BICYCLIC HETEROCYCLES AS FGFR INHIBITORS

FIELD OF THE INVENTION

The present disclosure relates to bicyclic heterocycles, and pharmaceutical compositions of the same, that are inhibitors of the FGFR enzymes and are useful in the treatment of FGFR-associated diseases such as cancer.

BACKGROUND OF INVENTION

The Fibroblast Growth Factor Receptors (FGFR) are receptor tyrosine kinases that bind to fibroblast growth factor (FGF) ligands. There are four FGFR proteins (FGFR1-4) that are capable of binding ligands and are involved in the regulation of many physiological processes including tissue development, angiogenesis, wound healing, and metabolic regulation. Upon ligand binding, the receptors undergo dimerization and phosphorylation leading to stimulation of the protein kinase activity and recruitment of many intracellular docking proteins. These interactions facilitate the activation of an array of intracellular signaling pathways including Ras-MAPK, AKT-PI3K, and phospholipase C that are important for cellular growth, proliferation and survival (Reviewed in Eswarakumar et al. Cytokine & Growth Factor Reviews, 2005).

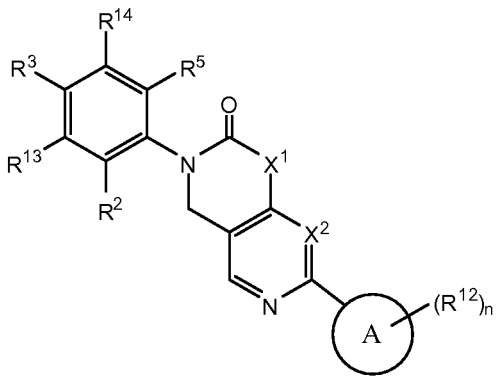
Aberrant activation of this pathway either through overexpression of FGF ligands or FGFR or activating mutations in the FGFRs can lead to tumor development, progression, and resistance to conventional cancer therapies. In human cancer, genetic alterations including gene amplification, chromosomal translocations and somatic mutations that lead to ligand-independent receptor activation have been described. Large scale DNA sequencing of thousands of tumor samples has revealed that components of the FGFR pathway are among the most frequently mutated in human cancer. Many of these activating mutations are identical to germline mutations that lead to skeletal dysplasia syndromes. Mechanisms that lead to aberrant ligand-dependent signaling in human disease include overexpression of FGFs and changes in FGFR splicing that lead to receptors with more promiscuous ligand binding abilities (Reviewed in Knights and Cook Pharmacology & Therapeutics, 2010; Turner and Grose, Nature Reviews Cancer, 2010). Therefore, development of inhibitors targeting FGFR may be useful in the clinical treatment of diseases that have elevated FGF or FGFR activity.

The cancer types in which FGF/FGFRs are implicated include, but are not limited to: carcinomas (e.g., bladder, breast, cervical, colorectal, endometrial, gastric, head and neck, kidney, liver, lung, ovarian, prostate); hematopoietic malignancies (e.g., multiple myeloma, chronic lymphocytic lymphoma, adult T cell leukemia, acute myelogenous leukemia, non-Hodgkin lymphoma, myeloproliferative neoplasms, and Waldenstrom's Macroglubulinemia); and other neoplasms (e.g., glioblastoma, melanoma, and rhabdosarcoma). In addition to a role in oncogenic neoplasms, FGFR activation has also been implicated in skeletal and chondrocyte disorders including, but not limited to, achrondroplasia and craniosynostosis syndromes.

The FGFR4-FGF19 signaling axis, specifically, has been implicated in the pathogenesis of a number of cancers including hepatocellular carcinoma (Heinzle et al., Cur. Pharm. Des. 2014, 20:2881). Ectopic expression of FGF19 in transgenic mice was shown to lead to tumor formation in the liver and a neutralizing antibody to FGF19 was found to inhibit tumor growth in mice. In addition, overexpression of FGFR4 has been observed in a multiple tumor types including hepatocellular carcinoma, colorectal, breast, pancreatic, prostate, lung, and thyroid cancers. Furthermore, activating mutations in FGFR4 have been reported in rhabdomyosarcoma (Taylor et al. JCI 2009,119:3395). Targeting FGFR with selective small molecule inhibitors may therefore prove beneficial in the treatment of cancers and other diseases.

SUMMARY OF INVENTION

In one aspect, the present disclosure relates to compounds having Formula (I'):



(I')

or a pharmaceutically acceptable salt thereof, wherein constituent variables are defined herein.

In another aspect, the present disclosure provides pharmaceutical compositions comprising a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient.

In another aspect, the present disclosure provides methods for inhibiting an FGFR3 and/or FGFR4 enzyme. The method includes contacting the enzyme with a compound of Formula (I'), or a pharmaceutically acceptable salt thereof or a composition comprising compounds of Formula (I').

In another aspect, the present disclosure provides a method for treating a disease associated with abnormal activity or expression of an FGFR enzyme, such as an FGFR3 and/or an FGFR4. The method includes administering an effective amount of a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formula (I'), to a patient in need thereof.

In yet another aspect, the present disclosure provides compounds of Formula (I') for use in treating a disease associated with abnormal activity or expression of an FGFR3 and/or FGFR4 enzyme.

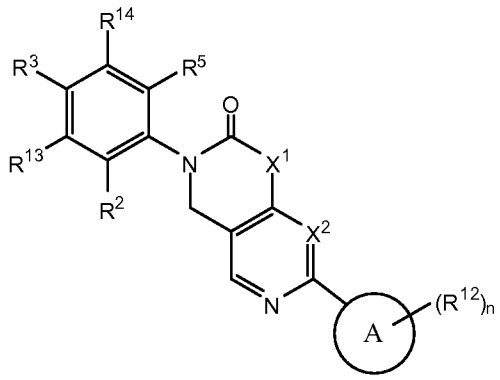
In another aspect, the present disclosure provides a method for treating a disorder mediated by an FGFR3 and/or FGFR4 enzyme, or a mutant thereof, in a patient in need thereof. The method includes administering to the patient a compound as described herein or pharmaceutically acceptable salts thereof or a composition comprising a compound as described herein.

In another aspect, the present disclosure provides the use of compounds of Formula (I') in the preparation of a medicament for use in therapy.

DETAILED DESCRIPTION

Compounds

In one aspect, the present disclosure provides a compound having Formula (I'):



or a pharmaceutically acceptable salt thereof, wherein:

ring A is a C_{6-10} aryl or 5- to 10-membered heteroaryl having carbon and 1 to 4 heteroatoms as ring members selected from O, N, and S, wherein the N and S are each optionally oxidized;

each R^{12} is independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^a, SR^a, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NR^aR^a, NR^aOR^a, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- are each optionally substituted with 1, 2, 3, or 4 independently selected R^b substituents;

or two adjacent R^{12} substituents on ring A taken together with the atoms to which they are attached form a fused 5- or 6-membered cycloalkyl ring, 5 to 6-membered heterocycloalkyl ring, phenyl or 5 to 6-membered heteroaryl ring, wherein the heterocycloalkyl or heteroaryl has 1-2 heteroatoms as ring members selected from O, N, and S;

each R^a is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10}

cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^a are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^d substituents;

or any two R^a substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

each R^b is independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$, and $S(O)_2NR^cR^c$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^b are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^f substituents;

each R^c is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^c are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^f substituents;

or any two R^c substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

each R^d is independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, CN, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$;

each R^f is independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, CN, OR^g, SR^g, $C(O)R^g$, $C(O)NR^gR^g$, $C(O)OR^g$, $OC(O)R^g$, $OC(O)NR^gR^g$, NR^gR^g, $NR^gC(O)R^g$, $NR^gC(O)NR^gR^g$, $NR^gC(O)OR^g$, $C(=NR^g)NR^gR^g$, $NR^gC(=NR^g)NR^gR^g$, $S(O)R^g$, $S(O)NR^gR^g$, $S(O)_2R^g$, $NR^gS(O)_2R^g$, $NR^gS(O)_2NR^gR^g$, and $S(O)_2NR^gR^g$;

each R^h is independently selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{1-6} haloalkyl, halo, CN, OR^i, SR^i, $C(O)R^i$, $C(O)NR^iR^i$, $C(O)OR^i$, $OC(O)R^i$, $OC(O)NR^iR^i$, NR^iR^i, $NR^iC(O)R^i$, $NR^iC(O)NR^iR^i$, $NR^iC(O)OR^i$, $C(=NR^i)NR^iR^i$, $NR^iC(=NR^i)NR^iR^i$, $S(O)R^i$, $S(O)NR^iR^i$, $S(O)_2R^i$, $NR^iS(O)_2R^i$, $NR^iS(O)_2NR^iR^i$, and $S(O)_2NR^iR^i$, wherein said C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, and 5-6 membered heteroaryl of R^h are optionally substituted by 1, 2, or 3 independentlys selected R^j substituents;

each R^j is independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, CN, OR^k, SR^k, $C(O)R^k$, $C(O)NR^kR^k$, $C(O)OR^k$, $OC(O)R^k$, $OC(O)NR^kR^k$, NR^kR^k, $NR^kC(O)R^k$, $NR^kC(O)NR^kR^k$, $NR^kC(O)OR^i$, $C(=NR^k)NR^kR^k$, $NR^kC(=NR^k)NR^kR^k$, $S(O)R^k$, $S(O)NR^kR^k$, $S(O)_2R^k$, $NR^kS(O)_2R^k$, $NR^kS(O)_2NR^kR^k$, and $S(O)_2NR^kR^k$;

each R^e, R^g, R^i or R^k is independently selected from H, C_{1-4} alkyl, C_{6-10}aryl, C_{1-4} haloalkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, wherein the C_{1-4} alkyl, C_{6-10}aryl, C_{2-4} alkenyl or C_{2-4} alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

or any two R^e substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^g substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^i substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

X^1 is $-CR^{10}R^{11}-$ or $-NR^7-$

X^2 is N or CR^6;

R^{13} is H, CN, $NR^{c4}R^{d4}$, OR^1 or $-C(O)NHR^e$, wherein R^1 is C_{1-3} alkyl or C_{1-3} haloalkyl;

R^2 is H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, CN, or C_{1-3} alkoxy;

R^3 is H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, CN, or C_{1-3} alkoxy;

R^{14} is H, CN, $NR^{c4}R^{d4}$, OR^4 or $-C(O)NHR^g$, wherein R^4 is C_{1-3} alkyl or C_{1-3} haloalkyl;

R^5 is H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, CN, or C_{1-3} alkoxy;

R^6 is selected from H, halo, CN, OR^{a4}, SR^{a4}, $C(O)NR^{c4}R^{d4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $S(O)_2NR^{c4}R^{d4}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl groups of R^6 are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10A};

R^7 is selected from H, $C(O)NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $S(O)_2NR^{c4}R^{d4}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, 5- to 10-membered heteroaryl having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, 4- to 10-membered heterocycloalkyl having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5- to 10-membered heteroaryl, 4-7 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- groups of R^7 are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10A}; or two R^{10A} substituents attached to the adjacent ring atoms of the aryl or heteroaryl ring of R^7, taken together with the atoms to which they are attached, form a fused C_{5-6} cycloalkyl ring or a fused 5- to 6-membered heterocycloalkyl ring having 1-2 heteroatoms as ring members independently selected from O, N and S, wherein the nitrogen and sulfur atoms are each optionally oxidized and the fused C_{5-6} cycloalkyl ring or fused 5 to 6-membered heterocycloalkyl is optionally substituted with 1 or 2 independently selected R^{19} groups;

