 - 2.11 (m, 1H), 0.68 - 0.50 (m, 6H).
(**I-327**)	576.5	LCMS: m/z MM-ES+APCI, Positive [M+H] + 576.5	1H NMR (499 MHz, DMSO-d6, 297 K) δ (ppm) 10.99 - 10.94 (m, 1H), 8.78 - 8.75 (m, 1H), 8.47 - 8.45 (m, 2H), 8.26 - 8.22 (m, 1H), 8.06 - 8.02 (m, 1H), 7.97 - 7.94 (m, 1H), 7.93 - 7.89 (m, 1H), 7.73 - 7.69 (m, 2H), 7.61 - 7.57 (m, 2H), 6.20 – 5.91 (t, J = 55 Hz, 1H) 4.14 (dd, J = 4.9, 12.6 Hz, 1H), 3.68 - 3.59 (m, 2H), 2.91 (m, 1H), 2.82 - 2.72 (m, 1H), 2.70 (m, 1H), 2.66 - 2.60 (m, 1H), 2.59 - 2.53 (m, 1H), 2.47 - 2.33 (m, 2H), 2.20 - 2.07 (m, 2H), 2.04 - 1.93 (m, 1H), 1.55 (br d, J = 13.1 Hz, 1H), 1.49 - 1.32 (m, 1H), 1.23 (br, 3H), 0.85 (m, 1H)
(**I-424**)	586.6	LCMS: m/z MM-ES+APCI,	1H NMR (499 MHz, DMSO-d6, 297 K) δ ppm 11.03 - 10.96 (m, 1H), 8.87 - 8.84 (m,

		Positive [M+H] + 586.6	1H), 8.43 - 8.40 (m, 1H), 8.36 - 8.32 (m, 1H), 8.10 - 8.04 (m, 1H), 7.89 - 7.83 (m, 1H), 7.71 (s, 2H), 7.61 - 7.57 (m, 2H), 5.31 - 5.24 (m, 1H), 4.26 - 4.19 (m, 1H), 3.72 - 3.67 (m, 1H), 3.64 - 3.59 (m, 1H), 3.52 - 3.45 (m, 2H), 3.19 - 3.10 (m, 4H), 3.10 - 3.05 (m, 2H), 2.81 - 2.71 (m, 1H), 2.71 - 2.66 (m, 1H), 2.65 - 2.58 (m, 2H), 2.39 - 2.34 (m, 1H), 2.27 - 2.22 (m, 1H), 2.17 - 2.10 (m, 1H), 1.72 - 1.67 (m, 1H), 1.48 - 1.42 (m, 1H), 1.30 - 1.20 (m, 2H), 1.19 - 1.07 (m, 1H)
3-(6-(10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)quinolin-3-yl)piperidine-2,6-dione (**I-702**)	552	LCMS: m/z HESI, positive [M+H]+= 552	1H NMR (500 MHz, DMSO-d6) δ (ppm) = 11.02 (s, 1H), 10.38 - 10.18 (m, 1H), 8.96 (s, 1H), 8.58 (br s, 1H), 8.15 - 8.07 (m, 2H), 8.07 - 8.02 (m, 1H), 7.98 (d, J = 8.2 Hz, 2H), 7.89 (d, J = 8.2 Hz, 2H), 5.73 (br s, 1H), 4.58 - 4.47 (m, J = 4.9, 4.9 Hz, 2H), 4.22 (dd, J = 4.7, 12.9 Hz, 1H), 3.40 - 3.29 (m, 2H), 3.04 - 2.87 (m, 3H), 2.84 - 2.72 (m, 1H), 2.69 - 2.59 (m, 1H), 2.48 - 2.43 (m, 1H), 2.22 - 2.12 (m, 1H), 2.12 - 2.02 (m, 1H), 1.96 - 1.88 (m, 2H), 1.44 (m, 1H), 1.31 - 1.17 (m, 2H), 1.13 (m, 1H), 0.95 - 0.82 (m, 1H), 0.80 - 0.67 (m, 1H).
3-(5-fluoro-6-(5-hydroxy-2-isobutyl-9-oxa-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)piperidine-2,6-dione (**I-782**)	484	LCMS: m/z HESI, positive [M+H]+= 484	1H NMR (500 MHz, DMSO-d6) δ (ppm) = 11.01 (s, 1H), 9.66 - 9.48 (m, 1H), 8.96 (d, J = 2.2 Hz, 1H), 8.48 (dd, J = 1.6, 7.1 Hz, 1H), 8.11 (br t, J = 8.5 Hz, 1H), 7.96 (d, J = 9.3 Hz, 1H), 6.09 (br s, 1H), 4.28 (dd, J = 4.9, 12.6 Hz, 1H), 3.85 (br d, J = 12.6 Hz, 1H), 3.66 - 3.57 (m, 1H), 3.54 - 3.41 (m, 4H), 3.38 - 3.30 (m, 1H), 3.28 - 3.09 (m, 2H), 3.02 - 2.92 (m, 1H), 2.82 - 2.71 (m, 1H), 2.68 - 2.51 (m, 3H), 2.41 - 2.28 (m, 1H), 2.23 - 2.07 (m, 1H), 2.05 - 1.88 (m, 1H), 1.66 - 1.51 (m, 1H), 1.40 - 1.27 (m, 1H), 1.27 - 1.12 (m, 2H), 1.05 - 0.99 (m, 6H).
1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((1-methyl-1H-pyrazol-5-yl)methyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-797**)	481	LCMS: m/z HESI, positive [M+H]+= 481	1H NMR (500 MHz, DMSO-d6) δ (ppm) = 10.63 (s, 1H), 10.51 - 10.32 (m, 1H), 9.01 (d, J = 2.7 Hz, 1H), 8.38 (d, J = 2.2 Hz, 1H), 8.05 (t, J = 8.8 Hz, 1H), 7.91 (d, J = 9.3 Hz, 1H), 7.53 (d, J = 1.6 Hz, 1H), 6.71 (d, J = 2.2 Hz, 1H), 6.04 - 5.84 (m, 1H), 4.53 (br d, J = 4.4 Hz, 2H), 4.00 (t, J = 6.6 Hz, 2H), 3.97 (s, 3H), 3.48 - 3.38 (m, 3H), 3.37 - 3.20 (m, 1H), 2.98 (m, 1H), 2.80 (t, J = 6.6 Hz, 2H), 2.02 (m, 1H), 1.16 - 1.08 (m, 3H), 0.79 (s, 3H).

1-(6-(1-(4-chlorobenzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-566**)	511	LCMS: m/z HESI, positive [M+H]+= 511	1H NMR (500 MHz, DMSO-d6) δ (ppm) = 10.63 (s, 1H), 10.07 (br s, 1H), 9.00 (d, J = 2.2 Hz, 1H), 8.35 (d, J = 2.2 Hz, 1H), 8.03 (t, J = 8.8 Hz, 1H), 7.89 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 8.2 Hz, 2H), 7.57 (d, J = 8.2 Hz, 2H), 6.02 - 5.83 (m, 1H), 4.46 - 4.34 (m, 2H), 4.00 (t, J = 6.6 Hz, 2H), 3.43 - 3.32 (m, 3H), 3.28 - 3.19 (m, J = 11.5, 11.5 Hz, 1H), 2.89 - 2.82 (m, J = 11.5 Hz, 1H), 2.80 (t, J = 6.6 Hz, 2H), 2.03 - 1.97 (m, J = 13.7 Hz, 1H), 1.07 (br s, 3H), 0.76 (s, 3H).
1-(5-fluoro-6-(9-hydroxy-6-methyl-6-azaspiro[3.5]nonan-9-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-877**)	413	LCMS: m/z HESI, positive [M+H]+= 413	1H NMR (500 MHz, DMSO-d6) δ (ppm) = 10.64 (s, 1H), 9.83 (br s, 1H), 9.03 (d, J = 2.7 Hz, 1H), 8.38 (d, J = 2.2 Hz, 1H), 8.24 - 8.07 (m, 1H), 7.97 (d, J = 9.3 Hz, 1H), 5.93 (br s, 1H), 4.06 - 3.97 (m, 2H), 3.72 - 3.66 (m, 1H), 3.65 - 3.55 (m, 1H), 3.40 - 3.33 (m, 1H), 3.10 - 2.99 (m, 1H), 2.86 (d, J = 4.4 Hz, 3H), 2.81 (t, J = 6.6 Hz, 2H), 2.28 - 2.20 (m, 1H), 2.01 - 1.93 (m, 2H), 1.87 - 1.73 (m, 2H), 1.73 - 1.63 (m, 1H), 1.56 - 1.35 (m, 1H), 1.02 - 0.93 (m, 1H).
1-(5-fluoro-6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-9-oxa-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-458**)	587	LCMS: m/z HESI, positive [M+H]+= 587	1H NMR (500 MHz, DMSO-d6) δ (ppm) = 10.79 (br s, 1H), 10.63 (s, 1H), 9.10 - 8.94 (m, 1H), 8.36 (d, J = 2.2 Hz, 1H), 8.08 - 7.97 (m, 3H), 7.94 - 7.87 (m, 3H), 6.00 (br s, 1H), 4.56 (br d, J = 4.4 Hz, 2H), 4.01 (t, J = 6.8 Hz, 2H), 3.86 - 3.81 (m, 1H), 3.59 - 3.47 (m, 3H), 3.44 - 3.35 (m, 2H), 3.28 - 3.15 (m, 2H), 2.84 - 2.75 (m, 2H), 2.70 - 2.61 (m, 1H), 2.02 - 1.91 (m, 1H), 1.64 - 1.45 (m, 1H), 1.37 - 1.21 (m, 1H), 1.21 - 1.13 (m, 1H).
1-(5-fluoro-6-(5-hydroxy-2-isobutyl-9-oxa-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-814**)	485	LCMS: m/z HESI, positive [M+H]+= 485	1H NMR (500 MHz, DMSO-d6) δ (ppm) = 10.63 (s, 1H), 9.65 (br s, 1H), 9.03 (d, J = 2.7 Hz, 1H), 8.38 (d, J = 2.2 Hz, 1H), 8.06 (br t, J = 8.8 Hz, 1H), 7.93 (d, J = 9.3 Hz, 1H), 6.25 - 5.97 (m, 1H), 4.04 - 3.99 (m, 2H), 3.88 - 3.83 (m, 1H), 3.64 - 3.57 (m, 1H), 3.55 - 3.41 (m, 4H), 3.37 - 3.32 (m, 1H), 3.27 - 3.08 (m, 2H), 3.03 - 2.90 (m, 1H), 2.80 (t, J = 6.6 Hz, 2H), 2.65 - 2.57 (m, 1H), 2.40 - 2.29 (m, 1H), 2.01 - 1.92 (m, 1H), 1.65 - 1.52 (m, 1H), 1.42 - 1.28 (m, 1H), 1.26 - 1.14 (m, 1H), 1.02 (t, J = 6.8 Hz, 6H).
1-(6-(2-(4-(1,2,4-oxadiazol-3-yl)benzyl)-5-hydroxy-9-oxa-2-azaspiro[5.5]unde	587	LCMS: m/z HESI, positive [M+H]+= 587	1H NMR (500 MHz, DMSO-d6) δ (ppm) = 10.62 (s, 1H), 9.70 (s, 1H), 8.98 (d, J = 2.7 Hz, 1H), 8.34 (d, J = 2.2 Hz, 1H), 8.13 - 7.98 (m, 3H), 7.87 (d, J = 9.3 Hz, 1H), 7.58 (d, J = 8.2 Hz, 2H), 5.28 (br s, 1H), 4.01 (t, J = 6.6

can-5-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-460**)			Hz, 2H), 3.74 (br d, J = 13.7 Hz, 1H), 3.58 (br d, J = 13.7 Hz, 1H), 3.51 - 3.45 (m, 1H), 3.42 - 3.39 (m, 1H), 3.19 - 3.06 (m, 4H), 2.80 (t, J = 6.6 Hz, 2H), 2.76 - 2.70 (m, 1H), 2.67 - 2.60 (m, 1H), 2.39 - 2.32 (m, 1H), 2.31 - 2.22 (m, 1H), 1.78 - 1.68 (m, 1H), 1.49 - 1.42 (m, 1H), 1.29 - 1.21 (m, 2H), 1.19 - 1.07 (m, 1H). (one extra aliphatic hydrogen, maybe salt?)
1-(5-fluoro-6-(5-hydroxy-2-(4-(oxetan-3-yl)benzyl)-9-oxa-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-730**)	575	LCMS: m/z HESI, positive [M+H]+= 575	1H NMR (500 MHz, DMSO-d6) δ (ppm) = 10.61 (s, 1H), 8.98 (d, J = 2.2 Hz, 1H), 8.33 (d, J = 2.2 Hz, 1H), 8.06 (t, J = 8.8 Hz, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.40 - 7.33 (m, 4H), 6.79 - 6.36 (m, 1H), 5.24 (s, 1H), 4.94 (dd, J = 6.0, 8.2 Hz, 2H), 4.65 - 4.59 (m, 2H), 4.25 (quin, J = 7.5 Hz, 1H), 4.01 (t, J = 6.6 Hz, 2H), 3.67 - 3.55 (m, 1H), 3.52 - 3.38 (m, 3H), 3.22 - 3.05 (m, 3H), 2.80 (t, J = 6.6 Hz, 2H), 2.73 - 2.66 (m, 1H), 2.61 - 2.52 (m, 1H), 2.34 - 2.27 (m, 1H), 2.27 - 2.21 (m, 1H), 1.73 - 1.65 (m, 1H), 1.51 - 1.38 (m, 1H), 1.24 (dt, J = 5.2, 13.3 Hz, 1H), 1.17 - 1.05 (m, 1H)
1-(5-fluoro-6-(5-hydroxy-2-isobutyl-9-oxa-2-azaspiro[5.5]undecan-5-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-669**)	499	LCMS: m/z HESI, positive [M+H]+= 499	1H NMR (500 MHz, DMSO-d6) δ (ppm) = 10.60 (s, 1H), 9.87 - 9.72 (m, 1H), 8.63 (br d, J = 11.0 Hz, 1H), 8.16 - 8.10 (m, 1H), 7.96 (br d, J = 9.3 Hz, 1H), 6.26 - 5.96 (m, 1H), 4.02 (dt, J = 5.5, 11.0 Hz, 2H), 3.90 - 3.79 (m, 1H), 3.75 - 3.66 (m, 1H), 3.64 - 3.56 (m, 1H), 3.55 - 3.39 (m, 5H), 3.25 - 3.09 (m, 2H), 3.00 - 2.85 (m, 2H), 2.82 - 2.73 (m, 1H), 2.70 - 2.62 (m, 4H), 2.42 - 2.27 (m, 1H), 2.01 - 1.92 (m, 1H), 1.62 - 1.54 (m, 1H), 1.36 - 1.27 (m, 1H), 1.21 - 1.12 (m, 1H), 1.05 - 0.99 (m, 6H).
1-(5-fluoro-6-(5-hydroxy-2-(4-(trifluoromethyl)benzyl)-9-oxa-2-azaspiro[5.5]undecan-5-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**I-532**)	601	LCMS: m/z HESI, positive [M+H]+= 601	1H NMR (500 MHz, DMSO-d6) δ (ppm) = 10.98 - 10.78 (m, 1H), 10.58 (s, 1H), 8.55 (br d, J = 7.7 Hz, 1H), 8.04 (br d, J = 8.2 Hz, 3H), 7.89 (d, J = 8.2 Hz, 3H), 6.01 (br s, 1H), 4.55 (br d, J = 3.8 Hz, 2H), 4.04 - 3.96 (m, 3H), 3.87 - 3.78 (m, 2H), 3.73 - 3.66 (m, 1H), 3.58 - 3.52 (m, 1H), 3.52 - 3.46 (m, 1H), 3.42 - 3.37 (m, 1H), 3.28 - 3.14 (m, 2H), 2.94 - 2.83 (m, 1H), 2.80 - 2.64 (m, 2H), 2.63 (s, 3H), 2.02 - 1.91 (m, 1H), 1.60 - 1.48 (m, 1H), 1.32 - 1.20 (m, 1H), 1.20 - 1.07 (m, 1H).
(I-517)	476.4		1H-NMR (400 MHz, DMSO-d6): δ ppm 11.00 (s, 1H), 9.41 (s, 1H), 8.89 (s, 1H), 8.37 (s, 1H), 8.06 (t, J = 8.40 Hz, 1H), 7.90 (d, J =

			9.20 Hz, 1H), 7.65 (s, 2H), 7.51 (s, 2H), 5.90 (s, 1H), 4.47-4.42 (m, 2H), 4.26-4.22 (m, 1H), 3.38-3.25 (m, 4H), 2.94 (d, J = 10.20 Hz, 1H), 2.64-2.81 (m, 1H), 2.55-2.42 (m, 3H), 2.13-1.98 (m, 2H), 1.01 (s, 3H), 0.77 (s, 3H).
(I-1062)	595.1		1H-NMR (400 MHz, DMSO-d6): δ ppm 10.98 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.56 (d, J = 4.00 Hz, 1H), 8.33 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.90-7.83 (m, 2H), 7.35-7.32 (m, 2H), 5.14 (s, 1H), 4.23 (dd, J = 4.80, 12.80 Hz, 1H), 3.64 (d, J = 14.40 Hz, 1H), 3.51 (d, J = 14.00 Hz, 1H), 3.21-3.17 (m, 1H), 3.14-2.80 (m, 2H), 2.77-2.73 (m, 3H), 2.22-2.01 (m, 3H), 1.76-1.62 (m, 1H), 1.24 (s, 3H), 0.68 (s, 3H).
(I-1085)	557.4		1H-NMR (400 MHz, DMSO-d6): δ ppm 10.98 (s, 1H), 8.85 (d, J = 2.0 Hz, 1H), 8.44 (s, 1H), 8.33 (s, 1H), 8.17 (s, 1H), 8.10 (q, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.72 (d, J = 8.40 Hz, 2H), 7.40 (d, J = 8.00 Hz, 2H), 5.11 (s, 1H), 4.23 (dd, J =12.8, 4.80 Hz, 1H), 3.60 (d, J = 13.60 Hz, 1H), 3.47 (d, J = 13.60 Hz, 1H), 3.32-3.16 (m, 1H), 2.77-2.69 (m, 2H), 2.68-2.63 (m, 2H), 2.58-2.51 (m, 5H), 2.18-2.13 (m, 2H), 1.71 (d, J = 12.40 Hz, 1H), 1.01 (s, 3H), 0.68 (m, 3H).
(I-1142)	590.2		1H-NMR (400 MHz, DMSO-d6): δ ppm 10.98 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.34 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.78-7.73 (m, 2H), 7.50 (s, 1H), 7.38-7.35 (m, 1H), 6.70 (d, J = 2.40 Hz, 1H), 5.14 (s, 1H), 4.25-4.21 (m, 1H), 3.91 (s, 3H), 3.62 (d, J = 13.60 Hz, 1H), 3.49 (d, J = 13.60 Hz, 1H), 3.20-3.14 (m, 1H), 2.78-2.71 (m, 3H), 2.68-2.62 (m, 3H), 2.34-2.21 (m, 2H), 1.81-1.71 (m, 1H), 1.02 (s, 3H), 0.69 (s, 3H).
(I-1180)	556.3		1H-NMR (400 MHz, DMSO-d6): δ ppm 10.98 (s, 1H), 8.84 (s, 1H), 8.34 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.75 (d, J = 8.40 Hz, 2H), 7.44 (d, J = 8.00 Hz, 2H), 6.32 (d, J = 2.00 Hz, 1H), 5.12 (s, 1H), 4.23 (dd, J = 4.80, 12.80 Hz, 1H), 3.60 (d, J = 13.60 Hz, 1H), 3.48 (d, J = 13.60 Hz, 1H), 3.18-3.13 (m, 1H), 2.81-2.72 (m, 4H), 2.33-2.18 (m, 6H), 1.91 (s, 3H), 1.76-1.24 (m, 1H), 1.01 (s, 3H), 0.68 (s, 3H).
(I-1163)	616.2		1H-NMR (400 MHz, DMSO-d6): δ ppm 10.99 (s, 1H), 8.85 (s, 1H), 8.43 (s, 1H), 8.34

			(s, 1H), 8.12-8.07 (m, 1H), 7.87-7.83 (m, 2H), 7.57 (d, J = 8.00 Hz, 1H), 7.48 (s, 1H), 7.34-7.32 (m, 1H), 5.13 (d, J = 1.20 Hz, 1H), 4.31-4.25 (m, 1H), 3.82-3.72 (m, 1H), 3.60-3.32 (m, 2H), 3.20-3.11 (s, 1H), 2.92-2.48 (m, 6H), 2.22-2.12 (m, 2H), 1.76-1.65 (m, 1H), 1.11-0.98 (m, 7H), 0.69 (s, 3H).
(I-1183)	610.6		1H-NMR (400 MHz, DMSO-d6):δ ppm 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.34 (s, 1H), 8.19 (t, J = 9.20 Hz, 1H), 8.12-8.06 (m, 3H), 7.84 (d, J = 9.20 Hz, 2H), 7.34 (d, J = 9.60 Hz, 1H), 5.14 (s, 1H), 4.46 (t, J = 2.80 Hz, 1H), 4.24-4.21 (m, 1H), 3.66 (d, J = 14.00 Hz, 1H), 3.55 (d, J = 14.00 Hz, 1H), 3.22-3.13 (m, 1H), 2.74-2.57 (m, 5H), 2.48-2.33 (m, 2H), 2.27-2.13 (m, 1H), 1.68 (d, J = 8.00 Hz, 1H), 1.03 (s, 3H), 0.86 (t, J = 6.00 Hz, 2H), 0.79 (dd, J = 6.40, 7.60 Hz, 2H), 0.69 (s, 3H).
(I-1093)	588.2		1H-NMR (400 MHz, DMSO-d6): δ ppm 10.99 (s, 1H), 8.84 (s, 1H), 8.32 (s, 1H), 8.05 (t, J = 8.40 Hz, 1H), 7.82 (d, J = 9.20 Hz, 1H), 7.72 (t, J = 4.00 Hz, 2H), 7.60 (d, J = 5.20 Hz, 2H), 5.01 (d, J = 14.80 Hz, 1H), 4.23 (d, J = 13.60 Hz, 1H), 3.76 (t, J = 9.20 Hz, 3H), 3.25 (d, J = 8.40 Hz, 3H), 3.14-3.15 (m, 2H), 2.95-2.73 (m, 4H), 2.51-2.34 (m, 1H), 2.15-2.05 (m, 2H), 1.72-1.61 (m, 1H), 1.01-0.95 (m, 3H), 0.68-0.61 (m, 3H).
(I-1337)	566.2		1H-NMR (400 MHz, DMSO-d6):δ ppm 10.97 (s, 1H), 8.75 (d, J = 2.40 Hz, 1H), 8.21 (s, 1H), 8.17 (s, 1H), 8.00 (s, 1H), 7.95-7.92 (m, 4H), 7.57 (d, J = 8.40, Hz, 2H), 4.86 (s, 1H), 4.16-4.11 (m, 1H), 3.61 (d, J = 14.00 Hz, 1H), 3.43 (d, J = 14.00 Hz, 1H), 2.95-2.73 (m, 3H), 2.57-2.50 (m, 2H), 2.48-2.32 (m, 2H), 2.29-2.24 (m, 1H), 2.19-2.11 (m, 2H), 1.56 (d, J = 13.20 Hz, 1H), 1.19-1.11 (m, 4H), 0.92 (s, 3H), 0.68 (s, 3H).
(I-1173)	557.4		1H-NMR (400 MHz, DMSO-d6): δ ppm 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.51 (s, 1H), 8.34 (s, 1H), 8.10 (s, 1H), 7.96 (d, J = 8.00 Hz, 2H), 7.84 (d, J = 9.20 Hz, 1H), 7.45 (d, J = 8.40 Hz, 2H), 5.13 (s, 1H), 4.23 (dd, J = 4.80, 12.60 Hz, 1H), 3.92 (s, 3H), 3.61 (d, J = 13.60 Hz, 1H), 3.50 (d, J = 13.60 Hz, 1H), 3.20-3.16 (m, 1H), 3.16-2.70 (m, 3H), 2.69-2.60 (m, 3H), 2.16 (dd, J = 4.80, 9.00 Hz, 2H), 1.72 (d, J = 12.00 Hz, 1H), 1.02 (s, 3H), 0.68 (s, 3H).

(I-1099)	629.3		1H-NMR (400 MHz, DMSO-d6): δ ppm 10.98 (s, 1H), 8.83 (d, J = 2.00 Hz, 1H), 8.32 (s, 1H), 8.24 (s, 1H), 8.05-7.99 (m, 1H), 7.81 (d, J = 9.20 Hz, 1H), 7.71 (d, J = 8.00 Hz, 2H), 7.54 (d, J = 8.00 Hz, 2H), 4.93 (d, J = 15.20 Hz, 1H), 4.24-4.16 (m, 2H), 3.09-3.01 (m, 3H), 2.91-2.89 (m, 2H), 2.85-2.76 (m, 2H), 2.76-2.67 (m, 5H), 2.34-2.15 (m, 4H), 1.64 (d, J = 13.20 Hz, 1H), 1.24 (s, 1H), 0.95 (d, J = 7.20 Hz, 3H), 0.64 (s, 3H),
(I-1003)	594.2		1H-NMR (400 MHz, DMSO-d6):δ ppm 10.97 (s, 1H), 8.76 (d, J = 2.00 Hz, 1H), 8.21 (s, 1H), 8.06 (d, J = 8.40 Hz, 2H), 8.01 (s, 1H), 7.94 (s, 2H), 7.63 (d, J = 8.40 Hz, 2H), 4.87 (s, 1H), 4.14 (dd, J = 4.80, 12.00 Hz, 1H), 3.70-3.67 (m, 2H), 2.89 (t, J = 2.40 Hz, 1H), 2.77-2.67 (m, 4H), 2.51-2.44 (m, 2H), 2.20-2.15 (m, 2H), 1.57 (d, J = 13.20 Hz, 1H), 0.93 (s, 3H), 0.69 (s, 3H).
(I-1092)	574.3		^{1}H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.84 (s, 1H), 8.32 (s, 1H), 8.18 (s, 1H), 8.08 (t, J = 8.40 Hz, 1H), 7.82 (d, J = 8.80 Hz, 1H), 7.71 (d, J = 7.60 Hz, 2H), 7.58 (d, J = 3.20 Hz, 2H), 5.00 (d, J = 20.00 Hz, 1H), 4.53 (s, 1H), 4.23 (d, J = 2.40 Hz, 1H), 3.80-3.79 (m, 3H), 3.59-3.54 (m, 1H), 3.15 (t, J = Hz, 2H), 2.91-2.89 (m, 2H), 2.81-2.76 (m, 3H), 2.40-2.33 (m, 1H), 2.14 (d, J = 5.20 Hz, 1H), 1.64 (dd, J = 12.80, 40.20 Hz, 1H), 1.00 (d, J = 27.60 Hz, 3H), 0.65 (d, J = 35.20 Hz, 3H)
(I-1088)	574.2		^{1}H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.84 (s, 1H), 8.31 (s, 1H), 8.05 (t, J = 8.80 Hz, 1H), 7.82 (d, J = 8.80 Hz, 1H), 7.72 (d, J = 8.00 Hz, 2H), 7.59 (d, J = 8.00 Hz, 2H), 4.97 (s, 1H), 4.53 (s, 1H), 4.23 (q, J = 4.80 Hz, 1H), 3.90 (s, 1H), 3.77 (t, J = 6.00 Hz, 1H), 3.59 (m, J = 6.40 Hz, 1H), 3.06 (t, J = 12.80 Hz, 1H), 2.77-2.73 (m, 1H), 2.66 (d, J = 13.20 Hz, 3H), 2.43 (d, J = 8.80 Hz, 3H), 2.16-2.12 (d, 1H), 1.63 (d, J = Hz, 1H), 1.03 (s, 3H), 0.69 (s, 3H)
(I-1089)	574.3		^{1}H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.84 (s, 1H), 8.33 (s, 1H), 8.05 (t, J = 8.80 Hz, 1H), 7.82 (d, J = 9.20 Hz, 1H), 7.71 (d, J = 8.40 Hz, 2H), 7.58 (d, J = 8.00 Hz, 2H), 5.02 (s, 1H), 4.53 (s, 1H), 4.23 (d, J = 4.80 Hz, 1H), 3.80 (s, 2H), 3.54 (t, J = 5.60 Hz, 1H), 3.17 (t, J = Hz, 1H), 2.93 (d, J = 8.00 Hz, 1H), 2.77 (m, 1H), 2.65 (d, J = 3.60

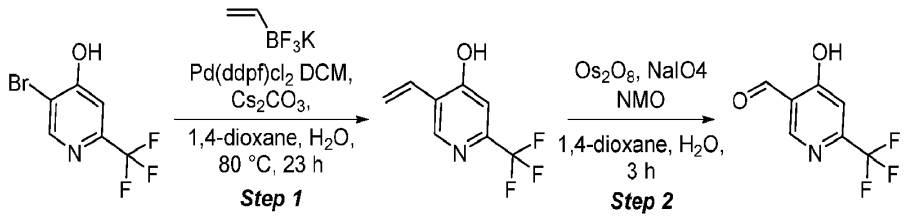
			Hz, 2H), 2.34 (d, J = 2.00 Hz, 2H), 2.14 (d, J = 4.80 Hz, 1H), 2.05 (d, J = 10.80 Hz, 1H), 1.71 (d, J = 12.80 Hz, 1H), 0.96 (s, 3H), 0.60 (s, 3H).
(I-1237)	600.5		1H-NMR (400 MHz, DMSO-d6): δ 10.99 (s, 1H), 8.86 (s, 1H), 8.34 (s, 1H), 8.07 (d, J = 8.40 Hz, 2H), 8.14 (s, 1H), 7.85 (d, J = 8.40 Hz, 2H), 7.43 (d, J = -8.40 Hz, 2H), 5.12 (s, 1H), 4.26-4.21 (m, 1H), 3.74-3.72 (m, 1H), 3.41-3.64 (m, 2H), 3.18-3.17 (m, 1H), 2.69-2.67 (m, 6H), 2.16-2.12 (m, 2H), 1.64-1.74 (m, 1H), 1.09-1.00 (m, 7H), 0.68 (s, 3H).
(I-1338)	557.4		^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 9.14 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.85 (d, J = 8.80 Hz, 1H), 7.54-7.48 (m, 4H), 5.12 (s, 1H), 4.23 (dd, J = 4.40, 12.60 Hz, 1H), 3.56 (m, 2H), 3.33 (m, 2H), 3.17 (t, J = 10.00 Hz, 1H), 2.80-2.76 (m, 2H), 2.72-2.67 (m, 2H), 2.41 (s, 3H), 2.34-2.33 (m, 1H), 2.16-2.12 (m, 1H), 1.75 (d, J = 11.20 Hz, 1H), 1.02 (s, 3H), 0.70 (s, 3H).
(I-1339)	583.3		1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 9.09 (d, J = 6.80 Hz, 1H), 8.85 (d, J = 2.40 Hz, 1H), 8.84 (s, 1H), 8.13 (t, J = 8.80 Hz, 1H), 7.94 (d, J = 8.40 Hz, 1H), 7.49 (d, J = 8.40 Hz, 2H), 7.60 (d, J = 8.00 Hz, 2H), 5.13 (s, 1H), 4.23 (dd, J = 4.80, 12.60 Hz, 1H), 3.62 (d, J = 13.60 Hz, 1H), 3.51 (d, J = 13.60 Hz, 1H), 3.33-3.16 (m, 1H), 2.74-2.50 (m, 7H), 2.22 (d, J = 10.40 Hz, 1H), 2.02-1.98 (m, 2H), 1.73-1.70 (m, 1H), 1.07-1.02 (m, 6H), 0.69 (s, 3H).
(I-1340)	606.3		^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.34 (d, J = 2.40 Hz, 1H), 8.20 (s, 1H), 8.12-8.08 (m, 2H), 7.84 (d, J = 9.20 Hz, 1H), 7.47 (d, J = 8.00 Hz, 2H), 7.40 (d, J = 8.40 Hz, 2H), 7.06 (t, J = 53.60 Hz, 1H), 5.12 (s, 1H), 4.23 (dd, J = 4.80, 12.80 Hz, 1H), 3.92 (s, 3H), 3.60-3.47 (m, 2H), 3.19-3.16 (m, 2H), 2.72-2.67 (m, 3H), 2.55-2.51 (m, 2H), 2.23-2.14 (m, 2H), 1.71 (d, J = 12.80 Hz, 1H), 1.02 (s, 3H), 0.69 (s, 3H).
(I-1251)	624.4		1H-NMR (400 MHz, DMSO-d6):δ ppm 10.98 (s, 1H), 8.85 (s, 1H), 8.84 (s, 1H), 8.22-7.98 (m, 2H), 7.84 (d, J = 9.20 Hz, 1H), 7.58-7.56 (m, 4H), 5.13 (s, 1H), 4.25-4.21 (m, 1H), 3.96-3.57 (m, 2H), 3.49-3.32 (m, 2H), 3.16-3.13 (m, 1H), 2.77-2.72 (m, 2H),

			2.67-2.63 (m, 2H), 2.34-0.20 (m, 4H), 1.91 (s, 1H), 1.76-1.70 (m, 1H), 1.02 (s, 3H), 0.69 (s, 3H).
(I-1258)	609.4		1H-NMR (400 MHz, DMSO-d6):δ ppm 10.98 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.49 (s, 1H), 8.33 (s, 1H), 8.17 (s, 1H), 8.12-8.07 (m, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.62 (dd, J = 8.00, Hz, 2H), 7.37 (dd, J = 8.00, Hz, 2H), 5.11 (s, 1H), 4.25-4.21 (m, 1H), 3.62-3.58 (m, 1H), 3.46-3.43 (m, 1H), 3.16 (m, 1H), 2.77-2.70 (m, 2H), 2.68-2.63 (m, 2H), 2.52-2.51 (m, 2H), 2.20-2.15 (m, 2H), 2.05 (s, 6H), 1.73-1.70 (m, 1H), 1.00 (s, 3H), 0.67 (s, 3H).
(I-1265)	600.4		1H-NMR (400 MHz, DMSO-d6):δ ppm 10.99 (s, 1H), 8.85 (d, J = 2.40 Hz, 1H), 8.33 (s, 1H), 8.21 (s, 1H), 8.10 (d, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.51 (d, J = 8.00 Hz, 2H), 7.38 (d, J = 8.00 Hz, 2H), 5.11 (s, 1H), 4.25-4.21 (m, 1H), 3.67-3.65 (m, 1H), 3.60-3.67 (m, 1H), 3.47-3.43 (m, 2H), 3.43-3.33 (m, 1H), 2.68-2.67 (m, 1H), 2.67-2.64 (m, 2H), 2.47-2.45 (m, 2H), 2.34-2.17 (m, 2H), 1.72-1.67 (m, 1H), 1.06-1.05 (m, 2H), 1.04-1.00 (m, 2H), 0.97 (s, 3H), 0.68 (s, 3H).
(I-1272)	566.5		1H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.84 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.36-7.31 (m, 4H), 5.86 (t, J = 56.40 Hz, 1H), 5.11 (s, 1H), 4.23 (dd, J = 4.40, 12.60 Hz, 1H), 3.56-3.45 (m, 3H), 3.13-2.64 (m, 1H), 2.60-2.34 (m, 3H), 2.50-2.34 (m, 2H), 2.14-2.12 (m, 2H), 1.69 (d, J = 12.80 Hz, 1H), 1.12-1.10 (m, 2H), 1.01-0.96 (m, 5H), 0.68 (s, 3H).
(I-1341)	591.2		^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.51-7.46 (m, 4H), 5.13 (s, 1H), 4.23 (dd, J = 4.80, 12.60 Hz, 1H), 3.58-3.52 (m, 6H), 3.15 (m, 2H), 2.77-2.68 (m, 3H), 2.64-2.59 (m, 2H), 2.21-2.13 (m, 2H), 1.85 (s, 3H), 1.76-1.60 (m, 1H), 1.02 (s, 3H), 0.68 (s, 3H).
(I-1293)	561.1		1H-NMR (400 MHz, DMSO-d6): δ ppm 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (d, J =2.00 Hz, 1H), 8.17 (d, J =8.80 Hz, 1H), 8.12-8.08 (m, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.45 (t, J = 8.80 Hz, 1H), 7.29-7.26 (m,

			3H), 5.14 (s, 1H), 4.25 (dd, J = 4.80, Hz, 1H), 3.58-3.42 (m, 2H), 3.19-3.13 (m, 1H), 2.77-2.68 (m, 3H), 2.34-2.17 (m, 2H), 2.13-1.70 (m, 8H), 1.02 (s, 3H), 0.65 (s, 3H).
(I-1300)	585.4		1H-NMR (400 MHz, DMSO-d6): δ ppm 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.33 (s, 1H), 8.24 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.84 (d, J = 9.20 Hz, 1H), 7.53 (d, J = 8.40 Hz, 2H), 7.44 (s, 2H), 5.12 (s, 1H), 4.23 (dd, J = 4.80, 12.80 Hz, 1H), 4.03 (d, J = 11.60 Hz, 2H), 3.69 (t, J = 9.20 Hz, 2H), 3.65-3.56 (m, 2H), 3.16 (t, J = 12.40 Hz, 1H), 2.77-2.67 (m, 2H), 2.64-2.60 (m, 2H), 2.51-2.34 (m, 2H), 2.21-2.10 (m, 6H), 1.71 (d, J = 12.40 Hz, 1H), 1.02 (s, 3H), 0.68 (s, 3H).
(I-1307)	594.5		^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 9.63 (s, 1H), 8.88 (s, 1H), 8.36 (s, 1H), 8.25 (d, J = 8.00 Hz, 2H), 8.17-8.14 (m, 1H), 8.06 (t, J = 8.80 Hz, 1H), 7.89 (d, J = 8.80 Hz, 1H), 7.82 (d, J = 8.00 Hz, 2H), 7.64 (d, J = 8.80 Hz, 1H), 5.92 (s, 1H), 4.50 (s, 2H), 4.24 (dd, J = 4.80, 12.80 Hz, 1H), 3.44-3.39 (m, 2H), 3.34-3.24 (m, 1H), 3.00 (d, J = 11.60 Hz, 1H), 2.77-2.72 (m, 1H), 2.68-2.63 (m, 1H), 2.51-2.48 (m, 2H), 2.34-2.31 (m, 1H), 2.14-2.01 (m, 2H), 1.24 (s, 1H), 1.14-1.12 (m, 4H), 1.12 (s, 3H), 0.79 (s, 3H).
(I-1314)	596.4		^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.34 (s, 1H), 8.27-8.09 (m, 4H), 7.84 (d, J = 9.20 Hz, 1H), 7.71 (d, J = 8.80 Hz, 1H), 7.54 (d, J = 8.00 Hz, 2H), 5.14 (s, 1H), 4.23 (dd, J = 4.40, 12.60 Hz, 1H), 3.69-3.54 (m, 2H), 3.18 (t, J = 10.80 Hz, 1H), 2.77-2.73 (m, 2H), 2.68-2.64 (m, 2H), 2.60-2.51 (m, 3H), 2.23 (d, J = 10.80 Hz, 1H), 2.16-2.13 (m, 1H), 1.73 (d, J = 13.20 Hz, 1H), 1.35 (d, J = 7.20 Hz, 6H), 1.04 (s, 3H), 0.69 (s, 3H).
(I-1324)	600.4		1H-NMR (400 MHz, DMSO-d6): δ ppm 10.98 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.34 (s, 1H), 8.10 (t, J = 8.80 Hz, 1H), 7.88-7.83 (m, 3H), 7.24 (t, J = 9.20 Hz, 2H), 6.58 (d, J = 2.40 Hz, 1H), 5.13 (s, 1H), 4.25-4.21 (m, 1H), 3.79 (t, J = 3.60 Hz, 1H), 3.64-3.60 (m, 1H), 3.50-3.47 (m, 1H), 3.32-3.17 (m, 1H), 2.74-2.71 (m, 2H), 2.68-2.60 (m, 4H), 2.18-2.14 (m, 2H), 1.72 (d, J = 12.40 Hz, 1H), 1.11 (s, 2H), 1.10-1.00 (m, 5H), 0.68 (s, 3H).

(I-1331)	598.4		1H-NMR (400 MHz, DMSO-d6): δ ppm 10.99 (s, 1H), 8.85 (d, J = 2.00 Hz, 1H), 8.34 (s, 1H), 8.18 (s, 1H), 8.12 (d, J = 8.80 Hz, 1H), 8.05 (d, J = 8.40 Hz, 2H), 7.84 (d, J = 9.20 Hz, 1H), 7.52 (d, J = 8.40 Hz, 2H), 7.29 (d, J = 9.20 Hz, 1H), 5.14 (s, 1H), 4.54 (q, J = 6.80 Hz, 2H), 4.26-4.21 (m, 1H), 3.66 (d, J = 9.20 Hz, 1H), 3.55 (d, J = 9.20 Hz, 2H), 3.20-3.18 (m, 1H), 2.77-2.72 (m, 3H), 2.68-2.64 (m, 2H), 2.24-2.22 (m, 1H), 2.16-2.16 (m, 1H), 1.73 (d, J = 4.00 Hz, 1H), 1.42 (t, J = 7.20 Hz, 3H), 1.03 (s, 3H), 0.69 (s, 3H).

Example 92: Synthesis of 4-hydroxy-6-(trifluoromethyl) nicotinaldehyde (ALD-1)



Step 1: **Synthesis of 2-(trifluoromethyl)-5-vinylpyridin-4-ol**

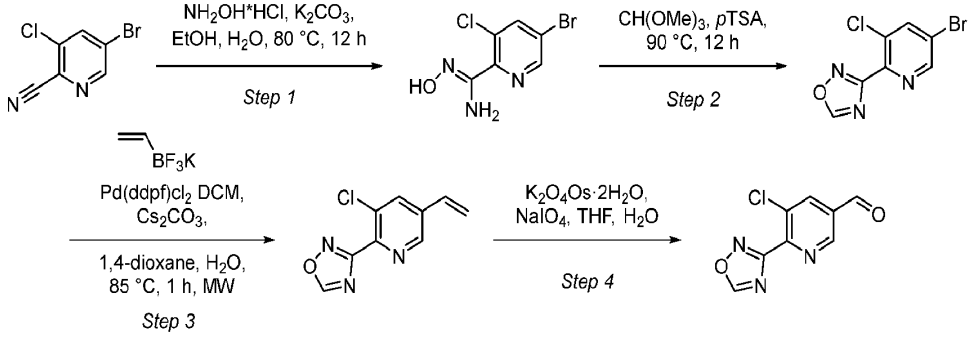
To a stirred solution of 5-bromo-2-(trifluoromethyl) pyridin-4-ol (0.2 g, 0.83 mmol) and trifluoro(vinyl)-l4-borane, potassium salt (0.133 g, 0.99 mmol) in 1,4-dioxane (0.9 mL)/water (0.1 mL) was added cesium carbonate (0.539 g, 1.65 mmol) at room temperature. The reaction mixture was sparged with argon for 10 min., followed by the addition of Pd(dppf)Cl_2·DCM (0.067 g, 0.083 mmol). The mixture was sparged with argon for 10 min and then stirred at 80 °C for 23 h. After completion of reaction, the mixture was cooled and concentrated under reduced pressure. The combined crude compound was purified by flash column chromatography using Biotage Isolera (silica gel cartridge, 250 g) using 30% EtOAc in hexane as the eluent. The collected pure fractions were concentrated under reduced pressure to afford 2-(trifluoromethyl)-5-vinylpyridin-4-ol (150 mg, 0.76 mmol, 92% yield). LCMS: m/z: MM-ES+APCI, $[M+H]^+$ 190.0. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.74 (s, 1H), 8.65 (s, 1H), 7.22 (s, 1H), 6.87 (dd, *J*= 17.8, 11.6 Hz, 1H), 6.10 (d, *J* = 18.8 Hz, 1H), 5.49 (d, *J* = 11.6 Hz, 1H).

Step 2: **Synthesis of 4-hydroxy-6-(trifluoromethyl) nicotinaldehyde (ALD-1)**

To a stirred solution of 2-(trifluoromethyl)-5-vinylpyridin-4-ol (130 mg, 0.68 mmol) in 1,4-dioxane (4 mL) and water (1 mL) were added sodium periodate (294 mg, 1.38 mmol) and 4-methylmorpholine *N*-oxide (40.3 mg, 0.34 mmol) at room temperature. Osmium tetroxide was then added (437 mg, 0.069 mmol) dropwise at 0 °C and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with water (50 mL) and extracted with EtOAc (2 x 150 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude residue.

The crude residue was triturated with MTBE wash and dried under reduced pressure to yield 4-hydroxy-6-(trifluoromethyl) nicotinaldehyde (**ALD-1**, 100 mg, 0.49 mmol, 72% yield). LCMS: m/z: MM-ES+APCI, $[M+H]^+$ 192.1. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.34 (s, 1H), 8.77 (s, 1H), 7.32 (s, 1H), 3.57 (s, H).

Example 93: Synthesis of 5-chloro-6-(1,2,4-oxadiazol-3-yl) nicotinaldehyde (ALD-2)



Step 1: **Synthesis of (*Z*)-5-bromo-3-chloro-*N*'-hydroxypicolinimidamide**

To a stirred solution of 5-bromo-3-chloropicolinonitrile (5 g, 22.99 mmol) in ethanol (40 mL) and water (4 mL) was added hydroxylamine (4.79 g, 69.0 mmol) and potassium carbonate (K_2CO_3, 15.89 g, 115 mmol) at room temperature. The resulting reaction mixture was stirred at 80 °C for 12 h. The reaction mixture was cooled to room temperature, quenched with water (100 mL), and stirred for 15 min. The resulting precipitate was filtered and washed with water (2 x 30 mL). The solid was dried under reduced pressure to afford (*Z*)-5-bromo-3-chloro-*N*'-hydroxypicolinimidamide (3 g, 9.10 mmol, 39% yield). LCMS: m/z: MM-ES+APCI, $[M+H]^+$ 249.8, 251.8. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.90 (s, 1H), 8.71 (s, 1H), 8.40 (s, 1H), 5.87 (s, 2H).

Step 2: **Synthesis of 3-(5-bromo-3-chloropyridin-2-yl)-1,2,4-oxadiazole**

To a stirred solution of 5-bromo-3-chloro-*N*-methylpicolinimidamide (3 g, 12.07 mmol) in triethyl orthoformate (89 g, 604 mmol) was added pyridinium *p*-toluene sulfonate (1.52 g, 6.04 mmol) at room temperature. The resulting reaction mixture was stirred at 120 °C for 12 h. The mixture was cooled to room temperature and quenched with ice-cold water (100 mL), then extracted with EtOAc (2 x 50 mL). The organic layer was dried over the Na_2SO_4 filtered, and concentrated under reduced pressure. The crude compound was purified by flash column chromatography using a Biotage Isolera system with a silica gel (230-400 mesh) cartridge (120 g), eluting with 18-20% EtOAc in hexanes. The pure fractions were collected and concentrated under reduced pressure to afford 3-(5-bromo-3-chloropyridin-2-yl)-1,2,4-oxadiazole (700 mg, 2.39 mmol, 29% yield). LCMS: m/z: MM-ES+APCI, $[M+H]^+$ 260.9, 261.9. ^{1}H-NMR (400 MHz, DMSO-*d6*): δ 9.88 (s, 1H), 8.91 (s, 1H), 8.65 (s, 1H).

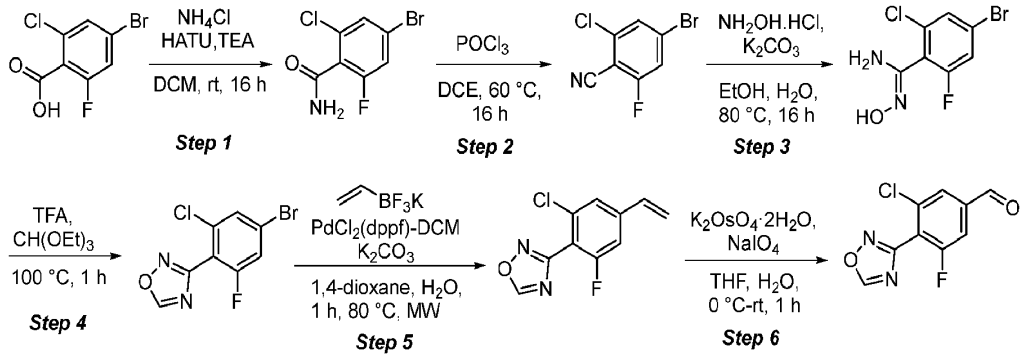
Step 3: **Synthesis of 3-(3-chloro-5-vinylpyridin-2-yl)-1,2,4-oxadiazole**

To a stirred solution of 3-(5-bromo-3-chloropyridin-2-yl)-1,2,4-oxadiazole (350 mg, 1.34 mmol) in 1,4-dioxane (9.5 mL) and water (0.5 mL) was added potassium trifluoroborate (254 mg, 2.016 mmol) and potassium carbonate (371 mg, 2.69 mmol) at room temperature. The reaction mixture was sparged with nitrogen for 10 min, and $PdCl_2$(dppf) (98 mg, 0.13 mmol) was added. The resulting reaction mixture was irradiated in the microwave at 85 °C for 1 h. The mixture was then concentrated under reduced pressure to obtain the crude product. The crude compound was extracted with EtOAc (2 x 100 mL) and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the crude product. The crude compound was purified by silica gel flash column chromatography eluting with 5% EtOAc in hexanes. The collected pure fractions were concentrated under reduced pressure to afford 3-(3-chloro-5-vinylpyridin-2-yl)-1,2,4-oxadiazole (135 mg, 0.57 mmol, 42% yield). LCMS: MM-ES+APCI, $[M+H, M+2H]^+$ 208, 210. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.85 (s, 1H), 8.85 (d, *J*=1.60 Hz, 1H), 8.38 (d, *J*=2.0 Hz, 1H), 6.87 (dd, *J* =17.8, 10.80 Hz, 1H), 6.28 (d, *J* = 17.60 Hz, 1H), 5.63 (d, *J* = 10.80 Hz, 1H).

Step 4: **Synthesis of 5-chloro-6-(1,2,4-oxadiazol-3-yl) nicotinaldehyde (ALD-2)**

To a stirred solution of 3-(3-chloro-5-vinylpyridin-2-yl)-1,2,4-oxadiazole (120 mg, 0.578 mmol) in tetrahydrofuran (THF, 5 mL) and water (1.667 mL) were added potassium osmate dihydrate (5.32 mg, 0.014 mmol) and sodium periodate (185 mg, 0.867 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 1 h. The progress of the reaction was monitor by LCMS. After completion of reaction, the reaction mixture was concentrated under reduced pressure to obtain the crude product. The water (50 mL) was added and extracted with EtOAc (2 x 50 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford 5-chloro-6-(1,2,4-oxadiazol-3-yl) nicotinaldehyde (**ALD-102**, 60 mg, 0.23 mmol, 40% yield). The product was analyzed by ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.19 (s, 1H), 9.93 (s, 1H), 9.19 (d, *J*=1.60 Hz, 1H), 8.63 (d, *J*=1.60 Hz, 1H).

Example 94: Synthesis of 3-chloro-5-fluoro-4-(1,2,4-oxadiazol-3-yl) benzaldehyde (ALD-3)



Step 1: **Synthesis of 4-bromo-2-chloro-6-fluorobenzamide**

To a stirred solution of 4-bromo-2-chloro-6-fluorobenzoic acid (5.0 g, 19.73 mmol) in DMF (40 mL) was added TEA (9.98 g, 99 mmol), HATU (9.00 g, 23.67 mmol), and ammonium chloride (3.17 g, 59.2 mmol) at room temperature and the reaction mixture was stirred for 16 h. After completion of reaction, the reaction mixture was quenched with water and extracted with DCM (2 x 100 mL). The organic layer was washed with sodium bicarbonate solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain the crude compound. The crude product was purified to afford 4-bromo-2-chloro-6-fluorobenzamide (2.5 g, 7.40 mmol, 38% yield). LCMS: m/z: MM-ES+APCI, $[M+H]^+$ 253.99. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.14 (s, 1H), 7.91 (s, 1H), 7.70 (s, 2H).

Step 2: **Synthesis of 4-bromo-2-chloro-6-fluorobenzonitrile**

To a stirred solution of 4-bromo-2-chloro-6-fluorobenzamide (2.5 g, 9.90 mmol) in DCE (5 mL) was added $POCl_3$ (7.59 g, 49.5 mmol) at room temperature and the resulting reaction mixture stirred at 60 °C for 5 h. The reaction mixture was cooled to room temperature and EtOAc (100 mL) was added. The EtOAc layer was washed with ice cold water. The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure to obtained crude compound. The crude was purified by normal phase column chromatography using (100-200 silica mesh) eluting with 15% of EtOAc in hexanes. The pure fractions were concentrated under reduced pressure to afford 4-bromo-2-chloro-6-fluorobenzonitrile (1.3 g, 5.54 mmol, 56% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.72 (s, 1H), 7.56 (s, 1H).

Step 3: **Synthesis of (*Z*)-4-bromo-2-chloro-6-fluoro-N'-hydroxybenzimidamide**

To a stirred solution of hydroxylamine (206 mg, 2.99 mmol) in ethanol (4 mL) was added sodium bicarbonate (627 mg, 7.46 mmol) at room temperature and stirred for 15 min. The 4-bromo-2-chloro-6-fluorobenzonitrile (700 mg, 2.99 mmol) in ethanol (4 mL) was added, and reaction mixture and stirred at 100 °C for 16 h. After completion of reaction, cooled the reaction mixture and filtered and washed with EtOAc (50 mL), filtrate was concentrated under reduced pressure to obtained as crude compound. The crude compound was purified by isolera biotage column chromatography using 100-200 silica gel mesh, eluted with 20% EtOAc in petroleum ether. The collected pure fractions were concentrated under reduced pressure to afford (*Z*)-4-bromo-2-chloro-6-fluoro-*N*'-hydroxybenzimidamide (270 mg, 1.009 mmol, 34% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.57 (s, 1H), 7.72 (s, 1H), 7.70 (s, 1H), 5.98 (s, 2H).

Step 4: **Synthesis of 3-(4-bromo-2-chloro-6-fluorophenyl)-1,2,4-oxadiazole**

To a stirred solution of 4-bromo-2-chloro-6-fluoro-*N*-hydroxybenzimidamide (270 mg, 1.01 mmol) in triethyl orthoformate (449 mg, 3.03 mmol) was added TFA (115 mg, 1.01 mmol) at room temperature. The reaction mixture allowed to stir at 100 °C for 1 h. The reaction concentrated under reduced pressure and the crude compound was purified by silica gel flash column chromatography eluting with 50% EtOAc in hexanes. The collected pure fractions were concentrated under reduced pressure to

afford 3-(4-bromo-2-chloro-6-fluorophenyl)-1,2,4-oxadiazole (120 mg, 0.43 mmol, 43% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.95 (s, 1H), 7.96-7.94 (m, 2H).

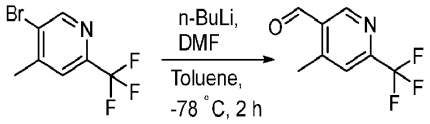
Step 5: **Synthesis of 3-(2-chloro-6-fluoro-4-vinylphenyl)-1,2,4-oxadiazole**

To a stirred solution of 3-(4-bromo-2-chloro-6-fluorophenyl)-1,2,4-oxadiazole (150 mg, 0.54 mmol) and trifluoro(vinyl)-l4-borane potassium salt (109 mg, 0.81 mmol) in 1,4-dioxane (4 mL) and water (0.1 mL) was added potassium carbonate 149 mg, 1.08 mmol) at room temperature. The resulting reaction mixture was sparged with argon for 10 min and then $PdCl_2$(dppf)-CH_2Cl_2 adduct (44.1 mg, 0.054 mmol) was added. The mixture was sparged with argon again for 5 min and heated to 80 °C for 1 h. The reaction mixture was filtered through a pad of celite, and the pad was washed with EtOAc (100 mL). The filtrate was concentrated under reduced pressure and the crude compound was purified by silica gel flash column chromatography eluting with 20% EtOAc in hexanes. The collected pure fractions were concentrated under reduced pressure to afford 3-(2-chloro-6-fluoro-4-vinylphenyl)-1,2,4-oxadiazole (100 mg, 0.45 mmol, 82% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.92 (s, 1H), 7.74 (s, 1H), 7.68 (dd, *J*=10.6, 1.2 Hz, 1H), 6.82 (dd, *J*=17.6, 11.2 Hz, 1H), 6.19 (d, *J* = 17.60 Hz, 1H), 5.57 (d, *J* = 10.80 Hz, 1H).

Step 6: **Synthesis of 3-chloro-5-fluoro-4-(1,2,4-oxadiazol-3-yl) benzaldehyde (ALD-3)**

To a stirred solution of 3-(2-chloro-6-fluoro-4-vinylphenyl)-1,2,4-oxadiazole (100 mg, 0.45 mmol) in THF (1 mL) and water (0.2 mL) were added sodium periodate (143 mg, 0.67 mmol) and potassium osmate dihydrate (4.10 mg, 0.011 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, followed by addition of water (50 mL) and extraction with EtOAc (2 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4 filtered concentrated under reduced pressure, and purified by silica gel flash column chromatography eluting with 100% EtOAc. The collected pure fractions were concentrated under reduced pressure to afford 3-chloro-5-fluoro-4-(1,2,4-oxadiazol-3-yl) benzaldehyde (**ALD-3**, 30 mg, 0.132 mmol, 30% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.06 (s, 1H), 10.06 (s, 1H), 8.13 (s, 1H), 7.98 (s, 1H).

Example 95: Synthesis of 4-methyl-6-(trifluoromethyl) nicotinaldehyde (ALD-4)

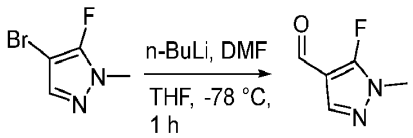


Step 1

To a stirred solution of 5-bromo-4-methyl-2-(trifluoromethyl) pyridine (200 mg, 0.83 mmol) in toluene (2 mL) was added *n*-butyllithium in hexane (0.500 mL, 1.25 mmol) at -78 °C. The resulting reaction mixture was stirred at -78 °C for 30 min, and DMF (73.1 mg, 1.00 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. After completion of the

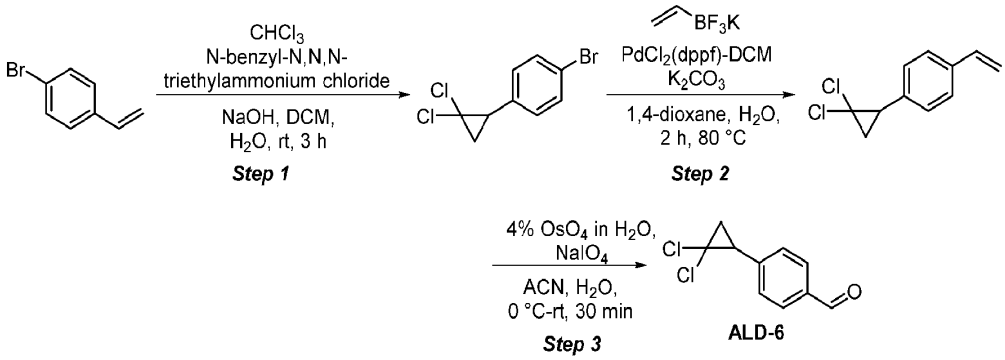
reaction, the reaction mixture was quenched with saturated ammonium chloride solution and extracted with EtOAc (2 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product. The crude compound was purified by flash column chromatography using a Biotage Isolera system with a silica gel (100-200 mesh) cartridge (1 g), eluting with 10% EtOAc in hexanes. The pure fractions were collected and concentrated under reduced pressure to afford 4-methyl-6-(trifluoromethyl) nicotinaldehyde (**ALD-4**, 80 mg, 0.28 mmol, 34% yield). LCMS m/z: MM-ES+APCI, positive $[M+H]^+$ 189.9. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.40 (s, 1H), 9.06 (s, 1H), 7.64 (s, 1H), 2.80 (s, 3H).

Example 96: Synthesis of 5-fluoro-1-methyl-1*H*-pyrazole-4-carbaldehyde (ALD-5)



To a stirred solution of 4-bromo-5-fluoro-1-methyl-1*H*-pyrazole (300 mg, 1.68 mmol) in THF (3 mL) was added *n*-butyllithium (1.00 mL, 2.51 mmol) at -78 °C and the reaction mixture was stirred for 30 min. DMF (368 mg, 5.03 mmol) was then added at -78 °C. The resulting reaction mixture was stirred at -78 °C for 1 h. After completion of the reaction, as confirmed by TLC and LCMS, the reaction mixture was quenched with water (10 mL) and extracted with 10% IPA in DCM (40 mL). The combined organic layers were concentrated under reduced pressure to afford 5-fluoro-1-methyl-1H-pyrazole-4-carbaldehyde (**ALD-5**, 300 mg, 2.34 mmol, quantitative yield). The crude aldehyde was used without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.771 (s, 1H), 7.799 (s, 1H), 3.724 (s, 3H).

Example 97: Synthesis of 4-(2,2-dichlorocyclopropyl) benzaldehyde (ALD-6)



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 x 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 (4 g, 12.58 mmol, 46% yield). ^{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).

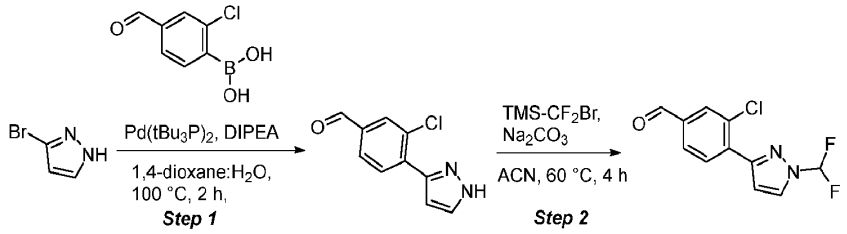
Step 2: **Synthesis of 1-(2,2-dichlorocyclopropyl)-4-vinylbenzene**

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 EtOAc (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 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 (1.3 g, 4.99 mmol, 66% yield). ^{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-6)**

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 (3 x 50 mL). The combined organic layer was dried, over Na_2SO_4 and concentrated under reduced pressure to obtain the crude compound. The crude compound was purified by flash column chromatography, eluting with EtOAc in hexane (10 to 12%) to obtain 4-(2,2-dichlorocyclopropyl)benzaldehyde (**ALD-6**, 0.09 g, 0.36 mmol, 18% yield). 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 98: Synthesis of 3-chloro-4-(1-(difluoro methyl)-1H-pyrazol-3-yl)benzaldehyde (ALD-7)



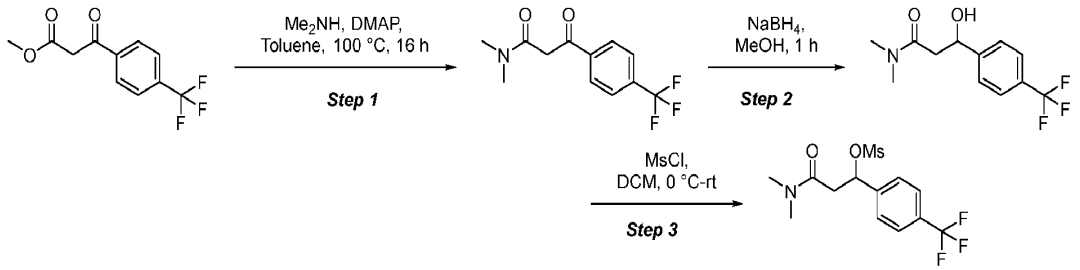
Step 1: **Synthesis of 3-chloro-4-(1*H*-pyrazol-3-yl) benzaldehyde**

To a stirred solution of(2-chloro-4-formylphenyl) boronic acid (1.0 g, 5.32 mmol) and 3-bromo-1*H*-pyrazole (1.21 g, 7.97 mmol) in water (0.7 mL) and 1,4-dioxane (2 mL) under nitrogen atmosphere was added DIPEA (2.08 g, 15.95 mmol) at room temperature. The reaction mixture was sparged with nitrogen for 10 min, and bis (tri-tertbutyl phosphine) palladium (0) (0.27 g, 0.53 mmol) was added. The resulting reaction mixture was stirred at 100°C for 2 h. Water (50 mL) was added to quench and the aqueous solution was extracted with EtOAc (2 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by Biotage using silica gel chromatography (100-200), eluting with 30% EtOAc in hexane. Fractions were concentrated to afford 3-chloro-4-(1*H*-pyrazol-3-yl) benzaldehyde (650 mg, 3.11 mmol, 59% yield). LCMS: m/z: MM-ES+APCI, [M+H, M+2H]$^+$ 207.2, 209.2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.02 (s, 1H), 8.01 (d, J = 6.40 Hz, 2H), 7.92 (d, J = 57.20 Hz, 1H), 7.83 (s, 1H), 7.28 (s, 1H), 6.97 (s, 1H).

Step 2: **Synthesis of 3-chloro-4-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)benzaldehyde (ALD-7)**

To a stirred solution of 3-chloro-4-(1*H*-pyrazol-3-yl) benzaldehyde (300 mg, 1.45 mmol) in acetonitrile (5 mL) was added sodium carbonate (462 mg, 4.36 mmol), followed by bromotrifluoroethylene trimethyl silane (590 mg, 2.90 mmol) and the reaction mixture was stirred at 60 °C for 3 h. Water (50 mL) was added and the mixture was extracted with EtOAc (2 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography, eluting with 10% EtOAc in hexane to afford 3-chloro-4-(1-(difluoro methyl)-1*H*-pyrazol-3-yl) benzaldehyde (**ALD-7**, 170 mg, 0.63 mmol, 43% yield). LCMS: m/z: MM-ES+APCI, [M+H, M+2H]$^+$ 257.0, 259.0. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.07 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 1.60 Hz, 1H), 7.94 (d, J = 6.80 Hz, 1H), 7.86 (dd, J = 8.0, 1.60 Hz, 1H), 7.30 (t, J = 53.6 Hz, 1H), 7.11 (d, J = 1.60 Hz, 1H).

Example 99: Synthesis of 3-(dimethylamino)-3-oxo-1-(4-(trifluoromethyl)phenyl)propyl methanesulfonate (ALD-8)



Step 1: **Synthesis of *N,N*-dimethyl-3-oxo-3-(4-(trifluoromethyl)phenyl)propenamide**

To a stirred solution of methyl 3-oxo-3-(4-(trifluoromethyl)phenyl)propanoate (2.0 g, 8.12 mmol) in toluene (20 mL) was added DMAP (0.099 g, 0.812 mmol) at room temperature. The reaction mixture was stirred at 100 °C for 16 h. The reaction was then cooled, quenched with cold ice water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to obtained solid crude. The crude compound was purified by flash column chromatography (silica-gel, 230-400 mesh size) using 10% EtOAc in hexane as eluent. The pure fractions were evaporated and dried under high vacuum to afford as *N,N*-dimethyl-3-oxo-3-(4-(trifluoromethyl)phenyl)propanamide (500 mg, 1.72 mmol, 21% yield). LCMS: m/z: MM-ES+APCI, $[M+H]^+$ 260.3.

Step 2: **Synthesis of *N,N*-dimethyl-3-oxo-3-(4-(trifluoromethyl)phenyl)propenamide**

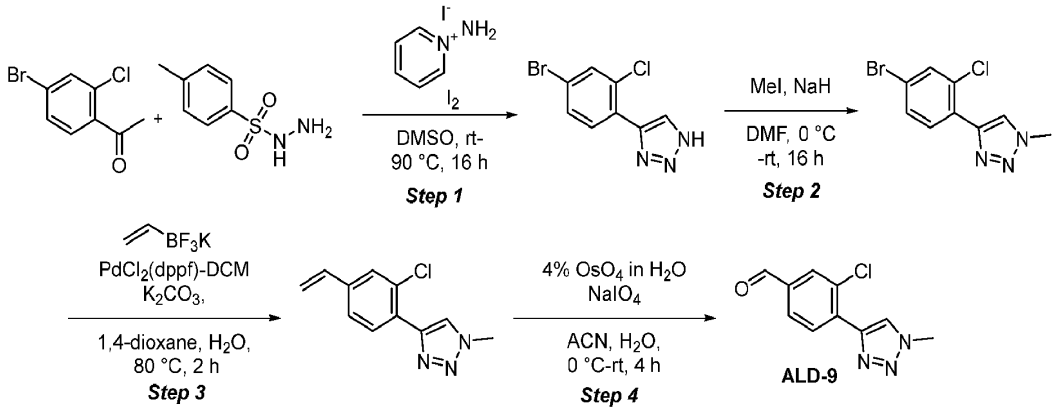
To a stirred solution of methyl 3-oxo-3-(4-(trifluoromethyl) phenyl) propanoate (2.0 g, 8.12 mmol) in toluene (20 mL) was added DMAP (0.099 g, 0.81 mmol) at room temperature. The reaction mixture was stirred at 100 °C for 1 h. The reaction mixture was quenched with ice cold water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4 filtered and concentrated. The crude residue was purified by flash column chromatography (silica-gel, 230-400 mesh size) using 10% EtOAc in hexane as eluent. The pure fractions were evaporated and dried under high vacuum to afford as *N, N*-dimethyl-3-oxo-3-(4-(trifluoromethyl)phenyl)-propenamide (500 mg, 1.72 mmol, 21% yield). LCMS: m/z: MM-ES+APCI, $[M+H]^+$ 262.3. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.11-8.07 (m, 2H), 7.86-7.80 (m, 2H), 5.86 (s, 1H), 3.12 (s, 6H), 3.11-3.02 (m, 2H).

Step 3: **Synthesis of 3-(dimethylamino)-3-oxo-1-(4-(trifluoromethyl)phenyl)propyl methanesulfonate (ALD-8)**

To a stirred solution of 3-hydroxy-*N,N*-dimethyl-3-(4-(trifluoromethyl)phenyl)-propanamide (140 mg, 0.54 mmol) in DCM (3 mL), were added TEA (163 mg, 1.61 mmol) and methanesulfonyl chloride (0.062 mL, 0.804 mmol) at 0 °C. The reaction was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution (10 mL) and the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4

and filtered. The solvent was removed under reduced pressure and the crude compound was purified by silica gel flash column chromatography, eluting with 10% MeOH in DCM to afford 3-(dimethylamine)-3-oxo-1-(4-(trifluoromethyl) phenyl) propyl methane sulfonate (**ALD-8**, 130 mg, 0.146 mmol, 27% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.68 (d, J = 8.40 Hz, 2H), 7.62 (d, J = 8.40 Hz, 2H), 6.15 (d, J = 8.60, 4.00 Hz, 1H), 3.39 (s, 1H), 3.17-3.12 (m, 4H), 3.07 (s, 3H), 2.99 (s, 3H).

Example 100: Synthesis of 3-chloro-4-(1-methyl-1H-1,2,3-triazol-4-yl)benzaldehyde (ALD-9)



Step 1: **Synthesis of 4-(4-bromo-2-chlorophenyl)-1*H*-1,2,3-triazole**

To a stirred solution of 1-(4-bromo-2-chlorophenyl) ethan-1-one (2.0 g, 8.57 mmol) in DMSO (10 mL) were added 4-methylbenzenesulfonohydrazide (1.595 g, 8.57 mmol), 1-aminopyridinium iodide (1.902 g, 8.57 mmol), and iodine (3.48 g, 13.71 mmol) at room temperature. The reaction was stirred at 90 °C for 16 h. The reaction mixture was quenched with saturated aqueous sodium thiosulfate solution (10 mL) and diluted with brine (25 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic extract was dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the crude compound was purified by silica gel flash column chromatography, eluting with 10% EtOAc in hexane to afford 4-(4-bromo-2-chlorophenyl)-1*H*-1,2,3-triazole (500mg, 1.65 mmol, 19% yield). LCMS: m/z: MM-ES+APCI, $[M+H, M+2H]^+$ 258, 260. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1H), 7.88 (d, J = 7.20 Hz, 1H), 7.67 (d, J = 8.40 Hz, 1H), 7.28 (s, 1H).

Step 2: **Synthesis of 4-(4-bromo-2-chlorophenyl)-1-methyl-1*H*-1,2,3-triazole**

To a stirred solution of 4-(4-bromo-2-chlorophenyl)-1*H*-1,2,3-triazole (0.5 g, 1.934 mmol) in DMF (5 mL) was added NaH (0.155 g, 3.87 mmol) at 0 °C and stirred for 10 min. MeI (0.181 mL, 2.90 mmol) was then added and the reaction mixture stirred at room temperature for 16 h. The reaction mixture quenched with water (100 mL), extracted with EtOAc (2x50 mL), and the organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude compound was purified by silica gel flash column chromatography, eluting with 10% EtOAc in hexane to afford 4-(4-bromo-2-chlorophenyl)-1-methyl-1*H*-1,2,3-triazole (0.2 g, 0.72 mmol, 37% yield). LCMS: m/z: MM-ES+APCI, $[M+H, M+2H]^+$

272, 274. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.67 (s, 1H), 8.03 (d, *J* =8.40 Hz, 1H), 7.86 (d, *J* =2.0 Hz, 1H), 7.68 (dd, *J* =8.40, 2.00 Hz, 1H), 4.14 (s, 3H).

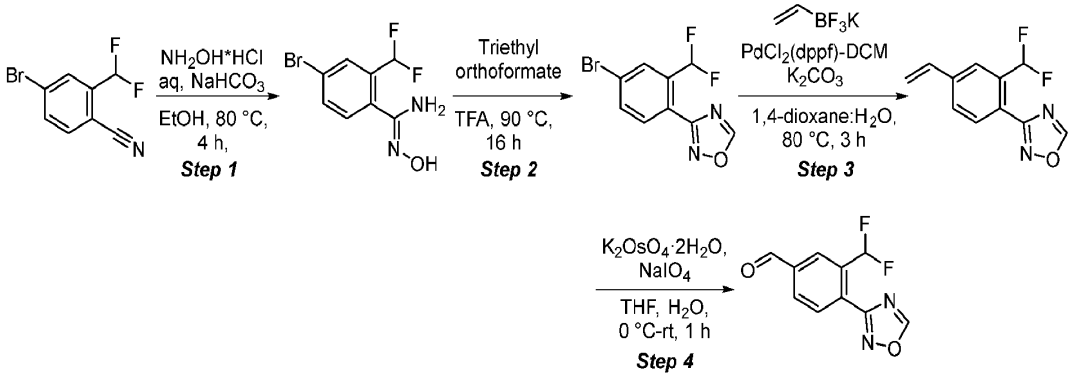
Step 3: **Synthesis of 4-(2-chloro-4-vinylphenyl)-1-methyl-1*H*-1,2,3-triazole**

To a stirred solution of 4-(4-bromo-2-chlorophenyl)-1-methyl-1*H*-1,2,3-triazole (150 mg, 0.55 mmol) in 1,4-dioxane (3 mL) and water (1.500 mL) under nitrogen atmosphere was added potassium trifluoro(vinyl)borate (111 mg, 0.83 mmol) and K_2CO_3 (114 mg, 0.83 mmol) at room temperature. The reaction mixture was sparged with nitrogen for 10 min, then $PdCl_2$(dppf)-DCM (45 mg, 0.055 mmol) was added, and the resulting reaction mixture was was heated at 80 °C for 2 h. The reaction was diluted with water, filtered through a pad of celite, and washed with EtOAc. The filtrate obtained was extracted with EtOAc (2x70 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography using Biotage Isolera (silica gel cartridge 40 g) using 15% EtOAc in hexanes as eluent. Collected pure fractions were concentrated to afford 4-(2-chloro-4-vinylphenyl)-1-methyl-1*H*-1,2,3-triazole (100 mg, 0.41 mmol, 74% yield). LCMS: m/z: MM-ES+APCI, [M+H, M+2H]$^+$ 220, 222. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.25 (d, *J* = 8.40 Hz, 1H), 8.20 (s, 1H), 7.75 (d, *J*=1.60 Hz, 1H)7.74 (dd, *J* = 8.20, 2.0 Hz, 1H), 6.71 (dd, *J* = 17.4, 11.2 Hz, 1H), 5.84 (dd, *J* = 17.40, 0.80 Hz, 1H), 5.36 (d, *J* =11.20, 0.40 Hz, 1H), 4.20 (s, 3H).

Step 4: **Synthesis of 3-chloro-4-(1-methyl-1*H*-1,2,3-triazol-4-yl) benzaldehyde (ALD-9)**

To a stirred solution of 4-(2-chloro-4-vinylphenyl)-1-methyl-1*H*-1,2,3-triazole (100 mg, 0.46 mmol) in acetonitrile (2 mL) and water (0.5 mL) was added sodium periodate (97 mg, 0.46 mmol) followed by osmium tetroxide (0.014 mL, 0.046 mmol) at 0 °C. The reaction was stirred at room temperature for 4 h. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (2 X 50 mL). The organic layer was dried over Na_2SO_4 filtered, and concentrated under reduced pressure. The crude compound was purified by silica gel flash column chromatography, eluting with 25% EtOAc in hexanes to afford 3-chloro-4-(1-methyl-1*H*-1,2,3-triazol-4-yl) benzaldehyde (**ALD-9**, 50 mg, 0.22 mmol, 47% yield). LCMS: m/z: MM-ES+APCI, [M+H]$^+$ 222.2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.03 (s, 1H), 8.53 (d, *J* = 8.00 Hz, 1H), 8.35 (s, 1H), 8.00 (d, *J* =1.60 Hz, 1H), 7.90 (dd, *J* = 8.0, 1.60 Hz, 1H).

Example 101: Synthesis of 3-(difluoromethyl)-4-(1,2,4-oxadiazol-3-yl) benzaldehyde (ALD-10)



Step 1: **Synthesis of (*Z*)-4-bromo-2-(difluoromethyl)-*N*'-hydroxybenzimidamide**

A solution of hydroxylamine (4.49 g, 64.6 mmol) and potassium carbonate (8.93 g, 64.6 mmol) in water (20 mL) and ethanol (100 mL) was stirred at room temperature for 30 min. 4-bromo-2-(difluoro methyl) benzonitrile (5 g, 21.55 mmol) was added, and the reaction mixture was heated at 80 °C for 12 h. The reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography (silica gel 100-200 mesh, Biotage Isolera, flow rate of 35 mL/min, 0-100% EtOAc in petroleum ether) to yield (*Z*)-4-bromo-2-(difluoro methyl)-*N*'-hydroxybenzimidamide (5.0 g, 18.30 mmol, 85% yield). LCMS: m/z: MM-ES+APCI, $[M+H, M+2H]^+$ 265.1, 267.1. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.87 (s, 1H), 7.82 (s, 1H), 7.81 (d, J = 3.60 Hz, 1H), 7.54 (d, J = 3.60 Hz, 1H), 7.26 (t, J = 54.80 Hz, 1H), 6.04 (s, 2H).

Step 2: **Synthesis of 3-(4-bromo-2-(difluoromethyl) phenyl)-1,2,4-oxadiazole**

To a stirred solution of (*Z*)-4-bromo-2-(difluoromethyl)-*N*'-hydroxybenzimidamide (5 g, 18.86 mmol) in triethyl orthoformate (50 mL) was added *p*-TsOH (500 mg, 2.63 mmol) and the reaction mixture stirred at 90 °C for 16 h. The reaction mixture was quenched with water (150 mL) and extracted with EtOAc (2 x 150 mL). The organic layer was washed with water (150 mL), brine solution (150 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel 100-200 mesh, Isolera, flow rate of 35 mL/min, 0-100% EtOAc in petroleum ether) to afford 3-(4-bromo-2-(difluoromethyl) phenyl)-1,2,4-oxadiazole (4.0 g, 14.25 mmol, 76% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.85 (s, 1H), 8.06-8.04 (m, 2H), 7.79-7.77 (m, 1H), 7.52 (t, J = 54.40 Hz, 1H).

Step 3: **Synthesis of 3-(2-(difluoromethyl)-4-vinylphenyl)-1,2,4-oxadiazole**

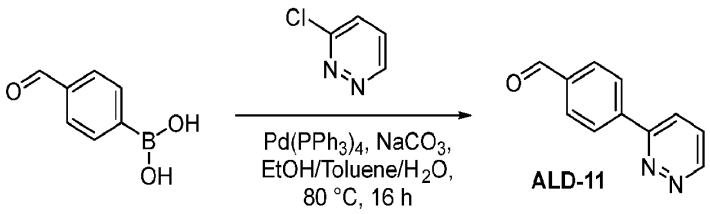
A stirred solution of 3-(4-bromo-2-(difluoro methyl)phenyl)-1,2,4-oxadiazole (500 mg, 1.818 mmol), trifluoro(vinyl)-l4-borane, potassium salt (243 mg, 1.82 mmol) and potassium carbonate (K_2CO_3, 251 mg, 1.82 mmol) in 1,4-dioxane (15 mL) and water (2 mL) was sparged with nitrogen for 15 min. $PdCl_2$(dppf).CH_2Cl_2 adduct (742 mg, 0.91 mmol) was then added at room temperature. The resulting reaction mixture was stirred at 80 °C for 2 h. The reaction was quenched with water (50 mL) and

extracted with EtOAc (2 x 100 mL). The organic layer was washed with water (50 mL) and brine solution (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel 100-200 mesh, Isolera, flow rate of 35 mL/min, 0-100% EtOAc in petroleum ether) to afford 3-(2-(difluoro methyl)-4-vinylphenyl)-1,2,4-oxadiazole (200 mg, 0.78 mmol, 43% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.83 (s, 1H), 8.14 (d, J = 8.00 Hz, 1H), 7.93 (s, 1H), 7.78-7.62 (m, 2H), 6.82 (dd, J = 17.6,10.80 Hz, 1H), 5.97 (d, J = 17.60 Hz, 1H), 5.53 (d, J = 10.80 Hz, 1H).

Step 4: **Synthesis of 3-(difluoromethyl)-4-(1,2,4-oxadiazol-3-yl) benzaldehyde (ALD-10)**

To a stirred solution of 3-(2-(difluoromethyl)-4-vinylphenyl)-1,2,4-oxadiazole (400 mg, 1.80 mmol) in THF (10 mL) and water (2 mL) at 0 °C was added sodium periodate (385 mg, 1.80 mmol), followed by osmium tetroxide (458 mg, 1.80 mmol). The resulting reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, mesh size 100-200) using EtOAc in hexane (0 to 10%) as eluent to afford 3-(difluoromethyl)-4-(1,2,4-oxadiazol-3-yl) benzaldehyde (**ALD-10**, 220 mg, 0.69 mmol, 38% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.18 (s, 1H), 8.91 (s, 1H), 8.42 (s, 1H), 8.38 (d, J = 8.0 Hz, 1H), 8.33 (d, J = 33.20 Hz, 1H), 8.17 (dd, J =8.0, 0.8 Hz, 1H), 7.68 (t, J = 54.80 Hz, 1H).

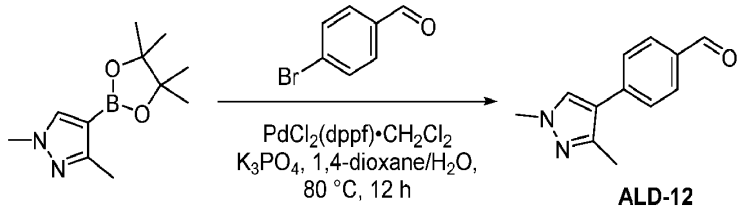
Example 102: Synthesis of 4-(pyridazin-3-yl) benzaldehyde (ALD-11)



To a stirred solution of 3-chloropyridazine (0.5 g, 4.37 mmol) and (4-formylphenyl)-boronic acid (1.178 g, 7.86 mmol) in ethanol (3 mL) and toluene (10 mL), 1M aqueous Na_2CO_3 (13.1 mL, 13.1 mmol) was added at room temperature. The mixture stirred for 10 minutes under nitrogen. Then, $Pd(PPh_3)_4$ (0.303 g, 0.262 mmol) was added at room temperature. The resulting reaction mixture was stirred at 80 °C for 16 h. The reaction was quenched with water (50 mL) and extracted with EtOAc (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by reverse phase chromatography, eluted with 50% acetonitrile in water, and the pure fraction was concentrated under reduced pressure to afford 4-(pyridazin-3-yl) benzaldehyde (**ALD-11**, 120 mg, 0.65 mmol, 15% yield). LCMS: m/z MM-ES+ APCI, Positive $[M+H]^+$ 185.1, ^{1}H-NMR (400 MHz,

$CDCl_3$): δ 10.15 (s, 1H), 9.26 (q, J = 1.60 Hz, 1H), 8.30 (d, J = 8.40 Hz, 2H), 8.08 (dd, J = 1.60, 6.80 Hz, 2H), 7.97 (dd, J = 1.60, 8.80 Hz, 1H), 7.66-7.62 (m, 1H).

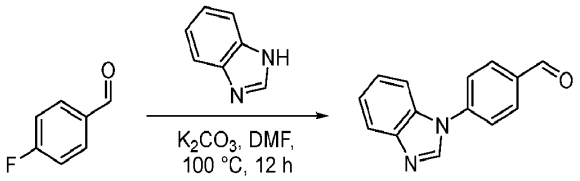
Example 103: Synthesis of 4-(1,3-dimethyl-1*H*-pyrazol-4-yl) benzaldehyde (ALD-12)



ALD-12

To a stirred solution of 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (360 mg, 1.62 mmol) and 4-bromobenzaldehyde (250 mg, 1.351 mmol) in water (0.55 mL) and 1,4-dioxane (5 mL) under nitrogen purging, tripotassium phosphate (574 mg, 2.70 mmol) was added. The suspension was degassed with nitrogen for 5 minutes, then $PdCl_2$(dppf)-CH_2Cl_2 adduct (55.2 mg, 0.068 mmol) was added. The resulting reaction mixture was stirred at 80 °C for 12 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel 100-200 mesh, Isolera, flow rate of 35 mL/min, 40% EtOAc in petroleum ether to afford 4-(1,3-dimethyl-1H-pyrazol-4-yl) benzaldehyde (**ALD-12**, 240 mg, 1.18 mmol, 87% yield). LCMS: m/z MM-ES+ APCI, Positive $[M+H]^+$ 201.1, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.97 (s, 1H), 8.09 (s, 1H), 7.91 (d, J = 8.40 Hz, 2H), 7.66 (d, J = 8.00 Hz, 2H), 3.81 (s, 3H), 2.36 (s, 3H).

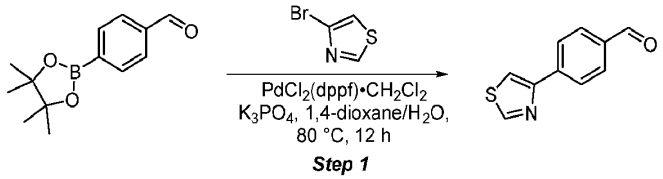
Example 104: Synthesis of 4-(1*H*-benzo[*d*]imidazol-1-yl)benzaldehyde (ALD-13)



Step 1

To a stirred solution of 4-fluorobenzaldehyde (0.1 g, 0.81 mmol) in DMF (1 mL) were added K_2CO_3 (0.223 g, 1.61 mmol) and 1H-benzo[d]imidazole (0.095 g, 0.81 mmol at room temperature. The reaction mixture was then stirred at 100 °C for 12 h. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure. The crude product was purified by combi-flash chromatography (eluent: 30-50% EtOAc in n-hexane). The pure fractions were concentrated under reduced pressure to yield 4-(1H-benzo[d]imidazol-1-yl)benzaldehyde (**ALD-13**, 0.11 g, 0.46 mmol, 58% yield). LCMS: m/z MM-ES+ APCI, Positive $[M+H]^+$ 223.2, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.11 (s, 1H), 8.72 (s, 1H), 8.17 (d, J = 6.80 Hz, 2H), 8.08 (d, J = 66.40 Hz, 2H), 7.83-7.76 (m, 2H), 7.42-7.34 (m, 2H).

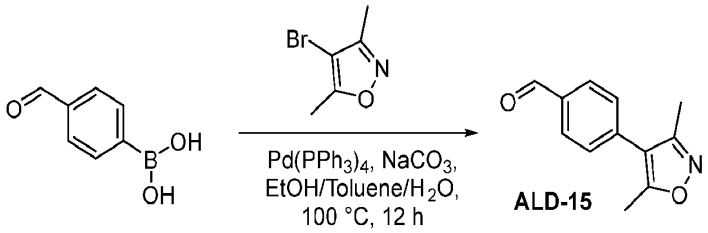
Example 105: Synthesis of 4-(thiazol-4-yl)benzaldehyde (ALD-14)



Step 1

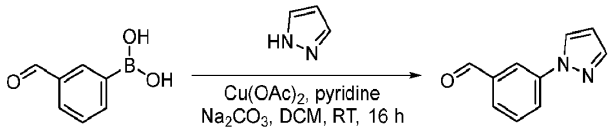
To a stirred solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (311 mg, 1.34 mmol) and 4-bromothiazole (0.110 mL, 1.22 mmol) in 1,4-dioxane (5 mL) and water (1 mL) under nitrogen purging, tripotassium phosphate (518 mg, 2.44 mmol) was added. The suspension was degassed with nitrogen for 5 minutes, then $PdCl_2(dppf)$-CH_2Cl_2 adduct (100 mg, 0.122 mmol) was added. The resulting reaction mixture was stirred at 80 °C for 12 h. The reaction mixture was concentrated under reduced pressure and tge crude residue was purified by Isolera (silica gel, 230-400 mesh) and eluted with 8% EtOAc in hexane to yield 4-(thiazol-4-yl) benzaldehyde (**ALD-14**, 200 mg, 0.83 mmol, 68% yield). LCMS: m/z MM-ES+ APCI, Positive $[M+H]^+$ 190.0, ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.07 (s, 1H), 8.95 (d, J = 1.60 Hz, 1H), 8.14 (t, J = 1.60 Hz, 2H), 7.99 (t, J = 4.80 Hz, 2H), 7.75 (d, J = 2.00 Hz, 1H).

Example 106: Synthesis of 4-(3,5-dimethylisoxazol-4-yl)benzaldehyde (ALD-15)



To a stirred solution of 4-bromo-3,5-dimethylisoxazole (0.5 g, 2.84 mmol) and (4-formylphenyl)boronic acid (0.767 g, 5.11 mmol) in ethanol (3 mL) and toluene (10 mL) was added Na_2CO_3 (8.52 mL, 8.52 mmol) at room temperature. The mixture was degassed with N_2 for 10 min and $Pd(PPh_3)_4$ (0.197 g, 0.170 mmol) was then added at RT. The resulting reaction mixture was stirred at 100 °C for 12 h. The reaction was quenched with water and extracted with EtOAc (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by reverse phase chromatography, eluting with 50% acetonitrile in H_2O. The pure fractions were concentrated to afford 4-(3,5-dimethylisoxazol-4-yl) benzaldehyde (**ALD-15**, 0.1 g, 0.45 mmol, 16% yield). LCMS: m/z MM-ES+ APCI, Positive $[M+H]^+$ 202.1, ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.08 (s, 1H), 7.99 (d, J = 2.00 Hz, 2H), 7.46 (d, J = 8.40 Hz, 2H), 2.48 (s, 3H), 2.33 (s, 3H).

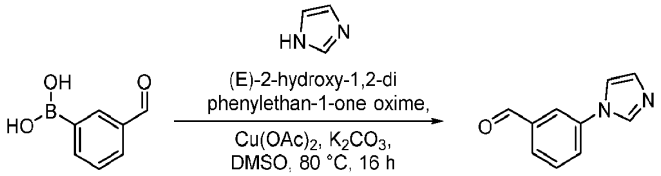
Example 107: Synthesis of 3-(1*H*-pyrazol-1-yl)benzaldehyde (ALD-16)



Step 1

To a stirred solution of 1H-pyrazole (500 mg, 7.34 mmol) and (3-formylphenyl)boronic acid (2.20 g, 14.69 mmol) in DCM (20 mL), pyridine (1162 mg, 14.69 mmol) and copper(II) acetate (2.0 g, 11.02 mmol) were added. The mixture was stirred at room temperature under an oxygen bladder for 16 h. The reaction mixture was concentrated under reduced and the crude residue was purified by column chromatography (silica gel 100-200 mesh, Isolera, flow rate of 35 mL/min, 5-6% EtOAc in petroleum ether). The isolated product was re-purified using reverse phase column chromatography (C18) cartridge (25 g), eluted with 5 to 100% acetonitrile in 0.1% formic acid in water. The pure fractions were collected and dried to afford 3-(1H-pyrazol-1-yl)benzaldehyde (**ALD-16**, 260 mg, 1.51 mmol, 21% yield). LCMS: m/z MM-ES+ APCI, Positive $[M+H]^+$ 173.0, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.09 (s, 1H), 8.65 (d, J = 2.40 Hz, 1H), 8.38 (d, J = 2.00 Hz, 1H), 8.37-8.18 (m, 1H), 7.86-7.72 (m, 3H), 6.61-6.60 (m, 1H).

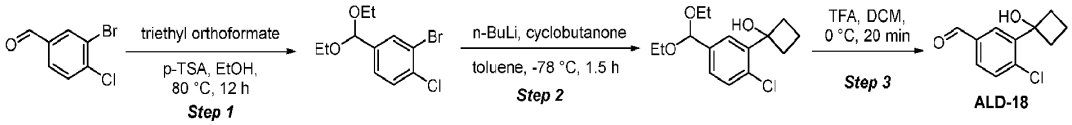
Example 108: Synthesis of 3-(1H-imidazol-1-yl)benzaldehyde (ALD-17)



Step 1

To a stirred solution of (3-formylphenyl)boronic acid (500 mg, 3.33 mmol) in DMSO (5 mL), 1H-imidazole (454 mg, 6.67 mmol), tripotassium phosphate (1416 mg, 6.67 mmol), (E)-2-hydroxy-1,2-diphenylethan-1-one oxime (76 mg, 0.333 mmol), and copper(II) acetate (60.6 mg, 0.333 mmol) were added at room temperature. The mixture was then stirred at 80 °C for 16 h. The reaction mixture was added to EtOAc (100 mL) and water (100 mL), and the organic layers were separated. The aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with water (100 mL) and brine solution (100 mL), dried over Na_2SO_4 filtered, and concentrated under reduced pressure to obtain a crude residue. The crude residue was purified by flash column chromatography using Biotage Isolera using a 100-200 mesh silica gel cartridge (100 g) with EtOAc in hexane (80%) as eluent. The isolated product was re-purified using a reverse phase Grace C18 cartridge (40 g) with acetonitrile in water (0.1% formic acid) (40-50%) as the eluent. The pure fractions were collected and dried to obtain 3-(1H-imidazol-1-yl)benzaldehyde (**ALD-17**, 120 mg, 0.58 mmol, 17% yield). LCMS: m/z MM-ES+ APCI, Positive $[M+H]^+$ 173.0, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.09 (s, 1H), 8.39 (s, 1H), 8.31 (s, 1H), 8.19-8.19 (m, 1H), 8.04-8.02 (m, 1H), 7.77 (t, J = 8.00 Hz, 2H), 7.16 (s, 1H).

Example 109: Synthesis of 4-chloro-3-(1-hydroxycyclobutyl) benzaldehyde (ALD-18)



Step 1: **Synthesis of 2-bromo-1-chloro-4-(diethoxymethyl)benzene**

To a stirred solution of 3-bromo-4-chlorobenzaldehyde (1 g, 4.56 mmol) in ethanol (10 mL), was added p-toluene sulfonic acid monohydrate (0.087 g, 0.46 mmol), followed by triethyl orthoformate (0.76 mL, 4.56 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 12 h. The reaction mixture was quenched with water (30 mL) and extracted with EtOAc (2 x 50 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by neutral alumina column chromatography, eluting with 2% EtOAc in petroleum ether, to yield 2-bromo-1-chloro-4-(diethoxymethyl)benzene (1.1 g, 3.75 mmol, 82% yield). 1H-NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 2.00 Hz, 1H), 7.45 (d, J = 8.40 Hz, 1H), 7.37 (dd, J = 2.00, 8.20 Hz, 1H), 5.48 (s, 1H), 3.60-3.57 (m, 4H), 1.26 (t, J = 7.20 Hz, 6H).

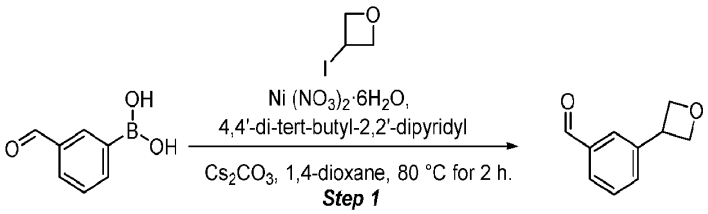
Step 2: **Synthesis of 1-(2-chloro-5-(diethoxymethyl)phenyl)cyclobutan-1-ol**

To a stirred solution of 2-bromo-1-chloro-4-(diethoxymethyl)benzene (0.1 g, 0.34 mmol) in toluene (1 mL) was added n-BuLi (2.5 M in THF) (0.14 mL, 0.34 mmol) dropwise at -78 °C and the reaction was stirred at -78 °C for 20 minutes. After 20 minutes, cyclobutanone (0.024 g, 0.34 mmol) was added to the reaction mixture and stirred at -78 °C for 30 min. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 25 mL). The combined organic layers were dried over Na_2SO_4. The crude compound was purified using 100-200 mesh silica gel, eluting with 20% EtOAc in hexane, to obtain 1-(2-chloro-5-(diethoxymethyl)phenyl)cyclobutan-1-ol (70 mg, 0.25 mmol, 72% yield). 1H-NMR (400 MHz, DMSO-d6): δ 7.41-7.37 (m, 2H), 7.29-7.27 (m, 1H), 5.49 (s, 1H), 5.41 (s, 1H), 3.57-3.47 (m, 4H), 2.55-2.51 (m, 2H), 2.33-2.34 (m, 2H), 1.28-1.27 (m, 2H), 1.12 (t, J = 13.20 Hz, 6H).

Step 3: **Synthesis of 4-chloro-3-(1-hydroxycyclobutyl)benzaldehyde (ALD-18)**

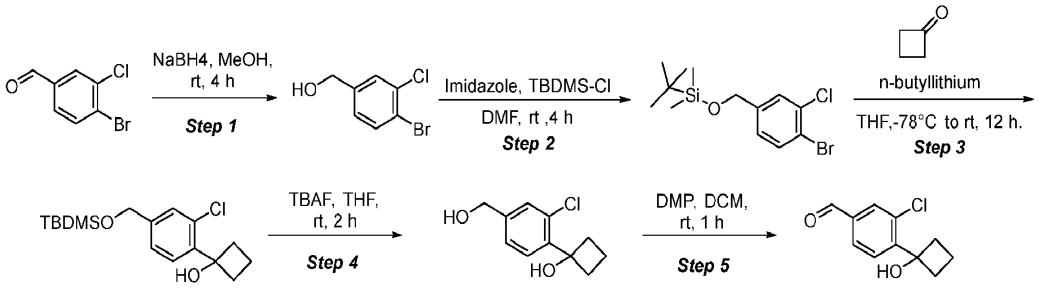
To a stirred solution of 1-(2-chloro-5-(diethoxymethyl)phenyl)cyclobutan-1-ol (70 mg, 0.26 mmol) in DCM (1 mL) was added TFA (0.114 mL, 1.48 mmol) dropwise at 0 °C and the reaction was stirred at 0 °C for 20 min. After completion, the reaction mixture was diluted with $NaHCO_3$ solution (20 mL) and extracted with DCM (2 x 25 mL). The combined organic layers were dried and concentrated to obtain 4-chloro-3-(1-hydroxycyclobutyl)benzaldehyde (**ALD-18**, 40 mg, 0.190 mmol, 77% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.94-7.82 (m, 1H), 7.80 (d, J = 2.00 Hz, 1H), 7.62 (d, J = 8.80 Hz, 1H), 5.57 (s, 1H), 4.10 (s, 1H), 2.62-2.62 (m, 2H), 2.50-2.50 (m, 2H), 1.29-1.28 (m, 2H).

Example 110: Synthesis of 3-(oxetan-3-yl)benzaldehyde (ALD-19)



A stirred solution of (3-formylphenyl)boronic acid (500 mg, 3.33 mmol), 3-iodooxetane (1.23 g, 6.67 mmol), and Cs_2CO_3 (2.17 g, 6.67 mmol) in 1,4-dioxane (10 mL) was degassed with nitrogen at room temperature for 15 minutes. After that, nickel (II) nitrate hexahydrate (79 mg, 0.33 mmol) and 4,4′-di-tert-butyl-2,2′-dipyridyl (90 mg, 0.33 mmol) were added and the reaction mixture was stirred at 80 °C for 2 h. The reaction mixture was filtered through a pad of Celite, and the pad was washed with EtOAc (100 mL). The filtrate was concentrated under reduced pressure. The crude compound was purified by Isolera Biotage column chromatography using 100-200 mesh silica gel, eluting with 50% EtOAc in petroleum ether. The collected pure fractions were concentrated under reduced pressure to yield 3-(oxetan-3-yl) benzaldehyde (**ALD-19**, 60 mg, 0.36 mmol, 11% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.05 (s, 1H), 7.97 (s, 1H), 7.83 (d, J = 7.60 Hz, 1H), 7.76 (d, J = 7.60 Hz, 1H), 7.62 (t, J = 7.60 Hz, 1H), 4.99 (q, J = 6.00 Hz, 2H), 4.65 (t, J = 6.40 Hz, 2H), 4.37 (t, J = 7.20 Hz, 1H).

Example 111: Synthesis of 3-chloro-4-(1-hydroxycyclobutyl)benzaldehyde (ALD-20)



Step 1: **Synthesis of (4-bromo-3-chlorophenyl)methanol**

To a stirred solution of 4-bromo-3-chlorobenzaldehyde (1 g, 4.56 mmol) in methanol (15 mL) under a nitrogen atmosphere was added sodium borohydride (0.345 g, 9.11 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated and quenched with ice water (30 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure to afford the crude compound (4-bromo-3-chlorophenyl)methanol (1.00 g, 4.47 mmol, 98% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.71 (d, J = 8.00 Hz, 1H), 7.55 (s, 1H), 7.23-7.21 (m, 1H), 5.40 (s, 1H), 4.48 (s, 2H).

Step 2: **Synthesis of (4-bromo-3-chlorobenzyl)oxy)(tert-butyl)dimethylsilane**

To a stirred solution of (4-bromo-3-chlorophenyl)methanol (1.0 g, 4.52 mmol) in DMF(10 mL) under a nitrogen atmosphere was added imidazole (0.369 g, 5.42 mmol) and TBDMSCl (0.817 g, 5.42 mmol) at 0 °C. The resulting reaction mixture was stirred at 25 °C for 4 h. The reaction mixture was quenched with water (100 mL) and extracted with EtOAc (2 x 200 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude compound was purified by flash column chromatography using Biotage Isolera (neutral alumina silica gel cartridge, 120 g) using 10% EtOAc in hexane as the eluent. The collected pure fractions were concentrated under reduced pressure to afford ((4-bromo-3-chlorobenzyl) oxy)(tert-butyl)dimethylsilane (987 mg, 2.94 mmol, 65% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$336.9, 338.9; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.74 (d, J = 8.40 Hz, 1H), 7.53 (t, J = 0.80 Hz, 1H), 7.24-7.21 (m, 1H), 4.70 (s, 2H), 0.91 (s, 9H), 0.09 (s, 6H).

Step 3: **Synthesis of 1-(4-(((tert-butyldimethylsilyl)oxy)methyl)-2-chlorophenyl)cyclobutan-1-ol**

To a stirred solution of ((4-bromo-3-chlorobenzyl)oxy)(tert-butyl)dimethylsilane (650 mg, 1.94 mmol) in tetrahydrofuran (1.0 mL) was added n-butyllithium (1.33 mL, 2.13 mmol) at -78 °C. The reaction mixture was stirred at the -78 °C for 30 minutes, followed by the addition of cyclobutanone (149 mg, 2.13 mmol) at 0 °C. The reaction mixture was then stirred at room temperature for 12 h. The reaction was quenched with saturated NH_4Cl solution (100 mL) and extracted with EtOAc (2 x 100 mL). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by flash column chromatography using Biotage Isolera (silica gel cartridge 20 g, neutral alumina) using 0% to 10% EtOAc in hexane as the eluent. The collected fractions were concentrated under reduced pressure to yield 1-(4-(((tert-butyldimethylsilyl) oxy)methyl)-2-chlorophenyl)cyclobutan-1-ol (225 mg, 0.68 mmol, 35% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.39 (d, J = 8.00 Hz, 1H), 7.30 (s, 1H), 7.23-7.21 (m, 1H), 5.33 (s, 2H), 4.70 (s, 2H), 2.32-2.29 (m, 1H), 2.32-2.29 (m, 1H), 2.29-2.00 (m, 1H), 1.50-1.58 (m, 1H), 0.93-0.87 (m, 10H), 0.13-0.09 (m, 6H).