R^{10} and R^{11} are each independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, a 5-10 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-10 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently

selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl groups of R^{10} and R^{11} are each optionally substituted with 1, 2, or 3, R^{10A};

alternatively, R^{10} and R^{11} together with the carbon atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl group or a 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl group; wherein said 3-, 4-, 5-, 6-, or 7-membered cycloalkyl group and 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl group are each optionally substituted with 1, 2, 3 or 4 R^{10A};

each R^{10A} is independently selected from halo, CN, NO_2, OR^{a4}, SR^{a4}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $S(O)_2NR^{c4}R^{d4}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl group of R^{10A} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{19};

each R^{a4}, R^{b4}, R^{c4}, and R^{d4} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl group of R^{a4}, R^{b4}, R^{c4}, and R^{d4} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{19};

alternatively, R^{c4} and R^{d4} together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group which is optionally substituted with 1, 2 or 3 substituents independently selected from R^{19};

each R^{e4} is independently H or C_{1-4} alkyl;

each R^{19} is independently selected from halo, CN, NO_2, OR^{a9}, SR^{a9}, $C(O)R^{b9}$, $C(O)NR^{c9}R^{d9}$, $C(O)OR^{a9}$, $OC(O)R^{b9}$, $OC(O)NR^{c9}R^{d9}$, $NR^{c9}R^{d9}$, $NR^{c9}C(O)R^{b9}$,

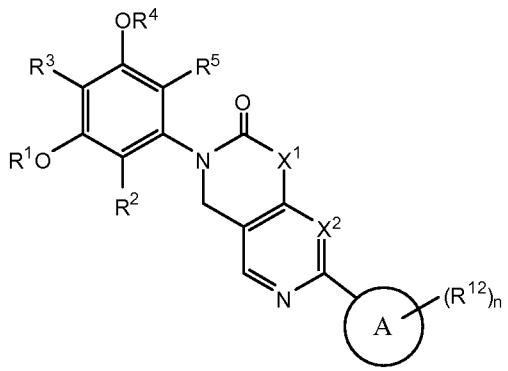
$NR^{c9}C(O)OR^{a9}$, $NR^{c9}C(O)NR^{c9}R^{d9}$, $NR^{c9}S(O)R^{b9}$, $NR^{c9}S(O)_2R^{b9}$, $NR^{c9}S(O)_2NR^{c9}R^{d9}$, $S(O)R^{b9}$, $S(O)NR^{c9}R^{d9}$, $S(O)_2R^{b9}$, $S(O)_2NR^{c9}R^{d9}$, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6}cycloalkyl and C_{1-4} haloalkyl; wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6}-cycloalkyl and C_{1-4} haloalkyl of R^{19} are each further optionally substituted with 1 or 2 R^{20} substituents independently selected from H, halo, CN, NO_2, OR^q, SR^q, $C(O)R^q$, $C(O)NR^qR^q$, $C(O)OR^q$, $OC(O)R^q$, $OC(O)NR^qR^q$, NR^qR^q, $NR^qC(O)R^q$, $NR^qC(O)OR^q$, $NR^qC(O)NR^qR^q$, $NR^qS(O)R^q$, $NR^qS(O)_2R^q$, $NR^qS(O)_2NR^qR^q$, $S(O)R^q$, $S(O)NR^qR^q$, $S(O)_2R^q$, $S(O)_2NR^qR^q$, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6}cycloalkyl and C_{1-4} haloalkyl, wherein each R^q is independently H or C_{1-4}alkyl;

each R^{a9}, R^{c9}, and R^{d9} is independently selected from H and C_{1-4} alkyl;

each R^{b9} is independently C_{1-4} alkyl; and

the subscript n is 0, 1, 2 or 3.

In some embodiments, the present disclosure provides a compound having Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

ring A is a C_{6-10} aryl or 5 to 6-membered heteroaryl having carbon and 1 to 4 heteroatoms as ring members selected from O, N, and S;

each R^{12} is independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^a, SR^a, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NR^aR^a, NR^aOR^a, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$,

$NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- are each optionally substituted with 1, 2, 3, or 4 independently selected R^b substituents;

or two adjacent R^{12} substituents on ring A taken together with the atoms to which they are attached form a fused 5- or 6-membered cycloalkyl ring, 5- to 6-membered heterocycloalkyl ring, phenyl or 5 to 6-membered heteroaryl ring, wherein the heterocycloalkyl or heteroaryl has 1-2 heteroatoms as ring members selected from O, N, and S;

each R^a is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^a are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^d substituents;

or any two R^a substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

each R^b is independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, CN, NO_2, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$, and $S(O)_2NR^cR^c$;

each R^c is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^f substituents;

or any two R^c substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents, wherein the C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl or 5-6 membered heteroaryl as R^h is optionally substituted with 1, 2, or 3 independently selected R^j substituents;

each R^d is independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, CN, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$;

each R^f is independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, CN, OR^g, SR^g, $C(O)R^g$, $C(O)NR^gR^g$, $C(O)OR^g$, $OC(O)R^g$, $OC(O)NR^gR^g$, NR^gR^g, $NR^gC(O)R^g$, $NR^gC(O)NR^gR^g$, $NR^gC(O)OR^g$, $C(=NR^g)NR^gR^g$, $NR^gC(=NR^g)NR^gR^g$, $S(O)R^g$, $S(O)NR^gR^g$, $S(O)_2R^g$, $NR^gS(O)_2R^g$, $NR^gS(O)_2NR^gR^g$, and $S(O)_2NR^gR^g$;

each R^h is independently selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{1-6} haloalkyl, halo, CN, OR^i, SR^i, $C(O)R^i$, $C(O)NR^iR^i$, $C(O)OR^i$, $OC(O)R^i$, $OC(O)NR^iR^i$, NR^iR^i, $NR^iC(O)R^i$, $NR^iC(O)NR^iR^i$, $NR^iC(O)OR^i$, $C(=NR^i)NR^iR^i$, $NR^iC(=NR^i)NR^iR^i$, $S(O)R^i$, $S(O)NR^iR^i$, $S(O)_2R^i$, $NR^iS(O)_2R^i$, $NR^iS(O)_2NR^iR^i$, and $S(O)_2NR^iR^i$, wherein said C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, and 5-6 membered heteroaryl are optionally substituted by 1, 2, or 3 independentlys selected R^j substituents;

each R^j is independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, CN, OR^k, SR^k, $C(O)R^k$, $C(O)NR^kR^k$, $C(O)OR^k$, $OC(O)R^k$, $OC(O)NR^kR^k$, NR^kR^k, $NR^kC(O)R^k$, $NR^kC(O)NR^kR^k$, $NR^kC(O)OR^i$, $C(=NR^k)NR^kR^k$, $NR^kC(=NR^k)NR^kR^k$, $S(O)R^k$, $S(O)NR^kR^k$, $S(O)_2R^k$, $NR^kS(O)_2R^k$, $NR^kS(O)_2NR^kR^k$, and $S(O)_2NR^kR^k$;

each R^e, R^g, R^i or R^k is independently selected from H, C_{1-4} alkyl, C_{6-10}aryl, C_{1-4} haloalkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, wherein the C_{1-4} alkyl, C_{6-10}aryl, C_{2-4} alkenyl or C_{2-4} alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

or any two R^e substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^g substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^i substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

X^1 is $-CR^{10}R^{11}-$ or $-NR^7-$

X^2 is N or CR^6;

R^1 is C_{1-3} alkyl or C_{1-3} haloalkyl;

R^2 is H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, CN, or C_{1-3} alkoxy;

R^3 is H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, CN, or C_{1-3} alkoxy;

R^4 is C_{1-3} alkyl or C_{1-3} haloalkyl;

R^5 is H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, CN, or C_{1-3} alkoxy;

R^6 and R^7 are each independently selected from H, halo, CN, OR^{a4}, SR^{a4}, $C(O)NR^{c4}R^{d4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $S(O)_2NR^{c4}R^{d4}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl groups of R^6 and R^7 are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10A};

R^{10} and R^{11} are each independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, a 5-10 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-10 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl groups of R^{10} and R^{11} are each optionally substituted with 1, 2, or 3, R^{10A};

alternatively, R^{10} and R^{11} together with the carbon atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl group or a 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl group; wherein said 3-, 4-, 5-, 6-, or 7-membered cycloalkyl

group and 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl group are each optionally substituted with 1, 2, 3 or 4 R^{10A};

each R^{10A} is independently selected from halo, CN, NO_2, OR^{a4}, SR^{a4}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $S(O)_2NR^{c4}R^{d4}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl group of R^{10A} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{19};

each R^{a4}, R^{b4}, R^{c4}, and R^{d4} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl group of R^{a4}, R^{b4}, R^{c4}, and R^{d4} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{19};

alternatively, R^{c4} and R^{d4} together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group which is optionally substituted with 1, 2 or 3 substituents independently selected from R^{19};

each R^{e4} is independently H or C_{1-4} alkyl;

each R^{19} is independently selected from halo, CN, NO_2, OR^{a9}, SR^{a9}, $C(O)R^{b9}$, $C(O)NR^{c9}R^{d9}$, $C(O)OR^{a9}$, $OC(O)R^{b9}$, $OC(O)NR^{c9}R^{d9}$, $NR^{c9}R^{d9}$, $NR^{c9}C(O)R^{b9}$, $NR^{c9}C(O)OR^{a9}$, $NR^{c9}C(O)NR^{c9}R^{d9}$, $NR^{c9}S(O)R^{b9}$, $NR^{c9}S(O)_2R^{b9}$, $NR^{c9}S(O)_2NR^{c9}R^{d9}$, $S(O)R^{b9}$, $S(O)NR^{c9}R^{d9}$, $S(O)_2R^{b9}$, $S(O)_2NR^{c9}R^{d9}$, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, and C_{1-4} haloalkyl; wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, and C_{1-4} haloalkyl are each further optionally substituted with 1 or 2 R^{20} substituents independently selected from H, halo, CN, NO_2, OR^q, SR^q, $C(O)R^q$, $C(O)NR^qR^q$, $C(O)OR^q$, $OC(O)R^q$, $OC(O)NR^qR^q$, NR^qR^q, $NR^qC(O)R^q$, $NR^qC(O)OR^q$, $NR^qC(O)NR^qR^q$,

$NR^qS(O)R^q$, $NR^qS(O)_2R^q$, $NR^qS(O)_2NR^qR^q$, $S(O)R^q$, $S(O)NR^qR^q$, $S(O)_2R^q$, $S(O)_2NR^qR^q$, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl and C_{1-4} haloalkyl, wherein each R^q is independently H or C_{1-4}alkyl;

each R^{a9}, R^{c9}, and R^{d9} is independently selected from H and C_{1-4} alkyl;

each R^{b9} is independently C_{1-4} alkyl; and

the subscript n is 0, 1, 2 or 3.

In some embodiments of compounds of Formula (I') or (I):

ring A is a C_{6-10} aryl or 5 to 6-membered heteroaryl having carbon and 1 to 4 heteroatoms as ring members selected from O, N, and S;

each R^{12} is independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^a, SR^a, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NR^aR^a, NR^aOR^a, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- are each optionally substituted with 1, 2, 3, or 4 independently selected R^b substituents;

or two adjacent R^{12} substituents on ring A taken together with the atoms to which they are attached form a fused 5- or 6-membered cycloalkyl ring, 5 to 6-membered heterocycloalkyl ring, phenyl or 5 to 6-membered heteroaryl ring, wherein the heterocycloalkyl or heteroaryl have 1-2 heteroatoms as ring members selected from O, N, and S;

each R^a is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-

as R^a are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^d substituents;

or any two R^a substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

each R^b is independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, CN, NO_2, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$, and $S(O)_2NR^cR^c$;

each R^c is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^f substituents;

or any two R^c substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

each R^d is independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, CN, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$;

each R^f is independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, CN, OR^g, SR^g, $C(O)R^g$, $C(O)NR^gR^g$, $C(O)OR^g$, $OC(O)R^g$, $OC(O)NR^gR^g$, NR^gR^g, $NR^gC(O)R^g$, $NR^gC(O)NR^gR^g$, $NR^gC(O)OR^g$, $C(=NR^g)NR^gR^g$, $NR^gC(=NR^g)NR^gR^g$, $S(O)R^g$, $S(O)NR^gR^g$, $S(O)_2R^g$, $NR^gS(O)_2R^g$, $NR^gS(O)_2NR^gR^g$, and $S(O)_2NR^gR^g$;

each R^h is independently selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{1-6} haloalkyl, halo, CN, OR^i, SR^i, $C(O)R^i$, $C(O)NR^iR^i$, $C(O)OR^i$, $OC(O)R^i$, $OC(O)NR^iR^i$, NR^iR^i, $NR^iC(O)R^i$, $NR^iC(O)NR^iR^i$, $NR^iC(O)OR^i$, $C(=NR^i)NR^iR^i$, $NR^iC(=NR^i)NR^iR^i$, $S(O)R^i$, $S(O)NR^iR^i$, $S(O)_2R^i$, $NR^iS(O)_2R^i$, $NR^iS(O)_2NR^iR^i$, and $S(O)_2NR^iR^i$, wherein said C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered

heterocycloalkyl, C_{6-10} aryl, and 5-6 membered heteroaryl are optionally substituted by 1, 2, or 3 independentlys selected R^j substituents;

each R^j is independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, CN, OR^k, SR^k, $C(O)R^k$, $C(O)NR^kR^k$, $C(O)OR^k$, $OC(O)R^k$, $OC(O)NR^kR^k$, NR^kR^k, $NR^kC(O)R^k$, $NR^kC(O)NR^kR^k$, $NR^kC(O)OR^i$, $C(=NR^k)NR^kR^k$, $NR^kC(=NR^k)NR^kR^k$, $S(O)R^k$, $S(O)NR^kR^k$, $S(O)_2R^k$, $NR^kS(O)_2R^k$, $NR^kS(O)_2NR^kR^k$, and $S(O)_2NR^kR^k$;

each R^e, R^g, R^i or R^k is independently selected from H, C_{1-4} alkyl, C_{6-10}aryl, C_{1-4} haloalkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, wherein the C_{1-4} alkyl, C_{6-10}aryl, C_{2-4} alkenyl or C_{2-4} alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

or any two R^e substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^g substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^i substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

X^1 is $-CR^{10}R^{11}-$ or $-NR^7-$

X^2 is N or CR^6;

R^1 is C_{1-3} alkyl or C_{1-3} haloalkyl;

R^2 is H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, CN, or C_{1-3} alkoxy;

R^3 is H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, CN, or C_{1-3} alkoxy;

R^4 is C_{1-3} alkyl or C_{1-3} haloalkyl;

R^5 is H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, CN, or C_{1-3} alkoxy;

R^6 is selected from H, halo, CN, OR^{a4}, SR^{a4}, $C(O)NR^{c4}R^{d4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $S(O)_2NR^{c4}R^{d4}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl having carbon and 1, 2, or 3 heteroatoms independently selected

from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl groups of R^6 are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10A};

R^7 is selected from H, $C(O)NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $S(O)_2NR^{c4}R^{d4}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl groups of R^7 are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10A};

R^{10} and R^{11} are each independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, a 5-10 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-10 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl groups of R^{10} and R^{11} are each optionally substituted with 1, 2, or 3, R^{10A};

alternatively, R^{10} and R^{11} together with the carbon atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl group or a 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl group; wherein said 3-, 4-, 5-, 6-, or 7-membered cycloalkyl group and 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl group are each optionally substituted with 1, 2, 3 or 4 R^{10A};

each R^{10A} is independently selected from halo, CN, NO_2, OR^{a4}, SR^{a4}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $S(O)_2NR^{c4}R^{d4}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered

heterocycloalkyl group of R^{10A} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{19};

each R^{a4}, R^{b4}, R^{c4}, and R^{d4} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl group of R^{a4}, R^{b4}, R^{c4}, and R^{d4} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{19};

alternatively, R^{c4} and R^{d4} together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group which is optionally substituted with 1, 2 or 3 substituents independently selected from R^{19};

each R^{e4} is independently H or C_{1-4} alkyl;

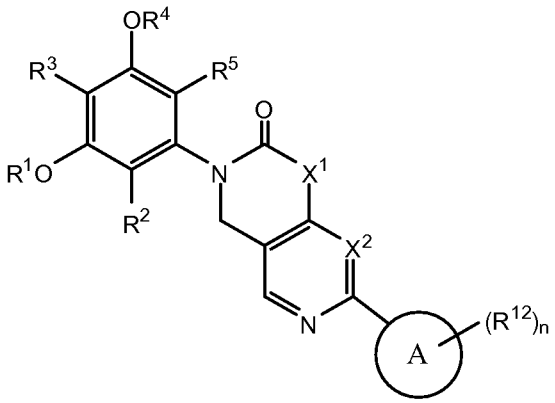
each R^{19} is independently selected from halo, CN, NO_2, OR^{a9}, SR^{a9}, $C(O)R^{b9}$, $C(O)NR^{c9}R^{d9}$, $C(O)OR^{a9}$, $OC(O)R^{b9}$, $OC(O)NR^{c9}R^{d9}$, $NR^{c9}R^{d9}$, $NR^{c9}C(O)R^{b9}$, $NR^{c9}C(O)OR^{a9}$, $NR^{c9}C(O)NR^{c9}R^{d9}$, $NR^{c9}S(O)R^{b9}$, $NR^{c9}S(O)_2R^{b9}$, $NR^{c9}S(O)_2NR^{c9}R^{d9}$, $S(O)R^{b9}$, $S(O)NR^{c9}R^{d9}$, $S(O)_2R^{b9}$, $S(O)_2NR^{c9}R^{d9}$, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6}cycloalkyl and C_{1-4} haloalkyl; wherein C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6}cycloalkyl and C_{1-4} haloalkyl are each further optionally substituted with 1 or 2 R^{20} substituents independently selected from H, halo, CN, NO_2, OR^q, SR^q, $C(O)R^q$, $C(O)NR^qR^q$, $C(O)OR^q$, $OC(O)R^q$, $OC(O)NR^qR^q$, NR^qR^q, $NR^qC(O)R^q$, $NR^qC(O)OR^q$, $NR^qC(O)NR^qR^q$, $NR^qS(O)R^q$, $NR^qS(O)_2R^q$, $NR^qS(O)_2NR^qR^q$, $S(O)R^q$, $S(O)NR^qR^q$, $S(O)_2R^q$, $S(O)_2NR^qR^q$, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6}cycloalkyl and C_{1-4} haloalkyl, wherein each R^q is independently H or C_{1-4}alkyl

each R^{a9}, R^{c9}, and R^{d9} is independently selected from H and C_{1-4} alkyl;

each R^{b9} is independently C_{1-4} alkyl; and

the subscript n is 0, 1, 2 or 3.

In one aspect, the present disclosure provides a compound having Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

ring A is a C_{6-10} aryl or 5 to 6-membered heteroaryl having carbon and 1 to 4 heteroatoms as ring members selected from O, N, and S;

each R^{12} is independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^a, SR^a, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NR^aR^a, NR^aOR^a, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- are each optionally substituted with 1, 2, 3, or 4 independently selected R^b substituents;

or two adjacent R^{12} substituents on ring A taken together with the atoms to which they are attached form a fused 5- or 6-membered cycloalkyl ring, 5 to 6-membered heterocycloalkyl ring, phenyl or 5 to 6-membered heteroaryl ring, wherein the heterocycloalkyl or heteroaryl have 1-2 heteroatoms as ring members selected from O, N, and S;

each R^a is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-

, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- as R^a are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^d substituents;

or any two R^a substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

each R^b is independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, CN, NO_2, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$, and $S(O)_2NR^cR^c$;

each R^c is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^f substituents;

or any two R^c substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents, wherein the C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl or 5-6 membered heteroaryl as R^h is optionally substituted with 1, 2, or 3 independently selected R^j substituents;

each R^d is independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, CN, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$;

each R^f is independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, CN, OR^g, SR^g, $C(O)R^g$, $C(O)NR^gR^g$, $C(O)OR^g$, $OC(O)R^g$, $OC(O)NR^gR^g$, NR^gR^g, $NR^gC(O)R^g$, $NR^gC(O)NR^gR^g$, $NR^gC(O)OR^g$, $C(=NR^g)NR^gR^g$, $NR^gC(=NR^g)NR^gR^g$, $S(O)R^g$, $S(O)NR^gR^g$, $S(O)_2R^g$, $NR^gS(O)_2R^g$, $NR^gS(O)_2NR^gR^g$, and $S(O)_2NR^gR^g$;

each R^h is independently selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{1-6} haloalkyl, halo, CN, OR^i, SR^i,

$C(O)R^i$, $C(O)NR^iR^i$, $C(O)OR^i$, $OC(O)R^i$, $OC(O)NR^iR^i$, NR^iR^i, $NR^iC(O)R^i$, $NR^iC(O)NR^iR^i$, $NR^iC(O)OR^i$, $C(=NR^i)NR^iR^i$, $NR^iC(=NR^i)NR^iR^i$, $S(O)R^i$, $S(O)NR^iR^i$, $S(O)_2R^i$, $NR^iS(O)_2R^i$, $NR^iS(O)_2NR^iR^i$, and $S(O)_2NR^iR^i$, wherein said C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, and 5-6 membered heteroaryl are optionally substituted by 1, 2, or 3 independentlys selected R^j substituents;

each R^j is independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, CN, OR^k, SR^k, $C(O)R^k$, $C(O)NR^kR^k$, $C(O)OR^k$, $OC(O)R^k$, $OC(O)NR^kR^k$, NR^kR^k, $NR^kC(O)R^k$, $NR^kC(O)NR^kR^k$, $NR^kC(O)OR^i$, $C(=NR^k)NR^kR^k$, $NR^kC(=NR^k)NR^kR^k$, $S(O)R^k$, $S(O)NR^kR^k$, $S(O)_2R^k$, $NR^kS(O)_2R^k$, $NR^kS(O)_2NR^kR^k$, and $S(O)_2NR^kR^k$;

each R^e, R^g, R^i or R^k is independently selected from H, C_{1-4} alkyl, C_{6-10}aryl, C_{1-4} haloalkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, wherein the C_{1-4} alkyl, C_{6-10}aryl, C_{2-4} alkenyl or C_{2-4} alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

or any two R^e substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^g substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^i substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

X^1 is $-CR^{10}R^{11}-$ or $-NR^7-$

X^2 is N or CR^6;

R^1 is C_{1-3} alkyl or C_{1-3} haloalkyl;

R^2 is H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, CN, or C_{1-3} alkoxy;

R^3 is H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, CN, or C_{1-3} alkoxy;

R^4 is C_{1-3} alkyl or C_{1-3} haloalkyl;

R^5 is H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, CN, or C_{1-3} alkoxy;

R^6 and R^7 are each independently selected from H, halo, CN, OR^{a4}, SR^{a4}, $C(O)NR^{c4}R^{d4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$,

$S(O)_2NR^{c4}R^{d4}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl groups of R^6 and R^7 are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10A};

R^{10} and R^{11} are each independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, a 5-10 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-10 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl groups of R^{10} and R^{11} are each optionally substituted with 1, 2, or 3, R^{10A};

alternatively, R^{10} and R^{11} together with the carbon atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl group or a 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl group; wherein said 3-, 4-, 5-, 6-, or 7-membered cycloalkyl group and 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl group are each optionally substituted with 1, 2, 3 or 4 R^{10A};

each R^{10A} is independently selected from halo, CN, NO_2, OR^{a4}, SR^{a4}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $S(O)_2NR^{c4}R^{d4}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl group of R^{10A} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{19};

each R^{a4}, R^{b4}, R^{c4}, and R^{d4} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7

membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl group of R^{a4}, R^{b4}, R^{c4}, and R^{d4} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{19};

alternatively, R^{c4} and R^{d4} together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group which is optionally substituted with 1, 2 or 3 substituents independently selected from R^{19};

each R^{e4} is independently H or C_{1-4} alkyl;

each R^{19} is independently selected from halo, CN, NO_2, OR^{a9}, SR^{a9}, $C(O)R^{b9}$, $C(O)NR^{c9}R^{d9}$, $C(O)OR^{a9}$, $OC(O)R^{b9}$, $OC(O)NR^{c9}R^{d9}$, $NR^{c9}R^{d9}$, $NR^{c9}C(O)R^{b9}$, $NR^{c9}C(O)OR^{a9}$, $NR^{c9}C(O)NR^{c9}R^{d9}$, $NR^{c9}S(O)R^{b9}$, $NR^{c9}S(O)_2R^{b9}$, $NR^{c9}S(O)_2NR^{c9}R^{d9}$, $S(O)R^{b9}$, $S(O)NR^{c9}R^{d9}$, $S(O)_2R^{b9}$, $S(O)_2NR^{c9}R^{d9}$, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{1-4} haloalkyl;

each R^{a9}, R^{c9}, and R^{d9} is independently selected from H and C_{1-4} alkyl;

each R^{b9} is independently C_{1-4} alkyl; and

the subscript n is 0, 1, 2 or 3.