Step 4: **Synthesis of (4-bromo-3-chlorophenyl)methanol**

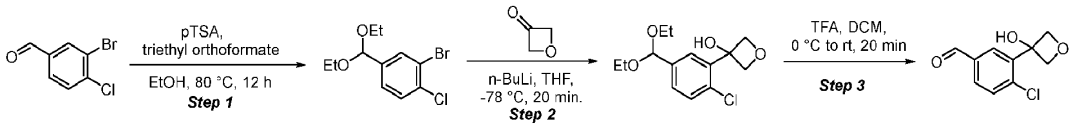
To a stirred solution of 1-(4-(((tert-butyldimethylsilyl)oxy)methyl)-2-chlorophenyl)-cyclobutan-1-ol (225 mg, 0.688 mmol) in tetrahydrofuran (1 mL), TBAF (0.69 mL, 0.69 mmol) was added at 0 °C and the reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the crude (90 mg). The crude compound was purified by flash column chromatography using Biotage Isolera (silica gel cartridge 20 g, neutral alumina) using 0% to 10% EtOAc in hexane as the eluent. The collected fractions were concentrated under reduced pressure to yield 1-(2-chloro-4-(hydroxymethyl)phenyl)cyclobutan-1-ol (50 mg, 0.19 mmol, 27% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.37-7.32 (m, 1H), 7.31-7.30 (m, 1H), 7.23-7.21 (m, 1H), 5.31-5.27

(m, 2H), 4.48-4.47 (m, 2H), 2.53 (d, J = 3.60 Hz, 2H), 2.24-2.19 (m, 2H), 2.14-2.09 (m, 1H), 1.56 (m, 1H).

Step 5: **Synthesis of 3-chloro-4-(1-hydroxycyclobutyl)benzaldehyde (ALD-20)**

To a stirred solution of 1-(2-chloro-4-(hydroxymethyl)phenyl)cyclobutan-1-ol (40 mg, 0.188 mmol) in DCM (2 mL) was added DMP (120 mg, 0.282 mmol) at 0 °C. The resulting reaction mixture was allowed to stir at 25 °C for 1 h. The reaction mixture was quenched with Na_2CO_3 solution, extracted with EtOAc (30 mL x 2), and the combined organic layer was dried over anhydrous Na_2SO_4 filtered, and concentrated. The crude obtained was washed with MTBE to get 3-chloro-4-(1-hydroxycyclobutyl)benzaldehyde (**ALD-20**, 39 mg, 0.19 mmol, quantitative yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.98 (s, 1H), 7.90-7.83 (m, 3H), 5.61 (s, 1H), 2.51-2.50 (m, 2H), 2.35-2.33 (m, 2H), 2.12-2.08 (m, 1H), 1.91-1.62 (m, 1H).

Example 112: Synthesis of 4-chloro-3-(3-hydroxyoxetan-3-yl)benzaldehyde (ALD-21)



Step 1: **Synthesis of 2-bromo-1-chloro-4-(diethoxymethyl)benzene**

To a stirred solution of 3-bromo-4-chlorobenzaldehyde (1 g, 4.56 mmol) in ethanol (10 mL), was added p-toluene sulfonic acid monohydrate (0.087 g, 0.46 mmol) and triethyl orthoformate (0.675 g, 4.56 mmol) at room temperature and the reaction mixture was stirred at 80 °C for 12 h. The reaction mixture was quenched with water (30 mL) and extracted with EtOAc (2 x 50 mL). The organic layers were dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure to obtain a crude residue. The crude product was purified by neutral alumina column chromatography, eluting with 2% EtOAc in pet ether, to yield 2-bromo-1-chloro-4-(diethoxymethyl)benzene (1.1 g, 3.75 mmol, 82% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.76 (d, J = 2.00 Hz, 1H), 7.45 (d, J = 8.40 Hz, 1H), 7.38-7.36 (m, 1H), 5.48 (s, 1H), 3.61-3.55 (m, 4H), 1.26 (t, J = 7.20 Hz, 6H).

Step 2: **Synthesis of 3-(2-chloro-5-(diethoxymethyl)phenyl)oxetan-3-ol**

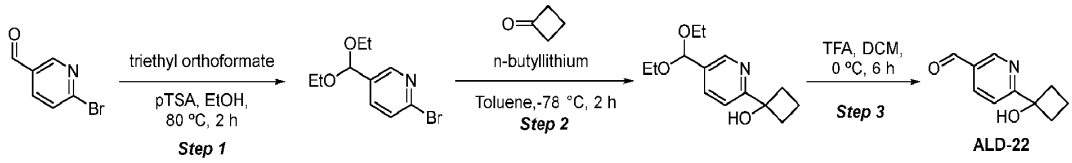
To stirred solution of 2-bromo-1-chloro-4-(diethoxymethyl)benzene (0.5 g, 1.70 mmol) in THF (2 mL) was added n-BuLi (1.6 M in hexane) (1.06 mL, 1.70 mmol) at -78 °C dropwise and stirred the reaction at -78 °C for 20 min. After 20 min, oxetan-3-one (0.123 g, 1.70 mmol) was added and the reaction stirred at -78 °C for 30 min. The reaction was quenched with NH_4Cl solution and extracted with EtOAc (2 x 25 mL). The combined organic layer was dried with anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure. The crude compound was purified through 100-200 silica gel column, 20% EtOAc in petroleum ether as eluent to get 3-(2-chloro-5-(diethoxymethyl)phenyl)oxetan-3-ol (70 mg, 0.17 mmol, 10% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ7.45-7.42 (m, 3H), 6.31 (s, 1H),

5.56-5.49 (m, 2H), 5.05-4.03 (m, 2H), 4.38-4.29 (m, 2H), 4.70-4.72 (m, 2H), 4.30 (s, 1H), 1.16-1.14 (m, 6H).

Step 3: **Synthesis of 4-chloro-3-(3-hydroxyoxetan-3-yl)benzaldehyde (ALD-21)**

To stirred solution of 3-(2-chloro-5-(diethoxymethyl)phenyl)oxetan-3-ol (0.07 g, 0.24 mmol) in DCM (1 mL) was added TFA (0.167 g, 1.465 mmol) at 0 °C dropwise and stirred at 0 °C for 20 min. The reaction was diluted with $NaHCO_3$ solution (20 mL) and extracted with DCM (2 x 25 mL). The combined organic layer was dried and concentrated to get 4-chloro-3-(3-hydroxyoxetan-3-yl)benzaldehyde (**ALD-21**, 0.05 g, 0.24 mmol, 96% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.11 (s, 1H), 7.95-7.88 (m, 3H), 5.76 (s, 1H), 5.12-5.12 (m, 2H), 4.76-4.40 (m, 2H).

Example 113: Synthesis of 6-(1-hydroxycyclobutyl)nicotinaldehyde (ALD-22)



Step 1: **Synthesis of 2-bromo-5-(diethoxymethyl)pyridine**

To a stirred solution of 6-bromonicotinaldehyde (1 g, 5.38 mmol) in ethanol (10 mL) was added p-toluenesulfonic acid monohydrate (0.102 g, 0.538 mmol), followed by triethyl orthoformate (2.69 mL, 16.13 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 2 h. The reaction mixture was quenched with water (100 mL), extracted with EtOAc (2 x 100mL), dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressue. The crude residue was purified by CombiFlash chromatography over neutral alumina, eluting with 30% EtOAc/hexane to afford 2-bromo-5-(diethoxymethyl)pyridine (1.25 g, 4.34 mmol, 81% yield). LCMS: m/z MM-ES+APCI, Positive [M+H, M+2H]$^+$ 260.1, 262.2 1H-NMR (400 MHz, DMSO-d_6): δ 8.40 (d, J = 2.40 Hz, 1H), 7.75-7.72 (m, 1H), 7.67 (d, J = 0.40 Hz, 1H), 5.59 (s, 1H), 3.57-3.52 (m, 4H), 1.16 (t, J = 7.20 Hz, 6H).

Step 2: **Synthesis of 1-(5-(diethoxymethyl)pyridin-2-yl)cyclobutan-1-ol**

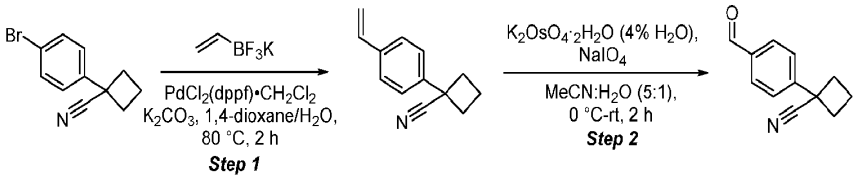
To a stirred solution of 2-bromo-5-(diethoxymethyl)pyridine (353 mg, 1.36 mmol) in toluene (4 mL) was added n-butyllithium (0.542 mL, 1.355 mmol) at -78 °C and stirred for 1 h. Cyclobutanone (95 mg, 1.35 mmol) was then added at -78 °C and the reaction mixture was stirred for at -78 °C 1 h. The reaction was quenched with ammonium chloride solution (10 mL) and the compound was extracted with DCM (2 x 50 mL). The solvent was evaporated under reduced pressure and the crude product was purified by Combi Flash chromatography over neutral alumina, eluting with 30% EtOAc/hexane. Pure fractions were combined to yield 1-(5-(diethoxymethyl)pyridin-2-yl)cyclobutan-1-ol (100 mg, 0.39 mmol, 28% yield). LCMS: m/z MM-ES+APCI, Positive [M+H]$^+$ 252.2, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.54

(d, J = 2.00 Hz, 1H), 7.74 (d, J = 2.00 Hz, 1H), 7.57 (d, J = 0.40 Hz, 1H), 5.73 (s, 1H), 5.57 (s, 1H), 3.59-3.55 (m, 4H), 2.23-2.20 (m, 2H), 1.93-1.91 (m, 2H), 1.87 (m, 2H), 1.16 (t, J = 6.80 Hz, 6H).

Step 3: **Synthesis of 6-(1-hydroxycyclobutyl)nicotinaldehyde (ALD-22)**

To a stirred solution of 1-(5-(diethoxymethyl)pyridin-2-yl)cyclobutan-1-ol (90 mg, 0.36 mmol) in DCM (1 mL) was added trifluoroacetic acid (0.55 mL, 7.16 mmol) at 0 °C and the reaction mixture was stirred for 6 h at room temperature. The reaction mixture was cooled to 0 °C and aqueous sodium bicarbonate solution (10 mL) was added. The mixture was extracted with DCM (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get 6-(1-hydroxycyclobutyl) nicotinaldehyde (**ALD-22**, 78 mg, 0.36 mmol, 99% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.10 (s, 1H), 9.07 (d, J = 1.20 Hz, 1H), 8.24-8.21 (m, 1H), 7.79 (d, J = 8.00 Hz, 1H), 5.76 (s, 1H), 2.57-2.52 (m, 2H), 2.28-2.23 (m, 2H), 1.98-1.87 (m, 2H).

Example 114: Synthesis of 1-(4-formylphenyl)cyclobutane-1-carbonitrile (ALD-23)



Step 1: **Synthesis of 1-(4-vinylphenyl)cyclobutane-1-carbonitrile**

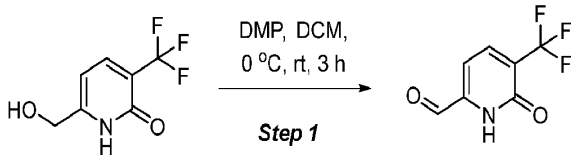
To a stirred solution of 1-(4-bromophenyl)cyclobutane-1-carbonitrile (0.4 g, 1.69 mmol), trifluoro(vinyl)-λ4-borane, potassium salt (0.340 g, 2.54 mmol), and K_2CO_3 (0.702 g, 5.08 mmol) in 1,4-dioxane (8 mL) and water (0.8 mL) was added $PdCl_2$dppf)-CH_2Cl_2 adduct (0.138 g, 0.169 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 2 h. The reaction mixture was concentrated under reduced pressure to obtain a crude residue. The crude product was purified by column chromatography using 100-200 mesh silica gel and 15% EtOAc in petroleum ether. The pure fractions were dried under reduced pressure to yield 1-(4-vinyl-phenyl)cyclobutane-1-carbonitrile (0.23 g, 1.13 mmol, 67% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.48-7.29 (m, 4H), 6.74 (dd, J = 10.80, 17.60 Hz, 1H), 5.79 (d, J = 0.80 Hz, 1H), 5.31 (d, J = 0.80 Hz, 1H), 2.89-2.82 (m, 2H), 2.68-2.60 (m, 2H), 2.49-2.42 (m, 1H), 2.14-2.08 (m, 1H).

Step 2: 1-(4-formylphenyl)cyclobutane-1-carbonitrile (ALD-23)

To a stirred solution of 1-(4-vinylphenyl)cyclobutane-1-carbonitrile (230 mg, 1.26 mmol) in water (0.5 mL) and acetonitrile (8 mL) was added sodium periodate (268 mg, 1.26 mmol) and 4% osmium tetroxide in water (0.197 mL, 0.025 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The reaction was diluted with water (50 mL) and extracted with DCM (2 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by Combi Flash chromatography over neutral alumina,

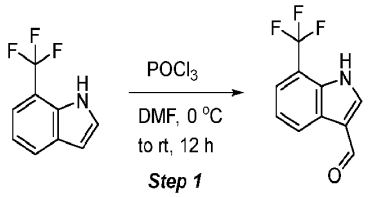
eluting with 30% EtOAc in hexane to afford 1-(4-formylphenyl)cyclobutane-1-carbonitrile (**ALD-23**, 120 mg, 0.65 mmol, 52% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.06 (s, 1H), 7.95 (d, J = 6.40 Hz, 1H), 7.63 (d, J = 8.40 Hz, 1H), 7.40 (d, J = 9.60 Hz, 2H), 2.53-2.88 (m, 4H), 2.06-2.15 (m, 2H).

Example 115: Synthesis of 6-oxo-5-(trifluoromethyl)-1,6-dihydropyridine-2-carbaldehyde (ALD-24)



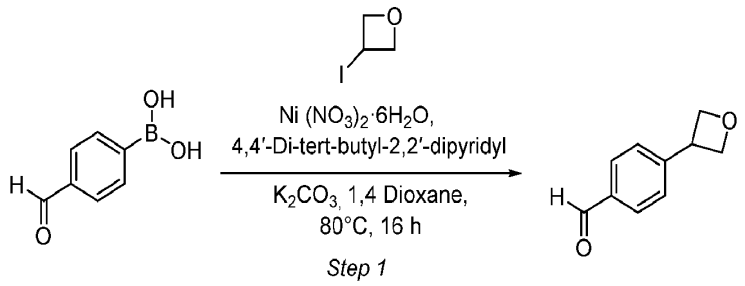
To a stirred solution of 6-(hydroxymethyl)-3-(trifluoromethyl)pyridin-2(1H)-one (0.20 g, 1.04 mmol) in DCM (5 mL) was added DMP (0.44 g, 1.04 mmol) at 0 °C and stirred at the same temperature for 3 h. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to obtain the crude compound. The crude compound was purified by column chromatography, eluting with 4% MeOH in DCM, to afford 6-oxo-5-(trifluoromethyl)-1,6-dihydropyridine-2-carbaldehyde (**ALD-24**, 40 mg, 0.16 mmol, 16% yield). LCMS: m/z MM-ES+APCI, Negative $[M-H]^-$ 190.7, 1H-NMR (400 MHz, DMSO-d_6): δ 12.57 (s, 1H), 9.69 (s, 1H), 8.18 (d, J = 6.80 Hz, 1H), 7.03 (br s, 1H).

Example 116: Synthesis of 7-(trifluoromethyl)-1H-indole-3-carbaldehyde (ALD-25)



A solution of $POCl_3$ (0.497 g, 3.24 mmol) in DMF (5 mL) was stirred for 30 min. 7-(trifluoromethyl)-1H-indole (0.5 g, 2.70 mmol) in DMF (2 mL) was then added at 0 °C and stirred at 25 °C under a nitrogen atmosphere for 12 h. The reaction was diluted with 10% $NaHCO_3$ solution (25 mL) and extracted with EtOAc (2 x 20 mL). The organic layer was dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure. The crude compound was purified by column chromatography using 60-120 silica gel and 40% EtOAc in hexane as the eluent to obtain 7-(trifluoromethyl)-1H-indole-3-carbaldehyde (**ALD-25**, 0.2 g, 0.94 mmol, 35% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 214.1, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.48 (s, 1H), 10.03 (s, 1H), 8.42 (t, J = 8.00 Hz, 2H), 7.64 (d, J = 7.60 Hz, 1H), 7.42 (t, J = 7.60 Hz, 1H).

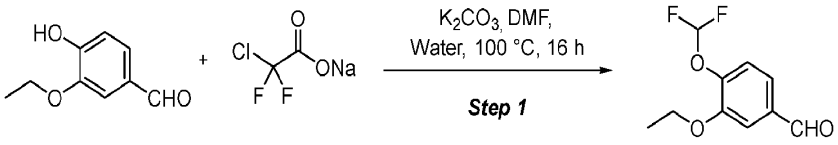
Example 117: Synthesis of 4-(oxetan-3-yl)benzaldehyde (ALD-26)



Step 1

A stirred solution of (4-formylphenyl)boronic acid (250 mg, 1.67 mmol, 1 eq), 3-iodooxetane (614 mg, 3.33 mmol, 2 eq), and K_2CO_3 (691 mg, 5.00 mmol, 3 eq) in 1,4-dioxane (20 mL) was degassed with nitrogen for 15 minutes. Then, 4,4′-di-tert-butyl-2,2′-dipyridyl (44.8 mg, 0.17 mmol, 0.1 eq) and nickel(II) nitrate hexahydrate (39.6 mg, 0.17 mmol, 0.1 eq) were added at room temperature and degassed with nitrogen for 5 minutes. The reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was diluted with EtOAc (50 mL) and the aqueous portion was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over Na_2SO_4 filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 100-200 mesh, gradient EtOAc in hexane). The compound was eluted with 20% EtOAc in hexane. The pure fraction was concentrated under reduced pressure to yield 4-(oxetan-3-yl)benzaldehyde (**ALD-26**, 220 mg, 1.36 mmol, 81% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.00 (s, 1H), 7.94 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H), 4.99-4.94 (m, 2H), 4.66-4.61 (m, 2H), 4.40-4.32 (m, 1H).

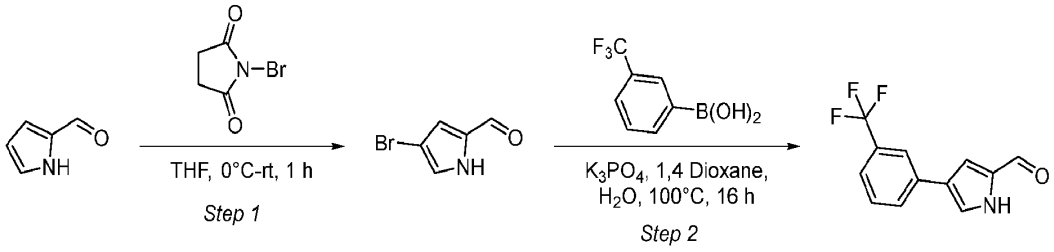
Example 118: Synthesis of 4-(difluoromethoxy)-3-ethoxybenzaldehyde (ALD-27)



Step 1

To a stirred solution of 3-ethoxy-4-hydroxybenzaldehyde (1 g, 6.02 mmol) in DMF (2 mL) and water (6 mL) was added sodium 2-chloro-2,2-difluoroacetate (1.37 g, 9.03 mmol) and K_2CO_3 (2.079 g, 15.04 mmol) at room temperature. The reaction mixture was stirred at 100 °C for 16 h. The reaction mixture was poured into ice-cold water (100 mL) and the compound was extracted with EtOAc (2 x 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude compound was purified by silica gel flash column chromatography eluting with 15% EtOAc in petroleum ether. The collected pure fractions were concentrated under reduced pressure to yield 4-(difluoromethoxy)-3-ethoxybenzaldehyde (**ALD-27**, 190 mg, 0.87 mmol, 15% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.96 (s, 1H), 7.51 (d, J = 1.60 Hz, 1H), 7.47 (dd, J = 2.00, 8.00 Hz, 1H), 7.33 (d, J = 8.40 Hz, 1H), 7.28 (s, 1H), 4.21 (q, J = 6.80 Hz, 2H), 1.51 (t, J = 6.80 Hz, 3H).

Example 119: Synthesis of 4-bromo-1H-pyrrole-2-carbaldehyde (ALD-28)



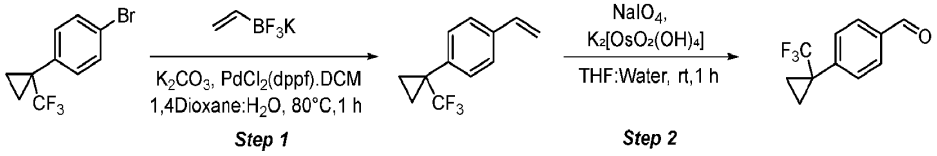
Step 1: **Synthesis of 4-bromo-1H-pyrrole-2-carbaldehyde**

To a stirred solution of 1H-pyrrole-2-carbaldehyde (100 mg, 1.05 mmol) in THF (4 mL) at 0 °C, was added 1-bromopyrrolidine-2,5-dione (187 mg, 1.05 mmol) and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the crude residue was diluted with water (5 mL) and extracted with EtOAc (2 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 100-200 mesh, gradient EtOAc in hexane). The compound was eluted with 10% EtOAc in hexane and the pure fractions were concentrated under reduced pressure to yield 4-bromo-1H-pyrrole-2-carbaldehyde (180 mg, 0.75 mmol, 72% yield). LCMS: m/z MM-ES+APCI, Negative [M-H, M-2H]$^-$ 172.1 174.1; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.47 (s, 1H), 9.45 (s, 1H), 7.38 (s, 1H), 7.01 (s, 1H).

Step 2: **Synthesis of 4-(3-(trifluoromethyl)phenyl)-1H-pyrrole-2-carbaldehyde (ALD-28)**

To a stirred solution of 4-bromo-1H-pyrrole-2-carbaldehyde (25 mg, 0.14 mmol) in 1,4-dioxane (1 mL) and water (0.1 mL) was added (3-(trifluoromethyl)phenyl)boronic acid (32.7 mg, 0.17 mmol) and potassium phosphate tribasic (76 mg, 0.36 mmol) at 25 °C. The solution was then sparged with N_2 for 10 min. Methanesulfonato(diadamantyl-n-butylphosphino)-2'-amino-1,1'-biphenyl-2-yl)palladium(II) dichloromethane adduct (1.05 mg, 1.44 µmol) was added and then the mixture was sparged with N_2 for 5 min. The reaction was heated at 100 °C for 16 h. The reaction was then filtered through a celite bed and washed with EtOAc (50 mL). The filtrate was concentrated under reduced pressure and the crude was purified by MPLC (manually packed cartridge; SiO2 230-400 mesh size; eluting 10-15% EtOAc in hexane) to afford 4-(3-(trifluoro-methyl)phenyl)-1H-pyrrole-2-carbaldehyde (**ALD-28**, 80 mg, 0.28 mmol, 58% yield). LCMS: m/z MM-ES+APCI, Negative [M-H]$^-$ 238.3; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.63 (s, 2H), 8.04 (s, 1H), 7.78 (s, 1H), 7.72 (t, J = 2.40 Hz, 1H), 7.53 (q, J = 2.00 Hz, 2H), 7.47 (t, J = 1.60 Hz, 1H).

Example 120: Synthesis of 4-(1-(trifluoromethyl)cyclopropyl)benzaldehyde (ALD-29)



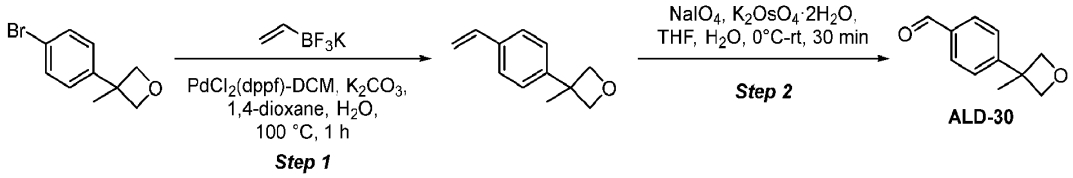
Step 1: **Synthesis of 1-(1-(trifluoromethyl)cyclopropyl)-4-vinylbenzene**

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 sparged 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 sparged 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 EtOAc (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 (100 mg, 0.47 mmol, quantitative yield) 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-29)**

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 EtOAc (20 mL), then washed with water (10 mL). The organic layer was dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure to afford the crude product 4-(1-(trifluoromethyl)cyclopropyl)benzaldehyde (**ALD-29**, 100 mg, 0.29 mmol, 62% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 215.

Example 121: Synthesis of 4-(3-methyloxetan-3-yl)benzaldehyde (ALD-30)



Step 1: **Synthesis of 3-methyl-3-(4-vinylphenyl)oxetane**

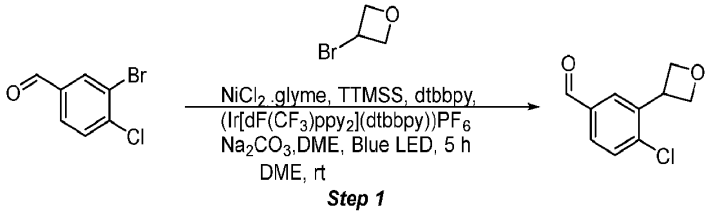
A solution of 3-(4-bromophenyl)-3-methyloxetane (200 mg, 0.88 mmol), trifluoro(vinyl)-l4-borane, potassium salt (177 mg, 1.30 mmol), K_2CO_3 (243 mg, 1.76 mmol) in 1,4-dioxane (5 mL) and water (0.5 mL) was degassed with N_2 for 10 mins. Bis(diphenylphosphino)-ferrocenedichloro palladium(II) dichloromethane complex (64.4 mg, 0.088 mmol) was added into the reaction mixture. The reaction was stirred at 100 °C for 1 h. The reaction mixture was poured in cooled water (50 mL), extracted with EtOAc (2 x 50 mL), and the combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by Biotage Isolera column chromatography using 230-400 mesh silica gel mesh, eluting with 50% EtOAc in petroleum

ether. The collected pure fractions were concentrated under reduced pressure to afford 3-methyl-3-(4-vinylphenyl)-oxetane (180 mg, 1.033 mmol, quantitative yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.49 (d, J = 2.00 Hz, 2H), 7.20 (d, J = 2.00 Hz, 2H), 6.77-6.70 (m, 1H), 5.79-5.74 (m, 1H), 5.26 (d, J = 0.80 Hz, 1H), 4.95 (s, 2H), 4.66 (s, 2H), 1.74 (s, 3H).

Step 2: **Synthesis of 4-(3-methyloxetan-3-yl)benzaldehyde (ALD-30)**

To a stirred solution of 3-methyl-3-(4-vinylphenyl)oxetane (150 mg, 0.86 mmol) in THF (1 mL) and water (0.2 mL) was added sodium periodate (276 mg, 1.29 mmol) and potassium osmate dihydrate (7.93 mg, 0.022 mmol) at 0 °C. The resulting reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was poured into cold water (50 mL) and extracted with EtOAc (2 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by flash column chromatography Biotage Isolera with silica gel using EtOAc in hexane (5-10%) as eluent. Pure fractions were concentrated under reduced pressure to afford 4-(3-methyloxetan-3-yl) benzaldehyde (**ALD-30**, 70 mg, 0.37 mmol, 43% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 177.0, ^{1}H-NMR (400 MHz, CDCl3): δ 10.03 (s, 1H), 7.91 (dd, J = 2.00, 5.00 Hz, 2H), 7.38 (dd, J = 1.60, 6.60 Hz, 2H), 4.97 (q, J = 5.60 Hz, 2H), 4.68 (q, J = 5.60 Hz, 2H), 1.76 (s, 3H).

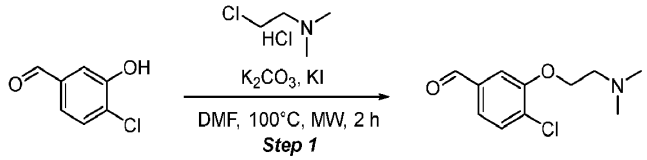
Example 122: Synthesis of 4-chloro-3-(oxetan-3-yl)benzaldehyde (ALD-31)



Step 1

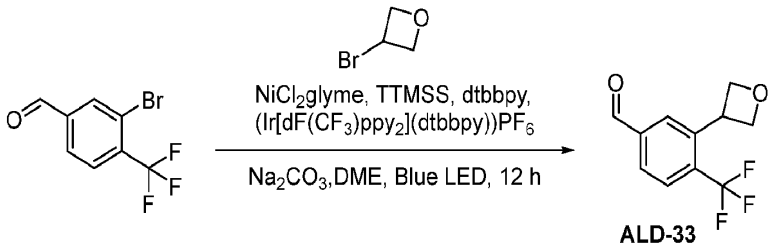
To a stirred solution of 3-bromo-4-chlorobenzaldehyde (250 mg, 1.14 mmol) and 3-bromooxetane (156 mg, 1.14 mmol) in DME (4 mL) was added Na_2CO_3 (241 mg, 2.28 mmol) at rt. The reaction mixture was sparged with argon for 5 min. Then, $Ir[dF(CF3)ppy]_2(dtbbpy)PF_6$ (32.0 mg, 0.028 mmol), dichloronickel; 1,2-dimethoxyethane (7.51 mg, 0.034 mmol), 1,1,1,3,3,3-hexamethyl-2-(trimethylsilyl)trisilane (8.50 mg, 0.034 mmol), 4,4'-di-tert-butyl-2,2'-bipyridyl (9.17 mg, 0.034 mmol) were added and reaction mixture was stirred while being irradiated by blue LED lights at 25 °C for 5 h. The reaction mixture was filtered through a pad of celite, rinsed with EtOAc (100 mL), and the filtrate was concentrated under reduced pressure. The crude compound was purified by column chromatography using 100-200 silica gel mesh, eluting with 60% EtOAc in petroleum ether. The collected pure fractions were concentrated under reduced pressure to afford 4-chloro-3-(oxetan-3-yl)benzaldehyde (**ALD-31**, 30 mg, 0.13 mmol, 11% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.05 (s, 1H), 8.00 (d, J = 2.00 Hz, 1H), 7.85 (d, J = 9.20 Hz, 1H), 7.71 (d, J = 4.40 Hz, 1H), 4.98-4.82 (m, 2H), 4.81-4.63 (m, 2H), 3.71-3.69 (m, 1H).

Example 123: Synthesis of 4-chloro-3-(2-(dimethylamino)ethoxy)benzaldehyde: (ALD-32)



To a stirred solution of 4-chloro-3-hydroxybenzaldehyde (150 mg, 0.96 mmol) in DMF (5 mL) was added K_2CO_3 (397 mg, 2.87 mmol) followed by 2-chloro-N,N-dimethylethan-1-amine (276 mg, 1.92 mmol) and potassium iodate (205 mg, 0.96 mmol). The reaction mixture was stirred in a microwave at 100 °C for 3 h. The reaction was quenched with water (5 mL) and extracted with 10% MeOH in DCM. 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 230-400 mesh silica gel, eluting with 5% MeOH in DCM, to yield 4-chloro-3-(2-(dimethylamino)ethoxy)benzaldehyde (250 mg, 0.55 mmol, 57% yield). LCMS: m/z M-ES+APCI, Positive $[M+H, M+2H]^+$ 228.0, 230.0. ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.98 (s, 1H), 7.70 (d, J = 8.00 Hz, 1H), 7.64 (d, J = 1.60 Hz, 1H), 7.53 (t, J = 1.60 Hz, 1H), 4.26 (t, J = 5.60 Hz, 2H), 3.17 (t, J = 8.40 Hz, 2H), 2.32 (s, 6H).

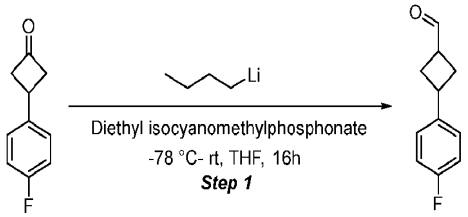
Example 124: Synthesis of 3-(oxetan-3-yl)-4-(trifluoromethyl)benzaldehyde (ALD-33)



ALD-33

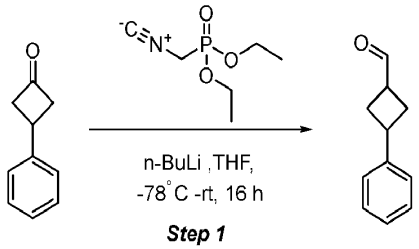
To a stirred solution of 3-bromo-4-(trifluoromethyl)benzaldehyde (250 mg, 0.99 mmol) and 3-bromooxetane (135 mg, 0.99 mmol) in DME (7 mL) was added Na_2CO_3 (209 mg, 1.98 mmol) at room temperature. The reaction mixture was degassed with argon for 5 min. Then, $Ir[dF(CF3)ppy]_2(dtbbpy)PF_6$ (27.7 mg, 0.025 mmol), dichloronickel; 1,2-dimethoxyethane (6.51 mg, 0.030 mmol), 1,1,1,3,3,3-hexamethyl-2-(trimethylsilyl)trisilane (7.37 mg, 0.030 mmol), and 4,4'-di-tert-butyl-2,2'-bipyridyl (7.96 mg, 0.030 mmol) were added. The reaction mixture was stirred with irradiation from blue strip LED lights at 25 °C for 12 h. The reaction mixture was filtered through pad of celite, rinsed with EtOAc (100 mL), and the filtrate was concentrated under reduced pressure. The crude compound was purified by column chromatography using 100-200 silica gel mesh, eluted with 55% EtOAc in petroleum ether. The collected pure fractions were concentrated under reduced pressure to afford 3-(oxetan-3-yl)-4-(trifluoromethyl)benzaldehyde (30 mg, 0.099 mmol, 10% yield). LCMS: m/z M-ES+APCI, Positive $[M+H]^+$ 231.2, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.15 (s, 1H), 8.20 (d, J = 12.80 Hz, 1H), 8.04-7.97 (m, 2H), 4.76-4.73 (m, 1H), 3.70-3.58 (m, 4H).

Example 125: Synthesis of 3-(4-fluorophenyl)cyclobutane-1-carbaldehyde (ALD-34)



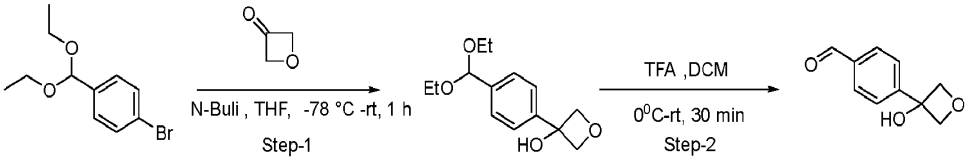
To a stirred solution of diethyl isocyanomethylphosphonate (108 mg, 0.61 mmol) in THF (10 mL) was added n-butyllithium (0.244 mL, 0.61 mmol) was added at -78 °C and stirred under a nitrogen atmosphere for 1 h. Then, 3-(4-fluorophenyl)cyclobutan-1-one (100 mg, 0.61 mmol) in THF (2 mL) was added to the reaction mixture at -78 °C and stirred at room temperature for 4 h. The reaction mixture was then quenched with concentrated HCl and stirred at room temperature for 16 h. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (2 x 30 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain 3-(4-fluorophenyl)cyclobutane-1-carbaldehyde (70 mg, 0.39 mmol, 65% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.70 (d, J = 5.60 Hz, 1H), 7.27-7.25 (m, 2H), 7.14-7.11 (m, 2H), 3.92-3.90 (m, 2H), 3.67-3.57 (m, 4H).

Example 126: Synthesis of 3-phenylcyclobutane-1-carbaldehyde (ALD-35)



To a stirred solution of diethyl isocyanomethylphosphonate (0.121 g, 0.68 mmol) in THF (10 mL) was added n-butyllithium (0.27 mL, 0.68 mmol) at -78 °C and the mixture was stirred under a nitrogen atmosphere for 1 h. Then, a solution of 3-phenylcyclobutan-1-one (0.1 g, 0.68 mmol) in THF (2 mL) was added to the reaction mixture at -78 °C and allowed to warm to room temperature, stirring for an additional 4 h. The reaction was then treated with 1.5 N HCl and stirred at room temperature for 16 h. The reaction was quenched by adding water (10 mL) and the mixture was extracted with EtOAc (2 x 25 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to yield a 3-phenylcyclobutane-1-carbaldehyde (**ALD-35**, 20 mg, 0.68 mmol, 18% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.32-7.28 (m, 5H), 9.71 (s, 1H), 3.53-3.51 (m, 4H), 2.07 (m, 2H).

Example 127: Synthesis of 4-(3-hydroxyoxetan-3-yl)benzaldehyde (ALD-36)



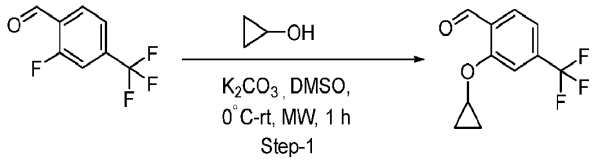
Step 1: **Synthesis of 3-(4-(diethoxymethyl)phenyl)oxetan-3-ol**

To a stirred solution of 1-bromo-4-(ethoxy(methoxy)methyl)benzene (1 g, 4.08 mmol) in THF (10 mL), nBuLi (3.06 mL, 4.90 mmol) was added dropwise at -78 °C. The reaction was allowed to proceed for 20 minutes, after which oxetan-3-one (0.294 g, 4.08 mmol) was added at the same temperature and stirred for 1 h. The reaction mixture was quenched with water (50 mL) and the product was extracted with EtOAc (2 x 150 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. This crude product was purified by normal phase column chromatography using 100-200 silica mesh and eluting with 11% EtOAc in hexane. The pure fractions were concentrated under reduced pressure to afford 3-(4-(diethoxymethyl)-phenyl)oxetan-3-ol (400 mg, 1.59 mmol, 39% yield). 1H-NMR (400 MHz, DMSO-d_6): δ 7.60 (d, J = 2.00 Hz, 2H), 7.42 (d, J = 8.40 Hz, 2H), 6.34 (s, 1H), 5.49 (s, 1H), 4.77 (d, J = 6.80 Hz, 2H), 4.68 (d, J = 6.80 Hz, 2H), 3.57-3.53 (m, 4H), 1.17 (t, J = 2.40 Hz, 6H).

Step 2: **Synthesis of 4-(3-hydroxyoxetan-3-yl)benzaldehyde**

To stirred solution of 3-(4-(diethoxymethyl)phenyl)oxetan-3-ol (60 mg, 0.24 mmol) in DCM (1.5 mL) was added TFA (29.8 mg, 0.262 mmol) at 25 °C for 30 min. The reaction was quenched with $NaHCO_3$ (5 mL) and extracted with DCM (2 x 25 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get 4-(3-hydroxyoxetan-3-yl)benzaldehyde (**ALD-36**, 40 mg, 0.238 mmol, 94% yield). 1H-NMR (400 MHz, $CDCl_3$): δ 10.07 (s, 1H), 7.97 (d, J = 2.00 Hz, 2H), 7.86 (s, 2H), 4.97-4.91 (m, 4H).

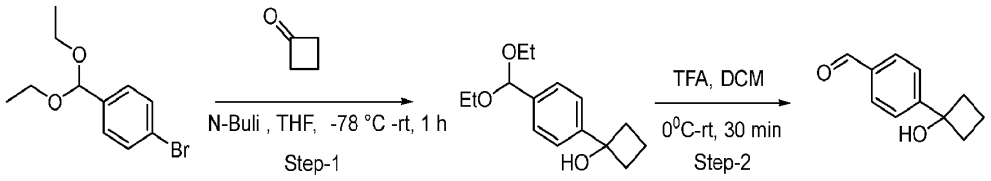
Example 128: Synthesis of 2-cyclopropoxy-4-(trifluoromethyl)benzaldehyde (ALD-37)



To a stirred solution of cyclopropanol (166 mg, 2.86 mmol) in DMSO (8 mL) under nitrogen atmosphere, 2-fluoro-4-(trifluoromethyl) benzaldehyde (500 mg, 2.60 mmol) was added at rt and stirred for 5 min. Then, K2CO3 (432 mg, 3.12 mmol) was added and stirred at rt for 5 min. Then reaction mixture was stirred under microwave at 100 °C for 1 h. The reaction mixture was poured in cooled water (100 mL), and the compound was extracted with EtOAc (2 x 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude compound was purified by silica gel flash column chromatography eluting with 50% EtOAc in hexane. The collected pure

fractions were concentrated under reduced pressure to get 2-cyclopropoxy-4-(trifluoromethyl)benzaldehyde (**ALD-37**, 50 mg, 0.22 mmol, 8% yield). a1H-NMR (400 MHz, DMSO-d6): δ 10.48 (s, 1H), 7.87-7.78 (m, 3H), 4.23-4.22 (m, 1H), 0.49-0.48 (m, 4H).

Example 129: Synthesis of 4-(1-hydroxycyclobutyl)benzaldehyde (ALD-38)



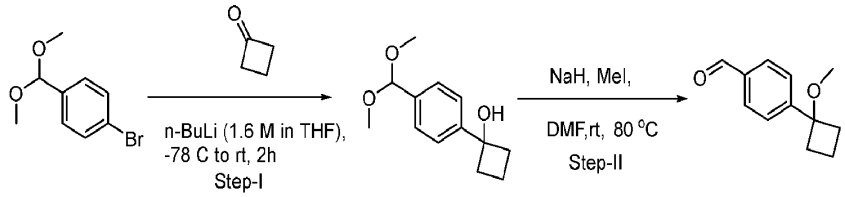
Step 1: Synthesis of 1-(4-(diethoxymethyl)phenyl)cyclobutan-1-ol

To a stirred solution of 1-bromo-4-(diethoxymethyl)benzene (500 mg, 1.93 mmol) and cyclobutanone (0.147 mL, 1.93 mmol) in THF (2 mL) was added n-butyllithium in hexane (1.16 mL, 2.89 mmol) at -78 °C. The resulting reaction mixture was stirred at -78 °C for 1 h. The reaction mixture was quenched with saturated ammonium chloride solution (50 mL), and extracted with EtOAc (50 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to afford crude 1-(4-(diethoxymethyl)phenyl)cyclobutan-1-ol (300 mg, 1.198 mmol, 62% yield). LCMS: ES+APCI, Positive [M+H]+ 251 1H-NMR (400 MHz, DMSO-d6): δ 7.49 (t, J = 3.60 Hz, 2H), 7.39-7.34 (m, 2H), 5.47 (s, 1H), 3.55-3.47 (m, 2H), 3.23 (s, 1H), 2.50 (t, J = 1.60 Hz, 2H), 2.37 (m, 2H), 2.27 (q, J = 2.40 Hz, 2H), 1.95 (s, 2H), 1.18-1.13 (m, 6H).

Step 2: Synthesis of 4-(1-hydroxycyclobutyl)benzaldehyde (ALD-38)

To a stirred solution of 1-(4-(diethoxy methyl)phenyl)cyclobutan-1-ol (300 mg, 1.198 mmol) in DCM (2 mL) was added TFA (137 mg, 1.198 mmol) at 0 °C. The resulting reaction mixture was stirred at 25°C. After completion of reaction, the reaction mixture was concentrated under reduced pressure. The crude residue was purified by flash column chromatography Biotage Isolera with silica gel (100-200 mesh) cartridge (20 g) using EtOAc in hexane (5-10%) as eluent. Pure fractions were concentrated under reduced pressure to afford 4-(1-hydroxycyclobutyl) benzaldehyde (**ALD-38**, 60 mg, 0.297 mmol, 25% yield). LCMS: ES+APCI, Positive [M+H]+ 177, 1H-NMR (400 MHz, DMSO-d6): δ 10.00 (s, 1H), 7.89 (q, J = 1.60 Hz, 2H), 7.72 (d, J = 8.00 Hz, 2H), 2.52-2.50 (m, 1H), 2.33-2.28 (m, 2H), 1.99-1.91 (m, 2H), 1.73 (t, J = 6.80 Hz, 2H).

Example 130: Synthesis of 4-(1-methoxycyclobutyl)benzaldehyde (ALD-39)



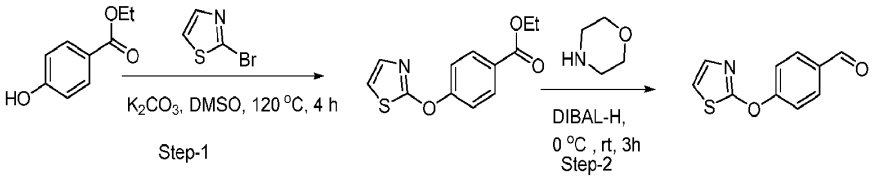
Step 1: **Synthesis of 1-(4-(dimethoxymethyl)phenyl)cyclobutan-1-ol**

To the stirred solution of 1-bromo-4-(dimethoxymethyl)benzene (500 mg, 2.164 mmol) in THF (1.0 mL) was added n-butyllithium in hexane (2.028 mL, 3.25 mmol) at-78 °C. The resulting reaction mixture was stirred at -78 °C for 30 mins. Then, cyclobutanone (303 mg, 4.33 mmol) was added and the resulting reaction mixture was stirred at -78 °C to 25 °C. The reaction mixture was quenched with water (50 mL), and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic extract was dried over anhydrous Na_2SO_4 and filtered the solvent was removed under reduced pressure to afford the crude compound. The crude compound was purified by silica gel flash column chromatography, eluting with 0-10% EtOAc in Hexane to afford 1-(4-(dimethoxymethyl)phenyl)cyclobutan-1-ol (120 mg, 0.540 mmol, 25% yield. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ No ionization. 1H-NMR (400 MHz, DMSO-d6): δ 1H-NMR (400 MHz, DMSO-d6): δ 7.89 (d, J = 1.60 Hz, 2H), 7.72 (d, J = 8.40 Hz, 2H), 5.482 (s, 1H), 4.23 (1H), 3.324 (s, 6H), 2.38-2.34 (m, 2H), 2.00-1.92 (m, 2H), 1.66-1.61 (m, 2H).

Step 2: **Synthesis of 4-(1-methoxycyclobutyl)benzaldehyde (ALD-39)**

To stirred solution of 1-(4-(dimethoxymethyl)phenyl)cyclobutan-1-ol (0.7 g, 3.15 mmol) in DMF (2.0 mL) was added NaH (0.091 g, 3.78 mmol) at 0 °C and continue for 30 min. Then was added MeI (0.591 mL, 9.45 mmol) then the reaction mixture was stirred at 80 °C for 12 h. The progress of reaction was monitored by TLC/LCMS. After completion of reaction, the reaction mass was quenched with ice cold water (50 mL) and the compound was extracted by EtOAc (30*3) and dried over anhydrous Na_2SO_4, the organic layer concentrate under reduced pressure to afford gummy crude. The crude was purified by normal phase column chromatography using (100-200 silica mesh) eluting with 20% of ethyl in hexane as an eluent to afford 4-(1-methoxy-cyclobutyl)benzaldehyde **(ALD-39)** (150 mg, 0.788 mmol, 25% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ No ionization. 1H-NMR (400 MHz, DMSO-d6): δ 1H-NMR (400 MHz, DMSO-d6): δ 10.03 (s, 1H), 7.95 (dd, J = 2.00, 6.60 Hz, 2H), 7.65 (d, J = 8.00 Hz, 2H), 2.87 (s, 3H), 2.36 (t, J = 7.20 Hz, 2H), 1.92-1.89 (m, 2H), 1.69-1.62 (m, 2H).

Example 131: Synthesis of 4-(thiazol-2-yloxy)benzaldehyde (ALD-40)



Step 1: **Synthesis of 1 ethyl 4-(thiazol-2-yloxy)benzoate**

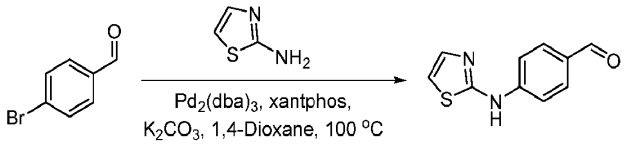
To the stirred solution of 2-bromothiazole (1.0 g, 6.10 mmol)in DMSO (10 mL) were added ethyl 4-hydroxybenzoate (1.013 g, 6.10 mmol), potassium carbonate (2.53 g, 18.29 mmol) at room temperature. The resulting reaction mixture was stirred at 120 °C for 4 h. The progress of reaction was monitored by TLC/LCMS. After completion of reaction, the reaction mixture was cooled to room temperature, diluted

with hexane (200 mL), water (400 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 solvents were removed by vacuum to obtained crude (1.5g). The obtained crude was purified by flash chromatography using 40g (230-400 mesh) column 0-10% EtOAc in hexane as eluent. Pure fractions were concentrated to afford ethyl 4-(thiazol-2-yloxy)benzoate (0.75 g, 2.99 mmol, 49% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 250.1. 1H-NMR (400 MHz, DMSO-d6): δ 8.15-8.11 (m, 2H), 7.38-7.35 (m, 2H), 7.29 (t, J = 4.00 Hz, 1H), 6.92 (d, J = 4.00 Hz, 1H), 4.40 (q, J = 6.80 Hz, 2H), 1.42 (t, J = 6.80 Hz, 3H).

Step 2: **Synthesis of 4-(thiazol-2-yloxy)benzaldehyde (ALD-40)**

A dry and argon-flushed flask, equipped with a magnetic stirring bar and a septum, was charged with morpholine (257 mg, 2.95 mmol) and THF (5 mL). After cooling to 0°C, DIBAL-H (2.340 mL, 2.81 mmol) was added dropwise, and the mixture was stirred at 0°C for 3 h. Ethyl 4-(thiazol-2-yloxy)benzoate (350 mg, 1.404 mmol) in THF (5.00 mL) was added slowly to the reaction mixture, which was stirred for 20 min. Then, DIBAL-H (1.287 mL, 1.544 mmol) was added, and the mixture was stirred for 20 min. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was quenched with 1N HCl (20 mL), extracted with EtOAc (2 X 30 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, solvents were removed by vacuum to obtained crude material. The crude material was purified by flash chromatography using 40g (230-400 mesh) column 0-15% EtOAc in hexane as eluent. Pure fractions were concentrated to afford 4-(thiazol-2-yloxy)benzaldehyde **(ALD-40)** (190 mg, 0.888 mmol, 63% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 206.1. 1H-NMR (400 MHz, DMSO-d6): δ 1H-NMR (400 MHz, DMSO-d6): δ 10.02 (s, 1H), 7.97 (dd, J = 2.00, 6.80 Hz, 2H), 7.48 (dd, J = 1.60, 6.80 Hz, 2H), 7.32 (d, J = 3.60 Hz, 1H), 6.96 (d, J = 4.00 Hz, 1H).

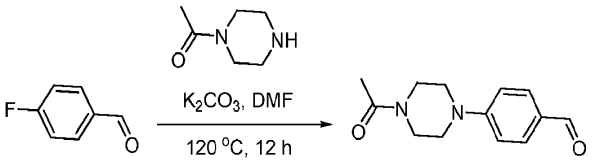
Example 132: Synthesis of 4-(thiazol-2-ylamino)benzaldehyde (ALD-41)



To a stirred solution of thiazol-2-amine (200 mg, 1.997 mmol) and 4-bromobenzaldehyde (370 mg, 1.997 mmol) in 1,4-Dioxane (5 mL) was added by K_2CO_3 (414 mg, 3.00 mmol) at RT. The reaction mixture was sparged with argon for 10 min and was added by $Pd_2(dba)_3$ (183 mg, 0.200 mmol) followed by Xantphos (57.8 mg, 0.100 mmol) and sparged with argon for 10 min. Then reaction mixture was irradiated at 100 °C for 1 h. The progress of reaction was monitored by TLC/LCMS. After completion of reaction mixture, the reaction mixture was concentrated under reduced pressure to get crude. The crude compound was purified by silica gel flash column chromatography eluting with EtOAc to afford 4-(thiazol-2-ylamino)benzaldehyde **(ALD-41)** (150 mg, 0.700 mmol, 35% yield). LCMS: m/z MM-

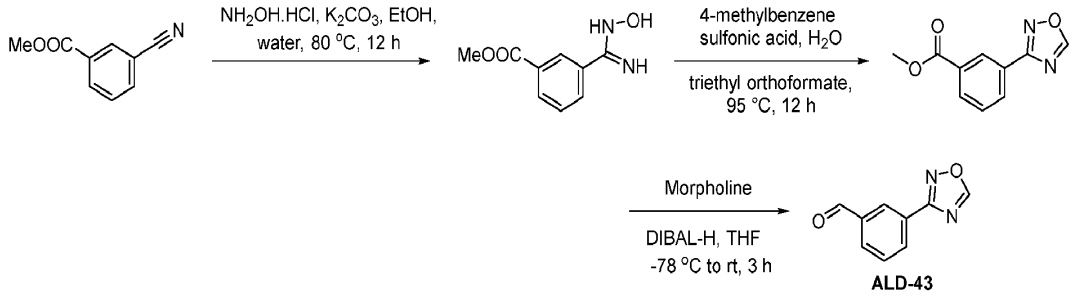
ES+APCI, Positive $[M+H]^+$ 205.0. 1H-NMR (400 MHz, DMSO-d6): δ 1H-NMR (400 MHz, DMSO-d6): δ 10.77 (s, 1H), 9.83 (s, 1H), 7.87-7.82 (m, 4H), 7.37 (d, J = 3.60 Hz, 1H), 7.08 (d, J = 3.60 Hz, 1H).

Example 133: Benzyl 4-(4-acetylpiperazin-1-yl)benzaldehyde (ALD-42)



To a stirred solution of 1-(piperazin-1-yl)ethan-1-one (200 mg, 1.560 mmol) in DMF (5 mL) was added 4-fluorobenzaldehyde (232 mg, 1.872 mmol) followed by K_2CO_3 (323 mg, 2.341 mmol) at RTand the reaction mixture was stirred at 120 °C for 12 h. The progress of reaction was monitored by TLC/LCMS. After completion of reaction, the reaction mixture was concentrated under reduced pressure to get crude. The crude material was purified by silica gel flash column chromatography eluting with EtOAc to afford benzyl 4-(4-acetylpiperazin-1-yl)-benzaldehyde (180 mg, 0.649 mmol, 42% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 233.0. 1H-NMR (400 MHz, DMSO-d6): δ 1H-NMR (400 MHz, DMSO-d6): δ 9.73 (s, 1H), 7.74 (d, J = 8.80 Hz, 2H), 7.05 (d, J = 9.20 Hz, 2H), 3.59-3.17 (m, 8H), 2.05 (s, 3H).

Example 134: Synthesis of 3-(1,2,4-oxadiazol-3-yl)benzaldehyde (ALD-43)



Step 1: Synthesis of 3-bromo-N-hydroxybenzimidamide

To a stirred solution of hydroxylamine hydrochloride, H2O (1.086 g, 12.41 mmol) in Water (2.5 mL) were added sodium bicarbonate (1.043 g, 12.41 mmol) at RT and resulting reaction mixture was stirred at RT for 10 min. Then followed by the addition a solution of methyl 3-cyanobenzoate (1 g, 6.21 mmol) in MeOH (2.5 mL) at RT. Then resulting reaction mixture was stirred at RT for 16 h. The progress of reaction as confirmed by TLC and LCMS. After completion of the reaction, the reaction mixture was directly concentrated under reduced pressure to give crude compound. the crude compound was dissolved in EtOAc (50 mL) and washed with water (2 x 20 mL), organic layer dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude compound. The crude compound was washed with Hexane (2 x 10 mL) to afford methyl 3-(N-hydroxycarbamimidoyl)benzoate (1.0 g, 5.06

mmol, 81% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ 194.9. 1H-NMR (400 MHz, DMSO-d6): 1H-NMR (400 MHz, DMSO-d6): δ 9.77 (s, 1H), 8.30 (t, J = 1.60 Hz, 1H), 7.97-7.93 (m, 2H), 7.54 (t, J = 11.60 Hz, 1H), 5.94 (s, 1H), 3.88 (s, 3H).

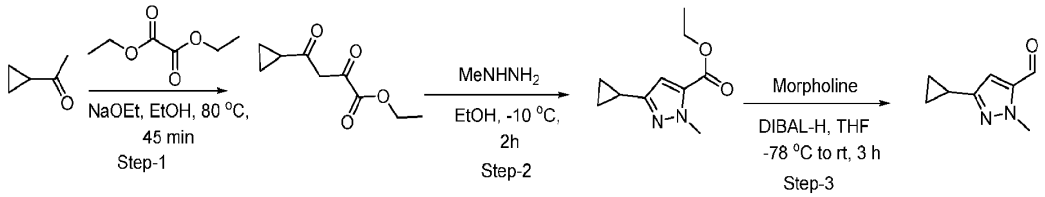
Step 2: **Synthesis of methyl 3-(1,2,4-oxadiazol-3-yl)benzoate**

To a stirred solution of methyl 3-(N-hydroxycarbamimidoyl)benzoate (800 mg, 4.12 mmol) in triethyl orthoformate (9158 mg, 61.8 mmol) was added 4-methylbenzenesulfonic acid, H2O (78 mg, 0.412 mmol) at room temperature and resulting reaction mixture was stirred at 95 °C for 12 h. After completion of the reaction, the reaction mixture was directly concentrated under reduced pressure to give crude compound. The crude compound was purified by Isolera column chromatography (silica gel, 230-400 mesh) and eluted with 10% EtOAc in Hexane to afford methyl 3-(1,2,4-oxadiazol-3-yl)benzoate (770 mg, 3.06 mmol, 74% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 204.9. 1H-NMR (400 MHz, DMSO-d6): δ 1H-NMR (400 MHz, DMSO-d6): δ 9.79 (s, 1H), 8.59 (d, J = 1.60 Hz, 1H), 8.32 (dd, J = 1.60, 4.60 Hz, 1H), 8.19 (dd, J = 1.20, 6.60 Hz, 1H), 7.77 (t, J = 7.60 Hz, 1H), 3.92 (s, 3H).

Step 3: **Synthesis of 3-(1,2,4-oxadiazol-3-yl)benzaldehyde (ALD-43)**

A dry and argon-flushed flask, equipped with a magnetic stirring bar and a septum, was charged with morpholine (0.444 mL, 5.14 mmol) and THF (10 mL). After cooling to 0°C, DIBAL-H (4.08 mL, 4.90 mmol) was added dropwise, and the mixture was stirred for 3 h at the same temperature. methyl 3-(1,2,4-oxadiazol-3-yl)benzoate (500 mg, 2.449 mmol) in THF (5 mL) was added slowly to the reaction mixture, which was stirred for 20 min. Then, DIBAL-H (2.245 mL, 2.69 mmol) was added, and the mixture was stirred for 20 min. After completion of reaction, the reaction mixture was quenched with 1N HCl (40 mL), extracted with EtOAc (2 X 150 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 solvents were concentrated under reduced pressure to get crude residue. The crude was purified by flash chromatography using 40g (230-400 mesh) column 0-15% EtOAc in hexane as eluent to afford 3-(1,2,4-oxadiazol-3-yl)benzaldehyde (0.2 g, 1.068 mmol, 44% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ No ionisation. 1H-NMR (400 MHz, DMSO-d6): δ 1H-NMR (400 MHz, DMSO-d6): δ 10.14 (s, 1H), 9.80 (s, 1H), 8.54 (t, J = 1.60 Hz, 1H), 8.37-8.15 (m, 1H), 8.15-8.13 (m, 1H), 7.83 (t, J = 7.60 Hz, 1H).

Example 135: 3-cyclopropyl-1-methyl-1H-pyrazole-5-carbaldehyde (ALD-44)



Step 1: Synthesis of ethyl 4-cyclopropyl-2,4-dioxobutanoate

To a stirred solution of sodium ethoxide (0.809 g, 11.89 mmol) in Ethanol (20 mL) was added 1-cyclopropylethan-1-one (1.0 g, 11.89 mmol) and diethyl oxalate (1.737 g, 11.89 mmol) dropwise at 0 °C, then reaction mixture was stirred at 0 °C-RT for 1 h. After 1h, reaction mixture was stirred at 80 °C for 45 min. After completion reaction mixture was cooled to room temperature, solvent was distilled out, then neutralized with 2N H_2SO_4 solution and extracted with EtOAc. The Organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford ethyl 4-cyclopropyl-2,4-dioxobutanoate (1.5 g, 7.17 mmol, 60% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 185. 1H-NMR (400 MHz, DMSO-d6): δ 1H-NMR (400 MHz, DMSO-d6): δ 4.68 (s, 2H), 4.44-4.35 (m, 2H), 2.28-1.44 (m, 1H), 1.42-1.38 (m, 3H), 1.28-1.25 (m, 2H), 1.11-1.09 (m, 2H).

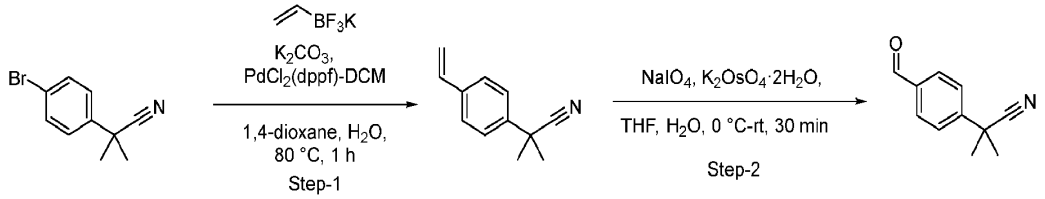
Step 2: Synthesis of ethyl 3-cyclopropyl-1-methyl-1H-pyrazole-5-carboxylate

To a stirred solution of ethyl 4-cyclopropyl-2,4-dioxobutanoate (1.5 g, 8.14 mmol) in Ethanol (15 mL) was added methylhydrazine (0.609 mL, 9.77 mmol) at -10 °C. Then reaction mixture was stirred at same temperature for 2 h. After completion reaction mixture was distilled out diluted with water and compound was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure to get crude. The crude was purified by combi-flash chromatography (Eluent 0-20% EtOAc in n-Hexane) to afford ethyl 3-cyclopropyl-1-methyl-1H-pyrazole-5-carboxylate (0.3 g, 1.455 mmol, 18% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 195.1. 1H-NMR (400 MHz, DMSO-d6): δ 1H-NMR (400 MHz, DMSO-d6): δ 6.56 (s, 1H), 4.27 (t, J = 7.20 Hz, 2H), 3.98 (s, 3H), 1.89-1.31 (m, 1H), 1.29 (t, J = 6.80 Hz, 3H), 0.88 (t, J = 2.40 Hz, 2H), 0.85 (t, J = 3.60 Hz, 2H).

Step 3: Synthesis of 3-cyclopropyl-1-methyl-1H-pyrazole-5-carbaldehyde (ALD-44)

To a stirred solution of morpholine (0.217 g, 2.487 mmol) in THF (2 mL) was added DIBAL-H (1.974 mL, 2.368 mmol) at 0 °C. Then reaction mixture was stirred at 0 °C for 3 h. After that ethyl 3-cyclopropyl-1-methyl-1H-pyrazole-5-carboxylate (0.23 g, 1.184 mmol) in THF (2.000 mL) was added and stirred for 5 min then DIBAL-H (1.085 mL, 1.303 mmol) was added at 0 °C and resulting reaction mixture was stirred at 0 °C for 1 h. After completion reaction was quenched with saturated NH_4Cl solution (20 mL) and compound was extracted with EtOAc (2 x 30 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude. The crude was purified by combi-flash chromatography (Eluent 5-10% EtOAc in n-Hexane to afford 3-cyclopropyl-1-methyl-1H-pyrazole-5-carbaldehyde (0.11 g, 0.635 mmol, 54% yield). 86.75. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 151.0. 1H-NMR (400 MHz, DMSO-d6): δ 1H-NMR (400 MHz, DMSO-d6): δ 9.79 (s, 1H), 6.56-6.50 (m, 1H), 4.36-4.29 (m, 3H), 1.99-1.94 (m, 1H), 0.99-0.96 (m, 2H), 0.77 (t, J = 2.00 Hz, 2H).

Example 136: Synthesis of 4-(1,2,4-oxadiazol-3-yl)benzaldehyde (ALD-45)



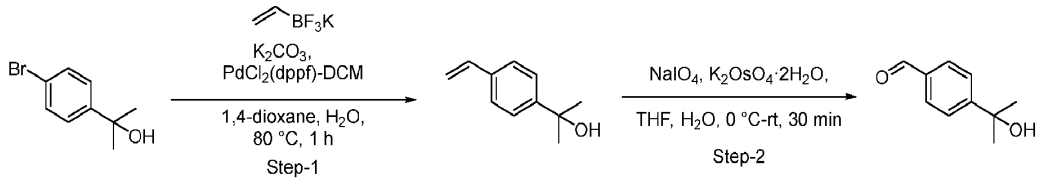
Step 1: **Synthesis of Methyl 4-(1,2,4-oxadiazol-3-yl)benzoate**

To a stirred solution of 2-(4-bromophenyl)-2-methylpropanenitrile (200 mg, 0.892 mmol) in 1,4-dioxane (3 mL) and water (0.333 mL) in a 20 mL vial under a nitrogen atmosphere, trifluoro(vinyl)borane potassium salt (239 mg, 1.785 mmol) and K_2CO_3 (370 mg, 2.68 mmol) were added at room temperature. The resulting reaction mixture was sparged with nitrogen for 10 minutes, then $PdCl_2(dppf)\cdot CH_2Cl_2$ adduct (72.9 mg, 0.089 mmol) was added. The reaction mixture was irradiated under microwave at 80 °C for 1 h. After completion of the reaction as confirmed by LCMS/TLC, the reaction mixture was quenched with water (10 mL), extracted with EtOAc (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude product. The crude product was purified by combi flash chromatography on 230-400 silica, eluting with 10% EtOAc in hexane, to afford 4-bromo-3-chloro-2-fluorobenzonitrile (450 mg, 1.862 mmol, 15% yield). ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.45 (s, 4H), 6.74 (dd, J = 11.20, 17.60 Hz, 1H), 5.81-5.77 (m, 1H), 5.32-5.29 (m, 1H), 1.75 (s, 6H).

Step 2: **Synthesis of 2-(4-formylphenyl)-2-methylpropanenitrile (ALD-45)**

To a stirred solution of 2-methyl-2-(4-vinylphenyl)propanenitrile (140 mg, 0.785 mmol) in water (0.600 mL) and tetrahydrofuran (3 mL), sodium periodate (168 mg, 0.785 mmol) and potassium osmate dihydrate (289 mg, 0.785 mmol) were added at room temperature and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (2 x 50 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated to afford the crude product. The crude product was purified by combi flash chromatography over neutral alumina, eluting with 30% EtOAc in hexane, to afford 2-(4-formylphenyl)-2-methylpropanenitrile (30 mg, 0.170 mmol, 22% yield). LCMS: ES+APCI, Positive $[M+H]^+$ 174.13. ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.06 (s, 1H), 7.95 (d, J = 4.80 Hz, 2H), 7.69 (d, J = 1.60 Hz, 2H), 1.79 (s, 6H).

Example 137: Synthesis of 4-(2-hydroxypropan-2-yl)benzaldehyde (ALD-46)



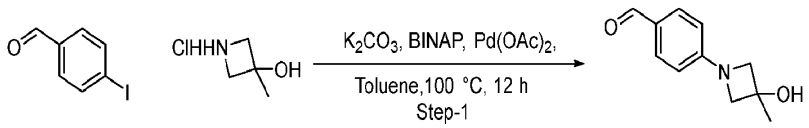
Step 1: **Synthesis of 2-(4-vinylphenyl)propan-2-ol**

To a stirred solution of 2-(4-bromophenyl)propan-2-ol (500 mg, 2.325 mmol) in 1,4-dioxane (6 mL) and water (0.750 mL) in a 20 mL vial under a nitrogen atmosphere, vinyl trifluoroborate (320 mg, 1.262 mmol) and K2CO3 (964 mg, 6.97 mmol) were added at room temperature. The resulting reaction mixture was sparged with nitrogen for 10 minutes, then $PdCl_2(dppf)\cdot CH_2Cl_2$ adduct (190 mg, 0.232 mmol) was added and the reaction mixture was stirred at 100 °C for 1 h. The reaction mixture was quenched with water (50 mL), extracted with EtOAc (2 x 50 mL), and dried over anhydrous Na_2SO_4, filtered, and solvent was evaporated under reduced pressure to afford the crude product. The crude product was purified by combi flash chromatography on 230-400 silica, eluting with 10% EtOAc in hexane, to afford 2-(4-vinylphenyl) propan-2-ol (320 mg, 1.262 mmol, 54% yield). ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.47-0.40 (m, 4H), 6.71 (dd, J = 11.20, 17.80 Hz, 1H), 5.80-5.75 (m, 1H), 5.22-5.19 (m, 1H), 5.00 (s, 1H), 1.17 (s, 6H).

Step 2: Synthesis of 4-(2-hydroxypropan-2-yl)benzaldehyde (ALD-46)

To a stirred solution of 2-(4-vinylphenyl)propan-2-ol (321 mg, 1.266 mmol) in THF (2 mL) and water (0.400 mL), sodium periodate (298 mg, 1.393 mmol) and potassium osmate dihydrate (233 mg, 0.633 mmol) were added at room temperature and the reaction mixture was stirred at room temperature for 1 h. After completion as confirmed by TLC, the reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (2 x 50 mL). The solvent was evaporated under reduced pressure to afford the crude product. The crude product was purified by combi flash chromatography over neutral alumina, eluting with 30% EtOAc in hexane, to afford 4-(2-hydroxypropan-2-yl)benzaldehyde (50 mg, 0.289 mmol, 23% yield). LCMS: ES+APCI, Positive $[M+H]^+$ 165.0, ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.98 (s, 1H), 7.85 (d, J = 8.40 Hz, 2H), 7.70 (d, J = 8.40 Hz, 2H), 5.23 (s, 1H), 1.45 (s, 6H).

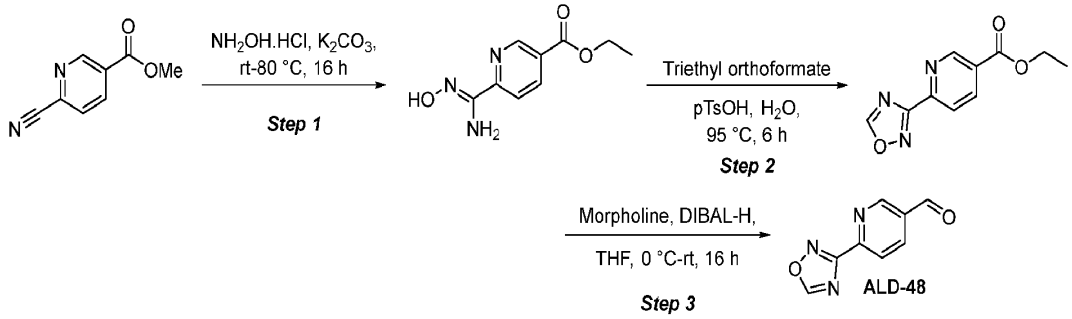
Example 138: Synthesis of 4-(3-hydroxy-3-methylazetidin-1-yl)benzaldehyde (ALD-47)



To a stirred solution of 4-iodobenzaldehyde (500 mg, 2.155 mmol) in toluene (5 mL), 3-methylazetidin-3-ol (346 mg, 2.80 mmol) and K_2CO_3 (596 mg, 4.31 mmol) were added at room temperature. Then, BINAP (268 mg, 0.431 mmol) was added, followed by Pd(OAc)2 (48.4 mg, 0.215 mmol) at RTand the reaction mixture was stirred at 100 °C for 12 h. The reaction mixture was quenched with water (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 filtered and concentrated under reduced pressure to obtain the crude product. The crude product was purified by column chromatography to yield 4-(3-hydroxy-3-methylazetidin-1-yl)benzaldehyde (350 mg, 1.756 mmol, 81% yield). ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.89 (s, 1H), 7.29

(d, J = 2.00 Hz, 2H), 6.39 (d, J = 2.00 Hz, 2H), 5.52 (s, 1H), 3.68 (d, J = 6.00 Hz, 2H), 3.58 (d, J = 11.60 Hz, 2H), 1.36 (s, 3H).

Example 139: Synthesis of 6-(1,2,4-oxadiazol-3-yl)nicotinaldehyde (ALD-48)



Step 1: **Synthesis of ethyl (Z)-6-(N'-hydroxycarbamimidoyl)nicotinate**

To a stirred solution of methyl 6-cyanonicotinate (2 g, 12.33 mmol) in ethanol (20 mL) and water (20 mL), hydroxylamine hydrochloride (2.15 g, 24.67 mmol) and K_2CO_3 (3.41 g, 24.67 mmol) were added at room temperature and stirred at 80 °C for 16 h. The reaction mixture was concentrated under reduced pressure to obtain the crude product. EtOAc (50 mL) and water (50 mL) were added, the layers were separated, and the aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product. The crude product was purified via chromatography to obtain ethyl (Z)-6-(N'-hydroxycarbamimidoyl) nicotinate (0.9 g, 2.94 mmol, 24% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 210.0, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.23 (d, J = 2.80 Hz, 1H), 9.06 (s, 1H), 8.30-8.27 (m, 1H), 8.00 (d, J = 8.40 Hz, 1H), 5.95 (s, 2H), 4.39-4.34 (m, 1H), 3.91 (s, 1H), 1.35 (t, J = 7.20 Hz, 3H).

Step 2: **Synthesis of ethyl 6-(1,2,4-oxadiazol-3-yl)nicotinate**

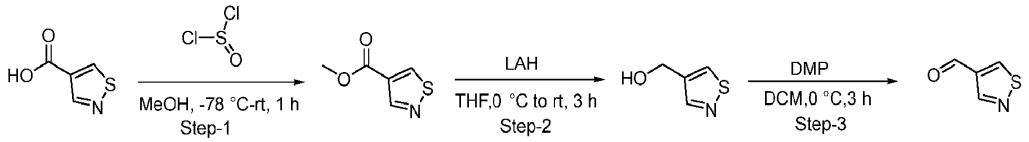
To a stirred solution of ethyl (Z)-6-(N'-hydroxycarbamimidoyl)nicotinate (0.9 g, 4.3 mmol) in triethyl orthoformate (14.33 mL, 86 mmol), 4-methylbenzenesulfonic acid monohydrate (0.082 g, 0.43 mmol) was added at room temperature. The resulting reaction mixture was stirred at 95°C for 6 h. The reaction mixture was concentrated under reduced pressure to obtain the crude product. EtOAc (50 mL) and water (50 mL) were added, the layers were separated, and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the crude product. The crude compound was purified by flash column chromatography using Biotage Isolera using a 50 g silica gel cartridge (100-200 mesh), eluting with 20% EtOAc in hexane. The pure fractions were concentrated to yield ethyl 6-(1,2,4-oxadiazol-3-yl) nicotinate (0.65 g, 2.48 mmol, 58% yield). LCMS:

m/z MM-ES+APCI, Positive $[M+H]^+$ 220.0, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.86 (s, 1H), 9.25 (d, J = 1.20 Hz, 1H), 8.55-8.51 (m, 1H), 8.28 (d, J = 8.00 Hz, 1H), 4.43-4.38 (m, 2H), 1.37 (t, J = 7.20 Hz, 3H).

Step 3: **Synthesis of 6-(1,2,4-oxadiazol-3-yl)nicotinaldehyde (ALD-48)**

To a stirred solution of morpholine (1.93 g, 22.18 mmol) in THF (10 mL), DIBAL-H (18.48 mL, 22.18 mmol) was added at 0 °C and stirred for 2 h. Methyl 6-(1,2,4-oxadiazol-3-yl)nicotinate (0.65 g, 3.17 mmol) in THF (5 mL) was then added and stirred for 30 min. Then, DIBAL-H (13.20 mL, 15.84 mmol) was added at 0 °C, and the mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was quenched with 1.5 N HCl solution and extracted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, filtered, 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 g silica gel cartridge (100-200 mesh), eluting with 10% IPA in DCM. The pure fractions were concentrated to yield 6-(1,2,4-oxadiazol-3-yl)nicotinaldehyde (**ALD-48**, 0.15 g, 0.78 mmol, 25% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 176.1, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 9.87 (s, 1H), 9.27 (d, J = 1.20 Hz, 1H), 8.50-8.48 (m, 1H), 8.34 (d, J = 8.00 Hz, 1H).

Example 140: Synthesis of isothiazole-4-carbaldehyde (ALD-49)



Step 1: Synthesis of methyl isothiazole-4-carboxylate

To a stirred solution of isothiazole-4-carboxylic acid (0.2 g, 1.549 mmol) in methanol (2 mL), $SOCl_2$ (0.226 mL, 3.10 mmol) was added at room temperature and the reaction mixture was stirred at room temperature for 1 h. After completion of the reaction as confirmed by TLC, the reaction mixture was then concentrated and diluted with $NaHCO_3$ solution, followed by extraction with EtOAc (2 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude methyl isothiazole-4-carboxylate (0.2 g, 1.384 mmol, 89% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 143.9, 1H-NMR (400 MHz, DMSO-d6): δ 9.31 (s, 1H), 8.93 (s, 1H), 3.94 (s, 3H).

Step 2: Synthesis of isothiazol-4-ylmethanol

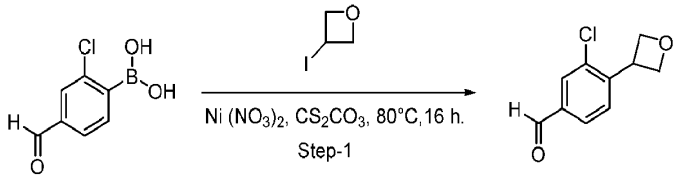
To a stirred solution of methyl isothiazole-4-carboxylate (0.2 g, 1.397 mmol) in tetrahydrofuran (10 mL), LAH (2 M in THF, 1.746 mL, 3.49 mmol) was added at 0 °C and stirred for 3 h. After completion of the reaction as confirmed by TLC, the reaction mixture was quenched with saturated Na_2SO_4 solution, diluted with water (25 mL), and extracted with EtOAc (2 x 25 mL). The combined

organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get isothiazol-4-ylmethanol (60 mg, 0.427 mmol, 31% yield). 1H-NMR (400 MHz, DMSO-d6): δ 8.81 (t, J = 0.80 Hz, 1H), 8.52 (s, 1H), 5.29 (t, J = 5.60 Hz, 1H), 4.60 (d, J = 5.20 Hz, 2H).

Step 3: Synthesis of isothiazole-4-carbaldehyde (ALD-49)

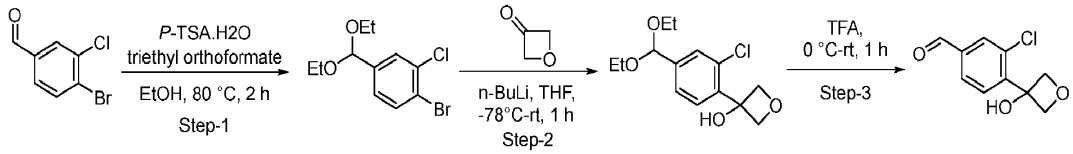
To a stirred solution of isothiazol-4-ylmethanol (60 mg, 0.521 mmol) in dichloromethane (10 mL), Dess-Martin periodinane (332 mg, 0.782 mmol) was added at 0 °C and stirred for 3 h. After completion of the reaction as confirmed by TLC, the reaction mixture was diluted with saturated $NaHCO_3$ solution, stirred for 10 min, and extracted with dichloromethane (2 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get isothiazole-4-carbaldehyde (22 mg, 0.194 mmol, 37% yield). 1H-NMR (400 MHz, DMSO-d6): δ 10.14 (s, 1H), 9.36 (s, 1H), 8.99 (s, 1H).

Example 141: Synthesis of 3-chloro-4-(oxetan-3-yl)benzaldehyde (ALD-50)



To a stirred solution of (2-chloro-4-formylphenyl)boronic acid (100 mg, 0.542 mmol), 3-iodooxetane (200 mg, 1.085 mmol), and Cs_2CO_3 (530 mg, 1.627 mmol) in 1,4-dioxane (2 mL), the mixture was degassed with nitrogen for 15 min. Then, Nickel (II) nitrate hexahydrate (12.89 mg, 0.054 mmol) and 4,4′-di-tert-butyl-2,2′-dipyridyl (14.56 mg, 0.054 mmol) were added at room temperature and the reaction mixture was stirred at 80 °C for 16 h. After completion of the reaction as confirmed by TLC, the reaction mixture was concentrated under reduced pressure, and the compound was purified by silica gel flash column chromatography eluting with 20% EtOAc in petroleum ether. The collected pure fractions were concentrated under reduced pressure to yield 3-chloro-4-(oxetan-3-yl)benzaldehyde (30 mg, 0.125 mmol, 23% yield). 1H-NMR (400 MHz, DMSO-d6): δ 10.00 (s, 1H), 7.97-7.93 (m, 2H), 7.79 (d, J = 8.00 Hz, 1H), 5.01-4.97 (m, 2H), 4.75 (t, J = 6.40 Hz, 2H), 1.35-1.10 (m, 1H).

Example 142: Synthesis of 3-chloro-4-(3-hydroxyoxetan-3-yl)benzaldehyde (ALD-51)



Step 1: Synthesis of 1-bromo-2-chloro-4-(diethoxymethyl)benzene

To a stirred solution of 4-bromo-3-chlorobenzaldehyde (1 g, 4.56 mmol) in ethanol (10 mL), triethyl orthoformate (0.675 g, 4.56 mmol) and p-toluenesulfonic acid monohydrate (0.087 g, 0.456

mmol) were added at room temperature and the reaction mixture was stirred at 80 °C for 2 h. The progress of the reaction was monitored by LCMS. After completion of the reaction as confirmed by LCMS, the reaction mixture was quenched with water (10 mL) and extracted with EtOAc (2 x 50 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the crude residue. The crude compound was purified by flash column chromatography using Biotage Isolera using a 40 g silica gel cartridge, eluting with 10% EtOAc in hexane. The collected pure fractions were concentrated under reduced pressure to afford 1-bromo-2-chloro-4-(diethoxymethyl)benzene (0.8 g, 2.398 mmol, 53% yield). 1H-NMR (400 MHz, DMSO-d6): δ 7.78 (d, J = 8.40 Hz, 1H), 7.58 (d, J = 2.00 Hz, 1H), 7.31-7.29 (m, 1H), 5.50 (s, 1H), 3.47-3.55 (m, 4H), 76.59 (m, 6H).

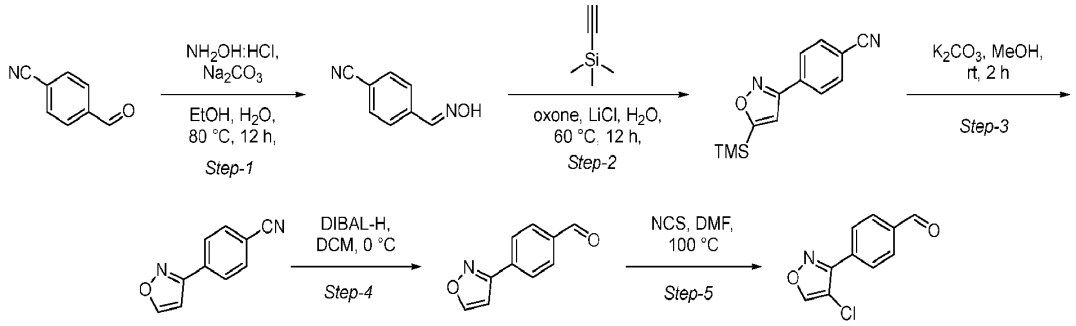
Step 2: Synthesis of 3-(2-chloro-4-(diethoxymethyl)phenyl)oxetan-3-ol

To a stirred solution of 1-bromo-2-chloro-4-(diethoxymethyl)benzene (200 mg, 0.681 mmol) in THF (3 mL), butyllithium (0.511 mL, 0.817 mmol) was added at -78 °C. After 30 min, oxetan-3-one (54.0 mg, 0.749 mmol) was introduced at the -78 °C. The reaction mixture was then stirred at room temperature for 1 h. After completion of the reaction as confirmed by TLC, the reaction was quenched with ammonium chloride solution (5 mL) and extracted with EtOAc (2 x 50 mL). The organic layer was concentrated under reduced pressure to yield crude 3-(2-chloro-4-(diethoxymethyl) phenyl)oxetan-3-ol (180 mg, 0.628 mmol, 92% yield). 1H-NMR (400 MHz, DMSO-d6): δ 7.42-7.40 (m, 3H), 6.27 (s, 1H), 5.05 (s, 1H), 4.37 (m, 2H), 3.58 (m, 2H), 3.50-3.33 (m, 4H), 1.18-1.14 (m, 6H).

Step 3: Synthesis of 3-chloro-4-(3-hydroxyoxetan-3-yl)benzaldehyde (ALD-51)

To a stirred solution of 3-(2-chloro-4-(diethoxymethyl)phenyl)oxetan-3-ol (200 mg, 0.697 mmol) in DCM (1 mL), TFA (0.059 mL, 0.767 mmol) was added at 0 °Cand the reaction mixture was stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure to obtain a crude residue. This crude compound was then purified using a Biotage Isolera system with a 40 g silica gel cartridge, employing 40% EtOAc in hexane as the eluent. The collected pure fractions were concentrated under reduced pressure to yield 3-chloro-4-(3-hydroxyoxetan-3-yl) benzaldehyde (**ALD-51**, 80 mg, 0.35 mmol, 51% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ 213.1, 215.1; ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.01 (s, 1H), 7.96 (d, J = 1.60 Hz, 1H), 7.90-7.88 (m, 1H), 7.65 (d, J = 8.00 Hz, 1H), 6.49 (s, 1H), 5.09 (d, J = 7.60 Hz, 2H), 4.73 (d, J = 8.00 Hz, 2H).

Example 143: Synthesis of 4-(4-chloroisoxazol-3-yl) benzaldehyde (ALD-52)



Step 1: Synthesis of (*Z*)-4-((hydroxyimino)methyl) benzonitrile

To a stirred solution of sodium carbonate (4.61 g, 43.5 mmol) in water (50 mL) was added hydroxylamine hydrochloride (3.02 g, 43.5 mmol), followed by the addition of 4-formylbenzonitrile (5 g, 36.2 mmol) in ethanol (50 mL) at room temperature and the reaction mixture was stirred at room temperature for 16 h. The progress of the reaction was monitored by TLC and LCMS. After completion of reaction, the excess solvent was removed under reduced pressure, and water (100 mL) was added. The resulting emulsion was filtered and washed with water and hexanes, then dried under reduced pressure to afford the crude compound (Z)-4-((hydroxyimino)methyl) benzonitrile (4.0 g, 26.4 mmol, 73% yield). LCMS m/z: MM-ES+APCI, $[M+H]^+$ 147. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.73 (s, 1H), 8.25 (s, 1H), 7.87 (dd, *J* = 6.60, 2.00, 2H), 7.78 (dd, *J* = 6.80, 1.20, 2H).

Step 2: Synthesis of 4-(5-(trimethylsilyl) isoxazol-3-yl) benzonitrile

To a stirred solution of (Z)-4-((hydroxyimino)methyl) benzonitrile (0.8 g, 5.47 mmol) in water (15 mL) was added lithium chloride (0.232 g, 5.47 mmol), Oxone (5.05 g, 8.21 mmol), and trimethylsilyl acetylene (1.152 mL, 8.21 mmol) at room temperature and the reaction mixture was stirred at 60 °C for 16 h. The progress of the reaction was monitored by TLC and LCMS. After completion of reaction, the reaction mixture was poured into cooled water (100 mL). The compound was extracted with EtOAc (2 x 100 mL), and the organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the crude compound. The crude compound was purified by silica gel flash column chromatography eluting with 5% EtOAc in hexanes. The collected pure fractions were concentrated under reduced pressure to afford 4-(5-(trimethylsilyl) isoxazol-3-yl) benzonitrile (300 mg, 1.052 mmol, 19% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.33 (dd, *J* = 3.20 Hz, 2H), 7.97 (dd, *J* = 4.60, 2.40 Hz, 2H), 6.79 (s, 1H), 0.36 (s, 9H).

Step 3: Synthesis of 4-(isoxazol-3-yl) benzonitrile

To a stirred solution of 4-(5-(trimethylsilyl) isoxazol-3-yl) benzonitrile (2.4 g, 9.31 mmol) in methanol (30 mL) was added potassium carbonate (1.930 g, 13.96 mmol) at 0 °C under a nitrogen atmosphere. The reaction mixture was then stirred at room temperature for 1 h. The reaction mixture was poured into cooled water (100 mL). The compound was extracted with EtOAc (2 x 500 mL), and the

organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the crude compound. The crude compound was purified by silica gel flash column chromatography eluting with 25% EtOAc in petroleum ether. The collected pure fractions were concentrated under reduced pressure to yield 4-(isoxazol-3-yl) benzonitrile (1.2 g, 6.83 mmol, 73% yield). LCMS: m/z: MM-ES+APCI, $[M+H]^+$ 171.0. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.56 (d, *J* = 1.60 Hz, 1H), 7.98 (dd, *J* = 6.0, 1.6 Hz, 2H), 7.79 (dd, *J* = 4.0, 0.80 Hz, 2H), 6.74 (d, *J* = 2.00 Hz, 1H).

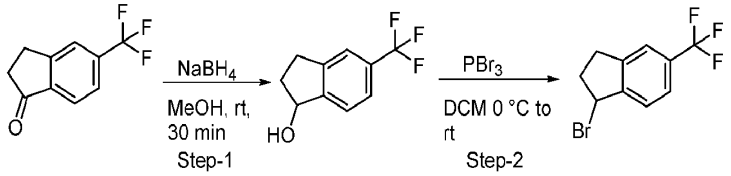
Step 4: Synthesis of 4-(isoxazol-3-yl) benzaldehyde

To a stirred solution of 4-(isoxazol-3-yl) benzonitrile (0.4 g, 2.351 mmol) in dichloromethane (5 mL) was added diisobutylaluminum hydride (DIBAL-H, 2.351 mL, 2.351 mmol, 1 M in toluene) at 0 °C under a nitrogen atmosphere and the reaction mixture was stirred at room temperature for 1 h. Additional DIBAL-H (2.351 mL, 2.351 mmol, 1 M in toluene) was added portion wise, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with 1.5 N HCl solution (50 mL) and extracted with DCM (2 x 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product. The crude compound was purified by flash column chromatography eluting with EtOAc in hexane (2-4%) to afford 4-(isoxazol-3-yl) benzaldehyde (0.2 g, 1.086 mmol, 46% yield) LCMS: m/z: MM-ES+APCI, $[M+H]^+$ 174. $_1$H-NMR (400 MHz, $CDCl_3$): δ 10.11 (s, 1H), 8.55 (d, *J* = 1.60 Hz, 1H), 8.06 (dd, *J* = 4.40, 3.80 Hz, 2H), 8.01 (dd, *J* = 0.80, 4.00 Hz, 2H), 6.77 (d, *J* = 1.60 Hz, 1H).

Step 5: Synthesis of 4-(4-chloroisoxazol-3-yl) benzaldehyde (ALD-52)

To a stirred solution of 4-(isoxazol-3-yl) benzaldehyde (200 mg, 1.155 mmol) in trifluoroacetic acid (TFA, 5 mL), cooled to 0 °C, was added *N*-chlorosuccinimide (771 mg, 5.77 mmol) at 0 °C. The resulting reaction mixture was stirred at 80 °C for 3 h. The reaction was concentrated under reduced pressure to obtain a crude residue. The crude residue was purified by silica gel flash column chromatography eluting with 5% EtOAc in hexanes. The collected pure fractions were concentrated under reduced pressure to yield 4-(4-chloroisoxazol-3-yl) benzaldehyde (**ALD-52**, 90 mg, 0.41 mmol, 35% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.13 (s, 1H), 8.61 (s, 1H), 8.11 (dd, *J* = 6.80, 1.60 Hz, 2H), 8.04 (dd, *J* = 6.60, 1.60 Hz, 2H).

Example 144: Synthesis of 1-bromo-5-(trifluoromethyl)-2,3-dihydro-1*H*-indene: (ALD-53)



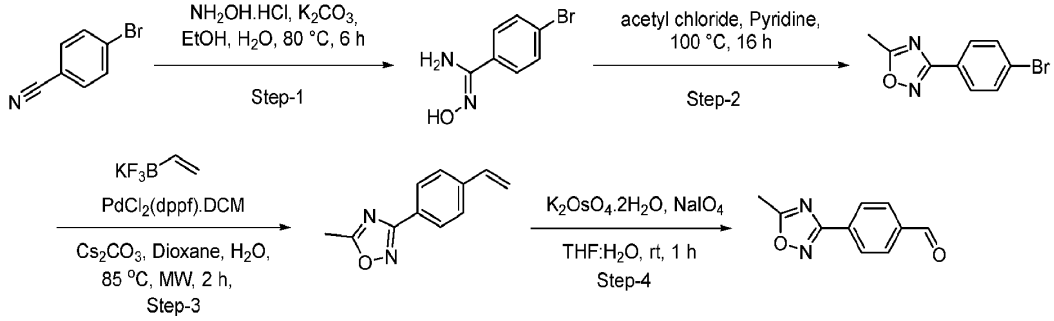
Step 1: Synthesis of 5-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-ol

To a stirred solution of 5-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-one (500 mg, 2.498 mmol) in methanol (5 mL) was added sodium borohydride (189 mg, 5.00 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 30 min. The mixture was quenched with water (10 mL) and extracted with dichloromethane (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure to afford crude 5-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-ol (430 mg, 2.040 mmol, 82% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.02 (s, 1H), 7.74 (d, *J* = 9.20 Hz, 1H), 7.53-7.31 (m, 1H), 5.45 (d, *J* = 6.00 Hz, 1H), 5.11-5.09 (m, 1H), 3.00-2.97 (m, 1H), 2.81-2.77 (m, 1H), 2.42-2.40 (m, 1H), 1.79-1.79 (m, 1H).

Step 2: Synthesis of 1-bromo-5-(trifluoromethyl)-2,3-dihydro-1H-indene (ALD-53)

To a stirred solution of 5-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-ol (430 mg, 2.127 mmol) in dichloromethane (10 mL), cooled to 0 °C, phosphorus tribromide (0.261 mL, 2.76 mmol) was added at 0 °C. The resulting reaction mixture was stirred at room temperature for 2 h and progress of reaction was monitored by (TLC). After completion of reaction, the reaction mixture was poured into cooled water (10 mL) and extracted with EtOAc (100 mL). The organic layer was dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure to yield crude 1-bromo-5-(trifluoromethyl)-2,3-dihydro-1*H*-indene (90 mg, 0.301 mmol, 14% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.55-7.51 (m, 3H), 5.57 (t, *J* = 4.00 Hz, 1H), 3.30-3.24 (m, 1H), 3.01-2.99 (m, 1H), 2.71-2.66 (m, 2H).

Example 145: Synthesis of 4-(5-methyl-1,2,4-oxadiazol-3-yl)benzaldehyde (ALD-54)



Step 1: Synthesis of (Z)-4-bromo-N'-hydroxybenzimidamide

To a stirred solution of 4-bromobenzonitrile (500 mg, 2.75 mmol) in ethanol (5 mL) and water (0.5 mL), hydroxylamine hydrochloride (573 mg, 8.24 mmol) and K_2CO_3 (1898 mg, 13.73 mmol) were added at 25 °C. The resulting reaction mixture was stirred at 80 °C for 6 h. The reaction mixture was concentrated under reduced pressure. The crude residue was taken up in water (50 mL) and the mixture was extracted with ethyl acetate (2 x 50 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield (Z)-4-bromo-N'-hydroxybenzimidamide (450 mg, 2.007 mmol, 73% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H_2]^+$ 216.6, ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.74 (s, 1H), 7.62-7.56 (m, 4H), 5.87 (s, 2H).

Step 2: Synthesis of 3-(4-bromophenyl)-5-methyl-1,2,4-oxadiazole

To a stirred solution of (Z)-4-bromo-N'-hydroxybenzimidamide (2 g, 9.30 mmol) in pyridine (2.21 g, 27.9 mmol) was added acetyl chloride (1.10 g, 14.0 mmol) and the mixture was stirred at 100 °C for 16 h. The cooled reaction mixture was concentrated under reduced pressure to obtain the crude product. Ethyl acetate (100 mL) and water (100 mL) were added to the crude product. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography, eluting with 10% ethyl acetate in hexane to yield 3-(4-bromophenyl)-5-methyl-1,2,4-oxadiazole (3 g, 10.86 mmol, 117% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H_2]^+$ 240.8, ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.83 (dd, J = 8.80, 36.60 Hz, 4H), 2.71 (s, 3H).

Step 3: Synthesis of 5-methyl-3-(4-vinylphenyl)-1,2,4-oxadiazole

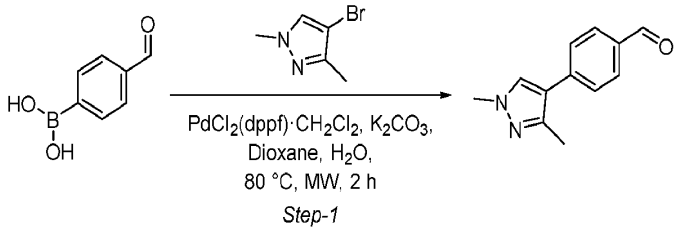
To a stirred solution of 3-(4-bromophenyl)-5-methyl-1,2,4-oxadiazole (500 mg, 2.091 mmol) in 1,4-dioxane (10 mL) and water (1 mL), trifluoro(vinyl)borane potassium salt (420 mg, 3.14 mmol) and K_2CO_3 (723 mg, 5.23 mmol) were added at 25 °C. The reaction mixture was degassed with nitrogen for 10 minutes. $PdCl_2(dppf)\cdot CH_2Cl_2$ adduct (171 mg, 0.209 mmol) was then added, and the mixture was degassed again with nitrogen for 5 minutes. The reaction was irradiated under microwave at 85 °C for 2 h. The progress of the reaction was monitored by LCMS. After completion of the reaction as confirmed by LCMS, the reaction mixture was filtered through a Celite pad and concentrated under reduced pressure to obtain the crude product. The crude compound was purified by flash column chromatography using Biotage Isolera using a 50 g silica gel cartridge (100-200 mesh), eluting with 50% EtOAc in hexane. The pure fractions were concentrated under reduced pressure to yield 5-methyl-3-(4-vinylphenyl)-1,2,4-oxadiazole (320 mg, 1.414 mmol, 68% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 187.2, ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.98 (d, J = 8.00 Hz, 2H), 7.67 (d, J = 8.40 Hz, 2H), 6.86-6.79 (m, 1H), 5.98 (d, J = 17.60 Hz, 1H), 5.41 (d, J = 11.20 Hz, 1H), 2.67 (s, 3H).

Step 4: Synthesis of 4-(5-methyl-1,2,4-oxadiazol-3-yl)benzaldehyde (ALD-54)

To a stirred solution of 5-methyl-3-(4-vinylphenyl)-1,2,4-oxadiazole (320 mg, 1.718 mmol) in tetrahydrofuran (5 mL) and water (1 mL), sodium periodate (551 mg, 2.58 mmol) was added at 25 °C. Then, potassium osmate dihydrate (15.83 mg, 0.043 mmol) was added, and the resulting reaction mixture was stirred at 25 °C for 1 h. After completion of the reaction as confirmed by TLC, the reaction mixture was filtered through a Celite bed and concentrated under reduced pressure to obtain the crude product. The crude compound was purified by flash column chromatography using Biotage Isolera column chromatography using 100-200 mesh silica gel, eluting with 50% EtOAc in n-hexane. The collected pure fractions were concentrated under reduced pressure to yield 4-(5-methyl-1,2,4-oxadiazol-3-yl)

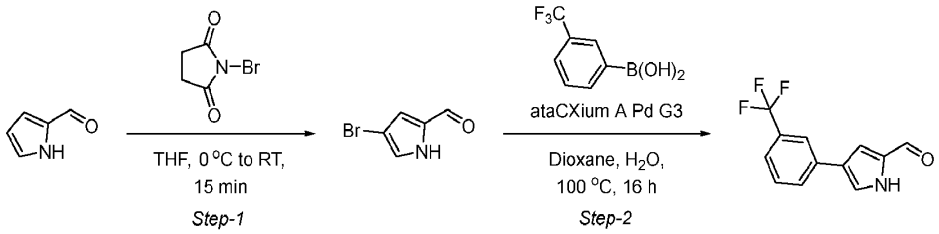
benzaldehyde (100 mg, 0.526 mmol, 31% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 189.2, ^{1}H-NMR (400 MHz, CDCl3): δ 10.12 (s, 1H), 8.27 (d, J = 8.00 Hz, 2H), 8.02 (d, J = 8.40 Hz, 2H), 2.71 (s, 3H).

Example 146: Synthesis of 4-(1,3-dimethyl-1H-pyrazol-4-yl)benzaldehyde (ALD-55)



To a stirred solution of (4-formylphenyl)boronic acid (1.5 g, 10.00 mmol) in 1,4-dioxane (12 mL) and water (1.2 mL) at rt were added 4-bromo-1,3-dimethyl-1H-pyrazole (1.75 g, 10.0 mmol) and K_2CO_3 (2.77 g, 20.1 mmol). The reaction mixture was sparged with nitrogen for 5 min, then $PdCl_2(dppf)\cdot CH_2Cl_2$ adduct (0.81 g, 1.00 mmol) was added and the reaction mixture was stirred at 80 °C under microwave irradiation for 2 h. The cooled reaction mixture was filtered through a Celite bed and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography, eluting with 34% ethyl acetate in hexane to afford 4-(1,3-dimethyl-1H-pyrazol-4-yl) benzaldehyde (800 mg, 3.81 mmol, 38% yield) as solid. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 201.0, ^{1}H-NMR (400 MHz, CDCl3): δ 10.02 (s, 1H), 7.91 (d, J = 8.00 Hz, 2H), 7.56 (t, J = 0.00 Hz, 3H), 3.92 (s, 3H), 2.47 (s, 3H).

Example 147: Synthesis of 4-(3-(trifluoromethyl)phenyl)-1H-pyrrole-2-carbaldehyde (ALD-56)



Step 1: Synthesis of 4-bromo-1H-pyrrole-2-carbaldehyde

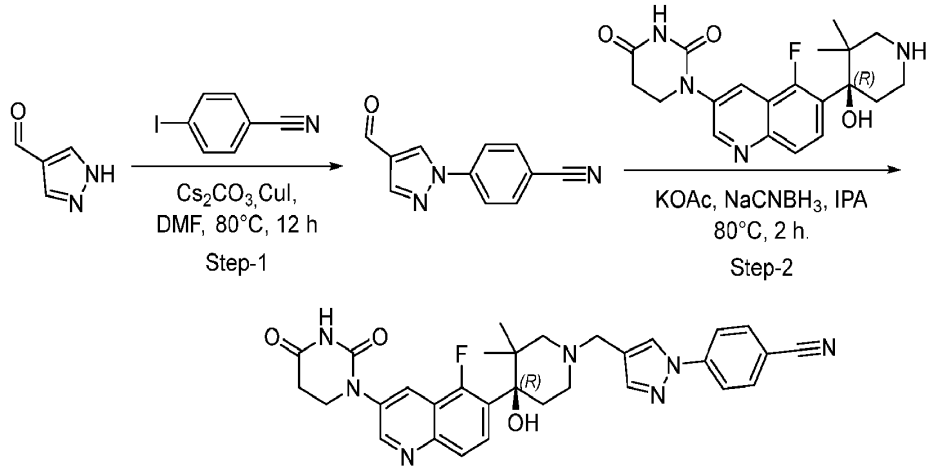
To a stirred solution of 1H-pyrrole-2-carbaldehyde (100 mg, 1.052 mmol) in THF (4 mL) at 0 °C was added NBS (187 mg, 1.05 mmol) and the reaction mixture was stirred at rt for 15 minutes. The reaction mixture was concentrated under reduced pressure. The crude residue was diluted with water (10 mL) and the mixture was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product residue was purified by silica gel flash chromatography, eluting with 5% ethyl acetate in n-hexane to yield 4-bromo-1H-pyrrole-2-carbaldehyde (180 mg, 0.754 mmol, 72% yield). LCMS: m/z MM-ES+APCI,

Positive [M-2, M-]⁻172.1, 174.1; ^{1}H-NMR (400 MHz, DMSO-d6): δ 12.47 (s, 1H), 9.46 (d, J = 0.80 Hz, 1H), 7.21 (d, J = 1.60 Hz, 1H), 7.00 (d, J = 2.40 Hz, 1H).