In some embodiments, R^7 is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl groups of R^7 are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10A}.

In some embodiments, R^7 is C_{1-6} alkyl, phenyl, benzyl, C_{3-6} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, 4- to 10-membered heterocycloalkyl, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, 5- to 10-membered heteroaryl, or (5- to 10-membered heteroaryl)-C_{1-4} alkyl-, each of which is optionally substituted with 1, 2, or 3 independently selected R^{10A} substituents; or two R^{10A} substituents attached to the adjacent ring atoms of the aryl or heteroaryl ring of R^7 are optionally taken together with the atoms to which they are attached form a fused C_{5-6} cycloalkyl ring or a fused 5 to 6-membered heterocycloalkyl ring having 1-2 heteroatoms as ring members independently selected from O, N and S, wherein

the nitrogen and sulfur atoms are each optionally oxidized and the fused C_{5-6} cycloalkyl ring or fused 5 to 6-membered heterocycloalkyl is optionally substituted with 1 or 2 independently selected R^{19} groups.

R^7 is C_{1-6} alkyl, cyclopropylmethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-fluorobenzyl, tetrahydrofuran-3-yl, (3-methylisoxazol-5-yl)methyl, (tetrahydro-2H-pyran-4-yl)methyl, (5-cyclopropylisoxazol-3-yl)methyl, 5-methylisoxazol-3-yl)methyl, 4-fluorophenyl, (1-ethylpyrazol-4-yl)methyl, benzothiazol-6-yl, 1-methyl-5-oxopyrrolidin-3-yl, 1-acetylpiperidin-4-yl, 2,3-dihydro-1,4-benzodioxin-6-ylmethyl, 1-t-butoxycarbonylpiperidin-4-yl, 4-cyanophenyl, 4-pyrimidinyl, 2-pyrimidinyl, 5-pyrimidinyl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, (1,5-dimethylpyrazol-4-yl)methyl, or (5-methyl-1,3,4-oxadiazol-2-yl)methyl.

In some embodiments, R^7 is C_{1-6} alkyl, cyclopropylmethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-fluorobenzyl, (3-methylisoxazol-5-yl)methyl, (5-cyclopropylisoxazol-3-yl)methyl, 4-fluorophenyl, (1-ethylpyrazol-4-yl)methyl, 1-acetylpiperidin-4-yl, 2,3-dihydro-1,4-benzodioxin-6-ylmethyl, 1-t-butoxycarbonylpiperidin-4-yl, 4-cyanophenyl, 4-pyrimidinyl, 2-pyrimidinyl, 5-pyrimidinyl, 1-methylpyrazol-3-yl, (1,5-dimethylpyrazol-4-yl)methyl, or (5-methyl-1,3,4-oxadiazol-2-yl)methyl.

In some embodiments, R^7 is C_{1-6} alkyl, cyclopropylmethyl, cyclopentyl, 4-fluorobenzyl, tetrahydrofuran-3-yl, (3-methylisoxazol-5-yl)methyl, (tetrahydro-2H-pyran-4-yl)methyl, (5-cyclopropylisoxazol-3-yl)methyl, 5-methylisoxazol-3-yl)methyl, 4-fluorophenyl, (1-ethylpyrazol-4-yl)methyl, benzothiazol-6-yl, 1-methyl-5-oxopyrrolidin-3-yl, 1-acetylpiperidin-4-yl, 2,3-dihydro-1,4-benzodioxin-6-ylmethyl, 4-cyanophenyl, 4-pyrimidinyl, (1,5-dimethylpyrazol-4-yl)methyl, or (5-methyl-1,3,4-oxadiazol-2-yl)methyl.

In some embodiments, R^7 is methyl, isopropyl, pyridazin-4-yl, (2-methoxypyridin-4-yl)methyl, (6-methoxypyridin-3-yl)methyl, 3-cyanophenyl, pyrimidin-5-yl, isoquinolin-7-yl, 4-methylcarbamoylbenzyl, (5-ethylisoxazol-3-yl)methyl, pyrimidin-4-ylmethyl, 3-cyano-4-fluorophenyl, (5-ethyl-1,3,4-oxadiazol-2-yl)methyl, (2-methylpyridin-4-yl)methyl, pyridin-4-ylmethyl, pyrazin-2-yl, 1-(methylsulfonyl)piperidin-4-yl, (1-methyl-1H-pyrazol-4-yl)methyl, 3,4-difluorobenzyl, 2-cyano-5-pyridyl, 2-methylbenzo[d]oxazol-6-yl, 4-(1H-pyrazol-1-yl)phenyl, 3-cyano-5-fluorophenyl, 5-cyano-2-pyridyl, oxazol-5-ylmethyl, 4-cyano-5-methoxyphenyl, (5-methyloxazol-2-yl)methyl, cyclopropyl, pyrimidin-5-ylmethyl, pyrazin-2-ylmethyl, pyridin-3-yl, 6-methylpyrazin-2-yl, pyridazin-3-ylmethyl, 3-(1-methyl-1H-1,2,3-triazol-5-yl)phenyl, 1-cyanocyclopropyl, 2-pyridyl, (5-isopropylisoxazol-3-yl)methyl,

pyridin-2-ylmethyl, (2-methylthiazol-4-yl)methyl, (1-methyl-5-oxopyrrolidin-3-yl)methyl, 4-(cyanomethyl)phenyl, 4-(methylsulfonyl)phenyl, 3-fluorophenyl, 1-methyl-1H-pyrazol-3-yl, (1,3-dimethyl-1H-pyrazol-4-yl)methyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 4-methoxyphenyl, pyrimidin-2-yl, 5-ethylpyrazin-2-yl, 5-methylpyrazin-2-yl, (tetrahydrofuran-3-yl)methyl, 3-methoxyphenyl, 2-fluorophenyl, 3-(methylsulfamoyl)phenyl, 5-methoxypyrazin-2-yl, 4-(dimethylcarbamoyl)phenyl, 2-(1-methyl-1H-pyrazol-4-yl)ethyl, 5-methyl-1,3,4-oxadiazol-2-yl, (2-ethoxypyridin-4-yl)methyl, (1-methyl-2-oxo-1,2-dihydropyridin-4-yl)methyl, (1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)methyl, 2-oxoindolin-5-yl, 2-methyl-3-oxoisoindolin-5-yl, (2-methylpyrimidin-4-yl)methyl, 1-(methylcarboxy)piperidin-4-yl, 4-(methoxycarbonylamino)phenyl, (1-cyclopropyl-1H-pyrazol-4-yl)methyl, (1-cyanomethyl-1H-pyrazol-4-yl)methyl, (1-cyclopropylmethyl-1H-pyrazol-4-yl)methyl, (1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)methyl, 1H-pyrazol-4-yl, 1-cyclopropyl-1H-pyrazol-4-yl, 1-ethyl-1H-pyrazol-4-yl, 1-propyl-1H-pyrazol-4-yl, 1H-indazol-6-yl, 1H-indazol-5-yl, pyrimidin-4-yl, cyclobutyl, 3-pyridyl, 2-methoxyethyl, cyclopropylmethyl, ethyl, 4-cyanophenyl, (1-ethyl-1H-pyrazol-4-yl)methyl, (5-methyl-1,3,4-oxadiazol-2-yl)methyl, or 1-methyl-1H-pyrazol-4-yl.

In some embodiments, compounds of Formula (I') or (I) have selective inhibitory activity on FGFR4 enzyme or any mutant thereof over other FGFR enzymes. In other embodiments, compounds of Formula (I') or (I) have selective inhibitory activity on FGFR3 enzyme or any mutant thereof over other FGFR enzymes. In other embodiments, compounds of Formula (I') or (I) have selective dual inhibitory activity on both FGFR3 and FGFR4 enzymes or any mutant thereof.

In some embodiments of compounds of Formula (I') or (I), ring A is C_{6-10} aryl. In certain instances, ring A is phenyl. In one instance, ring A is 1-naphthyl or 2-naphthyl.

In some embodiments of compounds of Formula (I') or (I), ring A is phenyl and two adjacent R^{12} substituents on the phenyl ring taken together with the carbon atoms to which they are attached form a fused 3 to 7-membered cycloalkyl. In some instances, ring A is phenyl and two adjacent R^{12} substituents on the phenyl ring taken together with the carbon atoms to which they are attached form a fused cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

In some embodiments of compounds of Formula (I') or (I), ring A is phenyl and two adjacent R^{12} substituents on the phenyl ring taken together with the carbon atoms to which they are attached form a fused 4 to 6-membered heterocycloalkyl. In some instances, ring A

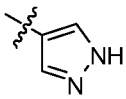
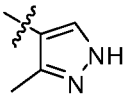
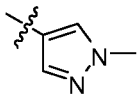
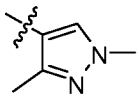
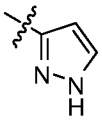
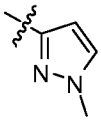
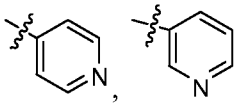
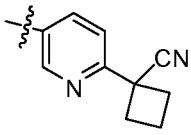
is phenyl and two adjacent R^{12} substituents on the phenyl ring taken together with the carbon atoms to which they are attached form a fused 2-oxetanyl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 1,1-dioxotetrahydrothiophen-2-yl, 1,1-dioxotetrahydrothiophen-3-yl, 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl, 3,6-dihydro-2H-pyranyl, 3,4-dihydro-2H-pyranyl, 1-azetidinyl, 2-azetidinyl, 3-azetidinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-oxo-pyrrolidin-1-yl, 2-oxo-pyrrolidin-3-yl, 2-oxo-pyrrolidin-4-yl, 2-oxo-pyrrolidin-5-yl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 2-oxo-piperidin-1-yl, 2-oxo-piperidin-3-yl, 2-oxo-piperidin-4-yl, 2-oxo-piperidin-5-yl, 2-oxo-piperidin-6-yl, 1-piperazinyl, 2-piperazinyl, 4-morpholinyl, 3-morpholinyl or 2-morpholinyl.

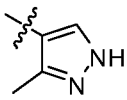
In some embodiments of compounds of Formula (I') or (I), ring A is 5-membered heteroaryl. In some embodiments, ring A is 5-membered heteroaryl selected from pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, thiophenyl, thiazolyl, isoxazolyl, isothiazolyl, or furanyl. In some embodiments, ring A is pyrazolyl or imidazolyl. In some embodiments, ring A is pyrazolyl. In some embodiments, ring A is 4-pyrazolyl.

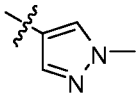
In some embodiments of compounds of Formula (I') or (I), ring A is 5-membered heteroaryl selected from 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 2-oxazolyl, 4- oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3- isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 1 ,2,3-triazol- 1 -yl, 1 ,2,3-triazol-2-yl, 1 ,2,3-triazol-3-yl, l ,2,3-triazol-4-yl, 1 ,2,3-triazol-5-yl, 1 ,2,4-triazol-l -yl, 1 ,2,4-triazol-2-yl, l,2,4-triazol-3-yl, 1 ,2,4-triazol-4-yl, l,2,4-triazol-5-yl, l -oxa-2,3-diazol-4-yl, l -oxa-2,3-diazol-5-yl, l-oxa-2,4-diazol-3-yI, 1 - oxa-2,4-diazol-5-yl, l -oxa-2,5-diazol-3-yl, l -oxa-2,5-diazol-4-yl, l -thia-2,3-diazol-4-yl, l -thia-2,3- diazol-5-yl, l -thia-2,4-diazol-3-yl, l -thia-2,4-diazol-5-yl, l -thia-2,5-diazol-3-yl, 1 -thia-2,5-diazol-4- yl, 1-tetrazolyl, 3-tetrazolyl, l H-5-tetrazolyl, 3H-5-tetrazolyl, 2-furanyl, 3-furanyl, 2-thiopenyl, and 3-thiophenyl.

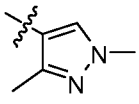
In some embodiments of compounds of Formula (I') or (I), ring A is 6-membered heteroaryl. In certain embodiments, ring A is selected from pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, and triazinyl. In some embodiments of compounds of Formula (I') or (I), ring A is 6-membered heteroaryl selected from 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrazinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 1,2,3-triazin-4-yl, 1,2,3-triazin-5-yl, 1,3,5-triazin-2-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, and 1,2,4-triazin-6-yl.

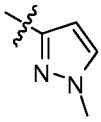
In some embodiments, ring A is pyridyl. In other embodiments, ring A is phenyl or 6-membered heteroaryl. In other embodiments, ring A is phenyl or pyridyl.

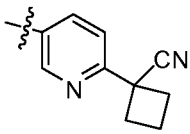
In some embodiments, ring A is  ,  ,  ,  ,  ,  ,  , or  , each of which is optionally substituted with 1 or 2 R^{12} substituents as defined herein.

In some embodiments, ring A is  substituted with R^{12} as defined herein.

In some embodiments, ring A is  ,optionally substituted with R^{12}.

In some embodiments, ring A is  .

In some embodiments, ring A is  , optionally substituted with R^{12}.

In some embodiments, ring A is  .

In some embodiments of compounds of Formula (I'), R^{13} is H, CN, $NR^{c4}R^{d4}$, OR^1 or -C(O)NHR^e, wherein R^1 is C_{1-3} alkyl or C_{1-3} haloalkyl and R^{14} is H, CN, $NR^{c4}R^{d4}$, OR^4 or -C(O)NHR^g, wherein R^4 is C_{1-3} alkyl or C_{1-3} haloalkyl. In other embodiments, R^{13} is OR^1 and R^{14} is OR^4. In other embodiments, R^{13} is -C(O)NHR^e and R^{14} is OR^4. In other embodiments, R^{13} and R^{14} are each OCH_3. In other embodiments, R^{13} is -C(O)NHR^e and R^{14} is OR^4. In some embodiments, R^{13} and R^{14} are each independently selected form C_{1-4} alkyl-NHC(O)- and OCH_3. In one embodiment, R^{13} is -C(O)NHC_{1-6} alkyl and R^{14} is OR^4. In another embodiment, R^{13} is -C(O)NHC_{1-6}alkyl and R^{14} is OCH_3. In another embodiment, R^{13} is -C(O)NHCH_3 and R^{14} is OCH_3. In some embodiments, R^{13} is H and R^{14} is CN, $NR^{c4}R^{d4}$, OR^4 or -C(O)NHR^g.

In some embodiments of compounds of Formula (I') or (I), R^2 and R^5 are each independently H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, CN, or C_{1-3} alkoxy. In other embodiments,

R^2 and R^5 are each independently halogen. In some instances, R^2 and R^5 are halogen. In a preferred embodiment, R^2 and R^5 are F.

In some embodiments of compounds of Formula (I') or (I), R^1 and R^4 are each independently C_{1-3} alkyl or C_{1-3} haloalkyl. In some instances, R^1 and R^4 are each independently C_{1-3} alkyl. In other instances, R^1 and R^4 are each independently methyl, ethyl, propyl, CF_3, CF_2H or CFH_2. In a preferred embodiment, R^1 and R^4 are CH_3.

In some embodiments of compounds of Formula (I') or (I), R^3 is H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, CN, or C_{1-3} alkoxy. In some instances, R^3 is H, F, Cl, C_{1-3}alkyl, CF_3, CF_3O, CFH_2, CHF_2, $OCFH_2$ or $OCHF_2$. In a preferred embodiment, R^3 is H.

In some embodiments of compounds of Formula (I') or (I), R^{10} and R^{11} are each independently C_{1-6} alkyl. In some instances, R^{10} and R^{11} are methyl. In some embodiments, R^{10} and R^{11} taken together with the carbon atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl group, which is optionally substituted with 1 or 2 independently selected R^{10A} groups. In some instances, R^{10} and R^{11} taken together with the carbon atom to which they are attached form cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, each of which is optionally substituted with from 1-3 R^{10A} groups. In a preferred embodiment, R^{10} and R^{11} together with the carbon atom to which they are attached form a cyclopropyl, optionally substituted with 1 or 2 independently selected R^{10A} groups. In some embodiments, R^{10} and R^{11} are H. In certain embodiments, R^{10} and R^{11} are each independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{1-6} haloalkyl; wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2 or 3 substituents independently selected from R^{10A}.

In some embodiments of compounds of Formula (I') or (I), R^{10} and R^{11} taken together with the carbon atom to which they are attached form 4-, 5-, 6-, or 7-membered heterocycloalkyl group, which is optionally substituted with 1 or 2 independently selected R^{10A} groups. In some instances, R^{10} and R^{11} together with the carbon atom to which they are attached form 2-oxetanyl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl, 3,6-dihydro-2H-pyranyl, 3,4-dihydro-2H-pyranyl, 1-azetidinyl, 2-azetidinyl, 3-azetidinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 1-piperazinyl, 2-piperazinyl, 4-morpholinyl, 3-morpholinyl or 2-morpholinyl, 1-azepanyl, 2-azepanyl, 3-azepanyl, 4-azepanyl, 2-oxepanyl, 3-oxepanyl or 4-oxepanyl, each of which is optionally substituted with 1 or 2 independently selected R^{10A}.

In some embodiments, R^{10A} is halo, CN, C_{1-6} alkyl, C_{3-6} cycloalkyl, -C(O)R^{b4}, or -C(O)OR^{b4}; or two R^{10A} substituents attached to the adjacent ring atoms of the aryl or heteroaryl ring of R^7 are optionally taken together with the atoms to which they are attached form a 5- to 6-membered heterocycloalkyl ring having 1-2 heteroatoms as ring members independently selected from O, N and S, wherein the nitrogen and sulfur atoms are each optionally oxidized.

In some embodiments, R^{10A} is F, Cl, CH_3, C_{1-6} alkyl, CN, -C(O)C_{1-4} alkyl or -C(O)OC_{1-4} alkyl; or two R^{10A} substituents attached to the adjacent ring atoms of the aryl or heteroaryl ring of R^7 are optionally taken together with the atoms to which they are attached form a tetrahydrofuran, tetrahydropyran, 1,4-dioxane, morpholine, tetrahydrothiopyran or tetrahydrothiophene ring, each of which is optionally substituted with 1 or 2 R^{19} substituents.

In some embodiments, R^{10A} is F, CH_3, CN, -C(O)CH_3, or cyclopropyl.

In some embodiments, R^{10} and R^{11} together with the carbon atom to which they are attached form a cyclopropyl.

In some embodiments of compounds of Formula (I') or (I), X^1 is -$CR^{10}R^{11}$- or –NR^7-. In one embodiment, X^1 is -$CR^{10}R^{11}$-. In another embodiment, X^1 is -NR^7-. In some instances, X^1 is CH_2 or NH.

In some embodiments of compounds of Formula (I') or (I), X^1 is NR^7, wherein R^7 is C_{1-6} alkyl, phenyl, benzyl, C_{3-6} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, 4- to 10-membered heterocycloalkyl, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, 5- to 10-membered heteroaryl, or (5- to 10-membered heteroaryl)-C_{1-4} alkyl-, each of which is optionally substituted with 1, 2, or 3 independently selected R^{10A} substituents; or two R^{10A} substituents attached to the adjacent ring atoms of the aryl or heteroaryl ring of R^7 are taken together with the atoms to which they are attached form a fused C_{5-6} cycloalkyl ring or a fused 5 to 6-membered heterocycloalkyl ring having 1-2 heteroatoms as ring members independently selected from O, N and S, wherein the nitrogen and sulfur atoms are each optionally oxidized; and wherein one or two ring atoms in the fused C_{5-6} cycloalkyl ring or fused 5 to 6-membered heterocycloalkyl are optionally replaced by a carbonyl group, and the fused C_{5-6} cycloalkyl ring or fused 5 to 6-membered heterocycloalkyl is optionally substituted with 1 or 2 independently selected R^{19} groups. In some instances, R^{10A} is halo, CN, C_{1-6}alkyl, C_{3-6}cycloalkyl, -C(O)R^{b4} or -C(O)OR^{b4}; or two R^{10A} substituents attached to the adjacent ring atoms of the aryl or heteroaryl ring of R^7 are taken together with the atoms to which they are attached form a 5- to 6-membered heterocycloalkyl ring having 1-2 heteroatoms as ring

members independently selected from O, N and S, wherein the nitrogen and sulfur atoms are each optionally oxidized. In other instances, R^{10A} is F, Cl, CH_3, C_{1-6} alkyl, CN, -C(O)C_{1-4} alkyl or -C(O)OC_{1-4} alkyl; or two R^{10A} substituents attached to the adjacent ring atoms of the aryl or heteroaryl ring of R^7 are taken together with the atoms to which they are attached form a tetrahydrofuran, tetrahydropyran, 1,4-dioxane, morpholine, tetrahydrothiopyran, or tetrahydrothiophene ring, each of which is optionally substituted with 1 or 2 R^{19} substituents.

In some embodiments of compounds of Formula (I') or (I), X^1 is NR^7, wherein R^7 is C_{1-6} alkyl, cyclopropylmethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-fluorobenzyl, (3-methylisoxazol-5-yl)methyl, (5-cyclopropylisoxazol-3-yl)methyl, 4-fluorophenyl, (1-ethylpyrazol-4-yl)methyl, 1-acetylpiperidin-4-yl, 2,3-dihydro-1,4-benzodioxin-6-ylmethyl, 1-t-butoxycarbonylpiperidin-4-yl, 4-cyanophenyl, 4-pyrimidinyl, 2-pyrimidinyl, 5-pyrimidinyl, 1-methylpyrazol-3-yl, (1,5-dimethylpyrazol-4-yl)methyl or (5-methyl-1,3,4-oxadiazol-2-yl)methyl.

In some embodiments of compounds of Formula (I') or (I), X^2 is N or CR^6. In other embodiments, X^2 is N or CH. In one preferred embodiment, X^2 is N. In another preferred embodiment, X^2 is CH.

In some embodiments of compounds of Formula (I') or (I), each R^{12} is independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OR^a, SR^a, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NR^aR^a, NR^aOR^a, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- are each optionally substituted with 1, 2 or 3 R^b substituents.

In some embodiments, each R^{12} is independently selected from F, Cl, CN, CH_3, CH_2CH_3, NH_2, OCH_3, -C(O)NH(C_{1-4} alkyl), $NHC(O)CH_3$, $NHS(O)_2CH_3$, $NHS(O)_2R^a$, $C(O)R^a$, $-CH_2C(O)R^a$, $-CH_2CH_2R^a$, morpholinosulfonyl, imidazolyl, 4-morpholinyl, (3-cyanopyrrolidin-1-yl)methyl, 2-cyanoprop-2-yl, 1-cyanocyclobutyl, 1-cyanocyclopropyl, benzyl, pyridylmethyl, 1,1-dioxothiolan-3-yl, 1-methylsulfonylazetidin-3-yl, 1-acetyl-3-(cyanomethyl)azetidin-3-yl, and $-CH_2$-(4-morpholinyl), wherein R^a is 4-morpholinyl.