Step 2: 4-(3-(trifluoromethyl)phenyl)-1H-pyrrole-2-carbaldehyde (ALD-56)

To a stirred solution of 4-bromo-1H-pyrrole-2-carbaldehyde (25 mg, 0.144 mmol) in dioxane (1 mL) and water (0.1 mL), (3-(trifluoromethyl)phenyl)boronic acid (32.7 mg, 0.172 mmol) and potassium phosphate tribasic (76 mg, 0.359 mmol) were added at 25 °C and the mixture was sparged with nitrogen for 10 min. Methanesulfonato(diadamantyl-n-butylphosphino)-2'-amino-1,1'-biphenyl-2-yl)palladium(II) dichloromethane adduct (1.05 mg, 1.44 µmol) was then added, and the mixture was sparged with nitrogen for an additional 5 min. The reaction mixture was stirred at 100 °C for 16 h, then the cooled reaction mixture was filtered through a Celite bed and washed with ethyl acetate (50 mL). The filtrate was concentrated under reduced pressure, and the crude residue was purified by silica gel flash chromatography, eluting with 10-15% ethyl acetate in hexane to afford 4-(3-(trifluoromethyl)phenyl)-1H-pyrrole-2-carbaldehyde (80 mg, 0.278 mmol, 193% yield). LCMS: m/z MM-ES+APCI, Positive [M-H]⁻ 238.3, 1H-NMR (400 MHz, CDCl3): δ 9.63 (s, 2H), 8.04 (s, 1H), 7.73 (s, 2H), 7.72 (d, J = 2.40 Hz, 2H), 7.53 (s, 1H).

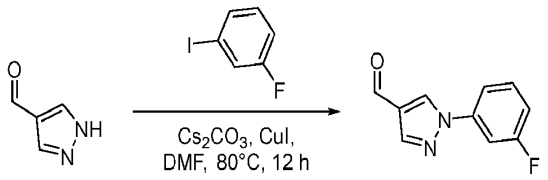
Example 148: Synthesis of 4-(4-formyl-1H-pyrazol-1-yl)benzonitrile (ALD-57)



A stirred mixture of 1H-pyrazole-4-carbaldehyde (500 mg, 5.20 mmol), 4-iodobenzonitrile (1430 mg, 6.24 mmol), DMF (5 mL), Cs_2CO_3 (2543 mg, 7.81 mmol) and copper(I) iodide (99 mg, 0.520 mmol) was sparged with nitrogen for 10 min. Copper(I) iodide (99 mg, 0.52 mmol) and (R, R)-(-)-N, N-dimethyl-1,2-cyclohexanediamine (74.0 mg, 0.520 mmol) were added, and the mixture was sparged with nitrogen for an additional 5 min. The reaction mixture was stirred at 80 °C for 12 h. The cooled reaction mixture was diluted with water (25 mL) and extracted with ethyl acetate (2 x 25 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The crude residue was purified by silica gel flash chromatography, eluting with 30% ethyl acetate in hexane to yield 4-(4-formyl-1H-

pyrazol-1-yl)benzonitrile (0.15 g, 0.730 mmol, 14% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 198.1, 1H-NMR (400 MHz, DMSO-d6): δ 10.02 (s, 1H), 8.54 (s, 1H), 8.24 (s, 1H), 7.93-7.91 (m, 2H), 7.85-7.83 (m, 2H).

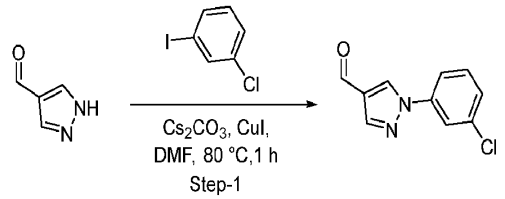
Example 149: Synthesis of 1-(3-fluorophenyl)-1H-pyrazole-4-carbaldehyde (ALD-58)



Step-1

To a stirred solution of 1H-pyrazole-4-carbaldehyde (500 mg, 5.2 mmol) in DMF (5 mL) were added 1-fluoro-3-iodobenzene (1386 mg, 6.24 mmol) and Cs_2CO_3 (2543 mg, 7.81 mmol) at 25 °C, and the mixture was sparged with N_2 for 10 min. To this reaction mixture were added copper(I) iodide (99 mg, 0.52 mmol) and (R,R)-(-)-N,N -Dimethyl-1,2-cyclohexanediamine (74.0 mg, 0.52 mmol) and the mixture was again sparged with N_2 for 5 min. The resulting reaction mixture was stirred at 80 °C for 12 h. Water (50 mL) was added, and the resulting solid precipitate was collected by filtration and dried to afford 1-(3-fluorophenyl)-1H-pyrazole-4-carbaldehyde (300 mg, 1.577 mmol, 30% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H_2]^+$ 191.0. 1H-NMR (400 MHz, DMSO-d6): δ 9.93 (s, 1H), 9.32 (s, 1H), 8.32 (s, 1H), 7.85-7.81 (m, 2H), 7.64-7.59 (m, 1H), 7.64-7.59 (m, 1H), 3.32 (s, 1H).

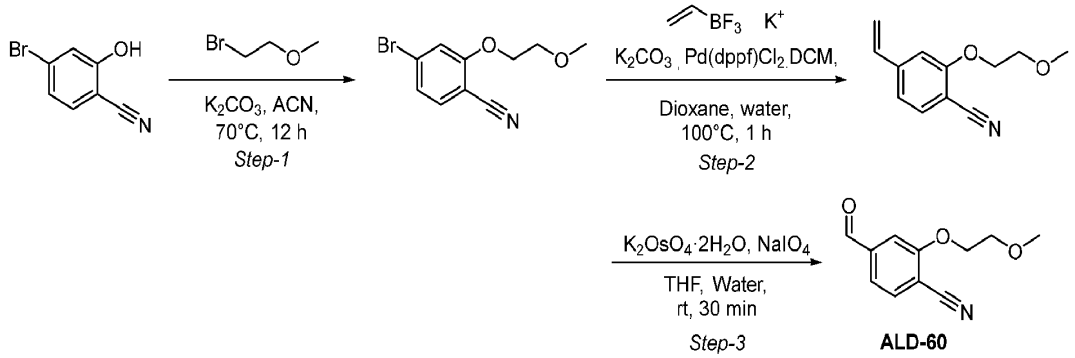
Example 150: Synthesis of 1-(3-chlorophenyl)-1H-pyrazole-4-carbaldehyde (ALD-59)



Step-1

A stirred mixture of 1H-pyrazole-4-carbaldehyde (500 mg, 5.2 mmol), DMF (5 mL), 1-chloro-3-iodobenzene (1489 mg, 6.24 mmol) and Cs_2CO_3 (2543 mg, 7.81 mmol) was sparge with nitrogen for 10 min. Then, copper(I) iodide (99 mg, 0.52 mmol) and (R,R)-(-)-N,N-dimethyl-1,2-cyclohexanediamine (74.0 mg, 0.52 mmol) were added and the mixture was sparged with nitrogen for an additional 5 min. The reaction mixture was stirred at 80 °C for 1 h, then water was added to the cooled mixture. The resulting solid precipitate was collected via filtration and dried to afford 1-(3-chlorophenyl)-1H-pyrazole-4-carbaldehyde (400 mg, 1.762 mmol, 34% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ 207.0, 209.0. 1H-NMR (400 MHz, DMSO-d6): δ 9.93 (s, 1H), 9.33 (s, 1H), 8.31 (s, 1H), 8.05 (d, J = 1.60 Hz, 1H), 7.97-7.92 (m, 1H), 7.61-7.51 (m, 1H), 7.50-7.48 (m, 1H).

Example 151: Synthesis of 4-formyl-2-(2-methoxyethoxy)benzonitrile (ALD-60)



Step 1: **Synthesis of 4-bromo-2-(2-methoxyethoxy)benzonitrile**

A mixture of 4-bromo-2-hydroxybenzonitrile (2 g, 10.1 mmol), 1-bromo-2-methoxyethane (2.11 g, 15.2 mmol), acetonitrile (15 mL), and K_2CO_3 (1.40 g, 10.1 mmol) was stirred at 70 °C for 12 h. The cooled reaction mixture was poured into water, and the mixture was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure, and the crude residue was purified by silica gel flash chromatography, eluting with 50% EtOAc in petroleum ether to afford 4-bromo-2-(2-methoxyethoxy)benzonitrile (2.2 g, 7.82 mmol, 77% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 258.1. 1H-NMR (400 MHz, DMSO-d6): δ 7.69 (d, J = 8.40 Hz, 1H), 7.55 (d, J = 1.60 Hz, 1H), 7.33-7.31 (m, 1H), 4.33-4.31 (m, 2H), 3.71-3.68 (m, 2H), 3.33 (s, 3H).

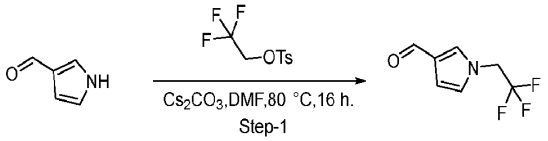
Step 2: Synthesis of 2-(2-methoxyethoxy)-4-vinylbenzonitrile

A stirred mixture of 4-bromo-2-(2-methoxyethoxy)benzonitrile (1 g, 3.9 mmol) and trifluoro(vinyl)borane potassium salt (0.523 g, 3.9 mmol) in 1,4-dioxane (5 mL) and water (0.5 mL), was sparged with nitrogen. Then, potassium carbonate (1.08 g, 7.81 mmol) was added, and the mixture was sparged with nitrogen again. 1,1'-Bis(diphenylphosphino)ferrocene dichloropalladium(II) dichloromethane complex (0.286 g, 0.39 mmol) was added, and the reaction mixture was stirred at 100 °C for 1 h. The cooled reaction mixture was poured into water, and the mixture was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography, eluting with 50% ethyl acetate in petroleum ether to yield 2-(2-methoxyethoxy)-4-vinylbenzonitrile (1.2 g, 4.84 mmol, 100% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 204.1. ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.70 (d, J = 16.00 Hz, 1H), 7.32 (s, 1H), 7.28-7.19 (m, 1H), 6.87-6.69 (m, 1H), 6.58-6.49 (m, 1H), 6.16-6.02 (m, 1H), 5.59-5.40 (m, 1H), 4.40-4.25 (m, 2H), 3.80-3.69 (m, 2H), 3.38-3.29 (m, 3H).

Step 3: Synthesis of formyl-2-(2-methoxyethoxy)benzonitrile

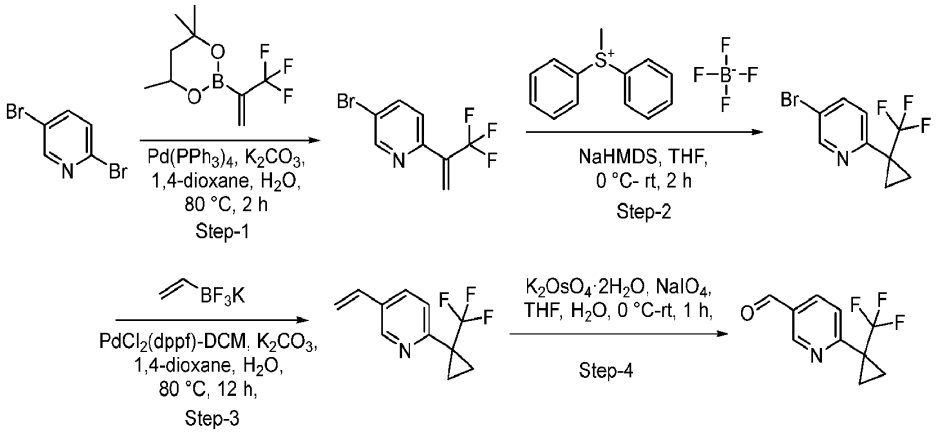
To a stirred solution of 2-(2-methoxyethoxy)-4-vinylbenzonitrile (600 mg, 2.95 mmol) in THF (5 mL) and water (0.5 mL) were added sodium periodate (947 mg, 4.43 mmol) and potassium osmate dihydrate (27.2 mg, 0.074 mmol) at rt. The resulting reaction mixture was stirred at rt for 30 min. The reaction mixture was poured into water, and the mixture was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography, eluting with 30% EtOAc in pet ether to afford 4-formyl-2-(2-methoxyethoxy)benzonitrile (100 mg, 0.478 mmol, 16% yield). LCMS: m/z MM-ES+APCI, Positive $[M-H]^+$ 206.12. 1H-NMR (400 MHz, DMSO-d6): δ 10.07 (s, 1H), 8.01 (d, J = 8.00 Hz, 1H), 7.73 (d, J = 0.80 Hz, 1H), 7.63 (d, J = 1.20 Hz, 1H), 4.40-4.38 (m, 2H), 3.76-3.73 (m, 2H), 3.33 (s, 3H).

Example 152: Synthesis of 1-(2,2,2-trifluoroethyl)-1H-pyrrole-3-carbaldehyde (ALD-61)



To a stirred solution of 1H-pyrrole-3-carbaldehyde (1 g, 10.52 mmol) and 2,2,2-trifluoroethyl 4-methylbenzenesulfonate (3.21 g, 12.62 mmol) in DMF (5 mL), cesium carbonate (6.85 g, 21.03 mmol) was added at ambient temperature. The resulting reaction mixture was stirred at 80 °C for 16 h. After completion, as confirmed by TLC, the reaction mixture was quenched with water (100 mL) and extracted with EtOAc (2 x 150 mL). The organic layer was concentrated under reduced pressure to obtain the crude compound, which was purified by flash column chromatography using Biotage Isolera column chromatography using 100-200 mesh silica gel, eluting with 20% EtOAc in petroleum ether. The collected pure fractions were concentrated under reduced pressure to yield 1-(2,2,2-trifluoroethyl)-1H-pyrrole-3-carbaldehyde (600 mg, 3.39 mmol, 32% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 178.2, 1H-NMR (400 MHz, DMSO-d6): δ 9.72 (s, 1H), 7.74 (s, 1H), 7.01 (s, 1H), 6.54-6.53 (m, 1H), 5.09-5.02 (m, 2H).

Example 153: Synthesis of 6-(1-(trifluoromethyl)cyclopropyl)nicotinaldehyde (ALD-62)



Step 1: **Synthesis of 5-bromo-2-(3,3,3-trifluoroprop-1-en-2-yl)pyridine**

To a stirred solution of 2,5-dibromopyridine (1.5 g, 6.33 mmol) and 4,4,6-trimethyl-2-(3,3,3-trifluoroprop-1-en-2-yl)-1,3,2-dioxaborinane (1.406 g, 6.33 mmol) in 1,4-dioxane (15 mL) and water (0.5 mL), K_2CO_3 (1.750 g, 12.66 mmol) was added. The reaction mixture was degassed with nitrogen gas for 5 min. Then, Pd (PPh3)$_4$ (0.146 g, 0.127 mmol) was added, and the reaction mixture was stirred at 80 °C for 2 h. The reaction mixture was filtered through a pad of Celite, and the pad was washed with EtOAc (100 mL). The filtrate was concentrated under reduced pressure to obtain the crude compound. The crude compound was purified by flash column chromatography using Biotage Isolera column chromatography using 230-400 mesh silica gel, eluting with 5% EtOAc in petroleum ether. The collected pure fractions were concentrated under reduced pressure to yield 5-bromo-2-(3,3,3-trifluoroprop-1-en-2-yl) pyridine (550 mg, 2.083 mmol, 33% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ 252.2, 254.1. 1H-NMR (400 MHz, DMSO-d6): δ 8.80-8.79 (m, 1H), 8.19-8.17 (m, 1H), 7.68 (t, J = 2.40 Hz, 1H), 6.65-6.64 (m, 1H), 6.32 (s, 1H).

Step 2: Synthesis of 5-bromo-2-(1-(trifluoromethyl)cyclopropyl)pyridine

To a stirred solution of 5-bromo-2-(3,3,3-trifluoroprop-1-en-2-yl)pyridine (550 mg, 2.182 mmol) in THF (15 mL), methyldiphenylsulfonium tetrafluoroborate (817 mg, 2.84 mmol) was added at 25 °C and stirred for 30 min. Then, sodium bis(trimethylsilyl)amide in THF (3.49 mL, 3.49 mmol) was then added at 0 °C, and the reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was poured into cooled water (100 mL) and the compound was extracted with EtOAc (2 x 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the crude compound. The crude compound was purified by flash column chromatography using Biotage Isolera column chromatography using 230-400 mesh silica gel, eluting with 50% EtOAc in petroleum ether. The collected pure fractions were concentrated under reduced pressure to yield 5-bromo-2-(1-(trifluoromethyl)cyclopropyl)pyridine (230 mg, 0.733 mmol, 34% yield). LCMS: m/z MM-ES+APCI,

Positive $[M+H, M+2+H]^+$ 266.1, 268.1. 1H-NMR (400 MHz, DMSO-d6): δ 8.69 (d, J = 2.00 Hz, 1H), 8.10-8.08 (m, 1H), 7.52 (d, J = 8.40 Hz, 1H), 1.51-1.32 (m, 4H).

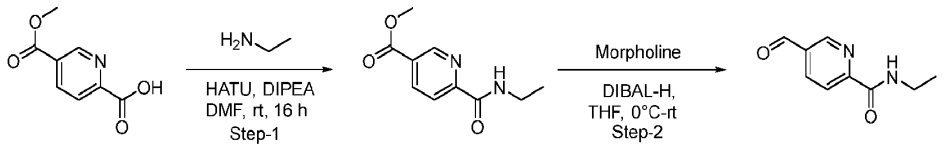
Step 3: Synthesis of 2-(1-(trifluoromethyl)cyclopropyl)-5-vinylpyridine

To a stirred solution of 5-bromo-2-(1-(trifluoromethyl)cyclopropyl)pyridine (210 mg, 0.789 mmol) and trifluoro(vinyl)borane potassium salt (127 mg, 0.947 mmol) in 1,4-dioxane (8 mL) and water (0.2 mL), K_2CO_3 (218 mg, 1.579 mmol) was added at 25 °C. The resulting reaction mixture was degassed with argon for 15 min. Then, $PdCl_2(dppf)\cdot CH_2Cl_2$ adduct (64.5 mg, 0.079 mmol) was then added at 25 °C, and the mixture was degassed with argon for an additional 5 minutesand the reaction mixture was stirred at 80 °C for 12 h. The reaction mixture was filtered through a pad of Celite, and the pad was washed with EtOAc (100 mL). The filtrate was concentrated under reduced pressure to obtain the crude compound. The crude compound was purified by flash column chromatography using Biotage Isolera column chromatography using 230-400 mesh silica gel, eluting with 5% EtOAc in petroleum ether. The collected pure fractions were concentrated under reduced pressure to yield 2-(1-(trifluoromethyl)cyclopropyl)-5-vinylpyridine (140 mg, 0.559 mmol, 71% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 214.0. 1H-NMR (400 MHz, DMSO-d6): δ 8.62 (d, J = 2.40 Hz, 1H), 7.97-7.95 (m, 1H), 7.52 (d, J = 8.00 Hz, 1H), 6.81-6.74 (m, 1H), 5.99 (dd, J = 0.80, 17.60 Hz, 1H), 5.42 (dd, J = 0.80, 10.80 Hz, 1H), 1.42-1.39 (m, 4H).

Step 4: Synthesis of 6-(1-(trifluoromethyl)cyclopropyl)nicotinaldehyde

To a stirred solution of 2-(1-(trifluoromethyl)cyclopropyl)-5-vinylpyridine (140 mg, 0.657 mmol) in THF (8 mL) and Water (2 mL) were added sodium periodate (211 mg, 0.985 mmol) and potassium osmate dihydrate (6.05 mg, 0.016 mmol) at 0 °C. The resulting reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was poured in cooled water (50 mL), compound was extracted in EtOAc (2 x 50 mL), organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get crude compound. The crude compound was purified by isolera biotage column chromatography using neutral alumina mesh, eluted with 5% EtOAc in pet ether. The collected pure fractions were concentrated under reduced pressure to afford 6-(1-(trifluoromethyl)cyclopropyl)nicotinaldehyde (80 mg, 0.372 mmol, 57% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 216.0, 1H-NMR (400 MHz, DMSO-d6): δ 10.10 (s, 1H), 9.05 (d, J = 1.60 Hz, 1H), 8.29-8.27 (m, 1H), 7.76 (d, J = 8.40 Hz, 1H), 1.58-1.54 (m, 4H).

Example 154: Synthesis of N-ethyl-5-formylpicolinamide (ALD-63)



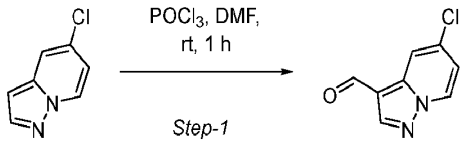
Step 1: Synthesis of methyl 6-(ethylcarbamoyl)nicotinate

To a stirred solution of 5-(methoxycarbonyl)picolinic acid (1) (500 mg, 2.76 mmol) in DMF (10 mL), DIPEA (1.446 mL, 8.28 mmol) and HATU (1574 mg, 4.14 mmol) were added, followed by ethanamine (2) (356 mg, 5.52 mmol)and the reaction mixture was stirred at 25 °C for 16 h. After completion of the reaction as confirmed by LCMS, the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain the crude product. The crude compound was purified by Isolera using EtOAc/hexane (0-30%) to afford methyl 6-(ethyl carbamoyl)nicotinate (3) (50 mg, 0.240 mmol, 9% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 209.1, $_1$H-NMR (400 MHz, DMSO-d6): δ 9.10 (d, J = 1.60 Hz, 1H), 8.99 (s, 1H), 8.49-8.46 (m, 1H), 8.17 (d, J = 8.00 Hz, 1H), 3.93 (s, 3H), 3.34 (t, J = 5.60 Hz, 2H), 1.14 (t, J = 7.20 Hz, 3H).

Step 2: Synthesis of N-ethyl-5-formylpicolinamide (ALD-63)

To a stirred solution of morpholine (0.961 mL, 11.05 mmol) in THF (2 mL), DIBAL-H (1.0 M in THF, 10.57 mL, 10.57 mmol) was added at 0 °C, and the reaction mixture was stirred for 3 h. Then, Methyl 6-(ethylcarbamoyl)nicotinate (1.0 g, 4.80 mmol) in THF (2 mL) was added to the reaction mixture and stirred at 0 °C for 10 min, followed by the addition of DIBAL-H (1.0 M in THF, 4.80 mL, 4.80 mmol) at 0 °Cand the reaction mixture was stirred at 25 °C for 15 min. The progress of the reaction was monitored by LCMS/TLC. After completion of the reaction as confirmed by LCMS/TLC, the reaction mixture was quenched with saturated NH_4Cl solution (30 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure to obtain the crude product. The crude compound was purified by Isolera using EtOAc/hexane (0-40%) to afford N-ethyl-5-formylpicolinamide **(ALD-63)** (170 mg, 0.754 mmol, 16% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 179.12. 1H-NMR (400 MHz, DMSO-d6): δ 10.20 (s, 1H), 9.13-9.13 (m, 1H), 9.02 (s, 1H), 8.45-8.42 (m, 1H), 8.22 (d, J = 8.00 Hz, 1H), 3.33 (s, 2H), 1.15 (t, J = 7.20 Hz, 3H).

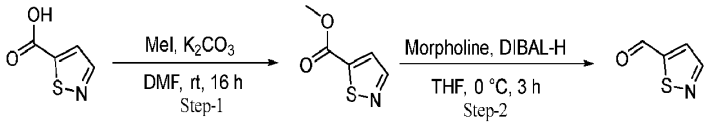
Example 155: Synthesis of 3-(4-formyl-1H-pyrazol-1-yl)benzonitrile (ALD-64)



To a stirred solution of $POCl_3$ (3.05 mL, 32.8 mmol) in DMF (30 mL) was stirred 10 mins at 0 °C. Then, a solution of 5-chloropyrazolo[1,5-a]pyridine (1.0 g, 6.55 mmol) in DMF was added to the reaction mixture at 0 °C. The resulting reaction mixture was stirred for 1 h. The reaction mixture was quenched with ice cold water (100 mL), then extracted with EtOAc (2 x 50 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to afford 5-chloropyrazolo[1,5-a]pyridine-3-carbaldehyde (301 mg, 1.610 mmol, 25% yield). LCMS: m/z MM-

ES+APCI, Positive $[M+H, M+2+H]^+$ 181.1, 183.1; ^{1}H-NMR (400 MHz, CDCl3): δ 10.04 (s, 1H), 8.51 (dd, J = 0.40, 7.40 Hz, 1H), 8.41 (s, 1H), 8.35 (d, J = 2.00 Hz, 1H), 7.07 (dd, J = 2.40, 7.20 Hz, 1H).

Example 156: Synthesis of isothiazole-5-carbaldehyde (ALD-65)



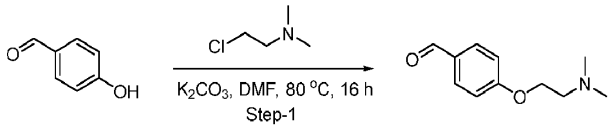
Step 1: Synthesis of methyl isothiazole-5-carboxylate

To a stirred solution of isothiazole-5-carboxylic acid (100 mg, 0.774 mmol) in DMF (2 mL) was added potassium carbonate (214 mg, 1.549 mmol) at RT. After that, methyl iodide (0.058 mL, 0.929 mmol) was added at 25 °C and stirred the reaction mixture for 16 h. The reaction was monitored by LCMS. After completion of reaction as confirmed by LCMS, the reaction mixture was quenched with water (10 mL), extracted with EtOAc (40 mL X 2), combine organic layer dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get crude compound methyl isothiazole-5-carboxylate (100 mg, 0.49 mmol, 63% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 144.2, 1H-NMR (400 MHz, DMSO-d6): δ 8.75 (d, J = 1.60 Hz, 1H), 7.97 (dd, J = 5.20 Hz, 1H), 3.90 (s, 3H).

Step 2: Synthesis of isothiazole-5-carbaldehyde (ALD-65)

To a stirred solution of Morpholine (140 mg, 1.607 mmol) in THF (2 mL) was added DIBAL-H (1.0M in THF) (1.537 mL, 1.537 mmol) at 0 °C and stirred for 3 h. After that methyl isothiazole-5-carboxylate (100 mg, 0.699 mmol) in THF (2 mL) was added to the above reaction mixture and stirred at 0 °C for 10 min, followed by DIBAL-H (1.0M in THF) (1.467 mL, 1.467 mmol) was added at same temperature. After completion of the reaction as confirmed by TLC, the rection mass quenched with 1N HCl in water and extracted with EtOAc (2 x 20 mL). The combined organic layer dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get isothiazole-5-carbaldehyde **(ALD-65)** (50 mg, 0.442 mmol, 63% yield). LCMS: Not recorded, ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.17 (s, 1H), 8.84 (dd, J = 2.00 Hz, 1H), 8.15 (dd, J = 2.00 Hz, 1H).

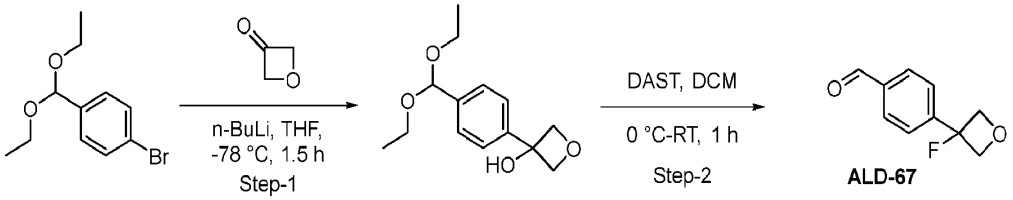
Example 157: Synthesis of 4-(2-(dimethylamino)ethoxy)benzaldehyde (ALD-66)



To a stirred solution of 4-hydroxybenzaldehyde (1 g, 8.19 mmol) in DMF (8 mL), 2-(dimethylamino)ethyl chloride hydrochloride (1.057 g, 9.83 mmol) and K_2CO_3 (2.263 g, 16.38 mmol) were added at 25 °C under a nitrogen atmosphere. The reaction mixture was then stirred at 80 °C for 16 h. After completion of the reaction as confirmed by LCMS, the reaction mixture was diluted with water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (25

mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the crude product. The crude compound was purified by Isolera using EtOAc/hexane (0-50%) to afford 4-(2-(dimethylamino)ethoxy)-benzaldehyde (200 mg, 0.963 mmol, 12% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 194.4. 1H-NMR (400 MHz, DMSO-d6): δ 9.87 (s, 1H), 7.96-7.85 (m, 2H), 7.16-7.12 (m, 2H), 4.17 (t, J = 5.60 Hz, 2H), 2.65 (t, J = 6.00 Hz, 2H), 2.22 (s, 6H).

Example 158: Synthesis of 4-(3-fluorooxetan-3-yl) benzaldehyde (ALD-67)



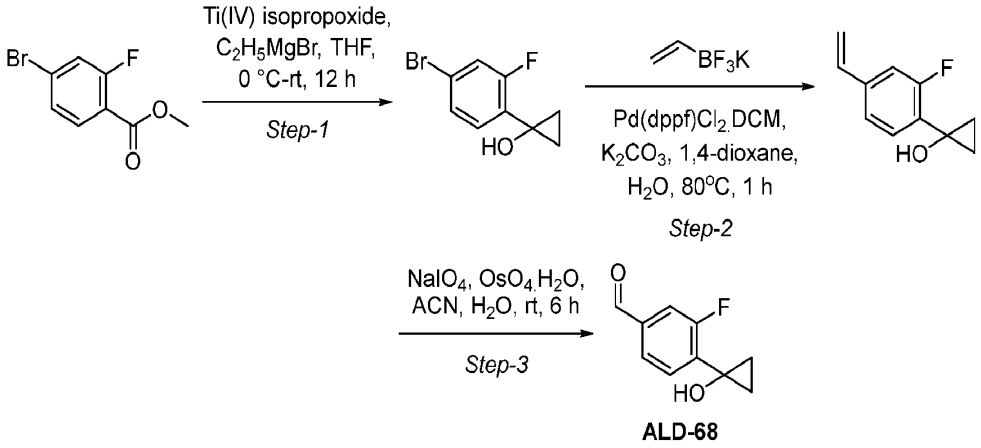
Step 1: **Synthesis of 3-(4-(diethoxymethyl)phenyl)oxetan-3-ol**

To a stirred solution of 1-bromo-4-(ethoxy(methoxy)methyl) benzene (1 g, 4.08 mmol) in THF (10 mL), n-BuLi (3.06 mL, 4.90 mmol) was added dropwise at -78 °C. The reaction was stirred at -78 °C for 20 min, after which oxetan-3-one (0.294 g, 4.08 mmol) was added at the -78 °C, and stirred for 1 h. After completion, of the reaction as confirmed by TLC, the reaction mixture was quenched with water (100 mL), and the product was extracted with EtOAc (2 x 150 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield a gummy crude product. This crude product was purified by normal phase column chromatography using 100-200 mesh silica gel, eluting with 11% EtOAc in hexane. The pure fractions were concentrated under reduced pressure to afford 3-(4-(diethoxymethyl)phenyl)oxetan-3-ol (400 mg, 1.585 mmol, 39% yield). 1H-NMR (400 MHz, DMSO-d6): δ 7.60 (d, J = 8.40 Hz, 2H), 7.42 (d, J = 8.00 Hz, 2H), 6.34 (s, 1H), 5.76 (s, 1H), 4.77 (d, J = 6.40 Hz, 2H), 4.68 (d, J = 6.40 Hz, 2H), 3.54-3.50 (m, 4H), 1.15 (s, 6H).

Step 2: Synthesis of 4-(3-fluorooxetan-3-yl) benzaldehyde

To stirred solution of 3-(4-(diethoxymethyl)phenyl)oxetan-3-ol (100 mg, 0.396 mmol) in DCM (3 mL) was added DAST (96 mg, 0.595 mmol) at 0 °Cand the reaction mixture was stirred at rt for 30 min. The Progress of reaction monitored by TLC. After completion of reaction of the reaction as confirmed by TLC, the reaction mass was quenched with $NaHCO_3$ solution (10 mL) and the compound was extracted by DCM (2 x 20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford gummy crude. The crude was purified by normal phase column chromatography using (100-200 silica mesh) eluting with 09% of ethyl in hexane as an eluent. Pure fractions were concentrated under reduced pressure to afford 4-(3-fluorooxetan-3-yl)benzaldehyde (35 mg, 0.194 mmol, 49% yield). 1H-NMR (400 MHz, DMSO-d6): δ 10.06 (s, 1H), 8.03 (d, J = 7.60 Hz, 2H), 7.81 (d, J = 8.00 Hz, 2H), 5.00-4.96 (m, 4H).

Example 159: Synthesis of 3-fluoro-4-(1-hydroxycyclopropyl)benzaldehyde (ALD-68)



ALD-68

Step 1: Synthesis of 1-(4-bromo-2-fluorophenyl)cyclopropan-1-ol

To a stirred solution of methyl 4-bromo-2-fluorobenzoate (5 g, 21.46 mmol) in THF (20 mL) under nitrogen at 25 °C, titanium(IV) isopropoxide (11.43 mL, 38.6 mmol) was added, followed by the dropwise addition of ethyl magnesium bromide (37.5 mL, 75 mmol) at 0 °C. The resulting reaction mixture was heated at 25 °C for 2 h. The progress of the reaction was monitored by LCMS/TLC. After completion of the reaction as confirmed by LCMS/TLC, the reaction was quenched with 1.5 N HCl (100 mL) and diluted with EtOAc (500 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure to obtain the crude compound. The crude compound was purified by flash column chromatography using Biotage Isolera (silica gel 100-200 mesh) and a linear gradient of 0-20% EtOAc in hexane as eluents to afford 1-(4-bromo-2-fluorophenyl)cyclopropan-1-ol (2.8 g, 8.12 mmol, 38% yield). ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.47-7.42 (m, 2H), 7.39-7.32 (m, 1H), 6.02 (s, 1H), 1.18-1.10 (m, 4H).

Step 2: Synthesis of 1-(2-fluoro-4-vinylphenyl)cyclopropan-1-ol

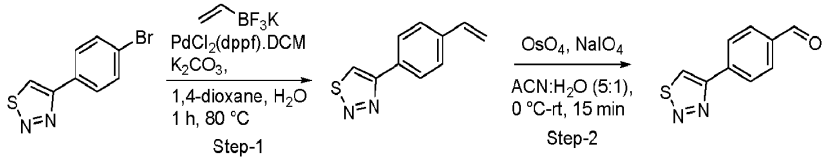
To a stirred solution of trifluoro(vinyl)-l4-borane, potassium salt (417 mg, 3.12 mmol), 1-(4-bromo-2-fluorophenyl)cyclopropan-1-ol (400 mg, 1.73 mmol), potassium salt (360 mg, 2.69 mmol) and K_2CO_3 (718 mg, 5.19 mmol) in 1,4-dDioxane (9 mL) and water (1 mL) was purged with N_2 at room temperature over 10 min. To this resulting mixture $PdCl_2$(dppf)-CH_2Cl_2adduct (141 mg, 0.173 mmol) was added in one lot and the reaction mixture was again sparged with N_2 for 10 min. The resulting reaction mixture was heated at 80°C for 16 h. The progress of the reaction was monitored by LCMS/TLC. After completion of the reaction as confirmed by LCMS/TLC, the reaction mixture was filtered through a pad of celite and washed with EtOAc (10 mL), the filtrate was concentrated under reduced pressure to get crude. The crude compound was purified by silica gel flash column chromatography, eluting with 0-20%

EtOAc in hexane to afford 1-(2-fluoro-4-vinylphenyl)-cyclopropan-1-ol (400 mg, 1.84 mmol, 106% yield). ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.49-7.44 (m, 1H), 7.43-7.40 (m, 1H), 7.39-7.32 (m, 1H), 6.74-6.67 (m, 1H), 6.02 (s, 1H), 5.91 (d, J = 10.00 Hz, 2H), 1.20-1.14 (m, 4H).

Step 3: Synthesis of 3-fluoro-4-(1-hydroxycyclopropyl) benzaldehyde (ALD-68)

To a stirred solution of 1-(2-fluoro-4-vinylphenyl) cyclopropan-1-ol (250 mg, 1.40 mmol) ACN (2.5 mL) and Water (0.25 mL) were added sodium iodide (50 mg, 0.33 mmol) at 25 °C. After 10 min osmium tetroxide 4% in water (0.07 mL, 0.223 mmol) was added at 0°C. The resulting reaction mixture was stirred at 25 °C for 6 h. The progress of the reaction was monitored by LCMS. After completion of the reaction as confirmed by LCMS, the reaction was quenched with water (10 mL) and diluted with DCM (50 mL). The layers were separated, and the aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure to get crude compound. The crude compound was purified by flash column chromatography using Biotag isolera (Neutral Alumina mesh) and a linear gradient of 0-30% EtOAc in hexane as eluents to afford 3-fluoro-4-(1-hydroxycyclopropyl)benzaldehyde (**ALD-68**) (37 mg, 0.168 mmol, 12% yield). ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.97 (d, J = 1.60 Hz, 1H), 7.81-7.73 (m, 2H), 7.62 (dd, J = 1.20, 11.40 Hz, 1H), 6.21 (s, 1H), 1.20-1.12 (m, 4H).

Example 160: Synthesis of 4-(1,2,3-thiadiazol-4-yl) benzaldehyde (ALD-69)



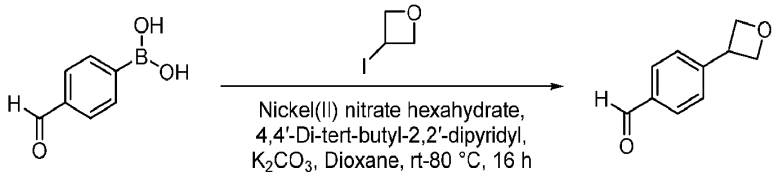
Step 1: Synthesis of 4-(4-vinylphenyl)-1,2,3-thiadiazole

To a stirred solution of 4-(4-bromophenyl)-1,2,3-thiadiazole (250 mg, 1.037 mmol) in dioxane (10 mL) and water (1 mL), potassium vinyl trifluoroborate (126 mg, 0.943 mmol) and K_2CO_3 (130 mg, 0.943 mmol) were added at room temperature. The reaction mixture was sparged with nitrogen for 10 minutes, followed by the addition of $PdCl_2(dppf)\cdot CH_2Cl_2$ adduct (77 mg, 0.094 mmol) at room temperature. The mixture was then irradiated under microwave conditions at 80°C for 1 h. The progress of the reaction was monitored by TLC and LCMS. Upon completion of the starting material, the reaction mixture was quenched with water, extracted with EtOAc (2 × 50 mL), and dried over anhydrous Na_2SO_4. The organic layer was filtered and concentrated under reduced pressure to yield the crude product. Purification by combi flash chromatography on silica gel (230-400 mesh) using 5% EtOAc/hexane afforded 4-(4-vinylphenyl)-1,2,3-thiadiazole (150 mg, 0.576 mmol, 61% yield). LCMS: ES+APCI, Positive $[M+H]^+$ 189. ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.70 (s, 1H), 8.15-7.78 (m, 2H), 7.68 (d, J = 8.00 Hz, 2H), 6.86-6.81 (m, 1H), 5.99-5.94 (m, 1H), 5.38-5.35 (m, 1H).

Step 2: **Synthesis of 4-(1,2,3-thiadiazol-4-yl) benzaldehyde (ALD-69)**

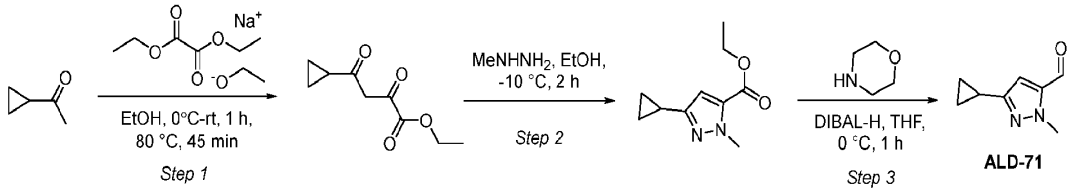
To a stirred solution of 4-(4-vinylphenyl)-1,2,3-thiadiazole (150 mg, 0.797 mmol) in water (0.8 mL) and acetonitrile (3 mL), sodium periodate (168 mg, 0.785 mmol) and osmium tetroxide (0.020 mL, 0.080 mmol) were added at 0°C. The reaction mixture was then stirred at room temperature for 15 minutes. Upon completion, as confirmed by TLC and LCMS, the reaction mixture was quenched with hypo solution and extracted with EtOAc (2 × 50 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated to yield the crude product. Purification by combi flash chromatography over neutral alumina, eluting with 5% EtOAc/hexane, afforded 4-(1,2,3-thiadiazol-4-yl) benzaldehyde (38 mg, 0.200 mmol, 25% yield). LCMS: ES+APCI, Positive $[M+H]^+$ Not ionized; ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.10 (s, 1H), 9.86 (s, 1H), 8.40 (d, J = 8.40 Hz, 2H), 8.10 (d, J = 2.00 Hz, 2H).

Example 161: Synthesis of 4-(oxetan-3-yl) benzaldehyde (ALD-70)



A stirred solution of (4-formylphenyl) boronic acid (0.4 g, 2.67 mmol), 3-iodooxetane (0.98 g, 5.34 mmol), and K_2CO_3 (1.11 g, 8.00 mmol) in 1,4-dioxane (1 mL) was degassed with nitrogen for 15 minutes. Nickel (II) nitrate hexahydrate (0.063 g, 0.27 mmol) and 4,4′-di-tert-butyl-2,2′-dipyridyl (0.072 g, 0.27 mmol) were then added at room temperature and the reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was concentrated under reduced pressure and the crude compound was purified by column chromatography, eluting with 60-75% EtOAc in hexane. The pure fractions were concentrated to afford 4-(oxetan-3-yl) benzaldehyde (**ALD-70**, 0.4 g, 1.97 mmol, 74% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 163.3. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.01 (s, 1H), 7.93 (dd, J = 8.40 Hz, 2H), 7.64 (dd, J = 8.00 Hz, 2H), 4.98 (d, J = 6.00 Hz, 2H), 4.41 (d, J = 0.80 Hz, 2H), 4.35-4.33 (m, 1H).

Example 162: Synthesis of cyclopropyl-1-methyl-1H-pyrazole-5-carbaldehyde (ALD-71)



Step 1: **Synthesis of (ethyl 4-cyclopropyl-2,4-dioxobutanoate)**

To a stirred solution of sodium ethoxide (0.809 g, 11.89 mmol) in ethanol (20 mL), 1-cyclopropylethan-1-one (1.0 g, 11.89 mmol) and diethyl oxalate (1.737 g, 11.89 mmol) were added dropwise at 0 °C. The reaction mixture was then stirred at 0 °C to room temperature for 1 h. Subsequently, the reaction mixture was heated to 80 °C and stirred for 45 minutes. The progress of the reaction was monitored by LCMS. Upon completion, the reaction mixture was cooled to room temperature, and the solvent was distilled off. The residue was neutralized with 2N H_2SO_4 solution and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield ethyl 4-cyclopropyl-2,4-dioxobutanoate (1.5 g, 7.17 mmol, 60% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 185.1.

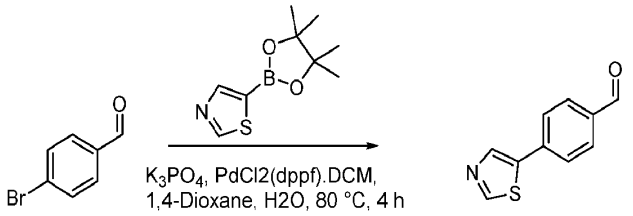
Step 2: Synthesis of ethyl 3-cyclopropyl-1-methyl-1H-pyrazole-5-carboxylate

To a stirred solution of ethyl 4-cyclopropyl-2,4-dioxobutanoate (1.5 g, 8.14 mmol) in ethanol (15 mL), methylhydrazine (0.609 mL, 9.77 mmol) was added at -10 °C. The reaction mixture was then stirred at the same temperature for 2 h. The progress of the reaction was monitored using TLC and LCMS. Upon completion, the reaction mixture was distilled, diluted with water, and the compound was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product. The crude product was purified by combi-flash chromatography (eluent: 0-20% EtOAc in n-hexane). The desired fractions were concentrated under reduced pressure to yield ethyl 3-cyclopropyl-1-methyl-1H-pyrazole-5-carboxylate (0.3 g, 1.455 mmol, 18% yield), which solidified to a solid. LCMS: m/z MM-ES+APCI, Positive $[M-H]^+$ 195.1.

Step 3: Synthesis of cyclopropyl-1-methyl-1H-pyrazole-5-carbaldehyde (ALD-71)

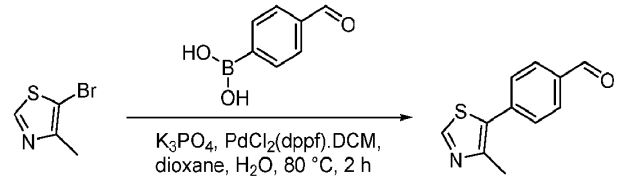
To a stirred solution of morpholine (0.217 g, 2.487 mmol) in THF (2 mL), DIBAL-H (1.974 mL, 2.368 mmol) was added at 0 °C and the reaction mixture was stirred at the same temperature for 3 h. Subsequently, ethyl 3-cyclopropyl-1-methyl-1H-pyrazole-5-carboxylate (0.23 g, 1.184 mmol) in THF (2.000 mL) was added and stirred for 5 minutes, followed by the addition of DIBAL-H (1.085 mL, 1.303 mmol) at 0 °C. The reaction mixture was then stirred at 0 °C for 1 h. The progress of the reaction was monitored by TLC and LCMS. Upon completion, the reaction was quenched with saturated ammonium chloride solution and the compound was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product. The crude product was purified by combi-flash chromatography (eluent: 5-10% EtOAc in n-hexane). The desired fractions were concentrated under reduced pressure to yield 3-cyclopropyl-1-methyl-1H-pyrazole-5-carbaldehyde (0.11 g, 0.635 mmol, 54% yield). LCMS: m/z MM-ES+APCI, Positive $[M-H]^+$ 151.0. ^{1}H-NMR (400 MHz, CDCL3): δ 9.78 (s, 1H), 6.49 (s, 1H), 4.11 (s, 3H), 1.99-1.93 (m,1H), 0.99-0.97(m, 2H), 0.96-0.95 (m, 2H).

Example 163: Synthesis of 4-(thiazol-5-yl)benzaldehyde (ALD-72)



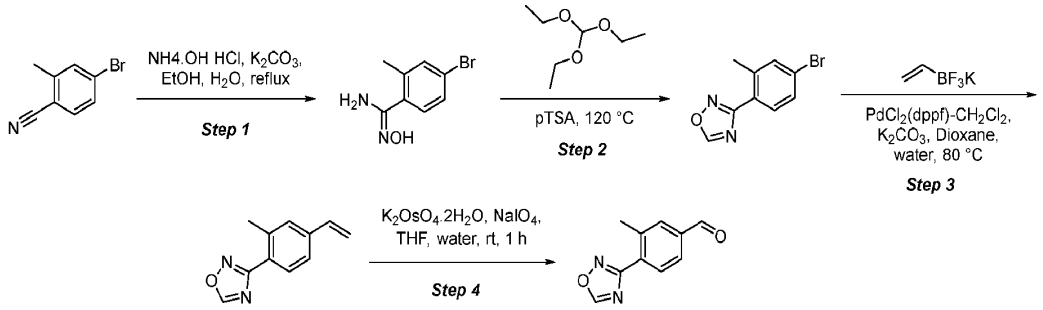
To a stirred solution of 4-bromobenzaldehyde (0.2 g, 1.081 mmol) in dioxane (2 mL) and water (0.4 mL) was added tripotassium phosphate (0.459 g, 2.162 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole (0.274 g, 1.297 mmol) at room temperature. The reaction mixture was sparged with nitrogen for 5 minutes. $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.044 g, 0.054 mmol) was then added, and the reaction mixture was stirred at 80 °C for 4 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 EtOAc. The filtrate was concentrated under reduced pressure to obtain a crude product. The crude compound was purified by combi-flash chromatography, eluting with 5-20% EtOAc in n-hexane. The desired fractions were concentrated under reduced pressure to yield 4-(thiazol-5-yl)benzaldehyde (0.18 g, 0.920 mmol, 85% yield). LCMS: m/z $^+$ 190.1; 1 H-NMR (DMSO): 1H-NMR (400 MHz, DMSO-d6): δ 10.03 (s, 1H), 9.21 (s, 1H), 8.53 (s, 1H), 8.00-7.94 (m, 4H).

Example 164: Synthesis of 4-(4-methylthiazol-5-yl) benzaldehyde (ALD-73)



To a stirred solution of 5-bromo-4-methylthiazole (300 mg, 1.685 mmol), (4-formylphenyl)boronic acid (278 mg, 1.853 mmol), and potassium phosphate, tribasic (894 mg, 4.21 mmol) in 1,4-dioxane (5 mL) and water (0.500 mL), degassed with N_2 for 5 minutes, $PdCl_2(dppf)\cdot DCM$ adduct (138 mg, 0.168 mmol) was added and the reaction mixture was stirred at 80 °C for 2 h.. The reaction mixture was concentrated under reduced pressure to obtain a crude residue. The crude compound was purified by flash column chromatography using Biotage Isolera (silica gel cartridge 40 g) using 11% EtOAc in hexane as the eluent. The pure fractions were concentrated under reduced pressure to afford 4-(4-methylthiazol-5-yl) benzaldehyde (240 mg, 0.897 mmol, 53% yield). LCMS: m/z $[M+H]^+$ 204.0. 1H-NMR (400 MHz, DMSO-d6): δ 10.06 (s, 1H), 9.11 (s, 1H), 8.02-8.00 (m, 2H), 7.75 (d, J = 8.40 Hz, 2H), 2.53-2.50 (m, 3H).

Example 165: Synthesis of 3-methyl-4-(1,2,4-oxadiazol-3-yl) benzaldehyde (ALD-75)



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 EtOAc (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 reduced pressure to afford (E)-4-bromo-N'-hydroxy-2-methylbenzimidamide (3.5 g, 14.58 mmol, 57% yield). 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 EtOAc (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 silica gel flash column chromatography eluting with 5% EtOAc in hexane. The collected pure fractions were concentrated to yield 3-(4-bromo-2-methylphenyl)-1,2,4-oxadiazole (2.5 g, 9.83 mmol, quantitative yield). ^{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**

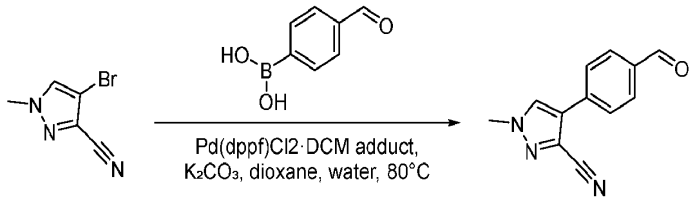
A stirred solution of 3-(4-bromo-2-methylphenyl)-1,2,4-oxadiazole (1.5 g, 6.27 mmol), potassium trifluoroborate (1.185 g, 9.41 mmol), K_2CO_3 (2.168 g, 15.69 mmol) in 1,4-dioxane (9.5 mL) and water (0.5 mL) was degassed with N_2 at room temperature. $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.512 g, 0.627 mmol) was added and the reaction mixture was stirred at 85 °C for 1 h in a microwave reactor. The reaction mixture was concentrated under reduced pressure to obtain the crude product. The crude compound was extracted with EtOAc (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 silica gel flash column chromatography eluting with 5% EtOAc in hexane. The collected pure fractions were concentrated under reduced pressure to yield 3-(2-methyl-4-vinylphenyl)-1,2,4-oxadiazole (0.5 g, 2.28 mmol, 36% yield). 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-75)**

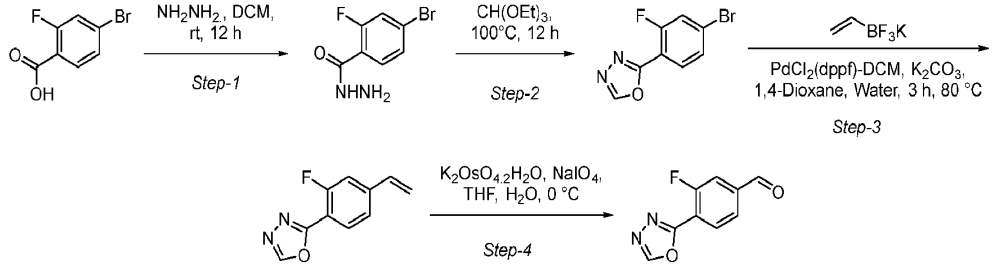
To a stirred solution of 3-(2-methyl-4-vinylphenyl)-1,2,4-oxadiazole (870 mg, 4.67 mmol) in THF (20 mL) and water (4.00 mL) was added sodium periodate (1499 mg, 7.01 mmol) at 25 °C. Potassium osmate dihydrate (43.0 mg, 0.12 mmol) was then added to the reaction mixture, which was stirred at 25 °C for 1 h. The reaction mixture was directly concentrated under reduced pressure to obtain the crude product. The crude compound was purified by silica gel flash column chromatography eluting with 5% EtOAc in hexane. The collected pure fractions were concentrated under reduced pressure to yield 3-methyl-4-(1,2,4-oxadiazol-3-yl) benzaldehyde (**ALD-75**, 365 mg, 1.75 mmol, 37% yield). 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 166: Synthesis of 4-(4-formylphenyl)-1-methyl-1H-pyrazole-3-carbonitrile (ALD-75)



To a stirred solution of (4-formylphenyl)boronic acid (300 mg, 2.001 mmol) and 4-bromo-1-methyl-1H-pyrazole-3-carbonitrile (372 mg, 2.001 mmol) in 1,4-dioxane (3 mL) and water (0.333 mL), potassium carbonate (415 mg, 3.00 mmol) was added at room temperature. The reaction mixture was sparged with argon for 10 minutes, followed by the addition of Pd(dppf)Cl_2·DCM adduct (146 mg, 0.200 mmol) at room temperature. The reaction mixture was again sparged with argon for 10 minutes. The reaction mixture was then irradiated at 80 °C for 1.5 h. The progress of the reaction was confirmed by TLC. The reaction mixture was concentrated under reduced pressure to obtain the crude product. The crude compound was purified by Isolera using 100-200 mesh silica gel. The product eluted in EtOAc, and the pure fractions were collected and concentrated under reduced pressure to afford 4-(4-formylphenyl)-1-methyl-1H-pyrazole-3-carbonitrile (280 mg, 1.320 mmol, 66% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 212.0. ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.03 (s, 1H), 8.58 (s, 1H), 8.03 (d, J = 8.40 Hz, 2H), 7.88 (d, J = 8.40 Hz, 2H), 4.01 (s, 3H).

Example 167: Synthesis of 3-fluoro-4-(1,3,4-oxadiazol-2-yl) benzaldehyde (ALD-76)



Step 1: Synthesis of 4-bromo-2-fluorobenzohydrazide

To a stirred solution of 4-bromo-2-fluorobenzoic acid (2.0 g, 9.13 mmol) in DCM (20 mL) at 0 °C under a nitrogen atmosphere, HOBt (2.098 g, 13.7 mmol) and EDC·HCl (2.63 g, 13.7 mmol) were added and the reaction mixture was stirred at the same temperature for 10 minutes, then hydrazine hydrate (0.488 mL, 10.05 mmol) was added, and the reaction mixture was stirred at room temperature for 12 h. The progress of the reaction was monitored by TLC. Upon completion, as confirmed by TLC, the reaction mixture was poured into cooled water (100 mL), and the compound was extracted with EtOAc (2 × 300 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the crude compound. LCMS no ionization. ^{1}H-NMR (400 MHz, DMSO-d6): δ 13.71 (s, 1H), 7.97 (d, J = 8.40 Hz, 1H), 7.71 (d, J = 8.40 Hz, 1H), 7.58-7.46 (m, 2H), 7.43 (t, J = 8.00 Hz, 1H).

Step 2: Synthesis of 2-(4-bromo-2-fluorophenyl)-1,3,4-oxadiazole

To a stirred solution of 4-bromo-2-fluorobenzohydrazide (600 mg, 2.57 mmol) in triethoxymethane (382 mg, 2.57 mmol) at 0 °C, the reaction mixture was stirred at 100 °C for 12 h. Upon completion, the reaction mixture was concentrated under reduced pressure to obtain the crude product. The crude product was added to water (20 mL) and extracted with EtOAc (2 × 40 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to obtain a solid crude product. This was purified by flash column chromatography (silica gel, 100-200 mesh) using 100% EtOAc as the eluent. The pure fractions were evaporated and dried under high vacuum to afford 2-(4-bromo-2-fluorophenyl)-1,3,4-oxadiazole (200 mg, 0.823 mmol, 32% yield). LCMS: No ionization. ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.45 (s, 1H), 8.01 (t, J = 8.00 Hz, 1H), 7.92 (dd, J = 1.60, 10.40 Hz, 1H), 7.69 (dd, J = 1.60, 8.40 Hz, 1H).

Step 3: Synthesis of 2-(2-fluoro-4-vinylphenyl)-1,3,4-oxadiazole

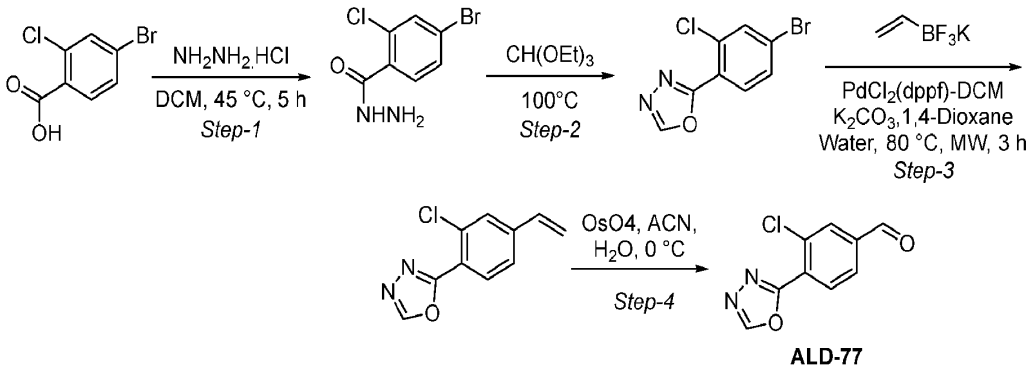
To a stirred solution of 2-(4-bromo-2-fluorophenyl)-1,3,4-oxadiazole (200 mg, 0.82 mmol) in 1,4-dioxane (3 mL), trifluoro(vinyl)-l4-borane, potassium salt (132 mg, 0.99 mmol) and K_2CO_3 (227 mg, 1.646 mmol) were added at 25 °C and degassed with N_2 for 10 minutes. After 10 minutes, $Pd(dppf)Cl_2$·DCM (67.2 mg, 0.082 mmol) was added, and the reaction mixture was stirred at 80 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to obtain the crude

product. The crude compound was added to water and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography eluting with 100% EtOAc in n-hexane. The collected pure fractions were concentrated under reduced pressure to yield 2-(2-fluoro-4-vinylphenyl)-1,3,4-oxadiazole (90 mg, 0.46 mmol, 55% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 191.0; ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.55 (d, J = 6.80 Hz, 1H), 8.07 (t, J = 8.00 Hz, 1H), 7.35-7.30 (m, 2H), 6.75 (dd, J = 10.80, 17.60 Hz, 1H), 5.93 (d, J = 17.20 Hz, 1H), 5.50 (d, J = 10.80 Hz, 1H).

Step 4: Synthesis of 3-fluoro-4-(1,3,4-oxadiazol-2-yl) benzaldehyde

To a stirred solution of 2-(2-fluoro-4-vinylphenyl)-1,3,4-oxadiazole (60 mg, 0.315 mmol) in THF (0.6 mL) and water (0.2 mL), potassium osmate dihydrate (2.91 mg, 7.89 µmol) was added at 0 °C. The resulting reaction mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to obtain the crude product. The crude compound was added to water and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography eluting with 100% EtOAc in n-hexane. The collected pure fractions were concentrated under reduced pressure to yield 3-fluoro-4-(1,3,4-oxadiazol-2-yl)benzaldehyde (35 mg, 0.159 mmol, 50% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 192.9. ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.10 (d, J = 1.60 Hz, 1H), 8.63 (s, 1H), 8.35 (dd, J = 6.40, 7.80 Hz, 1H), 7.87 (dd, J = 1.60, 8.00 Hz, 1H), 7.81 (dd, J = 1.20, 10.00 Hz, 1H).

Example 168: Synthesis of 3-chloro-4-(1,3,4-oxadiazol-2-yl) benzaldehyde (ALD-77)



ALD-77

Step 1: Synthesis of 4-bromo-2-chlorobenzohydrazide

To a stirred solution of 4-bromo-2-chlorobenzoic acid (0.5 g, 2.123 mmol) in dichloromethane (10 mL) at 0 °C under a nitrogen atmosphere, EDC·HCl (0.611 g, 3.19 mmol) and HOBt (0.488 g, 3.19 mmol) were added and the reaction mixture was stirred at room temperature for 5 minutes, then hydrazine hydrate (0.117 g, 2.336 mmol) was added, and the reaction mixture was stirred at room temperature for 12 h. Upon completion, the reaction mixture was diluted with water (20 mL) and extracted with DCM (2 × 40 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried over anhydrous

Na_2SO_4 and evaporated under reduced pressure to obtain the solid crude product. This was purified by flash column chromatography (silica gel, 100-200 mesh) using 100% EtOAc as the eluent. The pure fractions were evaporated and dried under high vacuum to afford 4-bromo-2-chlorobenzohydrazide (0.5 g, 2.004 mmol, 94% yield). LCMS: no mass ionization. ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.95 (d, J = 8.40 Hz, 1H), 7.66 (d, J = 2.00 Hz, 1H), 7.50 (t, J = 7.60 Hz, 1H), 7.42 (t, J = 0.80 Hz, 1H), 4.48 (s, 2H),

Step 2: Synthesis of 2-(4-bromo-2-chlorophenyl)-1,3,4-oxadiazole

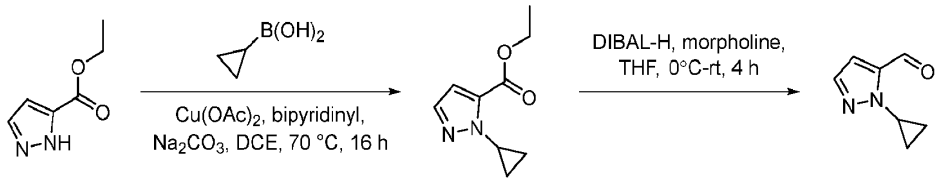
Solution of 4-bromo-2-chlorobenzohydrazide (800 mg, 3.21 mmol) in triethoxymethane (475 mg, 3.21 mmol) was stirred at 100 °C for 12 h. After completion of starting material, as monitored by TLC/LCMS. After completion of reaction, reaction mixture was concentrated under reduced pressure to get crude. Crude was quenched with water (50 mL) diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to get crude compound. crude which was purified by flash column chromatography (silica-gel, 100-200 mesh size) using (100% EtOAc as an eluent). The pure fractions were evaporated and dried under high vacuum to afford 2-(4-bromo-2-chlorophenyl)-1,3,4-oxadiazole (450 mg, 1.676 mmol, 52% yield). LCMS: m/z MM-ES+APCI, Positive $[M+2]^+$ 258.8, 260.8. ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.48 (s, 1H), 8.07 (s, 1H), 7.95 (d, J = 8.40 Hz, 1H), 7.82 (d, J = 2.00 Hz, 1H),

Step 3: Synthesis of 2-(2-chloro-4-vinylphenyl)-1,3,4-oxadiazole

To a stirred solution of 2-(4-bromo-2-chlorophenyl)-1,3,4-oxadiazole in 1,4-dioxane (3 mL), trifluoro(vinyl)-l4-borane, potassium salt (49.6 mg, 0.370 mmol) and K_2CO_3 (85 mg, 0.617 mmol) were added at 25 °C and degassed with N_2 for 10 minutes. After 10 minutes, $Pd(dppf)Cl_2$·DCM (25.2 mg, 0.031 mmol) was added, and the reaction mixture was stirred at 80 °C for 2 h. The progress of the reaction was monitored by LCMS. Upon completion, the reaction mixture was concentrated under reduced pressure to obtain the crude product. The crude product was quenched with water and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by silica gel flash column chromatography eluting with 100% EtOAc in n-hexane. The collected pure fractions were concentrated under reduced pressure to yield 2-(2-chloro-4-vinylphenyl)-1,3,4-oxadiazole (60 mg, 0.199 mmol, 65% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ 205.0, 207.0. ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.57 (s, 1H), 8.01 (d, J = 8.40 Hz, 1H), 7.60 (s, 1H), 7.46 (d, J = 1.60 Hz, 1H), 6.77-6.70 (m, 1H), 5.93 (d, J = 17.60 Hz, 1H), 5.49 (d, J = 11.20 Hz, 1H),

Step 4: Synthesis of 3-chloro-4-(1,3,4-oxadiazol-2-yl) benzaldehyde

Example 169: Synthesis of 1-cyclopropyl-1H-pyrazole-5-carbaldehyde (ALD-78)



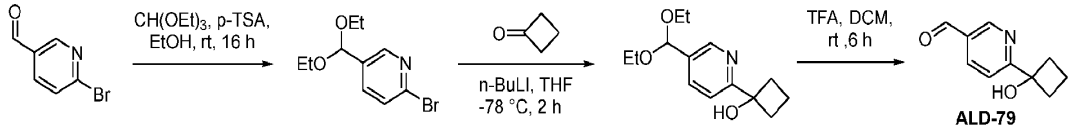
Step 1: Ethyl 1-cyclopropyl-1H-pyrazole-5-carboxylate

To a stirred solution of 1H-pyrazole-5-carboxylate (500 mg, 3.57 mmol) and cyclopropylboronic acid (613 mg, 7.14 mmol) in 1,2-dichloroethane (10 mL) were added bipyridinyl (111 mg, 0.714 mmol) and sodium carbonate (756 mg, 7.14 mmol) followed by copper(II) acetate monohydrate (142 mg, 0.714 mmol) at rt. The reaction mixture was stirred at 70 °C for 16 h. Water (50 mL) was added to the cooled reaction mixture, and the mixture was extracted with DCM (2 x 50 mL). The combined organic layers were concentrated under reduced pressure and purified by silica gel flash column chromatography, eluting with EtOAc in hexane (10%) to afford ethyl 1-cyclopropyl-1H-pyrazole-5-carboxylate (180 mg, 0.978 mmol, 27% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 181.3. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.50 (d, J = 1.60 Hz, 1H), 6.87 (d, J = 2.00 Hz, 1H), 4.35-4.28 (m, 3H), 1.32 (t, J = 7.20 Hz, 3H), 1.15-1.08 (m, 2H), 1.04-0.99 (m, 2H),

Step 2: 1-cyclopropyl-1H-pyrazole-5-carbaldehyde (ALD-78)

To a stirred solution of morpholine (0.383 mL, 4.44 mmol) in THF (5 mL), DIBAL-H (3.70 mL, 4.44 mmol) was added at 0 °C and stirred for 2 h. Then, ethyl 1-cyclopropyl-1H-pyrazole-5-carboxylate (160 mg, 0.888 mmol) in THF (2 mL) was added to the reaction mixture at 0 °C and stirred for 30 minutes. DIBAL-H (1.480 mL, 1.776 mmol) was added again at 0 °C and stirred for 1 h. The progress of the reaction was monitored by TLC and UPLC. Upon completion, as confirmed by TLC and UPLC, the reaction mixture was quenched with 1.5 N HCl (5 mL) and extracted with water (20 mL) and EtOAc (2 × 25 mL). The organic layer was concentrated under reduced pressure to obtain the crude product. The crude compound was purified by silica gel flash column chromatography eluting with 10% EtOAc in hexane to yield 1-cyclopropyl-1H-pyrazole-5-carbaldehyde (100 mg, 0.625 mmol, 70% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 137.1. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.05 (s, 1H), 7.56 (d, J = 2.00 Hz, 1H), 7.04 (d, J = 2.00 Hz, 1H), 4.25-4.22 (m, 1H), 1.18-1.16 (m, 2H), 1.08-1.06 (m, 2H).

Example 170: Synthesis of 6-(1-hydroxycyclobutyl)nicotinaldehyde (ALD-79)



Step 1: Synthesis of 2-bromo-5-(diethoxymethyl)pyridine

To a stirred solution of 6-bromonicotinaldehyde (2.5 g, 13.44 mmol) in ethanol (10 mL), p-toluene sulfonic acid monohydrate (0.256 g, 1.344 mmol) and triethyl orthoformate (5.98 g, 40.3 mmol)

were added at room temperature. The reaction mixture was then stirred at 80 °C for 2 h. Upon completion, the reaction mixture was quenched with water (100 mL), and the compound was extracted with EtOAc (2 × 300 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure to afford the crude compound. The crude product was purified by column chromatography using neutral alumina, eluted with 30% EtOAc/hexane. The collected pure fractions were evaporated under reduced pressure to afford 2-bromo-5-(diethoxymethyl)pyridine (2.45 g, 7.75 mmol, 58% yield). ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.47 (s, 1H), 7.68 (d, J = 2.40 Hz, 1H), 7.50 (d, J = 8.00 Hz, 1H), 5.55 (s, 1H), 3.65-3.60 (m, 4H), 1.28-1.26 (m, 6H).

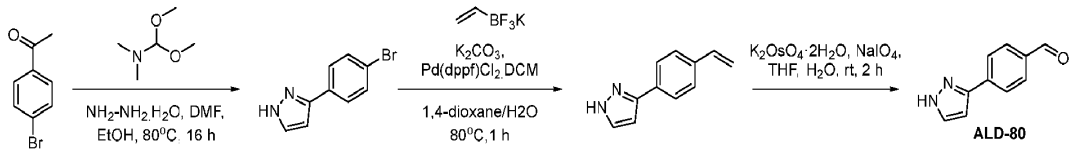
Step 2: Synthesis of 1-(5-(diethoxymethyl)pyridin-2-yl)cyclobutan-1-ol

To a stirred solution of 2-bromo-5-(diethoxymethyl)pyridine (1.3 g, 5.00 mmol) in toluene (4 mL), n-butyllithium (1.999 mL, 5.00 mmol) was added at -78 °C and stirred for 1 h. Cyclobutanone (0.350 g, 5.00 mmol) was then added at -78 °Cand the reaction mixture was stirred for 1 h at -78 °C. Upon completion, the reaction was quenched with water (50 mL) and the compound was extracted with DCM (2 × 250 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure to afford the crude compound. The crude product was purified by column chromatography using neutral alumina, eluted with 30% EtOAc/hexane, and evaporated to yield 1-(5-(diethoxymethyl)pyridin-2-yl)cyclobutan-1-ol (950 mg, 3.55 mmol, 71% yield). LCMS: m/z = (M+1) 252.5. ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.54 (s, 1H), 7.74 (d, J = 0.40 Hz, 1H), 7.57 (d, J = 0.80 Hz, 1H), 5.73 (s, 1H), 5.57 (s, 1H), 3.57-3.53 (m, 4H), 2.50 (m, 1H), 2.23-2.00 (m, 2H), 2.19-1.91 (m, 2H), 1.18-1.15 (m, 6H).

Step 3: Synthesis of 6-(1-hydroxycyclobutyl)nicotinaldehyde (ALD-79)

To a stirred solution of 1-(5-(diethoxymethyl)pyridin-2-yl)cyclobutan-1-ol (100 mg, 0.37 mmol) in DCM (5 mL), trifluoroacetic acid (0.566 mL, 7.40 mmol) was added at 0 °C and the reaction mixture was stirred at room temperature for 6 h. Upon completion, the reaction mixture was cooled to 0 °C and quenched with sodium bicarbonate solution (10 mL). The mixture was extracted with DCM (2 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure to obtain 6-(1-hydroxycyclobutyl)nicotinaldehyde (60 mg, 0.21 mmol, 57% yield). ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.10 (s, 1H), 9.07 (s, 1H), 8.21 (d, J = 2.00 Hz, 1H), 7.78 (d, J = 8.40 Hz, 1H), 6.07 (s, 1H), 2.52-2.51 (m, 2H), 2.30-2.26 (m, 2H), 1.97-1.94 (m, 2H).

Example 171: Synthesis of 4-(1H-pyrazol-3-yl) benzaldehyde (ALD-80)



Step 1: 3-(4-bromophenyl)-1H-pyrazole

To a stirred solution of 1-(4-bromophenyl)ethan-1-one (1 g, 5.02 mmol) in DMF (5 mL) under nitrogen at 25 °C, 1,1-dimethoxy-N,N-dimethylmethanamine (0.801 mL, 6.03 mmol) was added. The resulting reaction mixture was heated at 80 °C for 16 h. The reaction was quenched with water (10 mL) and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to obtain the crude compound. The crude compound was dissolved in ethanol (5.0 mL) and stirred for 10 minutes. To this reaction mixture, hydrazine monohydrate (0.735 mL, 15.07 mmol) was added dropwise at 25 °C. The resulting reaction mixture was heated at 80 °C for 2 h. The reaction was quenched with ice-cold water (10 mL) and evaporated under reduced pressure to afford the crude compound, 3-(4-bromophenyl)-1H-pyrazole (1 g, 4.44 mmol, 88% yield). LCMS: m/z MM-ES+APCI, Positive $[M+2]^+$ 223.1, 225.1; ^{1}H-NMR (400 MHz, DMSO-d6): 1H-NMR (400 MHz, DMSO-d6): δ 12.96 (s, 1H), 7.78 (d, J = 8.80 Hz, 2H), 7.60-7.48 (m, 3H), 6.73 (d, J = 11.60 Hz, 1H).

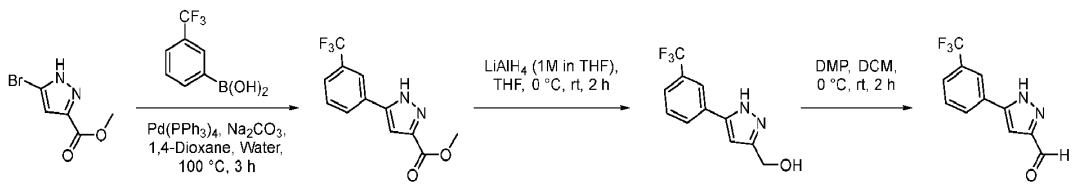
Step 2: 3-(4-vinylphenyl)-1H-pyrazole:

3-(4-Vinylphenyl)-1H-pyrazole was prepared following a procedure similar to **Example 168, ALD-77, Step 3.**

Step 3: 4-(1H-pyrazol-3-yl) benzaldehyde

To a stirred solution of 3-(4-vinylphenyl)-1H-pyrazole (150 mg, 0.881 mmol) in THF (5 mL) and water (1 mL), potassium osmate dihydrate (64.9 mg, 0.176 mmol) and sodium periodate (565 mg, 2.64 mmol) were added at 25 °C. The resulting reaction mixture was stirred at 25 °C for 2 h. The progress of the reaction was monitored by LCMS. The reaction was quenched with water (10 mL) and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to obtain the crude compound. The crude compound was purified by silica gel flash column chromatography eluting with 0-30% EtOAc in hexane to afford 4-(1H-pyrazol-3-yl) benzaldehyde (50 mg, 0.258 mmol, 29% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 172.8. ^{1}H-NMR (400 MHz, DMSO-d_6): 1H-NMR (400 MHz, DMSO-d6): δ 13.14 (s, 1H), 10.01 (s, 1H), 8.06 (d, J = 8.00 Hz, 2H), 7.99-7.94 (m, 2H), 6.93-6.88 (m, 1H), 5.44 (t, J = 8.00 Hz, 1H).

Example 172: Synthesis of 5-(3-(trifluoromethyl)phenyl)-1H-pyrazole-3-carbaldehyde (ALD-81)



Step 1: Synthesis of methyl 5-(3-(trifluoromethyl) phenyl)-1H-pyrazole-3-carboxylate

To a stirred solution of methyl 5-bromo-1H-pyrazole-3-carboxylate (2 g, 9.76 mmol) in 1,4-dioxane (18 mL) and water (2 mL) under nitrogen purging, (3-(trifluoromethyl) phenyl) boronic acid (2.223 g, 11.71 mmol) was added, followed by sodium carbonate (2.068 g, 19.51 mmol) at room temperature. After 2 minutes, $Pd(PPh_3)_4$ (1.127 g, 0.976 mmol) was added under nitrogen purging and the reaction mixture was stirred at 100 °C for 3 h. Upon completion, the reaction mixture was filtered through a Celite pad, washed, and the filtrate was concentrated to obtain the crude compound. The crude product was purified by flash column chromatography using SiO_2 (100-200 mesh) and 45-50% EtOAc in hexanes. The pure fractions were concentrated under reduced pressure to afford methyl 5-(3-(trifluoromethyl) phenyl)-1H-pyrazole-3-carboxylate (600 mg, 1.998 mmol, 21% yield). LCMS: m/z MM-ES+APCI, Positive $[M]^+$ 271.4; ^{1}H-NMR (400 MHz, DMSO-d6): δ 14.26 (s, 1H), 8.25-8.14 (m, 2H), 7.74-7.43 (m, 3H), 3.89 (s, 3H).

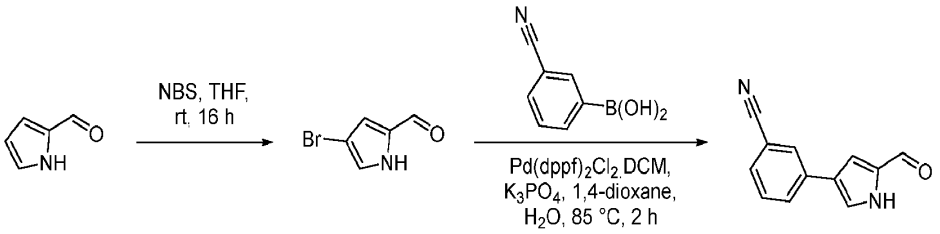
Step 2: Synthesis of (5-(3-(trifluoromethyl) phenyl)-1H-pyrazol-3-yl) methanol

To a stirred solution of methyl 5-(3-(trifluoromethyl) phenyl)-1H-pyrazole-3-carboxylate (1.5 g, 5.55 mmol) in THF (40 mL), $LiAlH_4$ (1M in THF, 16.7 mL, 16.7 mmol) was added at 0 °C and the reaction mixture was stirred under a nitrogen atmosphere at 25 °C for 2 h. Upon completion, the reaction mixture was quenched with NH_4Cl solution (20 mL) and stirred for 15 minutes. The mixture was then extracted with EtOAc (50 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure to afford (5-(3-(trifluoromethyl) phenyl)-1H-pyrazol-3-yl)methanol (1.62 g, 4.10 mmol, 74% yield). LCMS: m/z MM-ES+APCI, Positive $[M]^+$ 243.2; ^{1}H-NMR (400 MHz, DMSO-d6): δ 12.95 (s, 1H), 8.13-8.07 (m, 2H), 7.86-7.82 (m, 2H), 6.34 (s, 1H), 5.39 (s, 1H), 4.79 (s, 2H).

Step 3: 5-(3-(trifluoromethyl) phenyl)-1H-pyrazole-3-carbaldehyde

To a stirred solution of (5-(3-(trifluoromethyl) phenyl)-1H-pyrazol-3-yl) methanol (500 mg, 2.064 mmol) in DCM (8 mL) under a nitrogen atmosphere, Dess-Martin periodinane (1313 mg, 3.10 mmol) was added at 0 °C. The resulting reaction mixture was stirred at 25 °C for 2 h. Sodium bicarbonate solution was added and the mixture was extracted with DCM. The organic layer was separated and concentrated under reduced pressure to afford a crude residue. This crude product was triturated with MTBE and concentrated under reduced pressure to afford 5-(3-(trifluoromethyl) phenyl)-1H-pyrazole-3-carbaldehyde (46 mg, 0.134 mmol, 7% yield). LCMS: m/z MM-ES+APCI, Not ionized. ^{1}H-NMR (400 MHz, DMSO-d6): δ 12.57 (s, 1H), 9.75 (s, 1H), 8.99 (s, 1H), 7.87-7.81 (m, 1H), 7.69-7.65 (m, 1H), 7.50-7.44 (m, 1H), 6.76 (s, 1H).

Example 173: Synthesis of 3-(5-formyl-1H-pyrrol-3-yl)benzonitrile (ALD-82)



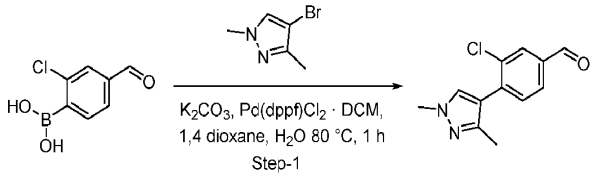
Step 1: 4-bromo-1H-pyrrole-2-carbaldehyde

To a stirred solution of 1H-pyrrole-2-carbaldehyde (1 g, 10.52 mmol) in THF (20 mL) at 0 °C, 1-bromopyrrolidine-2,5-dione (1.87 g, 10.52 mmol) was added as a single portion and the reaction mixture was stirred for 15 minutes at room temperature. Upon completion, the reaction mixture was concentrated under reduced pressure to obtain the crude product. The crude compound was added to water and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by silica gel flash column chromatography eluting with 5% EtOAc in n-hexane. The collected pure fractions were concentrated under reduced pressure to obtain 4-bromo-1H-pyrrole-2-carbaldehyde (1.5 g, 6.16 mmol, 59% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ 173.8, 175.8; ^{1}H-NMR (400 MHz, DMSO-d6): δ 12.59 (s, 1H), 9.48-9.45 (s, 1H), 7.38-7.22 (s, 1H), 7.08-6.99 (s, 1H).

Step 2: 3-(5-formyl-1H-pyrrol-3-yl) benzonitrile

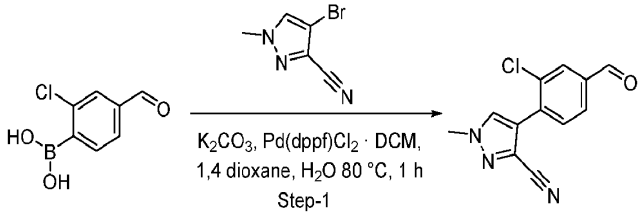
To a stirred solution of 4-bromo-1H-pyrrole-2-carbaldehyde (25 mg, 0.144 mmol) in 1,4-dioxane (1 mL) and water (0.1 mL), (3-cyanophenyl)boronic acid (25.3 mg, 0.172 mmol) and potassium phosphate, tribasic (76 mg, 0.359 mmol) were added at 25 °C. The reaction mixture was degassed with N_2 for 10 minutes, followed by the addition of methanesulfonato-(diadamantyl-n-butylphosphino)-2'-amino-1,1'-biphenyl-2-yl)palladium(II) dichloromethane adduct (5.23 mg, 7.18 µmol). The reaction mixture was further degassed with N_2 for 5 minutes. The resulting reaction mixture was allowed to stir at 100 °C for 16 h. The progress of the reaction was monitored by LCMS, which showed the desired product mass. Upon completion, the reaction mixture was concentrated under reduced pressure to obtain the crude product. The crude compound was added to water and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by silica gel flash column chromatography eluting with 5% EtOAc in n-hexane. The collected pure fractions were concentrated under reduced pressure to obtain 3-(5-formyl-1H-pyrrol-3-yl) benzonitrile (50 mg, 0.245 mmol, 100% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 197.2; ^{1}H-NMR (400 MHz, DMSO-d6): δ 12.42 (s, 1H), 9.54 (s, 1H), 8.07 (t, J = 8.00 Hz, 1H), 7.91-7.90 (m, 2H), 7.58-7.54 (m, 3H).

Example 175: Synthesis of 3-chloro-4-(1,3-dimethyl-1H-pyrazol-4-yl)benzaldehyde (ALD-85)



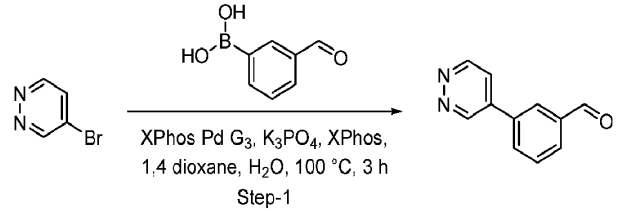
To a stirred solution of (2-chloro-4-formylphenyl)boronic acid (150 mg, 0.814 mmol) and 4-bromo-1,3-dimethyl-1H-pyrazole (142 mg, 0.814 mmol) in 1,4-dioxane (0.9 mL)/water (0.1 mL) were added potassium carbonate (169 mg, 1.220 mmol), at 25 °C and degassed with N_2 for 10 min. $Pd(dppf)Cl_2$ · DCM adduct (59.5 mg, 0.081 mmol) was added at 25 °C and the mixture was again degassed with N_2 for 10 min. The reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was filtered through a pad of celite and washed with EtOAc (2 x 30 mL). The combined organic layers were concentrated under reduced pressure, and the crude residue was purified by silica gel flash column chromatography, eluting with EtOAc in hexane (30%) to get 3-chloro-4-(1,3-dimethyl-1H-pyrazol-4-yl)benzaldehyde (100 mg, 0.413 mmol, 51% yield). LCMS: m/z MM-ES+APCI, Positive [M+H, M+2+H]$^+$ 234.9, 236.8. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.00 (s, 1H), 8.05 (d, J = 1.60 Hz, 1H), 7.93 (d, J = 2.00 Hz, 1H), 7.89-7.87 (m, 1H), 7.62-7.60 (m, 1H), 3.83 (s, 3H), 2.16 (s, 3H).

Example 176: Synthesis of 4-(2-chloro-4-formylphenyl)-1-methyl-1H-pyrazole-3-carbonitrile (ALD-86)



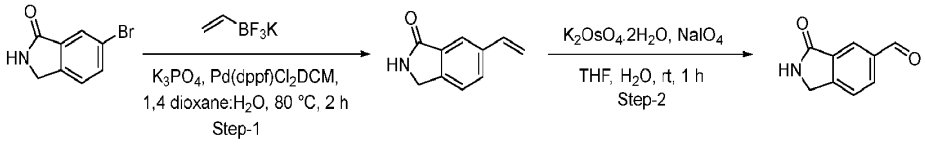
To a stirred solution of (2-chloro-4-formylphenyl)boronic acid (100 mg, 0.542 mmol) and 4-bromo-1-methyl-1H-pyrazole-3-carbonitrile (101 mg, 0.542 mmol) in 1,4-Dioxane (0.9 mL)/Water (0.1 mL) was added potassium carbonate (112 mg, 0.814 mmol), at 25 °C and degassed with N_2 for 10 min. Then, Pd(dppf)Cl2·DCM adduct (39.7 mg, 0.054 mmol) was added at 25 °C and degassed with N_2 for 10 min and the reaction mixture was stirred at 80 °C for 1 h. The reaction mixture filtered through a pad of celite and washed with EtOAc (2 x 30 mL), organic layer concentrated under reduced pressure to get crude. The crude compound was purified by silica gel flash column chromatography, eluting with EtOAc in hexane (30%) to get 4-(2-chloro-4-formylphenyl)-1-methyl-1H-pyrazole-3-carbonitrile (50 mg, 0.162 mmol, 30% yield). LCMS: m/z MM-ES+APCI, Positive [M+H, M+2+H]$^+$ 246.1, 248.0. 1H-NMR (400 MHz, DMSO-d6): δ 10.04 (s, 1H), 8.43 (s, 1H), 8.14 (s, 1H), 7.98 (d, J = 8.00 Hz, 1H), 7.78 (d, J = 8.00 Hz, 1H), 4.04 (s, 3H).

Example 177: Synthesis of 3-(pyridazin-4-yl)benzaldehyde (ALD-87)



To a stirred solution of 4-bromopyridazine, HBr (80 mg, 0.333 mmol) and (3-formylphenyl)boronic acid (60.0 mg, 0.400 mmol) in 1,4-Dioxane (0.9 mL)/Water (0.1 mL) was added potassium phosphate (106 mg, 0.500 mmol), at 25 °C and degassed with N_2 for 10 min. Then, XPhos (15.90 mg, 0.033 mmol) and XPhos Pd G_3 (26.2 mg, 0.033 mmol) were added at 25 °C and degassed with N_2 for 10 min and the reaction mixture was stirred at 100 °C for 3 h. The reaction mixture filtered through a pad of celite and washed with EtOAc (2 x 30 mL), organic layer was concentrated under reduced pressure to get crude. Crude compound was purified by silica gel flash column chromatography, eluting with EtOAc in hexane (70%) to get 3-(pyridazin-4-yl)benzaldehyde (50 mg, 0.269 mmol, 81% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 185.1, ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.14 (s, 1H), 9.74 (d, J = 1.20 Hz, 1H), 9.35 (dd, J = 0.80, 5.20 Hz, 1H), 8.48 (s, 1H), 8.29 (d, J = 8.00 Hz, 1H), 8.14-8.12 (m, 1H), 8.13 (dd, J = 2.40, 5.40 Hz, 1H), 7.82 (t, J = 7.60 Hz, 1H).

Example 178: Synthesis of 3-oxoisoindoline-5-carbaldehyde (ALD-88)



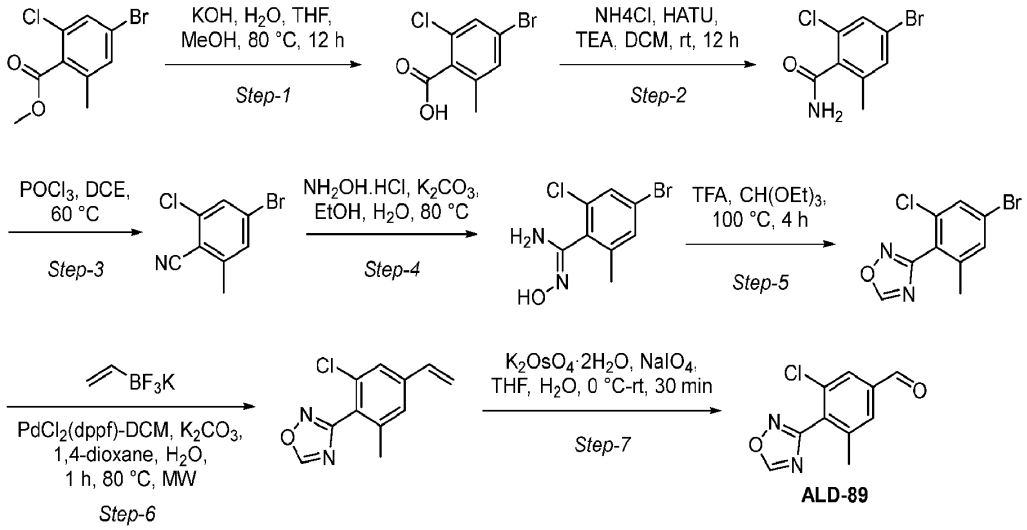
Step 1: Synthesis of **6-Vinylisoindolin-1-one**

To a stirred solution of 6-bromoisoindolin-1-one (500 mg, 2.358 mmol) and trifluoro(vinyl)-l4-borane, potassium salt (379 mg, 2.83 mmol) in 1,4-dioxane (0.9 mL)/water (0.1 mL) was added potassium phosphate tribasic (821 mg, 4.72 mmol) at 25 °C and degassed with N_2 for 10 min. Then, Pd(dppf)Cl2 · DCM (193 mg, 0.236 mmol) was added at 25 °C and degassed with N_2 for 10 min. Then reaction mixture was stirred at 80 °C for 2 h. The reaction mixture was filtered through a pad of celite and washed with EtOAc (2 x 30 mL). The combined organic layers were concentrated under reduced pressure, and the crude residue was purified by silica gel flash column chromatography, eluting with EtOAc in hexane (30%) to afford 6-vinylisoindolin-1-one (500 mg, 2.82 mmol, 120% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 160.0, ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.95 (d, J = 1.20 Hz, 1H), 7.63 (dd, J = 1.60, 7.80 Hz, 1H), 7.45 (d, J = 8.00 Hz, 1H), 6.86-6.72 (m, 2H), 5.88 (d, J = 17.60 Hz, 1H), 5.36 (d, J = 10.80 Hz, 1H), 4.49 (d, J = 4.00 Hz, 2H).

Step 2: **3-oxoisoindoline-5-carbaldehyde**

To a stirred solution of 6-vinylisoindolin-1-one (200 mg, 1.26 mmol) in THF (3.0 mL), Water (1.0 mL) were added sodium periodate (403 mg, 1.89 mmol) and potassium osmate dihydrate (11.6 mg, 0.03 mmol), at 0 °C. Then, the reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched with water (30 mL) and extracted with EtOAc (2 x 50 mL), organic layer was concentrated under reduced pressure to get crude. The crude was purified by silica gel flash column chromatography, eluting with EtOAc in hexane (100%) to afford 3-oxoisoindoline-5-carbaldehyde (55 mg, 0.29 mmol, 23% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 162.0. ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.15 (s, 1H), 8.39 (s, 1H), 8.17 (dd, J = 1.20, 8.00 Hz, 1H), 7.67 (d, J = 7.60 Hz, 1H), 6.47 (s, 1H), 4.59 (s, 2H).

Example 180: Synthesis of 3-chloro-5-methyl-4-(1,2,4-oxadiazol-3-yl) benzaldehyde (ALD-89)



Step 1: **Synthesis of 4-bromo-2-chloro-6-methylbenzoic acid**

To a stirred solution of methyl 4-bromo-2-chloro-6-methylbenzoate (3.8 g, 14.42 mmol) in tetrahydrofuran (5 mL), methanol (5 mL), and water (5 mL), KOH (2.427 g, 43.3 mmol) was added at 0 °C. The reaction mixture was heated at 80 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to obtain the crude product, which was extracted with EtOAc (2 × 1 mL). The aqueous layer was set aside, and the pH was adjusted to 4 with 1.5 M HCl solution. The mixture was then extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure to afford the crude product. The crude compound was purified to yield 4-bromo-2-chloro-6-methylbenzoic acid (2 g, 7.54 mmol, 52% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2+H]^-$ 248.8, 250.8; ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.58 (s, 1H), 7.49 (s, 1H), 2.27 (s, 3H).

Step 2: **Synthesis of 4-bromo-2-chloro-6-methylbenzamide**

To a stirred solution of 4-bromo-2-chloro-6-methylbenzoic acid (500 mg, 2.004 mmol) in dichloromethane (5 mL), TEA (811 mg, 8.02 mmol), HATU (914 mg, 2.405 mmol), and ammonium chloride (322 mg, 6.01 mmol) were added at room temperature. The mixture was stirred for 16 h at room temperature. Upon completion, the reaction mixture was quenched with water and extracted with DCM (2 × 100 mL). The combined organic layers were concentrated under reduced pressure to obtain the crude product. The crude compound was purified by silica gel flash column chromatography eluting with 50% EtOAc in n-hexane. The collected pure fractions were concentrated under reduced pressure to obtain 4-bromo-2-chloro-6-methylbenzamide (900 mg, 3.62 mmol, 181% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ 249.6, 251.8. ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.94 (s, 1H), 7.72 (s, 1H), 7.58 (s, 1H), 7.49 (s, 1H), 2.28 (s, 3H).

Step 3: **Synthesis of 4-bromo-2-chloro-6-methylbenzonitrile**

To a stirred solution of 4-bromo-2-chloro-6-methylbenzamide (700 mg, 2.82 mmol) in 1,2-dichloroethane (5 mL), $POCl_3$ (1.317 mL, 14.08 mmol) was added at room temperature and stirred for 5 h at 80 °C. Upon completion, the reaction mixture was quenched with water and extracted with DCM (2 × 100 mL). The combined organic layers were concentrated under reduced pressure to obtain the crude product. The crude compound was purified by silica gel flash column chromatography eluting with 50% EtOAc in n-hexane. The collected pure fractions were concentrated under reduced pressure to obtain 4-bromo-2-chloro-6-methylbenzonitrile (500 mg, 2.169 mmol, 77% yield). LCMS: No ionization; ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.94 (d, J = 1.20 Hz, 1H), 7.79 (s, 1H), 2.55 (s, 3H).

Step 4: **Synthesis of (Z)-4-bromo-2-chloro-N'-hydroxy-6-methylbenzimidamide**

To a stirred solution of hydroxylamine hydrochloride (150 mg, 2.169 mmol) in water (1 mL), K_2CO_3 (899 mg, 6.51 mmol) was added at room temperature and stirred for 15 minutes. Then, 4-bromo-2-chloro-6-methylbenzonitrile (500 mg, 2.169 mmol) in ethanol (4 mL) was added to the reaction mixture and stirred at 100 °C for 16 h. Upon completion, the reaction mixture was filtered, and the solid was collected. The solid was dried under reduced pressure to afford (Z)-4-bromo-2-chloro-N'-hydroxy-6-methylbenzimidamide (250 mg, 0.949 mmol, 44% yield). The crude product was used in the next step without purification. 1H-NMR (400 MHz, DMSO-d6): δ 7.49 (s, 1H), 7.65 (d, J = 55.20 Hz, 1H), 7.79 (s, 1H), 7.94 (s, 1H), 5.85 (s, 1H), 2.29 (s, 3H).

Step 5: **Synthesis of 3-(4-bromo-2-chloro-6-methylphenyl)-1,2,4-oxadiazole**

To a stirred solution of 4-bromo-2-chloro-N-hydroxy-6-methylbenzimidamide (200 mg, 0.759 mmol) in triethyl orthoformate (337 mg, 2.277 mmol) at 25 °C, TFA (87 mg, 0.759 mmol) was added at 25 °C. The resulting reaction mixture was stirred at 100 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to obtain the crude product. The crude compound was purified by silica gel flash column chromatography eluting with 50% EtOAc in n-hexane. The collected pure

fractions were concentrated under reduced pressure to obtain 3-(4-bromo-2-chloro-6-methylphenyl)-1,2,4-oxadiazole (100 mg, 0.350 mmol, 46% yield). LCMS: m/z MM-ES+APCI, Positive [M+H, M+2+H, M+4+H]$^+$ 272.8, 274.9, 276.8; ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.90 (s, 1H), 7.83 (d, J = 1.20 Hz, 1H), 7.71 (d, J = 0.80 Hz, 1H), 2.14 (s, 3H).

Step 6: **Synthesis of 3-(2-chloro-6-methyl-4-vinylphenyl)-1,2,4-oxadiazole**

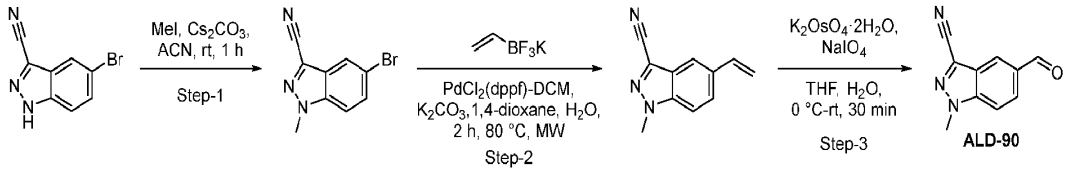
To a stirred solution of 3-(4-bromo-2-chloro-6-methylphenyl)-1,2,4-oxadiazole (200 mg, 0.731 mmol) and trifluoro(vinyl)-λ^4-borane, potassium salt (147 mg, 1.097 mmol) in 1,4-dioxane (5 mL) and water (0.2 mL), K_2CO_3 (202 mg, 1.462 mmol) was added at ambient temperature. The resulting reaction mixture was degassed with argon for 15 minutes, followed by the addition of $PdCl_2$(dppf)-CH_2Cl_2 adduct (59.7 mg, 0.073 mmol) at ambient temperature. The reaction mixture was degassed with argon for another 15 minutes. The reaction mixture was then irradiated in a microwave at 80 °C for 1 h. The progress of the reaction was monitored by TLC.

Upon completion, as confirmed by TLC, the reaction mixture was filtered through a pad of Celite, and the pad was washed with EtOAc (100 mL). The filtrate was concentrated under reduced pressure to obtain the crude compound. The crude product was purified by silica gel flash column chromatography eluting with 20% EtOAc in petroleum ether. The collected pure fractions were concentrated under reduced pressure to obtain 3-(2-chloro-6-methyl-4-vinylphenyl)-1,2,4-oxadiazole (190 mg, 0.373 mmol, 51% yield). LCMS: m/z MM-ES+APCI, Positive [M+H, M+2+H]$^+$ 221.0, 223.0; ^{1}H-NMR (400 MHz, CDCl3): δ 8.92 (d, J = 2.80 Hz, 1H), 7.56 (d, J = 1.20 Hz, 1H), 7.42 (s, 1H), 6.8 (t, J = 4.20 Hz, 1H), 5.84 (d, J = 3.20 Hz, 1H), 5.43 (d, J = 3.20 Hz, 1H), 2.22 (s, 3H).

Step 7: **Synthesis of 3-chloro-5-methyl-4-(1,2,4-oxadiazol-3-yl)benzaldehyde**

To a stirred solution of 3-(2-chloro-6-methyl-4-vinylphenyl)-1,2,4-oxadiazole (180 mg, 0.816 mmol) in THF (0.6 mL) and water (0.2 mL), sodium periodate (262 mg, 1.224 mmol) and potassium osmate dihydrate (7.51 mg, 0.020 mmol) were added at 0 °C. The resulting reaction mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to obtain the crude product. The crude compound was added to water and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by silica gel flash column chromatography eluting with 100% EtOAc in n-hexane. The collected pure fractions were concentrated under reduced pressure to obtain 3-chloro-5-methyl-4-(1,2,4-oxadiazol-3-yl) benzaldehyde (20 mg, 0.089 mmol, 11% yield). ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.05 (s, 1H), 9.95 (s, 1H), 8.02 (s, 1H), 7.93 (s, 1H), 2.24 (s, 3H).

Example 181: Synthesis of 5-formyl-1-methyl-1H-indazole-3-carbonitrile (ALD-90)



Step 1: **Synthesis of 5-bromo-1-methyl-1H-indazole-3-carbonitrile**

To a stirred solution of 5-bromo-1H-indazole-3-carbonitrile (1.0 g, 4.5 mmol) in 1,4-dioxane (18 mL), Cs_2CO_3 (4.40 g, 13.51 mmol) was added at ambient temperature, and the resulting reaction mixture was stirred for 15 minutes. Methyl iodide (0.34 mL, 5.4 mmol) was then added at ambient temperature and the reaction mixture was stirred for 2 h at 25 °C. Upon completion of the reaction, ice-cold water was added to the reaction mixture, causing the solid to precipitate. The solid was filtered to obtain the crude product. The crude product was triturated with hexane to afford 5-bromo-1-methyl-1H-indazole-3-carbonitrile (1.05 g, 3.36 mmol, 75% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ 236.06, 238.08; ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.17 (d, J = 1.20 Hz, 1H), 7.92-7.90 (m, 1H), 7.75-7.73 (m, 1H), 4.20 (s, 3H).