In some embodiments, each R^{12} is independently selected from F, Cl, CN, CH_3, CH_2CH_3, NH_2, -C(O)NH(C_{1-4} alkyl), NHC(O)CH_3, NHS(O)$_2CH_3$, C(O)R^a, -CH_2C(O)R^a, -$CH_2CH_2R^a$, morpholinosulfonyl, imidazolyl, 4-morpholinyl, (3-cyanopyrrolidin-1-yl)methyl, 2-cyanoprop-2-yl, 1-cyanocyclobutyl, pyridylmethyl, 1,1-dioxothiolan-3-yl, 1-acetyl-3-(cyanomethyl)azetidin-3-yl, and -CH_2-(4-morpholinyl), wherein R^a is 4-morpholinyl.

In some embodiments of compounds of Formula (I') or (I), each R^{12} is independently NH_2, CH_3, F, CN, 1-piperidinyl, 1-piperazinyl. or 4-morpholinyl.

In some embodiments, each R^{12} is independently selected from –NH_2, -NHOH, -NHOR^a, -NHR^a, -NHC(O)R^a, -NHC(O)NHR^a, -NHS(O)$_2R^a$, -C(O)R^a, -S(O)$_2R^a$, C_{1-6} alkyl, C_{1-6}alkoxy, C_{1-6} haloalkyl, C_{1-4} haloalkoxy, halo, CN, C_{3-6}cycloalkyl, phenyl-C_{1-4}alkyl, 5-6 membered heteroaryl, 5- to 6-membered heteroaryl-C_{1-4}alkyl, 4 to 6-membered heterocycloalkyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{1-6} alkyl, C_{3-6}cycloalkyl, phenyl-C_{1-4}alkyl, 5-6 membered heteroaryl, 4 to 6-membered heterocycloalkyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- is optionally substituted with from 1-3 R^b; and C_{1-6} alkoxy or C_{1-4} haloalkoxy is optionally substituted by 1-3 R^d.

In some embodiments, each R^{12} is independently F, Cl, CN, CH_3, NH_2, OCH_3, NHS(O)$_2R^a$, C(O)R^a, -CH_2C(O)R^a, imidazoyl, 4-morpholinyl, -CH_2-(4-morpholinyl), (3-cyanopyrrolidin-1-yl)methyl, 1-cycano-1-methyl-ethyl, 1-cyanocyclobutyl, 1-cyanocyclopropyl, benzyl, 1,1-dioxothiolan-3-yl, 1-methylsulfonylazetidin-3-yl, 1-acetyl-3-(cyanomethyl)azetidin-3-yl and -CH_2-(4-morpholinyl), wherein R^a is 4-morpholinyl.

In some embodiments, each R^{12} is independently F, Cl, CN, CH_3, NH_2, OCH_3, NHS(O)$_2R^a$, C(O)R^a, imidazoyl, 4-morpholinyl, and -CH_2-(4-morpholinyl), wherein R^a is 4-morpholinyl.

In some embodiments, R^{12} is H, methyl, ethyl, CN, cyanomethyl, 2-cyanoethyl, 1-cyanocyclobutyl, 3-morpholinopropyl, 1-(methylsulfonyl)pyrrolidin-3-yl, (1-(methylsulfonyl)piperidin-4-yl)ethyl, (4-methoxypiperidin-1-yl)ethyl, 2-morpholinoethyl, 2-morpholino-2-oxoethyl, dimethylamino, (3-methoxypyrrolidin-1-yl)ethyl, (1,1-dioxido-1,2-thiazinan-3-yl)methyl, 1-methylpyrrolidin-3-yl, (dimethylamino)ethyl, 2-(piperidin-4-yl)ethyl, (1-(methylsulfonyl)azetidin-3-yl)methyl, (1-acetylazetidin-3-yl)methyl, 1-acetylpyrrolidin-3-yl, (tetrahydro-2H-pyran-4-yl)methyl, ethylcarbamoyl, cyclopropylcarbamoyl, (2-hydroxyethyl)carbamoyl, propylcarbamoyl, isopropylcarbamoyl, 1-cycanocyclopropyl, carbamoyl, morpholino, 1-cyanomethylpyrrolidin-1-yl, or pyridin-3-ylmethyl.

In some embodiments, the subscript n is 0, 1, or 2. In some embodiments, the subscript n is 0. In some embodiments, the subscript n is 1. In another embodiment, the subscript n is 2. In another embodiment, the subscript n is 3.

In some embodiments:

Ring A is phenyl or a 6-membered heteroaryl ring;

R^{10} and R^{11} are C_{1-6} alkyl;

alternatively, R^{10} and R^{11} together with the carbon atom to which they are attached form a a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl group, which is optionally substituted with 1 or 2 independently selected R^{10A} groups.

each R^{12} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^a, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, NR^aR^a, NR^aOR^a, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)_2R^a$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- are each optionally substituted with 1-3 independently selected R^b substituents;

each R^b is independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, CN, NO_2, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$, and $S(O)_2NR^cR^c$; and

each R^c is independently selected from H and C_{1-6} alkyl; and

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

In some embodiments:

X^1 is $CR^{10}R^{11}$;

X^2 is CH;

Ring A is phenyl or a 6-membered heteroaryl ring;

R^{10} and R^{11} are C_{1-6} alkyl;

alternatively, R^{10} and R^{11} together with the carbon atom to which they are attached form a a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl group, which is optionally substituted with 1 or 2 independently selected R^{10A} groups.

each R^{12} is independently selected from halo, CN, NR^aR^a, NR^aOR^a, $NHC(O)R^a$, $NHS(O)_2R^a$, $C(O)R^a$, $S(O)_2R^a$, OR^a, C_{1-6} alkyl, C_{1-6} haloalkyl, 5-6 membered heteroaryl, and 4 to 6-membered heterocycloalkyl, wherein said C_{1-6} alkyl, 5-6 membered heteroaryl, or 4 to 6-membered heterocycloalkyl is optionally substituted with from 1-3 R^b;

each R^b is independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, CN, NO_2, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$, and $S(O)_2NR^cR^c$;

each R^c is independently selected from H and C_{1-6} alkyl; and

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

In some embodiments:

X^1 is $CR^{10}R^{11}$;

X^2 is CH;

Ring A is phenyl or pyridyl;

R^{10} and R^{11} are C_{1-6} alkyl;

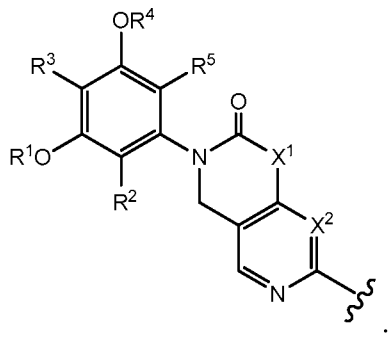
alternatively, R^{10} and R^{11} together with the carbon atom to which they are attached form a a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl group, which is optionally substituted with 1 or 2 independently selected R^{10A} groups;

each R^{12} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, (4-6 membered heterocycloalkyl)-C_{1-2} alkyl-, CN, OR^a, $C(O)R^a$, NR^aR^a, $NR^aS(O)_2R^a$, and $S(O)_2R^a$;

each R^a is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl; and

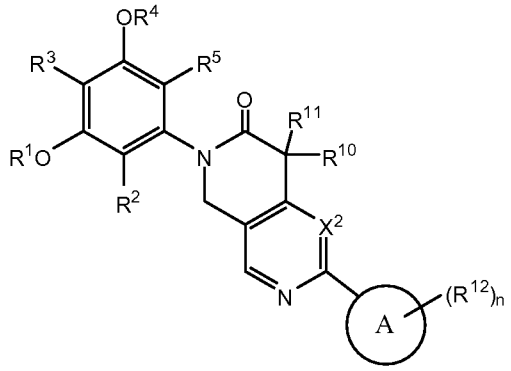
subscript n is 0, 1, 2, or 3.

In some embodiments, when ring A is a 5-6 membered heteroaryl ring, then ring A is connected by a carbon atom to the moiety below at the point indicated by the wavy line:



Subformulas

In some embodiments, compounds of Formula (I') or (I) have subformula (Ia):



(Ia)

or a pharmaceutically acceptable salt thereof, wherein the variables ring A, R^1, R^2, R^3, R^4, R^5, R^{10}, R^{11}, R^{12}, X^2 and n are as defined in any embodiment of compounds of Formula (I') or (I).

In some embodiments of compounds of Formula (Ia):

ring A is a C_{6-10} aryl or a 5 to 6-membered heteroaryl having carbon and 1 to 4 heteroatoms as ring members selected from O, N and S;

each R^{12} is independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^a, SR^a, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NR^aR^a, NR^aOR^a, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-

are each optionally substituted with 1, 2, 3, or 4 R^b substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, CN, NO_2, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$, and $S(O)_2NR^cR^c$; or two adjacent R^{12} substituents on ring A taken together with the atoms to which they are attached form a fused 5- or 6-member cycloalkyl ring, 5 to 6-membered heterocycloalkyl ring, phenyl or 5 to 6-membered heteroaryl ring, wherein the heterocycloalkyl or heteroaryl have 1-2 heteroatoms as ring members selected from O, N and S;

each R^a is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- is optionally substituted with 1, 2, 3, 4, or 5 R^d substituents independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, CN, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$;

each R^c is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- is optionally substituted with 1, 2, 3, 4, or 5 R^f substituents independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, CN, OR^g, SR^g, $C(O)R^g$, $C(O)NR^gR^g$, $C(O)OR^g$, $OC(O)R^g$, $OC(O)NR^gR^g$, NR^gR^g, $NR^gC(O)R^g$, $NR^gC(O)NR^gR^g$, $NR^gC(O)OR^g$, $C(=NR^g)NR^gR^g$, $NR^gC(=NR^g)NR^gR^g$, $S(O)R^g$, $S(O)NR^gR^g$, $S(O)_2R^g$, $NR^gS(O)_2R^g$, $NR^gS(O)_2NR^gR^g$, and $S(O)_2NR^gR^g$;

or any two R^a attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 R^h substituents independently selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{1-6} haloalkyl, halo, CN, OR^i, SR^i, $C(O)R^i$, $C(O)NR^iR^i$, $C(O)OR^i$, $OC(O)R^i$, $OC(O)NR^iR^i$, NR^iR^i, $NR^iC(O)R^i$, $NR^iC(O)NR^iR^i$, $NR^iC(O)OR^i$, $C(=NR^i)NR^iR^i$, $NR^iC(=NR^i)NR^iR^i$, $S(O)R^i$, $S(O)NR^iR^i$, $S(O)_2R^i$, $NR^iS(O)_2R^i$, $NR^iS(O)_2NR^iR^i$, and $S(O)_2NR^iR^i$, wherein said C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, and 5-6 membered heteroaryl are optionally substituted by 1, 2, or 3 R^j substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, CN, OR^k, SR^k, $C(O)R^k$, $C(O)NR^kR^k$, $C(O)OR^k$, $OC(O)R^k$, $OC(O)NR^kR^k$, NR^kR^k, $NR^kC(O)R^k$, $NR^kC(O)NR^kR^k$, $NR^kC(O)OR^i$, $C(=NR^k)NR^kR^k$, $NR^kC(=NR^k)NR^kR^k$, $S(O)R^k$, $S(O)NR^kR^k$, $S(O)_2R^k$, $NR^kS(O)_2R^k$, $NR^kS(O)_2NR^kR^k$, and $S(O)_2NR^kR^k$;

or any two R^c attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^e substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^g substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^i substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

each R^e, R^g, R^i or R^k is independently selected from H, C_{1-4} alkyl, C_{6-10}aryl, C_{1-4} haloalkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, wherein the C_{1-4} alkyl, C_{6-10}aryl, C_{2-4} alkenyl or C_{2-4} alkynyl, is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

X^2 is N or CR^6;

R^1 is C_{1-3} alkyl or C_{1-3} haloalkyl;

R^2 is H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, CN, or C_{1-3} alkoxy;

R^3 is H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, CN, or C_{1-3} alkoxy;

R^4 is C_{1-3} alkyl or C_{1-3} haloalkyl;

R^5 is H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, CN, or C_{1-3} alkoxy;