Step 2: **Synthesis of 1-methyl-5-vinyl-1H-indazole-3-carbonitrile**

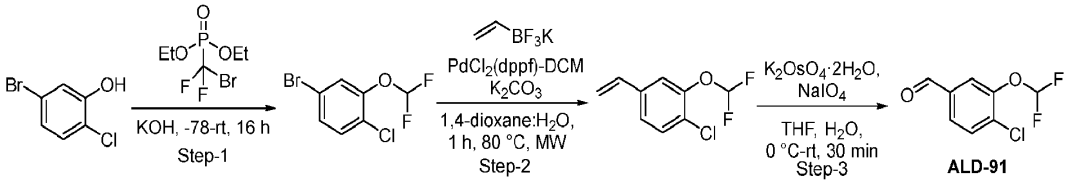
To a stirred solution of 5-bromo-1-methyl-1H-indazole-3-carbonitrile (500 mg, 2.118 mmol) and potassium vinyl trifluoroborate (426 mg, 3.18 mmol) in 1,4-dioxane (10 mL), K_2CO_3 (585 mg, 4.24 mmol) was added at ambient temperature. The resulting reaction mixture was degassed with argon for 15 minutes, followed by the addition of $PdCl_2$(dppf)-DCM adduct (173 mg, 0.212 mmol) at ambient temperature. The reaction mixture was degassed with argon for another 15 minutes. The reaction mixture was then irradiated in a microwave at 90 °C for 2 h. Upon completion, as confirmed by TLC, the reaction mixture was filtered through a pad of Celite, and the pad was washed with EtOAc (100 mL). The filtrate was concentrated under reduced pressure to obtain the crude compound. The crude product was purified by silica gel flash column chromatography eluting with 50% EtOAc in petroleum ether. The collected pure fractions were concentrated under reduced pressure to obtain 1-methyl-5-vinyl-1H-indazole-3-carbonitrile (320 mg, 1.568 mmol, 74% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 184. ^{1}H-NMR (400 MHz, CDCl3): δ 7.80 (s, 1H), 7.67 (dd, J = 1.60, 8.80 Hz, 1H), 7.48 (d, J = 8.80 Hz, 1H), 6.90-6.83 (m, 1H), 5.85 (d, J = 9.20 Hz, 1H), 5.37 (d, J = 9.20 Hz, 1H), 4.18 (s, 3H).

Step 3: **Synthesis of 5-formyl-1-methyl-1H-indazole-3-carbonitrile**

To a stirred solution of 1-methyl-5-vinyl-1H-indazole-3-carbonitrile (150 mg, 0.819 mmol) in THF (5 mL) and water (1.667 mL), potassium osmate dihydrate (7.54 mg, 0.020 mmol) and sodium periodate (263 mg, 1.228 mmol) were added at 0 °C. The resulting reaction mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to obtain the crude product. The crude compound was added to water and extracted with EtOAc. The organic layer was

dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by silica gel flash column chromatography eluting with 30% EtOAc in n-hexane. The collected pure fractions were concentrated under reduced pressure to obtain 5-formyl-1-methyl-1H-indazole-3-carbonitrile (80 mg, 0.372 mmol, 46% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 186. ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.15 (s, 1H), 8.61 (s, 1H), 8.09-8.02 (m, 2H), 4.26 (s, 3H).

Example 182: Synthesis of 4-chloro-3-(difluoromethoxy)benzaldehyde (ALD-91)



Step 1: **4-bromo-1-chloro-2-(difluoro methoxy) benzene**

To a stirred solution of 5-bromo-2-chlorophenol (2 g, 9.64 mmol) in acetonitrile (15 mL), KOH (12.44 g, 222 mmol) dissolved in water (10 mL) and diethyl (bromodifluoromethyl)-phosphonate (3.43 mL, 19.28 mmol) were added at -78 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. Upon completion, the reaction mixture was quenched with cooled water (100 mL) and the compound was extracted with EtOAc (2 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the crude compound. The crude product was purified by silica gel flash column chromatography eluting with 20% EtOAc in petroleum ether. The collected pure fractions were concentrated under reduced pressure to obtain 4-bromo-1-chloro-2-(difluoromethoxy) benzene (1.2 g, 3.84 mmol, 40% yield). LCMS: No mass ionization; ^{1}H-NMR (400 MHz, CDCl3): δ 7.43 (s, 1H), 7.34 (m, 2H), 6.74-6.38 (m, 1H).

Step 2: **1-chloro-2-(difluoromethoxy)-4-vinylbenzene**

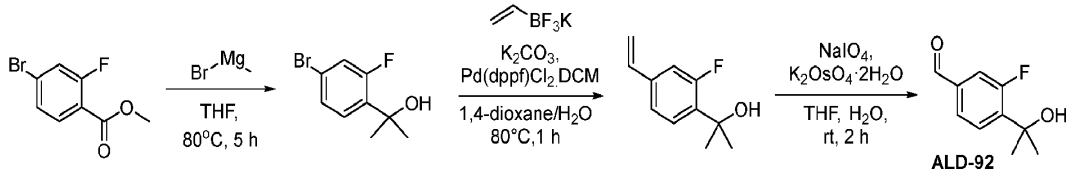
To a stirred solution of 4-bromo-1-chloro-2-(difluoromethoxy) benzene (500 mg, 1.942 mmol) and trifluoro(vinyl)-λ^4-borane, potassium salt (390 mg, 2.91 mmol) in 1,4-dioxane (10 mL) and water (0.5 mL), K_2CO_3 (537 mg, 3.88 mmol) was added at ambient temperature. The resulting reaction mixture was degassed with argon for 15 minutes, followed by the addition of $PdCl_2$(dppf)-CH_2Cl_2 adduct (159 mg, 0.194 mmol) at ambient temperature. The reaction mixture was degassed with argon for another 15 minutes. The reaction mixture was then irradiated in a microwave at 80 °C for 1 h. Upon completion, as confirmed by TLC, the reaction mixture was filtered through a pad of Celite, and the pad was washed with EtOAc (100 mL). The filtrate was concentrated under reduced pressure to obtain the crude compound. The crude product was purified by silica gel flash column chromatography eluting with 30% EtOAc in petroleum ether. The collected pure fractions were concentrated under reduced pressure to obtain 1-chloro-2-(difluoromethoxy)-4-vinylbenzene (230 mg, 0.727 mmol, 37% yield). LCMS: No mass

ionization; ^{1}H-NMR (400 MHz, CDCl3): δ 7.43-7.42 (m, 1H), 7.40 (s, 1H), 7.23 (dd, J = 2.00, 8.40 Hz, 1H), 6.74-6.68 (m, 1H), 6.65 (s, 1H), 5.78 (d, J = 17.60 Hz, 1H), 5.36 (d, J = 10.80 Hz, 1H).

Step 3: 4-Chloro-3-(difluoromethoxy)benzaldehyde

To a stirred solution of 1-chloro-2-(difluoromethoxy)-4-vinylbenzene (200 mg, 0.978 mmol) in THF (3 mL) and water (1 mL), sodium periodate (314 mg, 1.466 mmol) and potassium osmate dihydrate (9.00 mg, 0.024 mmol) were added at 0 °C. The resulting reaction mixture was stirred at 25 °C for 2 h. Upon completion, as confirmed by TLC, the reaction mixture was poured into cooled water (100 mL) and the compound was extracted with EtOAc (2 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the crude compound. The crude product was purified by Isolera Biotage column chromatography using 100-200 mesh neutral alumina, eluted with 0-100% EtOAc in petroleum ether. The collected pure fractions were concentrated under reduced pressure to obtain 4-chloro-3-(difluoromethoxy) benzaldehyde (45 mg, 0.190 mmol, 20% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ 204.9, 206.9. ^{1}H-NMR (400 MHz, CDCl3): δ 10.00 (s, 1H), 7.77 (s, 1H), 7.73 (dd, J = 1.60, 8.20 Hz, 1H), 7.67 (dd, J = 8.00 Hz, 1H), 6.83-6.47 (m, 1H).

Example 183: Synthesis of 3-fluoro-4-(2-hydroxypropan-2-yl) benzaldehyde (ALD-92)



Step 1: **2-(4-bromo-2-fluorophenyl) propan-2-ol**

To a stirred solution of methyl 4-bromo-2-fluorobenzoate (200 mg, 0.858 mmol) in THF (10 mL), methyl magnesium bromide in THF (3.07 mL, 4.29 mmol) was added at 0°C. The reaction mixture was then stirred at 80°C for 5 h. The progress of the reaction was monitored by TLC and LCMS. Upon completion, the reaction mixture was quenched with water and extracted with EtOAc (2 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product. Purification by silica gel flash column chromatography eluting with 5% EtOAc in petroleum ether, afforded 2-(4-bromo-2-fluorophenyl) propan-2-ol (70 mg, 0.247 mmol, 29% yield). ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.57 (t, J = 8.80 Hz, 1H), 7.41-7.39 (m, 2H), 5.37 (s, 1H), 1.46 (s, 6H).

Step 2: **2-(2-fluoro-4-vinylphenyl) propan-2-ol**

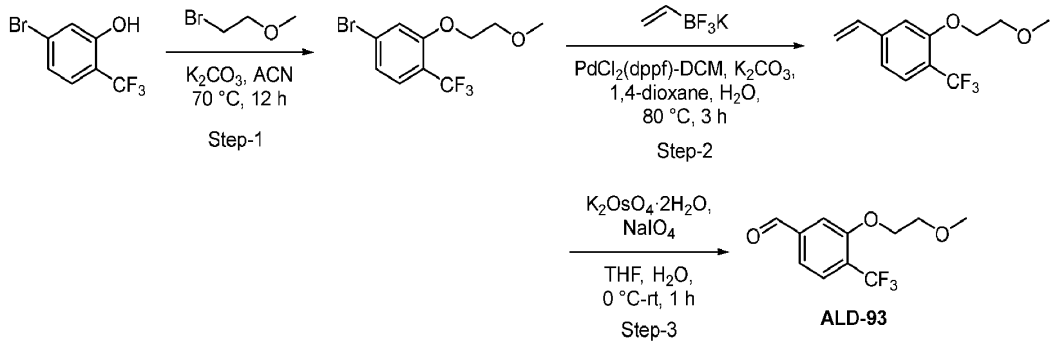
To a stirred solution of 2-(4-bromo-2-fluorophenyl) propan-2-ol (100 mg, 0.429 mmol) in 1,4-dioxane (3 mL) and water (0.333 mL), trifluoro(vinyl)-λ^4-borane, potassium salt (115 mg, 0.858 mmol) and K_2CO_3 (119 mg, 0.858 mmol) were added at room temperature. The reaction mixture was sparged with nitrogen for 10 minutes, followed by the addition of $PdCl_2(dppf)\cdot CH_2Cl_2$ adduct (35.0 mg, 0.043

mmol). The resulting mixture was stirred at 80°C for 1 h. The progress of the reaction was monitored by TLC and LCMS. Upon completion, as confirmed by TLC, the reaction mixture was filtered through a pad of Celite, and the pad was washed with EtOAc (100 mL). The filtrate was concentrated under reduced pressure to yield the crude product. Purification by silica gel flash column chromatography eluting with 5% EtOAc in petroleum ether, afforded 2-(2-fluoro-4-vinylphenyl) propan-2-ol (30 mg, 0.108 mmol, 25% yield). 1H-NMR (400 MHz, DMSO-d6): δ 7.58 (t, J = 4.80 Hz, 1H), 7.44 (dd, J = 2.00 Hz, 1H), 7.41 (dd, J = 4.40 Hz, 1H), 7.26-7.23 (m, 1H), 6.71-6.67 (m, 1H), 5.86 (d, J = 17.60 Hz, 1H), 5.34 (s, 1H), 1.47 (s, 6H).

Step 3: **3-fluoro-4-(2-hydroxypropan-2-yl) benzaldehyde**

To a stirred solution of 2-(2-fluoro-4-vinylphenyl) propan-2-ol (350 mg, 1.942 mmol) in THF (10 mL) and water (1.111 mL), sodium periodate (623 mg, 2.91 mmol) and potassium osmate dihydrate (35.8 mg, 0.097 mmol) were added at room temperature and the reaction mixture was stirred at 25°C for 2 h. The progress of the reaction was monitored by TLC and LCMS. Upon completion, as confirmed by TLC, the reaction mixture was poured into cooled water (100 mL) and extracted with EtOAc (2 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product. Purification by Isolera Biotage column chromatography using neutral silica gel, eluting with 25% EtOAc in petroleum ether, afforded 3-fluoro-4-(2-hydroxypropan-2-yl) benzaldehyde (150 mg, 0.796 mmol, 41% yield). LCMS: m/z MM-ES+APCI, Positive $[M+2]^+$ 183.2. ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.00 (s, 1H), 7.84 (t, J = 7.60 Hz, 1H), 7.68 (dd, J = 1.60, 8.00 Hz, 1H), 7.56 (dd, J = 1.60, 11.60 Hz, 1H), 2.08 (s, 1H), 1.68 (s, 6H).

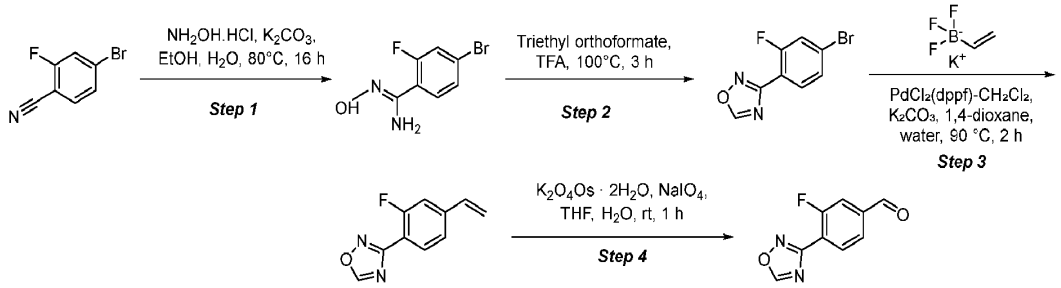
Example 184: Synthesis of 3-(2-methoxyethoxy)-4-(trifluoromethyl)benzaldehyde (ALD-93)



2-(2-Methoxyethoxy)-1-(trifluoromethyl)-4-vinylbenzene was prepared in two steps using a procedure similar to that of Ex 151, ALD-60, Steps 1 and 2. To a stirred solution of 2-(2-methoxyethoxy)-1-(trifluoromethyl)-4-vinylbenzene (200 mg, 0.812 mmol) in THF (2 mL) and water (0.2 mL) (10:1), sodium periodate (261 mg, 1.218 mmol) and potassium osmate dihydrate (7.48 mg, 0.020 mmol) were added at room temperature. The resulting reaction mixture was stirred at room temperature

for 30 minutes. The progress of the reaction was monitored by TLC. Upon completion, as confirmed by TLC, the reaction mixture was diluted with EtOAc (150 mL) and passed through a Celite bed. The collected filtrate was poured into cooled water (100 mL), and the compound was extracted with EtOAc (2 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the crude compound. The crude compound was purified by Isolera Biotage column chromatography using neutral silica gel (230-400 mesh), eluting with 50% EtOAc in petroleum ether. The collected pure fractions were concentrated under reduced pressure to yield 3-(2-methoxyethoxy)-4-(trifluoromethyl) benzaldehyde (50 mg, 0.191 mmol, 24% yield). ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.08 (s, 1H), 7.88 (d, J = 8.00 Hz, 1H), 7.75 (s, 1H), 7.65 (d, J = 8.00 Hz, 1H), 4.36 (t, J = 4.80 Hz, 2H), 3.71 (t, J = 8.80 Hz, 2H), 3.33 (s, 3H),

Example 185: Synthesis of 3-fluoro-4-(1,2,4-oxadiazol-3-yl)benzaldehyde (ALD-94)



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 (3.5 g, 15.02 mmol, 60% yield). 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, 2.15 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 EtOAc (2 x 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% EtOAc in petroleum ether. The collected pure fractions were concentrated under reduced pressure to afford 3-(4-bromo-2-fluorophenyl)-1,2,4-oxadiazole (170 mg, 0.68 mmol, 32% yield). 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).

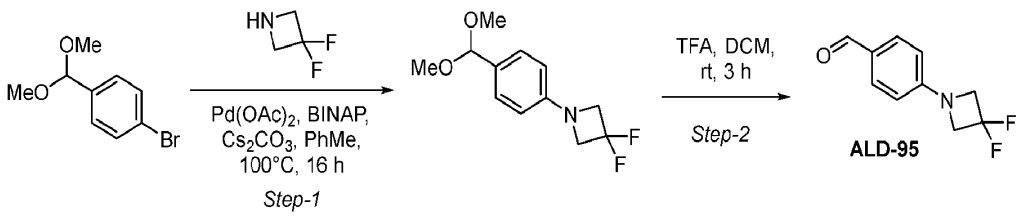
Step 3: **Synthesis of 3-(2-fluoro-4-vinylphenyl)-1,2,4-oxadiazole**

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 EtOAc (50 mL), and extracted with water (2 x 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% EtOAc in hexane. The collected pure fractions were concentrated under reduced pressure to afford 3-(2-fluoro-4-vinylphenyl)-1,2,4-oxadiazole (10 mg, 0.046 mmol, 22% yield). 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-94)**

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 EtOAc (2 x 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% EtOAc in petroleum ether. Pure fractions were concentrated under reduced pressure to afford 3-fluoro-4-(1,2,4-oxadiazol-3-yl)benzaldehyde (**ALD-94**, 55 mg, 0.27 mmol, 27% yield). 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 186: Synthesis of 4-(3,3-difluoroazetidin-1-yl)benzaldehyde (ALD-95)



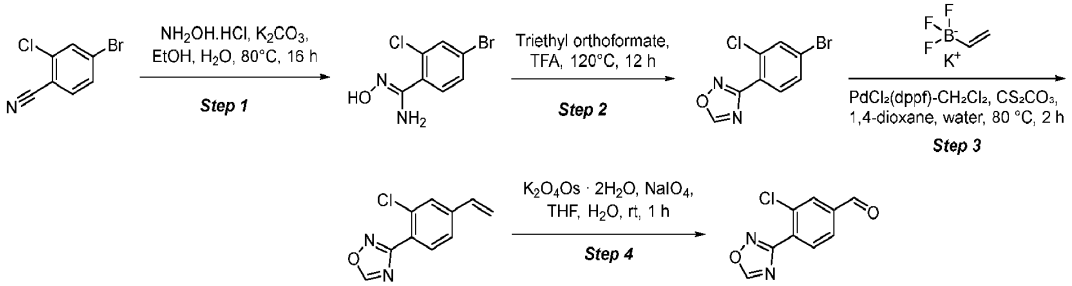
Step 1: **1-(4-(dimethoxymethyl)phenyl)-3,3-difluoroazetidine**

To a stirred solution of 1-bromo-4-(dimethoxy methyl) benzene (500 mg, 2.164 mmol) in toluene (8 mL) was added 3,3-difluoroazetidine hydrochloride (336 mg, 2.60 mmol) and cesium carbonate (1.41 g, 4.33 mmol). The reaction mixture was degassed with nitrogen for 10 minutes. Palladium (II) acetate (48.6 mg, 0.216 mmol) and BINAP (269 mg, 0.433 mmol) were then added, and the mixture was degassed with nitrogen for an additional 10 minutes. The resulting mixture was stirred at 100 °C for 12 h. The progress of the reaction was monitored by TLC and LCMS. Upon completion, as confirmed by TLC and LCMS, the reaction mixture was quenched; with water (50 mL) and extracted with EtOAc (2 × 200 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield a crude residue. The crude compound was purified by silica gel flash column chromatography, eluting with 10% EtOAc in hexane to afford 1-(4-(dimethoxy methyl) phenyl)-3,3-difluoroazetidine (70 mg, 0.140 mmol, 6% yield). LCMS: No ionization. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.24 (d, J = 8.40 Hz, 2H), 6.56 (d, J = 8.40 Hz, 2H), 5.29 (s, 1H), 4.43 (t, J = 0.00 Hz, 2H), 4.27 (t, J = 7.20 Hz, 2H), 3.21 (s, 6H).

Step 2: **4-(3,3-difluoroazetidin-1-yl)benzaldehyde**

To a stirred solution of 1-(4-(dimethoxymethyl) phenyl)-3,3-difluoroazetidine (70 mg, 0.13 mmol) in DCM (2 mL), TFA (9.98 µL, 0.13 mmol) was added at 0 °C. The progress of the reaction was monitored by TLC. Upon completion, as confirmed by TLC, the reaction mixture was quenched with saturated aqueous sodium bicarbonate solution (5 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure to afford 4-(3,3-difluoroazetidin-1-yl) benzaldehyde (50 mg, 0.245 mmol, 189% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 198.1; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.76 (s, 1H), 7.85 (d, J = 2.40 Hz, 2H), 6.66 (d, J = 8.40 Hz, 2H), 4.43 (t, J = 12.40 Hz, 4H).

Example 187: Synthesis of 3-chloro-4-(1,2,4-oxadiazol-3-yl)benzaldehyde (ALD-96)



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 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 EtOAc (2 x 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% EtOAc in hexane. The collected pure fractions were concentrated under reduced pressure to afford 3-(4-bromo-2-chlorophenyl)-1,2,4-oxadiazole (200 mg, 0.58 mmol, 32% yield). ^{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).

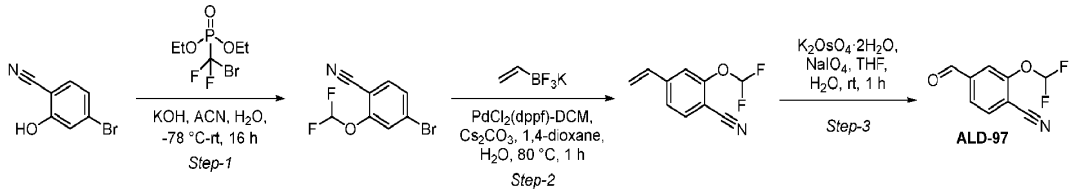
Step 3: **Synthesis of 3-(2-chloro-4-vinylphenyl)-1,2,4-oxadiazole**

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 sparged 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 sparged 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 (350 mg, 1.33 mmol, 68% yield). ^{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-96)**

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 EtOAc (2 x 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% EtOAc in hexane. The collected pure fractions were concentrated under reduced pressure to afford 3-chloro-4-(1,2,4-oxadiazol-3-yl) benzaldehyde (**ALD-96**, 75 mg, 0.36 mmol, 15% yield). ^{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 188: Synthesis of 2-(difluoromethoxy)-4-formylbenzonitrile (ALD-97)



Step 1: **Synthesis of 4-bromo-2-(difluoromethoxy)benzonitrile**

To a stirred solution of 4-bromo-2-hydroxybenzonitrile (2 g, 10.1 mmol) in ACN (15 mL), KOH (13.0 g, 232 mmol) dissolved in water (10 mL) and diethyl (bromodifluoromethyl)-phosphonate (3.6 mL, 20.2 mmol) were added at -78 °C. The resulting mixture was allowed to stir at rt for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 150 mL). The combined organic layers were washed with brine solution (100 mL), dried over Na_2SO_4 filtered, and concentrated to yield a crude product. The crude product was purified by Isolera chromatography using silica gel (100-200 mesh), eluting with 40-50% EtOAc in hexane. The collected fractions were concentrated under reduced pressure to afford 4-bromo-2-(difluoro methoxy) benzonitrile (1.5 g, 6.05 mmol, 60% yield). ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.91 (d, J = 8.40 Hz, 1H), 7.79 (s, 1H), 7.69 (d, J = 1.60 Hz, 2H).

Step 2: **Synthesis of 2-(difluoromethoxy)-4-vinylbenzonitrile**

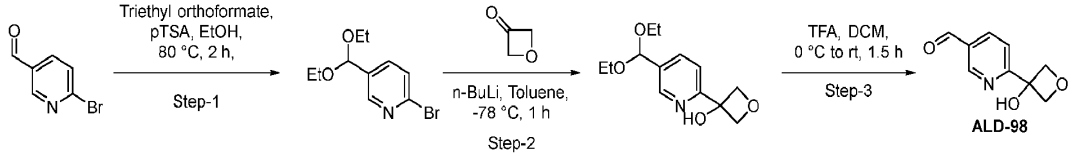
To a stirred solution of 4-bromo-2-(difluoromethoxy)benzonitrile (500 mg, 2.016 mmol) in dioxane (8 mL) and water (2 mL), II trifluoro(vinyl)-l4-borane, potassium salt (405 mg, 3.02 mmol), and Cs_2CO_3 (788 mg, 2.419 mmol) were added. The reaction mixture was sparged with N_2 for 10 min, followed by the addition of $PdCl_2$ (dppf)-CH_2Cl_2 adduct (32.9 mg, 0.040 mmol) at rt. The resulting reaction mixture was stirred at 80 °C for 1 h. The reaction mass was filtered through a celite pad. The filtrate was collected and concentrated under reduced pressure to yield a crude product. The crude product was purified by Isolera chromatography using silica gel (100-200 mesh), eluting with 20% EtOAc in hexane. The collected fractions were concentrated under reduced pressure to afford 2-(difluoromethoxy)-4-vinylbenzonitrile (400 mg, 1.783 mmol, 88% yield). LCMS: m/z MM-ES+ APCI, Positive $[M+H]^+$ 196.0, ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.79 (s, 1H), 7.79-7.67 (m, 1H), 7.57-7.48 (m, 1H), 7.31 (d, J = 9.20 Hz, 1H), 6.88-6.80 (m, 1H), 6.13 (d, J = 17.60 Hz, 1H), 5.57 (d, J = 10.80 Hz, 1H).

Step 3: **Synthesis of 2-(difluoromethoxy)-4-formylbenzonitrile**

To a stirred solution of 2-(difluoromethoxy)-4-vinylbenzonitrile (200 mg, 1.025 mmol) in THF (2 mL) and water (1 mL), sodium periodate (329 mg, 1.537 mmol) was added at rt. Then, potassium osmate dihydrate (7.55 mg, 0.020 mmol) was added at room temperature. The resulting reaction mixture was stirred at rt for 1 h. After completion of reaction as confirmed by TLC, the reaction mixture was quenched with water (10 mL) and extracted with EtOAc (2 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain a crude residue. The crude compound

was purified by silica gel flash column chromatography, eluting with 10% EtOAc in hexane to afford 2-(difluoromethoxy)-4-formylbenzonitrile (40 mg, 0.203 mmol, 20% yield). ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.10 (s, 1H), 8.21 (d, J = 7.60 Hz, 1H), 7.97-7.95 (m, 1H), 7.91 (m, 1H), 7.65-7.47 (m, 1H).

Example 189: Synthesis of 6-(3-hydroxyoxetan-3-yl) nicotinaldehyde (ALD-98)



Step 1: **2-bromo-5-(diethoxymethyl)pyridine**

To a stirred solution of 6-bromonicotinaldehyde (1.0 g, 5.38 mmol) in ethanol (20 mL) was added p-toluenesulfonic acid monohydrate (0.061 g, 0.323 mmol) at room temperature. Then, triethyl orthoacetate (4.96 mL, 26.9 mmol) was added at room temperature. The resulting reaction mixture was stirred at 80 °C for 2 h. The reaction mixture was concentrated under reduced pressure to get crude residue. The crude was purified by silica gel flash column chromatography, eluting with EtOAc in *n*-hexane (5-10%) to afford 2-bromo-5-(diethoxy methyl) pyridine (1.2 g, 1.409 mmol, 26% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 261.3. ^{1}H-NMR (400 MHz, CDCL3): δ 8.47 (s, 1H), 7.68-7.66 (m, 1H), 7.52-7.49 (m, 1H), 5.54 (s, 1H), 3.65-3.62 (m, 4H), 1.29 (t, J = 0.40 Hz, 6H).

Step 2: 3-(5-(diethoxymethyl) pyridin-2-yl)oxetan-3-ol

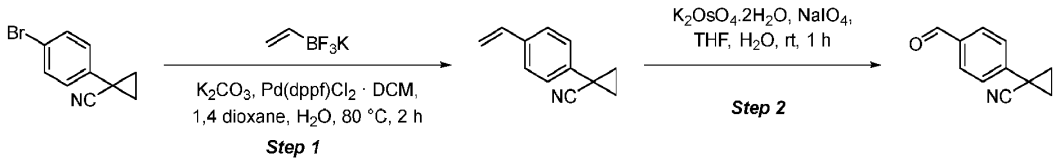
To a stirred solution of 2-bromo-5-(diethoxymethyl)pyridine (500 mg, 1.92 mmol) and oxetan-3-one (139 mg, 1.92 mmol) in toluene (5 mL), n-butyllithium in hexane (1.15 mL, 2.88 mmol) was added at -78 °C. The resulting reaction mixture was stirred at -78 °C for 1 h. The reaction mixture was quenched with saturated ammonium chloride solution (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield crude 3-(5-(diethoxymethyl)pyridin-2-yl)oxetan-3-ol (180 mg, 0.63 mmol, 33% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 254.4, ^{1}H-NMR (400 MHz, CDCL3): δ 8.61-8.61 (m, 1H), 8.01 (d, J = 1.20 Hz, 2H), 6.01 (s, 1H), 5.62 (s, 1H), 5.13 (d, J = 1.20 Hz, 2H), 4.74 (d, J = 1.20 Hz, 2H), 3.67-3.65 (m, 4H), 1.30 (t, J = 1.60 Hz, 6H).

Step 3: 6-(3-hydroxyoxetan-3-yl) nicotinaldehyde

To a stirred solution of 3-(5-(diethoxymethyl)pyridin-2-yl)oxetan-3-ol (180 mg, 0.71 mmol) in DCM (2 mL), TFA (81 mg, 0.71 mmol) was added at 0 °C. The resulting reaction mixture was stirred at 0 °C for 1.5 h. After completion of reaction as confirmed by TLC, the reaction mixture was quenched with saturated $NaHCO_3$ solution (30 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude product. The crude product was purified by silica gel flash column chromatography, eluting with 2.5%

EtOAc in n-hexane to afford 6-(3-hydroxyoxetan-3-yl) nicotinaldehyde (75 mg, 0.42 mmol, 59% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.14 (s, 1H), 9.16 (s, 1H), 8.29 (d, J = 2.00 Hz, 1H), 7.62 (d, J = 8.00 Hz, 1H), 5.61 (s, 1H), 4.39 (d, J = 6.40 Hz, 2H), 4.30 (d, J = 6.80 Hz, 2H).

Example 190: Synthesis of 1-(4-formylphenyl) cyclopropane-1-carbonitrile (ALD-99)



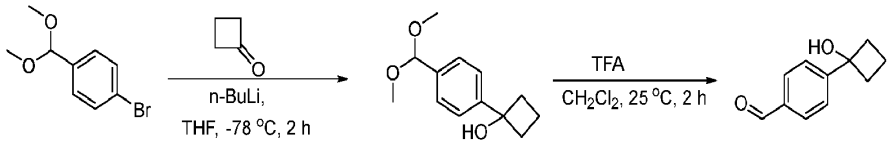
Step 1: **Synthesis of 1-(4-vinylphenyl) cyclopropane-1-carbonitrile**

To a stirred solution of 4-bromo-2-(2-methoxyethoxy) benzonitrile and trifluoro(vinyl)-λ^4-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 the mixture was 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 EtOAc (2 × 30 mL). The combined organic layers were concentrated under reduced pressure to obtain the crude product. The crude was purified by silica gel flash column chromatography, eluting with 2-5% EtOAc in hexane to obtain 1-(4-vinylphenyl) cyclopropane-1-carbonitrile (200 mg, 1.18 mmol, 53% yield). ^{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-99)**

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 h. The reaction mixture was quenched with water (30 mL) and extracted with EtOAc (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 silica gel flash column chromatography, eluting with 5-10% EtOAc in n-hexane to afford 1-(4-formylphenyl) cyclopropane-1-carbonitrile (**ALD-99**, 80 mg, 0.47 mmol, 23% yield). 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 191: Synthesis of 4-(1-hydroxycyclobutyl) benzaldehyde (ALD-100)



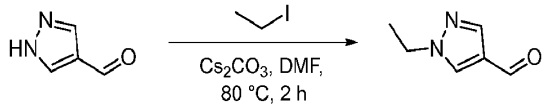
Step 1: Synthesis of 1-(4-(dimethoxymethyl)phenyl)cyclobutan-1-ol

To a stirred solution of 1-bromo-4-(dimethoxymethyl) benzene (500 mg, 2.164 mmol) in THF (6 mL) under a nitrogen atmosphere, n-butyllithium 2.5M in hexane (1.039 mL, 2.60 mmol) was added dropwise at -78 °C. The resulting reaction mixture was stirred at -78 °C for 30 minutes. Cyclobutanone (0.163 mL, 2.164 mmol) was then added dropwise, and the mixture was stirred for 2 h at 25 °C. Upon completion, the reaction mixture was quenched with water and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain a crude residue. This crude product was purified by silica gel flash column chromatography, eluting with 10% EtOAc in n-hexane to afford 1-(4-(dimethoxymethyl)phenyl)cyclobutan-1-ol (180 mg, 0.527 mmol, 24% yield). LCMS: m/z MM-ES+APCI, Positive $[M]^+$ = 223.0; ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.50 (d, J = -1.60 Hz, 2H), 7.48 (d, J = -1.60 Hz, 2H), 5.48 (s, 1H), 5.37 (s, 1H), 3.24 (s, 6H), 2.31-2.43 (m, 2H), 2.22-2.29 (m, 2H), 1.60-1.70 (m, 2H).

Step 2: 4-(1-hydroxycyclobutyl) benzaldehyde

To a stirred solution of 1-(4-(dimethoxymethyl) phenyl)cyclobutan-1-ol (180 mg, 0.810 mmol) in CH_2Cl_2 (3 mL) under a nitrogen atmosphere, TFA (0.062 mL, 0.810 mmol) was added dropwise at 0 °Cand the reaction mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was quenched with water and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford a crude residue. This crude product was purified by silica gel flash column chromatography, eluting with 10% EtOAc in n-hexane to afford 4-(1-hydroxycyclobutyl) benzaldehyde (80 mg, 0.454 mmol, 56% yield). LCMS: m/z MM-ES+APCI, $[M-H]^-$ = 174.9. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.72 (d, J = -6.80 Hz, 2H), 7.61 (d, J = -6.80 Hz, 2H), 5.74 (s, 1H), 2.39-2.45 (m, 4H), 1.93-1.99 (m, 2H).

Example 192: Synthesis of 1-ethyl-1H-pyrazole-4-carbaldehyde (ALD-101)

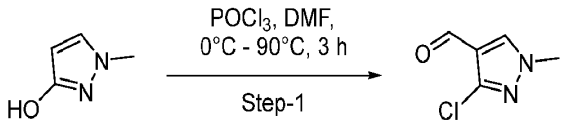


Step-1

To a stirred solution of 1H-pyrazole-4-carbaldehyde (500 mg, 5.20 mmol) in DMF (10 mL) under a nitrogen atmosphere, ethyl iodide (0.547 mL, 6.76 mmol) and Cs_2CO_3 (1695 mg, 5.20 mmol) were added at room temperature and the reaction mixture was stirred at 80 °C for 2 h. The reaction mixture was poured into cooled water (100 mL) and extracted with EtOAc (2 x 100 mL). The organic layer was dried

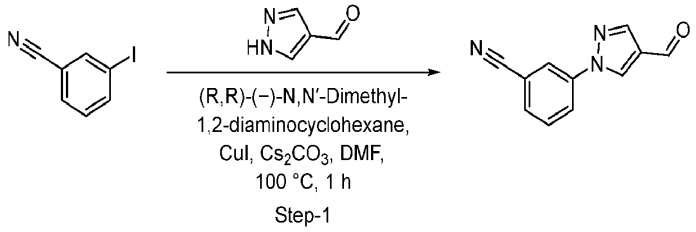
over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield a crude gummy compound. This crude product was purified by column chromatography using silica gel (100-200 mesh), eluting with 50% EtOAc in n-hexane. The collected pure fractions were concentrated under reduced pressure to afford 1-ethyl-1H-pyrazole-4-carbaldehyde (450 mg, 3.52 mmol, 68% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$125, ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.79 (s, 1H), 8.48 (s, 1H), 7.97 (d, J = 10.80 Hz, 1H), 4.23-4.17 (q, J = 7.20 Hz, 2H), 1.40 (t, J = 7.20 Hz, 3H).

Example 193: Synthesis of 3-chloro-1-methyl-*1H*-pyrazole-4-carbaldehyde (ALD-102)



To a stirred solution of $POCl_3$ (3.95 mL, 42.4 mmol) in DMF (2.5 mL) under nitrogen atmosphere was added 1-methyl-*1H*-pyrazol-3-ol (1 g, 10.19 mmol) at 0 °C to -10 °C. Then, the reaction mixture was stirred at 90 °C for 3 h. After completion of the reaction as confirmed by LCMS/TLC, the reaction mixture was diluted with EtOAc (100 mL) and reaction mixture was poured in 2M NaOH solution (~pH=8-9) (100 mL), compound was extracted in EtOAc (2 x 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The crude residue was purified by flash column chromatography using (100-200 mesh silica gel) 30-60% EtOAc in n-hexane as an eluent. The pure fractions were evaporated and dried under a high vacuum to afford compound 3-chloro-1-methyl-*1H*-pyrazole-4-carbaldehyde (500 mg, 3.46 mmol, 34% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$145, ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.75 (s, 1H), 8.50 (s, 1H), 3.30 (s, 3H).

Example 194: Synthesis of 3-(4-formyl-*1H*-pyrazol-1-yl)benzonitrile (ALD-103)

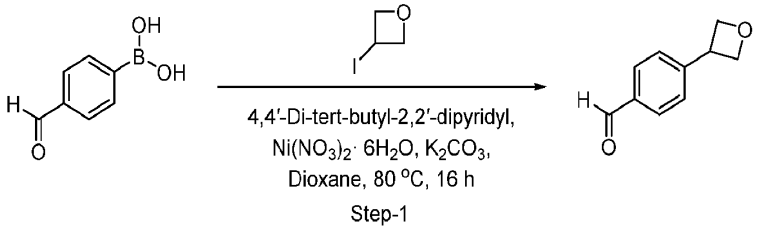


Step 1: 3-(4-formyl-*1H*-pyrazol-1-yl)benzonitrile

To a stirred solution of 3-iodobenzonitrile (100 mg, 0.437 mmol), *1H*-pyrazole-4-carbaldehyde (42.0 mg, 0.437 mmol) and cesium carbonate (356 mg, 1.092 mmol) in DMF (4 mL) was degassed for 15 min with N_2 followed by the addition of *(R,R)*-(−)-*N,N'*-Dimethyl-1,2-cyclohexanediamine (18.63 mg, 0.131 mmol) and copper(I) iodide (16.63 mg, 0.087 mmol) degassed with N_2 atmosphere for 5 min. The resulting reaction mixture was stirred at 100 °C for 1 h. The reaction was monitored by LCMS. After completion of the reaction as confirmed by LCMS, the reaction mixture was concentrated under reduced

pressure to get crude. The crude residue which was purified by normal phase column chromatography using (100-200 silica mesh) eluting with 15-20% of EtOAC in Hexane as an eluent. Then, pure fractions were evaporated and dried under a high vacuum to afford 3-(4-formyl-*1H*-pyrazol-1-yl) benzonitrile (32 mg, 0.161 mmol, 37% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 198.18, ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.02 (s, 1H), 8.50 (s, 1H), 8.23 (s, 1H), 8.11 (d, J = 1.60 Hz, 1H), 8.01-7.99 (m, 1H), 7.70-7.67 (m, 2H).

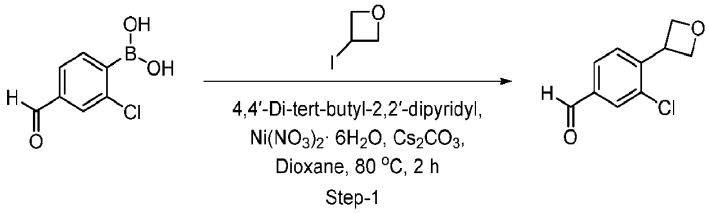
Example 195: Synthesis of 4-(oxetan-3-yl)benzaldehyde (ALD-104)



Step 1: Synthesis of 4-(oxetan-3-yl)benzaldehyde

To a stirred solution of (4-formylphenyl)boronic acid (250 mg, 1.667 mmol), 3-iodooxetane (614 mg, 3.33 mmol) and K_2CO_3 (691 mg, 5.0 mmol) in 1,4-dioxane (20 mL) was degassed for 15 min with N_2. Then were added 4,4′-Di-tert-butyl-2,2′-dipyridyl (44.8 mg, 0.17 mmol) and nickel (II) nitrate hexahydrate (39.6 mg, 0.17 mmol) at RT and degassed for 5 min with N_2 and the reaction mixture was stirred at 80 °C for 16 h. The reaction was monitored by LCMS. After completion of the reaction as confirmed by LCMS, the reaction mixture was diluted with EtOAc (50 mL), layers were separated, and aqueous portion was extracted with EtOAc (2 x 100 mL), The combine organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 100-200 mesh, gradient EtOAc/Hexane) compound was eluted at 20% EtOAc/Hexane as eluent get pure fraction. The pure fraction was concentrated under reduced pressure to obtained 4-(oxetan-3-yl) benzaldehyde (220 mg, 1.356 mmol, 81% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.00 (s, 1H), 7.94 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H), 4.99-4.94 (m, 2H), 4.66-4.61 (m, 2H), 4.40-4.32 (m, 1H).

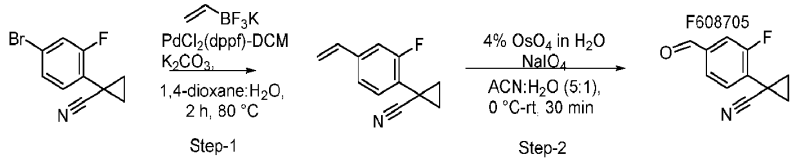
Example 196: Synthesis of 3-chloro-4-(oxetan-3-yl)benzaldehyde (ALD-105)



To a stirred solution of (2-chloro-4-formylphenyl)boronic acid (1 g, 5.4 mmol), 3-iodooxetane (1.996 g, 10.9 mmol) and Cs_2CO_3 (5.30 g, 16.3 mmol) in 1,4-dioxane (2 mL) was degassed for 15 min

with N_2.Were added nickel(II) nitrate hexahydrate (0.129 g, 0.54 mmol) and 4,4′-Di-tert-butyl-2,2′-dipyridyl (0.146 g, 0.54 mmol) and the reaction mixture was stirred at 80 °C for 2 h. The progress of reaction was monitored by LCMS. After completion of reaction as confirmed by LCMS, the resulting reaction mixture was concentrated under reduced pressure and compound was purified by isolera biotag column chromatography using (100-200 mesh silica gel mess), eluted with 20% EtOAc in pet ether. The collected pure fractions were concentrated under reduced pressure to obtained 3-chloro-4-(oxetan-3-yl)benzaldehyde (0.1 g, 0.34 mmol, 6% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 197.0; ^1H NMR (400 MHz, DMSO-d_6): δ 9.87 (s, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.48-7.44 (m, 1H), 4.97-4.75 (m, 2H), 4.28-4.25 (m, 2H), 4.17-4.11 (m, 1H).

Example 197: Synthesis of 1-(2-fluoro-4-formylphenyl) cyclopropane-1-carbonitrile (ALD-106)



Step 1: **1-(2-fluoro-4-vinylphenyl) cyclopropane-1-carbonitrile**

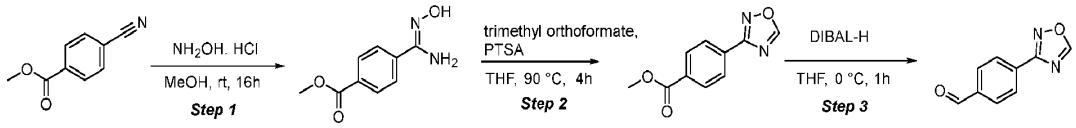
To a stirred solution of 1-(4-bromo-2-fluorophenyl) cyclopropane-1-carbonitrile (200 mg, 0.833 mmol) in dioxane (2.8 mL) and water (0.2 mL) in a microwave vial under a nitrogen atmosphere, K_2CO_3 (173 mg, 1.250 mmol) was added at room temperature. The reaction mixture was sparged with nitrogen for 10 minutes, followed by the addition of $PdCl_2(dppf)\cdot CH_2Cl_2$ adduct (68.0 mg, 0.083 mmol). The resulting mixture was irradiated under microwave conditions at 80°C for 30 minutes. The progress of the reaction was monitored by LCMS. Upon completion, as indicated by LCMS, the reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure to yield the crude product. Th crude was purified by silica gel flash column chromatography, eluting with 5% EtOAc in hexane to afford 1-(2-fluoro-4-vinylphenyl) cyclopropane-1-carbonitrile (150 mg, 0.801 mmol, 96% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 187.9 1H-NMR (400 MHz, DMSO-d6): δ 7.68 (d, J = 0.80 Hz, 2H), 7.30 (d, J = 1.60 Hz, 1H), 6.75 (t, J = 6.80 Hz, 1H), 5.96 (d, J = 17.20 Hz, 1H), 5.38 (d, J = 11.20 Hz, 1H), 1.43 (t, J = 7.60 Hz, 2H), 1.23 (t, J = 16.00 Hz, 2H).

Step 2: 1-(2-fluoro-4-formylphenyl) cyclopropane-1-carbonitrile

To a stirred solution of 1-(2-fluoro-4-vinylphenyl) cyclopropane-1-carbonitrile (100 mg, 0.497 mmol) in acetonitrile (1.8 mL) and water (0.2 mL), sodium periodate (106 mg, 0.497 mmol) and osmium tetroxide (1.579 mL, 0.248 mmol) were added at 0°C and the reaction mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by LCMS. Upon completion, the reaction mixture was quenched with water (10 mL) and extracted with EtOAc (2 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield the crude product.

Purification by Biotage Isolera (silica gel cartridge, 250 g) using 10% EtOAc in hexane as the eluent afforded 1-(2-fluoro-4-formylphenyl) cyclopropane-1-carbonitrile (35 mg, 0.185 mmol, 37% yield). LCMS: No ionization; ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.02 (s, 1H), 7.81-7.74 (m, 3H), 1.80-1.77 (m, 4H).

Example 198: Synthesis of (ALD-107)



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 (9 g, 45 mmol, 73% yield). 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**

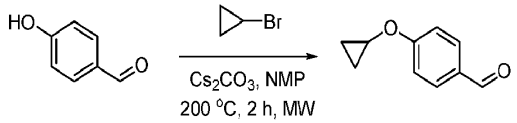
To the stirred solution of methyl 4-(N'-hydroxycarbamimidoyl)benzoate (9 g, 46 mmol) in THF (50 mL), trimethyl orthoformate (25.3 mL, 232 mmol) and toluene-4-sulfonic acid monohydrate (0.88 g, 4.63 mmol) were added at room temperature and the reaction mixture was stirred at 90 °C for 4 h. The reaction 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 (8 g, 39.1 mmol, 84% yield). 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-107)**

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-107**, 400 mg, 2.29 mmol, 47% yield). 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).

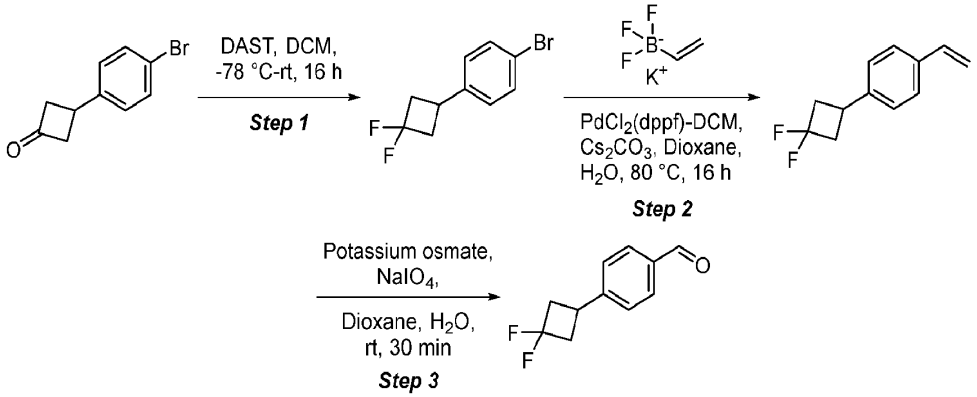
Example 199: Synthesis of 4-cyclopropoxybenzaldehyde (ALD-108):



Step 1

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 EtOAc (2 x 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 EtOAc and hexane (0-100%) as eluent. The pure fractions containing product were collected and concentrated to afford 4-cyclopropoxybenzaldehyde (**ALD-108**, 0.4 g, 2.17 mmol, 53% yield). 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 200: Synthesis of 4-(3,3-difluorocyclobutyl)benzaldehyde (ALD-109)



Step 1: **Synthesis of 1-bromo-4-(3,3-difluorocyclobutyl)benzene**

To a stirred solution of 3-(4-bromophenyl)cyclobutan-1-one (1.00 g, 4.44 mmol, 1 eq.) in DCM (30 mL) at -78 °C was added DAST (1.467 mL, 11.11 mmol, 2.5 eq.). The reaction mixture was then allowed to warm to 25 °C and stirred for 16 h. The reaction mixture was quenched with water and neutralized with a saturated aqueous sodium bicarbonate solution. The mixture was then extracted with DCM (2 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield 1-bromo-4-(3,3-difluorocyclobutyl)benzene (1.10 g, 3.22

mmol, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.45 (m, 2H), 7.17-7.09 (m, 2H), 3.13-2.93 (m, 2H), 2.75-2.53 (m, 2H).

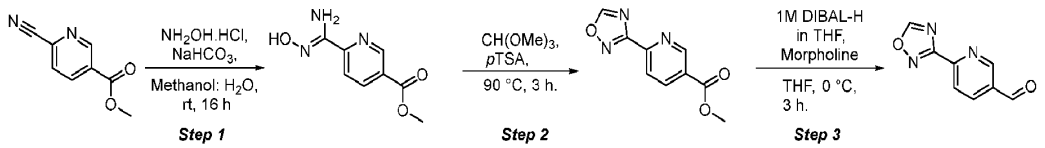
Step 2: **Synthesis of 1-(3,3-difluorocyclobutyl)-4-vinylbenzene**

To a stirred solution of 1-bromo-4-(3,3-difluorocyclobutyl)benzene (1.10 g, 4.45 mmol, 1 eq.) and potassium vinyl trifluoroborate (1.193 g, 8.90 mmol, 2 eq.) in 1,4-dioxane (10 mL) at 25 °C was added cesium carbonate (2.90 g, 8.90 mmol, 2 eq.). The reaction mixture was sparged with argon for 10 minutes. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (0.182 g, 0.22 mmol, 0.05 eq.) was then added at 25 °C. The reaction mixture was stirred at 80 °C for 16 h. The reaction was filtered through a Celite bed, and the filtrate was concentrated under reduced pressure to afford crude 1-(3,3-difluorocyclobutyl)-4-vinylbenzene (1.10 g, 2.83 mmol, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.38 (m, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 6.73 (dd, *J* = 10.8, 17.6 Hz, 1H), 5.76 (dd, *J* = 0.8, 17.6 Hz, 1H), 5.26 (dd, *J* = 0.8, 10.8 Hz, 1H), 3.10-2.93 (m, 2H), 2.78-2.57 (m, 2H).

Step 3: **Synthesis of 4-(3,3-difluorocyclobutyl)benzaldehyde (ALD-109)**

To a stirred solution of 1-(3,3-difluorocyclobutyl)-4-vinylbenzene (1.10 g, 5.66 mmol, 1 eq.) in THF (25 mL) and water (8 mL) at 0 °C was added sodium periodate (1.817 g, 8.50 mmol) followed by potassium osmate dihydrate (0.125 g, 0.34 mmol, 0.06 eq.) at 0 °C. The reaction mixture was then stirred at 25 °C for 30 minutes. The reaction mixture was diluted with water and extracted with EtOAc (2 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get the crude product. The crude product was purified by reverse-phase column chromatography using a C18 cartridge (120 g), eluted with a gradient of 30% acetonitrile in 0.1% formic acid in water. Pure fractions were concentrated under reduced pressure to afford 4-(3,3-difluorocyclobutyl)benzaldehyde (**ALD-109**, 0.35 g, 1.43 mmol, 25% yield). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 196.9; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.00 (s, 1H), 7.93-7.86 (m, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 3.13-2.98 (m, 2H), 2.84-2.67 (m, 2H).

Example 201: Synthesis of 6-(1,2,4-oxadiazol-3-yl)nicotinaldehyde (ALD-110)



Step 1: **Synthesis of methyl (Z)-6-(N'-hydroxycarbamimidoyl)nicotinate**

To a stirred solution of hydroxylamine hydrochloride (0.429 g, 6.17 mmol, 2 eq.) in water (5 mL) at 25 °C was added sodium bicarbonate (0.518 g, 6.17 mmol, 2 eq.). The mixture was stirred for 15 min. A solution of methyl 6-cyanonicotinate (0.5 g, 3.08 mmol, 1 eq.) 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 (0.55 g,

2.79 mmol, 90% yield). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 196.1; ^1H 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).

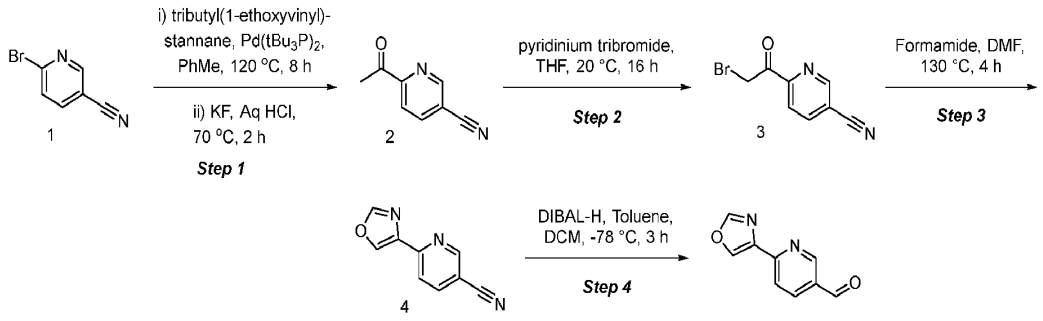
Step 2: **Synthesis of methyl 6-(1,2,4-oxadiazol-3-yl)nicotinate**

To a stirred solution of methyl 6-(N-hydroxycarbamimidoyl)nicotinate (2.00 g, 10.25 mmol, 1 eq.) in trimethyl orthoformate (8.50 mL, 77.0 mmol, 7.5 eq.) was added toluene-4-sulfonic acid monohydrate (0.195 g, 1.03 mmol, 0.1 eq.) 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 (2.10 g, 10.09 mmol, 98% yield). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 206.2; ^1H 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-110)**

To a stirred solution of morpholine (0.97 mL, 11.21 mmol, 2.3 eq.) in THF (12.5 mL) at 0 °C was added DIBAL-H (10.72 mL, 10.72 mmol, 2.2 eq.). 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 eq.) in THF (12.5 mL) was added to the reaction mixture, which was then stirred at 0 °C for 1 h. After that, DIBAL-H (5.85 mL, 5.85 mmol, 1.1 eq.) 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 EtOAc (EtOAc, 2 × 100 mL). The pooled organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, The crude compound was purified by silica gel flash column chromatography, eluting with EtOAc in hexane (40%-80%) to afford 6-(1,2,4-oxadiazol-3-yl)nicotinaldehyde (**ALD-110**, 0.210 g, 1.175 mmol, 24% yield). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 176.0; ^1H NMR (400 MHz, DMSO-d_6): δ ^1H 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 202: Synthesis of 6-(oxazol-4-yl)nicotinaldehyde (ALD-111)



Step 1: **Synthesis of 6-acetylnicotinonitrile**

To a stirred solution of 6-bromonicotinonitrile (5.00 g, 27.3 mmol, 1.00 eq.) in toluene (40 mL) was added tributyl(1-ethoxyvinyl)stannane (10.15 mL, 30.1 mmol, 1.10 eq.) 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 eq.) 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 EtOAc (2 × 200 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (100-200 mesh) using a gradient of EtOAc in hexane (0-20%) as the eluent to afford 6-acetylnicotinonitrile (3.50 g, 23.33 mmol, 85% yield). 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 eq.) in tetrahydrofuran (110 mL) was added pyridinium tribromide (7.44 g, 23.26 mmol, 1.00 eq.) 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 EtOAc (2 × 200 mL). The combined organic layers were dried over anhydrous Na_2SO_4, 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 EtOAc in hexane (0-20%) as the eluent to yield 6-(2-bromoacetyl)nicotinonitrile (2.57 g, 9.09 mmol, 39% yield. 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).

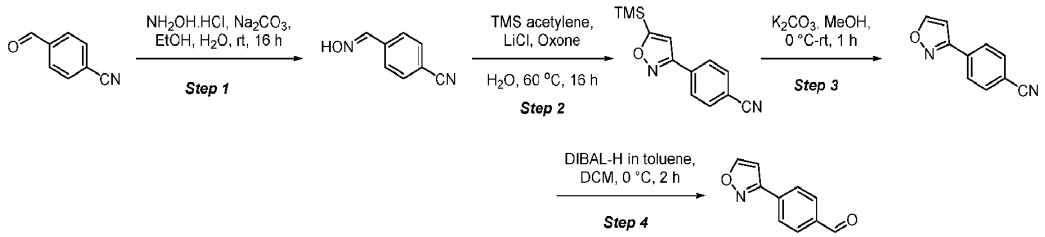
Step 3: **Synthesis of 6-(oxazol-4-yl)nicotinonitrile**

To a stirred solution of 6-(2-bromoacetyl)nicotinonitrile (2.57 g, 11.42 mmol, 1.00 eq.) in DMF (12.5 mL) at 25 °C, formamide (12.79 mL, 322 mmol, 28.2 eq.) 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 (0.57 g, 3.11 mmol, 27% yield). 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-111)**

To a stirred solution of 6-(oxazol-4-yl)nicotinonitrile (0.470 g, 2.47 mmol, 1 eq.) in DCM (15 mL) was added DIBAL-H in toluene (7.2 mL, 7.4 mmol, 3 eq.) 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 EtOAc (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-111**, 0.250 g, 0.919 mmol, 37% yield). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 175.1.

Example 203: Synthesis of 4-(isoxazol-3-yl)benzaldehyde (ALD-112)



Step 1: **Synthesis of (Z)-4-((hydroxyimino)methyl)benzonitrile**

To a stirred solution of sodium carbonate (4.85 g, 45.8 mmol, 1.2 eq.) in water (50 mL) was added hydroxylamine hydrochloride (3.18 g, 45.8 mmol, 1.2 eq.), followed by the addition of 4-formylbenzonitrile (5 g, 38.1 mmol, 1 eq.) 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 Na_2SO_4 filtered, and concentrated under reduced pressure to afford crude (Z)-4-((hydroxyimino)methyl)benzonitrile (4.5 g, 30.3 mmol, 79% yield). 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 eq.) was added to a solution of (Z)-4-((hydroxyimino)methyl)benzonitrile (2 g, 13.68 mmol, 1 eq.) in water (30 mL). Lithium chloride (0.580 g, 13.68 mmol, 1 eq.) was added portion-wise, followed by oxone (12.62 g, 20.53 mmol, 1.5 eq.) 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 EtOAc (2 × 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 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 EtOAc as the eluent to obtain the

desired product (2 g, 8.2 mmol, 62% yield). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 243.0; ^1H 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).

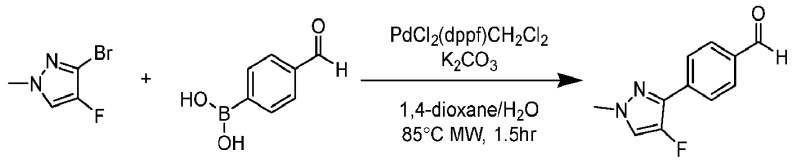
Step 3: **Synthesis of 4-(isoxazol-3-yl)benzonitrile**

To a stirred solution of 4-(5-(trimethylsilyl)isoxazol-3-yl)benzonitrile (1.3 g, 5.36 mmol, 1 eq.) in methanol (17 mL) at 0 °C under a nitrogen atmosphere, potassium carbonate (1.11 g, 8.05 mmol, 1.5 eq.) was added. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to afford the crude product. The crude product was then dissolved in water (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to yield 4-(isoxazol-3-yl)benzonitrile. Quantitative yield was assumed. LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 170.9; ^1H 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-112)**

To a stirred solution of 4-(isoxazol-3-yl)benzonitrile (0.4 g, 2.35 mmol, 1 eq.) 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 eq.). 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 eq.) 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 Na_2SO_4 and concentrated under reduced pressure to afford the crude product. The crude compound was purified by silica gel flash column chromatography, eluting with EtOAc in hexane (2-4%) to afford 4-(isoxazol-3-yl)benzaldehyde (**ALD-112**, 0.2 g, 1.15 mmol, 49% yield). LCMS: m/z: MM-ES+APCI, positive $[M+H]^+$ 174.0; ^1H 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).

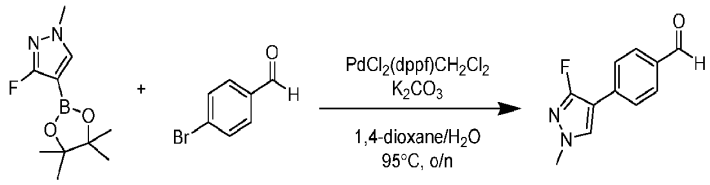
Example 204: Synthesis of 4-(4-fluoro-1-methyl-1H-pyrazol-3-yl)benzaldehyde (ALD-113)



A stirred mixture of 3-bromo-4-fluoro-1-methyl-1H-pyrazole (0.18 g, 1.0 mmol), (4-formylphenyl)boronic acid (0.18 g, 1.2 mmol), dioxane (3 mL), K_2CO_3 (0.21 g, 1.5 mmol, solution in 0.3 mL water), and $PdCl_2$(dppf)-DCM adduct (0.082 g, 0.1 mmol) was sparged with argon under sonication for 4 min, then the reaction vial was sealed and the mixture was stirred at 85 °C for 90 min under microwave irradiation. The cooled mixture was loaded onto silica gel and subject to purification via silica gel flash column chromatography, eluting with 20 to 80% EtOAc in heptane to afford 4-(4-fluoro-1-

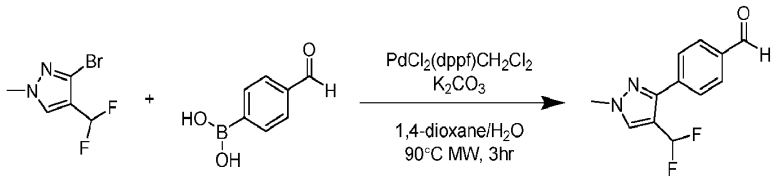
methyl-1H-pyrazol-3-yl)benzaldehyde (**ALD-113**, 0.115 g, 0.56 mmol, 56% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 205.0. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 10.01 (s, 1H), 8.03 (d, J = 4.38 Hz, 1H), 7.94-8.00 (m, 4H), 3.87 (s, 3H).

Example 205: Synthesis of 4-(3-fluoro-1-methyl-1H-pyrazol-4-yl)benzaldehyde (ALD-114)



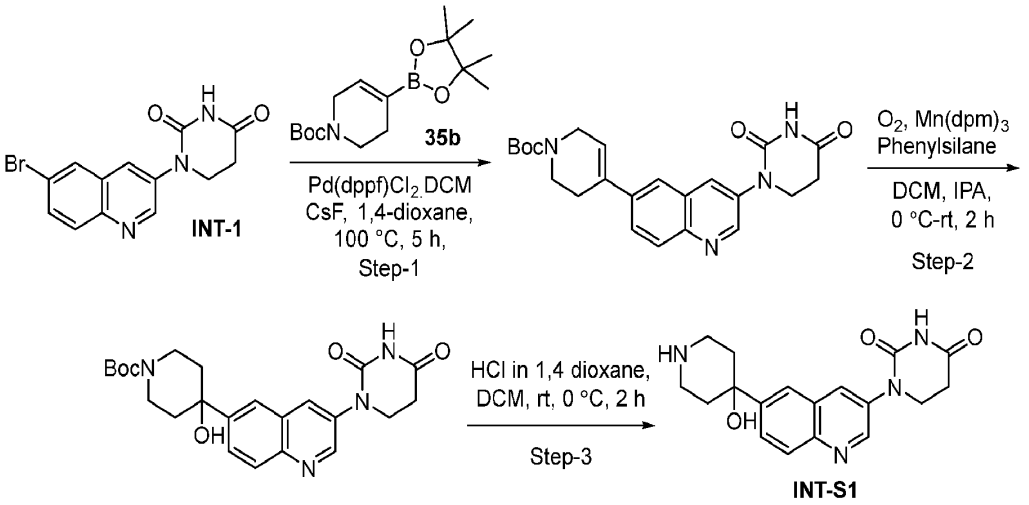
A mixture of 3-fluoro-1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.23 g, 1.0 mmol), 4-bromobenzaldehyde (0.15 g, 0.8 mmol), dioxane (3 ml), $PdCl_2$(dppf)-DCM adduct (0.08 g, 0.1 mmol), and K_2CO_3 (0.21 g, 1.5 mmol, solution in 0.3 mL water) was sparged with argon under sonication for 5 min, then reaction mixture was stirred at 95 °C for 16h. The cooled mixture was loaded onto silica gel and subject to purification via silica gel flash column chromatography, eluting with 20 to 80% EtOAc in heptane to afford 4-(3-fluoro-1-methyl-1H-pyrazol-4-yl)benzaldehyde (**ALD-114**, 0.146 g, 0.71 mmol, 71% yield). 4-(3-fluoro-1-methyl-1H-pyrazol-4-yl)benzaldehyde. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 205.1. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 9.97 (s, 1H), 8.33-8.34 (m, 1H), 8.30-8.32 (m, 1H), 7.88-7.99 (m, 2H), 7.74 (d, J = 8.21 Hz, 2H), 3.79 (s, 3H).

Example 206: Synthesis of 4-(4-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)benzaldehyde (ALD-115)



A mixture of 3-bromo-4-(difluoromethyl)-1-methyl-1H-pyrazole (0.21 g, 1.0 mmol), (4-formylphenyl)boronic acid (0.18 g, 1.2 mmol), dioxane (3 mL), K_2CO_3 (0.21 g, 1.5 mmol, solution in 0.3 mL water), and $PdCl_2$(dppf)-DCM adduct (0.082 g, 0.1 mmol) was sparged with argon under sonication for 4 min, then the reaction vial was sealed and the mixture was stirred at 90 °C for 3h under microwave irradiation. The cooled mixture was loaded onto silica gel and subject to purification via silica gel flash column chromatography, eluting with 20 to 80% EtOAc in heptane to afford 4-(4-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)benzaldehyde (**ALD-115**, 170 mg, 0.72 mmol, 72% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 237.1. ^1H NMR (500 MHz, DMSO-d6) δ ppm 10.04 (s, 1H), 8.20 (s, 1H), 7.97-8.00 (m, 2H), 7.88-7.92 (m, 2H), 7.00-7.49 (t, J = 55 Hz, 1H), 3.95 (s, 3H).

Example 207: Synthesis of 1-(6-(4-hydroxypiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (INT-S1)



Step 1: **Synthesis of *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)quinolin-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate**

To a stirred solution of 1-(6-bromoquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**INT-1**, 0.5 g, 1.56 mmol) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**35b**, 0.580 g, 1.87 mmol) in 1,4-dioxane (2 mL) and water (0.2 mL) was added DIPEA (0.544 mL, 3.12 mmol) at rt. The reaction mixture was sparged with nitrogen for 15 minutes. Then, Bis(tri-tert-butylphosphine)palladium(0) (0.080 g, 0.156 mmol) was added, and the resulting reaction mixture was stirred at 100 °C in a sealed vial for 5 h. The reaction mixture was diluted with EtOAc and passed through a Celite bed, and the filtrate was concentrated under reduced pressure. The crude residue was purified by reverse phase chromatography on a C18 column, eluting with 0.1% FA in water and acetonitrile to afford tert-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)quinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (320 mg, 2.18 mmol, 40% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 423.0. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.59 (s, 1H), 8.89 (d, J = 2.40 Hz, 1H), 8.24 (d, *J* = 2.40 Hz, 1H), 7.89-7.91 (m, 3H), 6.43 (s, 1H), 4.08 (s, 2h), 3.97 (t, *J* = 6.80 Hz, 2H), 3.61 (t, *J* = 5.60 Hz, 2H), 2.80 (t, *J* = 6.40 Hz, 2H), 2.61 (d, *J* = 1.60 Hz, 2H), 1.45 (s, 9H).

Step 2: **Synthesis of *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)quinolin-6-yl)-4-hydroxypiperidine-1-carboxylate**

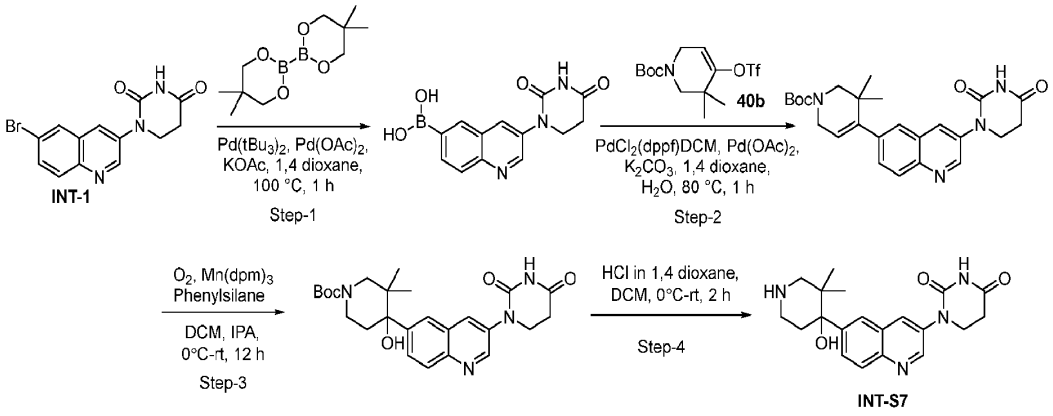
Tert-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)quinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (0.65 g, 1.539 mmol) was treated according to **General Procedure 3, Step C**. The reaction mixture was concentrated under reduced pressure. The crude residue was dissolved in EtOAc and passed through a Celite bed, and the filtrate was concentrated. The crude residue was purified by reverse phase chromatography on a C18 column, eluting with 0.1% FA in water and acetonitrile to afford tert-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)quinolin-6-yl)-4-hydroxypiperidine-1-carboxylate

(360 mg, 0.768 mmol, 50% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 441.0; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.59 (s, 1H), 8.89 (d, J = 2.40 Hz, 1H), 8.24 (d, *J* = 2.00 Hz, 1H), 8.03 (d, *J* = 1.60 Hz, 1H), 7.94 (d, *J* = 2.00 Hz, 1H), 7.88 (d, *J* = 2.00 Hz, 1H), 5.35 (s, 1H), 3.98-3.90 (m, 4H), 3.24-3.22 (m, 2H), 2.80 (t, *J* = 6.80 Hz, 2H), 1.93 (t, *J* = 8.40 Hz, 2H), 1.69 (d, *J* = 12.80 Hz, 2H), 1.44 (s, 9H).

Step 3: **Synthesis of 1-(6-(4-hydroxypiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (INT-S1)**

To a stirred solution of *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)quinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (0.32 g, 0.726 mmol) in DCM (5 mL) was added 4M HCl in dioxane (0.545 mL, 2.18 mmol) at 0 °C and the reaction mixture was allowed to stir at rt for 1 h. The reaction mixture was concentrated and dried under vacuum to afford 1-(6-(4-hydroxypiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**INT-S1**, 0.28 g, 0.550 mmol, 76% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 341.2; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.66 (s, 1H), 9.12-9.11 (m, 1H), 9.05 (d, *J* = 2.40 Hz, 1H), 8.98-8.97 (m, 1H), 8.50 (d, *J* = 1.60 Hz, 1H), 8.15-8.10 (m, 2H), 7.93 (dd, *J* = 2.00, 8.80 Hz, 1H), 4.00 (t, *J* = 6.80 Hz, 2H), 3.26 (s, 4H), 2.83-2.53 (m, 2H), 2.37-2.34 (m, 2H), 1.89-1.86 (m, 2H).

Example 208: Synthesis of 1-(6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (INT-S7)



Step 1: **Synthesis of (3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)quinolin-6-yl)boronic acid**

To a stirred solution of 1-(6-bromoquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**INT-1**, 600 mg, 1.874 mmol) in 1,4-dioxane (6 mL) were added 5,5,5',5'-tetramethyl-2,2'-bi(1,3,2-dioxaborinane) (847 mg, 3.75 mmol) and potassium acetate (552 mg, 5.62 mmol) at 25 °C, then the mixture was sparged with nitrogen for 10 min. To this reaction mixture were added tert-butyldiphenylphosphine (91 mg, 0.375 mmol) and palladium(II) acetate (42.1 mg, 0.187 mmol), then the mixture was sparged with nitrogen for 5 min. The resulting reaction mixture was heated at 100 °C for 1 h. The cooled reaction mixture was filtered through a Celite bed and washed with EtOAc (60 mL). The

filtrate was concentrated under reduced pressure to afford (3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)quinolin-6-yl)boronic acid (0.6 g, 1.60 mmol, 86% yield) which was used in the next step without purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 285.6. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.97 (s, 1H), 8.32 (s, 1H), 8.12-8.06 (m, 3H), 7.77 (s, 2H), 4.04 (t, J = 6.80 Hz, 2H), 2.96 (t, J = 6.40 Hz, 2H). (some NH resonances not observed)

Step 2: **Synthesis of *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)quinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate**

To a stirred solution of (3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)quinolin-6-yl)boronic acid (0.6 g, 2.11 mmol) in 1,4-dioxane (4 mL) and water (0.4 mL) were added tert-butyl 3,3-dimethyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (**40b**, 0.757 g, 2.11 mmol) and K_2CO_3 (0.582 g, 4.21 mmol) at room temperature, and the mixture was sparged with nitrogen for 10 min. To this reaction mixture was added $PdCl_2$(dppf).DCM adduct (0.086 g, 0.105 mmol), and the mixture was sparged with nitrogen for 5 min. The resulting reaction mixture was heated at 80 °C for 1 h. The cooled reaction mixture was filtered through a Celite bed and washed with EtOAc (2 × 50 mL). The filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by reverse phase column chromatography to afford tert-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)quinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (450 mg, 0.679 mmol, 32% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 451.8.

Step 3: **Synthesis of *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)quinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate**

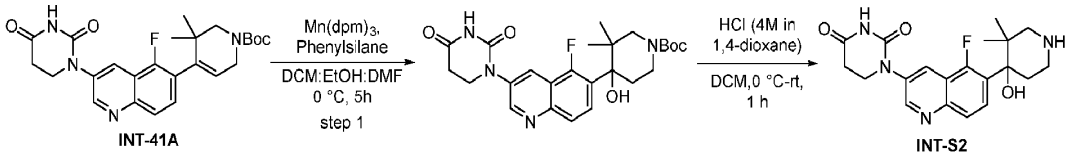
Tert-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)quinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (260 mg, 0.577 mmol) was treated according to **General Procedure 3, Step C**. The crude residue was purified by silica gel flash chromatography, eluting with 0-15% EtOAc in hexane to afford *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)quinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (120 mg, 0.195 mmol, 34% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 469.3; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.58 (s, 1H), 8.90 (s, 1H), 8.27 (s, 1H), 8.02 (s, 1H), 7.96-7.93 (m, 2H), 5.18 (s, H), 4.01 (m, 4H), 3.39-3.20 (m, 2H), 3.97 (t, J = 6.80 Hz, 2H), 2.82-2.80 (m, 2H), 1.50 (s, 9H), 0.85 (s, 3H), 0.75 (s, 3H).

Step 4: **Synthesis of 1-(6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (INT-S7)**

To a stirred solution of *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)quinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (120 mg, 0.256 mmol) in DCM (3 mL) was added HCl (4M in dioxane) (0.256 mL, 1.024 mmol) at 0 °C and the reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated under reduced pressure. The crude residue was triturated with MTBE,

filtered and dried to afford 1-(6-(4-hydroxy-3,3-dimethyl-piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (**INT-S7**, 110 mg, 0.173 mmol, 68% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 369.3. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.63 (s, 1H), 9.11 (s, 1H), 8.60-8.43 (m, 2H), 8.14-8.03 (m, 2H), 5.76 (s, 1H), 3.38-3.35 (m, 2H), 3.01-2.92 (m, 2H), 2.89-2.81 (m, 2H), 1.60 (m, 2H), 1.27-1.24 (m, 2H), 0.96 (s, 3H), 0.80 (s, 3H).

Example 209: Synthesis of 1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (INT-S2)



Step 1: **Synthesis of *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate**

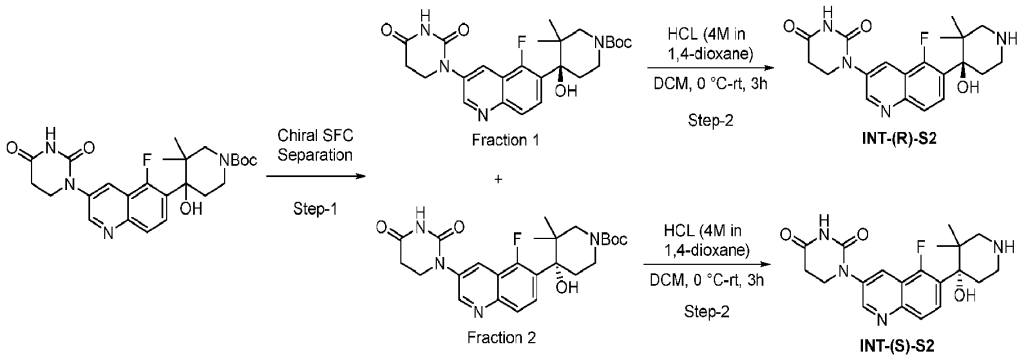
Tert-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-fluoroquinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2*H*)-carboxylate (**INT-41A,** 1.1g, 2.348 mmol) was treated according to **General Procedure 3, Step C**. The reaction mixture was diluted with DCM and filtered through a Celite bed. The filtrate was concentrated under reduced pressure, and the crude residue was purified by reverse phase chromatography on a C18 column, eluting with 0.1% FA in water and 0.1% FA IVin acetonitrile to afford *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (0.53 g, 1.04 mmol, 44% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 487.6: ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.61 (s, 1H), 8.98 (d, J = 2.4 Hz, 1H), 8.33 (d, J = 2.4 Hz, 1H), 8.06-8.10 (m, 1H), 7.87 (d, J = 8.8 Hz, 1H), 5.76 (s, 1H), 4.02-4.00 (m, 3H), 3.46-3.43 (m, 1H), 3.28-3.27 (m, 2H), 2.95-2.96 (m, 1H), 2.82-2.80 (m, 2H), 1.70-1.67 (m, 1H), 1.43 (s, 9H), 0.89 (s, 3H), 0.75 (s, 3H).

Step 2: **Synthesis of 1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (INT-S2)**

HCl (4M in 1,4-dioxane, 0.62 ml, 2.47 mmol) was added at 0 °C to a stirred solution of tert-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (80 mg, 0.164 mmol) in DCM (3 ml), and the reaction mixture was stirred at rt for 1 h. The reaction mixture was concentrated under reduced pressure to afford 1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**INT-S2**, 60 mg, 0.134 mmol, 83% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 387.4; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.63 (s, 1H), 9.10 (d, J = 10.8 Hz, 1H), 9.00 (d, J = 2.4 Hz, 1H), 8.35 (m, 2H), 8.04-8.09 (m, 1H), 7.91

(d, J = 8.8 Hz, 1H), 5.88 (s, 1H), 4.02 (d, J = 6.4 Hz, 2H), 3.25-3.22 (m, 4H), 2.97-2.94 (m, 1H), 2.83-2.81 (m, 2H), 1.91-1.91 (m, 1H), 0.99 (s, 3H), 0.79 (s, 3H).

Example 210: Synthesis of (*R*)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (INT-(R)-S2) and (*S*)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (INT-(S)-S2)



Step 1: **Chiral Separation of *tert*-butyl (R)-4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate and *tert*-butyl (S)-4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate**

Tert-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (from "Ex **INT-S2", Step 1**, 0.53 g, 1.035 mmol) was subjected to chiral SFC chromatography using the following method:

Instrument: PIC 22-027
Column: CHIRALPAK AS-H 250 x 30 mm, 5 µm
Mobile Phase: CO_2: 2-Propanol [70:30]
Total Flow: 120 mL/min
Back pressure: 120 bar
Wavelength: 254 nm
Cycle time: 6 min
Loading: 30 mg/injection

Two peaks obtained after chiral SFC were collected separately and lyophilized.

Fraction 1: *Tert*-butyl (R)-4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (180 mg). Retention time: 4.82 min. Chiral purity: 100 %, [Analysis Method: SFC Chiralpak-AS-H; Flow: 4.00 mL/min, Co-Solvent: 30 % IPA, Oven Temperature : 40 °C, BPR Pressure : 102.0 kgf/cm]. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 487.6: ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.61 (s, 1H), 8.98 (d, J = 2.4 Hz, 1H), 8.33 (d, J = 2.4 Hz, 1H), 8.06-

8.10 (m, 1H), 7.87 (d, *J* = 8.8 Hz, 1H), 5.76 (s, 1H), 4.02-4.00 (m, 3H), 3.46-3.43 (m, 1H), 3.28-3.27 (m, 2H), 2.95-2.96 (m, 1H), 2.82-2.80 (m, 2H), 1.70-1.67 (m, 1H), 1.43 (s, 9H), 0.89 (s, 3H), 0.75 (s, 3H)

Fraction 2: *Tert*-butyl (S)-4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (200 mg). Retention time: 7.14 min. Chiral purity: 98.29 %, [Analysis Method: SFC Chiralpak-AS-H; Flow: 4.00 mL/min, Co-Solvent : 30 % IPA, Oven Temperature : 40 oC, BPR Pressure : 102.0 kgf/cm]. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 487.6: ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.61 (s, 1H), 8.98 (d, *J* = 2.4 Hz, 1H), 8.33 (d, *J* = 2.4 Hz, 1H), 8.06-8.10 (m, 1H), 7.87 (d, *J* = 8.8 Hz, 1H), 5.76 (s, 1H), 4.02-4.00 (m, 3H), 3.46-3.43 (m, 1H), 3.28-3.27 (m, 2H), 2.95-2.96 (m, 1H), 2.82-2.80 (m, 2H), 1.70-1.67 (m, 1H), 1.43 (s, 9H), 0.89 (s, 3H), 0.75 (s, 3H).

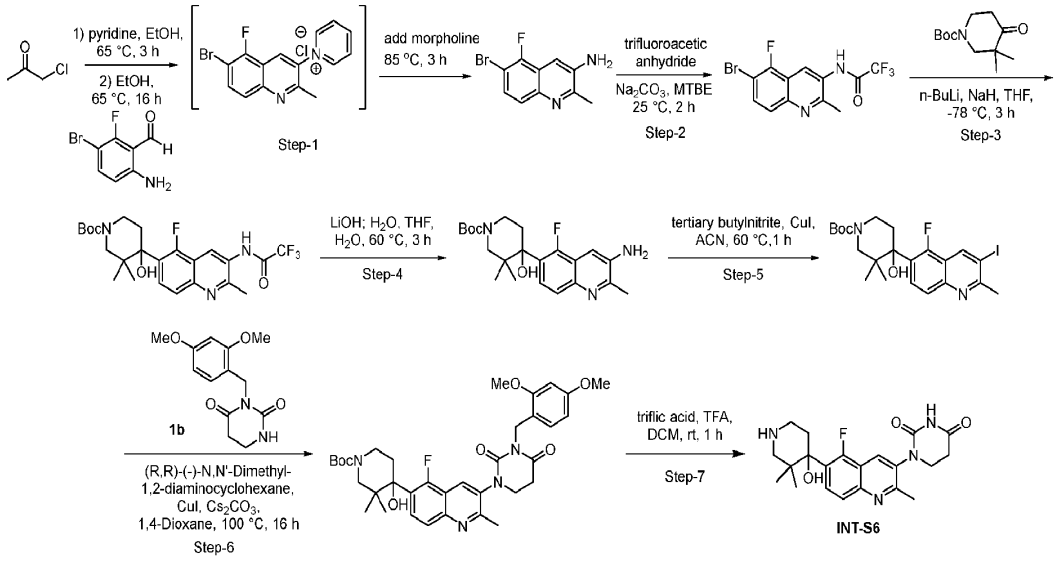
Note: Absolute stereochemistry was assigned arbitrarily

Step 2: **Synthesis of (*R*)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydro pyrimidine-2,4(1*H*,3*H*)-dione (INT-(R) S2)**

To a stirred solution of *tert*-butyl (*R*)-4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (the Fraction 1 product from Step 1, 50 mg, 0.103 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (176 mg, 1.54 mmol) at 0 °C under a nitrogen atmosphere, and the mixture was stirred at rt for 1 h. The reaction mixture was concentrated under reduced pressure to afford (*R*)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 387.4; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.63 (s, 1H), 9.01 (d, *J* = 2.4 Hz, 1H), 8.35 (m 2H), 8.04-8.09 (m, 1H), 7.91 (d, *J* = 8.8 Hz, 1H), 5.88 (s, 1H), 4.02 (d, *J* = 6.4 Hz, 2H), 3.25-3.22 (m, 4H), 2.97-2.94 (m, 1H), 2.83-2.81 (m, 2H), 1.91-1.91 (m, 1H), 0.99 (s, 3H), 0.79 (s, 3H).

Similarly prepared was **(*S*)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydro pyrimidine-2,4(1*H*,3*H*)-dione (INT-(S) S2)** starting from the Fraction 2 product from Step 1. LCMS: m/z MM-ES+APCI, $[M+H]^+$ 387; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.63 (s, 1H), 9.01-8.94 (m, 2H), 8.36-8.35 (m, 2H), 8.08 (d, *J* = 8.8 Hz, 1H), 7.90 (d, *J* = 8.8 Hz, 1H), 5.91 (s, 1H), 4.03-3.99 (m, 3H), 3.32-3.20 (m, 4H), 2.97-2.95 (m, 1H), 2.95-2.93 (m, 2H), 1.95-1.91 (m, 1H), 0.95 (s, 3H), 0.82 (s, 3H).

Example 211: Synthesis of 1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (INT-S6)



Step 1: **Synthesis of 6-bromo-5-fluoro-2-methylquinolin-3-amine**

To a stirred solution of pyridine (50 mL) in ethanol (500 mL) under a nitrogen atmosphere at rt was added 1-chloropropan-2-one (29.7 g, 321 mmol). The reaction mixture was heated to 65 °C for 3 h, then cooled to room temperature, and subjected to three cycles of vacuum followed by nitrogen backfill. Pyridine (50 mL) and 6-amino-3-bromo-2-fluorobenzaldehyde (50 g, 229 mmol) in ethanol (50 mL) were added. The reaction mixture was heated at 65 °C with stirring for 16 h and then was allowed to cool. Morpholine (55.9 g, 642 mmol) was added dropwise at rt, and the mixture was then stirred at 85 °C for 3 h. The reaction mixture was cooled to rt, water (500 mL) was added, and the mixture was extracted with ethyl acetate (2 x 500 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography, eluting with 0-45 % ethyl acetate in hexane to afford 6-bromo-5-fluoro-2-methylquinolin-3-amine. LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ 255.1, 257.1: ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.63 (d, J = 1.2 Hz, 1H), 7.60 (d, J = 1.2 Hz, 1H), 7.50 (s, 1H), 4.06 (s, 2H), 2.47 (s, 3H).

Step 2: **Synthesis of N-(6-bromo-5-fluoro-2-methylquinolin-3-yl)-2,2,2-trifluoroacetamide**

To a stirred mixture of 6-bromo-5-fluoro-2-methylquinolin-3-amine (70 g, 274 mmol), MTBE (2000 mL), and Na_2CO_3 (87 g, 823 mmol) at 0 °C was added trifluoroacetic anhydride (53.5 mL, 357 mmol) dropwise, then the reaction was allowed to warm to rt and stirred for 2 h. The reaction mixture was diluted with ice-cold water (300 mL) and extracted with ethyl acetate (2 x 300 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography, eluting with 0-60 % ethyl acetate in hexane to afford N-(6-bromo-5-fluoro-2-methylquinolin-3-yl)-2,2,2-trifluoroacetamide (89 g, 243 mmol, 89% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$

351.2, 353.3: 1H-NMR (400 MHz, DMSO-d6): δ 11.43 (s, 1H), 8.49 (s, 1H), 7.97-8.01 (m, 1H), 7.80 (d, J = 8.8 Hz, 1H), 2.63 (s, 3H).

Step 3: **Synthesis of 4-(5-fluoro-2-methyl-3-(2,2,2-trifluoroacetamido)quinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate**

To a stirred solution of N-(6-bromo-5-fluoro-2-methylquinolin-3-yl)-2,2,2-trifluoroacetamide (5 g, 14.2 mmol) in THF (40 mL) at 0 °C was added sodium hydride (0.68 g, 17 mmol), and the mixture was stirred for 30 minutes. The reaction mixture was cooled to -78 °C, and n-butyllithium (1.6 M in hexanes, 9.79 mL, 15.7 mmol) was added slowly dropwise and the reaction mixture was stirred for 15 minutes. This was followed by the addition of a solution of tert-butyl 3,3-dimethyl-4-oxopiperidine-1-carboxylate (4.21 g, 18.5 mmol) in THF (10 mL) at -78 °C, and the mixture was stirred for 3 h. A saturated solution of ammonium chloride (50 mL) was added, and the mixture was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography eluting with 0-30 % ethyl acetate in hexane to afford tert-butyl 4-(5-fluoro-2-methyl-3-(2,2,2-trifluoroacetamido)quinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (4 g, 7.2 mmol, 51% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 500.4; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.38 (s, 1H), 8.42 (s, 1H), 8.08 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 8.8 Hz, 1H), 5.76 (s, 1H), 4.06-4.05 (m, 4H), 3.26-3.23 (m, 2H), 2.61 (s, 3H), 1.43 (s, 9H), 0.87 (s, 3H), 0.73 (s, 3H).

Step 4: **Synthesis of *tert*-butyl 4-(3-amino-5-fluoro-2-methylquinolin-6-yl)-4-hydroxy-3,3-dimethyl piperidine-1-carboxylate.**

To a stirred solution of tert-butyl 4-(5-fluoro-2-methyl-3-(2,2,2-trifluoroacetamido)quinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (11 g, 22.0 mmol) in THF (110 mL) and water (110 mL) was added lithium hydroxide (1.58 g, 66 mmol) and the reaction mixture was heated to 60 °C for 3 h. The cooled reaction mixture was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was triturated with MTBE (50 mL), and the resulting solid was collected on a filter and dried to afford tert-butyl 4-(3-amino-5-fluoro-2-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (6.9 g, 16.7 mmol, 76% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 404.5: ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.63 (d, J = 8.8 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.29 (s, 1H), 5.59 (s, 2H), 5.22 (s, 1H), 4.03-3.96 (m, 1H), 3.50-3.44 (m, 1H), 3.34-3.34 (m, 2H), 3.24-3.21 (m, 1H), 2.90-2.95 (m, 3H), 1.64-1.61 (m, 1H), 1.43 (s, 9H), 0.81 (s, 3H), 0.71 (s, 3H).

Step 5: **Synthesis of *tert*-butyl 4-(5-fluoro-3-iodo-2-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate**

To a stirred solution of tert-butyl 4-(3-amino-5-fluoro-2-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (5 g, 12.4 mmol) in ACN (20 mL) was added copper(I) iodide (4.72 g,

24.8 mmol) at rt and the reaction mixture was stirred for 10 minutes. This was followed by the slow dropwise addition of a solution of tert-butyl nitrite (2.94 mL, 24.8 mmol) in ACN (3 mL) at rt. The reaction mixture was heated at 60 °C for 1 h. Water (30 mL) was added to the cooled reaction mixture, and the mixture was extracted with ethyl acetate (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography, eluting with 0-40 % ethyl acetate in hexane to afford tert-butyl 4-(5-fluoro-3-iodo-2-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (2.1 g, 3.68 mmol, 30% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 515.5: 1H-NMR (400 MHz, DMSO-d6): δ 8.84 (s, 1H), 8.09 (d, J = 8.8 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 5.76 (s, 1H), 4.06-4.01 (m, 4H), 3.26-3.24 (m, 2H), 2.55 (s, 3H), 1.42 (s, 9H), 0.81 (s, 3H), 0.71 (s, 3H).

Step 6: **Synthesis of *tert*-butyl 4-(3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-fluoro-2-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate**

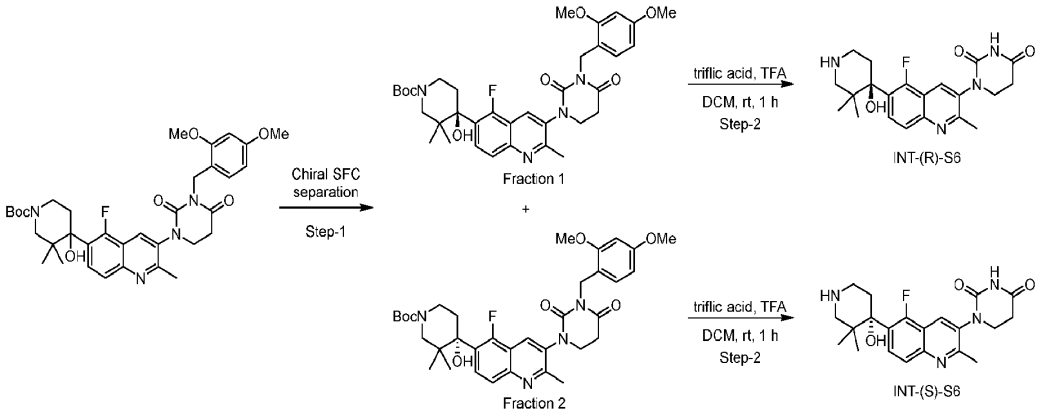
A mixture of tert-butyl 4-(5-fluoro-3-iodo-2-methylquinolin-6-yl)-4-hydroxy-3,3-dimethyl-piperidine-1-carboxylate (1.6 g, 3.1 mmol), 1,4-dioxane (10 mL), 3-(2,4-dimethoxybenzyl)-dihydropyrimidine-2,4(1H,3H)-dione (**1b**, 0.82 g, 3.1 mmol), cesium carbonate (2.03 g, 6.22 mmol), (R,R)-(-)-N,N'-Dimethyl-1,2-diaminocyclohexane (0.133 g, 0.93 mmol) and copper iodide (0.178 g, 0.933 mmol) was stirred under an argon atmosphere at 100 °C for 16 h. The reaction mixture was cooled and filtered through a Celite bed, rinsing with ethyl acetate (100 mL). The combined filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by reverse phase chromatography using a C-18 column, eluting with 50-55% acetonitrile in water to afford tert-butyl 4-(3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoro-2-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (0.93 g, 1.43 mmol, 46% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 651.5: ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.46 (m, 1H), 8.07 (d, J = 8.8 Hz, 1H), 7.80 (d, J = 8.8 Hz, 1H), 6.95 (d, J = 8.8 Hz, 1H), 6.57-6.56 (m, 1H), 6.49 (m, 1H), 5.46 (s, 1H), 4.81-4.79 (m, 2H), 4.06-4.03 (m, 2H), 3.81-3.75 (m, 8H), 3.59-3.51 (m, 1H), 3.07-2.67 (m, 4H), 2.58 (s, 3H), 1.67 (d, J = 13.6 Hz, 1H), 1.43 (s, 9H), 0.83 (s, 3H), 0.72 (s, 3H).

Step 7: **Synthesis of 1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (INT-S6)**

To a stirred solution of *tert*-butyl 4-(3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoro-2-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (3.35 g, 5.15 mmol) in DCM (30 mL) were added TFA (33 mL, 43 mmol) and trifluoromethanesulfonic acid (0.91 mL, 10.3 mmol) at 0 °C, and the mixture was stirred at rt for 1 h. The mixture was then concentrated under reduced pressure. The residue was purified by reverse phase chromatography using a C-18 column, eluting with 5-10% acetonitrile in water to afford 1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-

2-methylquinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione, (**INT-S6**, 1.7 g, 3.3 mmol, 64% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 401.1; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.43 (d, J = 8.8 Hz, 1H), 8.08 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 8. Hz, 1H), 4.02-4.01 (m, 1H), 3.71-3.70 (m, 1H), 3.00-3.17 (m, 4H), 2.87-2.91 (m, 2H), 2.60 (s, 3H), 1.77-1.76 (m, 2H), 0.98 (s, 3H), 0.73 (s, 3H) (Note: 3 proton resonances appear to be obscured by the solvent peak).

Example 212: Synthesis of (*R*)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (INT-(R)-S6) and (S)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (INT-(S)-S6)



Step 1: **Chiral Separation of *tert*-butyl (*R*)-4-(3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-fluoro-2-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate and *tert*-butyl (*S*)-4-(3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-fluoro-2-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate**

Tert-butyl 4-(3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoro-2-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (from "Ex **INT-S6, Step 6**, 1.0 g, 1.54 mmol) was subjected to chiral SFC chromatography using the following method:

Instrument:	PIC 22-027
Column:	Chiralpak-AS-H, IPA, 5μm, 250 x 30 mm
Mobile Phase:	CO_2: 0.2% FA in 1:1 IPA:ACN [70:30]
Total Flow:	120 mL/min
Back pressure:	120 bar
Wavelength:	220 nm
Cycle time:	7 min

Fraction 1: *Tert*-butyl (*R*)-4-(3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-fluoro-2-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate. Retention time: 4.83 min. Chiral Purity : 99.36 %, [Analysis Method: SFC Chiralpak-AS-H; Flow : 4.00 mL/min, Co-Solvent : 25 % IPA, Oven Temperature : 40 °C, BPR Pressure : 102.0 kgf/cm]. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 651.5; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.46 (d, *J* = 4.40 Hz, 1H), 8.07 (d, *J* = 8.80 Hz, 1H), 7.80 (d, *J* = 8.80 Hz, 1H), 6.95 (d, *J* = 8.80 Hz, 1H), 6.57-6.56 (m, 1H), 6.49-6.49 (m, 1H), 5.46 (s, 1H), 4.81-4.79 (m, 2H), 4.03-4.06 (m, 2H), 3.81-3.75 (m, 8H), 3.59-3.51 (m, 1H), 3.07-2.67 (m, 4H), 2.58 (s, 3H), 1.67 (d, *J* = 13.6 Hz, 1H), 1.43 (s, 9H), 0.83 (s, 3H), 0.72 (s, 3H).

Fraction 2: *Tert*-butyl (*S*)-4-(3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-fluoro-2-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate. Retention time: 6.86 min.. Chiral Purity : 98.16 %, [Analysis Method: SFC Chiralpak-AS-H; Flow : 4.00 mL/min, Co-Solvent : 25 % IPA, Oven Temperature : 40 °C, BPR Pressure : 102.0 kgf/cm}. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 651.5: ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.46 (d, *J* = 4.40 Hz, 1H), 8.07 (d, *J* = 8.80 Hz, 1H), 7.80 (d, *J* = 8.80 Hz, 1H), 6.95 (d, *J* = 8.80 Hz, 1H), 6.57-6.56 (m, 1H), 6.49-6.49 (m, 1H), 5.46 (s, 1H), 4.81-4.79 (m, 2H), 4.03-4.06 (m, 2H), 3.81-3.75 (m, 8H), 3.59-3.51 (m, 1H), 3.07-2.67 (m, 4H), 2.58 (s, 3H), 1.67 (d, *J* = 13.6 Hz, 1H), 1.43 (s, 9H), 0.83 (s, 3H), 0.72 (s, 3H).

Note: Absolute stereochemistry was assigned arbitrarily

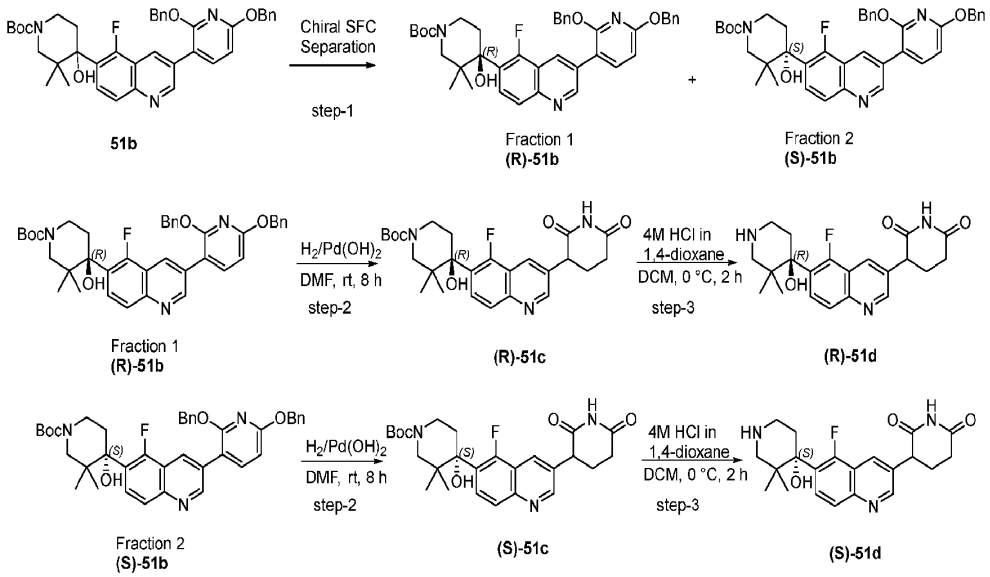
Step 2: **(*R*)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione((R)-S6)**

To a stirred solution of tert-butyl (*R*)-4-(3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoro-2-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (200 mg, 0.307 mmol) in DCM (3 ml) was added trifluoroacetic acid (350 mg, 3.07 mmol) followed by trifluoromethanesulfonic acid (138 mg, 0.922 mmol) at 0 °C under a nitrogen atmosphere and the mixture was stirred at rt for 4 h. The reaction mixture was concentrated under reduced pressure, and the crude residue was washed with hexane and then dried under vacuum to provide (*R*)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, TFA (150 mg, 0.226 mmol, 73% yield). LCMS : m/z MM-ES+APCI, Positive $[M+H]^+$ 401.1; ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.67 (s, 1H), 8.43 (s, 1H), 8.08 (d, *J* = 8.80 Hz, 1H), 7.81 (d, *J* = 8.80 Hz, 1H), 5.80 (s, 1H), 4.02-4.01 (m, 1H), 3.81-3.60 (m, 3H), 3.17-3.00 (m, 3H), 2.91-2.87 (m, 2H), 2.68 (s, 3H), 1.95 (d, J = 10.40 Hz, 1H), 1.25-1.16 (m, 1H), 0.98 (s, 3H), 0.73 (s, 3H).

Similarly prepared was (*S*)-**1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, TFA ((S)-S6)**, starting from ***tert*-butyl (*S*)-4-(3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-fluoro-2-methylquinolin-**

6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (the Fraction 2 product from Step 1). LCMS: m/z MM-ES+APCI, [M+H]+ 401.3; 1H-NMR (400 MHz, DMSO-d6): δ 10.57 (s, 1H), 8.45 (s, 1H), 8.08 (t, J = 8.40 Hz, 1H), 7.83 (d, J = 9.20 Hz, 1H), 5.81 (s, 1H), 4.01-3.98 (m, 1H), 3.81-3.67 (m, 3H), 3.19-3.11 (m, 2H), 2.98-2.79 (m, 2H), 2.68 (s, 3H), 1.93-1.82 (m, 1H), 1.28-1.23 (m, 1H), 1.02 (s, 3H), 0.78 (s, 3H).

Example 213: Synthesis of 3-(5-fluoro-6-((*R*)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione ((R)-51d) and 3-(5-fluoro-6-((*S*)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione ((S)-51d)



Step 1: **Chiral Separation of *tert*-butyl (*R*)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate and *tert*-butyl (*S*)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (**51b**, 6.3 g, 9.5 mmol) was subjected to chiral SFC chromatography using the following method:

Instrument:	PIC 22-027
Column:	I-cellulose Z 250 x 30 mm, 5μm
Mobile Phase:	CO_2: 0.2% FA in 1:1 IPA:ACN [70:30]
Total Flow:	120 ml/min
Back pressure:	120 bar
Wavelength:	220 nm
Cycle time:	7 min
Loading:	18 mg/injection

Two fractions obtained after chiral SFC were collected separately and lyophilized.

Fraction 1: *Tert*-butyl (*R*)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate ((**R)-51b**, 2.5 g, 3.66 mmol, 40 % yield). Retention time: 3.15 min;. LCMS: m/z MM-ES+APCI, $[M+H]^+$ 664.7. ^{1}H-NMR (400 MHz, DMSO-d_6; 9.14 (d, J = 2.0 Hz, 1H), 8.63 (d, J = 1.6 Hz, 1H), 8.10-8.05 (m, 2H), 7.85 (d, J = 8.8 Hz, 1H), 7.30-7.45 (m, 10H), 6.67 (d, J = 8.4 Hz, 1H), 5.50-5.42 (m, 5H), 3.99 (s, 1H), 3.34-2.97 (m, 4H), 1.68 (d, J = 13.6 Hz, 1H), 1.45 (m, 9H), 0.85 (s, 3H), 0.73 (s, 3H).

Fraction 2: *Tert*-butyl (*S*)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (**(S)-51b**, 2.6 g, 3.73 mmol, 41 % yield). Retention time: 4.50 min; LCMS: m/z MM-ES+APCI, $[M+H]^+$ 664.8. ^{1}H-NMR (400 MHz, DMSO-d_6; 9.15 (d, J = 2.0 Hz, 1H), 8.63 (d, J = 1.6 Hz, 1H), 8.16-8.06 (m, 2H), 7.85 (d, J = 8.8 Hz, 1H), 7.31-7.48 (m, 10H), 6.67 (d, J = 8.0 Hz, 1H), 5.50-5.42 (m, 5H), 3.99 (s, 1H), 3.34-2.97 (m, 4H), 1.68 (d, J = 13.6 Hz, 1H), 1.45 (s, 9H), 0.85 (s, 3H), -0.73 (s, 3H).

Step 2: **Synthesis of *tert*-butyl (4*R*)-4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate**

A stirred solution of tert-butyl (R)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (**(R)-51b**, the Fraction 1 product from Step 1, 1.25 g, 1.88 mmol) in N,N-dimethylformamide (15 mL) was sparged with nitrogen. Then palladium hydroxide (20% $Pd(OH)_2$/C, wet basis) (0.66 g, 0.94 mmol) was added at rt. The mixture was stirred at rt for 8h under a hydrogen atmosphere (1 atm). The hydrogen source was removed, then the mixture was sparged with nitrogen and filtered through a Celite bed, rinsing with 1:9 DMF/THF. The combined filtrate was concentrated under reduced pressure. The crude residue was purified by reverse phase chromatography using a C18 column, eluting with 50% acetonitrile in 0.1% FA in water to afford *tert*-butyl (4R)-4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (375 mg, 0.72 mmol, 38% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$486.6; ^{1}H-NMR (400 MHz, DMSO-d_6; 10.98 (s, 1H), 8.86 (d, J = 2.4 Hz, 1H), 8.33 (d, J = 2.0 Hz, 1H), 8.09 (t, J = 8.8 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 5.45 (s, 1H), 4.23 (dd, J = 4.40, 12.6 Hz, 1H), 3.51-3.32 (m, 4H), 3.01-2.92 (m, 1H), 2.72-2.48 (m, 3H), 2.16-2.12 (m, 1H), 1.68 (d, J = 13.2 Hz, 1H), 1.43 (s, 9H), 0.84 (s, 3H), 0.73 (s, 3H).

Similarly prepared was *tert*-butyl (4*S*)-4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate, starting from *tert*-butyl (S)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (**(S)-51b**, the Fraction 2 product from Step 1). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$486.2; ^{1}H-NMR (400 MHz, DMSO-d_6; 10.98 (s, 1H), 8.86 (d, J = 2.4 Hz, 1H), 8.33 (d, J = 2. Hz, 1H), 8.09 (t, J = 8.8 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 5.45 (s, 1H), 4.23 (dd, J = 4.4, 12.6 Hz, 1H), 3.51-3.32 (m, 4H), 3.01-2.92

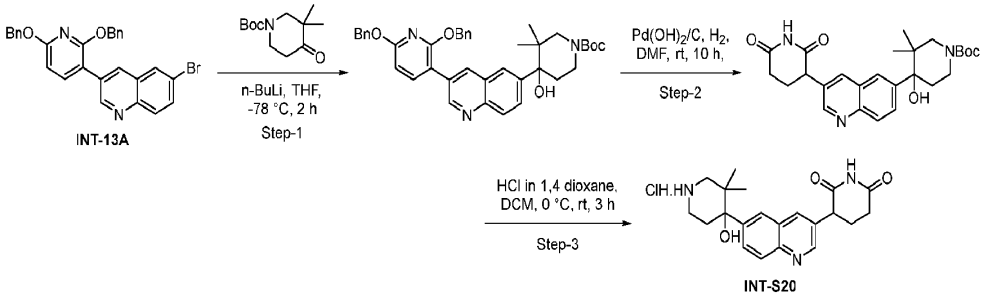
(m, 1H), 2.72-2.48 (m, 3H), 2.16-2.12 (m, 1H), 1.68 (d, *J* = 13.2 Hz, 1H), 1.43 (s, 9H), 0.84 (s, 3H), 0.73 (s, 3H).

Step 3: **3-(5-fluoro-6-((*R*)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione ((R)-51d)**

To a stirred solution of *tert*-butyl (4*R*)-4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (120 mg, 0.25 mmol) in dichloromethane (5 ml) at 0 °C was added HCl (4M in 1,4-dioxane, 0.62 ml, 2.5 mmol) and the mixture was stirred at rt for 2 h. The reaction mixture was concentrated under reduced pressure to afford 3-(5-fluoro-6-((*R*)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, 2HCl (90 mg, 0.193 mmol, 78% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$386.4; ^{1}H-NMR (400 MHz, DMSO-d_6; 11.01 (s, 1H), 9.39 (s, 1H), 8.96 (s, 1H), 8.73-8.47 (m, 2H), 8.13 (t, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 8.8 Hz, 1H), 5.90 (s, 1H), 4.30-4.16 (m, 1H), 3.22-3.15 (m, 4H), 2.68-2.89 (m, 3H), 2.16-2.13 (m, 1H), 1.93 (d, *J* = 11.6 Hz, 1H), 1.06 (s, 3H), 0.81 (s, 3H).

Similarly prepared was 3-(5-fluoro-6-((*S*)-4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, 2HCl (**(S)-51d**), starting from *tert*-butyl (4*S*)-4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate. LCMS: m/z MM-ES+APCI, Positive [M+H] +386.4; 1H-NMR (400 MHz, DMSO-d6 :11.01 (s, 1H), 9.31 (br s, 1H), 8.94 (s, 1H), 8.45 (s, 1H), 8.34 (s, 1H), 8.12 (t, J = 8.80 Hz, 1H), 7.93 (d, J = 9.2 Hz, 1H), 5.90 (s, 1H), 4.27 (dd, J = 4.4, 12.8 Hz, 1H), 3.23-3.08 (m, 4H), 2.65-2.77 (m, 3H), 2.15 (dd, J = 5.2, 9.2 Hz, 1H), 1.94-1.91 (m, 1H), 1.06 (s, 3H), 0.79 (s, 3H).

Example 214: Synthesis of 3-(6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (INT-S20)



Step 1: **Synthesis of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (3 g, 4.51 mmol, 45% yield) was synthesized according to **General Procedure 1, Step A** starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 5 g,

10.1 mmol) and *tert*-butyl 3,3-dimethyl-4-oxopiperidine-1-carboxylate (6.85 g, 30.2 mmol). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$646.5. ^{1}H-NMR (400 MHz, DMSO-d_6; 9.06 (d, J = 2.00 Hz, 1H), 8.52 (d, J = 2.00 Hz, 1H), 8.01-7.93 (m, 4H), 7.33-7.45 (m, 10H), 6.67 (d, J = 8.00 Hz, 1H), 5.46 (m, 2H), 5.44 (s, 2H), 5.17 (s, 1H), 4.05-4.03 (m, 1H), 2.71-3.33 (m, 5H), 1.44 (s, 9H), 0.76-0.74 (m, 6H).

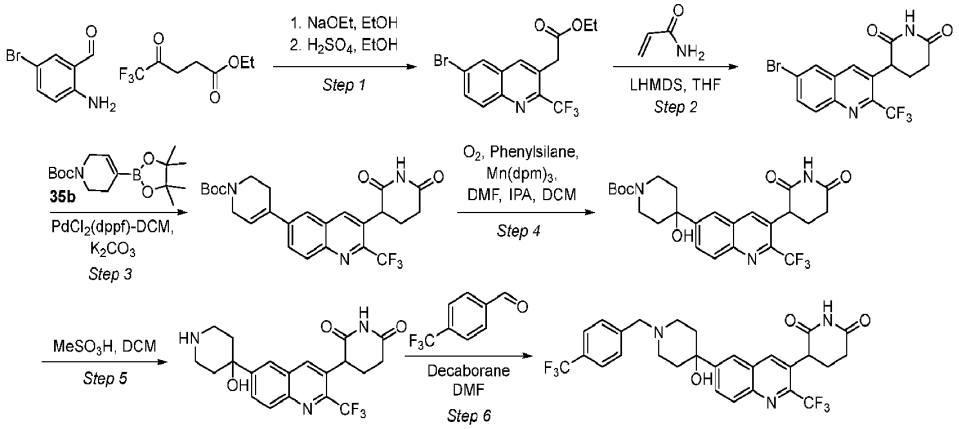
Step 2: **Synthesis of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (0.6 g, 1.21 mmol, 39% yield) was synthesized according to **General Procedure 1, Step B** starting from tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (2 g, 3.10 mmol) with a reaction time of 10h and using *Workup/Purification Procedure (a)*. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$468.4. ^{1}H-NMR (400 MHz, DMSO-d_6; 10.97 (s, 1H), 8.77 (d, J = 2.00 Hz, 1H), 8.22 (d, J = 2.00 Hz, 1H), 8.00-7.94 (m, 3H), 5.16 (s, 1H), 4.17-4.12 (m, 5H), 2.17-3.41 (m, 6H), 1.53-1.43 (m, 9H), 0.76-074 (m, 6H).

Step 3: **Synthesis of 3-(6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (INT-S20)**

3-(6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**INT-S20**, 3.5 g, 7.89 mmol, 100% yield) was synthesized according to **General Procedure 1, Step C** starting from tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (3.7 g, 7.91 mmol) using HCl in dioxane. The crude product was triturated with EtOAc to provide the title compound as an HCl salt. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$368.3. ^{1}H-NMR (400 MHz, DMSO-d_6; 11.09 (s, 1H), 9.66 (s, 1H), 9.22 (s, 1H), 8.99-8.31 (m, 2H), 8.29-8.19 (m, 3H), 6.85 (s, 1H), 4.36 (d, J = 12.00 Hz, 1H), 3.57 (s, 1H), 2.78-3.26 (m, 7H), 1.83-2.24 (m, 2H), 0.97 (s, 3H), 0.79 (s, 3H).

Example 215: Synthesis of 3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-(trifluoromethyl)quinolin-3-yl)piperidine-2,6-dione (I-887)



Step 1: **Synthesis of ethyl 2-(6-bromo-2-(trifluoromethyl)quinolin-3-yl)acetate**

Sodium ethoxide (245 mg, 3.6 mmol) was added to a solution of 2-amino-5-bromobenzaldehyde (600 mg, 3.0 mmol) and ethyl 5,5,5-trifluoro-4-oxopentanoate (594 mg, 3.0 mmol) in ethanol (6 mL) under argon, and the mixture was heated at 80 °C for 16h. The reaction mixture was concentrated in vacuo, then redissolved in ethanol (15 mL). Sulfuric acid (319 µL, 5.99 mmol) and 4 Å mol sieves were added and the reaction mixture was stirred at 90 °C for 1h. The cooled reaction mixture was diluted with EtOAc and filtered, and the filtrate was washed with saturated aqueous sodium bicarbonate solution and brine. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography, eluting with 0 to 100% EtOAc in heptane to provide ethyl 2-(6-bromo-2-(trifluoromethyl)quinolin-3-yl)acetate (802 mg, 2.21 mmol, 74%). LCMS: m/z HESI, positive $[M+H]^+ = 362$.

Step 2: **Synthesis of 3-(6-bromo-2-(trifluoromethyl)quinolin-3-yl)piperidine-2,6-dione**

LHMDS (2.65 mL, 1 molar, 2.65 mmol) was added to a solution of ethyl 2-(6-bromo-2-(trifluoromethyl)quinolin-3-yl)acetate (800 mg, 2.21 mmol) in anhydrous THF (11.0 mL, 0.2 molar) under an argon atmosphere at -78 °C. The mixture was stirred for 1 h at -78 °C before adding acrylamide (188 mg, 2.65 mmol), and the mixture was allowed to warm to rt and stirred for 2h. The reaction mixture was diluted with EtoAc and washed with 1 N HCl (2 x 50 mL) and brine (50 mL). The combined aqueous washes were washed with EtOAc, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography, eluting with 35% EtOAc in heptane to afford 3-(6-bromo-2-(trifluoromethyl)quinolin-3-yl)piperidine-2,6-dione (683 mg, 1.76 mmol, 80%). LCMS: m/z HESI, positive $[M+H]^+ = 387$.

Step 3: **Synthesis of tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-2-(trifluoromethyl)quinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate**

A solution of potassium carbonate in water (1.41 mL, 2 molar, 2.82 mmol) was added to a mixture of 3-(6-bromo-2-(trifluoromethyl)quinolin-3-yl)piperidine-2,6-dione (683 mg, 1.76 mmol), [1,1′-$PdCl_2$(dppf)• DCM (216 mg, 265 µmol), and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**35b**, 655 mg, 2.12 mmol) in dioxane (7 mL). The mixture was sparged with argon, and the reaction vial was sealed and the mixture stirred under microwave irradiation for 3h at 85 °C. The cooled reaction mixture was concentrated under reduced pressure, then the residue was purified by silica gel flash chromatography, eluting with 0 to 100% EtOAc in heptane to afford tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-2-(trifluoromethyl)quinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (691 mg, 1.41 mmol, 80%). LCMS: m/z HESI, positive $[M+H]^+ = 490$.

Step 4: **Synthesis of tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-2-(trifluoromethyl)quinolin-6-yl)-4-hydroxypiperidine-1-carboxylate**

Tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-3-(trifluoromethyl)quinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (690 mg, 1.41 mmol) was treated according to **General Procedure 3, Step C**. The reaction mixture was concentrated under reduced pressure, and the residue was purified via silica gel flash chromatography, eluting with 0 to 100% EtOAc in heptane to yield tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-3-(trifluoromethyl)quinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (138 mg, 272 μmol, 19%). LCMS: m/z HESI, positive $[M+H\text{-}Boc]^+ = 408$.

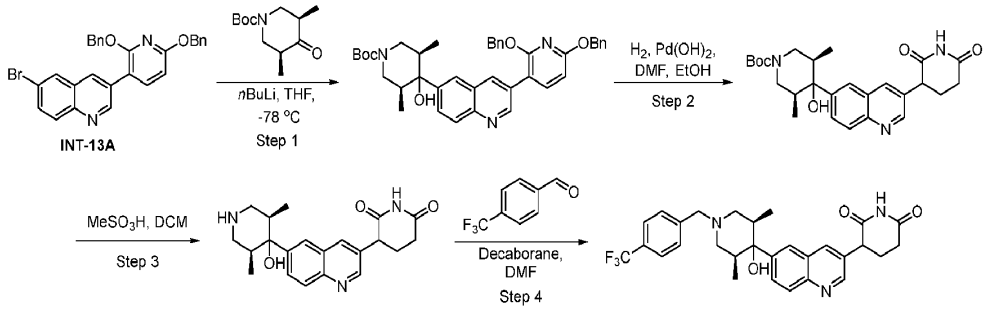
Step 5: **Synthesis of 3-(6-(4-hydroxypiperidin-4-yl)-2-(trifluoromethyl)quinolin-3-yl)piperidine-2,6-dione**

To a stirred mixture of tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-2-(trifluoromethyl)-quinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (137 mg, 270 μmol) in DCM (4.5 mL) at rt was added methanesulfonic acid (70.1 μL, 1.1 mmol) and the mixture was stirred at rt for 3h. TEA (188 μL, 1.35 mmol) was added, and the mixture was concentrated in vacuo to yield crude 3-(6-(4-hydroxypiperidin-4-yl)-2-(trifluoromethyl)quinolin-3-yl)piperidine-2,6-dione (110 mg), which was used in the next step without further purification. LCMS: m/z HESI, positive $[M+H]^+ = 408$.

Step 6: **Synthesis of 3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-(trifluoromethyl)quinolin-3-yl)piperidine-2,6-dione (I-887)**

3-(6-(4-hydroxypiperidin-4-yl)-2-(trifluoromethyl)quinolin-3-yl)piperidine-2,6-dione (110 mg, 270 μmol) was subjected to reaction with 4-(trifluoromethyl)benzaldehyde (41 μL, 297 μmol) and decaborane according to **General Procedure 1, Step D**, *Method A*. The crude was purified via *Purification Method (a)* followed by lyophilization with acetonitrile/HCl (aq) to yield 3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-2-(trifluoromethyl)quinolin-3-yl)piperidine-2,6-dione (**I-887**, 12 mg, 21 μmol, 8%). LCMS: m/z HESI, positive $[M+H]^+ = 566$. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 11.18 (br s, 1H), 11.05 (s, 1H), 8.71 (s, 1H), 8.18 (d, J = 8.8 Hz, 1H), 8.12 (d, J = 1.6 Hz, 1H), 8.00-7.93 (m, 3H), 7.91-7.86 (m, 2H), 6.54 (br s, 1H), 5.83 (s, 1H), 4.59-4.45 (m, 2H), 4.37-4.25 (m, 1H), 3.54-3.38 (m, 1H), 2.98-2.86 (m, 1H), 2.66-2.51 (m, 4H), 2.48-2.32 (m, 2H), 2.20-2.10 (m, 1H), 1.94-1.85 (m, 2H).

Example 216: Synthesis of 3-(6-((3R,5S)-4-hydroxy-3,5-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-917)



Step 1: **Synthesis of tert-butyl (3R,5S)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3,5-dimethylpiperidine-1-carboxylate**

Tert-butyl (3R,5S)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3,5-dimethylpiperidine-1-carboxylate (180 mg, 279 μmol, 56%) was synthesized according to **General Procedure 1, Step A** from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline **INT-13A**, (250 mg, 503 μmol) and *tert*-butyl (3R,5S)-3,5-dimethyl-4-oxopiperidine-1-carboxylate (149 mg, 653 μmol). The crude product was purified via silica gel chromatography eluting with 0 to 100% EtOAc in heptane. LCMS: m/z HESI, positive $[M+H]^+ = 646$.

Step 2: **Synthesis of tert-butyl (3R,5S)-4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3,5-dimethylpiperidine-1-carboxylate**

Tert-butyl (3R,5S)-4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3,5-dimethyl-piperidine-1-carboxylate (94 mg, 200 μmol, 75%) was prepared from *tert*-butyl (3R,5S)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3,5-dimethylpiperidine-1-carboxylate (173 mg, 268 μmol) according to **General Procedure 1, Step B**. The crude product was purified via preparative-HPLC [Method info: (Column: Phenomenex Luna C18 column (50 x 21.2mm); 5 μm); eluting with 0.1% formic acid in H_2O: 0.1% formic acid in MeCN. Flow rate: 50 mL/min]. LCMS: m/z HESI, positive $[M+H]^+ =$ 468.

Step 3: **Synthesis of 3-(6-((3R,5S)-4-hydroxy-3,5-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione**

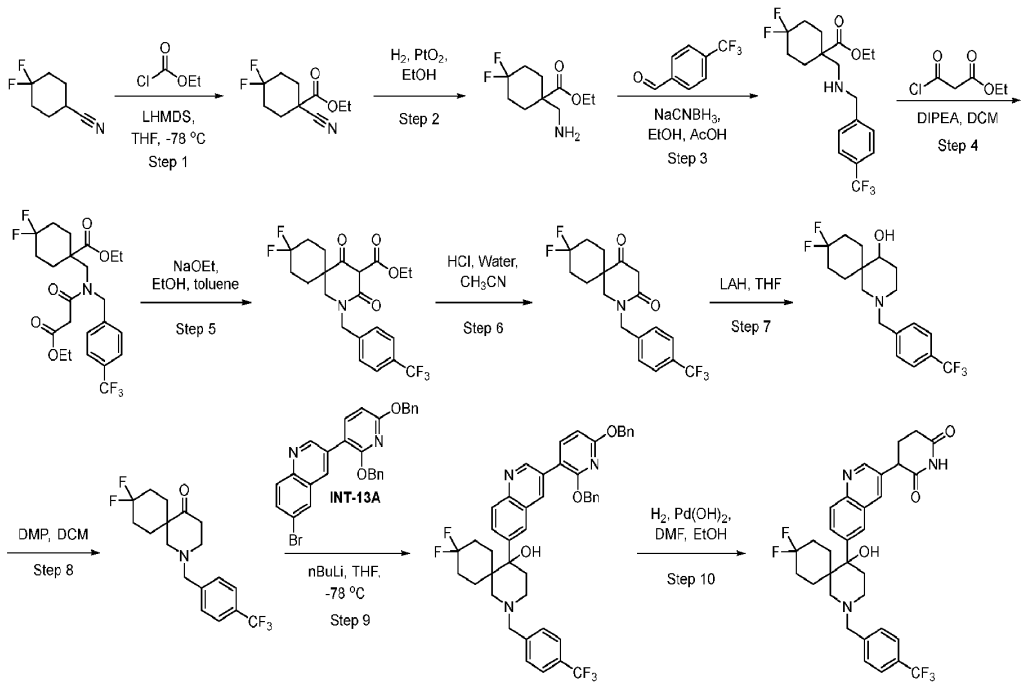
To a stirred mixture of tert-butyl (3R,5S)-4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3,5-dimethylpiperidine-1-carboxylate (50 mg, 0.11 mmol) in DCM (1.8 mL) was added methanesulfonic acid (28 μL, 0.43 mmol) and the mixture was stirred at rt for 2h. TEA (74 μL, 0.53 mmol) was added, and the mixture was concentrated under reduced pressure to provide crude 3-(6-((3R,5S)-4-hydroxy-3,5-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (39 mg), which was used in the next step without further purification. LCMS: m/z HESI, positive $[M+H]^+ = 368$.

Step 4: **Synthesis of 3-(6-((3R,5S)-4-hydroxy-3,5-dimethyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-917)**

Crude 3-(6-((3R,5S)-4-hydroxy-3,5-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (39 mg, 0.11 mmol) was subjected to reaction with 4-(trifluoromethyl)benzaldehyde (16 μL, 0.12 mmol) and decaborane according to **General Procedure 1, Step D**, *Method A*. The crude product was purified via *Purification Method (a)* followed by lyophilization with acetonitrile/HCl (aq) to afford 3-(6-((3R,5S)-4-hydroxy-3,5-dimethyl-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-917**, 30 mg, 58 μmol, 55%). LCMS: m/z HESI, positive $[M+H]^+ = 526$. ^{1}H NMR (500 MHz, DMSO-*d*6) δ (ppm) = 11.48 (br s, 1H), 11.01 (s, 1H), 8.89 (s, 1H), 8.39 (s, 1H), 8.18-8.04 (m, 2H), 7.94 (d, *J* =

8.2 Hz, 2H), 7.88 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 8.2 Hz, 1H), 5.39 (br s, 1H), 4.49 (d, *J* = 4.9 Hz, 2H), 4.21 (dd, *J* = 4.7, 12.9 Hz, 1H), 3.26-3.20 (m, 2H), 3.11-3.00 (m, 2H), 2.85-2.73 (m, 3H), 2.67-2.59 (m, 1H), 2.48-2.43 (m, 1H), 2.21-2.11 (m, 1H), 0.56-0.46 (m, 6H).

Example 217: Synthesis of 3-(6-(9,9-difluoro-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)piperidine-2,6-dione (I-177)



Step 1: **Synthesis of ethyl 1-cyano-4,4-difluorocyclohexane-1-carboxylate**

A solution of 4,4-difluorocyclohexane-1-carbonitrile (3.50 g, 24.1 mmol) in anhydrous THF (72 mL) was cooled to -78 °C was then treated with LHMDS (38.6 mL, 1 M in THF, 38.6 mmol). The mixture was stirred for 1 h at -78 °C, then ethyl chloroformate (3.69 mL, 38.6 mmol) was added and the mixture was allowed to warm to rt. Saturated aqueous sodium bicarbonate (100 ml) was added, and the mixture was extracted with EtOAc (3 X 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel flash chromatography, eluting with 0 to 40% EtOAc in heptane to afford ethyl 1-cyano-4,4-difluorocyclohexane-1-carboxylate (3.96 g, 18.2 mmol, 76%). LCMS: m/z HESI, positive no ions observed.

Step 2: **Synthesis of ethyl 1-(aminomethyl)-4,4-difluorocyclohexane-1-carboxylate**

A solution of ethyl 1-cyano-4,4-difluorocyclohexane-1-carboxylate (5.24 g, 24.1 mmol) in EtOH (66 mL) was added to platinum(IV) oxide (551 mg, 2.43 mmol) under an argon atmosphere. Acetic acid (66 mL) was added, and the mixture was stirred under 1 atmosphere of hydrogen for 16h. The reaction

mixture was filtered through a bed of celite and activated charcoal, and the filtrate was concentrated under reduced pressure. The crude residue was purified by reverse phase chromatography on a C18 column, eluting with 10 to 100% of 0.1% FA/acetonitrile in 0.1% FA/water to afford ethyl 1-(aminomethyl)-4,4-difluorocyclohexane-1-carboxylate (1.66 g, 7.50 mmol, 31%). LCMS: m/z HESI, positive $[M+H]^+ = 222$.

Step 3: **Synthesis of ethyl 4,4-difluoro-1-(((4-(trifluoromethyl)benzyl)amino)methyl)-cyclohexane-1-carboxylate**

A solution of ethyl 1-(aminomethyl)-4,4-difluorocyclohexane-1-carboxylate (1.66 g, 7.50 mmol) and 4-(trifluoromethyl)benzaldehyde (1.13 mL, 8.25 mmol) in EtOH (30 mL) and AcOH (429 µL, 7.50 mmol), was stirred for 1 h at 45 °C. Sodium cyanoborohydride (942 mg, 15.0 mmol) was added and the mixture was stirred at 45 °C for 15 min. The reaction mixture was concentrated under reduced pressure, and the residue was taken up in saturate aqueous sodium bicarbonate solution and extracted with DCM (3 x 50 mL). The combine organic layers were washed with saturated aqueous sodium bicarbonate solution and with brine, then were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was purified by silica gel flash chromatography, eluting with 0 to 10% MeOH in DCM to provide ethyl 4,4-difluoro-1-(((4-(trifluoromethyl)benzyl)amino)methyl)cyclohexane-1-carboxylate (1.74 g, 4.59 mmol, 61%). LCMS: m/z HESI, positive $[M+H]^+ = 380$.

Step 4: **Synthesis of ethyl 1-((3-ethoxy-3-oxo-N-(4-(trifluoromethyl)benzyl)propanamido)-methyl)-4,4-difluorocyclohexane-1-carboxylate**

A solution of ethyl 4,4-difluoro-1-(((4-(trifluoromethyl)benzyl)amino)methyl)-cyclohexane-1-carboxylate (1740 mg, 1 Eq, 4.59 mmol) and DIPEA (639 µL, 3.67 mmol) in DCM (23 mL) was added dropwise to a solution of ethyl 3-chloro-3-oxopropanoate (1.38 g, 9.17 mmol) in DCM (38 ml) at 0 °C with stirring. Following completion of the addition, the mixture was stirred for 90 min, then was diluted with DCM (50 mL) and poured into 1N HCl (aq) (200 mL). The aqueous layer was extracted with additional DCM (2 x 100 mL), then the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography, eluting with 0 to 80% EtOAc in heptane to provide ethyl 1-((3-ethoxy-3-oxo-N-(4-(trifluoromethyl)benzyl)-propanamido)methyl)-4,4-difluorocyclohexane-1-carboxylate (1.91 g, 2.34 mmol, 51%) as a mixture with diethyl 2-(((1-(ethoxycarbonyl)-4,4-difluorocyclohexyl)methyl)(4-(trifluoro-methyl)benzyl)-carbamoyl)-3-oxopentanedioate. LCMS: m/z HESI, positive $[M+H]^+ = 494$.

Step 5: **Synthesis of ethyl 9,9-difluoro-3,5-dioxo-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecane-4-carboxylate**

A solution of sodium ethoxide (191 mg, 2.81 mmol) in ethanol (5.8 mL) was added to a solution of ethyl 1-((3-ethoxy-3-oxo-N-(4-(trifluoromethyl)benzyl)propanamido)methyl)-4,4-difluorocyclohexane-1-carboxylate (1.15 g, 2.34 mmol) in toluene (5.8 mL) under argon, and the mixture

was stirred at 60 °C for 2h. The reaction mixture was concentrated under reduced pressure to give crude ethyl 9,9-difluoro-3,5-dioxo-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecane-4-carboxylate (1.05 g, 2.34 mmol) which was used in the next step without purification, assuming quantitative yield. LCMS: m/z HESI, positive $[M+H]^+ = 448$.

Step 6: **Synthesis of 9,9-difluoro-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecane-3,5-dione**

A solution of crude ethyl 9,9-difluoro-3,5-dioxo-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecane-4-carboxylate (1.05 g, 2.34 mmol) in acetonitrile (12 mL), water (1.7 mL, 94 mmol) and HCl (aq) (994 µL, 2 M, 1.99 mmol) was heated at 115 °C (bath temp) for 1 h. The cooled reaction mixture was concentrated under reduced pressure, then the crude residue was taken up in DCM (100 mL) and the solution was filtered through a fritted filter. The filtrate was concentrated in vacuo, and the residue was purified by silica gel flash chromatography, eluting with 0 to 100% EtOAc in heptane to afford 9,9-difluoro-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecane-3,5-dione (444 mg, 1.18 mmol, 51%). LCMS: m/z HESI, positive $[M+H]^+ = 376$.

Step 7: **Synthesis of 9,9-difluoro-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-ol**

To a stirred solution of 9,9-difluoro-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]-undecane-3,5-dione (875 mg, 1 Eq, 2.33 mmol) in THF (12 mL) at 0 °C was added LAH (4.66 mL, 1 M solution in THF, 4.66 mmol). The mixture was stirred at 60 °C for 5h. The cooled reaction mixture was diluted with ether, then further cooled to 0 °C, and quenched by adding 0.26 mL of water, followed by 0.26 mL of 15% NaOH (aq), followed by 0.80 mL of water. The stirred mixture was allowed to warm to rt, then excess magnesium sulfate was added and the solids were removed by filtration. The filtrate was concentrated in vacuo and the crude residue was purified by reverse phase chromatography on a C18 column, eluting with 10 to 100% acetonitrile in water to provide 9,9-difluoro-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]-undecan-5-ol (366 mg, 1.01 mmol, 43%). LCMS: m/z HESI, positive $[M+H]^+ = 364$.

Step 8: **Synthesis of 9,9-difluoro-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-one**

To a solution of 9,9-difluoro-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-ol (73 mg, 0.20 mmol) in DCM (1 ml) was added DMP (94 mg, 0.22 mmol) at rt and the mixture was stirred at rt for 2h. Saturated sodium thiosulfate (aq) (10 mL) was added, and the mixture was extracted with DCM (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography, eluting with 0 to 100% EtOAc in heptane to yield 9,9-difluoro-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-one (57 mg, 0.16 mmol, 79%). LCMS: m/z HESI, positive $[M+H]^+ = 362$.

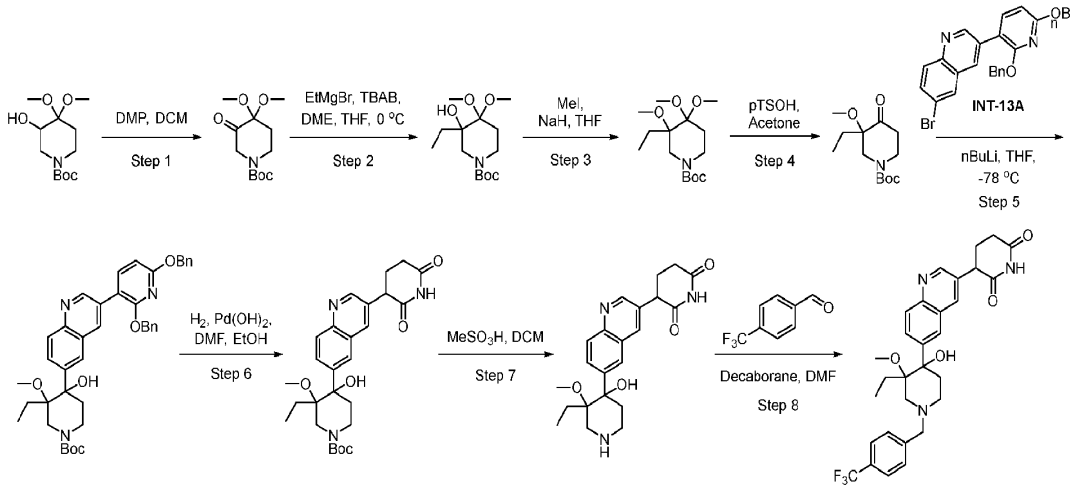
Step 9: **Synthesis of 5-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-9,9-difluoro-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-ol**

5-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-9,9-difluoro-2-(4-(trifluoromethyl)-benzyl)-2-azaspiro[5.5]undecan-5-ol (38.4 mg, 49.2 µmol, 26%) was synthesized from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 93.0 mg, 187 µmol) and 9,9-difluoro-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-one (68 mg, 187 µmol) according to **General Procedure 2, Step A**. The crude product was purified by silica gel flash chromatography, eluting with 0 to 100% EtOAc in heptane. LCMS: m/z HESI, positive $[M+H]^+ = 780$.

Step 10: **Synthesis of 3-(6-(9,9-difluoro-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)piperidine-2,6-dione (I-177)**

1-(3-(2,6-Bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-9,9-difluoro-4-(4-(trifluoromethyl)-benzyl)spiro[5.5]undecan-1-ol (38.4 mg, 1 Eq, 49.3 µmol) was treated according to **General Procedure 2, Step B**, *Purification Method (a)*, to provide 3-(6-(9,9-difluoro-5-hydroxy-2-(4-(trifluoromethyl)benzyl)-2-azaspiro[5.5]undecan-5-yl)quinolin-3-yl)piperidine-2,6-dione (**I-177**, 5.0 mg, 8.4 µmol, 17%). LCMS: m/z HESI, positive $[M+H]^+ = 602$. 1H NMR (500 MHz, DMSO-d_6) δ ppm: 10.97 (s, 1H), 8.76 (d, J = 2.2 Hz, 1H), 8.20 (s, 1H), 7.98 (s, 1H), 7.95-7.87 (m, 2H), 7.72 (d, J = 8.2 Hz, 2H), 7.61 (d, J = 7.7 Hz, 2H), 6.76 (br s, 1H), 5.02 (s, 1H), 4.14 (dd, J = 4.9, 12.6 Hz, 1H), 3.67 (d, J = 11.0 Hz, 2H), 2.87-2.79 (m, 2H), 2.79-2.68 (m, 2H), 2.65-2.56 (m, 2H), 2.47-2.36 (m, 3H), 2.20-2.11 (m, 1H), 1.87-1.78 (m, 1H), 1.74-1.63 (m, 2H), 1.57-1.49 (m, 2H), 1.23 (s, 1H), 1.03-0.92 (m, 1H). (No salt signals observed in ^{1}H NMR.)

Example 218: Synthesis of 3-(6-(3-ethyl-4-hydroxy-3-methoxy-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-179)



Step 1: **Synthesis of *tert*-butyl 4,4-dimethoxy-3-oxopiperidine-1-carboxylate**

To a solution of tert-butyl 3-hydroxy-4,4-dimethoxypiperidine-1-carboxylate (500 mg, 1.91 mmol) in DCM (10 ml) was added DMP (974 mg, 2.30 mmol) and the mixture was stirred at rt for 3h.

The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel flash chromatography, eluting with 0 to 100% EtOAc in heptane to yield tert-butyl 4,4-dimethoxy-3-oxopiperidine-1-carboxylate (273 mg, 1.05 mmol, 55%). LCMS: m/z HESI, positive $[M+H-Boc]^+ = 160$.

Step 2: **Synthesis of tert-butyl 3-ethyl-3-hydroxy-4,4-dimethoxypiperidine-1-carboxylate**

Ethylmagnesium bromide (526 µL, 3 M solution in ether, 1.58 mmol) was added to a solution of tetrabutylammonium bromide (33.9 mg, 0.1 Eq, 105 µmol) and DME (109 µL, 1.05 mmol) in THF (1.6 mL), at 0 °C under an argon atmosphere. The solution was stirred for 30 min at 0 °C before adding a solution of tert-butyl 4,4-dimethoxy-3-oxopiperidine-1-carboxylate (273 mg, 1.05 mmol) in THF (1.05 mL) dropwise at 0 °C. After 3h, the reaction mixture was diluted with EtOAc (25 mL) and washed with 1N HCl (aq) (50 mL). The combined aqueous layers were back extracted once with EtOAc (25mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified using silica gel flash chromatography, eluting with 0 to 100% EtOAc in heptane to provide tert-butyl 3-ethyl-3-hydroxy-4,4-dimethoxypiperidine-1-carboxylate (150 mg, 0.52 mmol, 49%). LCMS: m/z HESI, positive $[M-OMe-Boc]^+ = 158$.

Step 3: **Synthesis of tert-butyl 3-ethyl-3,4,4-trimethoxypiperidine-1-carboxylate**

NaH (31 mg, 60% Wt, 780 µmol) was added at rt to a solution of *tert*-butyl 3-ethyl-3-hydroxy-4,4-dimethoxypiperidine-1-carboxylate (150 mg, 520 µmol) in DMF (1.7 mL) and the mixture was stirred at rt for 30 min before adding iodomethane (45 µL, 730 µmol). After 90 min, an additional aliquot of iodomethane (23 µL, 370 µmol) was added, and the mixture was stirred for an additional 90 min. The reaction was concentrated in vacuo to provide crude *tert*-butyl 3-ethyl-3,4,4-trimethoxypiperidine-1-carboxylate (160 mg), which was used in the next step without purification. LCMS: m/z HESI, positive $[M-OMe-Boc]^+ = 172$.

Step 4: **Synthesis of tert-butyl 3-ethyl-3-methoxy-4-oxopiperidine-1-carboxylate**

A solution of crude *tert*-butyl 3-ethyl-3,4,4-trimethoxypiperidine-1-carboxylate (160 mg, 517 µmol) and *p*TSOH (9.8 mg, 52 µmol) in acetone (2.7 mL) was stirred at rt for 16h. The reaction mixture was concentrated under reduced pressure and resuspended in MTBE (25 mL). The solution was washed with saturated aqueous sodium bicarbonate solution and the aqueous layer was back extracted with EtOAc (25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel flash chromatography, eluting with 0 to 100% EtOAc in heptane to provide *tert*-butyl 3-ethyl-3-methoxy-4-oxopiperidine-1-carboxylate (79 mg, 310 µmol, 59% (over 2 steps). LCMS: m/z HESI, positive $[M+H-Boc]^+ = 158$.

Step 5: **Synthesis of tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-ethyl-4-hydroxy-3-methoxypiperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-ethyl-4-hydroxy-3-methoxypiperidine-1-carboxylate (93 mg, 0.14 mmol, 57%) was prepared according **to General Procedure 1, Step A**, starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 120 mg, 241 µmol) and tert-butyl 3-ethyl-3-methoxy-4-oxopiperidine-1-carboxylate (81 mg, 310 µmol). The crude product was purified by silica gel flash chromatography, eluting with 0 to 100% EtOAc in heptane. LCMS: m/z HESI, positive $[M+H]^+ = 676$.

Step 6: **Synthesis of tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3-ethyl-4-hydroxy-3-methoxypiperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-ethyl-4-hydroxy-3-methoxypiperidine-1-carboxylate (93 mg, 0.14 mmol) was subjected to hydrogenation according to **General Procedure 1, Step B**. The crude product was purified by reverse phase chromatography using a C18 column, eluting with 10-100% of 0.1% FA/acetonitrile in 0.1% FA/water to yield *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3-ethyl-4-hydroxy-3-methoxypiperidine-1-carboxylate (40 mg, 81 µmol, 59%). LCMS: m/z HESI, positive $[M+H]^+ = 498$.

Step 7: **Synthesis of 3-(6-(3-ethyl-4-hydroxy-3-methoxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione**

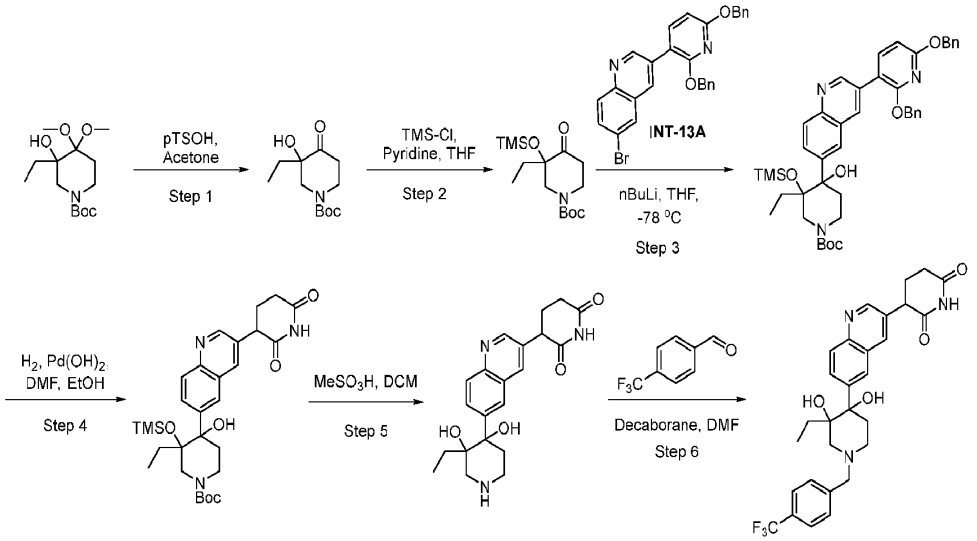
To a stirred mixture of tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3-ethyl-4-hydroxy-3-methoxypiperidine-1-carboxylate (40 mg, 81 µmol) in DCM (7 mL) at rt was added methanesulfonic acid (21 µL, 330 µmol). After 2h at rt, TEA (57 µL, 406 µmol) was added and the mixture was concentrated in vacuo to yield crude 3-(6-(3-ethyl-4-hydroxy-3-methoxy-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (32 mg). The crude product was used in the next step without further purification. LCMS: m/z HESI, positive $[M+H]^+ = 398$.

Step 8: **Synthesis of 3-(6-(3-ethyl-4-hydroxy-3-methoxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-179)**

Crude 3-(6-(3-ethyl-4-hydroxy-3-methoxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (32 mg, 81 µmol) was subjected to reaction with 4-(trifluoromethyl)benzaldehyde (12 µL, 89 µmol) and decaborane according to **General Procedure 1, Step D**, *Method A*. The crude product was purified via *Purification Method (a)* followed by lyophilization with acetonitrile/HCl (aq) to yield 3-(6-(3-ethyl-4-hydroxy-3-methoxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-179**, 26 mg, 47 µmol, 58%). LCMS: m/z HESI, positive [M+H]+ = 556. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 11.04 (s, 1H), 9.98 (br s, 1H), 9.03 (s, 1H), 8.68 (s, 1H), 8.24 (s, 1H), 8.19-8.11 (m, 2H), 8.11-8.05 (m, 1H), 8.00-7.97 (m, 1H), 7.93-7.87 (m, 2H), 6.17 (br s, 1H), 4.67-4.50 (m, 3H), 4.30-4.21 (m, 2H), 3.46-3.38 (m, 1H), 3.36-3.24 (m, 3H), 3.22-3.16 (m, 1H), 3.04 (s, 2H), 2.86-2.71 (m, 1H), 2.69-2.60

(m, 1H), 2.25-2.10 (m, 1H), 1.85-1.65 (m, 1H), 1.59-1.47 (m, 1H), 1.47-1.35 (m, 1H), 1.09-0.98 (m, 1H), 0.36-0.28 (m, 3H).

Example 219: Synthesis of 3-(6-(3-ethyl-3,4-dihydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-316)



Step 1: **Synthesis of tert-butyl 3-ethyl-3-hydroxy-4-oxopiperidine-1-carboxylate**

Tert-butyl 3-ethyl-3-hydroxy-4,4-dimethoxypiperidine-1-carboxylate (Prepared in **I-179,** Step 2 above, 460 mg, 59 mmol) was treated with *p*TSOH in acetone according to the procedure of **I-179,** Step 4 above, to yield *tert*-butyl 3-ethyl-3-hydroxy-4-oxopiperidine-1-carboxylate (280 mg, 1.15 mmol, 72%). LCMS: m/z HESI, positive $[M+H\text{-}Boc]^+ = 144$.

Step 2: **Synthesis of tert-butyl 3-ethyl-4-oxo-3-((trimethylsilyl)oxy)piperidine-1-carboxylate**

Chlorotrimethylsilane (150 µL, 1.18 mmol) was added to a solution of *tert*-butyl 3-ethyl-3-hydroxy-4-oxopiperidine-1-carboxylate (169 mg, 695 µmol) in DCM (3.5 ml) and pyridine (112 µL, 1.39 mmol) at rt and the mixture was stirred for 1h. Additional pyridine (2 eq) and TMSCl (2 eq) were added, and the mixture was stirred at 37 °C for 1h. The reaction mixture was concentrated in vacuo, and the crude residue was purified via silica gel flash chromatography, eluting with 0 to 100% EtOAc in heptane to afford *tert*-butyl 3-ethyl-4-oxo-3-((trimethylsilyl)-oxy)piperidine-1-carboxylate (162 mg, 695 µmol, 74%). $[M+H\text{-}Boc]^+ = 216$.

Step 3: **Synthesis of tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-ethyl-4-hydroxy-3-((trimethylsilyl)oxy)piperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-ethyl-4-hydroxy-3-((trimethylsilyl)oxy)piperidine-1-carboxylate (133 mg, 181 µmol, 50%) was prepared according to **General Procedure 1, Step A**, starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-quinoline (**INT-**

13A, 180 mg, 362 µmol) and *tert*-butyl 3-ethyl-4-oxo-3-((trimethylsilyl)oxy)-piperidine-1-carboxylate (160 mg, 507 µmol). The crude product was purified using silica gel flash chromatography, eluting with 0 to 100% EtOAc in heptane. LCMS: m/z HESI, positive $[M+H]^+ = 734$.

Step 4: **Synthesis of tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3-ethyl-4-hydroxy-3-((trimethylsilyl)oxy)piperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-ethyl-4-hydroxy-3-((trimethylsilyl)oxy)piperidine-1-carboxylate (133 mg, 181 µmol) was subjected to hydrogenation according to **General Procedure 1, Step B**. The crude product was purified by reverse phase chromatography using a C18 column, eluting with 10-100% of 0.1% FA/acetonitrile in 0.1% FA/water to yield *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3-ethyl-4-hydroxy-3-((trimethylsilyl)oxy)piperidine-1-carboxylate (60 mg, 0.11 mmol, 60%). LCMS: m/z HESI, positive $[M+H]^+ = 556$.

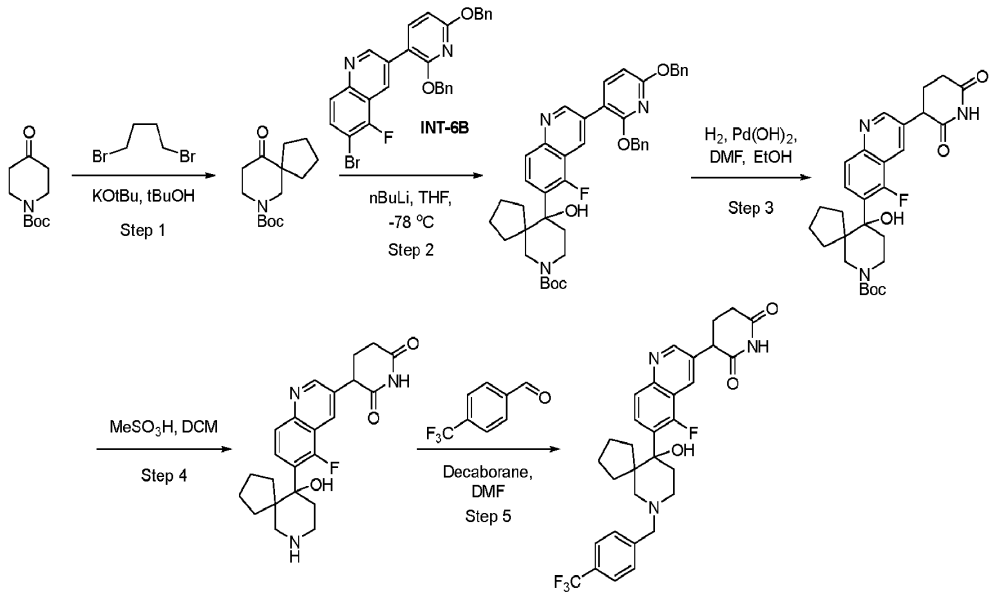
Step 5: **Synthesis of 3-(6-(3-ethyl-3,4-dihydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione**

A mixture of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3-ethyl-4-hydroxy-3-((trimethylsilyl)oxy)piperidine-1-carboxylate (60 mg, 0.11 mmol), methanesulfonic acid (28 µL, 430 µmol) and DCM (1.8 ml) was stirred at rt for 2h. TEA (75 µL, 538 µmol) was added, and the mixture was concentrated in vacuo to yield crude 3-(6-(3-ethyl-3,4-dihydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (49 mg), which was used in the next step without further purification. LCMS: m/z HESI, positive $[M+H]^+ = 384$.

Step 6: **Synthesis of 3-(6-(3-ethyl-3,4-dihydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-316)**

Crude 3-(6-(3-ethyl-4-hydroxy-3-((trimethylsilyl)oxy)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (49 mg, 108 µmol) was subjected to reaction with 4-(trifluoromethyl)-benzaldehyde (26.2 µL, 1.4 Eq, 151 µmol) and decaborane according to **General Procedure 1, Step D**, *Method A*. The crude product was purified via *Purification Method (a)* followed by lyophilization with acetonitrile/HCl (aq) to yield 3-(6-(3-ethyl-3,4-dihydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, (11 mg, 20 µmol, 19%). LCMS: m/z HESI, positive [M+H]+ = 542. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.13 (br s, 1H), 11.08 (s, 1H), 9.17 (s, 1H), 8.90 (s, 1H), 8.26-8.17 (m, 3H), 8.07-8.03 (m, J = 8.2 Hz, 2H), 7.92-7.88 (m, J = 8.2 Hz, 2H), 5.97 (br s, 1H), 4.64-4.57 (m, 1H), 4.50-4.44 (m, 1H), 4.36-4.28 (m, 2H), 3.52-3.46 (m, 1H), 3.40-3.25 (m, 2H), 3.12-3.03 (m, 2H), 2.97-2.74 (m, 2H), 2.70-2.62 (m, 1H), 2.47-2.37 (m, 1H), 2.25-2.13 (m, 2H), 2.09-2.02 (m, 1H), 0.50 (t, J = 7.1 Hz, 3H).

Example 220: Synthesis of 3-(5-fluoro-6-(10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)quinolin-3-yl)piperidine-2,6-dione (I-560)



Step 1: **Synthesis of tert-butyl 10-oxo-7-azaspiro[4.5]decane-7-carboxylate**

To a stirred mixture of tBuOH (50 ml), KOtBu (4.73 g, 42.2 mmol) and *tert*-butyl 4-oxopiperidine-1-carboxylate (4.00 g, 20.1 mmol) at 40 °C was added dropwise 1,4-dibromobutane (2.40 mL, 20.1 mmol). Following completion of the addition, the mixture was stirred at 40 °C for 2h. The cooled reaction mixture was diluted with EtOAc (100 mL) and washed with water (2 X 100 mL). The combined aqueous layer was extracted with EtOAc (3 x 50 mL), and then the combine organic layers were concentrated under reduced pressure. The crude residue was purified via silica gel flash chromatography, eluting with 0 to 25% EtOAc in heptane to give *tert*-butyl 10-oxo-7-azaspiro[4.5]decane-7-carboxylate (851 mg, 3.36 mmol, 17%). LCMS: m/z HESI, positive $[M+H- Boc]^+$ = 154.

Step 2: **Synthesis of tert-butyl 10-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-10-hydroxy-7-azaspiro[4.5]decane-7-carboxylate**

Tert-butyl 10-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-10-hydroxy-7-azaspiro[4.5]decane-7-carboxylate (314 mg, 456 µmol, 47%) was prepared according to **General Procedure 1, Step A**, starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-5-fluoroquinoline (**INT-6B** 500 mg, 1 Eq, 970 µmol) and *tert*-butyl 10-oxo-7-azaspiro[4.5]decane-7-carboxylate (369 mg, 1.46 mmol), with purification by silica gel flash chromatography with 0-100% EtOAc in heptane. LCMS: m/z HESI, positive $[M+H]^+$ = 690.

Step 3: **Synthesis of tert-butyl 10-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-10-hydroxy-7-azaspiro[4.5]decane-7-carboxylate**

Tert-butyl 10-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-10-hydroxy-7-azaspiro[4.5]decane-7-carboxylate (314 mg, 456 µmol) was subjected to hydrogenation according to **General Procedure 1, Step B**. The crude product was purified by reverse phase chromatography using a C18 column, eluting with 10-100% of 0.1% FA/acetonitrile in 0.1% FA/water to yield *tert*-butyl 10-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-10-hydroxy-7-azaspiro[4.5]decane-7-carboxylate (87 mg, 0.170 mmol, 37%). LCMS: m/z HESI, positive $[M+H]^+ = 512$.

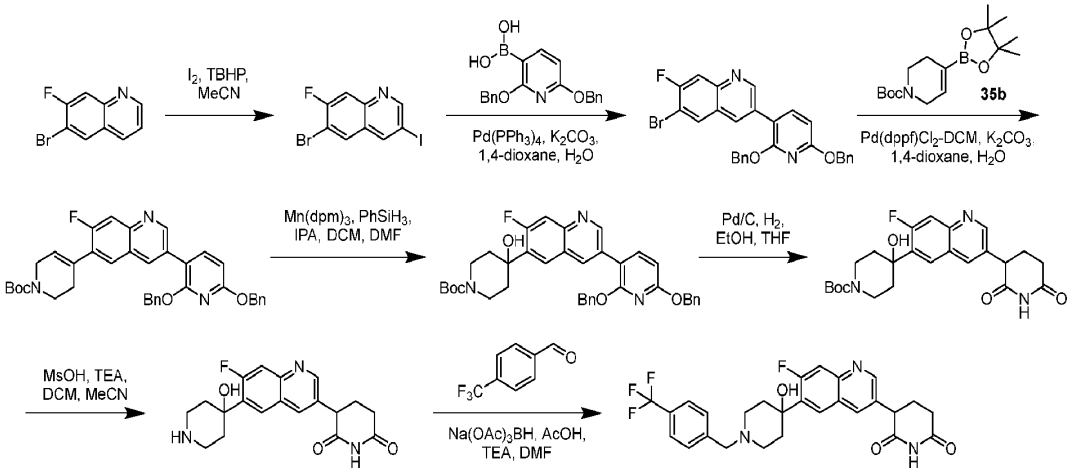
Step 4: **Synthesis of 3-(5-fluoro-6-(10-hydroxy-7-azaspiro[4.5]decan-10-yl)quinolin-3-yl)piperidine-2,6-dione**

A mixture of *tert*-butyl 10-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-10-hydroxy-7-azaspiro[4.5]decane-7-carboxylate (87 mg, 0.17 mmol) and methanesulfonic acid (44 µL, 0.68 mmol) in DCM (2.8 mL) was stirred at rt for 2h. TEA (118 µL, 0.86 mmol) was added and the reaction mixture was concentrated in vacuo to yield crude 3-(5-fluoro-6-(10-hydroxy-7-azaspiro[4.5]decan-10-yl)quinolin-3-yl)piperidine-2,6-dione (70 mg), which was used in the next step without further purification. LCMS: m/z HESI, positive $[M+H]^+ = 412$.

Step 5: **Synthesis of 3-(5-fluoro-6-(10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)quinolin-3-yl)piperidine-2,6-dione (I-560)**

Crude 3-(5-fluoro-6-(10-hydroxy-7-azaspiro[4.5]decan-10-yl)quinolin-3-yl)piperidine-2,6-dione (35 mg, 85 µmol) was subjected to reaction with 4-(trifluoromethyl)benzaldehyde (16 µL, 120 µmol) and decaborane according to **General Procedure 1, Step D**, *Method A*. The crude product was purified via *Purification Method (a)*, followed by lyophilization with acetonitrile/HCl (aq) to yield 3-(5-fluoro-6-(10-hydroxy-7-(4-(trifluoromethyl)benzyl)-7-azaspiro[4.5]decan-10-yl)quinolin-3-yl)piperidine-2,6-dione, (**I-560**, 10 mg, 18 µmol, 21%). LCMS: m/z HESI, positive [M+H]+ = 570. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.99 (s, 1H), 10.05 (br s, 1H), 8.90 (d, J = 1.6 Hz, 1H), 8.39 (t, J = 2.5 Hz, 1H), 8.13 (t, J = 8.8 Hz, 1H), 7.97-7.93 (m, 2H), 7.93-7.87 (m, 3H), 5.93 (br s, 1H), 4.56-4.49 (m, 2H), 4.27-4.21 (m, 1H), 3.46-3.24 (m, 2H), 3.09-3.02 (m, 1H), 2.82-2.69 (m, 2H), 2.67-2.58 (m, 2H), 2.24-2.18 (m, 1H), 2.17-2.09 (m, 1H), 2.09-2.02 (m, 1H), 1.92-1.71 (m, 2H), 1.41-1.26 (m, 3H), 1.21-1.11 (m, 2H), 0.87-0.75 (m, 1H).

Example 221: Synthesis of 3-(7-fluoro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-912)



Step 1: **Synthesis of 6-bromo-7-fluoro-3-iodoquinoline**

A mixture of 6-bromo-7-fluoroquinoline (0.50 g, 2.21 mmol), acetonitrile (35 mL), tert-butyl hydroperoxide (3.42 g, 3.81 mL of 70% Wt, 26.5 mmol) and iodine (674 mg, 2.65 mmol) was refluxed for 16h. The reaction mixture was concentrated in vacuo and diluted with aqueous sodium thiosulfate solution. The mixture was extracted with EtOAc, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel flash chromatography, eluting with EtOAc in heptane to yield 6-bromo-7-fluoro-3-iodoquinoline (85 mg, 240 µmol, 11%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 351.9.

Step 2: **Synthesis of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-7-fluoroquinoline**

To a mixture of 6-bromo-7-fluoro-3-iodoquinoline (74 mg, 0.21 mmol), (2,6-bis(benzyloxy)-pyridin-3-yl)boronic acid (78 mg, 0.23 mmol), tetrakis(triphenylphosphine)-palladium(0) (49 mg, 42 µmol) and dioxane (2 mL) was added a solution of potassium carbonate (58 mg, 0.42 mmol) in water (0.2 mL). The reaction mixture was stirred for 50 min at 80 °C, then the cooled reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography, eluting with EtOAc in heptane to yield 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-7-fluoroquinoline (77 mg, 0.15 mmol, 71%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 515.4.

Step 3: **Synthesis of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoroquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate**

To a mixture of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-7-fluoroquinoline (77 mg, 0.15 mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**35b**, 51 mg, 0.16 mmol), Pd(dppf)Cl_2-DCM adduct (18 mg, 22 µmol), and dioxane (2 mL) was added a solution of potassium carbonate (31 mg, 0.22 mmol) in water (0.2 mL). The reaction mixture was sparged with argon and was then stirred at 80 °C for 50 min. The cooled reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel flash chromatography, eluting with EtOAc in

heptane to provide tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoroquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (72 mg, 0.12 mmol, 78%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 618.5.

Step 4: **Synthesis of tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoroquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoroquinolin-6-yl)-3,6-dihydro-pyridine-1(2H)-carboxylate (0.072 g, 1 Eq, 0.12 mmol) was treated according to **General Procedure 3, Step C**. The crude product was purified by silica gel flash chromatography, eluting with EtOAc in heptane to provide *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-quinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (57.1 mg, 89.8 μmol, 77%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 636.4.

Step 5: **Synthesis of tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoroquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate**

A mixture of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoroquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (57.1 mg, 1 89.8 μmol), ethanol (5 mL), THF (7 mL) and Pd/C (9.6 mg, 90 μmol), was sparged with argon, then the mixture was sparged with hydrogen gas and then stirred under 1 atmosphere hydrogen pressure for 4h at rt. The reaction mixture was filtered through a pad of celite and concentrated in vacuo. The crude residue was purified via reverse phase chromatography on a C18 column, eluting with 0.1% FA/acetonitrile in 0.1% FA/water to yield *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoroquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (10 mg, 22 μmol, 24%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 458.3.

Step 6: **Synthesis of 3-(7-fluoro-6-(4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione**

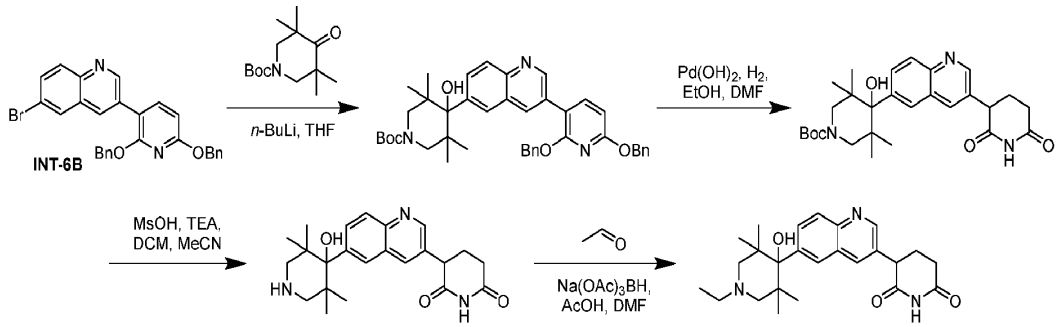
A solution of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoroquinolin-6-yl)-4-hydroxy-piperidine-1-carboxylate (10 mg, 22 μmol) and methanesulfonic acid (8.4 mg, 87 μmol) in DCM (700 μL) and MeCN (700 μL) was stirred at rt for 30 min. The reaction mixture was cooled to 0 °C and triethylamine (15 mg, 0.15 mmol) was added. The reaction mixture was then concentrated under reduced pressure and the entire crude product was used in the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 358.2.

Step 7: **Synthesis of 3-(7-fluoro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-912)**

To a solution of 3-(7-fluoro-6-(4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (15 mg crude from previous step) and 4-(trifluoromethyl)benzaldehyde (8 mg, 6 μL 0.04 mmol) in DMF (1.5 mL) at 0 °C was added acetic acid (52 mg, 0.87 mmol) and sodium triacetoxyborohydride (9 mg, 0.04 mmol). The reaction mixture was stirred at rt for 3h, then was concentrated under reduced pressure. The crude residue was purified using reverse phase chromatography on a C18 column, eluting with 0.1%

FA/acetonitrile in 0.1% FA/water to provide 3-(7-fluoro-6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (1.2 mg, 2.3 μmol, 10%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 516.4.

Example 222: Synthesis of 3-(6-(1-ethyl-4-hydroxy-3,3,5,5-tetramethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-909)



Step 1: **Synthesis of tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3,3,5,5-tetramethylpiperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3,3,5,5-tetramethyl-piperidine-1-carboxylate was synthesized according to **General Procedure 1, Step A**, starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-6B**, 249 mg, 0.500 mmol) and tert-butyl 3,3,5,5-tetramethyl-4-oxopiperidine-1-carboxylate (128 mg, 500 μmol). The crude product was purified by silica gel chromatography, eluting with 0-100% EtOAc in heptane.

Step 2: **Synthesis of tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3,3,5,5-tetramethylpiperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3,3,5,5-tetramethyl-piperidine-1-carboxylate (100 mg, 148 μmol) was subjected to hydrogenation according to **General Procedure 1, Step B**. The crude product was used in the next step without purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 496.4.

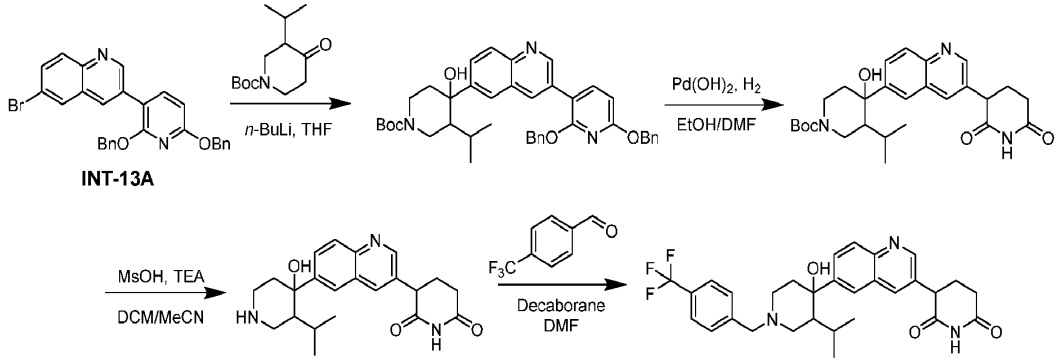
Step 3: **Synthesis of 3-(6-(4-hydroxy-3,3,5,5-tetramethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione**

A solution of t*ert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3,3,5,5-tetramethylpiperidine-1-carboxylate (74 mg, 149 μmol) and methanesulfonic acid (57 mg, 594 μmol) in DCM (700 μL) and MeCN (700 μL) was stirred at rt for 2h. Triethylamine (150 mg, 1.49 mmol) was added, then the reaction mixture was concentrated in vacuo. The entire crude product was used in the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 396.3.

Step 4: **Synthesis of 3-(6-(1-ethyl-4-hydroxy-3,3,5,5-tetramethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-909)**

A mixture of 3-(6-(4-hydroxy-3,3,5,5-tetramethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (59 mg, 148 μmol), acetaldehyde (6.5 mg, 150 μmol) DMF (1 mL), sodium triacetoxyborohydride (63 mg, 297 μmol) and acetic acid (52 mg, 0.87 mmol) was stirred at rt for 2h. The reaction mixture was filtered and directly loaded onto a C18 column for purification by reverse phase chromatography, eluting with 0.1% FA/acetonitrile in 0.1% FA/water to yield 3-(6-(1-ethyl-4-hydroxy-3,3,5,5-tetramethyl-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, formic acid **(I-909)** (6.5 mg, 15 μmol, 10%) LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 424.3 ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.96 (s, 1H), 8.74 (d, J = 2.2 Hz, 1H), 8.30 (s, 1H), 8.19-8.22 (m, 1H), 8.17 (s, 1H), 8.08 (br d, J = 8.2 Hz, 1H), 7.91 (d, J = 8.8 Hz, 1H), 4.13 (dd, J = 12.6, 4.9 Hz, 1H), 2.77 (m, 1H), 2.56-2.66 (m, 1H), 2.45-2.48 (m, 2H), 2.31-2.45 (m, 5H), 2.11-2.18 (m, 1H), 1.20-1.25 (m, 6H), 1.05 (t, J = 7.1 Hz, 3H), 0.75 (br s, 6H).

Example 223: Synthesis of 3-(6-(4-hydroxy-3-isopropyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-258)



Step 1: **Synthesis of tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3-isopropylpiperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3-isopropyl-piperidine-1-carboxylate (130 mg, 197 μmol, 62%) was synthesized according to **General Procedure 1, Step A**, starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-5-fluoro-quinoline (**INT-13A**, 0.17 g, 320 μmol) and *tert*-butyl 3-isopropyl-4-oxopiperidine-1-carboxylate (100 mg, 416 μmol). The crude product was purified by silica gel flash chromatography, eluting with EtOAc in heptane to yield LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 660.6.

Step 2: **Synthesis of tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3-isopropylpiperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3-isopropylpiperidine-1-carboxylate (0.130 g, 197 μmol) was hydrogenated according to **General Procedure 1, Step B**. The crude product was purified by reverse phase chromatography on a C18 column, eluting with 0.1% FA/acetonitrile in 0.1% FA/water to yield *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-

hydroxy-3-isopropylpiperidine-1-carboxylate (70 mg, 0.15 mmol, 74%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 482.5.

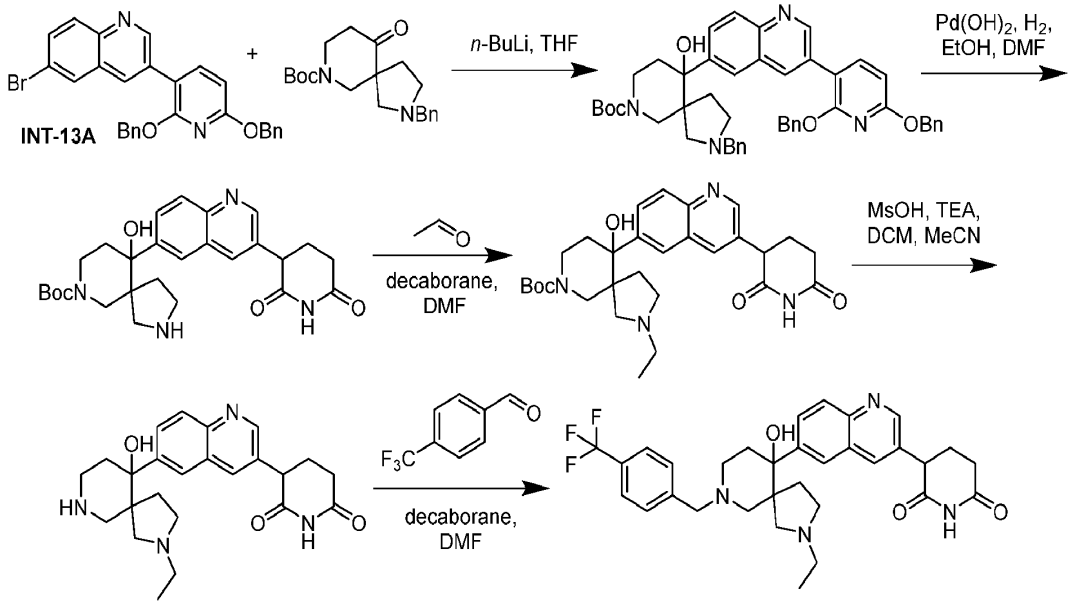
Step 3: **Synthesis of 3-(6-(4-hydroxy-3-isopropylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione**

A solution of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3-isopropyl-piperidine-1-carboxylate (35 mg, 73 μmol) and methanesulfonic acid (28 mg, 0.29 mmol) in DCM (1 mL) and MeCN (1 mL) was stirred at rt for 30 min. The reaction mixture was cooled to 0 °C and triethylamine (74 mg, 0.73 mmol) was added.. The reaction mixture was concentrated under reduced pressure. The entire crude product was used in the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 382.3.

Step 4: **Synthesis of 3-(6-(4-hydroxy-3-isopropyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-258)**

3-(6-(4-Hydroxy-3-isopropylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (0.028 g, μmol) was reacted with 4-(trifluoromethyl)benzaldehyde (26 mg, 0.15 mmol) and decaborane according to **General Procedure 1, Step D**, *Method A*. The crude product was purified by reverse phase chromatography on a C18 column, eluting with 0.1% FA/acetonitrile in 0.1% FA/water to yield 3-(6-(4-hydroxy-3-isopropyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, formic acid (8.9 mg, 16 μmol, 22%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 540.4. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.96 (s, 1H), 8.74 (d, J = 2.2 Hz, 1H), 8.36 (s, 1H), 8.20 (t, J = 2.5 Hz, 1H), 8.05 (s, 1H), 7.96 (d, J = 8.8 Hz, 1H), 7.86 (br s, 1H), 7.73-7.70 (m, J = 8.2 Hz, 2H), 7.62 (d, J = 8.2 Hz, 2H), 4.93 (br s, 1H), 4.13 (dd, J = 4.9, 12.6 Hz, 1H), 3.75 (br d, J = 13.7 Hz, 1H), 3.62 (br d, J = 13.7 Hz, 1H), 2.82-2.68 (m, 2H), 2.66-2.57 (m, 2H), 2.48-2.37 (m, 2H), 2.22-2.07 (m, 2H), 2.07-1.91 (m, 1H), 1.56 (br d, J = 13.1 Hz, 2H), 1.36 (m, 1H), 0.79 (d, J = 6.6 Hz, 3H), 0.62-0.55 (d, J = 6.6 Hz, 3H).

Example 224: Synthesis of 3-(6-(2-ethyl-10-hydroxy-7-(4-(trifluoromethyl)benzyl)-2,7-diazaspiro[4.5]decan-10-yl)quinolin-3-yl)piperidine-2,6-dione (I-898)



Step 1: **Synthesis of tert-butyl 2-benzyl-10-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-10-hydroxy-2,7-diazaspiro[4.5]decane-7-carboxylate**

Tert-butyl 2-benzyl-10-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-10-hydroxy-2,7-diazaspiro[4.5]decane-7-carboxylate (490 mg, 642 μmol, 64%) was synthesized according to **General Procedure 1, Step A**, starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-quinoline (**INT-13A**, 0.5 g, 1.0 mmol) and *tert*-butyl 2-benzyl-10-oxo-2,7-diazaspiro[4.5]decane-7-carboxylate (416 mg, 1.21 mmol). The crude product was purified by silica gel flash chromatography, eluting with EtOAc in heptane. LCMS: m/z MM-ES+sAPCI, Positive $[M+H]^+$ 763.5.

Step 2: **Synthesis of *tert*-butyl 10-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-10-hydroxy-2,7-diazaspiro[4.5]decane-7-carboxylate**

Tert-butyl 2-benzyl-10-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-10-hydroxy-2,7-diazaspiro[4.5]decane-7-carboxylate (490 mg, 642 μmol) was subjected to hydrogenation according to **General Procedure 1, Step B**. The crude product was purified by reverse phase chromatography on a C18 column, eluting with acetonitrile in water to afford *tert*-butyl 10-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-10-hydroxy-2,7-diazaspiro[4.5]decane-7-carboxylate (90 mg, 0.18 mmol, 28%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 495.4.

Step 3: **Synthesis of *tert*-butyl 10-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-2-ethyl-10-hydroxy-2,7-diazaspiro[4.5]decane-7-carboxylate**

Tert-butyl 10-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-10-hydroxy-2,7-diazaspiro[4.5]-decane-7-carboxylate (45 mg, 91 μmol) was reacted with acetaldehyde (4.0 mg, 91 μmol) and decaborane according to **General Procedure 1, Step D,** *Method A*. The crude product was purified by reverse phase

chromatography on a C18 column, eluting with acetonitrile in water to afford *tert*-butyl 10-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-2-ethyl-10-hydroxy-2,7-diazaspiro[4.5]decane-7-carboxylate (21.2 mg, 40.6 μmol, 45%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 523.5.

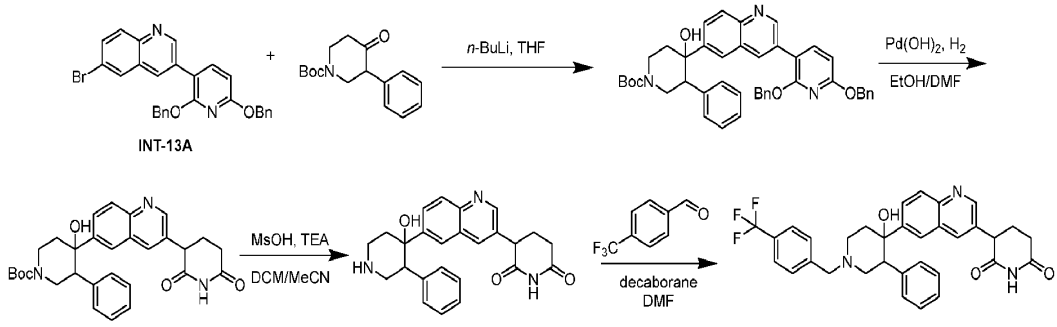
Step 4: **Synthesis of 3-(6-(2-ethyl-10-hydroxy-2,7-diazaspiro[4.5]decan-10-yl)quinolin-3-yl)piperidine-2,6-dione**

A solution of *tert*-butyl 10-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-2-ethyl-10-hydroxy-2,7-diazaspiro[4.5]decane-7-carboxylate (20 mg, 40.5 μmol) and methanesulfonic acid (15.6 mg, 162 μmol) in MeCN (1 mL) and DCM (1 mL) was stirred at rt for 30 min. The reaction mixture was cooled to 0 °C and then triethylamine (49.3 mg, 487 μmol) was added. The reaction mixture was concentrated in vacuo and the entire crude product was used in the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 423.4.

Step 5: **Synthesis of 3-(6-(2-ethyl-10-hydroxy-7-(4-(trifluoromethyl)benzyl)-2,7-diazaspiro[4.5]decan-10-yl)quinolin-3-yl)piperidine-2,6-dione (I-898)**

3-(6-(2-Ethyl-10-hydroxy-2,7-diazaspiro[4.5]decan-10-yl)quinolin-3-yl)piperidine-2,6-dione (17.1 mg, 1 Eq, 40.5 μmol) was reacted with 4-(trifluoromethyl)benzaldehyde (7.1 mg, 41 μmol) and decaborane according to **General Procedure 1, Step D**, *Method A*. The crude product was purified by reverse phase chromatography on a C18 column, eluting with 0.1% FA/acetonitrile in 0.1% FA/water to afford 3-(6-(2-ethyl-10-hydroxy-7-(4-(trifluoromethyl)-benzyl)-2,7-diazaspiro[4.5]decan-10-yl)quinolin-3-yl)piperidine-2,6-dione, formic acid (3.4 mg, 5.9 μmol, 14%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 581.5. ^{1}H NMR (500 MHz, DMSO-d6) δ ppm 11.00-10.95 (m, 1H), 8.77-8.74 (m, 1H), 8.37-8.34 (m, 2H), 8.22-8.19 (m, 1H), 8.09-8.06 (m, 1H), 8.05-8.01 (m, 1H), 7.95-7.90 (m, 1H), 7.73-7.69 (m, 2H), 7.63-7.58 (m, 2H), 4.16-4.12 (m, 1H), 3.69-3.65 (m, 1H), 3.61-3.56 (m, 2H), 2.70-2.66 (m, 2H), 2.66-2.62 (m, 3H), 2.61-2.57 (m, 2H), 2.46-2.42 (m, 2H), 2.30-2.26 (m, 1H), 2.11-2.07 (m, 1H), 2.04-1.97 (m, 2H), 1.93-1.85 (m, 2H), 1.83-1.77 (m, 1H), 1.64-1.59 (m, 1H), 0.78-0.73 (m, 3H).

Example 225: Synthesis of 3-(6-(4-hydroxy-3-phenyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-336)



Step 1: **Synthesis of tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3-phenylpiperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3-phenylpiperidine-1-carboxylate (261 mg, 376 μmol, 62%) was synthesized according to **General Procedure 1, Step A**, starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 0.3 g, 603 μmol) and *tert*-butyl 4-oxo-3-phenylpiperidine-1-carboxylate (216 mg, 784 μmol). The crude product was purified by silica gel flash chromatography, eluting with EtOAc in heptane. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 694.6.

Step 2: **Synthesis of tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3-phenylpiperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3-phenylpiperidine-1-carboxylate (261 mg, 376 μmol) was subjected to hydrogenation according to **General Procedure 1, Step B**. The crude product was purified by reverse phase chromatography using a C18 column, eluting with acetonitrile in water to yield tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3-phenylpiperidine-1-carboxylate (120 mg, 233 μmol, 62%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 516.5.

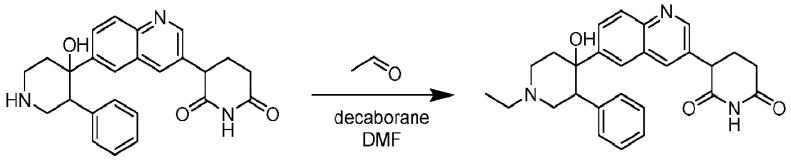
Step 3: **Synthesis of 3-(6-(4-hydroxy-3-phenylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione**

A solution of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3-phenylpiperidine-1-carboxylate (60 mg, 116 μmol) and methanesulfonic acid (44 mg, 466 μmol) in MeCN (1 mL) and DCM was stirred at rt for 30 min. Triethylamine (118 mg, 1.16 mmol) was added, and the reaction mixture was concentrated in vacuo. The entire crude product was used in the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 416.3.

Step 4: **Synthesis of 3-(6-(4-hydroxy-3-phenyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-336)**

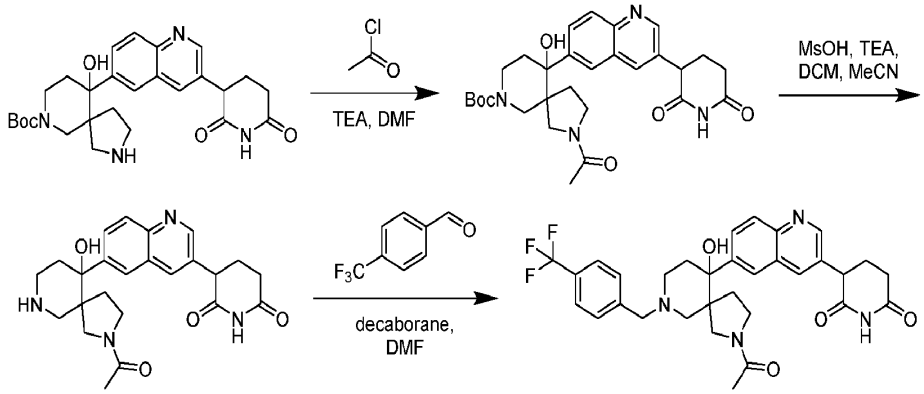
3-(6-(4-hydroxy-3-phenylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (48 mg, 0.12 mmol) was reacted with 4-(trifluoromethyl)benzaldehyde (20 mg, 0.12 mmol) and decaborane according to **General Procedure 1, Step D**, *Method A*. The crude product was purified by reverse phase chromatography on a C18 column, eluting with 0.1% FA/acetonitrile in 0.1% FA/water to yield 3-(6-(4-hydroxy-3-phenyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, formic acid **(I-336)** (23.8 mg, 41.5 μmol, 36%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 574.6. ^{1}H NMR (500 MHz, DMSO) δ (ppm) 10.97-10.92 (m, 1H), 8.67 (d, J = 2.2 Hz, 1H), 8.36-8.31 (m, 1H), 8.07-8.04 (m, 1H), 7.87-7.83 (m, 1H), 7.82-7.74 (m, 2H), 7.72-7.68 (m, 2H), 7.66-7.59 (m, 2H), 7.08-7.02 (m, 2H), 6.99-6.91 (m, 3H), 5.27-5.21 (m, 1H), 4.13-4.03 (m, 1H), 3.77-3.68 (m, 2H), 2.95-2.87 (m, 1H), 2.84-2.69 (m, 4H), 2.68-2.52 (m, 2H), 2.45-2.33 (m, 2H), 2.13-2.04 (m, 1H), 1.77-1.70 (m, 1H).

Example 226: Synthesis of 3-(6-(1-ethyl-4-hydroxy-3-phenylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-47)



3-(6-(4-Hydroxy-3-phenylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (prepared in **(I-336) step 3,** 48 mg, 0.12 mmol) was reacted with acetaldehyde (5.1 mg, 0.12 mmol) and decaborane according to **General Procedure 1, Step D**, *Method A*. The crude product was purified by reverse phase chromatography on a C18 column, eluting with 0.1% FA/acetonitrile in 0.1% FA/water to yield 3-(6-(1-ethyl-4-hydroxy-3-phenylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, formic acid (**I-47**, 18.7 mg, 42.2 µmol, 36%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 444.4 ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.94 (s, 1H), 8.67 (d, *J* = 2.2 Hz, 1H), 8.25 (s, 1H), 8.04 (s, 1H), 7.83 (s, 1H), 7.80-7.74 (m, 2H), 7.08 (m, 2H), 7.02-6.91 (m, 3H), 4.08 (dd, *J* = 4.7, 12.3 Hz, 1H), 3.32 (m, 4H), 2.89-2.69 (m, 4H), 2.65-2.54 (m, 2H), 2.43-2.33 (m, 2H), 2.13-2.04 (m, 1H), 1.77-1.70 (m, 1H), 1.07 (t, *J* = 7.4 Hz, 3H).

Example 227: Synthesis of 3-(6-(2-acetyl-10-hydroxy-7-(4-(trifluoromethyl)benzyl)-2,7-diazaspiro[4.5]decan-10-yl)quinolin-3-yl)piperidine-2,6-dione (I-900)



Step 1: **Synthesis of tert-butyl 2-acetyl-10-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-10-hydroxy-2,7-diazaspiro[4.5]decane-7-carboxylate**

Acetyl chloride (7.1 mg, 91 µmol) was added at 0 °C to a solution of *tert*-butyl 10-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-10-hydroxy-2,7-diazaspiro[4.5]decane-7-carboxylate (prepared in **Ex 224**, Step 2, 45 mg, 91 µmol) and TEA (41 mg, 0.41 mmol) in DMF (1 mL). After 15 min, the reaction mixture was filtered and loaded directly onto a C18 column for purification via reverse phase chromatography, eluting with 0.1% FA/acetonitrile in 0.1% FA/water to yield *tert*-butyl 2-acetyl-10-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-10-hydroxy-2,7-diazaspiro[4.5]decane-7-carboxylate (29 mg, 54 µmol, 59%) LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 537.5.

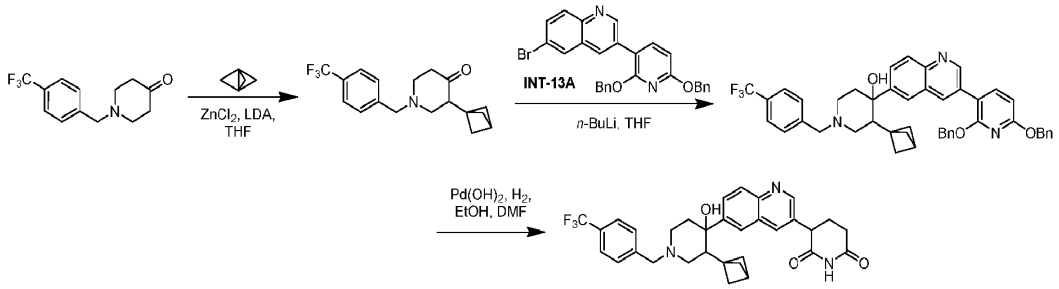
Step 2: **Synthesis of 3-(6-(2-acetyl-10-hydroxy-2,7-diazaspiro[4.5]decan-10-yl)quinolin-3-yl)piperidine-2,6-dione**

A solution of *tert*-butyl 2-acetyl-10-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-10-hydroxy-2,7-diazaspiro[4.5]decane-7-carboxylate (29 mg, 54 μmol) and methanesulfonic acid (21 mg, 0.22 mmol). in DCM (700 μL) and MeCN (700 μL) was stirred at rt for 1h. The reaction mixture was cooled to 0 °C and triethylamine (55 mg, 0.54 mmol) was added, then the reaction mixture was concentrated under reduced pressure. The entire crude product was used in the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 437.3.

Step 3: **Synthesis of 3-(6-(2-acetyl-10-hydroxy-7-(4-(trifluoromethyl)benzyl)-2,7-diazaspiro-[4.5]decan-10-yl)quinolin-3-yl)piperidine-2,6-dione (I-900)**

3-(6-(2-Acetyl-10-hydroxy-2,7-diazaspiro[4.5]decan-10-yl)quinolin-3-yl)piperidine-2,6-dione (24 mg, 55 μmol) was reacted with 4-(trifluoromethyl)benzaldehyde (9.6 mg, 55 μmol) and decaborane according to **General Procedure 1, Step D,** *Method A*. The crude product was purified by reverse phase chromatography on a C18 column, eluting with 0.1% FA/acetonitrile in 0.1% FA/water to provide 3-(6-(2-acetyl-10-hydroxy-7-(4-(trifluoromethyl)benzyl)-2,7-diazaspiro[4.5]decan-10-yl)quinolin-3-yl)piperidine-2,6-dione, formic acid (7.7 mg, 13 μmol, 24%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 595.5. ^{1}H NMR (500 MHz, DMSO-d6) δ ppm 11.01-10.94 (m, 1H), 8.79-8.74 (m, 1H), 8.47-8.41 (m, 1H), 8.24-8.19 (m, 1H), 8.12-8.08 (m, 1H), 8.01-7.92 (m, 2H), 7.76-7.66 (m, 2H), 7.64-7.56 (m, 2H), 4.18-4.12 (m, 1H), 3.76-3.57 (m, 3H), 2.92 (m, 3H), 2.85-2.70 (m, 4H), 2.67-2.56 (m, 4H), 2.45-2.36 (m, 2H), 2.18-2.10 (m, 1H), 2.03-1.88 (m, 1H), 1.76 (s, 1H), 1.73-1.62 (m, 2H), 1.54-1.50 (m, 1H).

Example 228: Synthesis of 3-(6-(3-(bicyclo[1.1.1]pentan-1-yl)-4-hydroxy-1-(4-(trifluoro-methyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-846)



Step 1: **Synthesis of 3-(bicyclo[1.1.1]pentan-1-yl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-one**

A solution of 1-(4-(trifluoromethyl)benzyl)piperidin-4-one (1.17 g, 4.54 mmol) in THF (1.5 mL) was added to a solution of LDA (4.7 mL of 2 molar solution in THF/heptane/ethylbenzene, 9.38 mmol) at -78 °C, After 30 min, a solution of anhydrous zinc chloride (5.3 mL of 2M solution in THF, 10.6 mmol) was added and the mixture was stirred for 5 min at -78 °C. Tricyclo[1.1.1.01,3]pentane (0.20 g, 3.78 mL of 0.8 M solution in THF, 3.03 mmol) was then added, and the reaction mixture was allowed to warm to rt

and was stirred for 1h. Saturated aqueous NH_4Cl solution was added, and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel flash chromatography, eluting with EtOAc in heptane to yield 3-(bicyclo[1.1.1]pentan-1-yl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-one (337 mg, 1.04 mmol, 34%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 324.3.

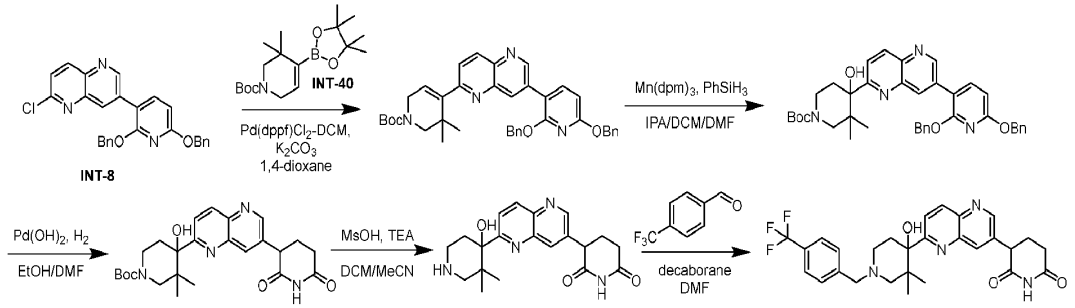
Step 2: **Synthesis of 3-(bicyclo[1.1.1]pentan-1-yl)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-ol**

3-(bicyclo[1.1.1]pentan-1-yl)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-ol (51 mg, 69 μmol, 34%) was synthesized according to **General Procedure 1, Step A**, starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 100 mg, 201 μmol) and 3-(bicyclo[1.1.1]pentan-1-yl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-one (78.0 mg, 241 μmol). The crude product was purified by silica gel flash chromatography, eluting with EtoAc in heptane. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 372.0 (half mass).

Step 3: **Synthesis of 3-(6-(3-(bicyclo[1.1.1]pentan-1-yl)-4-hydroxy-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-846)**

3-(Bicyclo[1.1.1]pentan-1-yl)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-1-(4-(trifluoro-methyl)benzyl)piperidin-4-ol (51 mg, 69 μmol) was subjected to hydrogenation according to **General Procedure 1, Step B**. The crude product was purified by reverse phase chromatography on a C18 column, eluting with 0.1% FA/acetonitrile in 0.1% FA/water to yield 3-(6-(3-(bicyclo[1.1.1]pentan-1-yl)-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, formic acid (2.1 mg, 3.7 μmol, 5.4%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 564.5 ^1H NMR (500 MHz, DMSO-d6) δ ppm 10.98-10.94 (m, 1H), 8.75-8.73 (m, 1H), 8.45-8.43 (m, 1H), 8.20-8.17 (m, 1H), 8.07-8.01 (m, 1H), 7.96-7.91 (m, 1H), 7.71 (s, 2H), 7.62-7.59 (m, 2H), 4.88-4.79 (m, 1H), 4.18-4.09 (m, 1H), 3.7 -3.71 (m, 1H), 3.63-3.57 (m, 1H), 2.81-2.73 (m, 1H), 2.67-2.61 (m, 2H), 2.61-2.55 (m, 2H), 2.47-2.40 (m, 3H), 2.33-2.29 (m, 1H), 2.19-2.12 (m, 1H), 2.0-1.94 (m, 1H), 1.34 (dd, J = 1.6, 9.6 Hz, 3H), 1.22 (s, 4H).

Example 229: Synthesis of 3-(6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-1,5-naphthyridin-3-yl)piperidine-2,6-dione (I-181)



Step 1; **Synthesis of tert-butyl 4-(7-(2,6-bis(benzyloxy)pyridin-3-yl)-1,5-naphthyridin-2-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate**

A solution of 7-(2,6-bis(benzyloxy)pyridin-3-yl)-2-chloro-1,5-naphthyridine (**INT-8**, 125 mg, 275 μmol), *tert*-butyl 3,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**INT-40**, 111 mg, 330 μmol), and $Pd(dppf)Cl_2$-DCM adduct (33.7 mg, 41.3 μmol) in dioxane (1.1 mL) was sparged with argon for 3 min. A solution of potassium carbonate (46 μl, 2M in water, 0.33 mmol) was added and the mixture was again sparged with argon for 3 min, then was stirred at 100 °C for 2h. The cooled reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel flash chromatography, eluting with EtOAc in heptane to provide *tert*-butyl 4-(7-(2,6-bis(benzyloxy)pyridin-3-yl)-1,5-naphthyridin-2-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (72.8 mg, 116 μmol, 42%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 629.6.

Step 2: **Synthesis of tert-butyl 4-(7-(2,6-bis(benzyloxy)pyridin-3-yl)-1,5-naphthyridin-2-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate**

Tert-butyl 4-(7-(2,6-bis(benzyloxy)pyridin-3-yl)-1,5-naphthyridin-2-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (72 mg, 115 μmol) was treated according to **General Procedure 3, Step C**. The crude produce was purified by reverse phase chromatography using a C18 column, eluting with 0.1% FA/acetonitrile in 0.1% FA/water to yield *tert*-butyl 4-(7-(2,6-bis(benzyloxy)pyridin-3-yl)-1,5-naphthyridin-2-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (75 mg, 0.12 mmol, 100%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 647.6.

Step 3: **Synthesis of tert-butyl 4-(7-(2,6-dioxopiperidin-3-yl)-1,5-naphthyridin-2-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate**

Tert-butyl 4-(7-(2,6-bis(benzyloxy)pyridin-3-yl)-1,5-naphthyridin-2-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (75 mg, 0.12 mmol) was hydrogenated according to **General Procedure 1, Step B**. The crude product was purified by reverse phase chromatography on a C18 column, eluting with acetonitrile/water to yield tert-butyl 4-(7-(2,6-dioxopiperidin-3-yl)-1,5-naphthyridin-2-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (10 mg, 21 μmol, 18%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 469.6.

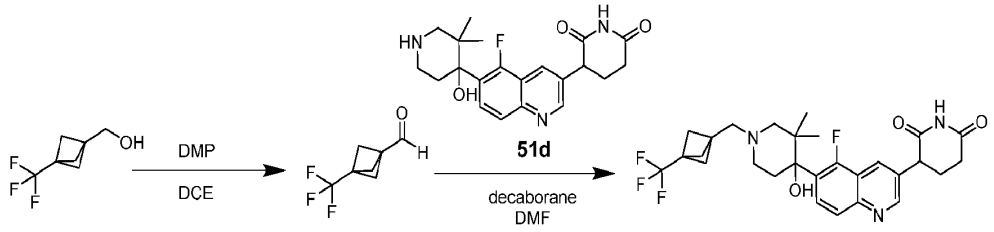
Step 4: **Synthesis of 3-(6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-1,5-naphthyridin-3-yl)piperidine-2,6-dione**

A solution of *tert*-butyl 4-(7-(2,6-dioxopiperidin-3-yl)-1,5-naphthyridin-2-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (10 mg, 21 μmol) and methanesulfonic acid (8.2 mg, 85 μmol) in MeCN (500 μL) and DCM (500 μL) was stirred at rt for 30 min, then was cooled to 0 °C and triethylamine (32 mg, 0.32 mmol) was added. The reaction mixture was concentrated in vacuo and the entire crude product was used in the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 369.3.

Step 5: **Synthesis of 3-(6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1,5-naphthyridin-3-yl)piperidine-2,6-dione (I-181)**

3-(6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-1,5-naphthyridin-3-yl)piperidine-2,6-dione (8 g, 0.02 mmol) was reacted with 4-(trifluoromethyl)benzaldehyde (6 mg, 0.03 mmol) and decaborane according to **General Procedure 1, Step D**, *Method A*. The crude product was purified by reverse phase chromatography on a C18 column, eluting with 0.1% FA/acetonitrile in 0.1% FA/water to provide 3-(6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1,5-naphthyridin-3-yl)piperidine-2,6-dione, formic acid (5.3 mg, 10 μmol, 50%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 527.5. ^{1}H NMR (500 MHz, DMSO, 298 K) δ ppm 11.03-10.97 (m, 1H), 8.90-8.85 (m, 1H), 8.46-8.43 (m, 2H), 8.39-8.36 (m, 1H), 8.25-8.22 (m, 1H), 8.09-8.05 (m, 1H), 7.70 (s, 2H), 7.62-7.58 (m, 2H), 5.32-5.25 (m, 1H), 4.27-4.21 (m, 1H), 3.69-3.63 (m, 2H), 3.60-3.54 (m, 2H), 3.18-3.08 (m, 2H), 2.82-2.72 (m, 2H), 2.65-2.59 (m, 1H), 2.21-2.12 (m, 2H), 1.58-1.51 (m, 1H), 0.93-0.88 (m, 3H), 0.73 (s, 3H).

Example 230: Synthesis of 3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((3-(trifluoromethyl)-bicyclo[1.1.1]pentan-1-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-848)



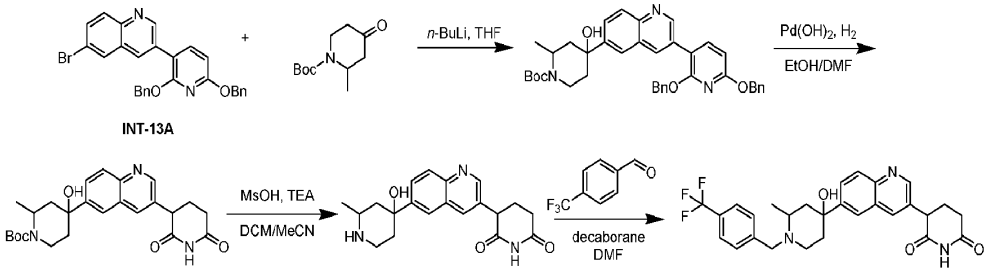
Step 1: **Synthesis of 3-(trifluoromethyl)bicyclo[1.1.1]pentane-1-carbaldehyde**

DMP (26 mg, 60 μmol) was added to a solution of [3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]methanol (0.01 g, 60 μmol) in DCE (0.5 ml) and the mixture was stirred at rt for 2h. The reaction mixture was filtered, and the filtrate was used directly in the next step as a solution in DCE. Quantitative yield is assumed for the reaction.

Step 2: **Synthesis of 3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((3-(trifluoromethyl)-bicyclo[1.1.1]pentan-1-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-848)**

To the stirred DCE solution of 3-(trifluoromethyl)bicyclo[1.1.1]pentane-1-carbaldehyde (from Step 1, 0.060 mmol) was added 3-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (8 mg, 0.02 mmol), followed by DMF (0.5 ml) and decaborane (1 mg, 8 µmol). The reaction mixture was stirred for 15 min at 70 °C. The cooled reaction mixture was concentrated under reduced pressure, then the residue was purified by reverse phase chromatography on a C18 column, eluting with 0.1% FA/acetonitrile in 0.1% FA/water to provide 3-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-((3-(trifluoromethyl)bicyclo[1.1.1-]pentan-1-yl)methyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, formic acid (6.2 g, 12 µmol, 60%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 534.3. 1H NMR (500 MHz, DMSO-d6) δ ppm 10.98 (s, 1H), 8.84 (d, J = 2.2 Hz, 1H), 8.44-8.36 (m, 1H), 8.35-8.28 (m, 1H), 8.11-8.06 (m, 1H), 7.86-7.81 (m, 1H), 5.11-5.06 (m, 1H), 4.25-4.19 (m, 1H), 3.14-3.06 (m, 2H), 2.79-2.71 (m, 1H), 2.68-2.61 (m, 2H), 2.61-2.54 (m, 1H), 2.25-2.19 (m, 1H), 2.16-2.09 (m, 1H), 1.94 (m, 5H), 1.68-1.59 (m, 1H), 1.28-1.19 (m, 2H), 1.01-0.95 (m, 3H), 0.73-0.65 (m, 3H) (peaks overlap with solvent).

Example 231: Synthesis of 3-(6-(4-hydroxy-2-methyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-903)



Step 1: **Synthesis of tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-2-methylpiperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-2-methyl-piperidine-1-carboxylate (113 mg, 178 µmol, 29.5%) was synthesized according to **General Procedure 1, Step A**, starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 0.3 g, 603 µmol) and *tert*-butyl 2-methyl-4-oxopiperidine-1-carboxylate (154 mg, 724 µmol). The crude product was purified by silica gel flash chromatography, eluting with EtOAc in heptane. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 632.6.

Step 2: **Synthesis of tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-2-methylpiperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-Bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-2-methyl-piperidine-1-carboxylate (0.11g, 178 µmol) was subjected to hydrogenation according to **General Procedure 1, Step B**. The crude product was purified by reverse phase chromatography on a C18 column, eluting with

acetonitrile/water to yield tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-2-methyl-piperidine-1-carboxylate (48 mg, 0.11 mmol, 59%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 454.4.

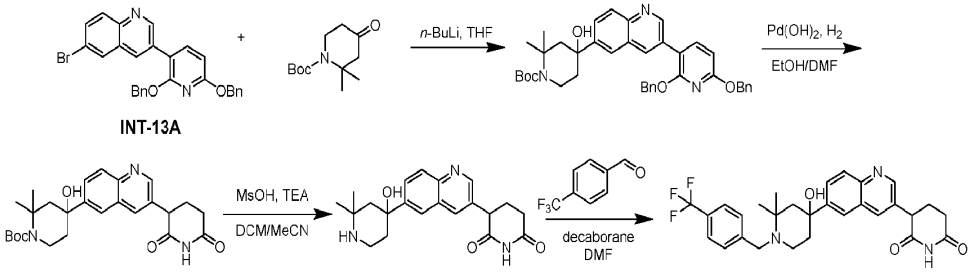
Step 3: **Synthesis of 3-(6-(4-hydroxy-2-methylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione**

A solution of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-2-methylpiperidine-1-carboxylate (24 mg, 53 µmol) and methanesulfonic acid (20 mg, 0.21 mmol) in MeCN (700 µL) and DCM (700 µL) was stirred at rt for 30 min, then was cooled to 0 °C. Triethylamine (80 mg, 0.79 mmol) was added, and the reaction mixture was concentrated. The entire crude product was used in the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 354.1.

Step 4: Synthesis of 3-(6-(4-hydroxy-2-methyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-903)

3-(6-(4-Hydroxy-2-methylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (19 mg, 53 µmol) was reacted with 4-(trifluoromethyl)benzaldehyde (14 mg, 81 µmol) and decaborane according to **General Procedure 1, Step D**, *Method A*. The crude product was purified via reverse phase chromatography on a C18 column, eluting with 0 to 100% of 0.1% FA/MeCN in 0.1% FA/water to yield 3-(6-(4-hydroxy-2-methyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, formic acid (1.4mg, 2.7 µmol, 5%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 512.2 ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.76 (s, 1H), 8.44 (s, 1H), 8.22 (m, 1H), 7.99 (m, 1H), 7.98-7.95 (s, 1H), 7.90 (dd, J = 1.9, 9.0 Hz, 1H), 7.67 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 8.2 Hz, 2H), 4.14 (dd, J = 4.7, 12.3 Hz, 1H), 3.92 (br d, J = 14.2 Hz, 1H), 2.83-2.72 (m, 2H), 2.71-2.57 (m, 2H), 2.46-2.33 (m, 2H), 2.32-2.21 (m, 1H), 2.20-2.10 (m, 1H), 2.12–2.05 (m, 1H), 2.03-1.95 (m, 1H), 1.81-1.69 (m, 2H), 1.23 (m, 4H).