R^6 is H, halo, CN, OR^{a4}, SR^{a4}, $C(O)NR^{c4}R^{d4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $S(O)_2NR^{c4}R^{d4}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl groups of R^6 are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10A};

R^{10} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, a 5-10 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-10 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl groups of R^{10} are each optionally substituted with 1, 2, 3, or 4 R^{10A};

each R^{10A} is independently selected from halo, CN, NO_2, OR^{a4}, SR^{a4}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $S(O)_2NR^{c4}R^{d4}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl group of R^{10A} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{19};

each R^{a4}, R^{b4}, R^{c4}, and R^{d4} are independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7

membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl group of R^{a4}, R^{b4}, R^{c4}, and R^{d4} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{19};

alternatively, R^{c4} and R^{d4} together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group which is optionally substituted with 1, 2 or 3 substituents independently selected from R^{19};

each R^{e4} is independently H or C_{1-4} alkyl;

R^{11} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{1-6} haloalkyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2 or 3 substituents independently selected from R^{19};

alternatively, R^{10} and R^{11} together with the carbon atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl group or a 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl group; wherein said 3-, 4-, 5-, 6-, or 7-membered cycloalkyl group and 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl group are each optionally substituted with 1, 2, 3 or 4 R^{10A};

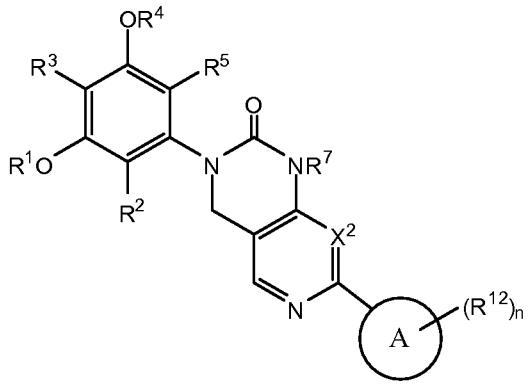
each R^{19} is independently selected from halo, CN, NO_2, OR^{a9}, SR^{a9}, $C(O)R^{b9}$, $C(O)NR^{c9}R^{d9}$, $C(O)OR^{a9}$, $OC(O)R^{b9}$, $OC(O)NR^{c9}R^{d9}$, $NR^{c9}R^{d9}$, $NR^{c9}C(O)R^{b9}$, $NR^{c9}C(O)OR^{a9}$, $NR^{c9}C(O)NR^{c9}R^{d9}$, $NR^{c9}S(O)R^{b9}$, $NR^{c9}S(O)_2R^{b9}$, $NR^{c9}S(O)_2NR^{c9}R^{d9}$, $S(O)R^{b9}$, $S(O)NR^{c9}R^{d9}$, $S(O)_2R^{b9}$, $S(O)_2NR^{c9}R^{d9}$, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{1-4} haloalkyl;

each R^{a9}, R^{c9}, and R^{d9} is independently selected from H and C_{1-4} alkyl;

each R^{b9} is independently C_{1-4} alkyl; and

n as an integer is 0, 1, 2, or 3. In some embodiments, compounds of Formula (Ia) have selective inhibitory activity on FGFR4 enzyme or any mutant thereof. In other embodiments, compounds of Formula (Ia) have selective inhibitory activity on FGFR3 enzyme or any mutant thereof. In other embodiments, compounds of Formula (Ia) have selective inhibitory activity on both FGFR3 and FGFR4 enzyme or any mutant thereof

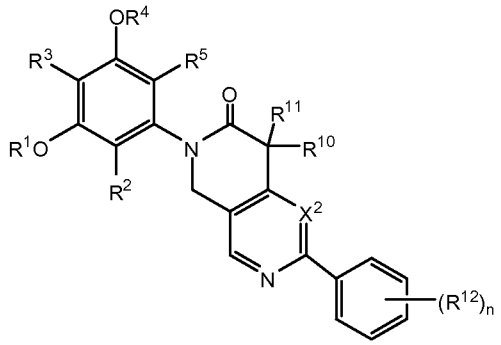
In some embodiments, compounds of Formula (I') or (I) have subformula (Ib):



(Ib)

or a pharmaceutically acceptable salt thereof, wherein the variables ring A, R^1, R^2, R^3, R^4, R^5,R^7, R^{12}, X^2 and n are as defined in any embodiment of compounds of Formula (I') or (I). In some embodiements, R^7 is H, halo, CN, or C_{1-6} alkyl. In one embodiment, R^7 is H or C_{1-6} alkyl.

In some embodiments, compounds of Formula (I') or (I) have subformula (Ic):



(Ic)

or a pharmaceutically acceptable salt thereof, wherein the variables R^1, R^2, R^3, R^4, R^5, R^{10}, R^{11}, R^{12}, X^2 and n are as defined in any embodiment of compounds of Formula (I') or (I).

In some embodiments,

R^2 is F or Cl;

R^5 is F or Cl;

R^{10} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, a 5-10 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-10 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered

heteroaryl, and 4-10 membered heterocycloalkyl groups of R^{10} are each optionally substituted with 1, 2, 3, or 4 R^{10A};

each R^{10A} is independently selected from halo, CN, NO_2, OR^{a4}, SR^{a4}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $S(O)_2NR^{c4}R^{d4}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl groups of R^{10a} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{19};

each R^{a4}, R^{b4}, R^{c4}, and R^{d4} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl groups of R^{a4}, R^{b4}, R^{c4}, and R^{d4} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{19};

alternatively, R^{c4} and R^{d4} together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group which is optionally substituted with 1, 2 or 3 substituents s independently selected from R^{19};

R^{e4} is H or C_{1-4} alkyl;

R^{11} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{1-6} haloalkyl;

alternatively, R^{10} and R^{11} together with the carbon atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl group or a 4-, 5-, 6-, or 7-membered heterocycloalkyl group; wherein said 3-, 4-, 5-, 6-, or 7-membered cycloalkyl group and 4-, 5-, 6-, or 7-membered heterocycloalkyl group are each optionally substituted with 1, 2, 3 or 4 R^{10A};

each R^{19} is independently selected from halo, CN, NO_2, OR^{a9}, SR^{a9}, $C(O)R^{b9}$, $C(O)NR^{c9}R^{d9}$, $C(O)OR^{a9}$, $OC(O)R^{b9}$, $OC(O)NR^{c9}R^{d9}$, $NR^{c9}R^{d9}$, $NR^{c9}C(O)R^{b9}$,

$NR^{c9}C(O)OR^{a9}$, $NR^{c9}C(O)NR^{c9}R^{d9}$, $NR^{c9}S(O)R^{b9}$, $NR^{c9}S(O)_2R^{b9}$, $NR^{c9}S(O)_2NR^{c9}R^{d9}$, $S(O)R^{b9}$, $S(O)NR^{c9}R^{d9}$, $S(O)_2R^{b9}$, $S(O)_2NR^{c9}R^{d9}$, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl,C_{3-6}cycloalkyl and C_{1-4} haloalkyl; wherein C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6}cycloalkyl and C_{1-4} haloalkyl are each further optionally substituted with 1 or 2 R^{20} substituents independently selected from H, halo, CN, NO_2, OR^q, SR^q, $C(O)R^q$, $C(O)NR^qR^q$, $C(O)OR^q$, $OC(O)R^q$, $OC(O)NR^qR^q$, NR^qR^q, $NR^qC(O)R^q$, $NR^qC(O)OR^q$, $NR^qC(O)NR^qR^q$, $NR^qS(O)R^q$, $NR^qS(O)_2R^q$, $NR^qS(O)_2NR^qR^q$, $S(O)R^q$, $S(O)NR^qR^q$, $S(O)_2R^q$, $S(O)_2NR^qR^q$, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6}cycloalkyl and C_{1-4} haloalkyl, wherein each R^q is independently H or C_{1-4}alkyl

each R^{a9}, R^{c9}, and R^{d9} are independently selected from H and C_{1-4} alkyl; and R^{b9} is C_{1-4} alkyl.

In some embodiments, X^2 is N.

In some embodiments, X^2 is CR^6.

In some embodiments, R^6 is H, halo, CN, or C_{1-6} alkyl. In some embodiments, R^6 is H.

In some embodiments, R^6 is C_{1-6} alkyl. In some embodiments, R^6 is methyl. In some embodiments, R^6 is halo. In some embodiments, R^6 is CN.

In some embodiments, R^1 is C_{1-3} alkyl. In some embodiments, R^1 is methyl.

In some embodiments, R^2 is halo. In some embodiments, R^2 is fluoro. In some embodiments, R^2 is chloro.

In some embodiments, R^3 is H.

In some embodiments, R^4 is C_{1-3} alkyl. In some embodiments, R^4 is methyl.

In some embodiments, R^5 is halo. In some embodiments, R^5 is fluoro. In some embodiments, R^5 is chloro.

In some embodiments, R^2 is fluoro and R^5 is fluoro. In some embodiments, R^2 is chloro and R^5 is chloro.

In some embodiments, R^1 is C_{1-3} alkyl; R^2 is halo; R^3 is H; R^4 is C_{1-3} alkyl; and R^5 is halo.

In some embodiments, R^1 is C_{1-3} alkyl; R^2 is F; R^3 is H; R^4 is C_{1-3} alkyl; and R^5 is F.

In some embodiments, R^1 is methyl; R^2 is F; R^3 is H; R^4 is methyl; and R^5 is F.

In some embodiments, R^1 is C_{1-3} alkyl; R^2 is Cl; R^3 is H; R^4 is C_{1-3} alkyl; and R^5 is Cl.

In some embodiments, R^1 is methyl; R^2 is Cl; R^3 is H; R^4 is methyl; and R^5 is Cl.

In some embodiments, R^{10} is C_{1-6} alkyl. In some embodiments, R^{10} is methyl.

In some embodiments, R^{11} is C_{1-6} alkyl. In some embodiments, R^{11} is methyl.

In some embodiments, R^{10} and R^{11} are each C_{1-6} alkyl. In some embodiments, R^{10} and R^{11} are each methyl.

In some embodiments, R^{10} and R^{11} together with the carbon atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl group. In some embodiments, R^{10} and R^{11} together with the carbon atom to which they are attached form a 3-, 4-, 5-, or 6-membered cycloalkyl group. In some embodiments, R^{10} and R^{11} together with the carbon atom to which they are attached form a 3-, 4-, or 5-membered cycloalkyl group.

In some embodiments, R^{10} and R^{11} together with the carbon atom to which they are attached form a cyclopropyl group. In some embodiments, R^{10} and R^{11} together with the carbon atom to which they are attached form a cyclobutyl group. In some embodiments, R^{10} and R^{11} together with the carbon atom to which they are attached form a cyclopentyl group. In some embodiments, R^{10} and R^{11} together with the carbon atom to which they are attached form a cyclohexyl group. In some embodiments, R^{10} and R^{11} together with the carbon atom to which they are attached form a cycloheptyl group.

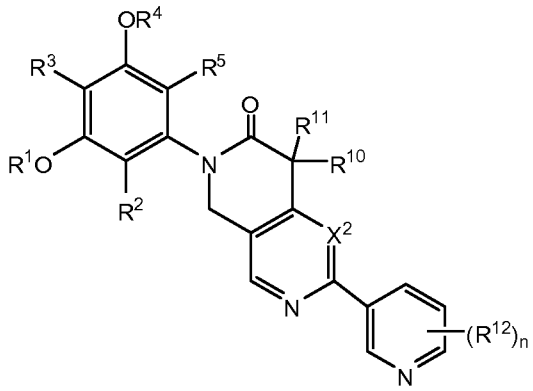
In some embodiments, R^{10} and R^{11} together with the carbon atom to which they are attached form a cyclopropyl group optionally substituted by 1 or 2 R^{10A}. In some embodiments, R^{10} and R^{11} together with the carbon atom to which they are attached form a cyclobutyl group optionally substituted by 1 or 2 R^{10A}. In some embodiments, R^{10} and R^{11} together with the carbon atom to which they are attached form a cyclopentyl group optionally substituted by 1 or 2 R^{10A}. In some embodiments, R^{10} and R^{11} together with the carbon atom to which they are attached form a cyclohexyl group optionally substituted by 1 or 2 R^{10A}.