Example 232: Synthesis of 3-(6-(4-hydroxy-2,2-dimethyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-923)



Step 1: **Synthesis of tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-2,2-dimethylpiperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-2,2-dimethyl-piperidine-1-carboxylate (102 mg, 158 µmol, 26%) was synthesized according to **General Procedure 1, Step A**, starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 0.3 g, 603 µmol)

and *tert*-butyl 2,2-dimethyl-4-oxopiperidine-1-carboxylate (165 mg, 724 μmol). The crude product was purified by silica gel flash chromatography, eluting with EtOAc in heptane. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 646.6.

Step 2: **Synthesis of tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-2,2-dimethylpiperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-2,2-dimethyl-piperidine-1-carboxylate (102 mg, 158 μmol) was hydrogenated according to **General Procedure 1, Step B**. The crude product was purified by reverse phase chromatography on a C18 column, eluting with acetonitrile/water to afford 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-2,2-dimethylpiperidine-1-carboxylate (32.3 mg, 69.1 μmol, 44%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 468.4.

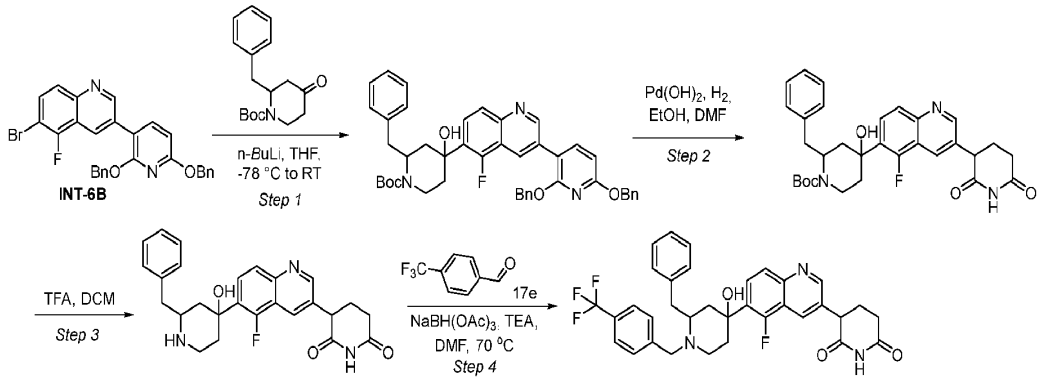
Step 3: **Synthesis of 3-(6-(4-hydroxy-2,2-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione**

A solution of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-2,2-dimethylpiperidine-1-carboxylate (16 mg, 34 μmol) and methanesulfonic acid (13 mg, 0.14 mmol) in DCM (700 μL) and MeCN (700 μL) was stirred at rt for 30 min, then was cooled to 0 °C. Triethylamine (52 mg, 0.051 mmol) was added, and the reaction mixture was concentrated. The entire crude product was used in the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 368.1.

Step 4: **Synthesis of 3-(6-(4-hydroxy-2,2-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-923)**

3-(6-(4-Hydroxy-2,2-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (13 mg, 34 μmol) was reacted with 4-(trifluoromethyl)benzaldehyde (9.2 mg, 53 μmol) and decaborane according to **General Procedure 1, Step D**, *Method A*. The crude product was purified via reverse phase chromatography on a C18 column, eluting with 0.1% FA/MeCN in 0.1% FA/water to yield 3-(6-(4-hydroxy-2,2-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, formic acid (2 mg, 4 μmol, 10%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 526.3.

Example 233: Synthesis of 3-(6-(2-benzyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (I-987)



Step 1: **Synthesis of *tert*-butyl 2-benzyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (100a)**

Tert-butyl 2-benzyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (190.0 mg, 0.26 mmol, 26% yield) was synthesized according to **General Procedure 1, Step A** starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-5-fluoroquinoline (**INT-6B**, 515 mg, 1.00 mmol) and *tert*-butyl 2-benzyl-4-oxopiperidine-1-carboxylate (347 mg, 1.20 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 726.4.

Step 2: **Synthesis of *tert*-butyl 2-benzyl-4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (100b)**

Tert-butyl 2-benzyl-4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (**100b**, 70 mg, 0.13 mmol, 77% yield) was synthesized according to **General Procedure 1, Step B** starting from *tert*-butyl 2-benzyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (**100a**, 120 mg, 1.65 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 548.3.

Step 3: **Synthesis of 3-(6-(2-benzyl-4-hydroxypiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (100c)**

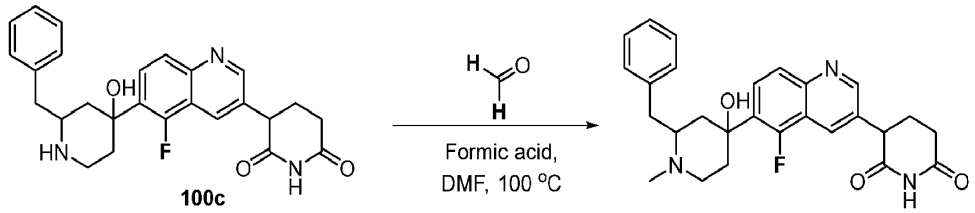
A stirred solution of *tert*-butyl 2-benzyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-quinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (**100b**, 30 mg, 1 eq., 0.055 mmol) in DCM (2 mL)and TFA (0.5 mL) was allowed to stir for 30 min at room temperature. The reaction mixture was concentrated under reduced pressure and used in the next step without purification. LCMS: m/z HESI, positive $[M+H]^+$ = 448.2.

Step 4: **Synthesis of 3-(6-(2-benzyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (I-987)**

To a stirred solution of **3-(6-(2-benzyl-4-hydroxypiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione** (**100c**, 0.055 mmol), triethylamine (33 mg, 46 µL, 0.33 mmol) and 4-(trifluoromethyl)benzaldehyde (**17e**, 13 mg, 0.077 mmol) in DMF (1 mL) was added sodium

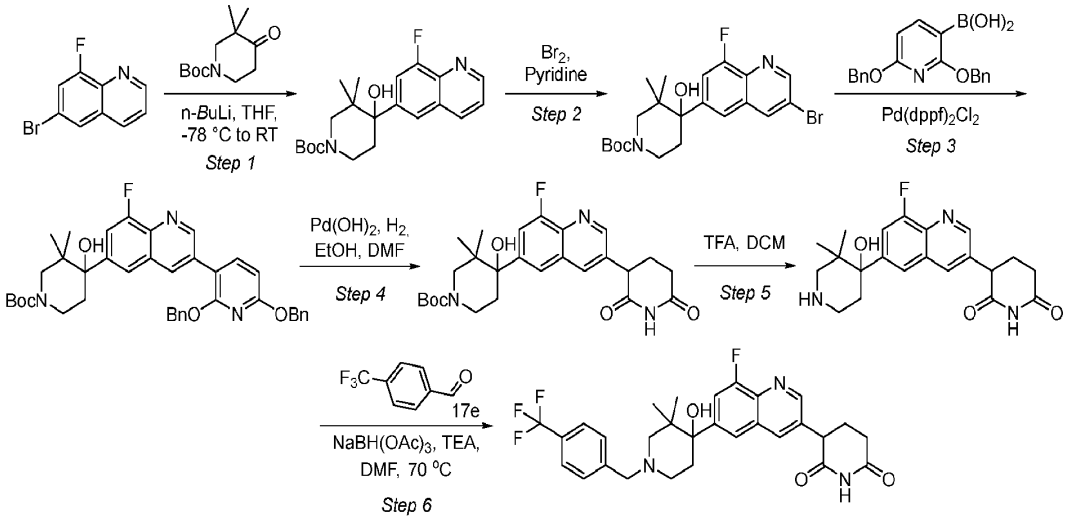
triacetoxyborohydride (16 mg, 77 μmol). The resulting mixture was stirred at 40 °C for 1 h. The reaction mixture was purified via **General Procedure 1, Step D** *Purification Method* (b) to give 3-(6-(2-benzyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, formic acid (**I-987**, 21 mg, 0.035 mmol, 63% yield). LCMS: m/z HESI, positive $[M+H]^+$ = 606.5; ^{1}H NMR (500 MHz, DMSO-d6) δ ppm 11.02-10.95 (m, 1H), 8.86-8.82 (m, 1H), 8.33-8.30 (m, 1H), 7.99-7.94 (m, 1H), 7.88-7.84 (m, 1H), 7.64 (d, J = 8.2 Hz, 2H), 7.50 (d, J = 7.7 Hz, 2H), 7.29-7.22 (m, 5H), 7.19-7.14 (m, 1H), 5.46-5.41 (m, 1H), 4.25-4.18 (m, 1H), 4.03-3.98 (m, 1H), 3.88-3.83 (m, 1H), 3.21-3.11 (m, 3H), 2.95-2.89 (m, 1H), 2.80-2.72 (m, 1H), 2.47-2.39 (m, 3H), 2.29-2.24 (m, 1H), 2.16-2.10 (m, 1H), 1.74-1.64 (m, 2H).

Example 234: Synthesis of 3-(6-(2-benzyl-4-hydroxy-1-methylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (I-1319)



To a stirred solution of **3-(6-(2-benzyl-4-hydroxypiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione** (**Example 233, I-987 Step 3**, 0.055 mmol) in DMF (0.67 mL) was added water (3 mL), aqueous formaldehyde solution (0.56 g, 36%, 6.7 mmol) and formic acid (62 mg, 1.3 mmol). The solution was stirred at 100 °C for 16 h. Purification via **General Procedure 1, Step D**, *Purification Method* (b) gave 3-(6-(2-benzyl-4-hydroxy-1-methylpiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione, formic acid (**I-1319,** 6 mg, 0.01 mmol, 20% yield). LCMS: m/z HESI, positive $[M+H]^+$ = 462.3; ^{1}H NMR (500 MHz, DMSO-d6) δ ppm 10.97 (s, 1H), 8.83 (s, 1H), 8.31-8.24 (m, 1H), 8.22-8.18 (m, 1H), 7.83-7.78 (m, 1H), 7.75-7.69 (m, 1H), 7.29 (d, J = 7.1 Hz, 2H), 7.28-7.25 (m, 2H), 7.19 (s, 1H), 4.25-4.19 (m, 1H), 3.04-3.00 (m, 1H), 2.98-2.93 (m, 1H), 2.85-2.72 (m, 2H), 2.65-2.60 (m, 1H), 2.59-2.55 (m, 1H), 2.52 (br s, 1H), 2.48-2.43 ((m, 1H), 2.35 (s, 3H), 2.32-2.24 (m, 1H), 2.23-2.16 (m, 1H), 2.16-2.09 (m, 1H), 1.84-1.76 (m, 1H), 1.59-1.51 (m, 1H).

Example 235: Synthesis of 3-(8-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-1320)



Step 1: **Synthesis of *tert*-butyl 4-(8-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (101a)**

Tert-butyl 4-(8-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (**101a**, 150 mg, 0.40 mmol, 5% yield) was synthesized according to **General Procedure 1, Step A** starting from 6-bromo-8-fluoroquinoline (1.92 g, 8.5 mmol) and *tert*-butyl 3,3-dimethyl-4-oxopiperidine-1-carboxylate (2.32 g, 10.2 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 375.2.

Step 2: **Synthesis of *tert*-butyl 4-(3-bromo-8-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (101b)**

A solution of *tert*-butyl 4-(8-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (**101a**, 150 mg, 401 µmol) in pyridine (222 mg, 2.80 mmol) and acetonitrile (2 mL) was heated at 70 °C and then treated with bromine (320 mg, 2.00 mmol). The reaction mixture was stirred at 70 °C for 80 min. The cooled reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel flash chromatography, eluting with 20-80% EtOAc in heptane to afford *tert*-butyl 4-(3-bromo-8-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (**101b**, 161 mg, 355 µmol, 89%). LCMS: m/z HESI, positive $[M+H]^+$ = 453.3.

Step 3: **Synthesis of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-8-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (101c)**

In a microwave vial equipped with a stir bar was added *tert*-butyl 4-(3-bromo-8-fluoro-quinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (**101b**, 151 mg, 333 µmol), $PdCl_2$(dppf)-DCM adduct (27.2 mg, 33.3 µmol), (2,6-bis(benzyloxy)pyridin-3-yl)boronic acid (201 mg, 600 µmol), potassium carbonate (92.1 mg, 666 µmol), 1,4-dioxane (3 mL), and water (0.3 mL). The reaction mixture was sparged with argon, then the vial was sealed and heated at 110 °C for 1 h in a microwave reactor. The cooled reaction mixture was filtered through a pad of celite and silica, and the filtrate was concentrated.

The crude residue was purified by silica gel flash chromatography, eluting with 0-100% EtOAc in heptane to afford *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-8-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (**101c**, 188 mg, 283 µmol, 85%). LCMS: m/z HESI, positive $[M+H]^+$ = 664.5.

Step 4: **Synthesis of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-8-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (101d)**

Tert-butyl 2-benzyl-4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-piperidine-1-carboxylate (**101d**) was synthesized according to **General Procedure 1, Step B** starting from *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-8-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (**101c**, 148 mg, 223 µmol). The crude material was used in the next step without purification. LCMS: m/z HESI, positive $[M+H]^+$ = 486.3.

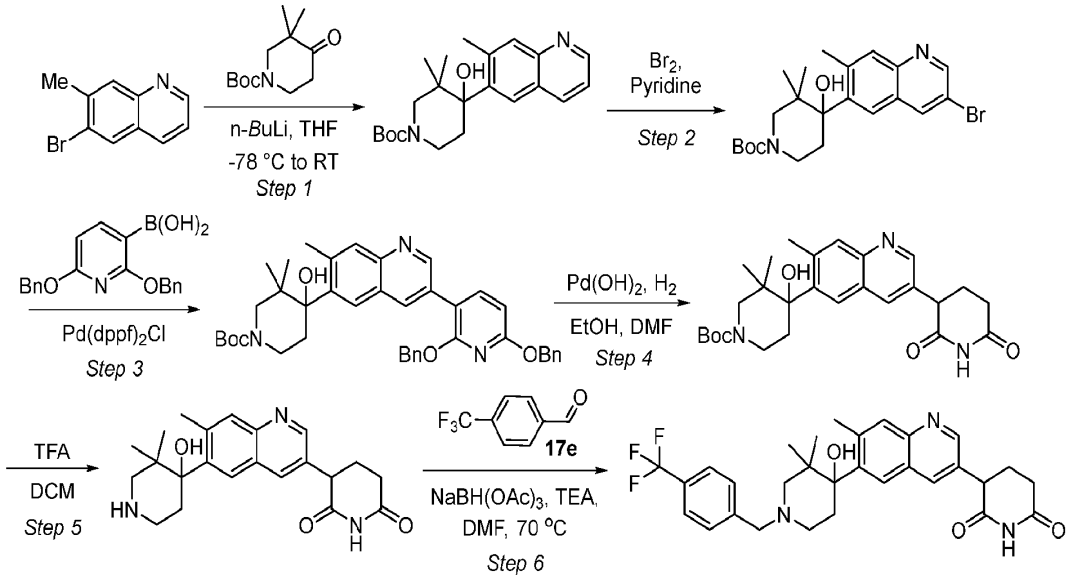
Step 5: **Synthesis of 3-(8-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (101e)**

A solution of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-8-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (directly from the previous step, **101d**) in DCM (2 mL) and TFA (0.5 mL) was stirred at 45 °C for 1 h. The reaction mixture was concentrated under reduced pressure, and the entire crude product was used in the next step without purification. LCMS: m/z HESI, positive $[M+H]^+$ = 386.2.

Step 6: **Synthesis of 3-(8-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-1320)**

To a stirred solution of **3-(8-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione** (directly from the previous step, **101e**), triethylamine (135 mg, 186 µL, 1.34 mmol) and 4-(trifluoromethyl)benzaldehyde (**17e**, 54.4 mg, 0.312 mmol) in DMF (1 mL) was added sodium triacetoxyborohydride (113 mg, 535 µmol). The resulting mixture was stirred at 40 °C for 1 h. The reaction mixture was purified via **General Procedure 1, Step D** *Purification Method* (b) to give **3-(8-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione** (**I-1320**, 40 mg, 0.074 mmol, 33% yield over 3 steps). LCMS: m/z HESI, positive $[M+H]^+$ = 544.35; ^{1}H NMR (500 MHz, DMSO-d6) δ ppm 10.99 (s, 1H), 8.81 (d, J = 2.2 Hz, 1H), 8.29 (d, J = 1.1 Hz, 1H), 7.83 (s, 1H), 7.70 (d, J = 8.2 Hz, 3H), 7.59 (d, J = 8.2 Hz, 2H), 5.04-4.91 (m, 1H), 4.22-4.12 (m, 1H), 3.67-3.63 (m, 1H), 3.58-3.54 (m, 1H), 2.88-2.70 (m, 3H), 2.52 (s, 3H), 2.48-2.38 (m, 1H), 2.18-2.12 (m, 2H), 1.58-1.51 (m, 1H), 0.93 (s, 3H), 0.68 (s, 3H).

Example 236: Synthesis of 3-(6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-7-methylquinolin-3-yl)piperidine-2,6-dione (I-1321)



Step 1: **Synthesis of *tert*-butyl 4-hydroxy-3,3-dimethyl-4-(7-methylquinolin-6-yl)piperidine-1-carboxylate (102a)**

tert-butyl 4-hydroxy-3,3-dimethyl-4-(7-methylquinolin-6-yl)piperidine-1-carboxylate (**102a**, 240 mg, 0.65 mmol, 8% yield) was synthesized according to **General Procedure 1, Step A** starting from 6-bromo-7-methylquinoline (1.89 g, 8.50 mmol) and *tert*-butyl 3,3-dimethyl-4-oxopiperidine-1-carboxylate (2.32 g, 10.2 mmol). LCMS: m/z HESI, positive $[M+H]^+$ = 371.2.

Step 2: **Synthesis of *tert*-butyl 4-(3-bromo-7-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (102b)**

A solution of ***tert*-butyl 4-hydroxy-3,3-dimethyl-4-(7-methylquinolin-6-yl)piperidine-1-carboxylate** (**102a**, 200 mg, 540 μmol) in pyridine (299 mg, 3.78 mmol) and acetonitrile (2 mL) was heated at 70 °C, and then was treated with bromine (431 mg, 2.70 mmol). The reaction mixture was stirred at 70 °C for 80 min. The reaction mixture was concentrated, and the residue was purified via silica gel flash chromatography, eluting with 20 to 80% EtOAc in heptane to afford ***tert*-butyl 4-(3-bromo-7-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate** (**102b**, 230 mg, 540 μmol, 95%) LCMS: m/z HESI, positive $[M+H]^+$ = 449.4.

Step 3: **Synthesis of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (102c)**

Tert-butyl 4-(3-bromo-7-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (**102b**, 220 mg, 490 μmol) and (2,6-bis(benzyloxy)pyridin-3-yl)boronic acid (295 mg, 881 μmol) were subjected to Suzuki coupling using the procedure of Ex 235**, (I-1320) Step 3** to afford *tert*-butyl 4-(3-

(2,6-bis(benzyloxy)pyridin-3-yl)-7-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (**102c**, 250 mg, 379 μmol, 77%). LCMS: m/z HESI, positive $[M+H]^+$ = 660.4.

Step 4: **Synthesis of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-7-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (102d)**

Tert-butyl 2-benzyl-4-(3-(2,6-dioxopiperidin-3-yl)-7-methylquinolin-6-yl)-4-hydroxy-piperidine-1-carboxylate (**102d**) was synthesized according to **General Procedure 1, Step B** starting from *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (**102c**, 202 mg, 306 μmol). The entire crude product was used in the next step without purification. LCMS: m/z HESI, positive $[M+H]^+$ = 482.4.

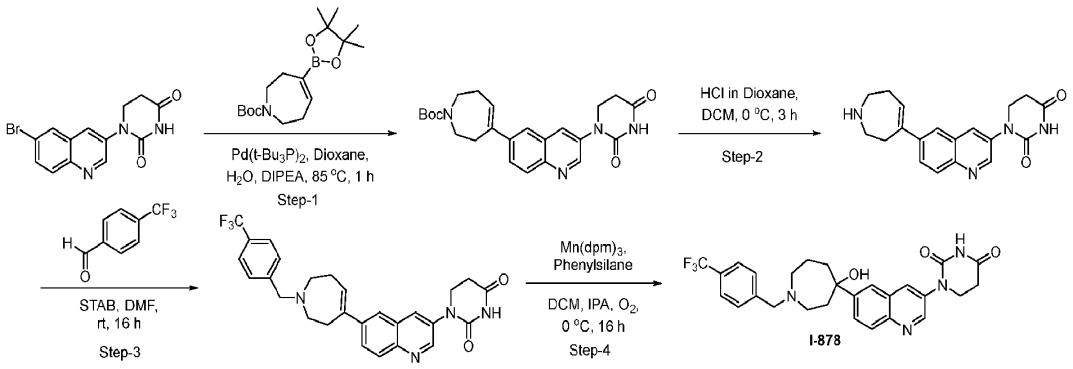
Step 5: **Synthesis of 3-(6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-7-methylquinolin-3-yl)piperidine-2,6-dione (102e)**

A solution of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-7-methylquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (directly from the previous step, **102d**) in DCM (2 mL) and TFA (0.5 mL) was stirred at 45 °C for 1 h. The reaction mixture was concentrated under reduced pressure and used in the next step without purification. LCMS: m/z HESI, positive $[M+H]^+$ = 382.3.

Step 6: **Synthesis of 3-(6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-7-methylquinolin-3-yl)piperidine-2,6-dione (I-1321)**

To a stirred solution of 3-(6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-7-methylquinolin-3-yl)piperidine-2,6-dione (**102e,** direct from the previous step), triethylamine (186 mg, 256 μL, 1.84 mmol) and 4-(trifluoromethyl)benzaldehyde (**17e**, 75 mg, 0.43 mmol) in DMF (1.5 mL) was added sodium triacetoxyborohydride (156 mg, 735 μmol). The resulting mixture was stirred at 40 °C for 1 h. The reaction mixture was purified via **General Procedure 1, Step D**, *Purification Method* (b) to give 3-(6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-7-methylquinolin-3-yl)piperidine-2,6-dione, formic acid (**I-1321**, 40 mg, 0.074 mmol, 24% yield over 3 steps). LCMS: m/z HESI, positive $[M+H]^+$ = 540.3; ^{1}H NMR (500 MHz, DMSO-d6) δ ppm 10.95 (s, 1H), 8.69 (d, J = 2.2 Hz, 1H), 8.14 (br s, 1H), 7.93-7.87 (m, 1H), 7.76-7.69 (m, 3H),7.66-7.58 (m, 2H), 5.03-4.72 (m, 1H), 4.13-4.06 (m, 1H), 3.79-3.59 (m, 2H), 3.04-2.96 (m, 1H), 2.81 (s, 3H), 2.80-2.56 (m, 5H), 2.43-2.33 (m, 1H), 2.26-2.09 (m, 2H), 1.69-1.59 (m, 1H), 0.96 (s, 3H), 0.74 (s, 3H).

Example 237: Synthesis of 1-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)azepan-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-878)



Step 1: **Synthesis of tert-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)quinolin-6-yl)-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate**

To a stirred solution of 1-(6-bromoquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**INT-1**, 500 mg, 1.56 mmol) in 1,4-dioxane (10 mL) and water (1 mL) were added tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate (757 mg, 2.34 mmol) and DIPEA (404 mg, 3.12 mmol). The reaction mixture was sparged with N_2 for 10 minutes. Bis(tri-tert-butylphosphine)palladium(0) (80 mg, 0.156 mmol) was then added. The resulting reaction mixture was heated at 85 °C for 1 h. The cooled reaction mixture was filtered through a celite pad, then the pad was rinsed with EtOAc and the combined filtrate was concentrated. The residue was purified by silica gel flash chromatography, eluting with 5% IPA in DCM to afford tert-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)quinolin-6-yl)-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate (0.53 g, 1.20 mmol, 77% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 437.3; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.58 (s, 1H), 8.88 (d, J = 4.0 Hz, 1H), 8.21 (d, J = 4.0 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 4.0 Hz, 1H), 7.79-7.76 (m, 1H), 6.52 (s, 1H), 6.24 (d, J = 8.0 Hz, 1H), 4.06-4.00 (m, 2H), 3.98-3.94 (m, 2H), 3.63-3.60 (m, 2H), 2.81-2.78 (m, 4H), 2.49-2.46 (m, 1H), 1.47 (s, 9H).

Step 2: **Synthesis of 1-(6-(2,3,6,7-tetrahydro-1H-azepin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione**

To a stirred solution of tert-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)quinolin-6-yl)-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate (1.1 g, 2.52 mmol) in DCM (10 mL) was added HCl (4.0 M in 14-dioxane) (4 mL, 16.0 mmol) at 0 °C. The reaction mixture was then stirred at 0 °C for 3 h. The reaction mixture was concentrated under reduced pressure. The crude residue was triturated with MTBE (100 mL), filtered and dried under reduced pressure to obtain 1-(6-(2,3,6,7-tetrahydro-1H-azepin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl (0.9 g, 1.933 mmol, 77% yield). MM-ES+APCI, Positive $[M+H]^+$ 337.3; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.68 (s, 1H), 9.45 (bs, 1H), 9.06 (s, 1H), 8.48 (s, 1H), 8.14-8.05 (m, 2H), 8.93 (d, J = 8.0 Hz, 1H), 6.40 (t, J = 8.0 Hz, 1H), 4.02-3.98 (m, 2H), 3.32-3.28 (m, 2H), 3.22-3.18 (m, 2H), 3.11-3.07 (m, 2H), 3.06-3.04 (m, 2H), 3.03-3.00 (m, 2H).

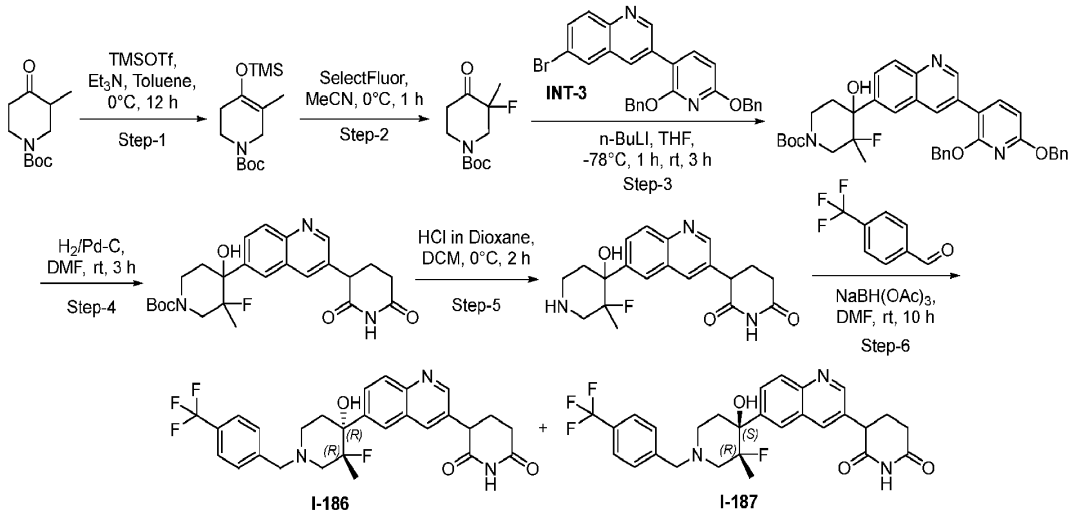
Step 3: **Synthesis of 1-(6-(1-(4-(trifluoromethyl)benzyl)-2,5,6,7-tetrahydro-1H-azepin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione**

To a stirred solution of 1-(6-(2,5,6,7-tetrahydro-1H-azepin-4-yl)quinolin-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione, HCl (500 mg, 1.34 mmol) in DMF (10 mL) was added 4-(trifluoromethyl)benzaldehyde (350 mg, 2.012 mmol) and the mixture was stirred at room temperature for 1h. Sodium triacetoxyborohydride (568 mg, 2.68 mmol) was added and the mixture stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography, eluting with 5% IPA in DCM to afford 1-(6-(1-(4-(trifluoromethyl)benzyl)-2,5,6,7-tetrahydro-1H-azepin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (500 mg, 0.90 mmol, 67% yield). m/z MM-ES+APCI, Positive $[M+H]^+$ 495.3; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.58 (s, 1H), 8.87 (d, J = 4.0 Hz, 1H), 8.19 (s, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.88-7.70 (m, 3H), 7.61 (d, J = 8.0 Hz, 2H), 6.36 (t, J = 8.0 Hz, 1H), 3.97-3.94 (m, 2H), 3.80-3.75 (m, 2H), 2.89-2.73 (m, 4H), 2.67-2.58 (m, 2H), 2.49-2.46 (m, 2H), 1.99-1.03 (m, 2H).

Step 4: **Synthesis of 1-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)azepan-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-878)**

To a stirred solution of 1-(6-(1-(4-(trifluoromethyl)benzyl)-2,5,6,7-tetrahydro-1H-azepin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (200 mg, 0.404 mmol) in DCM (5 mL) and 2-propanol (5 mL) were added phenylsilane (87 mg, 0.81 mmol) and $Mn(dpm)_3$ (74.0 mg, 0.121 mmol). The mixture was stirred under an O_2 bladder at 0 °C for 16 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by preparative-HPLC [(Column: X select C18 (150 x 19 mm) 5 µm, eluting with Mobile phase A: 0.05% HCl in H2O, Mobile phase B: Acetonitrile, flow rate: 15 mL/min)] to obtain 1-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)azepan-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (39 mg, 0.070 mmol, 16% yield). m/z MM-ES+APCI, Positive $[M+H]^+$ 513.4; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.20-11.05 (m, 1H), 10.63 (s, 1H), 8.99 (d, J = 2.4 Hz, 1H), 8.37 (d, J = 6.4 Hz, 1H), 8.14-7.86 (m, 7H), 5.01 (s, 2H), 4.53 (s, 2H), 3.80-3.27 (m, 5H), 2.84-2.79 (m, 3H), 2.34-2.25 (m, 2H), 2.03-1.97 (m, 1H), 1.91-1.83 (m, 2H).

Example 238: Synthesis of 3-(6-((3R,4R)-3-fluoro-4-hydroxy-3-methyl-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-186) and 3-(6-((3R,4S)-3-fluoro-4-hydroxy-3-methyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-187)



Step1: **Synthesis of *tert*-butyl 5-methyl-4-((trimethylsilyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate**

To a stirred solution of *tert*-butyl 3-methyl-4-oxopiperidine-1-carboxylate (3 g, 14.07 mmol) in toluene (20 mL) was added TEA (5.69 g, 56.3 mmol) at 0 °C followed by TMS-OTf (3.75 g, 16.9 mmol) at 0 °C drop wise and the reaction mixture was allowed to stir at 0 °C for 4 h. The reaction mixture was treated with saturated aqueous sodium bicarbonate solution and then extracted with EtOAc (2 x 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude tert-butyl 5-methyl-4-((trimethylsilyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (3.6 g, 5.0 mmol, 36% yield). LCMS: m/z MM-ES+APCI, No ionization; ^{1}H-NMR (400 MHz, DMSO-d6): δ 3.67 (s, 2H), 3.43 (t, J = 6.00 Hz, 2H), 2.05 (s, 2H), 1.50 (s, 3H), 1.42 (s, 9H), 0.18 (s, 9H).

Step 2: **Synthesis of tert-butyl 3-fluoro-3-methyl-4-oxopiperidine-1-carboxylate**

To a stirred solution of tert-butyl 5-methyl-4-((trimethylsilyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (3.8 g, 13.31 mmol) in ACN (12 mL) was added Selectfluor (5.19 g, 14.6 mmol) at 0 °C and the reaction mixture was allowed to stir at 0 °C for 1h. The reaction mixture was diluted with water (100 mL) and extracted with EtOAc (2X 100 mL) and the combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure The crude residue was purified by silica gel flash chromatography eluting with 0-100% EtOAc in hexane to afford tert-butyl 3-fluoro-3-methyl-4-oxopiperidine-1-carboxylate (1.3 g, 4.27 mmol, 32% yield).LCMS: No ionization; ^{1}H-NMR (400 MHz, DMSO-d6): δ 3.67-3.32 (m, 4H), 2.57-2.54 (m, 2H), 1.44 (s, 9H), 1.42-1.35 (m, 3H).

Step 3: **Synthesis of tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-fluoro-4-hydroxy-3-methylpiperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-fluoro-4-hydroxy-3-methylpiperidine-1-carboxylate (240 mg, 0.358 mmol, 71% yield) was synthesized according to **General Procedure 1, Step A** starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-quinoline (**INT-1**, 250 mg, 0.503 mmol) and *tert*-butyl 3-fluoro-3-methyl-4-oxopiperidine-1-carboxylate (174 mg, 0.754 mmol). The crude product was purified by silica gel flash chromatography, eluting with 0-50% EtOAc in hexane. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 650.5; ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.17 (s, 1H), 8.14 (s, 1H), 8.14-8.10 (m, 2H), 7.94-7.92 (m, 1H), 7.86-7.76 (m, 1H), 7.75-7.73 (m, 1H), 7.48-7.43 (m, 2H), 7.43-7.39 (m, 4H), 7.39-7.36 (m, 4H), 6.60 (d, J = 1.60 Hz, 2H), 5.46 (m, 4H), 4.15 (q, J = 7.20 Hz, 3H), 3.32 (s, 1H), 2.00 (m, 1H), 1.45 (s, 9H), 1.08-0.97 (m, 3H).

Step 4: **Synthesis of tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3-fluoro-4-hydroxy-3-methylpiperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-fluoro-4-hydroxy-3-methylpiperidine-1-carboxylate (240 mg, 0.369 mmol) Was treated according to **General Procedure 1, Step B**, The crude compound was washed with n-hexane (2 x 20 mL) and the resulting solid was dried under reduced pressure to provide *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3-fluoro-4-hydroxy-3-methylpiperidine-1-carboxylate (170 mg, 0.33 mmol, 89% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 472.4; 1H-NMR (400 MHz, DMSO-d6): δ 10.97 (s, 1H), 8.79 (s, 1H), 8.26 (d, J = 2.00 Hz, 1H), 8.19-8.13 (m, 1H), 7.99-7.97 (m, 2H), 5.86 (s, 1H), 4.18-4.17 (m, 1H), 3.28-3.24 (m, 2H), 2.75-2.67 (m, 2H), 2.50-2.41 (m, 2H), 2.16-2.14 (m, 1H), 1.62-1.59 (m, 1H), 1.44-1.41 (m, 9H), 0.89 (t, J = 2.40 Hz, 3H).

Step 5: **Synthesis of 3-(6-(3-fluoro-4-hydroxy-3-methylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione**

A solution of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-3-fluoro-4-hydroxy-3-methylpiperidine-1-carboxylate (150 mg, 0.318 mmol) in DCM (5 mL) and HCl (4M in 1,4-dioxane, 120 mg, 0.32 mmol) was stirred at rt for 2 h. The reaction mixture was concentrated under reduced pressure. The crude residue was triturated with n-hexane, and the resulting solid was dried under reduced pressure to provide 3-(6-(3-fluoro-4-hydroxy-3-methylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (130 mg, 0.29 mmol, 92% yield). LCMS m/z MM-ES+APCI, Positive $[M+H]^+$ 372.2. 1H-NMR (400 MHz, DMSO-d6): δ 11.04 (s, 1H), 9.75-9.56 (m, 1H), 9.22-8.89 (m, 2H), 8.63 (s, 1H), 8.25-8.19 (m, 2H), 8.09-8.00 (m, 1H), 6.45 (s, 1H), 4.28-4.24 (m, 1H), 3.46-3.39 (s, 3H), 3.39-3.29 (m, 3H), 2.90-2.81 (m, 1H), 2.76-2.50 (m, 1H), 2.21-2.17 (m, 1H), 1.91-1.86 (m, 1H), 1.29-1.03 (m, 3H).

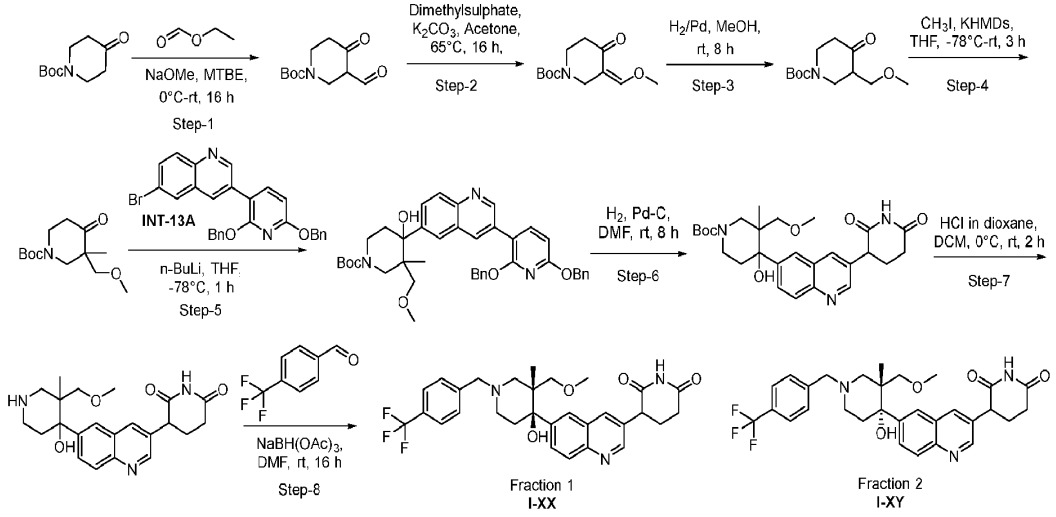
Step 6: **Synthesis of 3-(6-((3R,4R)-3-fluoro-4-hydroxy-3-methyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-186) and 3-(6-((3R,4S)-3-fluoro-4-hydroxy-3-methyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-187)**

3-(6-(3-fluoro-4-hydroxy-3-methylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (130 mg, 0.319 mmol) was treated with 4-(trifluoromethyl)benzaldehyde (83 mg, 0.48 mmol) and sodium triacetoxyborohydride according to **General Procedure 1, Step D** *Method (b)*. The crude residue was purified by preparative-HPLC [Method info: (SUNFIRE C18 column 150 x 21.2 mm; 5 um; eluting with 0.1% NH4OAc in H_2O: acetonitrile. Flow rate: 15 mL/min)] Two fractions were collected separately.

Fraction 1: 3-(6-((3R,4R)-3-fluoro-4-hydroxy-3-methyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-186**). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 530.3; 1H-NMR (400 MHz, DMSO-d6): δ 10.97 (s, 1H), 8.77 (s, 1H), 8.24 (s, 1H), 8.09 (s, 1H), 7.96 (s, 2H), 7.73 (d, J = 8.00 Hz, 2H), 7.62 (d, J = 8.00 Hz, 2H), 5.57 (s, 1H), 5.57 (d, J = 3.20 Hz, 1H), 3.38 (s, 2H), 2.78-2.76 (m, 4H), 2.68-2.67 (m, 4H), 2.51-2.50 (m, 1H), 1.84-1.76 (m, 1H), 0.97-9.93 (m, 3H).

Fraction 2: 3-(6-((3R,4S)-3-fluoro-4-hydroxy-3-methyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-187**) LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 530.3. 1H-NMR (400 MHz, DMSO-d6): δ 10.97 (s, 1H), 8.78 (s, 1H), 8.20 (s, 1H), 8.03-8.01 (m, 3H), 7.73 (d, J = 8.00 Hz, 2H), 7.60 (d, J = 8.00 Hz, 2H), 5.48 (s, 1H), 4.18-4.15 (m, 1H), 3.77-3.70 (m, 2H), 2.89-2.84 (m, 4H), 2.79-2.75 (m, 3H), 2.50-2.45 (m, 1H), 2.18-2.16 (m, 1H), 1.83-1.81 (m, 1H), 1.20-1.14 (m, 3H). Each fraction is a mixture of diastereomers; stereochemistry is arbitrarily assigned.

Example 239: Synthesis of 3-(6-((3R,4R)-4-hydroxy-3-(methoxymethyl)-3-methyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-805) and **3-(6-((3R,4S)-4-hydroxy-3-(methoxymethyl)-3-methyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-807)**



Step 1: **Synthesis of tert-butyl 3-formyl-4-oxopiperidine-1-carboxylate**

To a stirred solution of sodium methoxide (4.67 mL, 25.1 mmol) in methanol (5 mL) under a nitrogen atmosphere at 0 °C was added ethyl formate (3.04 mL, 37.6 mmol) dropwise, and the resulting

mixture was stirred at 0 ºC for 5 min. *Tert*-butyl 4-oxopiperidine-1-carboxylate (5 g, 25.1 mmol) was then added at 0 °C, and the mixture was allowed to warm and was stirred at rt for 16 h. The reaction mixture was concentrated under reduced pressure to yield crude *tert*-butyl 3-formyl-4-oxopiperidine-1-carboxylate (5 g, 22 mmol, 88% yield). LCMS: not ionized by LCMS; 1H-NMR (400 MHz, DMSO-d6): δ 9.14 (s, 1H), 3.91 (s, 2H), 3.64-3.59 (m, 1H), 3.38-3.35 (m, 2H), 2.37-2.33 (m, 1H), 1.95-1.91 (m, 2H), 1.40 (s, 9H).

Step 2: **Synthesis of tert-butyl-3-(methoxymethylene)-4-oxopiperidine-1-carboxylate**

A stirred mixture of tert-butyl 3-formyl-4-oxopiperidine-1-carboxylate (5 g, 22 mmol), acetone (50 mL), potassium carbonate (6.08 g, 44.0 mmol) and dimethyl sulfate (2.77 g, 22.0 mmol) was heated at 65 °C for 16 h. The cooled reaction mixture was concentrated under reduced pressure, and the residue was taken up in water (100 mL) and extracted with EtOAc (2 × 350 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by silica gel flash chromatography, eluting with 50-60% EtOAc in n-hexane to afford tert-butyl-3-(methoxymethylene)-4-oxopiperidine-1-carboxylate (2.5 g, 4.77 mmol, 22% yield). LCMS: not ionized by LCMS; ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.33 (s, 1H), 4.16 (s, 2H), 3.91-3.81 (m, 3H), 3.59-3.57 (m, 2H), 2.35 (t, J = 6.40 Hz, 2H), 1.43-1.37 (m, 9H).

Step 3: **Synthesis of tert-butyl 3-(methoxymethyl)-4-oxopiperidine-1-carboxylate**

A mixture of *tert*-butyl-3-(methoxymethylene)-4-oxopiperidine-1-carboxylate (2.5 g, 10.4 mmol), methanol (15 mL), and Pd/C (2.2 g, 2.07 mmol) was stirred under 1 atmosphere of hydrogen for 8 h. The reaction mixture was sparged with nitrogen and was then filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to provide *tert*-butyl 3-(methoxymethyl)-4-oxopiperidine-1-carboxylate (2.4 g, 96% yield) LCMS: m/z MM-ES+APCI, Positive $[M\text{-}Boc]^+$ 188.3; ^{1}H-NMR (400 MHz, DMSO-d6): δ 4.03-3.97 (m, 1H), 3.88-3.82 (m, 1H), 3.59-3.55 (m, 1H), 3.47-3.40 (m, 2H), 3.23 (s, 3H), 2.74-2.72 (m, 1H), 2.42-2.34 (m, 3H), 1.43 (s, 9H).

Step 4: **Synthesis of tert-butyl 3-(methoxymethyl)-3-methyl-4-oxopiperidine-1-carboxylate**

To a stirred solution of tert-butyl 3-(methoxymethyl)-4-oxopiperidine-1-carboxylate (500 mg, 2.1 mmol) in THF (20 mL) under a nitrogen atmosphere was added potassium bis(trimethylsilyl)amide (KHMDS) (2.466 mL, 2.466 mmol) at 0 °C, and the reaction mixture was stirred at the same temperature for 10 min. The reaction mixture was cooled to -78 °C, then iodomethane (438 mg, 3.08 mmol) was added dropwise. The mixture was allowed to warm to rt and stirred at rt for 3h. Saturated aqueous ammonium chloride solution was added, and the mixture was extracted with EtOAc (2 × 350 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude residue was purified by silica gel flash chromatography, eluting with 5-20% EtOAc in n-hexane to afford tert-butyl 3-(methoxymethyl)-3-methyl-4-oxopiperidine-1-carboxylate (120 mg, 0.47 mmol, 23% yield). LCMS Not

ionized; ^{1}H-NMR (400 MHz, DMSO-d6): δ 3.81-3.70 (m, 2H), 3.52-3.42 (m, 4H), 3.31 (m, 3H), 2.53-2.49 (m, 2H), 1.52-1.47 (s, 9H), 1.13-1.06 (m, 3H).

Step 5: **Synthesis of tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl) quinolin-6-yl)-4-hydroxy-3-(methoxymethyl)-3-methylpiperidine-1-carboxylate**

3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (200 mg, 0.40 mmol) was reacted with tert-butyl 3-(methoxymethyl)-3-methyl-4-oxopiperidine-1-carboxylate (**INT-13A**, 114 mg, 0.44 mmol) according to **General Procedure 1, Step A**, to provide tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3-(methoxymethyl)-3-methylpiperidine-1-carboxylate (60 mg, 0.051 mmol, 13% yield), following purification via silica gel flash chromatography (40-50% EtOAc in hexane as eluant). LCMS: m/z MM-ES+APCI, [M+H]$^+$676. 1H-NMR (400 MHz, DMSO-d6): δ 9.07 (s, 1H), 8.51 (s, 1H), 8.00-7.89 (m, 4H), 7.30-7.44 (m, 11H), 6.67 (d, J = 8.40 Hz, 1H), 5.46-5.44 (m, 4H), 4.35-3.89 (m, 2H), 3.77-3.56 (m, 2H), 3.13-2.88 (m, 3H), 2.71 (m, 2H), 1.43 (m, 9H), 0.79 (m, 3H).

Step 6: **Synthesis of tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl) quinolin-6-yl)-4-hydroxy-3-(methoxymethyl)-3-methylpiperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl) quinolin-6-yl)-4-hydroxy-3-(methoxymethyl)-3-methylpiperidine-1-carboxylate (65 mg, 0.098 mmol, 55% yield) was synthesized according to **General Procedure 1, Step B**, starting from *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl) quinolin-6-yl)-4-hydroxy-3-(methoxymethyl)-3-methylpiperidine-1-carboxylate (120 mg, 0.178 mmol). The crude product was purified by trituration with MTBE/pentane. LCMS: m/z MM-ES+APCI, Positive [M+H]$^+$ 484.4; ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.97 (s, 1H), 8.76 (s, 1H), 8.22-8.19 (m, 1H), 7.96-7.87 (m, 3H), 5.35-5.22 (m, 1H), 4.34 (d, J = 4.40 Hz, 1H), 4.17-4.13 (m, 2H), 3.79-3.76 (m, 1H), 3.23 (s, 3H), 2.87-2.68 (m, 5H), 2.55-2.33 (m, 1H), 2.33-2.16 (m, 1H), 1.47 (s, 9H), 1.05-1.03 (m, 4H), 0.79-0.74 (m, 3H).

Step 7: **Synthesis of 3-(6-(4-hydroxy-3-(methoxymethyl)-3-methylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione**

A solution of tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl) quinolin-6-yl)-4-hydroxy-3-(methoxymethyl)-3-methylpiperidine-1-carboxylate (398 mg, 0.800 mmol) in dichloromethane (5 mL) and 4.0 M HCl in dioxane (0.2 mL, 0.80 mmol) was stirred at rt for 2 h. The reaction mixture was concentrated under reduced pressure to afford 3-(6-(4-hydroxy-3-(methoxymethyl)-3-methylpiperidin-4-yl) quinolin-3-yl) piperidine-2,6-dione (50 mg, 0.078 mmol, 10% yield), which was used in the next step without further purification. LCMS: m/z MM-ES+APCI, Positive [M+H]$^+$ 398.3.

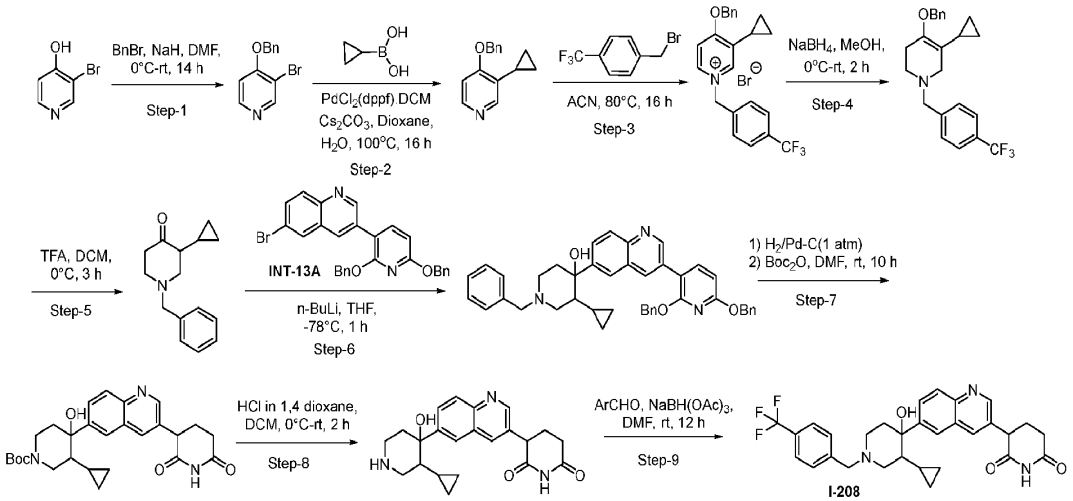
Step 8: **Synthesis of 3-(6-((3R,4R)-4-hydroxy-3-(methoxymethyl)-3-methyl-1-(4-(trifluoromethyl) benzyl) piperidin-4-yl) quinolin-3-yl) piperidine-2,6-dione (I-805, Fraction 1) and 3-(6-((3R,4S)-4-hydroxy-3-(methoxymethyl)-3-methyl-1-(4-(trifluoromethyl) benzyl) piperidin-4-yl) quinolin-3-yl) piperidine-2,6-dione (I-807, Fraction 2)**

3-(6-(4-Hydroxy-3-(methoxymethyl)-3-methylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione hydrochloride (50 mg, 0.115 mmol) was treated with 4-(trifluoromethyl)benzaldehyde (40.1 mg, 0.230 mmol) and sodium triacetoxyborohydride according to **General Procedure 1, Step D**. The crude product was purified by reverse phase chromatography on a C18 column, eluting with Mobile phase A: 0.1% NH_4OAc in H_2O, Mobile phase B: Acetonitrile, eluted with 50% ACN in Water (0.1%HCOOH)]. And. Two fractions were collected separately.

Fraction 1: 3-(6-((3R,4R)-4-hydroxy-3-(methoxymethyl)-3-methyl-1-(4-(trifluoro-methyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-805) (4.5 mg, 8.0 µmol, 7% yield); LCMS: m/z MM-ES+APCI, Postive $[M+H]^+$ 556.4; ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.97 (s, 1H), 8.77 (s, 1H), 8.22 (s, 1H), 7.99-7.88 (m, 3H), 7.69 (d, J = 8.00 Hz, 2H), 7.59 (d, J = 8.00 Hz, 2H), 4.98 (s, 1H), 4.15 (d, J = 4.80 Hz, 1H), 3.97 (d, J = 8.00 Hz, 1H), 3.71 (d, J = 14.40 Hz, 1H), 3.52 (d, J = 14.40 Hz, 1H), 3.12 (s, 3H), 2.90-2.89 (m, 1H), 2.87-2.81 (m, 2H), 2.75-2.51 (m, 4H), 2.27 (d, J = 10.40 Hz, 1H), 2.17-2.13 (m, 1H), 1.75 (s, 1H), 1.61 (d, J = 13.20 Hz, 1H), 0.71 (s, 3H)

Fraction 2: 3-(6-((3R,4S)-4-hydroxy-3-(methoxymethyl)-3-methyl-1-(4-(trifluoro-methyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-807) (2.0 mg, 3.6 µmol, 3% yield); LCMS: m/z MM-ES+APCI, Postive $[M+H]^+$ 556.4 ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.76 (s, 1H), 8.22 (s, 1H), 7.99-7.96 (m, 2H), 7.93-7.91 (m, 1H), 7.72 (d, J = 8.00 Hz, 2H), 7.60 (d, J = 8.00 Hz, 2H), 5.10 (s, 1H), 4.28-4.12 (m, 2H), 3.70 (d, J = 14.00 Hz, 1H), 3.54-3.52 (m, 2H), 3.07 (s, 3H), 2.86 (d, J = 9.20 Hz, 2H), 2.75-2.74 (m, 2H), 2.68-2.49 (m, 4H), 2.17-2.14 (m, 1H), 1.52 (d, J = 13.20 Hz, 1H), 1.00 (s, 3H).

Example 240: Synthesis of 3-(6-(3-cyclopropyl-4-hydroxy-1-(4-(trifluoromethyl) benzyl) piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-208)



Step 1: **Synthesis of 4-(benzyloxy)-3-bromopyridine**

To a stirred solution of 3-bromopyridin-4-ol (5.0 g, 28.7 mmol) in DMF (40 mL) at 0 °C was added NaH (1.72 g, 43.1 mmol), and the reaction mixture was stirred for 15 min at 0 °C. Benzyl bromide (5.90 g, 34.5 mmol) was added and the rection mixture was allowed to warm to rt and stirred. Water was added and the mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 filtered and concentrated under reduced pressure. The crude residue was triturated with hexane, and the resulting solid was collected via filtration and dried to afford 4-(benzyloxy)-3-bromopyridine (7.5 g, 19 mmol, 66% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 265; ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.44 (d, J = 2.40 Hz, 1H), 7.86 (d, J = 5.20 Hz, 1H), 7.41-7.35 (m, 5H), 6.25 (s, 1H), 5.13 (s, 2H).

Step 2: **Synthesis of 4-(benzyloxy)-3-cyclopropylpyridine**

A stirred mixture of cyclopropylboronic acid (244 mg, 2.84 mmol). 4-(benzyloxy)-3-bromopyridine (500 mg, 1.893 mmol). dioxane (5 mL), Cs_2CO_3 (1850 mg, 5.68 mmol), and water (0.75 mL) was sparged with nitrogen for 5 minutes. $PdCl_2$(dppf)-CH_2Cl_2 adduct (155 mg, 0.189 mmol) was added and the reaction mixture was sparged with nitrogen for another 5 minutes. The reaction mixture was stirred at 100°C for 16 h, then the cooled mixture was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography eluting with DCM/methanol to afford 4-(benzyloxy)-3-cyclopropylpyridine (0.38 g, 1.5 mmol, 79% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 226.3; ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.42-7.40 (m, 3H), 7.39 (d, J = 4.00 Hz, 1H), 7.27 (d, J = 2.40 Hz, 2H), 7.01 (s, 1H), 6.39 (d, J = 7.60 Hz, 1H), 4.93 (s, 2H), 2.05-2.02 (m, 1H), 0.92 (q, J = 1.60 Hz, 2H), 0.51 (q, J = 4.00 Hz, 2H).

Step 3: **Synthesis of 4-(benzyloxy)-3-cyclopropyl-1-(4-(trifluoromethyl)benzyl)pyridin-1-ium bromide**

A solution of 4-(benzyloxy)-3-cyclopropylpyridine (3.8 g, 16.87 mmol) and 4-(trifluoromethyl)benzyl bromide (4.03 g, 16.87 mmol) in acetonitrile (40 mL) was stirred at 100 °C for 16 h. The cooled reaction mixture was concentrated under reduced pressure, and the crude residue was triturated with acetone, collected via filtration, and dried to afford 4-(benzyloxy)-3-cyclopropyl-1-(4-(trifluoromethyl)benzyl)pyridin-1-ium bromide (5.2g, 9.8 mmol, 58% yield. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 384.5; ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.96-8.93 (m, 1H), 8.75 (s, 1H), 7.84 (d, J = 8.40 Hz, 2H), 7.77-7.67 (m, 3H), 7.51 (d, J = 2.00 Hz, 2H), 7.49-7.40 (m, 3H), 5.64 (m, 4H), 2.13-2.10 (m, 3H), 0.93 (q, J = 2.00 Hz, 2H).

Step 4: **Synthesis of 4-(benzyloxy)-5-cyclopropyl-1-(4-(trifluoromethyl) benzyl)-1,2,3,6-tetrahydropyridine**

To a stirred solution of 4-(benzyloxy)-3-cyclopropyl-1-(4-(trifluoromethyl)benzyl)-pyridin-1-ium bromide (5.0g, 10.8 mmol) in MeOH (40 mL) at 0 °C was added $NaBH_4$ (2.04 g, 53.8 mmol), and the reaction mixture was stirred for 2 h at rt. Ice cold water was added, and the mixture was extracted with EtOAc (4 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography eluting with 0-40% EtOAc in hexane to afford 4-(benzyloxy)-5-cyclopropyl-1-(4-(trifluoromethyl) benzyl)-1,2,3,6-tetrahydropyridine (2.6 g, 5.33 mmol, 49% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 388.8; ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.64 (d, J = 8.40 Hz, 2H), 7.54 (d, J = 8.00 Hz, 2H), 7.33-7.27 (m, 5H), 4.91 (s, 2H), 3.58 (s, 2H), 2.71 (s, 2H), 2.63 (t, J = 5.60 Hz, 2H), 2.33-2.30 (m, 2H), 1.91-1.87 (m, 1H), 0.59 (q, J = 2.40 Hz, 2H), 0.46 (q, J = 1.20 Hz, 2H).

Step 5: **Synthesis of 1-benzyl-3-cyclopropylpiperidin-4-one**

To a stirred solution of 4-(benzyloxy)-5-cyclopropyl-1-(4-(trifluoromethyl) benzyl)-1,2,3,6-tetrahydropyridine (500 mg, 1.07 mmol) in DCM (5 mL) at 0 °C was added TFA (0.33 mL, 4.3 mmol), then the reaction mixture was allowed to warm to rt and was stirred for 3 h. The mixture was concentrated under reduced pressure, then was taken up in EtOAc (20 mL) and washed with saturated NaHCO3 (2 x 10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography, eluting with 0-20% ethyl acetate in hexane to afford 1-benzyl-3-cyclopropylpiperidin-4-one (153 mg, 0.515 mmol, 48% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 230.6; ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.35-7.29 (m, 5H), 3.66 (d, J = 13.20 Hz, 1H), 3.57 (d, J = 13.20 Hz, 1H), 2.93-2.90 (m, 2H), 2.51-2.45 (m, 4H), 1.78 (t, J = 5.20 Hz, 1H), 0.90 (t, J = 4.40 Hz, 1H), 0.48 (t, J = 4.40 Hz, 1H), 0.34 (t, J = 3.60 Hz, 1H), 0.10-0.07 (m, 2H). (Under the acidic conditions of the reaction, the benzyl and 4-trifluoromethylbenzyl groups were scrambled, and the isolated product was 1-benzyl-3-cyclopropylpiperidin-4-one.)

Step 6: **Synthesis of 1-benzyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl) quinolin-6-yl)-3-cyclopropylpiperidin-4-ol**

1-benzyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-cyclopropylpiperidin-4-ol (250 mg, 0.324 mmol, 32% yield) was synthesized according to **General Procedure 1, Step A** starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 500 mg, 1.00 mmol) and 3-cyclopropyl-1-(4-(trifluoromethyl) benzyl) piperidin-4-one (359 mg, 1.21 mmol). The crude product was purified by silica gel flash column chromatography, eluting with 0-50% EtOAc in hexane to afford the title compound. LCMS m/z MM-ES+APCI, Positive $[M+H]^+$ 649.4; ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.06 (s, 1H), 8.47 (s, 1H), 8.06 (s, 1H), 7.98 (s, 2H), 7.48 (s, 1H), 7.40-7.33 (m, 15H), 6.66 (d, J = 8.00 Hz,

1H), 5.43 (s, 2H), 5.47 (s, 2H), 5.10 (s, 1H), 4.50 (s, 1H), 3.72 (m, 2H), 3.14 (m, 2H), 1.92 (s, 2H), 0.70-0.68 (m, 2H), 0.16 (s, 1H), -0.27 (s, 2H), -0.88 (s, 2H).

Step 7: **Synthesis of *tert*-butyl-3-cyclopropyl-4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxypiperidine-1-carboxylate**

To a stirred solution of 1-benzyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-cyclopropylpiperidin-4-ol (220 mg, 0.340 mmol) in DMF (4 mL) was added di-tert-butyl dicarbonate (148 mg, 0.68 mmol) and 10% Pd/C (150 mg, 0.340 mmol) at rt, and the reaction mixture was stirred under 1 atmosphere of hydrogen for 10 h. The reaction mixture was filtered through Celite, rinsing with DMF followed by EtOAc. The combined filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography, eluting with EtOAc/Hexane to provide *tert*-butyl 3-cyclopropyl-4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (75 mg, 0.16 mmol, 39% yield). m/z MM-ES+APCI, Positive $[M+H]^+$ 480.5; 1H-NMR (400 MHz, DMSO-d6): δ 10.97 (s, 1H), 8.75 (d, J = 2.00 Hz, 1H), 8.18 (d, J = 2.00 Hz, 1H), 8.12 (s, 1H), 7.94 (m, 2H), 7.83 (d, J = 8.80 Hz, 1H), 5.31 (s, 1H), 4.13 (d, J = 4.80 Hz, 1H), 3.89-3.86 (m, 2H), 3.34-3.30 (m, 1H), 2.90 (s, 2H), 2.77-2.68 (m, 3H), 2.17-2.15 (m, 1H), 1.44 (s, 9H), 1.29-1.27 (m, 1H), 0.88-0.84 (m, 1H), 0.23-0.19 (m, 2H), -0.22--0.30 (m, 2H).

Step 8: **Synthesis of 3-(6-(3-cyclopropyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione**

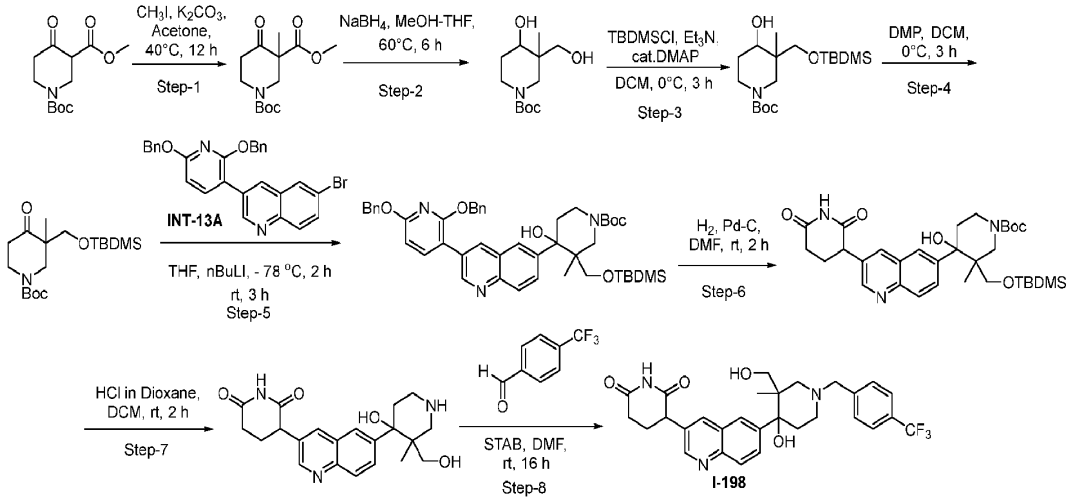
A solution of tert-butyl 3-cyclopropyl-4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (75 mg, 0.16 mmol) in DCM (5 mL) and 4M HCl in dioxane (0.3 mL, 1.20 mmol) was stirred at 0 °C for 2 h. The reaction mixture was concentrated under reduced pressure, and the crude residue was washed with pentane to afford 3-(6-(3-cyclopropyl-4-hydroxypiperidin-4-yl) quinolin-3-yl) piperidine-2,6-dione (65 mg, 0.14 mmol, 90% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 380.3; ^{1}H-NMR (400 MHz, DMSO-d6): δ 11.04 (s, 1H), 8.98 (s, 1H), 8.93 (s, 1H), 8.56 (s, 1H), 8.15-8.09 (m, 2H), 7.88 (d, J = 8.80 Hz, 1H), 4.27 (d, J = 4.40 Hz, 1H), 3.29-3.22 (m, 4H), 2.77-2.70 (m, 1H), 2.68-2.67 (m, 1H), 2.33 (t, J = 2.00 Hz, 1H), 1.83-1.78 (m, 1H), 1.63-1.52 (m, 3H), 0.73-0.64 (m, 1H), 0.28-0.22 (m, 1H), -0.12--0.25 (m, 2H), -8.82--0.86 (m, 1H).

Step 9: **Synthesis of 3-(6-(3-cyclopropyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-208)**

3-(6-(3-cyclopropyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (60 mg, 0.14 mmol) was treated with 4-(trifluoromethyl)benzaldehyde (38 mg, 0.22 mmol) and sodium triacetoxyborohydride according to General Procedure 1, Step 4. The crude product was triturated with MTBE/pentane, then the resulting crude solid was further purified by reverse phase chromatography using a C-18 column, eluting with 0.1% HCl in H_2O: Acetonitrile as eluant to afford 3-(6-(3-cyclopropyl-4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-208**, 15 mg,

0.026 mmol, 18% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 538.4; ^{1}H-NMR (400 MHz, DMSO-d6): δ 11.07 (s, 1H), 11.02 (s, 1H), 8.94 (s, 1H), 8.49 (s, 1H), 8.10 (d, J = 8.40 Hz, 2H), 7.97-7.89 (m, 4H), 7.85 (d, J = 8.80 Hz, 1H), 5.80 (s, 1H), 4.62 (d, J = 9.20 Hz, 1H), 4.52 (d, J = 5.60 Hz, 1H), 4.23 (d, J = 4.40 Hz, 1H), 3.39-3.27 (m, 4H), 2.79-2.76 (m, 1H), 2.68-2.66 (m, 2H), 2.46 (s, 1H), 2.18 (d, J = 3.20 Hz, 1H), 1.85-1.82 (m, 2H), 0.69 (d, J = 3.60 Hz, 1H), 0.25 (d, J = 5.60 Hz, 1H), -0.12--0.28 (m, 2H), -8.82--0.86 (m, 1H).

Example 241: Synthesis of 3-(6-(4-hydroxy-3-(hydroxymethyl)-3-methyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-198)



Step 1: **Synthesis of 1-(tert-butyl) 3-methyl 3-methyl-4-oxopiperidine-1,3-dicarboxylate**

To a stirred mixture of 1-(tert-butyl) 3-methyl 4-oxopiperidine-1,3-dicarboxylate (5 g, 19.43 mmol) and potassium carbonate (4.12 g, 68.0 mmol) in acetone (50 mL) at rt was added iodomethane (4.97 g, 35.0 mmol). The reaction mixture was stirred at 40 °C for 12 h. The cooled reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The crude residue was dissolved in EtOAc, and the organic layer was washed with water followed by brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by trituration with n-pentane to yield 1-(tert-butyl) 3-methyl 3-methyl-4-oxopiperidine-1,3-dicarboxylate. (7.5 g, 20.4 mmol, 53% yield). LCMS: MM-ES+APCI, Positive $[M-56+H]^+$ 216.06; ^{1}H-NMR (400 MHz, DMSO-d6): δ 4.28 (dd, J = 2.00, 13.60 Hz, 1H), 3.95 (d, J = 8.00 Hz, 1H), 3.65 (s, 3H), 3.35-3.22 (m, 2H), 2.61-2.58 (m, 1H), 2.48-2.41 (m, 1H), 1.42 (s, 9H), 1.19 (s, 3H).

Step 2: **Synthesis of tert-butyl 4-hydroxy-3-(hydroxymethyl)-3-methylpiperidine-1-carboxylate**

To a stirred solution of 1-(tert-butyl) 3-methyl 3-methyl-4-oxopiperidine-1,3-dicarboxylate (4 g, 14.7 mmol) in THF (60 mL) and methanol (15 mL) at 0 °C was added sodium borohydride (1.39 g, 36.9 mmol). The reaction mixture was stirred at 70 °C for 16 h. The reaction mixture was concentrated under

reduced pressure, then crude residue was diluted with water and extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography eluting with 20% EtOAc in hexane to afford tert-butyl 4-hydroxy-3-(hydroxymethyl)-3-methylpiperidine-1-carboxylate (2.5 g, 9.3 mmol, 63% yield). LCMS: m/z MM-ES+APCI, Negative $[M-H-BOC]^-$ 144.1; ^{1}H-NMR (400 MHz, DMSO-d6): δ 4.49-4.44 (m, 2H), 3.83-3.77 (m, 1H), 3.56-3.46 (m, 2H), 3.31-3.22 (m, 2H), 2.76-2.63 (m, 2H), 1.56-1.51 (m, 1H), 1.42 (m, 1H), 1.38 (s, 9H), 0.70 (s, 3H).

Step 3: **Synthesis of tert-butyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-4-hydroxy-3-methylpiperidine-1-carboxylate**

To a stirred solution of tert-butyl 4-hydroxy-3-(hydroxymethyl)-3-methylpiperidine-1-carboxylate (0.5 g, 2.038 mmol), triethylamine (0.390 mL, 2.85 mmol) and DMAP (0.025 g, 0.204 mmol) in THF at 0 °C was added TBDMS-Cl (0.40 g, 2.65 mmol). The reaction mixture was allowed to warm to rt and was stirred for 16 h. The mixture was concentrated under reduced pressure. The crude residue was diluted with water and extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography, eluting with EtOAc in hexane to afford tert-butyl 3-(((tert-butyldimethylsilyl)-oxy)methyl)-4-hydroxy-3-methylpiperidine-1-carboxylate (0.28 g, 0.58 mmol, 28% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 360.2; ^{1}H-NMR (400 MHz, DMSO-d6): δ 4.30 (d, J = 4.80 Hz, 1H), 3.82 (d, J = 13.60 Hz, 1H), 3.64-3.61 (m, 1H), 3.50-3.42 (m, 3H), 2.82-2.78 (m, 1H), 2.69 (d, J = 10.00 Hz, 1H), 1.60-1.44 (m, 2H), 1.42 (s, 9H), 0.91 (s, 9H), 0.78 (s, 3H), 0.05 (s, 6H).

Step 4: **Synthesis of tert-butyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-3-methyl-4-oxopiperidine-1-carboxylate**

To a stirred solution of tert-butyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-4-hydroxy-3-methylpiperidine-1-carboxylate (1.7 g, 4.73 mmol) in dichloromethane (30 mL) at 0 °C was added Dess-Martin periodinane (3.01 g, 7.09 mmol). The reaction mixture was stirred at rt for 3 h. The mixture was poured into ice water and extracted with dichloromethane (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel flash chromatography, eluting with 0-5% EtOAc in hexane to afford tert-butyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-3-methyl-4-oxopiperidine-1-carboxylate (1 g, 2.8 mmol, 59% yield). LCMS: MM-ES+APCI, Positive $[M-BOC+H]^+$ 258.1; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.86-3.53 (m, 6H), 2.49 (br s, 2H), 1.51 (s, 9H), 1.09 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

Step 5: **Synthesis of tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-(((tert-butyldimethylsilyl)oxy)methyl)-4-hydroxy-3-methylpiperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-(((tert-butyldimethylsilyl)oxy)methyl)-4-hydroxy-3-methylpiperidine-1-carboxylate (350 mg, 0.45 mmol, 45% yield) was synthesized according to **General Procedure 1, Step A** starting from 3-(2,6-bis(benzyl-oxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 500 mg, 1.00 mmol) and *tert*-butyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-methyl-4-oxopiperidine-1-carboxylate (431 mg, 1.21 mmol). The crude product was purified by silica gel flash chromatography eluting with 0-50% EtOAc in hexane to afford the title compound. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 777.5; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.07 (d, J = 4.0 Hz, 1H), 8.49 (s, 1H), 8.03-7.87 (m, 4H), 7.48-7.29 (m, 11H), 6.66 (d, J = 8.0 Hz, 1H), 5.47-5.20 (m, 5H), 4.10-3.90 (m, 3H), 3.15-2.60 (m, 4H), 1.42 (s, 9H), 0.82 (s, 9H), 0.74 (s, 3H), -0.02 (s, 3H), -0.20 (s, 3H).

Step 6: **Synthesis of tert-butyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3-methylpiperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-(((tert-butyldimethylsilyl)oxy)methyl)-4-hydroxy-3-methylpiperidine-1-carboxylate (500 mg, 0.644 mmol) was treated according to **General Procedure 1, Step B.** The crude product was purified by silica gel flash chromatography, eluting with 10% IPA in DCM to afford *tert*-butyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3-methylpiperidine-1-carboxylate (180 mg, 0.28 mmol, 44% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 598.5; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.97 (s, 1H), 8.77 (s, 1H), 8.20 (d, J = 8.0 Hz, 2H), 8.00-7.86 (m, 1H), 5.76 (bs, 1H), 4.16-4.12 (m, 1H), 3.89-3.85 (m, 4H), 2.77-2.71 (m, 3H), 2.68-2.59 (m, 2H), 2.57-2.53 (m, 2H), 2.48-2.43 (m, 1H), 2.20-2.16 (m, 1H), 1.47 (s, 9H), 1.41 (s, 3H), 0.80 (s, 9H), -0.02 (s, 3H), -0.18 (s, 3H).

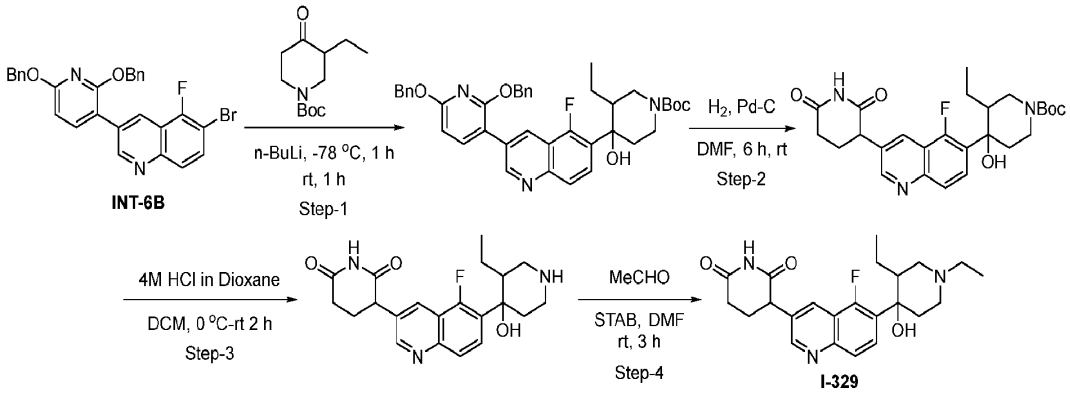
Step 7: **Synthesis of 3-(6-(4-hydroxy-3-(hydroxymethyl)-3-methylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione**

A solution of *tert*-butyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3-methylpiperidine-1-carboxylate (160 mg, 0.27 mmol) in DCM (5 mL) and HCl (4 M in dioxane, 0.34 mL, 1.34 mmol) was stirred at rt for 2 h. The reaction mixture was concentrated under reduced pressure, and the resulting crude residue was washed with MTBE/pentane and dried to afford 3-(6-(4-hydroxy-3-(hydroxymethyl)-3-methylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (120 mg, 0.27 mmol, 100% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 384.0; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 8.87 (bs, 1H), 8.84 (s, 1H), 8.39 (s, 1H), 8.07-8.02 (m, 2H), 7.89 (d, J = 8.0 Hz, 1H), 5.99 (bs, 1H), 4.21-4.17 (m, 2H), 3.68-3.65 (s, 1H), 3.57-3.19 (m, 1H), 3.09-3.00 (m, 1H), 2.98-2.74 (m, 1H), 2.67-2.60 (m, 2H), 2.33-2.18 (m, 2H), 1.91-1.60 (m, 2H), 1.35-1.24 (m, 2H), 0.93 (s, 3H).

Step 8: **Synthesis of 3-(6-(4-hydroxy-3-(hydroxymethyl)-3-methyl-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-198)**

3-(6-(4-hydroxy-3-(hydroxymethyl)-3-methylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (70 mg, 0.167 mmol) was treated with 4-(trifluoromethyl)benzaldehyde (44 mg, 0.25 mmol) and sodium triacetoxyborohydride according to **General Procedure 1, Step D**. The crude product was purified by reverse phase chromatography using a C-18 column, eluting with 0.1% HCl in H_2O and acetonitrile to afford 3-(6-(4-hydroxy-3-(hydroxymethyl)-3-methyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-198**, 20 mg, 0.034 mmol, 21% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 542.7; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 8.90 (bs, 1H), 8.47 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 8.01-7.89 (m, 6H), 5.99 (bs, 1H), 4.60-4.56 (m, 2H), 4.22-4.17 (m, 1H), 3.68-3.43 (m, 3H), 3.08-2.95 (m, 3H), 2.79-2.68 (m, 2H), 2.67-2.55 (m, 1H), 2.43-2.33 (m, 2H), 2.18-2.16 (m, 2H), 0.97 (s, 3H).

Example 242: Synthesis of 3-(6-(1,3-diethyl-4-hydroxypiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (I-329)



Step 1: **Synthesis of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-3-ethyl-4-hydroxypiperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-3-ethyl-4-hydroxy-piperidine-1-carboxylate (250 mg, 0.372 mmol, 55% yield) was synthesized according to **General Procedure 1, Step A** starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-5-fluoroquinoline (**INT-6B**, 0.35 g, 0.679 mmol) and tert-butyl 3-ethyl-4-oxopiperidine-1-carboxylate (**28a**, 0.232 g, 1.019 mmol). The crude product was purified by silica gel flash chromatography, eluting with 15-20% EtOAc in hexane to afford the title compound. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 664.5; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.13 (s, 1H), 8.61 (d, J = 4.0 Hz, 1H), 8.06 (d, J = 8.0 Hz, 2H), 8.02 (d, J = 8.0 Hz, 1H), 7.50-7.30 (m, 10H), 6.67 (d, J = 8.0 Hz, 1H), 5.49-5.45 (m, 5H), 4.00-3.96 (m, 2H), 2.49-2.33 (m, 2H), 1.99-1.94 (m, 1H), 1.46 (s, 9H), 1.26-1.18 (m, 2H), 1.07-0.83 (m, 2H), 0.67 (t, J = 8.0 Hz, 3H).

Step 2: **Synthesis of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-3-ethyl-4-hydroxypiperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoroquinolin-6-yl)-3-ethyl-4-hydroxy-piperidine-1-carboxylate (250 mg, 0.377 mmol) was treated according to **General Procedure 1, Step B**. The crude product was purified by reverse phase chromatography on a C18 column, eluting with 5 to 100% acetonitrile to afford tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-3-ethyl-4-hydroxypiperidine-1-carboxylate (140 mg, 0.28 mmol, 75% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 486.2; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.98 (s, 1H), 8.85 (d, J = 4.0 Hz, 1H), 8.33 (d, J = 4.0 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 5.49 (s, 1H), 4.24-4.20 (m, 1H), 3.90-3.87 (m, 2H), 2.77-2.72 (m, 2H), 2.63-2.60 (m, 2H), 2.59-2.55 (m, 1H), 2.27-2.22 (m, 1H), 2.14-2.11 (m, 1H), 2.08-2.05 (m, 2H), 1.69-1.65 (m, 1H), 1.45 (m, 9H), 0.95-0.93 (m, 1H), 0.66 (t, J = 8.0 Hz, 3H).

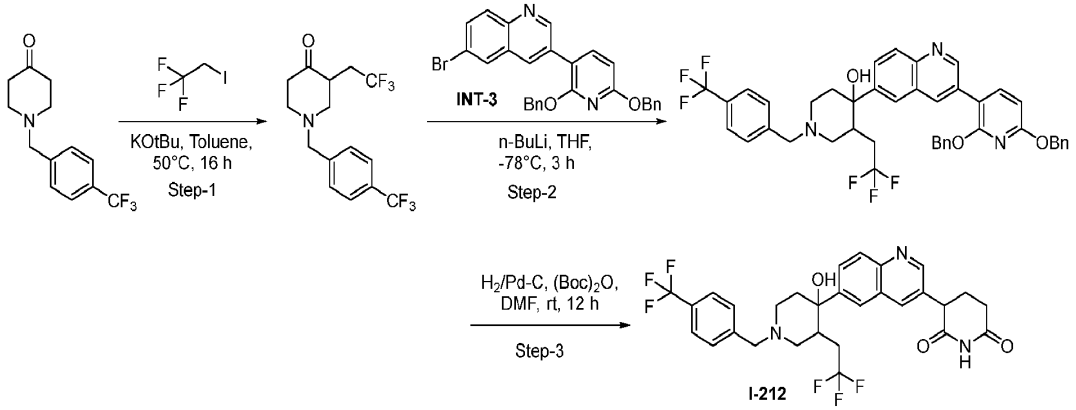
Step 3: **Synthesis of 3-(6-(3-ethyl-4-hydroxypiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione**

A solution of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoroquinolin-6-yl)-3-ethyl-4-hydroxy-piperidine-1-carboxylate (120 mg, 0.25 mmol) in DCM (5 mL) and HCl (4M in 1,4-dioxane, 0.7 ml, 2.80 mmol) was stirred at 0 °C for 2 h. The reaction mixture was concentrated under reduced pressure. The crude residue was washed with pentane to obtain 3-(6-(3-ethyl-4-hydroxypiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (100 mg, 0.23 mmol, 93% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 386.2; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 8.92 (s, 1H), 8.43-8.40 (m, 2H), 8.05 (d, J = 8.0 Hz, 1H), 7.97-7.94 (m, 2H), 6.00 (bs, 1H), 4.29-4.24 (m, 1H), 3.57-3.25 (m, 2H), 2.78-2.61 (m, 2H), 2.56-2.53 (m, 1H), 2.45-2.16 (m, 1H), 1.99-1.85 (m, 1H), 1.28-1.25 (m, 3H), 1.10-1.08 (m, 2H), 0.66 (t, J = 8.0 Hz, 3H).

Step 4: **Synthesis of 3-(6-(1,3-diethyl-4-hydroxypiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (I-329)**

3-(6-(3-ethyl-4-hydroxypiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (120 mg, 0.284 mmol) was treated with acetaldehyde (12.5 mg, 0.284 mmol) and sodium triacetoxyborohydride (151 mg, 0.711 mmol) according to **General Procedure 1, Step D**. The crude product was purified by prep-HPLC [Method info: (Column: X Select C18 (250 x19 mm), 5 µm, eluting with Mobile phase A: 0.05%HCl in H_2O, Mobile phase B: Acetonitrile, flow rate: 15 mL/min] to afford 3-(6-(1,3-diethyl-4-hydroxypiperidin-4-yl)-5-fluoroquinolin-3-yl)piperidine-2,6-dione (I-329) (30 mg, 0.066 mmol, 23% yield) solid. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 414.4; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.04 (s, 1H), 9.96 (bs, 1H), 8.89 (s, 1H), 8.38 (s, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 6.00 (bs, 1H), 4.27-4.23 (m, 1H), 3.49-3.20 (m, 4H), 3.05-3.02 (m, 1H), 2.78-2.56 (m, 4H), 2.33-2.08 (m, 2H), 1.95-1.91 (m, 1H), 1.31 (t, J = 8.0 Hz, 3H), 1.13-1.11 (m, 2H), 0.66 (t, J = 8.0 Hz, 3H).

Example 243: Synthesis of 3-(6-(4-hydroxy-3-(2,2,2-trifluoroethyl)-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-212)



Step 1: **Synthesis of 3-(2,2,2-trifluoroethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-one**

To a stirred solution of 1-(4-(trifluoromethyl)benzyl)piperidin-4-one (5 g, 19 mmol) in toluene (100 mL) under nitrogen atmosphere at 0°C was added potassium tert-butoxide (4.32 g, 23.3 mmol). After 40 min, at the same temperature, 1,1,1-trifluoro-2-iodoethane (4.90 g, 23.3 mmol) was added. The reaction mixture was stirred at 50°C for 16 h. The cooled reaction mixture was diluted with saturated aqueous NH_4Cl solution (100 mL) and then extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography, eluting with 0-10% EtOAc in hexane to afford 3-(2,2,2-trifluoroethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-one (1.3 g, 3.7 mmol, 19% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 340.2; ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.72 (d, J = 8.00 Hz, 2H), 7.61 (d, J = 8.00 Hz, 2H), 3.77 (AB, J = 13.60 Hz, 2H), 3.18-3.13 (m, 1H), 3.05-3.01 (m, 1H), 2.94-2.91 (m, 1H), 2.72-2.80 (m, 2H), 2.50-2.47 (m, 1H), 2.48-2.30 (m, 2H), 2.28-2.16 (m, 1H).

Step 2: **Synthesis of 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-(2,2,2-trifluoroethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-ol**

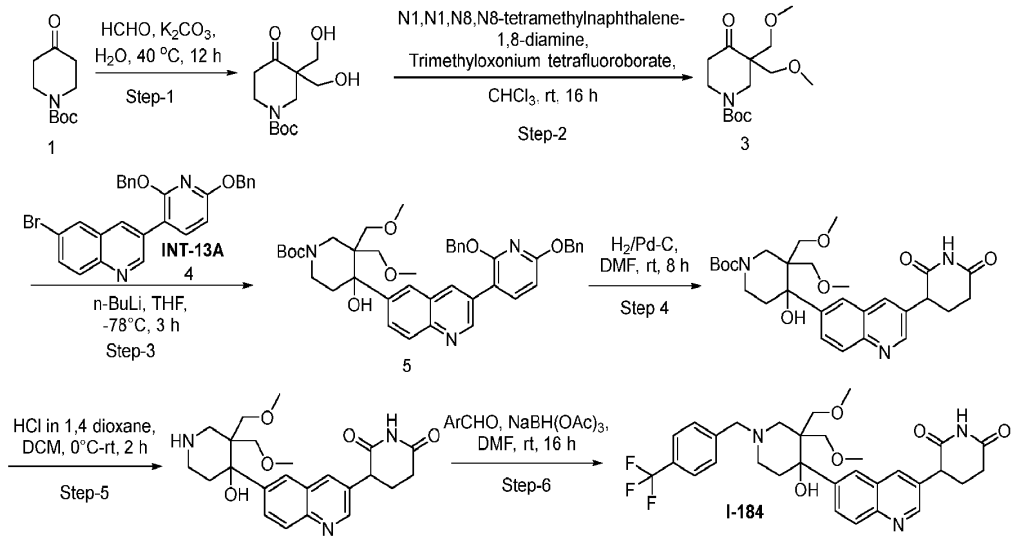
4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-(2,2,2-trifluoroethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-ol (210 mg, 0.211 mmol, 42% yield) was synthesized according to **General Procedure 2, Step A** starting from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (250 mg, 0.503 mmol) and 3-(2,2,2-trifluoroethyl)-1-(4-(trifluoromethyl)-benzyl)piperidin-4-one (205 mg, 0.603 mmol). The crude product was purified by silica gel flash chromatography, eluting with 0-60% EtOAc in hexane to afford the title compound. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 759.2; ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.08 (s, 1H), 8.49 (d, J = 1.60 Hz, 1H), 8.10 (s, 1H), 7.93-7.99 (m, 4H), 7.74-7.70 (m, 2H), 7.64-7.59 (m, 2H), 7.32-7.42 (m, 9H), 6.67 (d, J = 8.00 Hz, 1H), 5.47 (s, 2H), 5.44 (s,

2H), 3.71 (AB, J = 13.60 Hz, 2H), 2.89-2.75 (m, 2H), 2.68-2.59 (m, 2H), 2.51-2.50 (m, 1H), 2.34-2.28 (m, 1H), 2.25-2.07 (m, 1H), 1.77-1.68 (m, 2H).

Step 3: **Synthesis of 3-(6-(4-hydroxy-3-(2,2,2-trifluoroethyl)-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-212)**

4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-(2,2,2-trifluoroethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-ol (100 mg, 0.132 mmol) was treated according to General Procedure 2, Step B. The crude product was purified by Preparative-HPLC [Method info: Column: X Select (150 mm x 19 mm) 5um, eluting with Mobile phase A: 0.1%AA H_2O, Mobile phase B: ACN, Flow rate: 15 mL/min] to afford 3-(6-(4-hydroxy-3-(2,2,2-trifluoroethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-212**, 12.9 mg, 0.022 mmol, 17% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 580.1; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H), 8.78 (d, J = 2.00 Hz, 1H), 8.22 (s, 1H), 8.07 (s, 1H), 8.00 (d, J = 8.80 Hz, 1H), 7.88 (d, J = 1.60 Hz, 1H), 7.86 (d, J = 1.60 Hz, 1H), 7.73 (d, J = 8.40 Hz, 2H), 7.62 (d, J = 8.00 Hz, 2H), 5.40 (s, 1H), 4.15 (dd, J = 4.80, 12.40 Hz, 1H), 3.71 (q, J = 14.00 Hz, 2H), 2.88-2.79 (m, 1H), 2.78-2.74 (m, 1H), 2.68-2.60 (m, 2H), 2.46-2.39 (m, 3H), 2.34-2.16 (m, 2H), 2.15-2.13 (m, 1H), 1.91 (s, 1H), 1.76-1.67 (m, 2H).

Example 244: Synthesis of 3-(6-(4-hydroxy-3,3-bis(methoxymethyl)-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-184)



Step 1: **Synthesis of tert-butyl 3,3-bis(hydroxymethyl)-4-oxopiperidine-1-carboxylate**

A stirred mixture of *tert*-butyl 4-oxopiperidine-1-carboxylate (10.0 g, 50.2 mmol), water (30 mL), potassium carbonate (0.104 g, 0.753 mmol) and formaldehyde (7.10 mL, 95 mmol) heated at 40 °C for 16 h. Water was added to the cooled reaction mixture, and the mixture was extracted with EtOAc (2 × 500 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The

crude residue was purified by silica gel flash chromatography, eluting with 0-50% EtOAc in n-hexane to afford tert-butyl 3,3-bis(hydroxymethyl)-4-oxopiperidine-1-carboxylate (2.30 g, 7.46 mmol, 15% yield). LCMS: m/z MM-ES+APCI, Positive $[M\text{-}Boc]^+$ 160.1. 1H-NMR (400 MHz, DMSO-d6): δ 6.62 (t, J = 5.60 Hz, 2H), 3.61-3.52 (m, 8H), 2.37 (t, J = 6.40 Hz, 2H), 1.41 (s, 9H).

Step 2: **Synthesis of tert-butyl 3,3-bis(methoxymethyl)-4-oxopiperidine-1-carboxylate**

To a stirred solution of tert-butyl 3,3-bis(hydroxymethyl)-4-oxopiperidine-1-carboxylate (4.5 g, 17.35 mmol) and N1,N1,N8,N8-tetramethylnaphthalene-1,8-diamine (22.32 g, 104 mmol) in chloroform (80 mL) at rt was added trimethyl oxonium tetrafluoroborate (12.8 g, 87 mmol), and the resulting reaction mixture was stirred at rt for 16 h. The reaction mixture was filtered through a Celite pad and washed with dichloromethane (100 mL). The combined filtrate was washed with 1N aqueous hydrochloric acid (2 × 100 mL) followed by saturated aqueous sodium bicarbonate solution (70 mL). The organic layer was dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography, eluting with 0-10% EtOAc in n-hexane to afford *tert*-butyl 3,3-bis(methoxymethyl)-4-oxopiperidine-1-carboxylate (2.5 g, 6.63 mmol, 38% yield). LCMS: m/z MM-ES+APCI, Positive $[M\text{-}Boc]^+$ 188.0; ^{1}H-NMR (400 MHz, DMSO-d6): δ 3.63-3.58 (m, 4H), 3.43 (s, 4H), 3.22 (s, 6H), 2.41 (t, J = 6.40 Hz, 2H), 1.44 (s, 9H).

Step 3: **Synthesis of tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3,3-bis(methoxymethyl)piperidine-1-carboxylate**

n-Butyllithium (1.6 M in hexane) (0.75 mL, 1.2 mmol) was added dropwise at -78 °C to a stirred solution of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 500 mg, 1.005 mmol) and *tert*-butyl 3,3-bis(methoxymethyl)-4-oxopiperidine-1-carboxylate (433 mg, 1.508 mmol) in THF (5 mL) under a nitrogen atmosphere. The reaction mixture was allowed to warm to rt and was stirred for 3 h. Saturated aqueous ammonium chloride solution was added, and the mixture was extracted with EtOAc (2 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel flash chromatography, eluting with 0-25% EtOAc in n-hexane to afford tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3,3-bis(methoxymethyl)piperidine-1-carboxylate (180 mg, 0.253 mmol, 25% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 706.5; ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.06 (s, 1H), 8.47 (s, 1H), 7.97-7.85 (m, 4H), 7.30-7.43 (m, 10H), 6.67 (d, J = 8.00 Hz, 1H), 5.44 (d, J = 12.00 Hz, 5H), 4.06-4.01 (m, 2H), 3.33-3.22 (m, 5H), 3.07 (s, 6H), 1.82-1.73 (m, 1H), 1.49-1.38 (m, 11H).

Step 4: **Synthesis of tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3,3-bis(methoxymethyl)piperidine-1-carboxylate**

Tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-4-hydroxy-3,3-bis(methoxymethyl)piperidine-1-carboxylate (160 mg, 0.227 mmol) was treated according to **General**

Procedure 1, Step B. The crude product was purified by trituration with DCM/hexane, and the resulting solid was collected by filtration and dried to afford tert-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3,3-bis(methoxymethyl)piperidine-1-carboxylate (105 mg, 0.17 mmol, 75% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 528.4; ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.97 (s, 1H), 8.76 (s, 1H), 8.20 (s, 1H), 7.94-7.86 (m, 3H), 5.40 (s, 1H), 4.17-4.02 (m, 3H), 3.23-3.08 (m, 12H), 2.82-2.79 (m, 2H), 2.77-2.63 (m, 2H), 2.59-2.50 (m, 1H), 2.05-2.01 (m, 1H), 1.44 (s, 9H).

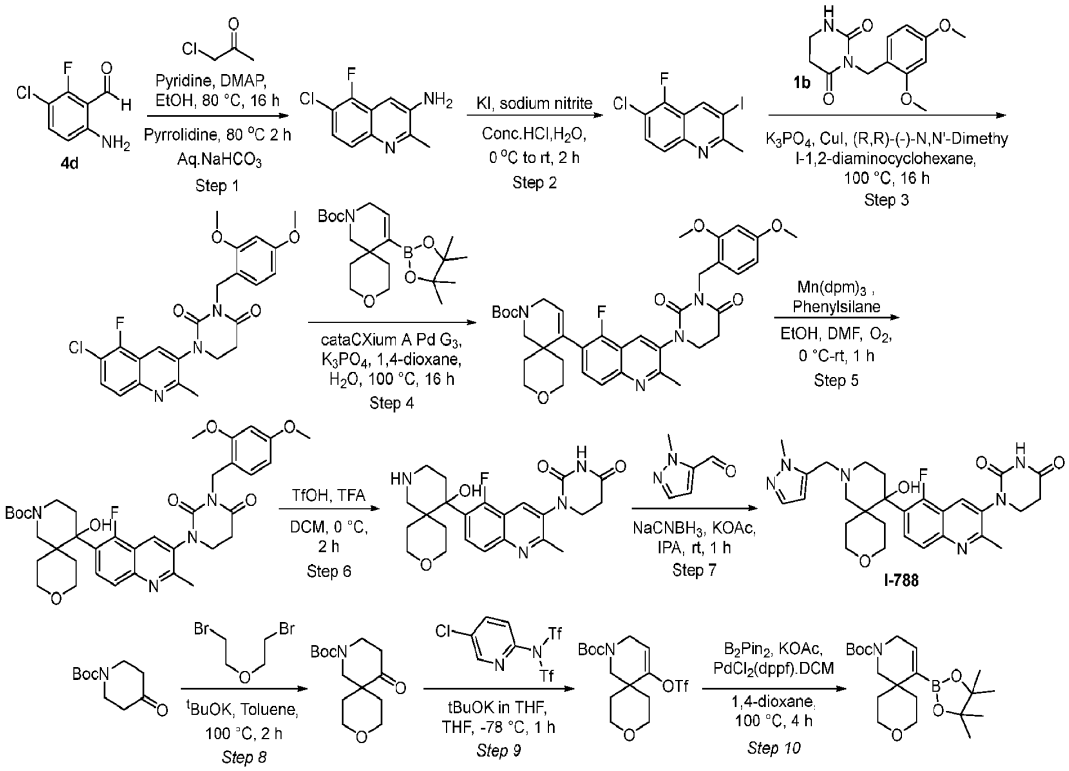
Step 5: **Synthesis of 3-(6-(4-hydroxy-3,3-bis(methoxymethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione**

A solution of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxy-3,3-bis(methoxymethyl)piperidine-1-carboxylate (100 mg, 0.190 mmol) in dichloromethane (5 mL) and 4M HCl in dioxane (0.47 mL, 1.9 mmol) was stirred at rt for 2 h. The mixture was concentrated under reduced pressure to afford 3-(6-(4-hydroxy-3,3-bis(methoxymethyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (82 mg, 0.16 mmol, 84% yield), which was used in the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 428.4; ^{1}H-NMR (400 MHz, DMSO-d6): δ 11.00 (s, 1H), 9.06-9.02 (m, 1H), 8.87 (s, 1H), 8.39 (s, 1H), 8.06 (d, J = 8.80 Hz, 1H), 8.00 (s, 1H), 7.87 (d, J = 7.60 Hz, 1H), 7.55-7.42 (m, 1H), 5.84 (s, 1H), 4.21-4.16 (m, 1H), 3.57-3.54 (m, 2H), 3.39-3.09 (m, 12H), 2.99-2.95 (m, 1H), 2.68-2.66 (m, 2H), 2.20-2.13 (m, 1H), 1.81-1.76 (m, 1H).

Step 6: **Synthesis of 3-(6-(4-hydroxy-3,3-bis(methoxymethyl)-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-184)**

3-(6-(4-hydroxy-3,3-bis(methoxymethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (70 mg, 0.151 mmol) was treated with 4-(trifluoromethyl)benzaldehyde (0.027 mL, 0.196 mmol) and sodium triacetoxyborohydride according to **General Procedure 1, Step D.** The crude product was purified by preparative HPLC [Method: X Select C18 (250 x 19 mm), 5 μm; eluting with Mobile phase A: 0.1% FA in H_2O, Mobile phase B: Acetonitrile, flow rate: 15 mL/min] to afford 3-(6-(4-hydroxy-3,3-bis(methoxymethyl)-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**I-184**, 28.5 mg, 0.048 mmol, 32% yield. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 587.0; ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.97 (s, 1H), 8.75 (s, 1H), 8.20 (s, 1H), 7.94-7.85 (m, 3H), 7.71 (d, J = 8.00 Hz, 2H), 7.59 (d, J = 8.00 Hz, 2H), 5.27 (s, 1H), 4.14 (d, J = 4.80 Hz, 1H), 3.78-3.69 (m, 2H), 3.52 (d, J = 14.00 Hz, 1H), 3.38-3.33 (m, 2H), 3.16-3.13 (m, 2H), 3.05 (s, 6H), 2.90-2.75 (m, 1H), 2.67-2.62 (m, 2H), 2.51-2.50 (m, 3H), 2.43 (d, J = 3.60 Hz, 2H), 2.07-2.02 (m, 1H), 1.53 (d, J = 13.60 Hz, 1H).

Example 245: Synthesis of 1-(5-fluoro-6-(5-hydroxy-2-((1-methyl-1H-pyrazol-5-yl)methyl)-9-oxa-2-azaspiro[5.5]undecan-5-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-788)



Step 1: **Synthesis of 6-chloro-5-fluoro-2-methylquinolin-3-amine**

1-chloropropan-2-one (2.78 mL, 34.6 mmol) was added to a stirred solution of pyridine (2.80 mL, 34.6 mmol) in ethanol (20 mL) under continuous nitrogen sparging at rt, then the mixture heated at 80°C for 2 h. The reaction mixture was cooled to rt and subjected to three cycles of vacuum followed by nitrogen backfill. Pyridine (3.49 mL, 43.2 mmol) and 6-amino-3-chloro-2-fluorobenzaldehyde (5 g, 28.8 mmol) in ethanol (20 mL) were added, and the resulting mixture was heated at 80°C for 16 h. The reaction mixture was cooled to 70°C, pyrrolidine (5.96 mL, 72.0 mmol) was added, and the mixture was heated to 80°C for 2 h. The reaction mixture was concentrated under reduced pressure. Saturated aqueous sodium bicarbonate solution was added to the crude residue, and the mixture was extracted with DCM. The combined organic layers were concentrated under reduced pressure to obtain 6-chloro-5-fluoro-2-methylquinolin-3-amine (2.5 g, 11.9 mmol, 41% yield) LCMS: m/z MM-ES+APCI, Positive [M+H, M+2+H]$^+$ 211.0, 212.8; ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.59 (d, J = 9.20 Hz, 1H), 7.35 (d, J = 8.80 Hz, 1H), 7.25 (s, 1H), 5.88 (s, 2H), 1.92 (s, 3H).

Step 2: **Synthesis of 6-chloro-5-fluoro-3-iodo-2-methylquinoline**

To a stirred solution of 6-chloro-5-fluoro-2-methylquinolin-3-amine (2.5 g, 11.87 mmol) in concentrated HCl (15 mL) was added a solution of sodium nitrite (1.56 g, 22.6 mmol) dissolved in water

(8 mL) at 0°C, and the reaction was stirred at 0°C for 1 h. To this resulting mixture was added KI (4.93 g, 29.7 mmol) dissolved in water (8 mL) dropwise, and the reaction mixture was allowed to warm to rt over 2h. The reaction mixture was poured into 10% $NaHCO_3$ solution and the mixture was extracted with EtOAc (2 x 180 mL). The organic layer was washed with aqueous sodium hypochlorite solution (200 mL). The organic layer was concentrated under reduced pressure, and the crude residue was purified by silica gel flash chromatography, eluting with 0-6% EtOAc in hexane to afford 6-chloro-5-fluoro-3-iodo-2-methylquinoline (1.4 g, 4.35 mmol, 37% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ 321.9, 323.7; ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.90 (s, 1H), 7.89 (d, J = 9.20 Hz, 1H), 7.81 (d, J = 9.20 Hz, 1H), 2.85 (s, 3H).

Step 3: **Synthesis of 1-(6-chloro-5-fluoro-7-methylquinolin-3-yl)-3-(2,4-dimethoxybenzyl)-dihydropyrimidine-2,4(1H,3H)-dione**

A stirred mixture of 6-chloro-5-fluoro-3-iodo-7-methylquinoline (1.4 g, 4.35 mmol), 3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (1.726 g, 6.53 mmol), Cs_2CO_3 (3.55 g, 10.89 mmol), and 2-methyl-THF (15 mL) was sparged with argon for 15 minutes. Anhydrous copper(II) acetate (0.395 g, 2.177 mmol) and (1R,2R)-N,N'-dimethyl-1,2-cyclohexanediamine (0.433 g, 3.05 mmol) were then added at ambient temperature, and the reaction mixture was sparged with argon for another 15 minutes. The reaction mixture was stirred at 100°C for 16 h. The cooled reaction mixture was filtered through Celite, washing with EtOAc (200 mL), and the combined filtrates were washed with water (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography, eluting with 0-99% EtOAc in hexane to afford 1-(6-chloro-5-fluoro-7-methylquinolin-3-yl)-3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (850 mg, 1.71 mmol, 39% yield). LCMS m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ 458.4, 460.1; ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.53 (s, 1H), 7.89-7.87 (m, 2H), 6.95 (d, J = 8.00 Hz, 1H), 6.56 (s, 1H), 6.49 (d, J = 2.40 Hz, 1H), 4.83 (m, 2H), 4.09-4.06 (m, 1H), 3.80 (s, 6H), 3.33 (m, 1H), 3.09-3.05 (m, 2H), 2.68 (s, 3H).

Step 4: **Synthesis of tert-butyl 5-(3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoro-2-methylquinolin-6-yl)-9-oxa-2-azaspiro[5.5]undec-4-ene-2-carboxylate**

To a stirred solution of 1-(6-chloro-5-fluoro-2-methylquinolin-3-yl)-3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (400 mg, 0.87 mmol) and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9-oxa-2-azaspiro[5.5]undec-4-ene-2-carboxylate (530 mg, 1.40 mmol) in 1,4-dioxane (5 mL) and water (0.25 mL) at rt was added tri-potassium phosphate (167 mg, 0.79 mmol). The resulting reaction mixture was sparged with argon, then cataCXium A Pd G3 (32 mg, 0.044 mmol) was added. The reaction mixture was sparged with argon for 5 minutes and then stirred at 100 °C for 16 h. The cooled reaction mixture was filtered through a Celite, rinsing with EtOAc (2 × 50 mL). The

combined organic layers were concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography, eluting with 50-80% EtOAc in n-hexane to afford tert-butyl 5-(3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoro-2-methylquinolin-6-yl)-9-oxa-2-azaspiro[5.5]undec-4-ene-2-carboxylate (250 mg, 0.21 mmol, 24% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 675.5; ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.46 (s, 1H), 7.85 (s, 1H), 7.80 (d, J = 8.80 Hz, 1H), 7.49 (t, J = 8.40 Hz, 1H), 6.96 (d, J = 8.40 Hz, 1H), 6.75 (s, 1H), 6.55 (d, J = 2.40 Hz, 1H), 6.46 (dd, J = 10.40 Hz, 1H), 5.76 (s, 1H), 4.80 (d, J = 11.20 Hz, 1H), 4.68 (s, 2H), 4.06-4.01 (m, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.75-3.73 (m, 1H), 3.56-3.53 (m, 2H), 3.28 (t, J = 2.80 Hz, 1H), 3.08 (q, J = 6.00 Hz, 2H), 2.68 (t, J = 6.80 Hz, 2H), 2.60 (s, 3H), 1.60-1.58 (m, 2H), 1.57 (s, 9H).

Step 5: **Synthesis of tert-butyl 5-(3-(3-(3,5-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoro-2-methylquinolin-6-yl)-5-hydroxy-9-oxa-2-azaspiro[5.5]undecane-2-carboxylate**

Tert-butyl 5-(3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoro-2-methylquinolin-6-yl)-9-oxa-2-azaspiro[5.5]undec-4-ene-2-carboxylate (300 mg, 0.445 mmol) was treated according to **General Procedure 3, Step C**. The crude product was purified by reverse phase chromatography using a C18 column, eluting with 0.1% FA in water and acetonitrile to afford tert-butyl 5-(3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoro-2-methylquinolin-6-yl)-4-hydroxy-9-oxa-2-azaspiro[5.5]undec-4-ene-2-carboxylate (80 mg, 0.083 mmol, 19% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 693.8; ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.47 (s, 1H), 8.07 (d, J = 8.40 Hz, 1H), 7.84 (d, J = 8.80 Hz, 1H), 6.95 (d, J = 8.40 Hz, 1H), 6.56 (d, J = 2.40 Hz, 1H), 6.48 (dd, J = 2.00, 8.40 Hz, 1H), 5.78 (s, 1H), 5.57 (d, J = 9.60 Hz, 1H), 4.77 (d, J = 15.20 Hz, 2H), 4.40 (m, 1H), 4.07-4.02 (m, 2H), 3.81 (s, 3H), 3.73 (s, 3H), 3.59-3.56 (m, 3H), 3.07-3.06 (m, 4H), 2.68-2.55 (m, 4H), 1.68-1.65 (m, 1H), 1.51 (s, 9H), 1.19-1.08 (m, 3H).

Step 6: **Synthesis of 1-(5-fluoro-6-(5-hydroxy-9-oxa-2-azaspiro [5.5] undecan-5-yl)-2-methylquinolin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione**

To a stirred solution of tert-butyl 5-(3-(3-(3,5-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoro-2-methylquinolin-6-yl)-5-hydroxy-9-oxa-2-azaspiro[5.5]undecane-2-carboxylate (20 mg, 0.029 mmol) in DCM (1 mL) at 0 °C under nitrogen atmosphere were added TFA (5.56 µl, 0.072 mmol) and trifluoromethanesulfonic acid (5.13 µl, 0.058 mmol), and the reaction mixture was stirred at 0 °C for 2 h. The mixture was concentrated under reduced pressure, and the crude residue was triturated with MTBE. The resulting solid was collected and dried to provide 1-(5-fluoro-6-(5-hydroxy-9-oxa-2-azaspiro [5.5] undecan-5-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, TFA (10 mg, 0.012 mmol, 41% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 443.4; 1H-NMR (400 MHz, DMSO-d6): 10.5 (s, 1H), 8.48 (s, 1H), 8.13-8.05 (m, 1H), 6.55 (s, 1H), 5.99 (s, 1H), 4.36-4.25 (m, 2H), 4.00-3.96 (m, 2H), 3.80-3.71 (m, 1H), 3.38-3.16 (m, 2H), 2.90-2.89 (m, 2H), 2.80-2.75 (m, 2H), 2.68-

2.62 (m, 1H), 2.10 (d, J = 14.80 Hz, 2H), 1.90 (d, J = 13.60 Hz, 2H), 1.59 (d, J = 14.40 Hz, 2H), 1.30-1.24 (m, 2H), 1.11 (s, 2H).

Step 7: **Synthesis of 1-(5-fluoro-6-(5-hydroxy-2-((1-methyl-1H-pyrazol-5-yl)methyl)-9-oxa-2-azaspiro[5.5]undecan-5-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-788)**

1-(5-fluoro-6-(5-hydroxy-9-oxa-2-azaspiro[5.5]undecan-5-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, TFA (50 mg, 0.090 mmol) was reacted with 1-methyl-1H-pyrazole-5-carbaldehyde (11 mg, 0.099 mmol) and sodium triacetoxyborohydride according to **General Procedure 1, Step D**. The crude product was purified by preparative-HPLC [Method info: Column: X SELECTC18 (150 x 19 mm) 5 µm, eluting with Mobile phase A: 0.05% FA in H_2O, Mobile phase B: acetonitrile, flow rate: 15 mL/min)] to afford 1-(5-fluoro-6-(5-hydroxy-2-((1-methyl-1H-pyrazol-5-yl)methyl)-9-oxa-2-azaspiro[5.5]undecan-5-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-788) (2.4 mg, 4.44 µmol, 5% yield). LCMS m/z MM-ES+APCI, Positive $[M+H]^+$ 537.5; ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.55 (s, 1H), 8.41 (d, J = 5.20 Hz, 1H), 8.10-8.03 (m, 1H), 7.81 (d, J = 6.40 Hz, 1H), 7.50 (d, J = 2.00 Hz, 1H), 6.19 (s, 1H), 5.27 (d, J = 12.80 Hz, 1H), 4.07-3.97 (m, 1H), 3.76 (s, 3H), 3.68-3.63 (m, 2H), 3.59-3.53 (m, 4H), 3.49 (s, 3H), 3.25-3.14 (m, 2H), 2.88-2.79 (m, 1H), 2.75-2.74 (m, 2H), 2.59 (s, 3H), 2.12 (d, J = 12.80 Hz, 1H), 1.69 (d, J = 8.00 Hz, 1H), 1.47 (d, J = 13.20 Hz, 1H), 1.23 (t, J = 6.00 Hz, 1H), 1.09 (m, 1H).

Step 8: **Synthesis of tert-butyl 5-oxo-9-oxa-2-azaspiro [5.5] undecane-2-carboxylate**

To a stirred solution of tert-butyl 4-oxopiperidine-1-carboxylate (5 g, 25.09 mmol) in toluene (50 mL) under a nitrogen atmosphere was added potassium tert-butoxide (7.04 g, 62.7 mmol) portion-wise at rt, and the mixture was stirred for 1h. 1-Bromo-2-(2-bromoethoxy)ethane (6.40 g, 27.6 mmol) was then added dropwise and the reaction mixture was stirred at 100 °C for 2 h. The reaction mixture was allowed to cool to rt, then aqueous ammonium chloride solution (50 mL) was added, and the mixture was extracted with EtOAc (2 × 100 mL). The combined organic layers were concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography, eluting with 18-30% EtOAc in n-hexane to afford tert-butyl 5-oxo-9-oxa-2-azaspiro[5.5]undecane-2-carboxylate (650 mg, 2.15 mmol, 9% yield). LCMS m/z MM-ES+APCI, Positive $[M-56+H]^+$ 214.0; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.15-4.01 (m, 6H), 3.60 (s, 2H), 2.54-2.51 (m, 2H), 2.07-1.94 (m, 2H), 1.52 (s, 9H).

Step 9: **Synthesis of tert-butyl 5-(((trifluoromethyl)sulfonyl) oxy)-9-oxa-2-azaspiro[5.5]-undec-4-ene-2-carboxylate**

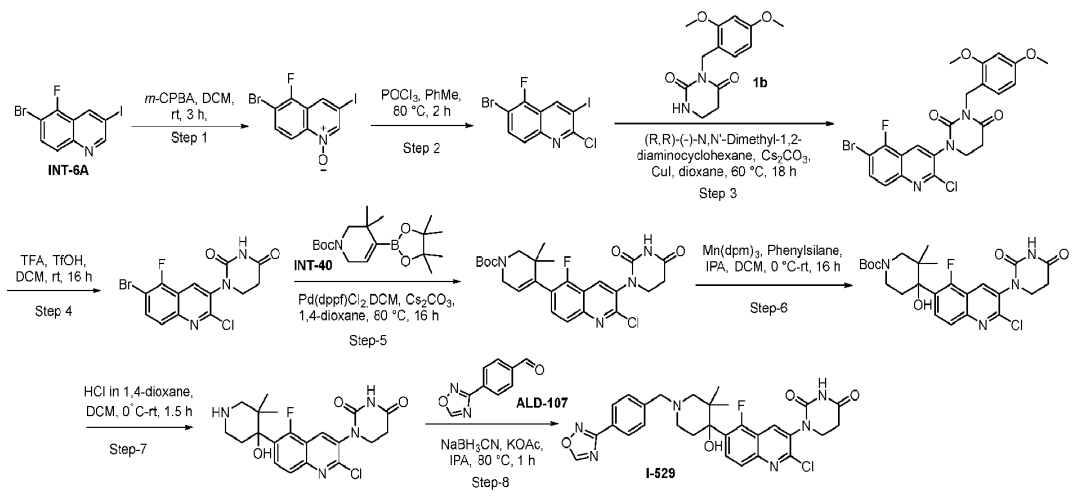
To a stirred solution of tert-butyl 5-oxo-9-oxa-2-azaspiro [5.5] undecane-2-carboxylate (300 mg, 1.11 mmol) in THF (5 mL) at -78 °C under a nitrogen atmosphere was added potassium tert-butoxide (1M in THF, 2.90 mL, 2.90 mmol), and the mixture was stirred at -50 °C for 1 h. The reaction mixture was again cooled to -78 °C, and a solution of N-(5-chloropyridin-2-yl)-1,1,1-trifluoro-N-

((trifluoromethyl)sulfonyl) methane sulfonamide (787 mg, 2.01 mmol) in THF (2 mL) was then added. The reaction mixture was warmed to 0 °C and stirred for 1h. Aqueous ammonium chloride solution (100 mL) was added, and the mixture was extracted with EtOAc (2 x 500 mL). The combined organic layers were washed with brine solution (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography, eluting with 15-20% EtOAc in hexane to afford tert-butyl 5-(((trifluoromethyl)sulfonyl) oxy)-9-oxa-2-azaspiro [5.5] undec-4-ene-2-carboxylate (290 mg, 0.71 mmol, 64% yield). LCMS m/z MM-ES+APCI, Positive $[M-56+H]^+$ 346.3; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.83-5.77 (m, 1H), 4.14 (d, J = 12.80 Hz, 2H), 4.09 (s, 2H), 3.74-3.60 (m, 4H), 2.06 (t, J = 9.20 Hz, 2H), 1.50 (s, 9H), 1.38 (d, J = 13.60 Hz, 2H).

Step 10: **Synthesis of tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9-oxa-2-azaspiro[5.5]undec-4-ene-2-carboxylate**

$PdCl_2$(dppf)-DCM adduct (0.224 g, 0.274 mmol) was added to a stirred mixture of tert-butyl 5-(((trifluoromethyl)sulfonyl)oxy)-9-oxa-2-azaspiro[5.5]undec-4-ene-2-carboxylate (1.1 g, 2.74 mmol), 1,4-dioxane (15 mL), bispinacolato diboron (1.39 g, 5.48 mmol), and potassium acetate (0.807 g, 8.22 mmol). The reaction mixture was sparged with nitrogen for 5 min, then stirred at 100 °C for 4 h. The cooled reaction mixture was filtered through Celite, rinsing with EtOAc (2 x 50 mL). The combined filtrate was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography, eluting with 0-30% EtOAc in hexane to afford tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9-oxa-2-azaspiro[5.5]undec-4-ene-2-carboxylate (800 mg, 1.75 mmol, 64% yield). LCMS m/z MM-ES+APCI, Positive $[M+H]^+$ 380.4. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.49-6.42 (m, 1H), 3.97 (d, J = 10.80 Hz, 2H), 3.90-3.82 (m, 2H), 3.74-3.57 (m, 5H), 2.25 (t, J = 4.80 Hz, 2H), 1.50 (s, 9H), 1.27 (s, 12H), 1.20 (d, J = 14.00 Hz, 1H).

Example 246: Synthesis of 1-(6-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethyl-piperidin-4-yl)-2-chloro-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-529)



Step 1: **Synthesis of 6-bromo-5-fluoro-3-iodoquinoline 1-oxide**

To a stirred solution of 6-bromo-5-fluoro-3-iodoquinoline (12 g, 34.1 mmol) in DCM (50 mL) was added m-CPBA (9.17 g, 40.9 mmol) at 0°C. The reaction mixture was allowed to stir at rt for 3 h. The reaction mixture was diluted with DCM (100 mL) and saturated aq $NaHCO_3$ (150 mL) was added. The separated organic layer was washed with brine (200 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography, eluting with 0-20% EtOAc in hexane to afford 6-bromo-5-fluoro-3-iodoquinoline 1-oxide (5 g, 10.8 mmol, 32% yield. LCMS m/z MM-ES+APCI, Positive $[M+H]^+$ 367.9; ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.09 (d, J = 2.00 Hz, 1H), 8.78 (d, J = 1.60 Hz, 1H), 7.85-7.79 (m, 2H).

Step 2: **Synthesis of 6-bromo-2-chloro-5-fluoro-3-iodoquinoline**

To a stirred solution of 6-bromo-5-fluoro-3-iodoquinoline 1-oxide (7.5 g, 20.38 mmol) in toluene (75 mL) at 0°C was added $POCl_3$ (9.50 mL, 102 mmol), and the reaction mixture was heated at 80°C for 2 h. The cooled reaction mixture was diluted with EtOAc (100 mL) and the pH was adjusted to 8 using saturated aq $NaHCO_3$ (50 mL). The organic layer was separated, washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography, eluting with 0-4% EtOAc in hexane to afford 6-bromo-2-chloro-5-fluoro-3-iodoquinoline (4.7 g, 9.73 mmol, 48% yield). LCMS m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ 386.0, 388.0; ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.07 (s, 1H), 8.11-8.05 (m, 1H), 7.78 (d, J = 9.20 Hz, 1H).

Step 3: **Synthesis of 1-(6-bromo-2-chloro-5-fluoroquinolin-3-yl)-3-(2,4-dimethoxybenzyl)-dihydropyrimidine-2,4(1H,3H)-dione**

A stirred mixture of 6-bromo-2-chloro-5-fluoro-3-iodoquinoline (300 mg, 0.776 mmol), and 3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (**1b**, 205 mg, 0.776 mmol), 1,4-dioxane (6

mL), and Cs_2CO_3 (506 mg, 1.553 mmol) was sparged for 15 min with argon. Copper(I) iodide (74 mg, 0.39 mmol) and (1R,2R)-N,N'-dimethyl-1,2-cyclohexanediamine (55 mg, 0.39 mmol) were then added at rt and the reaction mixture was stirred at 60°C for 18 h. The cooled reaction mixture was filtered through Celite, rinsing with EtOAc (250 mL). The filtrate was washed with water (2 x 250 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography, eluting with 0-45% EtOAc in hexane to afford 1-(6-bromo-2-chloro-5-fluoroquinolin-3-yl)-3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (130 mg, 0.236 mmol, 30% yield). LCMS m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ 522.0, 524.0; ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.81 (s, 1H), 8.13 (d, J = 1.20 Hz, 1H), 7.94 (d, J = 9.20 Hz, 1H), 6.95 (d, J = 8.40 Hz, 1H), 6.56 (s, 1H), 6.48 (d, J = 2.40 Hz, 1H), 4.81 (s, 2H), 3.99-3.96 (m, 1H), 3.90-3.80 (m, 1H), 3.75 (s, 3H), 3.32 (s, 3H), 3.05 (t, J = 7.60 Hz, 2H).

Step 4: **Synthesis of 1-(6-bromo-2-chloro-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione**

To a stirred solution of 1-(6-bromo-2-chloro-5-fluoroquinolin-3-yl)-3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (1.0 g, 1.91 mmol) in DCM (10 mL) at 0°C were added, TFA (2.06 mL, 26.8 mmol) and triflic acid (0.34 mL, 3.8 mmol) and the resulting reaction mixture was stirred at rt for 16 h. The reaction mixture was concentrated under reduced pressure, and saturated aq $NaHCO_3$ solution was added to the residue. The resulting solid was collected via filtration and dried to afford the crude product, which was purified by silica gel flash chromatography, eluting with 0-55% EtOAc in hexane to afford 1-(6-bromo-2-chloro-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (0.5 g, 1.16 mmol, 61% yield). LCMS m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ 372.0, 374.0; ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.43 (s, 1H), 8.71 (s, 1H), 8.07 (d, J = 7.60 Hz, 1H), 7.83 (d, J = 9.20 Hz, 1H), 3.85 (t, J = Hz, 2H), 2.84 (t, J = 6.80 Hz, 2H).

Step 5: **Synthesis of tert-butyl 4-(2-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate**

To a stirred solution of 1-(6-bromo-2-chloro-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (300 mg, 0.81 mmol) and tert-butyl 3,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**INT-40**, 407 mg, 1.21 mmol) in 1,4-dioxane (12 mL), $PdCl_2$(dppf)-CH_2Cl_2 adduct (66 mg, 0.081 mmol) was added, and the reaction mixture was sparged with nitrogen for 5 min. The reaction mixture was stirred at 80°C for 16 h. The cooled reaction mixture was filtered through a pad of celite, and the pad was washed with EtOAc (100 mL). The filtrate was concentrated under reduced pressure. The crude residue was purified by reverse phase column chromatography on a C18 column, eluting with 50% acetonitrile in 0.1% FA in H_2O to afford tert-butyl 4-(2-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-3,3-dimethyl-3,6-

dihydropyridine-1(2H)-carboxylate (100 mg, 0.19 mmol, 23% yield). LCMS m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ 503.2, 505.2; ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.66 (s, 1H), 8.72 (s, 1H), 7.84 (d, J = 8.80 Hz, 1H), 7.65 (t, J = 8.00 Hz, 1H), 5.64 (s, 1H), 4.04 (s, 2H), 3.89 (t, J = 6.00 Hz, 1H), 3.77 (t, J = 5.60 Hz, 1H), 3.39 (s, 2H), 2.85-2.80 (m, 2H), 1.46 (s, 9H), 1.00 (s, 6H).

Step 6: **Synthesis of tert-butyl 4-(2-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate**

Tert-butyl 4-(2-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (200 mg, 0.40 mmol) was treated according to **General Procedure 3, Step C.** The crude product was purified by silica gel flash chromatography, eluting with 5% IPA in DCM to afford tert-butyl 4-(2-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (100 mg, 0.130 mmol, 33% yield. LCMS m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ 521.2, 523.2.

Step 7: **Synthesis of 1-(2-chloro-5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione**

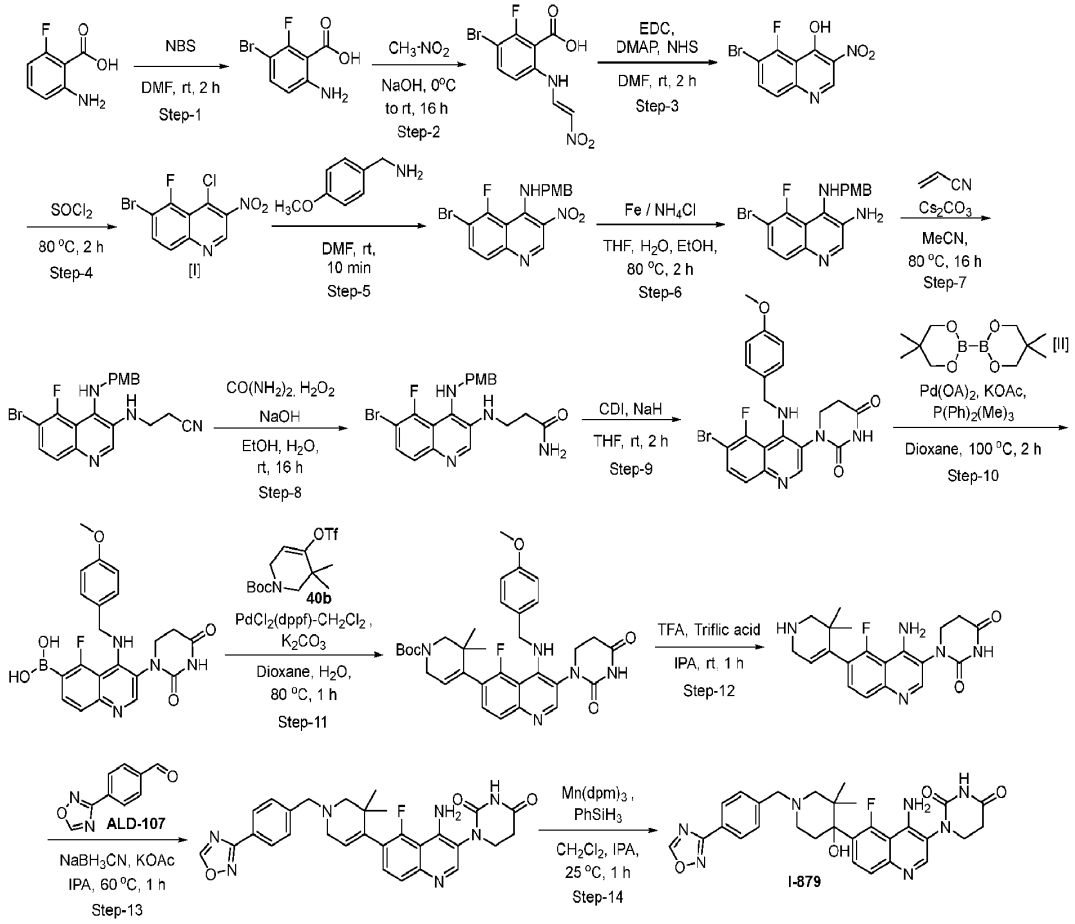
A solution of tert-butyl 4-(2-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (80 mg, 0.154 mmol) in DCM (3 mL) and HCl (4 M in dioxane, 0.1 mL, 0.400 mmol) was stirred at 0 °C for 1.5 h. The reaction mixture was concentrated under reduced pressure. The crude residue was triturated with pentane, collected and dried under vacuum to afford 1-(2-chloro-5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl (80 mg, 0.19 mmol, 84% yield). LCMS m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ 421.1, 423.2; ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.67 (s, 1H), 8.75 (s, 1H), 8.22 (d, J = 8.00 Hz, 1H), 7.89 (d, J = 4.00 Hz, 1H), 5.97 (s, 1H), 3.91 (t, J = 2.40 Hz, 2H), 3.80-3.74 (m, 2H), 3.44-3.15 (m, 3H), 2.94-2.81 (m, 3H), 1.92 (s, 1H), 1.07 (s, 9H).

Step 8: **Synthesis of 1-(6-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-2-chloro-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-529)**

To a stirred solution of 1-(2-chloro-5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl) quinolin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione, HCl (70 mg, 0.15 mmol) in 2-propanol (2 mL) was added 4-(1,2,4-oxadiazol-3-yl)benzaldehyde (**ALD-107**, 27 mg, 0.15 mmol) and potassium acetate (45.1 mg, 0.46 mmol) and the mixture was stirred at rt for 20 min. Sodium cyanoborohydride (29 mg, 0.46 mmol) was added and the reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was poured into cooled water (100 mL) and the mixture was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by preparative-HPLC [(Column: X select C18 (150 x 19 mm) 5 µm, eluting with Mobile phase A: 0.1% acetic acid in H_2O, Mobile phase B: Acetonitrile, flow rate: 15 mL/min)]. The resulting

product was dissolved in acetonitrile (5 mL) and 0.1M HCl (aq) and lyophilized to afford 1-(6-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-2-chloro-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl (I-529) (18.0 mg, 0.029 mmol, 19% yield). LCMS m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ 579.2, 581.2; ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.67 (s, 1H), 10.10 (s, 1H), 9.78 (s, 1H), 8.76 (s, 1H), 8.16 (d, J = 8.00 Hz, 3H), 7.90 (t, J = 9.20 Hz, 3H), 6.01 (d, J = 8.80 Hz, 1H), 4.54 (q, J = 3.20 Hz, 2H), 3.91 (t, J = 7.20 Hz, 1H), 3.87-3.86 (m, 2H), 3.40-3.27 (m, 2H), 2.95-2.85 (m, 3H), 2.08-2.03 (m, 2H), 1.09 (s, 3H), 0.77 (s, 3H).

Example 247: Synthesis of 1-(6-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethyl-piperidin-4-yl)-4-amino-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-879)



Step 1: **Synthesis of 6-amino-3-bromo-2-fluorobenzoic acid**

To a stirred a solution of 2-amino-6-fluorobenzoic acid (30 g, 193 mmol) in DMF (300 mL) at 0 °C was added NBS (34.4 g, 193 mmol). The reaction was stirred at 25 °C for 2 h. Water (500 mL) was added to the reaction mixture, and the resultant solid was collected by filtration and dried under vacuum to afford 6-amino-3-bromo-2-fluorobenzoic acid (40 g, 171 mmol, 88% yield). LCMS: m/z MM-

ES+APCI, Positive $[M+2+H]^+$ = 235.8; ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.38 (d, J = 8.80 Hz, 1H), 6.56 (d, J = 8.80 Hz, 1H). (Note: NH_2 and COOH protons were not observed in ^{1}H-NMR).

Step 2: **Synthesis of (E)-3-bromo-2-fluoro-6-((2-nitrovinyl)amino)benzoic acid**

In a 500 mL multi-neck round-bottom flask under a nitrogen atmosphere, NaOH (51.3 g, 1282 mmol) was dissolved in water (180 mL) and the solution cooled to 0 °C. To this solution, nitromethane (31.3 g, 513 mmol) was added dropwise resulting in an exothermic reaction. The mixture was then stirred at 45 °C for approximately 10 minutes. The reaction mixture was allowed to reach ambient temperature and was carefully poured into an ice (92 g, 5128 mmol) and HCl (395 mL, 4743 mmol) solution. This mixture was then added dropwise to a suspension of 6-amino-3-bromo-2-fluorobenzoic acid (30 g, 128 mmol) in water (750 mL) and HCl (660 mL, 7948 mmol). The resulting mixture was stirred at room temperature for 16 h. The obtained solids were collected via flitration and washed with water (300 mL) and methanol (300 mL) to yield (E)-3-bromo-2-fluoro-6-((2-nitrovinyl)amino)benzoic acid (17.5 g, 51.1 mmol, 40% yield). LCMS: m/z MM-ES+APCI, Positive $[M+2+H]^+$ = 306.9; ^{1}H-NMR (400 MHz, DMSO-d6): δ 14.1 (bs, 1H), 12.33 (d, J = 8.20 Hz, 1H), 7.93-8.03 (m, 2H), 7.53 (d, J = 9.60 Hz, 1H), 6.80 (d, J = 6.40 Hz, 1H).

Step 3: **Synthesis of 6-bromo-5-fluoro-3-nitroquinolin-4-ol**

To a stirred solution of (E)-3-bromo-2-fluoro-6-((2-nitrovinyl)amino)benzoic acid (15 g, 49.2 mmol) in DMF (150 mL) were added at rt n-hydroxysuccinimide (9.05 g, 79 mmol) and EDC (13.2 g, 68.8 mmol). The reaction was stirred for 1 h, after which DMAP (7.21 g, 59.0 mmol) was added. The reaction was stirred at rt for an additional 2 h, then the reaction mixture was added to water (1 L). The obtained solid was collected via filtration and dried under vacuum, and was then washed with MTBE/acetonitrile (1:1 ratio) and dried under vacuum to yield 6-bromo-5-fluoro-3-nitroquinolin-4-ol (4.4 g, 11 mmol, 22% yield). ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.10 (s, 1H), 7.95 (d, J = 9.20 Hz, 1H), 7.45 (d, J = 8.80 Hz, 1H). (Note: OH proton was not observed in ^{1}H-NMR).

Step 4: **Synthesis of 6-bromo-4-chloro-5-fluoro-3-nitroquinoline**

A mixture of 6-bromo-5-fluoro-3-nitroquinolin-4-ol (10 g, 35 mmol) and thionyl chloride (166 g, 1394 mmol) was stirred at 80 °C for 2 h. The reaction mixture was concentrated under reduced pressure to obtain crude 6-bromo-4-chloro-5-fluoro-3-nitroquinoline (10 g), which was used in the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 305.2; ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.12 (s, 1H), 8.06 (d, J = 9.20 Hz, 1H), 7.98 (d, J = 9.20 Hz, 1H).

Step 5: **Synthesis of 6-bromo-5-fluoro-N-(4-methoxybenzyl)-3-nitroquinolin-4-amine**

To a stirred solution of 6-bromo-4-chloro-5-fluoro-3-nitroquinoline (10 g, 32.7 mmol) in DMF (100 mL), at 0 °C was added 4-methoxybenzylamine (8.98 g, 65.5 mmol). The mixture was stirred and allowed to warm to rt over 10 minutes. Water (100 mL) was added, and the mixture was extracted with

EtOAc (500 mL). The combined organic layers were washed with water (500 mL) and brine (500 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography, eluting with 30% EtOAc in petroleum ether to afford 6-bromo-5-fluoro-N-(4-methoxybenzyl)-3-nitroquinolin-4-amine (6 g, 13.7 mmol, 42% yield). LCMS m/z MM-ES+APCI, Positive $[M+2+H]^+$ = 408.2'; ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.92 (s, 1H), 8.62 (br s, 1H), 8.07 (t, J = 7.80 Hz, 1H), 7.69 (d, J = 8.80 Hz, 1H), 7.17 (d, J = 8.80 Hz, 2H), 6.85 (d, J = 8.80 Hz, 2H), 4.47 (s, 2H), 3.72 (s, 3H).

Step 6: **Synthesis of 6-bromo-5-fluoro-N4-(4-methoxybenzyl)quinoline-3,4-diamine**

A stirred mixture of 6-bromo-5-fluoro-N-(4-methoxybenzyl)-3-nitroquinolin-4-amine (5 g, 12.3 mmol), THF (25 mL), ethanol (25 mL), water (5 mL), iron powder (4.12 g, 73.9 mmol), and ammonium chloride (3.95 g, 73.9 mmol) was stirred at 80 °C for 2 h. The cooled reaction mixture was filtered through celite, rinsing with ethanol (150 mL) and THF (150 mL), then the combined filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel chromatography, eluting with 0-60% EtOAc in petroleum ether to afford 6-bromo-5-fluoro-N4-(4-methoxybenzyl)quinoline-3,4-diamine (3.4 g, 8.22 mmol, 67% yield). LCMS: m/z MM-ES+APCI, Positive $[M+2+H]^+$ = 377.8; ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.45 (s, 1H), 7.49 (d, J = 4.00 Hz, 1H), 7.26 (d, J = 8.40 Hz, 2H), 6.84 (d, J = 8.40 Hz, 2H), 5.41 (s, 2H), 5.09-5.10 (m, 2H), 4.20 (d, J = 6.80 Hz, 2H), 3.71 (s, 3H).

Step 7: **Synthesis of 3-((6-bromo-5-fluoro-4-((4-methoxybenzyl)amino)quinolin-3-yl)amino)-propanenitrile**

A mixture of 6-bromo-5-fluoro-N4-(4-methoxybenzyl)quinoline-3,4-diamine (10 g, 26.6 mmol), cesium carbonate (10.4 g, 31.9 mmol), acrylonitrile (2.12 g, 39.9 mmol), and acetonitrile (100 ml) was stirred at rt for 2 h and then at 80 °C for 16 h. Water (300 mL) was added, and the mixture was extracted with EtOAc (300 mL). The combined organic layers were washed with water (300 mL) followed by brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by reverse phase column chromatography on a C18 column, eluting with 5 to 100% acetonitrile in 0.1% FA in water to afford 3-((6-bromo-5-fluoro-4-((4-methoxybenzyl)amino)quinolin-3-yl)amino)propanenitrile (7 g, 16.3 mmol, 61% yield). LCMS: m/z MM-ES+APCI, Positive $[M+2+H]^+$ = 431.3; ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.58 (s, 1H), 7.47-7.58 (m, 2H), 7.26 (d, J = 8.40 Hz, 2H), 6.84 (d, J = 8.40 Hz, 2H), 5.65-5.68 (m, 1H), 5.27-5.30 (m, 1H), 4.22 (t, J = 6.80 Hz, 2H), 3.71 (s, 3H), 3.59-3.64 (m, 2H), 2.85 (t, J = 6.40 Hz, 2H).

Step 8: **Synthesis of 3-((6-bromo-5-fluoro-4-((4-methoxybenzyl)amino)quinolin-3-yl)amino)-propanamide**

To a solution of 3-((6-bromo-5-fluoro-4-((4-methoxybenzyl)amino)quinolin-3-yl)amino)-propanenitrile (6.8 g, 15.84 mmol) in EtOH (68 mL) and water (102 mL) at rt was added urea hydrogen peroxide (17.9 g, 190 mmol) and NaOH (4.43 g, 111 mmol). The reaction mixture was stirred at rt for 16h, then water was added, and the resultant solid precipitate was collected by filtration. The crude product was purified by reverse phase column chromatography on a C18 column, eluting with 5 to 100% acetonitrile in 0.1% FA in water to yield 3-((6-bromo-5-fluoro-4-((4-methoxybenzyl)amino)quinolin-3-yl)amino)propenamide (2 g, 4.47 mmol, 30% yield). LCMS m/z MM-ES+APCI, Positive $[M+2+H]^+$ = 449.2; ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.57 (s, 1H), 7.45-7.62 (m, 3H), 7.27 (d, J = 8.80 Hz, 2H), 6.95 (d, J = 1.20 Hz, 1H), 6.83 (d, J = 4.80 Hz, 2H), 5.46 (t, J = 6.00 Hz, 1H), 5.11 (q, J = 7.20 Hz, 1H), 4.15 (d, J = 6.40 Hz, 2H), 3.71 (s, 3H), 3.52 (q, J = 6.40 Hz, 2H), 2.45 (t, J = 6.80 Hz, 2H).

Step 9: **Synthesis of 1-(6-bromo-5-fluoro-4-((4-methoxybenzyl)amino)quinolin-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione**

NaH (214 mg, 5.36 mmol) was added at 0 °C to a stirred solution of 3-((6-bromo-5-fluoro-4-((4-methoxybenzyl)amino)quinolin-3-yl)amino)propanamide (0.8 g, 1.79 mmol) in THF (20 mL) and the mixture was stirred for 15 min at 0 °C. CDI (870 mg, 5.36 mmol) was then added, and the reaction mixture was allowed to warm to rt over 2 h. The pH of the reaction mixture was adjusted with 4M HCl (aq) to approximately pH 6-7. The resultant solid precipitate was collected by filtration and triturated with MTBE (20 mL) to afford 1-(6-bromo-5-fluoro-4-((4-methoxybenzyl)amino)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (1.0 g, 2.1 mmol). LCMS m/z MM-ES+APCI, Positive $[M+2+H]^+$ = 475.1; ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.95 (s, 1H), 8.45 (s, 1H), 7.87 (d, J = 8.80 Hz, 1H), 7.65 (d, J = 8.80 Hz, 1H), 7.26 (d, J = 8.80 Hz, 2H), 6.90 (d, J = 8.80 Hz, 2H), 6.58-6.62 (m, 1H), 4.44-4.55 (m, 2H), 3.68-3.37 (m, 4H), 3.27-3.33 (m, 1H), 2.68-2.68 (m, 2H).

Step 10: **Synthesis of (3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoro-4-((4-methoxybenzyl)amino)quinolin-6-yl)boronic acid**

To a stirred solution of 1-(6-bromo-5-fluoro-4-((4-methoxybenzyl)amino)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (200 mg, 0.423 mmol) and 5,5,5',5'-tetramethyl-2,2'-bi(1,3,2-dioxaborinane) (191 mg, 0.845 mmol) in 1,4-dioxane (4 mL) was added potassium acetate (124 mg, 1.268 mmol), and the mixture was sparged with nitrogen for 10 minutes. *Tert*-butyldiphenylphosphine (20.5 mg, 0.085 mmol) and palladium(II) acetate (9.5 mg, 0.042 mmol) were added, and the reaction mixture was stirred at 100 °C for 2 h. The cooled reaction mixture was filtered through celite, washing with EtOAc, and the combined filtrate was concentrated under reduced pressure. The crude residue was triturated with hexane, collected by filtration and dried to afford (3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoro-4-((4-methoxybenzyl)-amino)quinolin-6-yl)boronic acid (0.21 g, 0.28 mmol, 66% yield). LCMS, m/z MM-ES+APCI, Positive $[M+H]^+$ = 438.9.

Step 11: **Synthesis of tert-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoro-4-((4-methoxybenzyl)amino)quinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate**

A stirred mixture of (3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoro-4-((4-methoxybenzyl)amino)quinolin-6-yl)boronic acid (175 mg, 0.399 mmol), *tert*-butyl 3,3-dimethyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (**40b**, 172 mg, 0.479 mmol), 1,4-dioxane (4 mL), water (0.4 mL), and potassium carbonate (110 mg, 0.799 mmol) was sparged with nitrogen for 10 min at rt. $PdCl_2(dppf)$-CH_2Cl_2 adduct (33 mg, 0.040 mmol) was added, and the reaction mixture was stirred at 80 °C for 1 h. Water was added to the cooled reaction mixture, and the mixture was extracted with DCM. The combined organic layers were concentrated under reduced pressure. The crude residue was purified by reverse phase chromatography on a C18 column, eluting with acetonitrile in 0.01% FA in water to provide *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoro-4-((4-methoxybenzyl)amino)-quinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (130 mg, 0.17 mmol, 44% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 604.3; ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.48 (s, 1H), 8.41 (s, 1H), 7.65 (d, J = 8.00 Hz, 1H), 7.41 (t, J = 8.00 Hz, 1H), 7.23 (d, J = 4.00 Hz, 2H), 6.85 (d, J = 6.00 Hz, 2H), 6.55 (d, J = 4.00 Hz, 1H), 5.55 (s, 1H), 4.46-4.56 (m, 1H), 4.36-4.44 (m, 1H), 4.04 (d, J = 4.00 Hz, 2H), 3.68-3.78 (m, 3H), 3.35-3.40 (m, 1H), 3.22-3.29 (m, 2H), 2.50-2.60 (m, 1H), 2.35-2.45 (m, 1H), 2.08-2.09 (m, 1H), 1.44 (s, 9H), 0.98 (s, 6H).

Step 12: **Synthesis of 1-(4-amino-6-(3,3-dimethyl-1,2,3,6-tetrahydropyridin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione**

To a stirred solution of tert-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoro-4-((4-methoxybenzyl)amino)quinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (50 mg, 0.083 mmol) in CH_2Cl_2 (4 mL) were added TFA (0.064 mL, 0.828 mmol) followed by trifluoromethanesulfonic acid (0.022 mL, 0.248 mmol) at 0 °C and stirred at this temperature for 1 h. After completion of the reaction as confirmed by TLC and LCMS, the reaction mixture was evaporated and triturated with hexane to afford a crude 1-(4-amino-6-(3,3-dimethyl-1,2,3,6-tetrahydropyridin-4-yl)-5-fluoroquinolin-3-yl)dihydro pyrimidine-2,4(1H,3H)-dione (21 mg, 55 mmol). The crude taken forward to the next step without further purification. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 384.1; ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.37 (s, 1H), 8.32 (s, 1H), 7.55 (d, J = 8.40 Hz, 1H), 7.33 (t, J = 8.40 Hz, 1H), 6.72 (s, 2H), 5.55 (t, J = 2.80 Hz, 1H), 3.78-3.68 (m, 3H), 3.56-3.51 (m, 1H), 2.95-2.85 (m, 1H), 2.69-2.60 (m, 4H), 1.00 (s, 6H).

Step 13: **Synthesis of 1-(6-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-3,3-dimethyl-1,2,3,6-tetrahydropyridin-4-yl)-4-amino-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione**

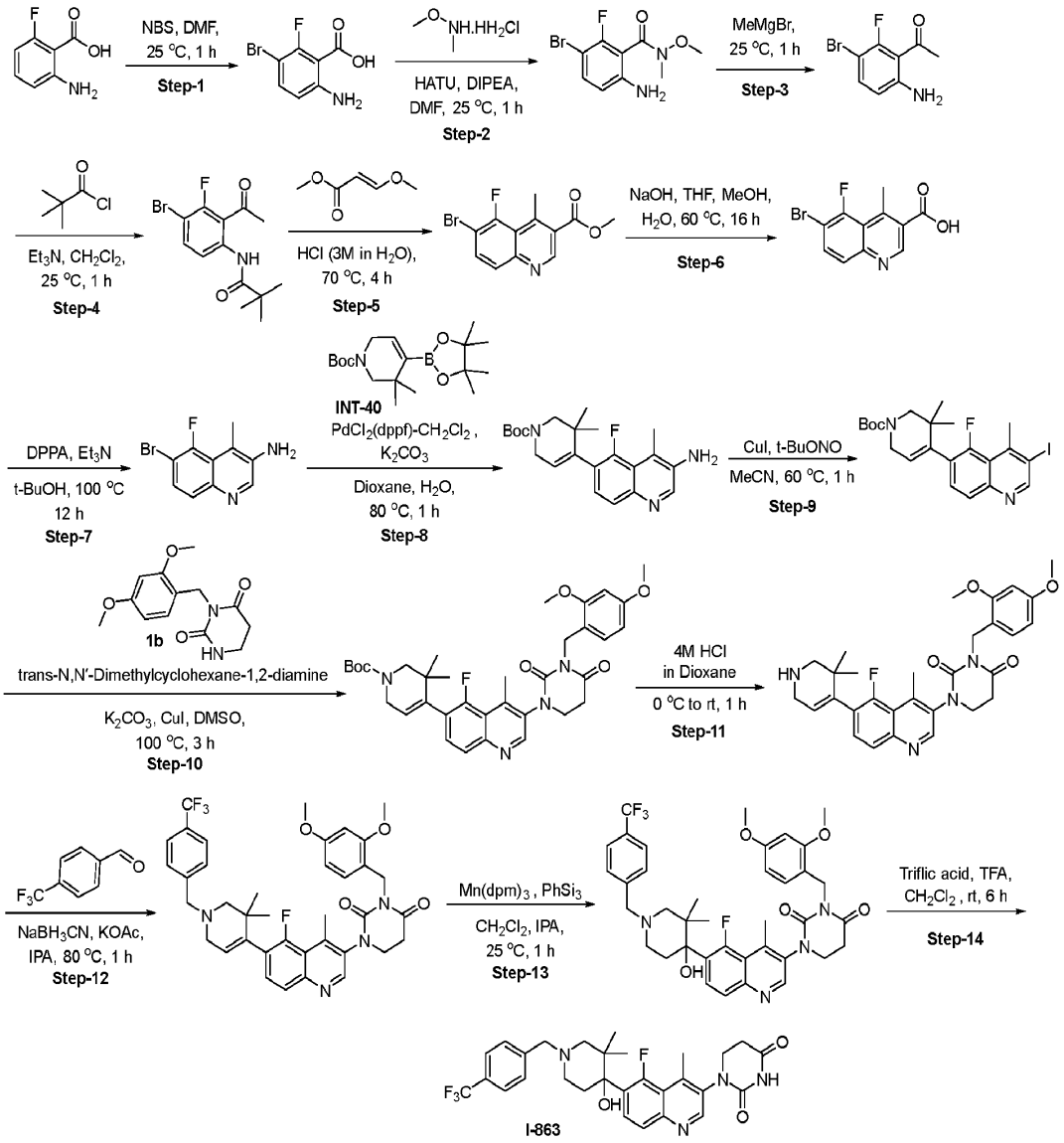
A mixture of 1-(4-amino-6-(3,3-dimethyl-1,2,3,6-tetrahydropyridin-4-yl)-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (35 mg, 0.091 mmol), 4-(1,2,4-oxadiazol-3-yl)benzaldehyde

(**74a**, 16 mg, 0.091 mmol), potassium acetate (26.9 mg, 0.274 mmol) and 2-propanol (1.5 mL) was stirred at rt for 1 h. Sodium cyanoborohydride (17.2 mg, 0.274 mmol) was then added and the reaction mixture was stirred at 60 °C for 1 h. The cooled reaction mixture was partitioned between water and 10% IPA/DCM, and the organic layer was collected and concentrated under reduced pressure. The crude residue was triturated with hexane and collected via filtration to afford 1-(6-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-3,3-dimethyl-1,2,3,6-tetrahydropyridin-4-yl)-4-amino-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (40 mg, 0.039 mmol). LCMS m/z MM-ES+APCI, Positive $[M+H]^+$ = 542.3.

Step 14: **Synthesis of 1-(6-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-amino-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-879)**

To a stirred solution of 1-(6-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-3,3-dimethyl-1,2,3,6-tetrahydropyridin-4-yl)-4-amino-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (40 mg, 0.074 mmol) in DCM (2 mL) and 2-propanol (1 mL) at 0 °C was added phenylsilane (0.028 mL, 0.22 mmol) followed by $Mn(dpm)_3$ (22.3 mg, 0.037 mmol) and the reaction mixture was stirred at rt for 1 h. Water was added and the mixture was extracted with DCM. The combined extracts were concentrated under reduced pressure, and the residue was purified by preparative-HPLC [Method info: (Column: X SELECT C18 (19 x 250 mm), 5 µm), eluting with Mobile phase A: 0.05% ammonium acetate in water, Mobile phase B: Acetonitrile, flow rate: 15 mL/min] to afford 1-(6-(1-(4-(1,2,4-oxadiazol-3-yl)benzyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-4-amino-5-fluoroquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-879) (0.81 mg, 1.4 µmol, 2% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 560.3; ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.37 (s, 1H), 9.70 (s, 1H), 8.30 (s, 1H), 8.03 (d, J = 8.00 Hz, 2H), 7.94 (t, J = 6.20 Hz, 1H), 7.55-7.59 (m, 3H), 6.71 (s, 2H), 5.06 (s, 1H), 3.50-3.76 (m, 4H), 2.65-2.70 (m, 2H), 1.56-1.75 (m, 6H), 1.04 (s, 3H), 0.68 (s, 3H).

Example 248: Synthesis of 1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)-4-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-863)



Step 1: **Synthesis of 6-amino-3-bromo-2-fluorobenzoic acid**

6-Amino-3-bromo-2-fluorobenzoic acid was prepared in **Example 247, I-879, Step 1.**

Step 2: **Synthesis of 6-amino-3-bromo-2-fluoro-N-methoxy-N-methylbenzamide**

To a stirred solution of 6-amino-3-bromo-2-fluorobenzoic acid (100 g, 427 mmol) in N,N-dimethylformamide (500 mL) 0°C were added DIPEA (166 g, 1282 mmol) and HATU (325 g, 855 mmol). After 30 min, N,O-dimethylhydroxylamine hydrochloride (62.5 g, 641 mmol) was added and the mixture was stirred at rt for 16 h. The reaction mixture was concentrated, then ice-cold water (3 L) was added and the mixture was extracted with 10% MeOH in DCM (2 x 1000 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was purified by

silica gel column chromatography, eluting with 40% EtOAc in hexanes to afford 6-amino-3-bromo-2-fluoro-N-methoxy-N-methylbenzamide (65 g, 167 mmol, 39% yield). LCMS m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ = 277.0, 278.9; ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.30 (d, J = 8.40 Hz, 1H), 6.50 (d, J = 8.80 Hz, 1H), 5.55 (s, 2H), 3.52 (s, 3H), 3.26 (s, 3H).

Step 3: **Synthesis of 1-(6-amino-3-bromo-2-fluorophenyl)ethan-1-one**

To a stirred solution of 6-amino-3-bromo-2-fluoro-N-methoxy-N-methylbenzamide (60 g, 217 mmol) in THF (600 mL) at rt was added methylmagnesium bromide (1.4 M in THF) (619 mL, 866 mmol) and the mixture was stirred at rt for 1 h. Ammonium chloride was added and the mixture was extracted with EtOAc. The combined organic layers were concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography, eluting with 0-10% EtOAc in hexane to afford 1-(6-amino-3-bromo-2-fluorophenyl)ethan-1-one (14.8 g, 63.8 mmol, 30% yield). LCMS m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ = 232.1, 234.3; ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.45-7.40 (m, 3H), 6.60 (d, J = 8.80 Hz, 1H), 2.51 (s, 3H).

Step 4: **Synthesis of N-(2-acetyl-4-bromo-3-fluorophenyl)pivalamide**

To a stirred solution of 1-(6-amino-3-bromo-2-fluorophenyl)ethan-1-one (2 g, 8.62 mmol) and triethylamine (1.80 mL, 12.9 mmol) in dichloromethane (30 mL) at 0°C was added pivaloyl chloride (1.161 mL, 9.48 mmol) and the mixture was stirred at 30°C for 1 h. Aqueous $NaHCO_3$ solution (50 mL) was added and the mixture was extracted with DCM (2 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 filtered and concentrated. The crude residue was purified by silica gel chromatography, eluting with 30% EtOAc in hexanes to afford N-(2-acetyl-4-bromo-3-fluorophenyl)-pivalamide (2 g, 5.95 mmol, 69% yield). LCMS m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ = 315.9, 318.0; ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.10 (s, 1H), 7.81 (m, 1H), 7.61 (d, J = 8.80 Hz, 1H), 2.53 (s, 3H), 1.18 (s, 9H).

Step 5: **Synthesis of methyl 6-bromo-5-fluoro-4-methylquinoline-3-carboxylate**

A mixture of N-(2-acetyl-4-bromo-3-fluorophenyl)pivalamide (2 g, 6.33 mmol), methyl (*E*)-3-methoxyacrylate (1.10 g, 9.49 mmol), MeOH (20 mL), and 3M HCl (aq) (10.5 mL, 31.6 mmol) was stirred at 70°C for 4 h. The mixture was concentrated under reduced pressure, and the residue was purified by reverse phase chromatography on a C18 column, eluting with 0.1% FA in H_2O and MeCN to afford methyl 6-bromo-5-fluoro-4-methylquinoline-3-carboxylate (0.8 g, 1.89 mmol, 30% yield). LCMS m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ = 297.9, 299.9; ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.07 (s, 1H), 8.12 (d, J = 9.20 Hz, 1H), 7.37 (d, J = 4.40 Hz, 1H), 3.98 (s, 3H), 2.95 (s, 3H).

Step 6: **Synthesis of 6-bromo-5-fluoro-4-methylquinoline-3-carboxylic acid**

A mixture of methyl 6-bromo-5-fluoro-4-methylquinoline-3-carboxylate (800 mg, 2.68 mmol), NaOH (215 mg, 5.37 mmol), THF (10 mL), MeOH (2 mL) and H_2O (2 mL) was stirred at 60 °C for 16 h.

The cooled reaction mixture was concentrated, diluted with water (50 mL), amd extracted with MTBE (2 x 25 mL). The aqueous layer was acidified with 1 N HCl resulting in a solid precipitate, which was collected via filtration to afford 6-bromo-5-fluoro-4-methylquinoline-3-carboxylic acid (0.65 g, 2.3 mmol, 85% yield). LCMS m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ = 283.9, 285.9; ^{1}H-NMR (400 MHz, DMSO-d6): δ 13.54 (s, 1H), 9.05 (s, 1H), 8.05 (d, J = 8.40 Hz, 1H), 7.82 (d, J = 8.80 Hz, 1H), 2.95 (s, 3H).

Step 7: **Synthesis of 6-bromo-5-fluoro-4-methylquinolin-3-amine**

A mixture of 6-bromo-5-fluoro-4-methylquinoline-3-carboxylic acid (3 g, 10.6 mmol), tert-BuOH (50 mL), triethylamine (2.97 mL, 21.1 mmol), and diphenylphosphoryl azide (4.36 g, 15.8 mmol) was stirred at 100°C for 12 h. The cooled reaction mixture was concentrated under reduced pressure. The resulting crude residue was taken up in DCM (25 mL), then concentrated HCl (10 mL) was added and the mixture was stirred for 1 h. The pH of the mixture was adjusted to 8 with $NaHCO_3$, and then the mixture was extracted with DCM (2 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 filtered and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography eluting with 1% MeOH in DCM to afford 6-bromo-5-fluoro-4-methylquinolin-3-amine (0.95 g, 2.87 mmol, 27% yield). LCMS m/z MM-ES+APCI, Positive $[M+H, M+2+H]^+$ = 255.0, 257.1; ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.48 (s, 1H), 7.58 (d, J = 0.80 Hz, 1H), 7.50 (d, J = 7.60 Hz, 1H), 5.84 (s, 2H), 2.45 (s, 3H).

Step 8: **Synthesis of tert-butyl 4-(3-amino-5-fluoro-4-methylquinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate**

A stirred mixture of 6-bromo-5-fluoro-4-methylquinolin-3-amine (850 mg, 3.33 mmol), tert-butyl 3,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**INT-40**, 1120 mg, 3.33 mmol, potassium phosphate tribasic (707 mg, 3.33 mmol), 1,4-dioxane (15 mL) and water (1.5 mL) was sparged with nitrogen for 10 min, then $PdCl_2$(dppf)-CH_2Cl_2 adduct (272 mg, 0.333 mmol) was added, and the resulting reaction mixture was stirred at 100 °C for 3 h. The cooled reaction mixture was diluted with water (50 mL) and extracted with DCM (2 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel flash column chromatography, eluting with 4% MeOH in DCM to afford tert-butyl 4-(3-amino-5-fluoro-4-methylquinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (0.95 g, 1.85 mmol, 56% yield). LCMS m/z MM-ES+APCI, Positive $[M+H]^+$ = 386.3; ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.45 (s, 1H), 7.53 (d, J = 12.80 Hz, 1H), 7.02 (d, J = 8.00 Hz, 1H), 5.63 (s, 2H), 4.04-4.01 (m, 3H), 3.93 (s, 2H), 2.44 (s, 3H), 1.42 (s, 9H), 0.98 (s, 6H).

Step 9: **Synthesis of tert-butyl 4-(5-fluoro-3-iodo-4-methylquinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate**

To a stirred solution of *tert*-butyl nitrite (428 mg, 4.15 mmol) in acetonitrile (10 mL) was added copper(I) iodide (790 mg, 4.15 mmol) at rt and the mixture was stirred for 10 min. *Tert*-butyl 4-(3-amino-5-fluoro-4-methylquinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (800 mg, 2.08 mmol) was added and the mixture was stirred at 60 °C for 1 h. The cooled reaction mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 filtered and concentrated to dryness. The crude residue was purified by silica gel flash chromatography, eluting with 0-20% EtOAc in hexane to afford tert-butyl 4-(5-fluoro-3-iodo-4-methylquinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (290 mg, 0.51 mmol, 24% yield). LCMS m/z MM-ES+APCI, Positive $[M+H]^+$ = 497.3; ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.14 (s, 1H), 7.82 (d, J = 8.80 Hz, 1H), 7.41 (d, J = 8.00 Hz, 1H), 5.58 (t, J = 0.80 Hz, 1H), 4.12-4.10 (m, 2H), 3.46 (s, 2H), 3.03 (s, 3H), 1.52 (s, 9H), 1.07 (s, 6H).

Step 10: **Synthesis of tert-butyl 4-(3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydro-pyrimidin-1(2H)-yl)-5-fluoro-4-methylquinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate**

A stirred mixture of tert-butyl 4-(5-fluoro-3-iodo-4-methylquinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (180 mg, 0.363 mmol), 3-(2,4-dimethoxybenzyl) dihydropyrimidine-2,4(1H,3H)-dione ((**1b**, 144 mg, 0.544 mmol) and K_2CO_3 (150 mg, 1.088 mmol) in DMSO (12 mL) was sparged with nitrogen for 2 min. Then copper(I) iodide (34.5 mg, 0.181 mmol) was added, and the resulting reaction mixture was stirred at 100 °C for 3 h. The cooled reaction mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. This crude residue was purified by reverse phase chromatography on a C18 column, eluting with 50% acetonitrile in 0.1% FA in water to yield *tert*-butyl 4-(3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoro-4-methylquinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (85 mg, 0.120 mmol, 33% yield). LCMS m/z MM-ES+APCI, Positive $[M+H]^+$ = 633.6; ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.83 (s, 1H), 7.84 (d, J = 8.40 Hz, 1H), 7.53 (t, J = 8.00 Hz, 1H), 7.18 (d, J = 5.8 Hz, 1H), 6.97 (d, J = 9.60 Hz, 1H), 6.48 (d, J = 8.00 Hz, 1H), 5.59 (s, 1H), 4.80 (s, 2H), 4.02-3.91 (m, 3H), 3.80 (s, 6H), 3.11-3.06 (m, 4H), 2.65-2.64 (m, 4H), 1.46 (s, 9H), 1.00 (s, 6H).

Step 11: **Synthesis of 3-(2,4-dimethoxybenzyl)-1-(6-(3,3-dimethyl-1,2,3,6-tetrahydropyridin-4-yl)-5-fluoro-4-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione**

A solution of tert-butyl 4-(3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydro pyrimidin-1(2H)-yl)-5-fluoro-4-methylquinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2H)-carboxylate (60 mg, 0.084 mmol) in dichloromethane (1 mL) and HCl (4 M in 1,4-dioxane, 0.063 mL, 0.25 mmol) was stirred at rt for 1 h. The reaction mixture was concentrated under reduced pressure to afford 3-(2,4-dimethoxybenzyl)-1-(6-(3,3-dimethyl-1,2,3,6-tetrahydropyridin-4-yl)-5-fluoro-4-methyl quinolin-3-

yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl (50 mg, 0.075 mmol, 88% yield). LCMS m/z MM-ES+APCI, Positive $[M+H]^+$ = 532.8; ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.99 (s, 2H), 8.86 (s, 1H), 7.89 (d, J = 8.40 Hz, 1H), 7.51 (t, J = 8.00 Hz, 1H), 6.97 (d, J = 6.80 Hz, 1H), 6.56 (d, J = 2.40 Hz, 1H), 6.47 (d, J = 2.00 Hz, 1H), 5.65 (s, 1H), 4.80 (s, 2H), 3.98-3.90 (m, 2H), 3.78-3.70 (m, 6H), 3.59 (s, 6H), 2.10 (s, 3H), 1.13 (s, 6H).

Step 12: **Synthesis of 3-(2,4-dimethoxybenzyl)-1-(6-(3,3-dimethyl-1-(4-(trifluoromethyl)-benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-fluoro-4-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione**

A mixture of 3-(2,4-dimethoxybenzyl)-1-(6-(3,3-dimethyl-1,2,3,6-tetrahydro pyridin-4-yl)-5-fluoro-4-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl (50 mg, 0.080 mmol), 4-(trifluoromethyl)benzaldehyde (20.8 mg, 0.120 mmol), potassium acetate (23 mg, 0.24 mmol), 2-propanol (1 mL), and $NaCNBH_4$ (15.0 mg, 0.24 mmol) was stirred at 80 °C for 1 h. The cooled reaction mixture was diluted with water (20 mL) and extracted with 10% IPA in CH_2Cl_2 (2 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was purified by silica gel flash chromatography, eluting with 5% IPA in DCM to afford 3-(2,4-dimethoxybenzyl)-1-(6-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-fluoro-4-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (50 mg, 0.047 mmol, 59% yield). LCMS m/z MM-ES+APCI, Positive $[M+H]^+$ = 691.6; ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.82 (s, 1H), 8.13 (d, J = 1.20 Hz, 1H), 8.00 (d, J = 7.60 Hz, 1H), 7.86-7.83 (m, 1H), 7.61-7.79 (m, 3H), 7.59 (d, J = 2.40 Hz, 1H), 7.29 (d, J = 6.40 Hz, 1H), 6.98 (d, J = 8.40 Hz, 1H), 5.40 (t, J = 5.60 Hz, 1H), 4.62 (s, 2H), 3.73 (s, 6H), 3.10-3.06 (m, 2H), 2.23 (s, 3H), 1.03 (s, 6H).

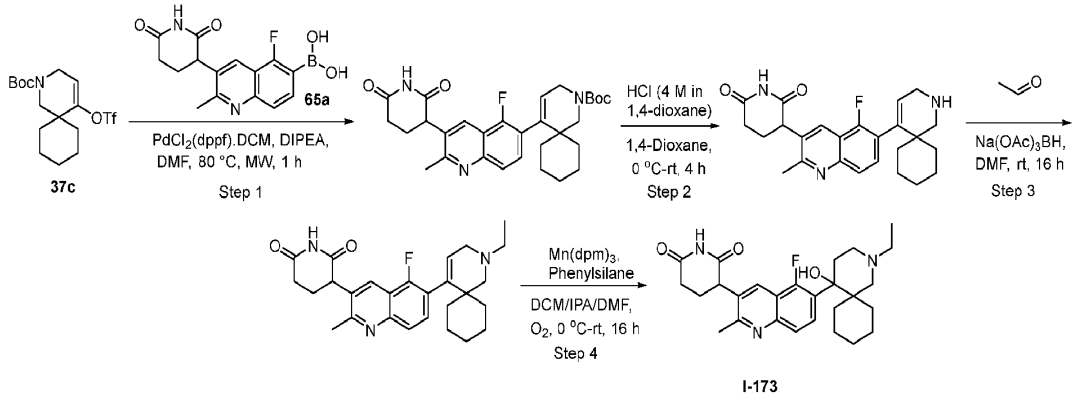
Step 13: **Synthesis of 3-(2,4-dimethoxybenzyl)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-methylquinolin-3-yl)dihydropyrimidine-2,4 (1H,3H)-dione**

3-(2,4-Dimethoxybenzyl)-1-(6-(3,3-dimethyl-1-(4-(trifluoromethyl) benzyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-fluoro-4-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (40 mg, 0.038 mmol) was treated according to **General Procedure 3, Step C**. The crude product was purified by reverse phase chromatography on a C18 column, eluting with 50% acetonitrile in 0.1% FA in water. The partially purified product was further purified by silica gel flash chromatography, eluting with 10% IPA in DCM to afford 3-(2,4-dimethoxybenzyl)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (18 mg, 0.011 mmol, 30% yield). LCMS m/z MM-ES+APCI, Positive $[M+H]^+$ = 709.6.

Step 14: **Synthesis of 1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)-4-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-863)**

To a stirred solution of 3-(2,4-dimethoxybenzyl)-1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-4-methylquinolin-3-yl)dihydropyrimidine-2,4-(1H,3H)-dione (18 mg, 0.011 mmol) and TFA (1.761 µl, 0.023 mmol) in DCM (2 mL) was added dropwise trifluoromethanesulfonic acid (2.0 µl, 0.023 mmol), and the resulting reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated, and the residue was purified by preparative-HPLC [Method info: (Column: X-Select C18 (19 x 250 mm), 5µm), eluting with Mobile phase A: 5 mM ammonium acetate in water, Mobile phase B: acetonitrile, flow rate=15 mL/min] to afford 1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)-4-methylquinolin-3-yl)dihydro pyrimidine-2,4(1H,3H)-dione (I-863) (0.8 mg, 1.4 µmol, 12% yield). LCMS m/z MM-ES+APCI, Positive $[M+H]^+$ = 559.2; ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.55 (s, 1H), 8.78 (s, 1H), 8.12 (t, J = 8.00 Hz, 1H), 7.83 (d, J = 9.20 Hz, 1H), 7.71 (d, J = 8.00 Hz, 2H), 7.61 (d, J = 8.00 Hz, 2H), 5.12 (s, 1H), 3.85-3.91 (m, 2H), 3.55-3.70 (m, 4H), 3.19 (s, 2H), 2.61-2.70 (m, 4H), 2.34 (s, 3H), 1.24 (s, 6H).

Example 249: Synthesis of 3-(6-(2-ethyl-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (I-173)



Step 1: **Synthesis of tert-butyl 5-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-2-azaspiro [5.5]undec-4-ene-2-carboxylate**

A mixture of (3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)boronic acid (**65a**, 250 mg, 0.79 mmol), *tert*-butyl 5-(((trifluoromethyl)sulfonyl)oxy)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (**37c**, 316 mg, 0.79 mmol), potassium phosphate, tribasic (165 mg, 0.95 mmol) and dioxane (5 mL) was sparged with nitrogen for 10 min at rt. $TPdCl_2(dppf)$-CH_2Cl_2 adduct (65 mg, 0.079 mmol) was added and the mixture was again sparged with nitrogen for 10 min. the mixture was sealed and stirred at 80 °C under microwave irradiation for 1 h. The cooled reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were concentrated under reduced pressure, and the crude residue was purified by silica gel flash chromatography, eluting with 0-80% EtOAc in hexane to afford *tert*-butyl 5-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylquinolin-6-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate

(400 mg, 0.54 mmol, 68%). LCMS m/z MM-ES+APCI, Positive $[M+H]^+$ 522.5; ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.96 (s, 1H), 8.30 (s, 1H), 7.74 (d, J = 3.60 Hz, 1H), 7.59-7.58 (m, 1H), 7.57-7.46 (m, 1H), 5.60-5.57 (m, 1H), 3.99 (s, 2H), 3.62 (s, 2H), 3.54 (s, 2H), 2.82 (t, J = 8.00 Hz, 1H), 2.68 (s, 3H), 2.12-2.11 (m, 1H), 1.56-1.46 (m, 10H), 0.75 (s, 9H).

Step 2: **Synthesis of 3-(5-fluoro-2-methyl-6-(2-azaspiro[5.5]undec-4-en-5-yl)quinolin-3-yl)piperidine-2,6-dione**

To a stirred solution of *tert*-butyl 5-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methyl-quinolin-6-yl)-2-azaspiro[5.5]undec-4-ene-2-carboxylate (600 mg, 1.15 mmol) in DCM (10 mL) at 0 °C was added HCl (4.0 M in 1,4-dioxane, 2.88 mL, 11.5 mmol) and the mixture was allowed to stir at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure, and the crude residue was triturated with MTBE (20 mL) and dried under vacuum to yield 3-(5-fluoro-2-methyl-6-(2-azaspiro[5.5]undec-4-en-5-yl)quinolin-3-yl)piperidine-2,6-dione, HCl (500 mg, 0.34 mmol, 29%). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 422.1; ^{1}H-NMR (400 MHz, DMSO-d6): δ 11.01 (s, 1H), 8.48 (s, 1H), 7.96-7.93 (m, 1H), 7.57-7.53 (m, 1H), 5.67 (s, 1H), 5.67 (s, 1H), 4.46-4.42 (m, 1H), 3.41-3.39 (m, 2H), 3.14 (s, 2H), 2.80 (s, 3H), 1.52-1.44 (m, 4H), 0.82-0.75 (m, 10H).

Step 3: **Synthesis of 3-(6-(2-ethyl-2-azaspiro[5.5]undec-4-en-5-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione**

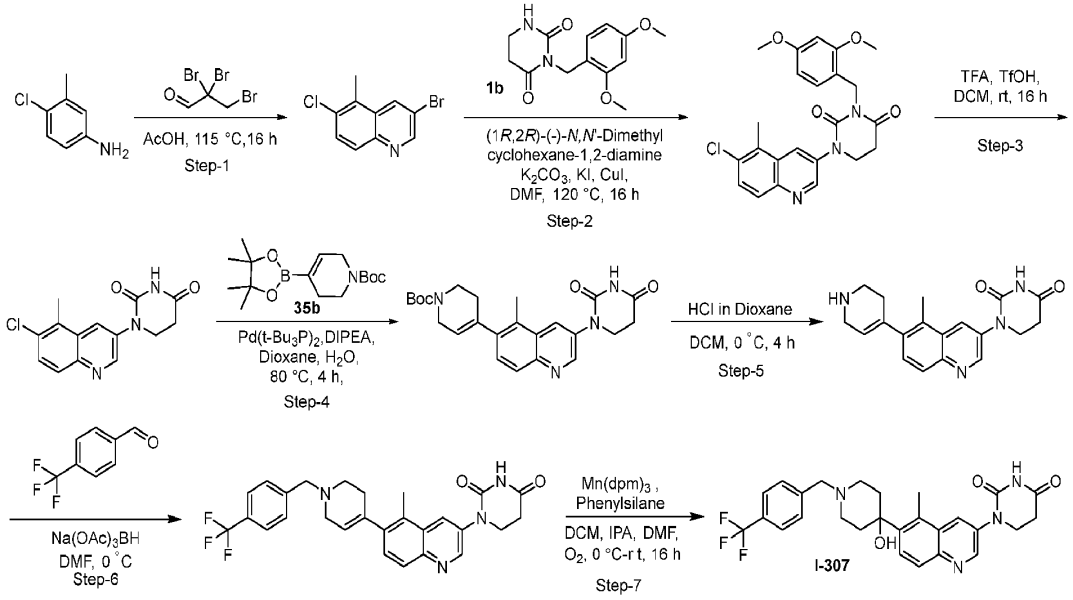
3-(5-Fluoro-2-methyl-6-(2-azaspiro[5.5]undec-4-en-5-yl)quinolin-3-yl)piperidine-2,6-dione (200 mg, 0.47 mmol) and acetaldehyde (0.027 mL, 0.47 mmol) were reacted with sodium triacetoxyborohydride according to **General Procedure 1, Step D**. The crude product was purified by reverse phase chromatography on a C18 column, eluting with acetonitrile and 0.1% FA in water to afford 3-(6-(2-ethyl-2-azaspiro[5.5]undec-4-en-5-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (80 mg, 0.10 mmol, 21%). LCMS m/z MM-ES+APCI, Positive $[M+H]^+$ 450.5.

Step 4: **Synthesis of 3-(6-(2-ethyl-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (I-173)**

3-(6-(2-ethyl-2-azaspiro[5.5]undec-4-en-5-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (51 mg, 0.113 mmol) was treated according to **General Procedure 3, Step C**. The reaction mixture was directly concentrated under reduced pressure, and the crude product was triturated with n-hexane and dried under vacuum. The crude product was further purified by preparative-HPLC [Method info: (Column: X Select C18 (150 mm × 19 mm), 5 µm, eluting with Mobile phase A: 0.1% HCl in water, and Mobile phase B: acetonitrile, flow rate: 10 mL/min] to afford 3-(6-(2-ethyl-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)-5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione, HCl (36 mg, 0.071 mmol, 29%). LCMS m/z MM-ES+APCI, Positive $[M+H]^+$ 468.4; ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.97 (s, 1H), 8.94 (br s, 1H). 8.28 (d, J = 5.60 Hz, 1H), 8.02 (t, J = 8.40 Hz, 1H), 7.82 (d, J = 8.80 Hz,

1H), 5.87 (s, 1H), 4.40-4.36 (m, 1H), 3.66 (d, J = 12.40 Hz, 1H), 3.29-3.20 (m, 4H), 2.85 (m, 1H), 2.68 (s, 4H), 2.68-2.60 (m, 1H), 2.34-2.33 (m, 1H), 2.12 (m, 1H), 1.96-1.93 (m, 2H), 1.46-1.32 (m, 10H), 0.96 (m, 3H).

Example 250: Synthesis of 1-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-methylquinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (I-307)



Step 1: **Synthesis of 3-bromo-6-chloro-5-methylquinoline**

A stirred solution of 4-chloro-3-methylaniline (2 g, 14.12 mmol) and 2,2,3-tribromopropanal (9.16 g, 31.1 mmol) in acetic acid (30 mL) was stirred at rt for 3 h, and then at 115 °C for 16 h. The cooled reaction mixture was concentrated under reduced pressure, and the crude residue was diluted with EtOAc and washed with water (2 x 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4 filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography, eluting with 3% EtOAc in hexanes to afford 3-bromo-6-chloro-5-methylquinoline (0.8 g, 14.1 mmol, 22% yield). LCMS: m/z MM-ES+APCI, POSITIVE $[M+H]^+$ 257.8. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.04-8.65 (m, 1H), 8.65-8.41 (m, 1H), 8.23 (d, J = 7.60 Hz, 1H), 7.65-7.62 (m, 1H), 2.52 (s, 3H).

Step 2: **Synthesis of 1-(6-chloro-5-methylquinolin-3-yl)-3-(2,4-dimethoxybenzyl)-dihydropyrimidine-2,4(1*H*,3*H*)-dione**

To a stirred solution of 3-bromo-6-chloro-5-methylquinoline (0.3 g, 1.17 mmol) in DMF (3 mL) under argon sparging was added 3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (**1b**, 0.309 g, 1.17 mmol), potassium carbonate (0.194 g, 1.40 mmol), and potassium iodide (0.233 g, 1.40 mmol), with sparging continued for 15 min. Copper (I) iodide (0.044 g, 0.23 mmol) and (1R,2R)-(-)-

N,N'-dimethylcyclohexane-1,2-diamine (0.033 g, 0.23 mmol) were added, and the reaction mixture was heated at 120 °C for 16 h. The cooled reaction mixture was filtered through a Celite bed, and the filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography eluting with 0-35% EtOAc in hexane to afford 1-(6-chloro-5-methylquinolin-3-yl)-3-(2,4-dimethoxybenzyl)-dihydropyrimidine-2,4(1H,3H)-dione (0.3 g, 1.17 mmol, 58% yield). LCMS: m/z MM-ES+APCI, POSITIVE $[M+H]^+$ 441.3. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.00 (dd, J = 1.60, 4.20 Hz, 1H), 8.64 (dd, J = 1.60, 8.80 Hz, 1H), 7.90 (s, 1H), 7.69 (d, J = 4.00 Hz, 1H), 7.11 (d, J = 9.20 Hz, 1H), 6.56-6.53 (m, 2H), 4.79 (s, 2H), 3.90 (s, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 3.02 (t, J = 6.40 Hz, 2H), 2.74 (s, 3H).

Step 3: **Synthesis of 1-(6-chloro-5-methylquinolin-3-yl)dihydropyrimidine-2,4(1*H*,3H)-dione**

To a stirred solution of 1-(6-chloro-5-methylquinolin-3-yl)-3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (0.3 g, 0.682 mmol) in DCM (3 mL) were added 2,2,2-trifluoroacetic acid (0.74 mL, 0.68 mmol) and trifluoromethanesulfonic acid (0.12 mL, 0.68 mmol) at 0 °C and the reaction mixture was stirred at rt for 16 h. The reaction mixture was concentrated under reduced pressure, and the crude residue was neutralized with sodium bicarbonate solution and extracted with EtOAc (2 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure to afford 1-(6-chloro-5-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (0.16 g, 0.50 mmol, 74% yield). LCMS: m/z MM-ES+APCI, POSITIVE $[M+H]^+$ 290.0. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.43 (s, 1H), 8.97 (dd, J = 1.60, 4.00 Hz, 1H), 8.64 (d, J = 7.20 Hz, 1H), 7.86 (s, 1H), 7.70-7.67 (m, 1H), 3.77 (t, J = 6.40 Hz, 2H), 2.80 (t, J = 6.40 Hz, 2H), 2.74 (s, 3H).

Step 4: **Synthesis of *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylquinolin-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate**

A stirred solution of 1-(6-chloro-5-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (120 mg, 0.41 mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**35b**, 128 mg, 0.414 mmol), and DIPEA (0.217 mL, 1.24 mmol) in 1,4-dioxane (5 mL) and water (0.5 mL) was sparged with nitrogen for 5 min. $Pd(t\text{-}Bu_3P)_2$ (21.2 mg, 0.041 mmol) was added and reaction mixture was stirred at 80 °C for 4 h. The cooled reaction mixture was concentrated under reduced pressure. The crude was purified by silica gel flash chromatography eluting with 0-70% EtOAc in hexane to afford tert-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-methyl-quinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (40 mg, 0.089 mmol, 39% yield). LCMS: MM-ES+APCI, POSITIVE $[M+H]^+$ m/z 437.4. ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.36 (s, 1H), 8.91 (d, J = 2.80 Hz, 1H), 8.57 (d, J = 1.60 Hz, 1H), 7.62 (dd, J = 4.00, 8.60 Hz, 1H), 7.55 (s, 1H), 5.69 (s, 1H), 4.03 (s, 2H), 3.80-3.60 (m, 4H), 2.79 (t, J = 6.40 Hz, 2H), 2.61 (s, 3H), 2.38 (t, J = 5.20 Hz, 2H), 1.31 (s, 9H).

Step 5: **Synthesis of 1-(5-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione**

To a stirred solution of *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methylquinolin-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (40 mg, 0.092 mmol) in 1,4-dioxane (2 mL) was added 4M HCl in 1,4-dioxane (0.18 mL, 0.73 mmol) at 0 °C. The mixture was stirred and allowed to warm to rt for 3 h. The reaction mixture was concentrated under reduced pressure to provide 1-(5-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, HCl LCMS: m/z MM-ES+APCI, POSITIVE $[M+H]^+$ 337.4. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.44 (s, 1H), 9.25 (s, 2H), 9.00 (d, J = 3.20 Hz, 1H), 8.73 (d, J = 7.60 Hz, 1H), 7.75-7.60 (m, 2H), 5.71 (s, 1H), 3.77-3.57 (m, 4H), 3.39 (t, J = 5.60 Hz, 2H), 2.82 (t, J = 6.40 Hz, 2H), 2.67 (s, 3H), 2.58-2.51 (m, 2H).

Step 6: **Synthesis of 1-(5-methyl-6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione**

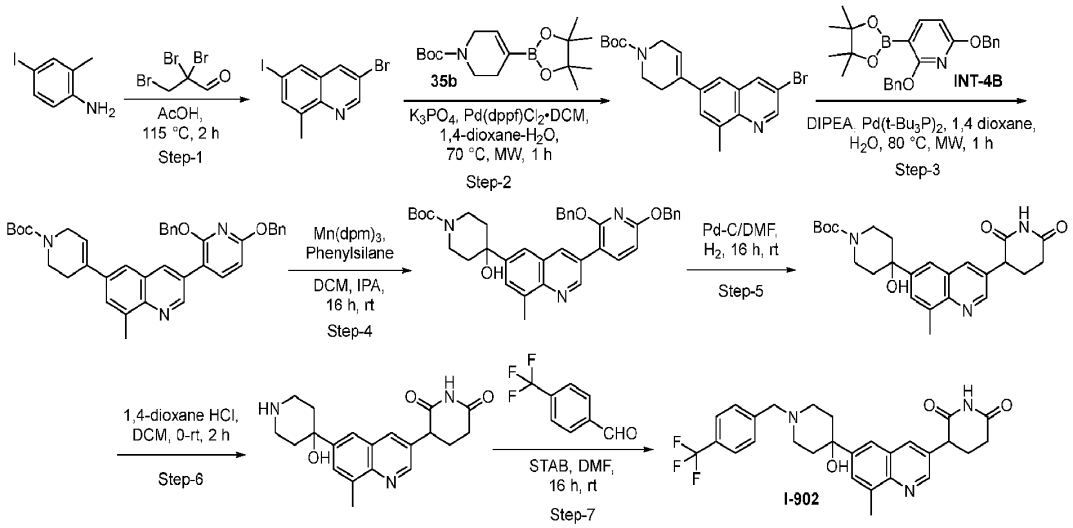
To a stirred solution of 1-(5-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione, HCl (0.032 g, 0.086 mmol) in DMF (2 mL) was added 4-(trifluoromethyl)benzaldehyde (0.014 mL, 0.103 mmol) and the mixture was stirred for 1 h at rt. Sodium triacetoxyborohydride (0.045 g, 0.215 mmol) was added in portions and the reaction mixture was stirred at rt for 16 h. The mixture was concentrated under reduced pressure, and the crude residue was purified by silica gel flash chromatography, eluting with 0-10% IPA in DCM to afford 1-(5-methyl-6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (25 mg, 0.045 mmol, 53% yield). LCMS: m/z MM-ES+APCI, POSITIVE $[M+H]^+$ 495.6.

Step 7: **Synthesis of 1-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-methylquinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (I-307)**

To a stirred solution of 1-(5-methyl-6-(1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (0.025 g, 0.051 mmol) in 2-propanol (5 mL) and DCM (1 mL) were added $Mn(dpm)_3$ (0.015 g, 0.025 mmol) and phenylsilane (0.012 mL, 0.101 mmol) at 0 °C and the reaction mixture was stirred at rt under 1 atmosphere O_2 for 16 h. The reaction mixture was quenched with saturated aqueous sodium thiosulphate (10 mL) and was then extracted with DCM (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by preparative-HPLC [Method info: (Column: ZORBAX C18 150 x 21.2), 7µm, eluting with Mobile phase A: 0.1 FA in H_2O:ACN, Mobile phase B: Acetonitrile, flow rate: 15 mL/min] to obtain 1-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-methylquinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (1.5 mg, 2.7 µmol, 5% yield). LCMS: m/z MM-ES+APCI, POSITIVE $[M+H]^+$ 513.3. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.32 (s, 1H), 8.89 (d, J = 1.60 Hz, 1H), 8.62 (d, J = 7.20 Hz, 1H), 8.48 (s, 1H), 7.91 (s, 1H), 7.70 (d, J = 8.00 Hz, 2H), 7.58 (d,

J = 4.40 Hz, 2H), 6.69 (s, 1H), 5.11 (s, 1H), 3.79-3.32 (m, 4H), 2.95 (s, 3H), 2.66-2.50 (m, 5H), 2.19-2.17 (m, 2H), 1.90 (d, 2H).

Example 251: Synthesis of 3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-8-methylquinolin-3-yl)piperidine-2,6-dione (I-902)



Step 1: **Synthesis of 3-bromo-6-iodo-8-methylquinoline**

A stirred solution of 4-iodo-2-methylaniline (5 g, 21.5 mmol) and 2,2,3-tribromopropanal (6.32 g, 21.5 mmol) in acetic acid (30 mL) was heated at 115 °C for 2 h. Saturated aqueous sodium bicarbonate (150 mL) was added and the mixture was extracted with EtOAc (2 × 75 mL). The combined organic layers were concentrated under reduced pressure, and the crude residue was purified by silica gel flash chromatography, eluting with 0-100% EtOAc in hexane to afford 3-bromo-6-iodo-8-methylquinoline (2.5 g, 5.3 mmol, 25% yield). LCMS: m/z MM-ES+APCI, POSITIVE $[M+H, M+2+H]^+$ 347.7, 349.6; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.00 (dd, *J* = 2.40, 7.60 Hz, 1H), 8.67 (dd, *J* = 2.00, 17.40 Hz, 1H), 8.29 (d, *J* = 1.60 Hz, 1H), 7.97 (d, *J* = 1.20 Hz, 1H), 2.68 (s, 3H).

Step 2: **Synthesis of *tert*-butyl 4-(3-bromo-8-methylquinolin-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate**

To a stirred solution of 3-bromo-6-iodo-8-methylquinoline (1 g, 2.87 mmol) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (**35b**, 0.355 g, 1.15 mmol) in 1,4-dioxane (10 mL) and water (1 mL) at rt was added tripotassium phosphate (1.22 g, 5.75 mmol) and the mixture was sparged with nitrogen for 10 min. Then was added $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.117 g, 0.144 mmol) and the mixture was again sparged with nitrogen for 10 min. The reaction vessel was sealed and the mixture heated with stirring under microwave irradiation at 70 °C for 1 h. The cooled mixture was filtered through a pad of Celite, rinsing with EtOAc (2 x 50 mL). The combined organic layers were concentrated under reduced pressure, and the crude residue was purified by silica gel

flash chromatography, eluting with 0-6% EtOAc in hexane to afford *tert*-butyl 4-(3-bromo-8-methylquinolin-6-yl)-3,6-dihydro-pyridine-1(2*H*)-carboxylate (340 mg, 0.79 mmol, 28% yield). LCMS: m/z MM-ES+APCI, POSITIVE $[M+2+H]^+$ 404.7; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.91 (d, J = 2.40 Hz, 1H), 8.65 (d, J = 2.40 Hz, 1H), 7.87 (s, 1H), 7.79 (s, 1H), 6.41 (s, 1H), 4.08 (m, 2H), 3.61-3.58 (m, 2H), 2.61 (s, 3H), 2.56 (m, 2H), 1.45 (s, 9H).

Step 3: **Synthesis of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-8-methylquinolin-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate**

To a stirred solution of tert-butyl 4-(3-bromo-8-methylquinolin-6-yl)-3,6-dihydro-pyridine-1(2H)-carboxylate (340 mg, 0.84 mmol) and 2,6-bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**INT-4B**, 352 mg, 0.843 mmol) in 1,4-dioxane (10.0 mL) and water (2.0 mL) was added DIPEA (0.294 mL, 1.686 mmol) at rt and the mixture was sparged with nitrogen for 10 min. Bis(tri-tert-butylphosphine)palladium(0) (21.5 mg, 0.042 mmol) was added and the mixture sparged again with nitrogen for 10 min. The reaction mixture was irradiated in a microwave at 80 °C for 1 h. The reaction mixture was filtered through a Celite pad and washed with EtOAc (2 × 50 mL). The organic layer was concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography, eluting with 25-30% EtOAc in hexanes as the eluent to provide tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-8-methylquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (320 mg, 0.508 mmol, 60% yield). LCMS: m/z MM-ES+APCI, POSITIVE $[M+H]^+$ 614.5. ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.07 (d, J = 2.00 Hz, 1H), 8.43 (d, J = 2.40 Hz, 1H), 7.97 (d, J = 8.00 Hz, 1H), 7.79 (dd, J = 13.20, Hz, 2H), 7.48-7.34 (m, 10H), 6.66 (d, J = 8.40 Hz, 1H), 6.39 (s, 1H), 5.45 (dd, J = 18.80, Hz, 4H), 4.08-4.01 (m, 4H), 3.61 (m, 2H), 2.68 (s, 3H), 1.45 (s, 9H).

Step 4: **Synthesis of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-8-methylquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate**

To a stirred solution of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-8-methylquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate (320 mg, 0.52 mmol) in DCM (20 mL)/IPA (10 mL) was added $Mn(dpm)_3$ (94 mg, 0.16 mmol), at 25 °C and the mixture was sparged with O_2 for 5 min. followed by addition of phenyl silane (0.162 mL, 1.30 mmol). The reaction mixture was stirred at rt under 1 atmosphere of oxygen for 16 h. The reaction mixture was filtered through a Celite pad and washed with EtOAc (2 x 50 mL). The combined filtrate was concentrated under reduced pressure, and the crude residue was purified by silica gel flash chromatography eluting with 30-35% EtOAc in hexanes to provide *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-8-methylquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (170 mg, 0.25 mmol, 47% yield). LCMS: m/z MM-ES+APCI, POSITIVE $[M+H]^+$ 632.7. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.08 (d, J = 2.40 Hz, 1H), 8.45 (d, J = 2.40 Hz, 1H), 7.97 (d, J = 8.00 Hz,

1H), 7.85 (s, 1H), 7.77 (s, 1H), 7.48-7.36 (m, 10H), 6.66 (d, *J* = 8.40 Hz, 1H), 5.76 (s, 1H), 5.45 (m, 4H), 3.93 (s, 2H), 2.74-2.73 (m, 4H), 1.94-1.91 (m, 2H), 1.44 (s, 9H), 1.08 (s, 3H).

Step 5: **Synthesis of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-8-methylquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate**

To a solution of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-8-methylquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (300 mg, 0.475 mmol) in DMF (5.0 mL) was added Pd/C (250 mg, 2.349 mmol), and the mixture was stirred under 1 atmosphere hydrogen pressure at rt for 16 h. The reaction mixture was filtered through celite, rinsing with EtOAc (2 x 25 mL). The combined filtrate was concentrated under reduced pressure to provide *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-8-methyl-quinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (200 mg, 0.410 mmol, 86% yield). LCMS: m/z MM-ES+APCI, POSITIVE $[M+H]^+$ 454.5. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.97 (s, 1H), 8.77 (d, *J* = 2.00 Hz, 1H), 8.15 (d, *J* = 2.00 Hz, 1H), 7.96-7.93 (m, 1H), 5.25 (s, 1H), 4.12 (m, 2H), 3.93 (m, 4H), 3.32-3.29 (m, 1H), 2.48-2.43 (m, 2H), 2.34-2.33 (m, 2H), 1.67 (d, *J* = 12.40 Hz, 2H), 1.43 (s, 9H), 1.41 (s, 3H).

Step 6: **Synthesis of 3-(6-(4-hydroxypiperidin-4-yl)-8-methylquinolin-3-yl)piperidine-2,6-dione**

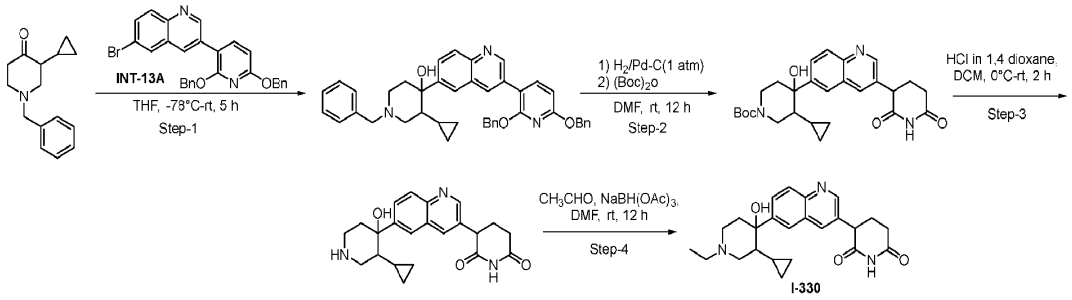
To a stirred solution of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-8-methylquinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (200 mg, 0.44 mmol) in DCM (10 mL) was added 4 M HCl in 1,4-dioxane (0.8 mL, 3.20 mmol) at 0 °C. The mixture was stirred and allowed to warm to rt over 2h. The reaction mixture was concentrated under reduced pressure to provide 3-(6-(4-hydroxypiperidin-4-yl)-8-methylquinolin-3-yl)piperidine-2,6-dione, HCl (150 mg, 0.32 mmol, 72% yield). LCMS: m/z MM-ES+APCI, POSITIVE $[M+H]^+$ 354.0. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 8.86 (d, *J* = 2.00 Hz, 1H), 8.79 (br s, 2H), 8.33 (s, 1H), 7.86 (s, 1H), 7.76 (s, 1H), 6.00 (s, 1H), 4.22-4.18 (m, 1H), 3.39-3.26 (m, 5H), 2.90-2.80 (m, 3H), 2.79 (s, 3H), 2.17-2.10 (m, 2H), 1.91-1.85 (m, 2H).

Step 7: **Synthesis of 3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-8-methylquinolin-3-yl)piperidine-2,6-dione (I-902)**

To a stirred solution of 3-(6-(4-hydroxypiperidin-4-yl)-8-methylquinolin-3-yl)piperidine-2,6-dione, HCl (150 mg, 0.39 mmol) in DMF (2.0 mL) was added 4-(trifluoromethyl)-benzaldehyde (80 mg, 0.46 mmol) and the mixture was stirred at rt for 1 h. Sodium triacetoxyborohydride (163 mg, 0.769 mmol) was added and the reaction mixture was stirred at rt for 16 h. The mixture was concentrated under reduced pressure, and the crude residue was purified by preparative-HPLC [Method info: (Column: X select (150 x19 mm), 5um, eluting with Mobile phase A: 0.1% HCl in H_2O, Mobile phase B: Acetonitrile, flow rate: 15 mL/min] to provide 3-(6-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-8-methylquinolin-3-yl)piperidine-2,6-dione, HCl (I-902) (44.1 mg, 0.080 mmol, 21% yield) LCMS: m/z MM-ES+APCI, POSITIVE $[M+H]^+$ 512.5. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 10.54 (br s, 1H), 8.83 (s, 1H), 8.26 (s, 1H), 7.88 (br s, 4H), 7.83 (s, 1H), 7.72 (s, 1H), 5.69 (br s, 1H), 4.54 (d, *J* = 5.20

Hz, 2H), 4.20-4.16 (m, 1H), 3.36 (br s, 4H), 2.77 (s, 3H), 2.64-2.61 (m, 2H), 2.60-2.59 (m, 1H), 2.46-2.41 (m, 1H), 2.46-2.41 (m, 1H), 1.93-1.89 (m, 2H).

Example 252: Synthesis of 3-(6-(3-cyclopropyl-1-ethyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-330)



Step 1: **Synthesis of 1-benzyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-cyclopropylpiperidin-4-ol**

1-benzyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-cyclopropylpiperidin-4-ol (290 mg, 0.421 mmol, 42% yield) was prepared from 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromoquinoline (**INT-13A**, 500 mg, 1.005 mmol) and 1-benzyl-3-cyclopropylpiperidin-4-one (prepared in Ex **240** Step 1, 300 mg, 1.307 mmol) according to **General Procedure 2, Step A**. The crude product was purified by silica gel flash chromatography, eluting with 0-50% EtOAc in hexanes. LCMS: ES+APCI, POSITIVE $[M+H]^+$ 648.9. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.04 (d, J = 2.40 Hz, 1H), 8.46 (d, J = 2.00 Hz, 1H), 8.07 (s, 1H), 7.98 (d, J = 8.40 Hz, 1H), 7.90-7.85 (m, 2H), 7.47-7.35 (m, 15H), 6.66 (d, J = 8.00 Hz, 1H), 5.45 (s, 4H), 5.01 (s, 1H), 3.60-3.55 (m, 1H), 3.37-3.32 (m, 1H), 2.68-2.65 (m, 2H), 2.51-2.49 (m, 1H), 2.37-2.33 (m, 1H), 1.46-1.30 (m, 1H), 1.20-1.16 (m, 1H), 0.98 (bs, 1H), 0.66-0.65 (m, 1H), 0.14-0.10 (m, 1H), -0.13--0.24 (m, 2H), -0.83--0.94 (m, 1H).

Step 2: **Synthesis of *tert*-butyl 3-cyclopropyl-4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxypiperidine-1-carboxylate**

To a stirred solution of 1-benzyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)quinolin-6-yl)-3-cyclopropylpiperidin-4-ol (280 mg, 0.432 mmol) in DMF (5 mL) was added Boc-anhydride (283 mg, 1.30 mmol) and Pd/C 10% (250 mg, 0.432 mmol), and the reaction mixture was stirred for 10 h at rt under 1 atmosphere hydrogen pressure. The reaction mixture was filtered through celite, rinsing with DMF and EtOAc. The combined filtrate was concentrated under reduced pressure, and the crude residue was purified by silica gel flash chromatography, eluting with IPA in DCM to afford *tert*-butyl 3-cyclopropyl-4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (90 mg, 0.19 mmol, 40% yield). LCMS: ES+APCI, POSITIVE $[M+H]^+$ 480.4. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.97 (s, 1H), 8.75 (d, J = 2.00 Hz, 1H), 8.18 (s, 1H), 8.03 (s, 1H), 7.92 (d, J = 9.20 Hz, 1H), 7.83 (d, J =

9.60 Hz, 1H), 5.31 (s, 1H), 4.17-4.12 (m, 1H), 3.89 (s, 1H), 3.20-3.15 (m, 2H), 2.90-2.81 (m, 1H), 2.78-2.74 (m, 1H), 2.67-2.62 (m, 1H), 2.16-2.03 (m, 1H), 1.63-1.59 (m, 1H), 1.44 (s, 11H), 1.11-0.84 (m, 2H), 0.65-0.63 (m, 1H), 0.12-0.10 (m, 1H), -0.13--0.24 (m, 2H), -0.83--0.94 (m, 1H).

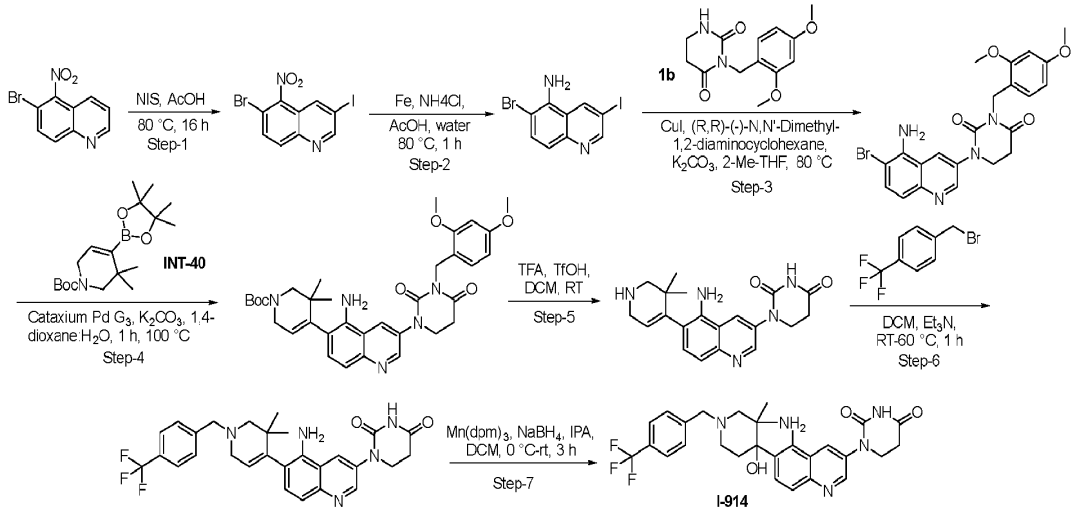
Step 3: **Synthesis of 3-(6-(3-cyclopropyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione**

To a stirred solution of *tert*-butyl 3-cyclopropyl-4-(3-(2,6-dioxopiperidin-3-yl)quinolin-6-yl)-4-hydroxypiperidine-1-carboxylate (80 mg, 0.17 mmol) in DCM (5 mL) was added 4M HCl in 1,4-dioxane (0.3 mL, 1.2 mmol) at 0 °C and reaction mixture was stirred for 2 h at 0 °C. The mixture was concentrated under reduced pressure, and the crude was washed with pentane to afford 3-(6-(3-cyclopropyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl (70 mg, 0.16 mmol, 97% yield). LCMS: ES+APCI, POSITIVE $[M+H]^+$ 380.3. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.04 (s, 1H), 9.01-8.95 (m, 3H), 8.61 (s, 1H), 8.16 (d, J = 8.40 Hz, 2H), 7.91 (d, J = 8.00 Hz, 1H), 5.76 (s, 1H), 4.28 (d, J = 4.40 Hz, 1H), 3.26-3.13 (m, 5H), 2.90-2.86 (m, 1H), 2.77-2.74 (m, 1H), 2.34-2.20 (m, 1H), 1.82-1.79 (m, 1H), 1.60-1.57 (m, 1H), 1.11-1.08 (m, 1H), 0.87-0.68 (m, 1H), 0.25-0.23 (m, 2H), -0.12--0.24 (m, 2H), -0.83--0.86 (m, 1H).

Step 4: **Synthesis of 3-(6-(3-cyclopropyl-1-ethyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-330)**

A mixture of 3-(6-(3-cyclopropyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl (60 mg, 0.14 mmol) DMF (2 mL) and acetaldehyde (12.7 mg, 0.29 mmol) was stirred at rt for 1 h. To this mixture was added sodium triacetoxyborohydride (92 mg, 0.433 mmol) and the reaction mixture was stirred at rt for 6 h. The mixture was concentrated under reduced pressure, and the crude residue was triturated with MTBE/pentane to give a crude solid. The crude solid was further purified by reverse phase chromatography using a C-18 column, eluting with acetonitrile in 0.1% FA in H_2O to afford 3-(6-(3-cyclopropyl-1-ethyl-4-hydroxypiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, formic acid (**I-330,** 5.8 mg, 0.013 mmol, 9% yield). LCMS: ES+APCI, POSITIVE $[M+H]^+$ 408.5. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.97 (s, 1H), 8.74 (d, J = 2.00 Hz, 1H), 8.18 (s, 2H), 8.03 (s, 1H), 7.93 (d, J = 8.80 Hz, 1H), 7.81 (d, J = 8.80 Hz, 1H), 5.07 (s, 1H), 4.17-4.12 (m, 1H), 2.81-2.75 (m, 3H), 2.68-2.64 (m, 1H), 2.63-2.59 (m, 2H), 2.19-2.16 (m, 2H), 1.66-1.63 (m, 1H), 1.28-1.24 (m, 1H), 1.13 (t, J = 7.20 Hz, 3H), 0.87-0.68 (m, 1H), 0.25-0.23 (m, 2H), -0.12--0.24 (m, 2H), -0.83--0.86 (m, H).

Example 253: Synthesis of 1-(5-amino-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)-benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-914)



Step 1: **Synthesis of 6-bromo-3-iodo-5-nitroquinoline**

To a stirred solution of 6-bromo-5-nitroquinoline (2.5 g, 9.88 mmol) in acetic acid (20 mL) was added N-iodosuccinimide (6.67 g, 29.6 mmol) at rt. The resulting reaction mixture was stirred at 80 °C for 16 h. The cooled reaction mixture was filtered through a Celite bed, rinsing with EtOAc (60 mL), and the combined filtrate was washed with water (30 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography, eluting with 30-40% EtOAc in hexanes to afford 6-bromo-3-iodo-5-nitroquinoline (1.8 g, 4.32 mmol, 44% yield). LCMS: m/z MM-ES+APCI, Positive [M+H, M+2+H]+ = 378.9, 380.8. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.18 (d, J = 1.60 Hz, 1H), 8.43 (d, J = 1.20 Hz, 1H), 8.12 (d, J = 9.20 Hz, 1H), 7.95 (d, J = 9.20 Hz, 1H).

Step 2: **Synthesis of 6-bromo-3-iodoquinolin-5-amine**

A stirred mixture of 6-bromo-3-iodo-5-nitroquinoline (3.5 g, 9.24 mmol), acetic acid (30 mL), water (3 mL), iron powder (3.09 g, 55.4 mmol), and ammonium chloride (0.99 g, 18.5 mmol) was stirred at 80 °C for 1h. The cooled reaction mixture was concentrated under reduced pressure. The crude residue was taken up in 10% IPA in DCM (40 mL) then washed with water (10 mL). The organic layer was concentrated under reduced pressure, and the crude residue was purified by silica gel flash chromatography, eluting with 0-100% EtOAc in hexane to afford 6-bromo-3-iodoquinolin-5-amine (1.7 g, 4.7 mmol, 51% yield). LCMS m/z MM-ES+APCI, POSITIVE $[M+H, M+2+H]^+$ = 349.7, 351.7; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.15 (d, J = 1.20 Hz, 1H), 8.96 (d, J = 2.00 Hz, 1H), 7.71 (d, J = 8.80 Hz, 1H), 7.12 (d, J = 8.80 Hz, 1H), 6.24 (s, 2H),

Step 3: **Synthesis of 1-(5-amino-6-bromoquinolin-3-yl)-3-(2,4-dimethoxybenzyl)-dihydropyrimidine-2,4(1*H*,3*H*)-dione**

To a stirred solution of 6-bromo-3-iodoquinolin-5-amine (500 mg, 1.43 mmol) in 2-methyl tetrahydrofuran (10 mL) at rt was added 3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (**1b**, 379 mg, 1.433 mmol) and potassium carbonate (K_2CO_3, 297 mg, 2.149 mmol) and the mixture was sparged with nitrogen for 10 min. To the reaction mixture were added copper(I) iodide (27.3 mg, 0.143 mmol) and (R,R)-(-)-N,N-dimethyl-1,2-cyclohexane-diamine (20.4 mg, 0.143 mmol), then the mixture was again sparged with nitrogen for 5 min. The reaction mixture was stirred at 80 °C for 2 h. The cooled reaction mixture was filtered through Celite, rinsing with EtOAc (80 mL). The combined filtrate was washed with water (30 mL), dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography on alumina, eluting with 70-80% EtOAc in hexane to afford 1-(5-amino-6-bromoquinolin-3-yl)-3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (0.5 g, 2.81 mmol, 69% yield). LCMS: m/z MM-ES+APCI, POSITIVE $[M+H, M+2+H]^+$ = 485.1, 487.0. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.87 (d, J = 2.40 Hz, 1H), 8.59 (d, J = 2.00 Hz, 1H), 7.67 (d, J = 8.80 Hz, 1H), 7.17 (d, J = 8.80 Hz, 1H), 6.94 (d, J = 8.40 Hz, 1H), 6.56 (d, J = 2.00 Hz, 1H), 6.46 (d, J = 2.40 Hz, 1H), 6.16 (s, 2H), 4.82 (s, 2H), 4.03 (t, J = 6.40 Hz, 2H), 3.79 (s, 3H), 3.75 (s, 3H), 3.03 (t, J = 6.40 Hz, 2H).

Step 4: **Synthesis of *tert*-butyl 4-(5-amino-3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)quinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2*H*)-carboxylate**

To a stirred solution of 1-(5-amino-6-bromoquinolin-3-yl)-3-(2,4-dimethoxybenzyl)-dihydropyrimidine-2,4(1H,3H)-dione (0.5 g, 1.03 mmol) and *tert*-butyl 3,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (**INT-40**, 0.347 g, 1.03 mmol) in 1,4-dioxane (5 mL) was added a solution of K_2CO_3 (0.142 g, 1.03 mmol) in water 2 (0.5 mL), followed by cataCXium A PdG3 (0.075 g, 0.103 mmol). The mixture was sparged with nitrogen, then was stirred at 100 °C for 1 h. The cooled reaction mixture was filtered through Celite, rinsing with 10% IPA in DCM. The combined filtrate was washed with water (100 mL), dried over Na_2SO_4 and concentrated. The crude residue was purified by reverse phase chromatography on a C18 column, eluting with 70% ACN in 0.05% FA in water to provide *tert*-butyl 4-(5-amino-3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)quinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2*H*)-carboxylate (0.2 g, 0.32 mmol, 24% yield). LCMS: m/z MM-ES+APCI, Positive $[M+1]^+$ = 616.9.

Step 5: **Synthesis of 1-(5-amino-6-(3,3-dimethyl-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione**

To a stirred solution of *tert*-butyl 4-(5-amino-3-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)quinolin-6-yl)-3,3-dimethyl-3,6-dihydropyridine-1(2*H*)-carboxylate (200 mg, 0.32 mmol) in DCM (4 mL) was added TFA (0.2 mL, 2.60 mmol) and triflic acid (0.2 mL, 2.3 mmol) under a nitrogen atmosphere at rt. The reaction mixture was stirred at 80°C for 1 h. The mixture was

concentrated under reduced pressure to provide 1-(5-amino-6-(3,3-dimethyl-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione, TFA (0.15 g, 0.31 mmol). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ = 366.2.

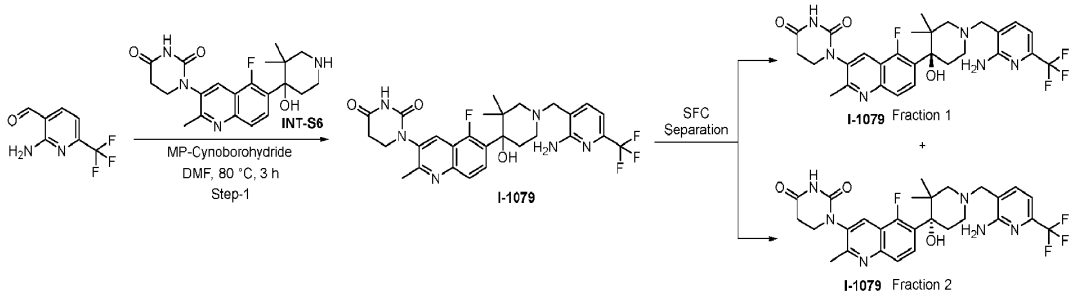
Step 6: **Synthesis of 1-(5-amino-6-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione**

To a stirred solution of 1-(5-amino-6-(3,3-dimethyl-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione, TFA (0.15 g, 0.313 mmol) in DCM (2 mL) were added 1-(bromomethyl)-4-(trifluoromethyl)benzene (0.090 g, 0.38 mmol) and TEA (0.16 g, 1.56 mmol) and the mixture was stirred at 60 °C for 1 h in a pressure vessel. The cooled reaction mixture was diluted with water (25 mL) and extracted with 10% IPA in DCM. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was purified by silica gel column chromatography, eluting with 10% IPA in DCM to provide 1-(5-amino-6-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (100 mg, 0.13 mmol, 43% yield). LCMS: m/z MM-ES+APCI, Positive $[M+1]^+$ = 524.3.

Step 7: **Synthesis of 1-(5-amino-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (I-914)**

1-(5-amino-6-(3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (100 mg, 0.134 mmol) was treated according to **General Procedure 3, Step C**. The crude product was purified by preparative-HPLC [Method info: (Column: Zorbax C18 (150 ×21.2mm), 5µm, eluting with Mobile phase B: 0.1% acetic acid in water, Mobile phase B: acetonitrile, flow rate: 15.0 mL/min] to afford 1-(5-amino-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (0.98 mg, 1.7 µmol, 1% yield). LCMS: m/z MM-ES+APCI, POSITIVE $[M+1]^+$ = 542.3. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.54 (s, 1H), 8.77 (d, J = 2.00 Hz, 1H), 8.41 (d, J = 2.00 Hz, 1H), 7.71 (d, J = 8.00 Hz, 2H), 7.60 (d, J = 8.00 Hz, 2H), 7.44 (d, J = 9.20 Hz, 1H), 7.15 (d, J = 8.80 Hz, 1H), 6.62 (s, 1H), 5.46 (s, 1H), 5.33 (s, 1H), 3.94 (t, J = 6.80 Hz, 2H), 3.63-3.61 (m, 3H), 3.41-3.39 (m, 2H), 2.09-1.98 (m, 3H), 1.77-1.72 (m, 1H), 1.54-1.49 (m, 1H), 1.00 (s, 3H), 0.85 (s, 3H).

Example 254: Synthesis of 1-(6-(1-((2-amino-6-(trifluoromethyl)pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (I-1079), R)-1-(6-(1-((2-amino-6-(trifluoromethyl)pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (I-1079-peak1) **and (S) 1-(6-(1-((2-amino-6-(trifluoromethyl)pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione** (I-1079-peak2)



Step 1: **Synthesis of 1-(6-(1-((2-amino-6-(trifluoromethyl)pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione**

To a stirred solution of 1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (**INT-S6**, 100 mg, 0.25 mmol) and 2-amino-6-(trifluoromethyl)nicotinaldehyde (48 mg, 0.25 mmol) in DMF (0.5 mL) was added MP-cyanoborohydride (100 mg, 0.25 mmol), and the reaction mixture was stirred for 1 h at 80 °C. The reaction mixture was concentrated under reduced pressure, and the crude residue was purified by preparative-HPLC [Method info: (Column: Shim-pack C18 (20 x 250 mm), 5µm, eluting with Mobile phase A: 5 mM ammonium acetate in water, Mobile phase B: acetonitrile, flow rate: 15 mL/min] to afford 1-(6-(1-((2-amino-6-(trifluoromethyl)pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (21.6 mg, 0.037 mmol, 15% yield). LCMS: ES+APCI, POSITIVE $[M+H]^+$ 575.4, ^{1}H-NMR (400 MHz, DMSO-d_6): ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.55 (s, 1H), 8.42 (s, 1H), 8.09 (t, J = 8.80 Hz, 1H), 7.79 (d, J = 9.20 Hz, 1H), 7.57 (d, J = 7.20 Hz, 1H), 6.96 (d, J = 7.20 Hz, 1H), 6.80 (s, 2H), 5.22 (d, J = 9.20 Hz, 2H), 3.99-3.97 (m, 1H), 3.71-3.68 (m, 1H), 3.48 (s, 2H), 3.33-3.11 (m, 1H), 2.88-2.80 (m, 1H), 2.79-2.67 (m, 1H), 2.65 (s, 3H), 2.54-2.51 (m, 1H), 2.35-2.33 (m, 1H), 1.76-1.71 (m, 1H), 1.24 (s, 1H), 0.98 (s, 3H), 0.97 (s, 3H).

Step 2: **Chiral SFC Separation of (R)-1-(6-(1-((2-amino-6-(trifluoromethyl)pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione and (S) 1-(6-(1-((2-amino-6-(trifluoromethyl)pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione**

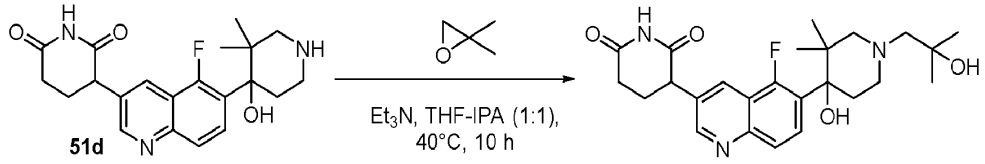
1-(6-(1-((2-amino-6-(trifluoromethyl)pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione was subjected to chiral SFC chromatography using methods similar those disclosed for other examples. Two fractions obtained after chiral SFC chromatography were collected separately and lyophilized. Each fraction was separately further purified by preparative-HPLC [Method info: (Column: Shim-pack C18 (20 x 250 mm)), 5µm, eluting with Mobile phase A: 0.1% FA in Water, Mobile phase B: Acetonitrile, flow rate: 15 mL/min].

Fraction 1 (**I-1079,** Peak-1): (*R*)-1-(6-(1-((2-amino-6-(trifluoromethyl)pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (4.1 mg, 7.1 µmol, 20 % yield). LCMS: ES+APCI, POSITIVE $[M+H]^+$ 575.2, ^{1}H-NMR (400 MHz, DMSO-d_6): ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.55 (s, 1H), 8.42 (s, 1H), 8.09 (t, *J* = 8.80 Hz, 1H), 7.79 (d, *J* = 9.20 Hz, 1H), 7.57 (d, *J* = 7.20 Hz, 1H), 6.96 (d, *J* = 7.60 Hz, 1H), 6.80 (s, 2H), 5.22 (d, *J* = 8.80 Hz, 1H), 4.01-3.98 (m, 1H), 3.71-3.68 (m, 1H), 3.48 (s, 2H), 3.48-3.12 (m, 1H), 2.88-2.85 (m, 1H), 2.85-2.75 (m, 1H), 2.69-2.65 (m, 1H), 2.63 (s, 3H), 2.54-2.51 (m, 1H), 2.34 (d, *J* = 2.00 Hz, 1H), 1.74-1.71 (m, 1H), 1.24 (s, 1H), 0.98 (s, 3H), 0.70 (s, 3H)

Fraction 2 (**I-1079**, Peak-2): (*S*)-1-(6-(1-((2-amino-6-(trifluoromethyl)pyridin-3-yl)methyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)-5-fluoro-2-methylquinolin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (4.1 mg, 7.1 µmol, 20 % yield). LCMS: ES+APCI, POSITIVE $[M+H]^+$ 575.4, ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.55 (s, 1H), 8.38 (s, 2H), 8.09 (t, *J* = 8.80 Hz, 1H), 7.79 (d, *J* = 8.80 Hz, 1H), 7.57 (d, *J* = 7.20 Hz, 1H), 6.96 (d, *J* = 7.20 Hz, 1H), 6.80 (s, 2H), 6.60 (s, 1H), 5.22 (d, J = 9.20 Hz, 1H), 3.99 (m, 1H), 3.70-3.47 (m, 2H), 3.32-3.21 (m, 1H), 2.88-2.80 (m, 2H), 2.79-2.75 (m, 1H), 2.68 (s, 3H), 2.34-2.33 (m, 1H), 1.74-1.71 (m, 1H), 1.24 (s, 1H), 0.97 (s, 3H), 0.70 (s, 3H).

Note: Absolute stereochemistry was assigned arbitrarily.

Example 255: Synthesis of 3-(5-fluoro-6-(4-hydroxy-1-(2-hydroxy-2-methylpropyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-217)

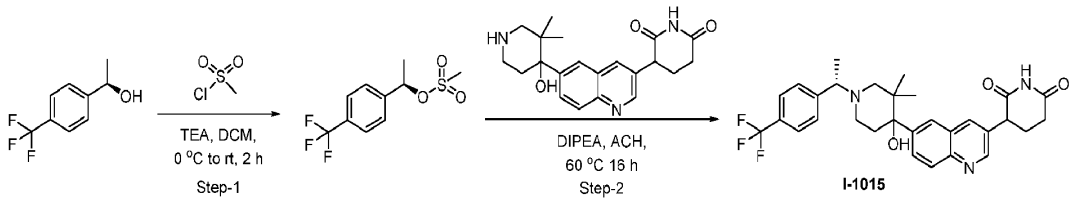


I-217

To a stirred solution of 3-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, HCl (**51d**, 50 mg, 0.119 mmol) in tetrahydrofuran (2 mL) and 2-propanol (2 mL) was added triethylamine (TEA, 36.0 mg, 0.36 mmol) at 25 °C and the mixture was stirred for 10 min. 2,2-dimethyloxirane (10.3 mg, 0.14 mmol) was added portion-wise over a period of 10 h. The reaction mixture was concentrated under reduced pressure. The crude residue was triturated with MTBE/pentane and then was further purified by reverse phase chromatography using a C18 column, eluting with acetonitrile in 0.1% formic acid in water to afford 3-(5-fluoro-6-(4-hydroxy-1-(2-hydroxy-2-methylpropyl)-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione, formic acid (**I-217**, 20 mg, 0.040 mmol, 33% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 458.5; ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1H), 8.84 (d, J = 2.00 Hz, 1H), 8.32 (s, 1H), 8.16 (s, 1H), 8.09 (t, J = 8.40 Hz, 1H), 7.83 (d, J = 9.20 Hz, 1H), 6.55 (bs, 1H), 5.04 (s, 1H), 4.23 (q, J = 4.40 Hz, 1H), 3.17 (t, J = 13.60

Hz, 1H), 2.76-2.60 (m, 5H), 2.48-2.44 (m, 1H), 2.25-2.14 (m, 3H), 1.64 (d, J = 13.20 Hz, 1H), 1.13 (m, 6H), 1.02 (s, 3H), 0.68 (s, 3H).

Example 256: Synthesis of 3-(6-(4-hydroxy-3,3-dimethyl-1-((S)-1-(4-(trifluoromethyl)-phenyl)ethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-1015)



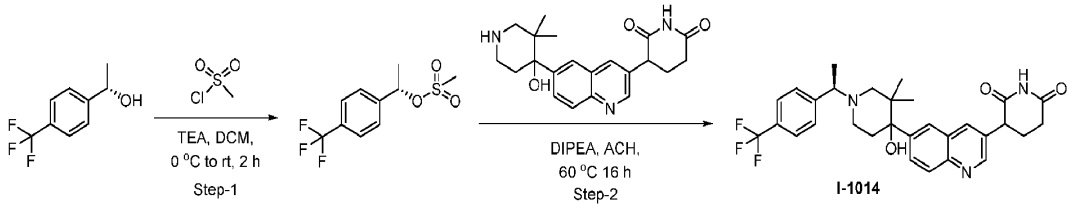
Step 1: **Synthesis of (R)-1-(4-(trifluoromethyl)phenyl)ethyl methanesulfonate**

To a stirred solution of (R)-1-(4-(trifluoromethyl)phenyl)ethan-1-ol (0.162 mL, 1.05 mmol) in dichloromethane (DCM, 3 mL) at 0 °C were added triethylamine (0.43 mL, 3.16 mmol) and methane sulfonyl chloride (0.122 mL, 1.58 mmol), and the reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography using neutral alumina, eluting with 0-5% EtOAc in hexane obtain (R)-1-(4-(trifluoromethyl)phenyl)ethyl methane sulfonate (200 mg, 0.653 mmol, 62% yield). LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ Not ionized; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.40 Hz, 2H), 7.55 (d, J = 8.40 Hz, 2H), 5.81 (q, J = 6.40 Hz, 1H), 2.87 (s, 3H), 1.75 (d, J = 6.40 Hz, 3H).

Step 2: **Synthesis of 3-(6-(4-hydroxy-3,3-dimethyl-1-((S)-1-(4-(trifluoromethyl)phenyl)-ethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-1015)**

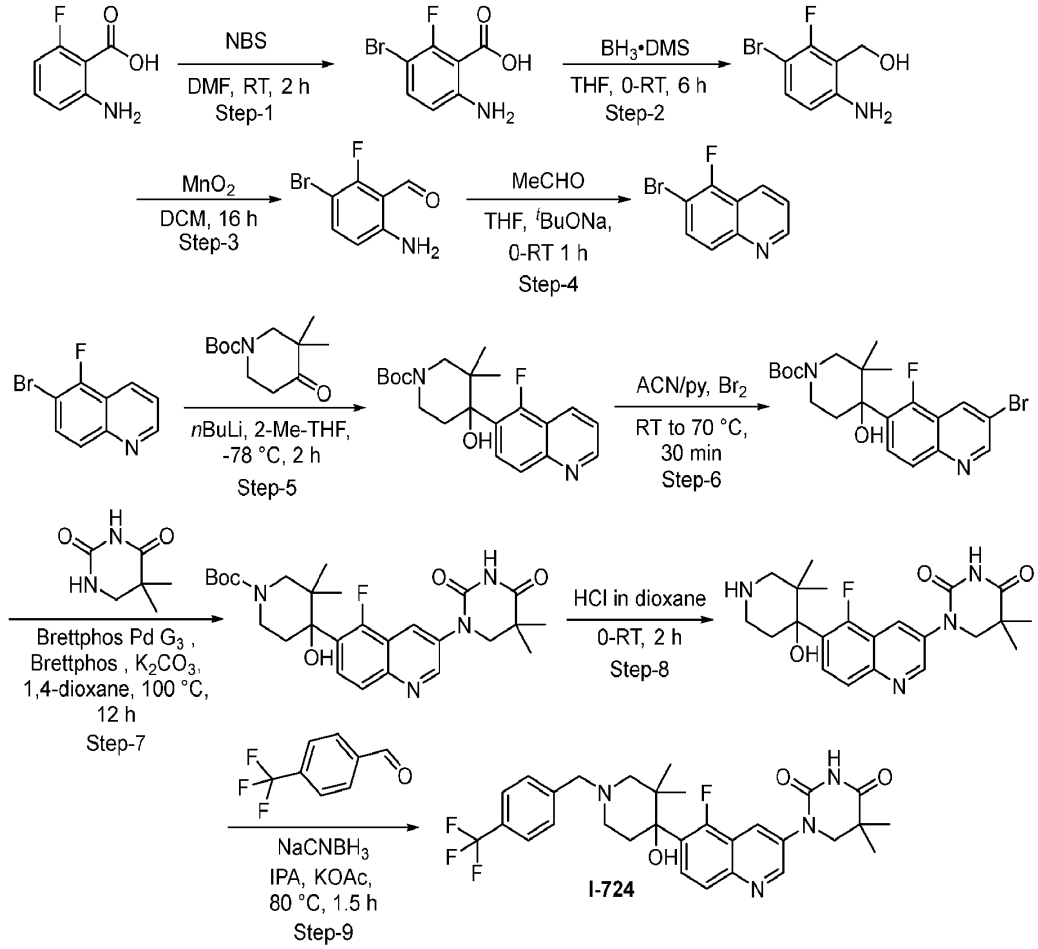
To a stirred solution of 3-(6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (**INT-S20**, 50 mg, 0.136 mmol) in acetonitrile (3 mL) at rt were added DIPEA (0.073 mL, 0.408 mmol) and (R)-1-(4-(trifluoromethyl)phenyl)ethyl methane sulfonate (73.0 mg, 0.272 mmol), and the reaction mixture was stirred at 60 °C for 16 h. The cooled reaction mixture was concentrated under reduced pressure, and the residue was purified by preparative-HPLC [Method info: (Column: Prudent C18, 20 × 250 mm), 5 µm, Mobile phase A: 0.1% FA in water, Mobile phase B: acetonitrile, flow rate = 15 mL/min] to afford 3-(6-(4-hydroxy-3,3-dimethyl-1-((S)-1-(4-(trifluoromethyl)phenyl)ethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-1015) (19 mg, 0.034 mmol, 25% yield. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 540.5; ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.96 (s, 1H), 8.75 (d, J = 1.60 Hz, 1H), 8.20 (s, 1H), 7.98-7.89 (m, 3H), 7.73-7.70 (m, 2H), 7.64-7.59 (m, 2H), 4.77 (d, J = 6.80 Hz, 1H), 4.16-4.12 (m, 1H), 2.82-2.73 (m, 3H), 2.60-2.59 (m, 2H), 2.51-2.50 (m, 2H), 2.34-2.29 (m, 1H), 2.17-2.10 (m, 2H), 1.36 (m, 1H), 1.35 (m, 3H), 0.92-0.87 (m, 3H), 0.71-0.63 (m, 3H).

Example 257: Synthesis of 3-(6-(4-hydroxy-3,3-dimethyl-1-((R)-1-(4-(trifluoromethyl)-phenyl)ethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione (I-1014)



3-(6-(4-hydroxy-3,3-dimethyl-1-((R)-1-(4-(trifluoromethyl)phenyl)ethyl)piperidin-4-yl)quinolin-3-yl)piperidine-2,6-dione **(I-1014)** was prepared in two steps similarly to **Example 256, I-1015**, starting from (S)-1-(4-(trifluoromethyl)phenyl)ethan-1-ol. LCMS: m/z MM-ES+APCI, Positive $[M+H]^+$ 540.3; ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.97 (s, 1H), 8.75 (s, 1H), 8.21-8.16 (m, 1H), 7.98-7.91 (m, 3H), 7.73-7.70 (m, 2H), 7.64-7.58 (m, 2H), 4.77 (d, J = 7.20 Hz, 1H), 4.16-4.12 (m, 1H), 3.65-3.33 (m, 1H), 2.89-2.73 (m, 3H), 2.68-2.59 (m, 2H), 2.44-2.41 (m, 2H), 2.17-2.07 (m, 2H), 1.57-1.43 (m, 1H), 1.35 (d, J = 6.40 Hz, 3H), 0.92-0.87 (m, 3H), 0.71-0.63 (m, 3H).

Example 258: Synthesis of 1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)-piperidin-4-yl)quinolin-3-yl)-5,5-dimethyldihydropyrimidine-2,4(1*H*,3*H*)-dione (I-724)



Step-1: **Synthesis of 6-amino-3-bromo-2-fluorobenzoic acid**

To a stirred solution of 2-amino-6-fluorobenzoic acid (50 g, 322 mmol) in DMF (500 mL) at 0 °C was added NBS (57.4 g, 322 mmol) and the reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was added to water (500 mL), and the resulting solid precipitate was collected via filtration and dried under vacuum to afford 6-amino-3-bromo-2-fluorobenzoic acid (60 g, 227 mmol, 71% yield). LCMS m/z MM-ES+APCI, POSITIVE $[M+H, M+2+H]^+$ 233.9, 235.6; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.78 (br s, 2H), 7.41-7.37 (m, 1H), 6.58-6.55 (m, 1H).

Step-2: **Synthesis of (6-amino-3-bromo-2-fluorophenyl)methanol**

To a stirred solution of 6-amino-3-bromo-2-fluorobenzoic acid (50 g, 214 mmol) in tetrahydrofuran (750 mL) was added BH_3·DMS (534 mL, 1068 mmol) dropwise at 0 °C and the reaction mixture was stirred at 25 °C for 6 h. The reaction mixture was quenched with methanol (1000 mL) at 0 °C and stirred for 30 min at 25 °C. The reaction mixture was concentrated under reduced pressure, and the crude residue was taken up in ethyl acetate (500 mL) and washed with water (2 × 200 mL). The aqueous layer was further extracted with ethyl acetate (2 × 300 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain (6-amino-3-bromo-2-fluorophenyl)methanol (45 g, 182 mmol, 85% yield). LCMS m/z MM-ES+APCI, POSITIVE $[M+H, M+2+H]^+$ 220, 222; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.31-7.17 (m, 1H), 6.45 (s, 1H), 5.48 (s, 2H), 5.06-5.04 (m, 1H), 4.55-4.46 (m, 2H).

Step-3: **Synthesis of 6-amino-3-bromo-2-fluorobenzaldehyde**

To a stirred solution of (6-amino-3-bromo-2-fluorophenyl)methanol (46 g, 209 mmol) in DCM (2800 mL) was added manganese dioxide (109 g, 1254 mmol) at 25 °C and the reaction mixture was stirred at 25 °C for 16 h. The reaction mixture was filtered through a Celite bed and was washed with DCM (2000 mL). The combined filtrate was concentrated under reduced pressure. The crude residue (40 g) was triturated with hexanes (120 mL) and dried under vacuum to afford 6-amino-3-bromo-2-fluorobenzaldehyde (37 g, 161 mmol, 77% yield). LCMS m/z MM-ES+APCI, POSITIVE $[M+H, M+2+H]^+$ 220.0, 218.0; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.14 (s, 1H), 7.63 (s, 2H), 7.52 (t, J = 8.00 Hz, 1H), 6.59 (d, J = 9.20 Hz, 1H).

Step-4: **Synthesis of 6-bromo-5-fluoroquinoline**

To a stirred solution of 6-amino-3-bromo-2-fluorobenzaldehyde (23 g, 105 mmol) in THF (350 mL) under nitrogen was added sodium tert-butoxide (2.028 g, 21.10 mmol) in portions at 0 °C. To this mixture was added acetaldehyde (31.6 mL, 158 mmol) dropwise at 0 °C and the reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched with Aq. NaCl solution (100 mL) and the mixture was extracted with ethyl acetate (2 x 200 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude residue was purified by silica gel

column chromatography eluting with 8 % ethyl acetate in hexane to afford 6-bromo-5-fluoroquinoline (24 g, 67% yield). LCMS: m/z MM-ES+APCI, POSITIVE $[M+H, M+2+H]^+$ 225.9, 227.9; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.03 (q, J = 1.60 Hz, 1H), 8.50 (d, J = 8.40 Hz, 1H), 7.99 (t, J = 7.60 Hz, 1H), 7.85 (d, J = 8.80 Hz, 1H), 7.71-7.68 (m, 1H).

Step-5: **Synthesis of *tert*-butyl 4-(5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate**

To a stirred solution of 6-bromo-5-fluoroquinoline (10 g, 44.2 mmol) in 2-methyl tetrahydrofuran (100 mL) was added dropwise n-butyllithium (2.5 M in hexane, 17.3 mL, 43.4 mmol) at -78 °C. The reaction mixture was stirred at -78 °C for 30 min, then *tert*-butyl 3,3-dimethyl-4-oxopiperidine-1-carboxylate (11.06 g, 48.7 mmol) in 2-methyl THF (50 mL) was added dropwise at -78 °C. The resulting reaction mixture was stirred at -78 °C for 2 h. The reaction mixture was quenched with aqueous ammonium chloride solution (50 mL) and diluted with ethyl acetate (100 mL). The organic layer was washed with water (100 mL). The aqueous layer was further extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography eluting with 0 to 60% ethyl acetate in hexane afford *tert*-butyl 4-(5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (10 g, 57% yield). LCMS: m/z MM-ES+APCI, POSITIVE $[M+H]^+$ 375; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.97-8.96 (m, 1H), 8.50 (d, J = 8.80 Hz, 1H), 8.11 (t, J = 8.80 Hz, 1H), 7.87 (d, J = 8.80 Hz, 1H), 7.64-7.60 (m, 1H), 5.43 (s, 1H), 4.06-3.98 (m, 1H), 3.53-3.43 (m, 1H), 3.33-3.16 (m, 2H), 2.99-2.96 (m, 1H), 1.64 (d, J = 4.80 Hz, 1H), 1.43 (s, 9H), 0.89 (s, 3H), 0.73 (s, 3H).

Step-6: **Synthesis of tert-butyl 4-(3-bromo-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate**

To a stirred solution of *tert*-butyl 4-(5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (5 g, 13.35 mmol) in ACN (50 mL) was added pyridine (7.39 g, 93 mmol) at 25 °C and the mixture was then stirred at 70 °C for 30 min. Bromine (10.7 g, 66.8 mmol) was added dropwise over 30 minutes at 70 °C and the mixture was stirred at 70 °C for 5 min following completion of the addition. The reaction mixture was cooled to 0 °C, aqueous $NaHCO_3$ solution was added, and the mixture was extracted with EtOAc (2x 50 mL). The combined organic layer was washed with sodium thiosulphate solution and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography eluting with 20-30% ethyl acetate in hexanes to obtain *tert*-butyl 4-(3-bromo-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (3.1 g, 51% yield). LCMS m/z MM-ES+APCI, POSITIVE $[M+H, M+2+H]^+$, 453, 455. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.01 (d, J = 2.00 Hz, 1H), 8.74 (d, J = 1.60 Hz, 1H), 8.15 (t, J = 8.80 Hz, 1H), 7.88 (d, J = 9.20 Hz, 1H),

5.49 (s, 1H), 4.04-3.98 (m, 1H), 4.04-3.98 (m, 1H), 3.33-3.22 (m, 2H), 2.95 (d, *J* = 11.60 Hz, 1H), 1.67 (d, *J* = 13.60 Hz, 1H), 1.43 (s, 9H), 0.95 (s, 3H), 0.83 (s, 3H).

Step-7: **Synthesis of tert-butyl 4-(3-(5,5-dimethyl-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate**

A stirred mixture of *tert*-butyl 4-(3-bromo-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (100 mg, 0.221 mmol), 1,4-dioxane (1 mL), 5,5-dimethyldihydropyrimidine-2,4(1*H*,3*H*)-dione (31.4 mg, 0.221 mmol) and K_2CO_3 (45.7 mg, 0.331 mmol) was sparged with nitrogen at rt for 10 min, then thereto were added Brettphos (11.84 mg, 0.022 mmol) followed by Brettphos PdG_3 (6.52 mg, 0.018 mmol). The resulting reaction mixture was stirred at 100 °C for 12 h. The crude reaction mixture was purified by silica gel flash chromatography eluting with 0-70 % ethyl acetate in hexane to afford *tert*-butyl 4-(3-(5,5-dimethyl-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (35 mg, 30% yield). LCMS: m/z MM-ES+APCI, POSITIVE $[M+H.]^+$ 515.4. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.59 (s, 1H), 9.03 (s, 1H), 8.31 (s, 1H), 8.09 (t, *J* = 8.80 Hz, 1H), 7.88 (d, *J* = 9.20 Hz, 1H), 5.76 (s, 1H), 3.98 (s, 1H), 3.18-2.96 (m, 4H), 1.69-1.67 (m, 1H), 1.43 (s, 9H), 1.28 (s, 6H), 1.27 (s, 3H), 0.87 (s, 3H), 0.79 (m, 2H).

Step-8: **Synthesis of 1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)-5,5-dimethyldihydropyrimidine-2,4(1*H*,3*H*)-dione**

To a stirred solution of *tert*-butyl 4-(3-(5,5-dimethyl-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-fluoroquinolin-6-yl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (60 mg, 0.117 mmol) in DCM (1 mL) under a nitrogen atmosphere was added HCl (4M in dioxane, 0.833 mL, 1.17 mmol) at 0 °C. The resulting reaction mixture was stirred at rt for 2 h, then was concentrated under reduced pressure. The crude residue was washed with MTBE, and then was dried under vacuum to provide 1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)-5,5-dimethyldihydropyrimidine-2,4(1*H*,3*H*)-dione, HCl (50 mg, 0.094 mmol, 81% yield) LCMS m/z MM-ES+APCI, POSITIVE $[M+H]^+$ 515.4. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.61 (s, 1H), 9.06 (d, *J* = 2.40 Hz, 1H), 9.06 (s, 1H), 8.67 (d, *J* = 2.80 Hz, 1H), 8.34 (d, *J* = 2.00 Hz, 1H), 7.91 (d, *J* = 9.20 Hz, 1H), 5.76 (s, 1H), 3.39-3.17 (m, 4H), 3.01 (s, 1H), 2.92 (d, *J* = 11.60 Hz, 1H), 1.99-1.91 (m, 1H), 1.40 (s, 1H), 1.27 (s, 6H), 1.08 (s, 6H).

Step-9: **Synthesis of 1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)-5,5-dimethyldihydropyrimidine-2,4(1*H*,3*H*)-dione**

To a stirred solution of 1-(5-fluoro-6-(4-hydroxy-3,3-dimethylpiperidin-4-yl)quinolin-3-yl)-5,5-dimethyldihydropyrimidine-2,4(1*H*,3*H*)-dione, HCl (50 mg, 0.111 mmol) in IPA (1 mL) was added 4-(trifluoromethyl)benzaldehyde (23.17 mg, 0.133 mmol) followed by potassium acetate (32.6 mg, 0.333 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 30 min. Then $NaCNBH_3$ (20.9 mg, 0.333 mmol) was added and the reaction mixture was stirred at 80 °C for 1 h. The cooled reaction

mixture was diluted with water (5 mL) and extracted with IPA: DCM (2 x 20 mL). The combined organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by reverse phase column chromatography on a C18 column, eluting with 5 to 100 % ACN in 0.1% acetic acid in water to afford a partially purified product (20 mg). This was further purified by preparative-HPLC [Method info: Column: X Select C18 (250 x 19mm), Mobile phase A: 0.1%HCl in water, Mobile phase B: acetonitrile, flow rate: 15 mL/min] to afford 1-(5-fluoro-6-(4-hydroxy-3,3-dimethyl-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)quinolin-3-yl)-5,5-dimethyldihydropyrimidine-2,4(1*H*,3*H*)-dione, HCl (**I-724**, 2.9 mg, 4.57 µmol, 4.1 % yield). LCMS: m/z MM-ES+APCI, POSITIVE $[M+H.]^+$ 573.3; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.61 (s, 1H), 9.33 (s, 1H), 9.05 (d, J = 2.40 Hz, 1H), 8.33 (d, J = 2.00 Hz, 1H), 8.05 (t, J = 8.80 Hz, 1H), 7.93-7.84 (m, 5H), 5.96 (s, 1H), 4.96 (m, 2H), 3.86 (s, 2H), 3.423-3.40 (m, 4H), 2.68 (t, J = 2.00 Hz, 1H), 2.33 (t, J = 1.60 Hz, 1H), 1.28 (m, 6H), 1.05 (s, 3H), 0.80 (s, 3H).

Example 259: General Method for Separation of Isomers of 3-(Quinolin-3-yl)-piperidine-2,6-dione-Containing Compounds

To obtain single enantiomers or diastereomers with defined stereochemistry at the 3-position of the piperidine-2,6-dione contained in certain compounds of the invention, chiral SFC purification can be applied using a method similar to the following:

Column: ChiralPak IH, 250 x 30mm, 10um; mobile phase: [CO2-EtOH], isocratic elution mode, with 0.1% HCl (aq) added to each fraction after SFC separation before concentrating by freeze drying.

Biological Assays and Data

The activity of a compound according to the present disclosure can be assessed by the following *in vitro* methods.

Example 260: 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 x 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).

Table 3 shows ARNT (HIF-1b) degradation activity of compounds of the disclosure in Pro-label assays in 7860-O. In Table 3 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 3: ARNT degradation activity of exemplary compounds of Formula (I)

Cmpd No.	ARNT DC_{50}	ARNT Dmax
I-1	A	A
I-5	A	A
I-8	A	A
I-9	C	B
I-10	B	C
I-11	C	B
I-12	B	A
I-13	B	A
I-14	B	A
I-16	B	A
I-17	B	A
I-18	B	A
I-19	B	A
I-20	B	A
I-21	B	B
I-22	B	B

Cmpd No.	ARNT DC_{50}	ARNT Dmax
I-23	B	A
I-24	B	A
I-25	A	A
I-26	A	A
I-27	A	A
I-28	A	A
I-29	A	A
I-30	A	A
I-31	A	A
I-33	A	A
I-34	A	B
I-35	A	A
I-36	A	A
I-37	A	A
I-38	A	A
I-39	C	C

Cmpd No.	ARNT DC_{50}	ARNT Dmax
I-40	A	A
I-43	A	A
I-44	A	A
I-45	A	A
I-46	A	A
I-47	C	C
I-48	A	A
I-49	A	A
I-50	A	A
I-51	B	B
I-52	A	A
I-55	A	A
I-56	A	A
I-57	A	A
I-58	A	A
I-59	A	A

Cmpd No.	ARNT DC_{50}	ARNT Dmax
I-62	A	A
I-63	A	A
I-64	A	A
I-67	A	A
I-68	A	A
I-69	A	A
I-74	A	A
I-75	A	A
I-76	A	A
I-79	A	A
I-82	A	A
I-83	B	B
I-84	A	A
I-85	C	C
I-86	A	A
I-87	A	A
I-88	C	C
I-89	A	A
I-92	A	A
I-95	A	A
I-98	A	A
I-101	A	A
I-104	A	A
I-107	A	A
I-110	A	A
I-113	A	A
I-116	A	A
I-119	A	A
I-122	A	A
I-124	A	A
I-129	A	A
I-132	A	A
I-133	A	A
I-139	A	A
I-142	A	A
I-145	A	A
I-146	A	A

Cmpd No.	ARNT DC_{50}	ARNT Dmax
I-149	A	A
I-155	A	A
I-158	A	A
I-164	A	A
I-167	C	C
I-168	B	B
I-169	B	A
I-170	A	A
I-173	A	A
I-176	B	A
I-177	B	A
I-178	A	A
I-179	A	A
I-181	B	A
I-184	B	A
I-187	A	A
I-189	C	B
I-198	A	A
I-199	A	B
I-200	B	A
I-201	A	B
I-202	C	C
I-203	A	A
I-206	A	B
I-207	A	B
I-208	A	A
I-210	A	A
I-212	C	A
I-213	A	A
I-217	A	C
I-218	A	A
I-221	A	A
I-222	A	A
I-225	A	A
I-228	A	A
I-231	A	A
I-234	B	A

Cmpd No.	ARNT DC_{50}	ARNT Dmax
I-235	A	A
I-238	A	A
I-242	A	A
I-243	A	A
I-244	A	A
I-247	A	A
I-250	A	A
I-255	A	A
I-256	A	A
I-258	A	A
I-259	C	B
I-260	B	A
I-261	A	A
I-262	B	B
I-265	A	A
I-268	A	A
I-271	A	A
I-272	A	A
I-273	A	A
I-274	A	A
I-291	A	A
I-293	A	A
I-294	A	A
I-295	A	A
I-297	A	A
I-299	A	A
I-306	C	B
I-307	C	C
I-308	B	B
I-311	A	B
I-313	B	B
I-314	C	C
I-316	C	B
I-317	A	A
I-318	C	C
I-319	A	A
I-324	A	A

Cmpd No.	ARNT DC_{50}	ARNT Dmax
I-327	B	A
I-329	A	A
I-330	C	B
I-334	C	C
I-335	A	A
I-336	B	A
I-337	A	A
I-338	B	B
I-339	A	A
I-342	A	A
I-345	A	A
I-348	A	A
I-351	A	A
I-354	A	A
I-357	A	A
I-360	A	A
I-364	A	A
I-365	A	A
I-366	A	A
I-369	A	A
I-372	A	A
I-375	A	A
I-378	A	A
I-381	A	A
I-384	A	A
I-387	A	A
I-389	A	A
I-394	A	A
I-397	A	A
I-400	A	A
I-403	A	A
I-406	A	A
I-408	A	A
I-409	A	A
I-412	A	A
I-415	A	A
I-418	A	A

Cmpd No.	ARNT DC_{50}	ARNT Dmax
I-419	A	A
I-422	C	C
I-424	A	A
I-428	A	A
I-431	C	C
I-432	A	A
I-433	A	A
I-438	A	A
I-441	A	A
I-454	A	A
I-455	A	A
I-458	A	A
I-459	A	A
I-460	A	A
I-465	A	A
I-471	A	A
I-473	A	A
I-475	A	A
I-479	A	A
I-484	A	A
I-519	A	A
I-526	A	A
I-529	A	A
I-532	A	A
I-535	A	A
I-538	A	A
I-541	A	A
I-542	A	A
I-543	A	A
I-545	B	A
I-546	A	A
I-549	A	A
I-556	A	A
I-559	A	A
I-560	A	A
I-561	A	A
I-566	A	A

Cmpd No.	ARNT DC_{50}	ARNT Dmax
I-569	C	A
I-572	A	A
I-575	A	A
I-578	A	A
I-579	A	A
I-581	A	A
I-584	A	A
I-591	A	A
I-594	A	A
I-597	A	A
I-598	B	A
I-599	C	B
I-600	A	A
I-603	A	A
I-606	A	A
I-613	A	A
I-616	A	A
I-619	A	A
I-622	A	A
I-625	A	A
I-628	A	A
I-631	A	A
I-632	A	A
I-635	A	A
I-640	A	A
I-643	A	A
I-650	A	A
I-651	A	A
I-656	A	A
I-659	A	A
I-662	A	A
I-665	A	A
I-668	A	A
I-669	A	A
I-674	A	A
I-675	A	A
I-678	A	A

Cmpd No.	ARNT DC_{50}	ARNT Dmax
I-679	A	A
I-680	A	A
I-687	A	A
I-688	A	A
I-689	B	A
I-692	A	A
I-697	A	A
I-698	A	A
I-701	A	A
I-702	A	A
I-705	A	A
I-708	A	A
I-709	A	A
I-712	A	A
I-713	A	A
I-716	A	A
I-717	A	A
I-720	A	A
I-723	A	A
I-726	A	A
I-729	A	A
I-730	A	A
I-731	A	A
I-732	A	A
I-733	A	A
I-734	A	A
I-737	A	A
I-740	A	A
I-743	A	A
I-746	A	A
I-747	B	A
I-748	A	A
I-749	A	A
I-752	A	A
I-755	A	A
I-758	A	A
I-759	A	A

Cmpd No.	ARNT DC_{50}	ARNT Dmax
I-760	A	A
I-763	A	A
I-766	A	A
I-769	A	A
I-770	B	A
I-771	A	A
I-774	A	A
I-775	A	A
I-776	A	A
I-777	A	A
I-778	A	A
I-779	A	A
I-780	A	A
I-781	A	A
I-782	A	A
I-783	A	A
I-784	A	A
I-785	A	A
I-786	A	A
I-787	A	A
I-788	B	A
I-789	B	A
I-790	A	A
I-791	A	A
I-792	A	A
I-793	A	A
I-794	A	A
I-795	A	A
I-796	A	A
I-797	A	A
I-798	B	A
I-799	A	A
I-800	A	A
I-802	C	A
I-804	B	A
I-814	A	A
I-815	B	A

Cmpd No.	ARNT DC_{50}	ARNT Dmax
I-816	B	A
I-817	A	A
I-818	B	A
I-819	A	A
I-820	A	A
I-821	A	A
I-822	A	A
I-823	A	A
I-824	A	A
I-825	A	A
I-829	C	C
I-830	A	A
I-831	A	A
I-832	A	A
I-833	B	A
I-834	A	A
I-835	A	A
I-836	B	A
I-837	A	A
I-838	A	A
I-839	A	A
I-840	A	A
I-841	A	A
I-842	B	A
I-843	A	A
I-844	B	A
I-845	A	A
I-846	B	A
I-847	A	A
I-848	A	A
I-849	A	A
I-850	B	A
I-851	A	A
I-852	A	A
I-853	B	A
I-854	A	A
I-855	A	A

Cmpd No.	ARNT DC_{50}	ARNT Dmax
I-856	B	A
I-857	A	A
I-858	A	B
I-859	A	B
I-860	A	B
I-861	B	B
I-862	B	B
I-863	B	B
I-864	B	B
I-865	B	B
I-866	B	B
I-867	A	B
I-868	A	B
I-869	B	B
I-870	B	B
I-871	B	B
I-872	B	B
I-873	B	B
I-874	B	B
I-875	B	B
I-876	B	B
I-877	B	B
I-878	B	B
I-879	C	A
I-880	C	A
I-881	C	B
I-882	C	B
I-883	C	B
I-884	C	B
I-885	C	C

Cmpd No.	ARNT DC_{50}	ARNT Dmax
I-886	C	C
I-887	C	C
I-888	C	C
I-889	C	C
I-890	B	C
I-891	C	C
I-892	C	C
I-893	C	C
I-894	C	C
I-895	C	C
I-896	C	C
I-897	B	C
I-898	C	C
I-899	C	C
I-900	C	C
I-901	C	C
I-902	C	C
I-903	C	C
I-908	C	C
I-909	C	C
I-910	C	C
I-911	C	C
I-912	C	C
I-913	C	C
I-914	C	C
I-915	C	C
I-916	C	C
I-917	C	C
I-918	C	C
I-919	C	C

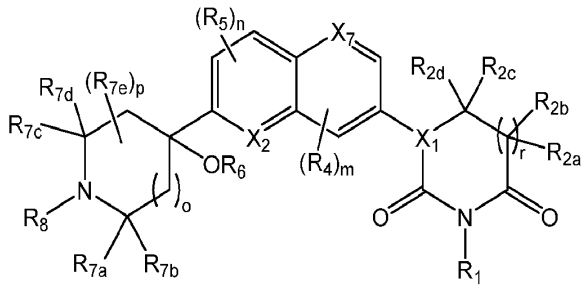
Cmpd No.	ARNT DC_{50}	ARNT Dmax
I-920	C	C
I-921	C	C
I-922	C	C
I-923	C	C
I-928	A	A
I-931	A	A
I-938	A	A
I-941	A	A
I-944	A	A
I-947	A	A
I-950	A	A
I-953	A	A
I-956	A	A
I-959	A	A
I-962	A	A
I-965	A	A
I-968	A	A
I-975	A	A
I-978	A	A
I-981	A	A
I-984	A	A
I-985	A	A
I-986	C	B
I-987	C	C
I-1190	A	A
I-1193	A	A
I-1196	A	A
I-1197	A	A
I-1200	A	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:

X_1 is N or CR_3;

X_2 is N, N(O), or CR_5;

X_7 is N and N(O);

R_1 is H, D, $-C(O)R_{11}$, $-CH_2OC(O)R_{11}$, $-CH_2OC(O)NHR_{12}$, $-CH_2OC(O)OR_{12}$, $-P(O)(OR_{12})_2$, $-CH_2OP(O)(OR_{12})_2$, $-CH_2OP(O)(OH)OR_{12}$, $-CH_2OP(O)(R_{12})_2$, $-CH_2OC(O)CH_2NHC(O)CH_2NH_2$, $-CH_2OC(O)CH(R_{12'})NHR_{12'}$, $-CH_2OC(O)(CH_2)_q-C(O)OR_{12'}$, 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 optionally substituted with one or more R_{40};

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 optionally substituted with one or more R_{40};

R_4 is D $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$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, or $-NR_9R_{10}$; wherein each alkyl, deuteroalkyl, haloalkyl, alkoxy, deuteoalkoxy, haloalkoxy, carbocyclyl, and heterocyclyl is optionally substituted with one or more R_{40};

R_5 is D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$deuteroalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$deuteroalkoxy, $(C_1$-$C_6)$haloalkoxy, $(C_3$-$C_7)$carbocyclyl, $O(C_3$-$C_7)$carbocyclyl, $(C_3$-$C_7)$carbocyclyl, 4- to 7-membered heterocyclyl comprising 1 to 4 heteroatoms selected from O, N, NH, and S; halogen, -OH, or

-NR_9R_{10}, wherein each alkyl, deuteroalkyl, haloalkyl, alkoxy, deuteoalkoxy, haloalkoxy, carbocyclyl, and heterocyclyl is optionally substituted with one or more R_{40};

R_6 is H, D, (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_{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_{7a}, R_{7b}, R_{7c}, and R_{7d} are each independently H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, or (C_1-C_2)haloalkyl; or

two of R_{7a}, R_{7b}, R_{7c}, and R_{7d} are taken together with the carbon atoms to which they are attached form (C_3-C_7)carbocyclyl, (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 carbocyclyl, spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one or more substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$;

each R_{7e} is independently at each occurrence D, (C_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_{19}, the aryl and heteroaryl are optionally substituted with one or more R_{21}, and the carbocyclyl and heterocyclyl are optionally substituted with one or more R_{22}; or

two R_{7e} together with the carbon atom to which they are attached form a (C_3-C_7)carbocyclyl, (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 carbocyclyl, spirocarbocyclyl and spiroheterocyclyl are optionally substituted with one or more substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$;

one R_{7e} is taken together with any one of R_{7a}, R_{7b}, R_{7c}, and R_{7d} 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_{22};

R_8 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)$NR_{32}R_{33}$, 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 $R_{15'}$;

R_9 and R_{10} are each independently at each occurrence H, D, (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, or (C_1-C_6)haloalkyl;

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

$R_{13'}$ is independently at each occurrence H, (C_1-C_6)alkyl or (C_1-C_6)haloalkyl;

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} and $R_{15'}$ 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_{16}, -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 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_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_{29}, $SO_2NR_{30}R_{31}$, -CN, and R_{19}; or

two R_{15}, 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_{17};

two $R_{15'}$, 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_{17}; or

two $R_{15'}$ 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_{17}; or

two $R_{15'}$ when on the same carbon atom form C=(O);

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

R_{17} is independently at each occurrence D, (C_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_{18}, or -CN;

R_{18} is H, (C_1-C_6)alkyl, or (C_1-C_6)haloalkyl;

each R_{19} is independently at each occurrence (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, -$NR_{20}R_{20'}$, -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 or more R_{23} and the aryl and heteroaryl are optionally substituted with one or more R_{24}; or

two R_{19} when on the same carbon atom form C=(O); or

two R_{19} 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_{17};

R_{20} and $R_{20'}$ are each independently at each occurrence H or (C_1-C_6)alkyl;

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_{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_{21}, 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_{15};

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_{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_{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_{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; 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;

each R_{24} 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_{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;

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 D, (C_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_{16}, -CN, -C(O)$NR_{32}R_{33}$, -C(O)OR_{32}, (C_3-C_7)carbocyclyl, -O(C_3-C_7)carbocyclyl, phenyl;

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

o is 0, 1 or 2;

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

q is 1, 2, or 3; and

r is 0 or 1.

2. The compound according to claim 1, wherein R_1 is H.

3. The compound according to claim 1, wherein R_{2a} is H.

4. The compound according to claim 1, wherein R_{2b} is H.

5. The compound according to claim 1, wherein R_{2c} is H.

6. The compound according to claim 1, wherein R_{2d} is H.

7. The compound according to claim 1, wherein one to four members of R_{2a}, R_{2b}, R_{2c}, and R_{2d} is CH_3.

8. The compound according to claim 1, wherein X_1 is CR_3.

9. The compound according to claim 1, wherein X_1 is N.

10. The compound according to claim 1, wherein X_2 is N.

11. The compound according to claim 1, wherein X_2 is CR_5.

12. The compound according to claim 1, wherein R_3 is H.

13. The compound according to claim 1, wherein R_3 is D.

14. The compound according to claim 1, wherein R_3 is CH_3.

15. The compound according to claim 1, wherein R_4 is independently in each instance $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, -OH, -O-$(C_1\text{-}C_6)$alkyl, $-NR_9R_{10}$, or halogen.

16. The compound according to claim 1, wherein R_4 is independently in each instance $-CH_3$, $-C_2H_5$, $-CF_3$, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, or -Cl.

17. The compound according to claim 1, wherein R_5 is independently in each instance $(C_1\text{-}C_6)$alkyl or halogen.

18. The compound according to claim 1, wherein R_5 is independently in each instance $-CH_3$, -F.

19. The compound according to claim 1, wherein R_5 is independently in each instance $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$carbocyclyl, -OH, -O-$(C_1\text{-}C_6)$alkyl, $-NR_9R_{10}$, or halogen.

20. The compound according to claim 1, wherein R_5 is independently in each instance $-CH_3$, cyclopropyl, -OH, $-OCH_3$, $-NH_2$, -F, -Cl.

21. The compound according to claim 1, wherein n is 0.

22. The compound according to claim 1, wherein n is 1.

23. The compound according to claim 1, wherein m is 0.

24. The compound according to claim 1, wherein m is 1.

25. The compound according to claim 1, wherein m is 2.

26. The compound according to claim 1, wherein R_6 is H.

27. The compound according to claim 1, wherein R_{7a} is H, or (C_1-C_6)alkyl.

28. The compound according to claim 1, wherein R_{7a} is -H, -CH_3, or -$CH(CH_3)_2$.

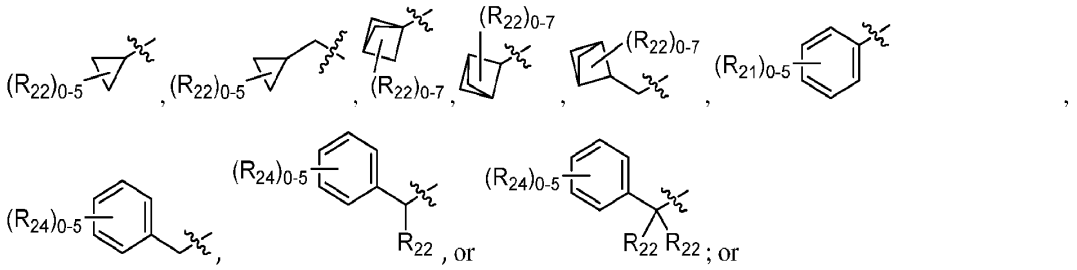
29. The compound according to claim 1, wherein R_{7b} is H.

30. The compound according to claim 1, wherein R_{7c} is H.

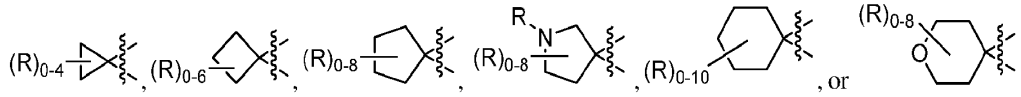
31. The compound according to claim 1, wherein R_{7d} is H.

32. The compound according to claim 1, wherein each R_{7e} is independently at each occurrence (C_1-C_6)alkyl, (C_1-C_6)deuteroalkyl, halogen, -OH, -O-(C_1-C_6)alkyl, (C_3-C_7)carbocyclyl, or phenyl wherein the alkyl is optionally substituted with one to six R_{19} and the carbocyclyl is optionally substituted with one to five R_{22} and the phenyl is optionally substituted with one to five R_{22}; or two R_{7e}, when on the same carbon atom, together with the carbon atom to which they are attached form a (C_3-C_7)spirocarbocyclyl or 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 substituents independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$.

33. The compound according to claim 1, wherein each R_{7e} is independently at each occurrence



two R_{7e}, when on the same carbon atom, together with the carbon atom to which they are attached, form

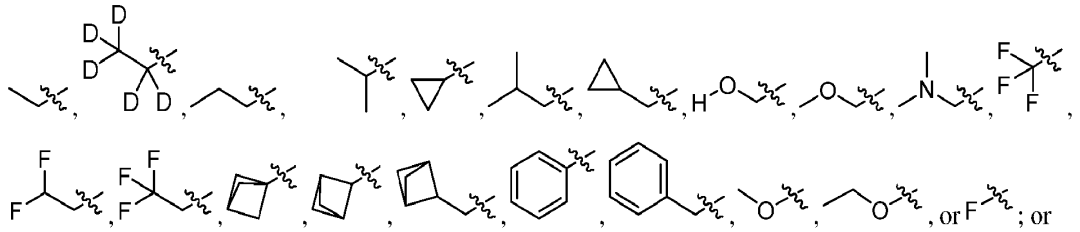


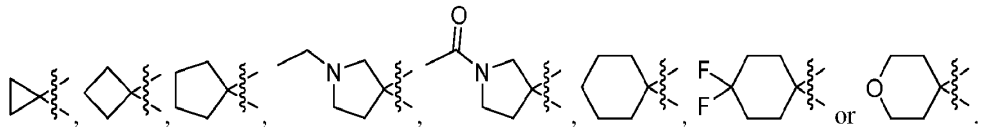
, wherein

R in each instance is independently selected from D, (C_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)$OR_{13'}$, -C(O)R_{13}, and -C(O)$NR_{13'}R_{13'}$; and

R_{21}, R_{22}, and R_{24} are defined as in claim 1.

34. The compound according to claim 1, wherein each R_{7e} is independently at each occurrence ,



two R_{7e}, when on the same carbon atom, together with the carbon atom to which they are attached, form .

35. The compound according to claim 1, wherein o is 2.

36. The compound according to claim 1, wherein o is 1.

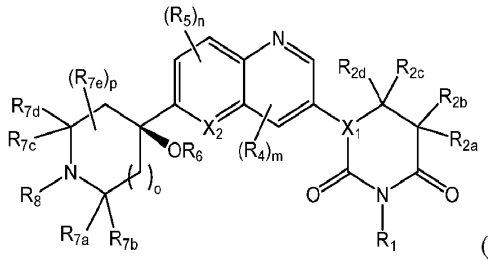
37. The compound according to claim 1, wherein p is 0.

38. The compound according to claim 1, wherein p is 1.

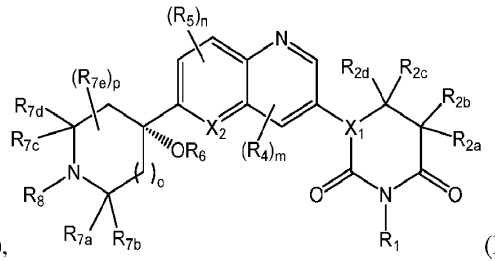
39. The compound according to claim 1, wherein p is 2.

40. The compound according to claim 1, wherein p is 4.

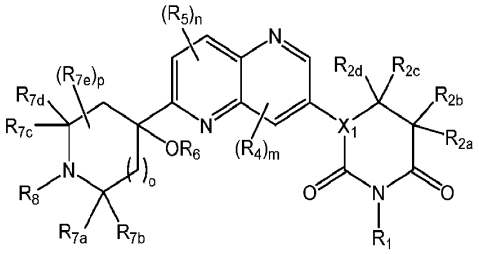
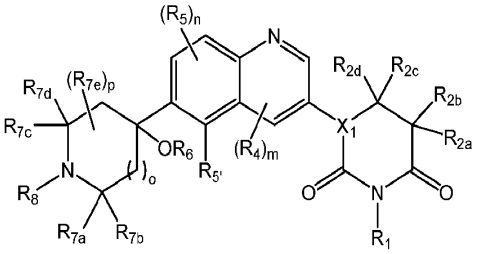
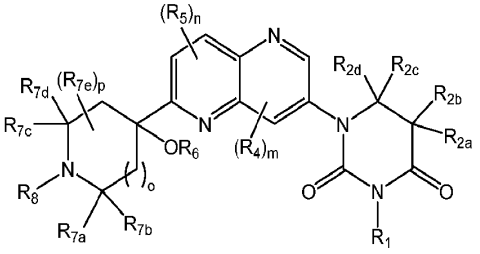
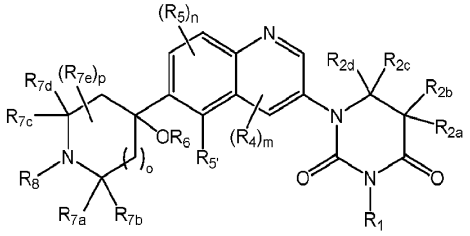
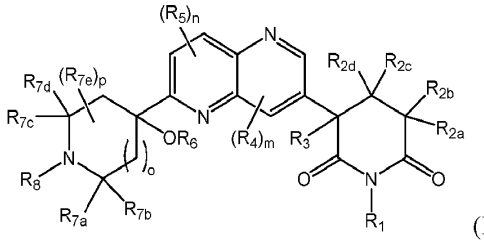
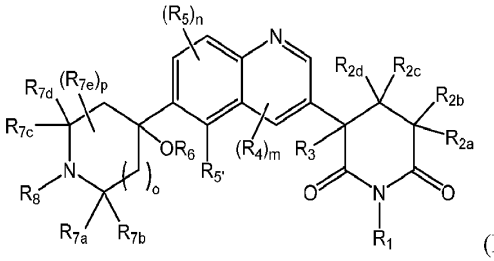
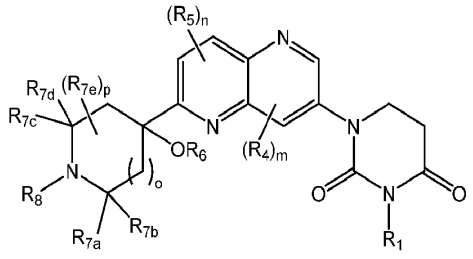
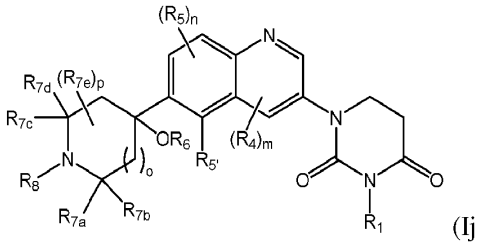
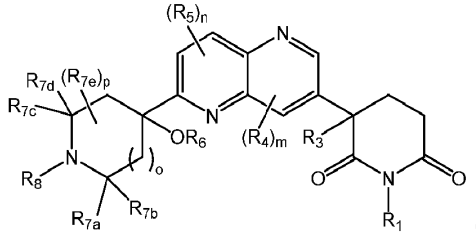
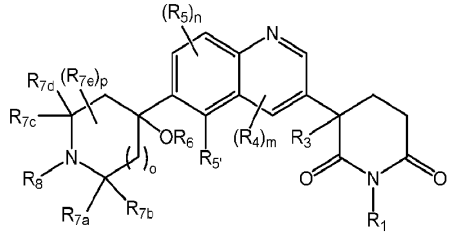
41. The compound according to claim 1, having a Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), or Formula (Il):



(Ia),

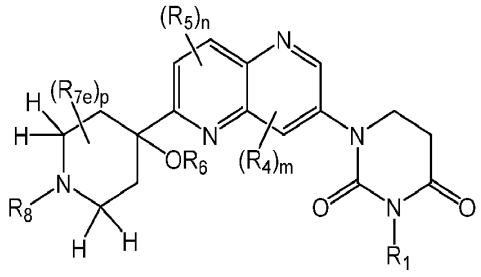


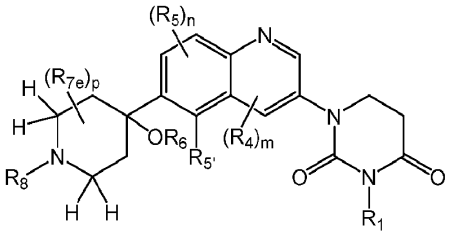
(Ib),

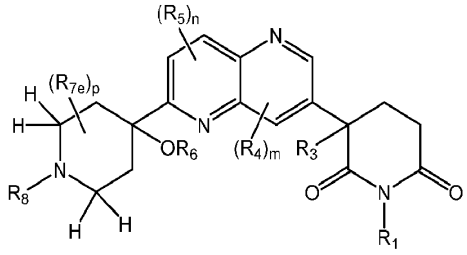

(Ic),

(Id),

(Ie),

(If),

(Ig),

(Ih),

(Ii),

(Ij),

(Ik), or

(Il),

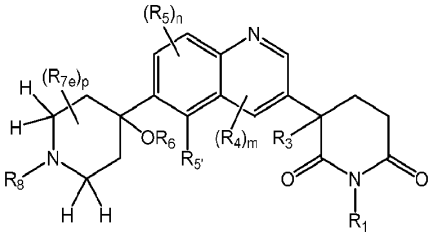
or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

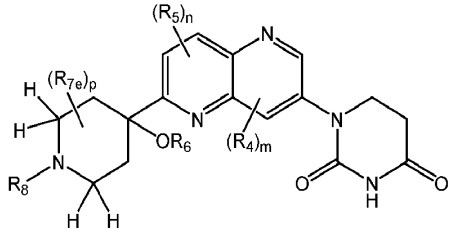
42. The compound according to claim 1, having a Formula (Im), Formula (Io), Formula (Ip), Formula (Iq), Formula (Ir), Formula (Iu), Formula (Iv), Formula (Iw), Formula (Ix), Formula (Iy), Formula (Iz), Formula (Iaa), Formula (Ibb), or Formula (Icc):

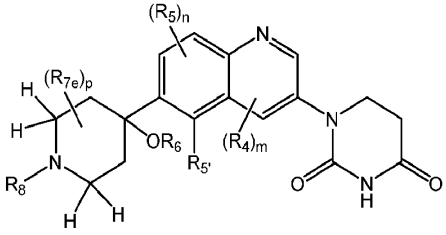

(Im),

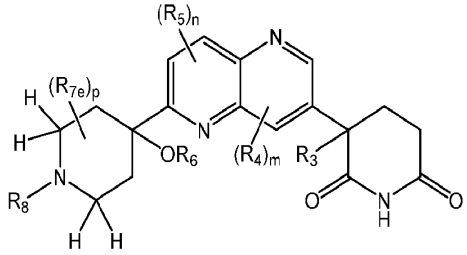

(Io),

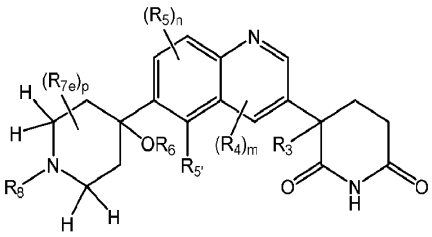

(Ip),

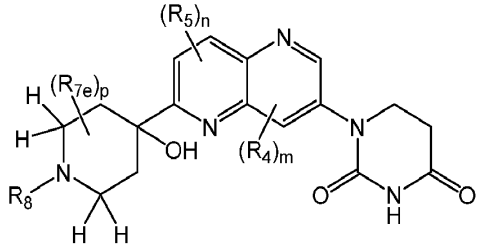

(Iq),

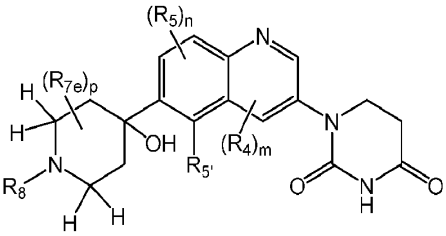

(Ir),

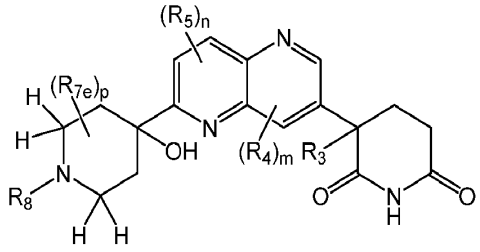

(Iu),

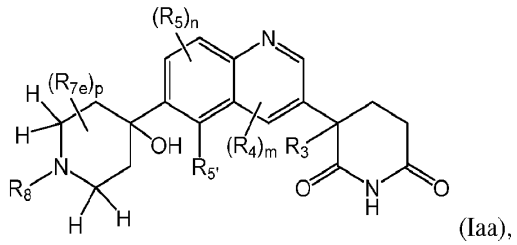

(Iv),

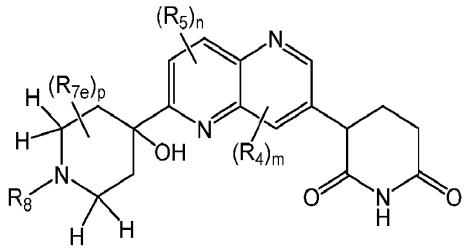

(Iw),

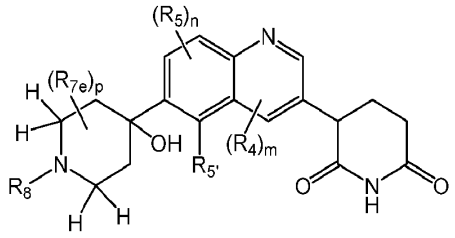

(Ix),


(Iy),


(Iz),

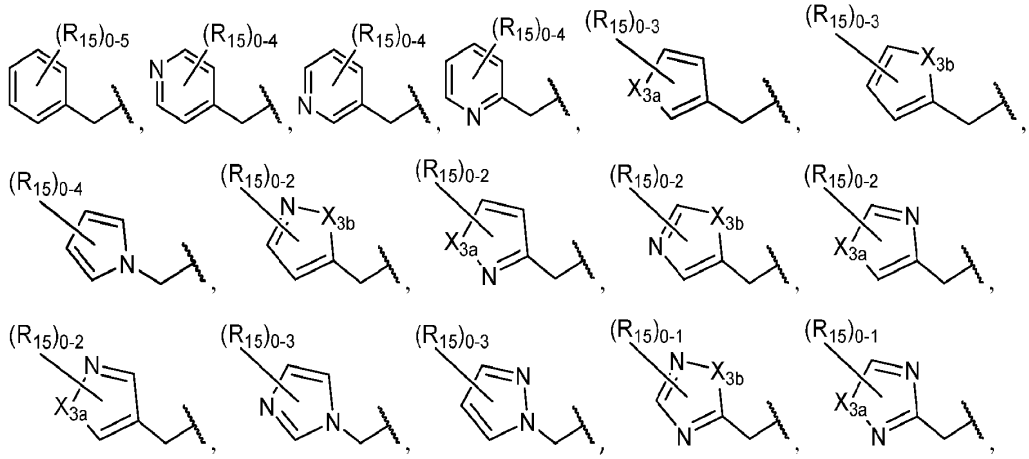

(Iaa),

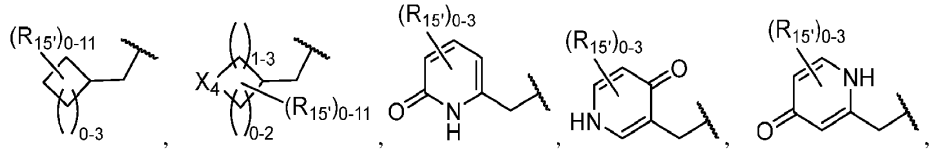

(Ibb), or


(Icc),

43. The compound according to claim 1, wherein R_8 is (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)alkyl optionally substituted with one to three 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 optionally substituted with one to three R_{15} and the carbocyclyl and heterocyclyl are optionally substituted with one to three $R_{15'}$.

44. The compound according to claim 1, wherein R_8 is selected from:





wherein

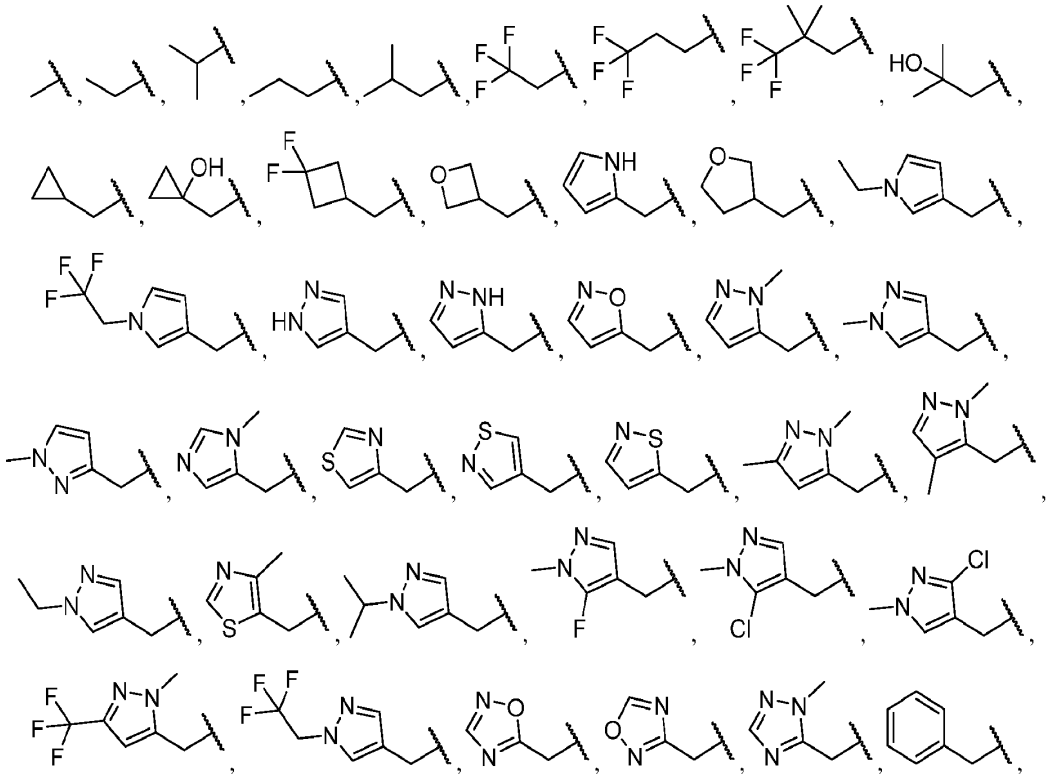
each of X_{3a} and X_{3b} is independently selected from O, S, NH, and NR_{15};

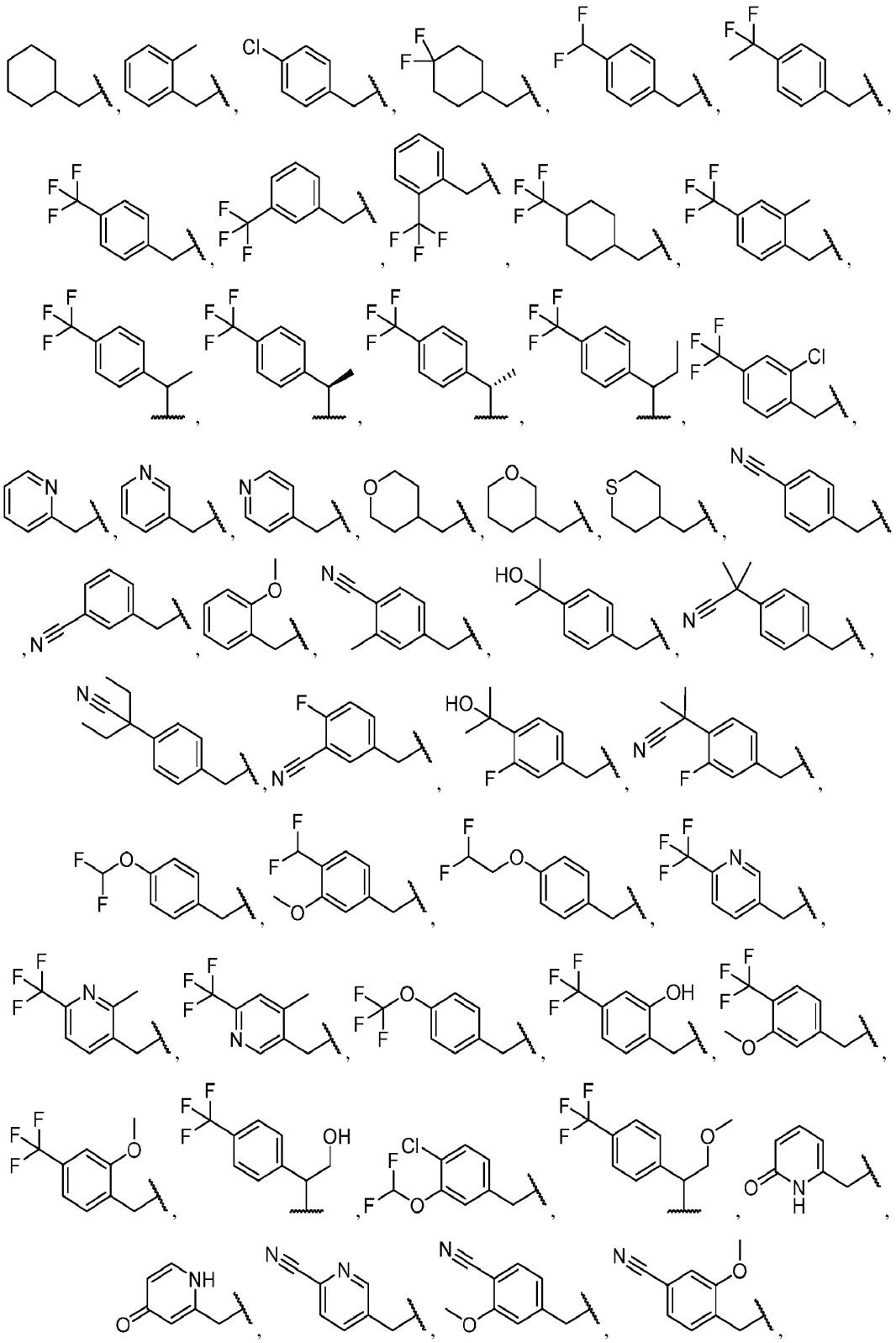
X_4 is O, S, NH, and $NR_{15'}$;

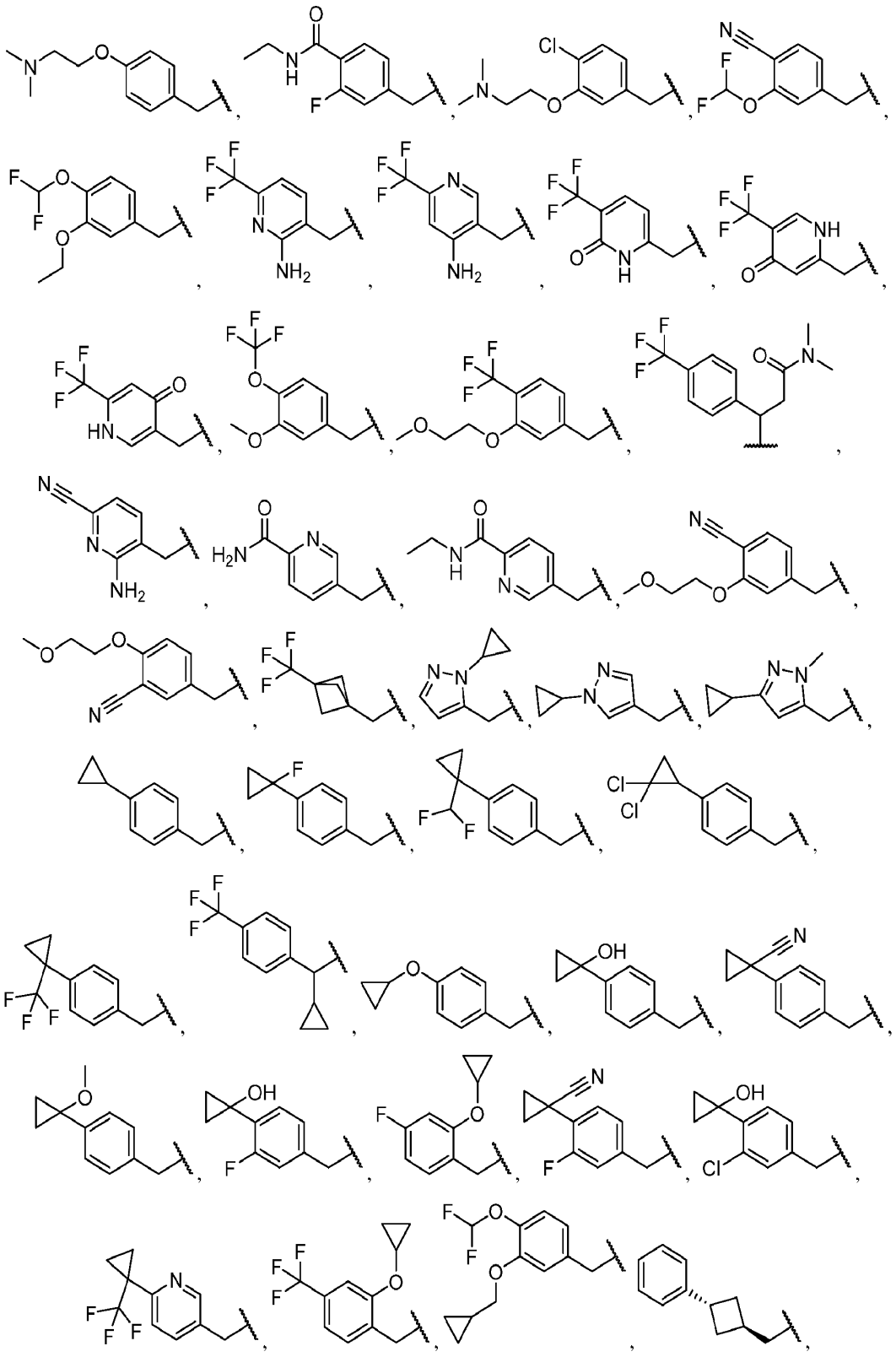
R is selected from $(C_1$-$C_5)$alkyl and $(C_3$-$C_7)$cycloalkyl, and is optionally substituted with one or more of D, hydroxy, halogen, alkoxy, imidazol-2-yl, and -C(O)$NR_{32}R_{33}$; and

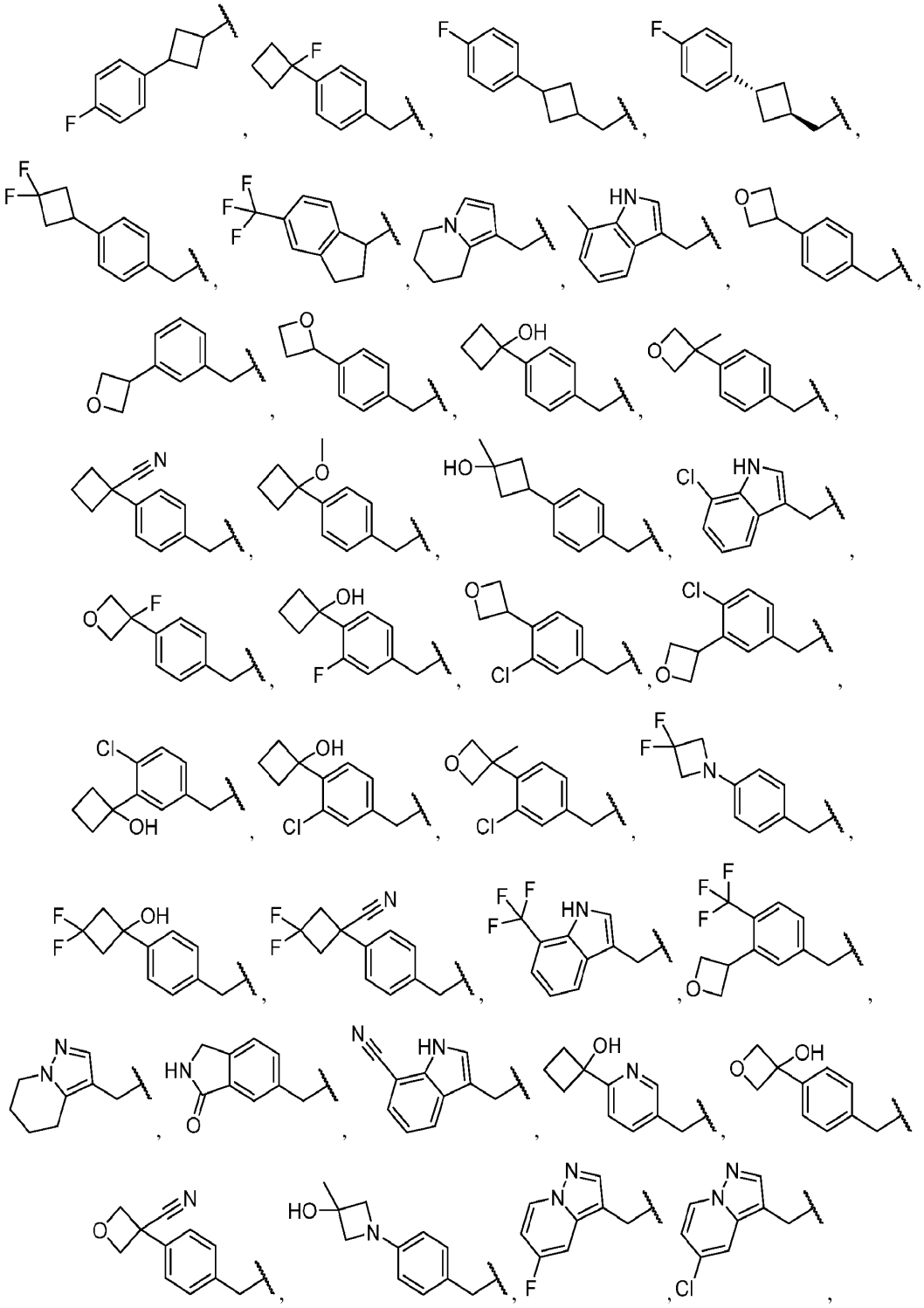
R_{15}, $R_{15'}$, R_{32}, and R_{33} are as defined in claim 1.

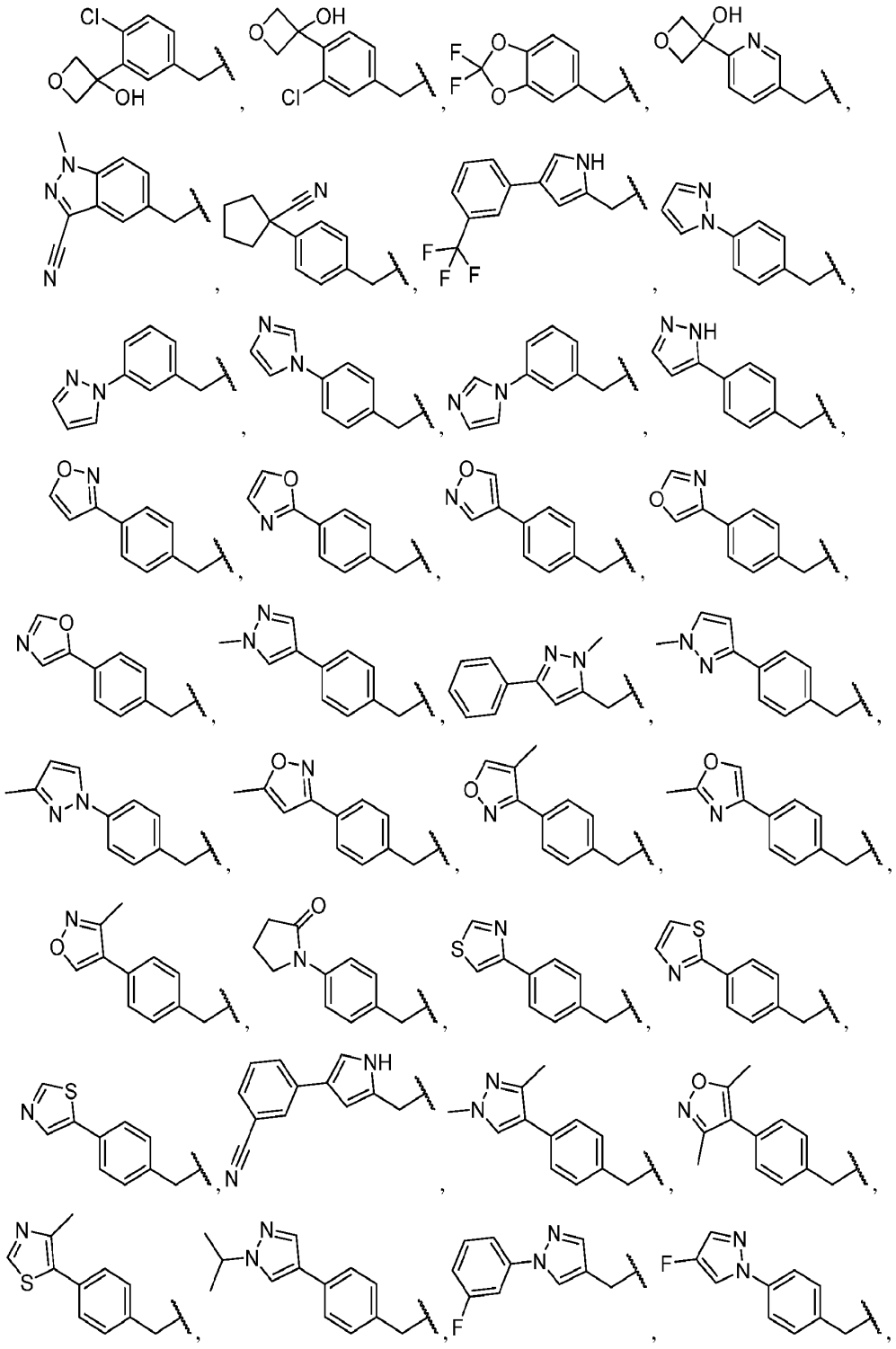
45. The compound according to claim 1, wherein R_8 is selected from:

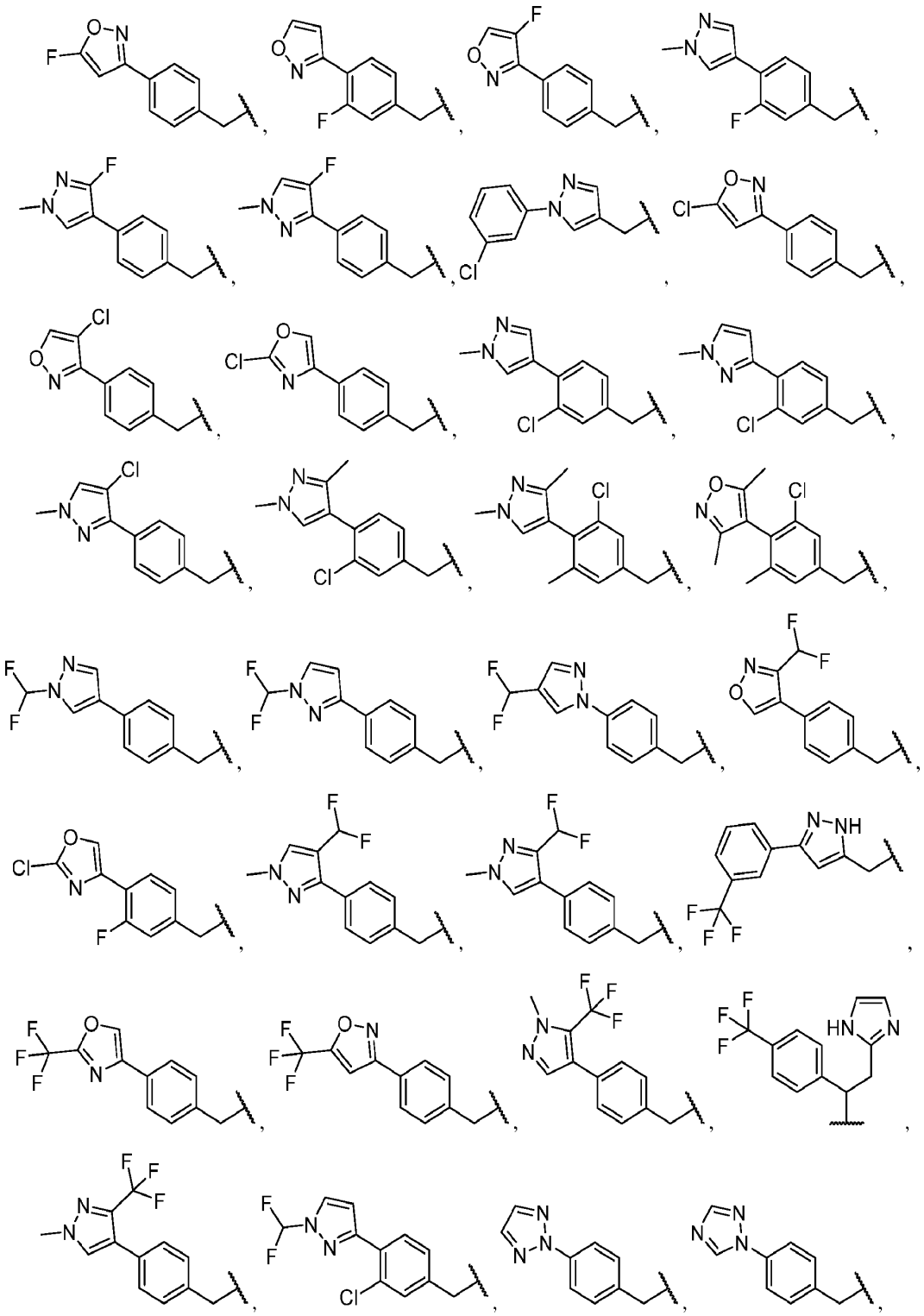


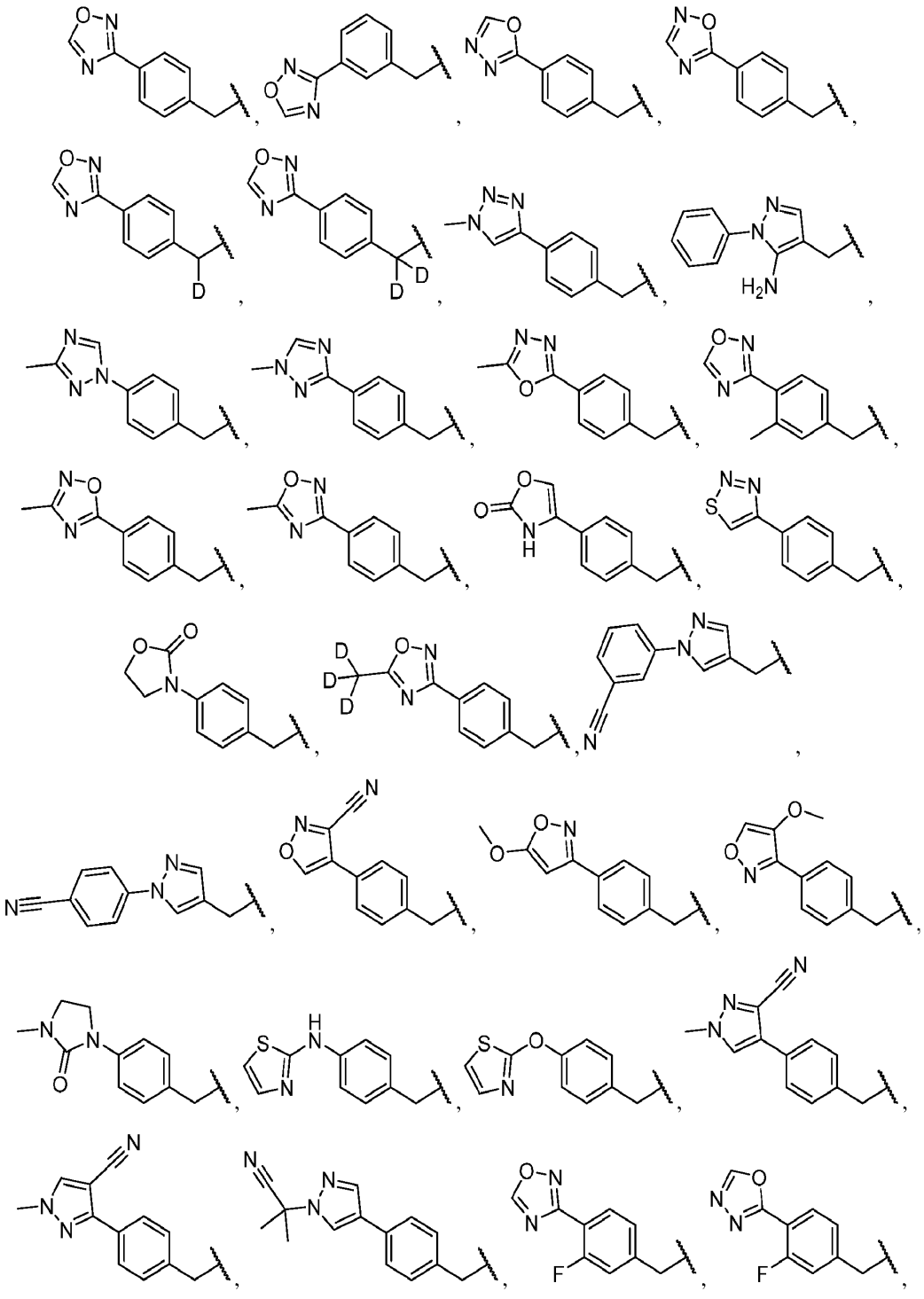


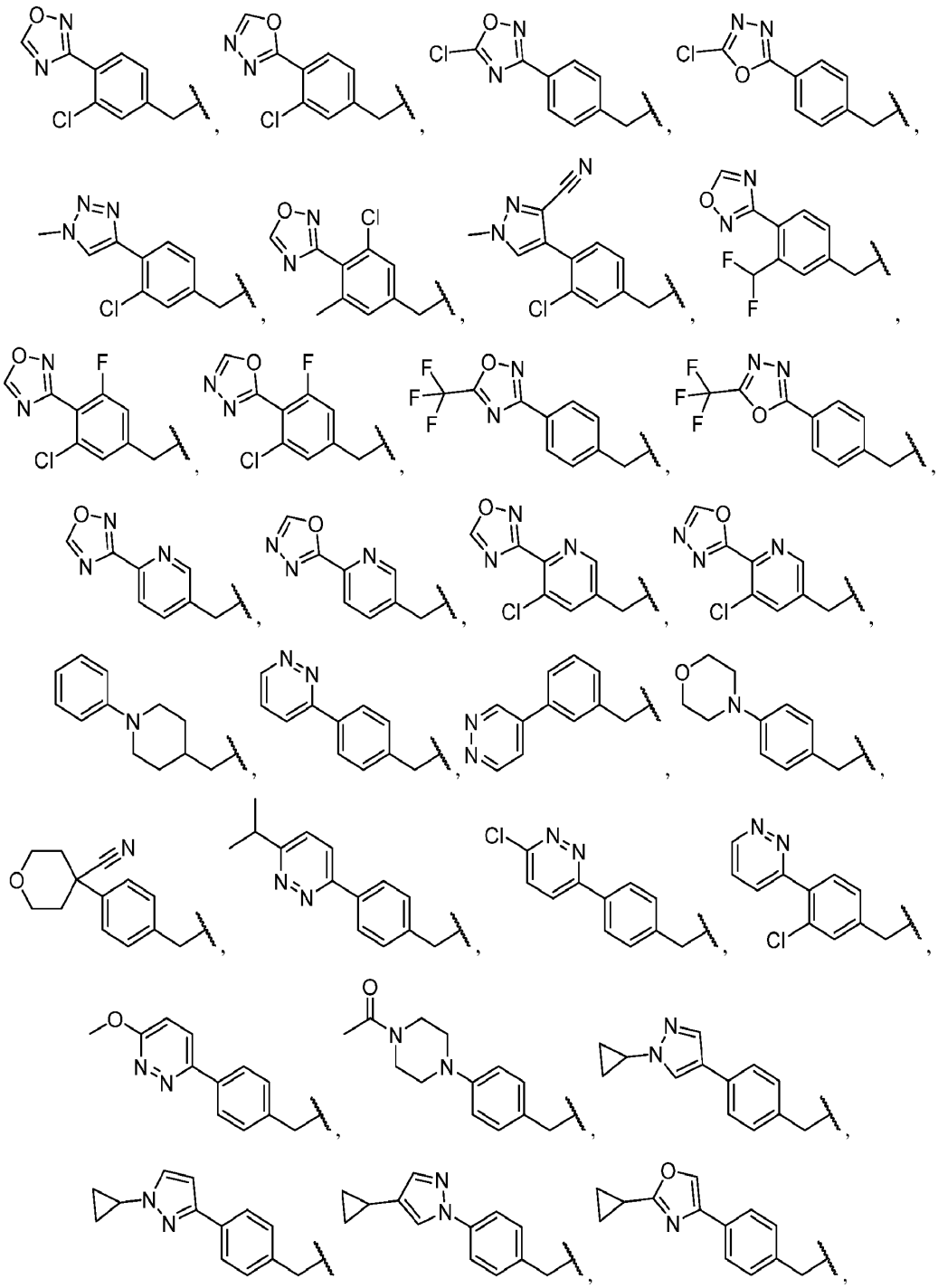


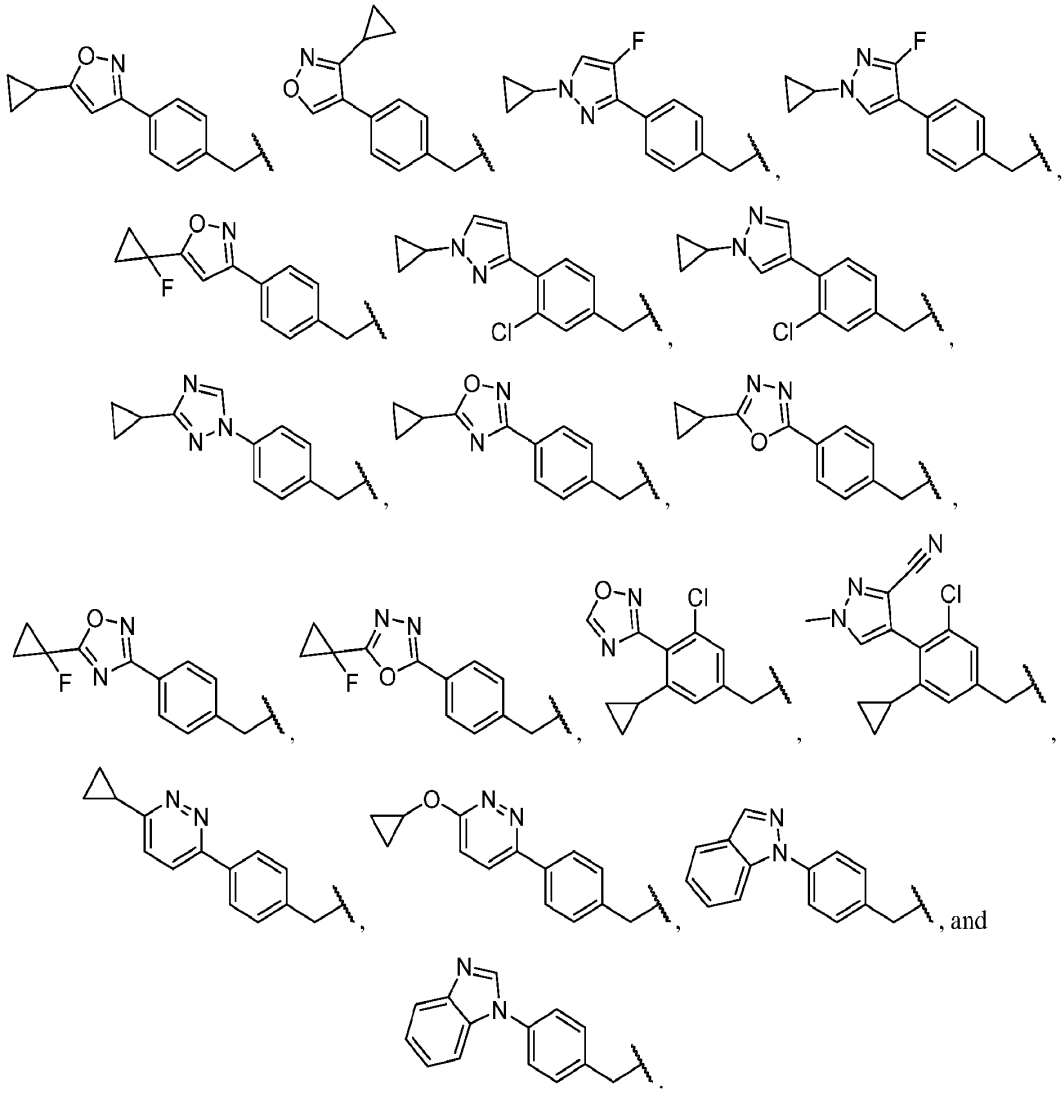












, and

46. The compound according to claim 1, wherein each R_{19} is independently at each occurrence (C_1-C_6)alkoxy, -$NR_{20}R_{20'}$, or (C_3-C_7)carbocyclyl wherein carbocyclyl is optionally substituted with two to four R_{23}.

47. The compound according to claim 1, wherein the compound is selected from any compound provided in Table 1, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

48. A pharmaceutical composition comprising a compound of claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier or excipient.

49. The pharmaceutical composition according to claim 48, further comprising at least one additional pharmaceutical agent.

50. The pharmaceutical composition according to claim 48 for use in the treatment of a disease or disorder that is affected by the reduction of HIF-1β levels.

51. A method of degrading HIF-1β, comprising administering to a patient in need thereof an effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

52. 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, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

53. 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, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

54. 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, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

55. The method according to claim 54, 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.

56. The method according to claim 54, 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.

57. A method of treating cancer, comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

58. The method according to claim 57, wherein the cancer is VHL-deficient cancer.

59. The method according to claim 57, 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.

60. 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, or a pharmaceutically acceptable salt thereof.

61. 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, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

62. 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, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

63. 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, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

64. The method of claim 63, wherein the renal cell carcinoma is clear cell renal cell carcinoma (ccRCC).

65. The method according to claim 54, wherein the administration is oral, parenteral, subcutaneous, by injection, or by infusion.

66. A compound according to claim 1, 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.

67. A compound according to claim 1, 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.

68. Use of a compound according to claim 1, 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.

69. Use of a compound according to claim 1, 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.

70. The compound for use according to claim 68 or 69 or the use according to claim 52 or 53, 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.