In some embodiments, R^{10} and R^{11} together with the carbon atom to which they are attached form 4-, 5-, 6-, or 7-membered heterocycloalkyl group.

In some embodiments, R^{10} and R^{11} together with the carbon atom to which they are attached form a tetrahydropyranyl group, a tetrahydrofuranyl group, tetrahydrothiophene group, a pyrrolidinyl group, or a piperidinyl group. In some embodiments, R^{10} and R^{11} together with the carbon atom to which they are attached form a tetrahydropyranyl group. In some embodiments, R^{10} and R^{11} together with the carbon atom to which they are attached form a tetrahydropyranyl group optionally substituted by 1 or 2 R^{10A}. In some embodiments, R^{10} and R^{11} together with the carbon atom to which they are attached form a tetrahydrofuranyl group. In some embodiments, R^{10} and R^{11} together with the carbon atom to which they are attached form a tetrahydrofuranyl group optionally substituted by R^{10A}. In

some embodiments, R^{10} and R^{11} together with the carbon atom to which they are attached form an azetidinyl group. In some embodiments, R^{10} and R^{11} together with the carbon atom to which they are attached form an azetidinyl group optionally substituted by R^{10A}.

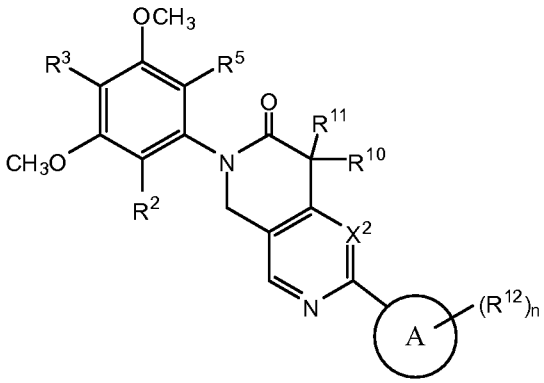
In some embodiments, compounds of Formula (I'), (I) or (Ia) have sub Formula (Id):



(Id)

or a pharmaceutically acceptable salt thereof, wherein X^2, R^1, R^2, R^3, R^4, R^5, R^{10}, R^{11}, R^{12} and n are as defined in any embodiment of Formula (I') or (I) as described herein.

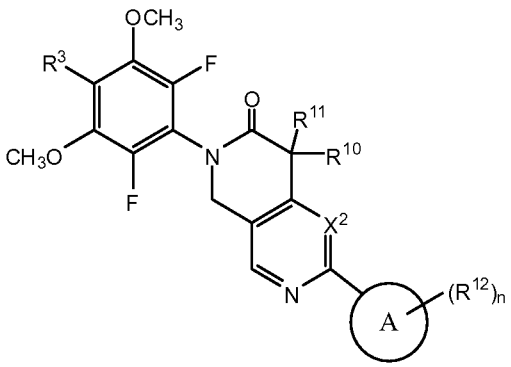
In some embodiments, compounds of Formula (I'), (I) or (Ia) have sub Formula (Ie):



(Ie)

or a pharmaceutically acceptable salt thereof, wherein ring A, R^2, R^3, R^5, R^{10}, R^{11}, R^{12}, X^2 and n are as defined in any embodiment of Formula (I') or (I) as described herein.

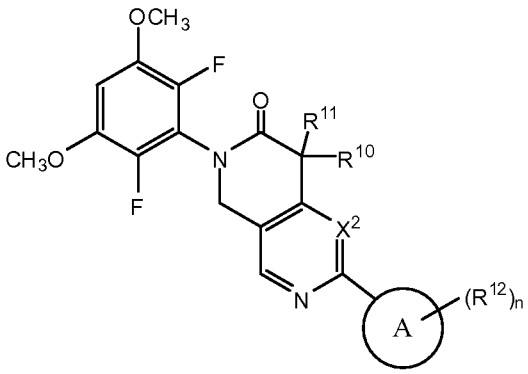
In some embodiments, compounds of Formula (I'), (I), (Ia) or (Ie) have sub Formula (If):



(If)

or a pharmaceutically acceptable salt thereof, wherein ring A, R^3, R^{10}, R^{11}, R^{12}, X^2 and n are as defined in any embodiment of compounds of Formula (I') or (I) as described herein.

In some embodiments, compounds of Formula (I'), (I), (Ie) or (If) have sub Formula (Ig):

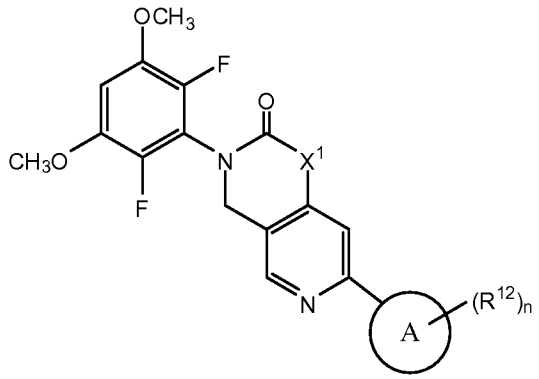


(Ig)

or a pharmaceutically acceptable salt thereof, wherein ring A, R^{10}, R^{11}, X, R^{12} and n are as defined in any embodiment of compounds of Formula (I') or (I) as described herein. In some embodiments of compounds of Formula (Ie), X^2 is N. In other embodiments, X^2 is CH. In one embodiment, ring A is phenyl. In another embodiment, ring A is 5-membered heteroaryl selected from 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 2-oxazolyl, 4- oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3- isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 1 ,2,3-triazol- 1 -yl, 1 ,2,3-triazol-2-yl, 1 ,2,3-triazol-3-yl, l ,2,3-triazol-4-yl, 1 ,2,3-triazol-5-yl, 1 ,2,4-triazol-l -yl, 1 ,2,4-triazol-2-yl, l,2,4-triazol-3-yl, 1 ,2,4- triazol-4-yl, l,2,4-triazol-5-yl, l -oxa-2,3-diazol-4-yl, l -oxa-2,3-diazol-5-yl, l-oxa-2,4-diazol-3-yI, 1 - oxa-2,4-diazol-5-yl, l -oxa-2,5-diazol-3-yl, l -oxa-2,5-diazol-4-yl, l -thia-2,3-diazol-4-yl, l -thia-

2,3- diazol-5-yl, 1 -thia-2,4-diazol-3-yl, 1 -thia-2,4-diazol-5-yl, 1 -thia-2,5-diazol-3-yl, 1 -thia-2,5-diazol-4- yl, 1 -tetrazolyl, 3-tetrazolyl, 1 H-5-tetrazolyl, 3H-5-tetrazolyl, 2-furanyl, 3-furanyl, 2-thiopenyl or 3- thiophenyl. In other embodiments, ring A is 2-pyridyl, 3-pyridyl or 4-pyridyl. In some embodiements of compounds of Formula (Ie), each R^{12} is independently selected from NH_2, CH_3, F, CN, 1-piperidinyl, methylcarbamoyl, 1-piperazinyl or 4-morpholinyl. In one embodiment, the subscript n is 0. In one embodiment, the subscript n is 1. In another embodiment, the subscript n is 2. In another embodiment, the subscript n is 3.

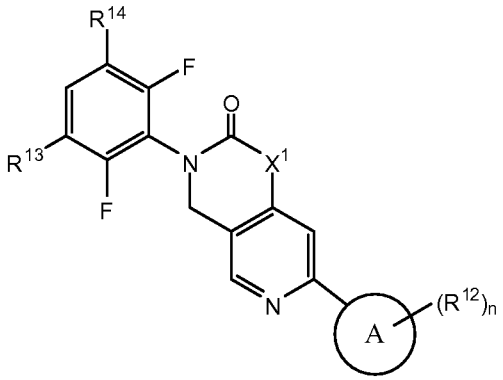
In some embodiments, compounds of Formula (I') or (I) have sub Formula (Ih):



(Ih)

The variables X^1, ring A, R^{12} and n are as defined in any embodiment of compounds of Formula (I') or (I) as described herein. In certain instances, X^1 is $-CR^{10}R^{11}-$ or $-NR^7-$. In some instances, X^1 is $-CR^{10}R^{11}-$, where R^{10} and R^{11} taken together form a C_{3-6} cycloalkyl ring. In one embodiment, R^{10} and R^{11} taken together form a cyclopropyl ring. In other instances, X^1 is $-NR^7-$. In one embodiment, R^7 is C_{1-6} alkyl. In one embodiment, R^7 is ethyl. In some instances, ring A is phenyl or 3-pyridyl. In one instance, ring A is 4-pyrazolyl.

In some embodiments, compounds of Formula (I') have sub Formula (Ih):



(Ij)

The variables R^{13}, R^{14}, X^1, ring A, R^{12} and n are as defined in any embodiment of compounds of formula (I') or (I) as described herein. In some instances, R^{13} is $-C(O)NHC_{1-6}$ alkyl and R^{14} is OCH_3. In certain instances, X^1 is $-CR^{10}R^{11}-$ or $-NR^7-$. In some instances, X^1 is $-CR^{10}R^{11}-$, where R^{10} and R^{11} taken together form a C_{3-6} cycloalkyl ring. In one embodiment, R^{10} and R^{11} taken together form a cyclopropyl ring. In other instances, X^1 is $-NR^7-$.

It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

Definitions

At various places in the present specification, substituents of compounds of the invention are disclosed in groups or in ranges. It is specifically intended that the invention include each and every individual subcombination of the members of such groups and ranges. For example, the term "C_{1-6} alkyl" is specifically intended to individually disclose methyl, ethyl, C_3 alkyl, C_4 alkyl, C_5 alkyl, and C_6 alkyl.

At various places in the present specification various aryl, heteroaryl, cycloalkyl, and heterocycloalkyl rings are described. Unless otherwise specified, these rings can be attached to the rest of the molecule at any ring member as permitted by valency. For example, the term "a pyridine ring" or "pyridinyl" may refer to a pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl ring.

The term "n-membered" where n is an integer typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n. For example, piperidinyl is an example of a 6-membered heterocycloalkyl ring, pyrazolyl is an example of a 5-membered heteroaryl ring, pyridyl is an example of a 6-membered heteroaryl ring, and 1,2,3,4-tetrahydro-naphthalene is an example of a 10-membered cycloalkyl group.

For compounds of the invention in which a variable appears more than once, each variable can be a different moiety independently selected from the group defining the variable. For example, where a structure is described having two R groups that are simultaneously present on the same compound, the two R groups can represent different moieties independently selected from the group defined for R.

As used herein, the phrase "optionally substituted" means unsubstituted or substituted.

As used herein, the term "substituted" means that a hydrogen atom is replaced by a non-hydrogen group. It is to be understood that substitution at a given atom is limited by valency.

As used herein, the term "C_{i-j}," where i and j are integers, employed in combination with a chemical group, designates a range of the number of carbon atoms in the chemical group with i-j defining the range. For example, C_{1-6} alkyl refers to an alkyl group having 1, 2, 3, 4, 5, or 6 carbon atoms.

As used herein, the term "alkyl," employed alone or in combination with other terms, refers to a saturated hydrocarbon group that may be straight-chain or branched. In some embodiments, the alkyl group contains 1 to 6, 1 to 4, or 1 to 3 carbon atoms. Examples of alkyl moieties include, but are not limited to, chemical groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, 2-methyl-1-butyl, 3-pentyl, *n*-hexyl, 1,2,2-trimethylpropyl, and the like. In some embodiments, the alkyl group is methyl, ethyl, or propyl.

As used herein, "alkenyl," employed alone or in combination with other terms, refers to an alkyl group having one or more carbon-carbon double bonds. In some embodiments, the alkenyl moiety contains 2 to 6 or 2 to 4 carbon atoms. Example alkenyl groups include, but are not limited to, ethenyl, *n*-propenyl, isopropenyl, *n*-butenyl, *sec*-butenyl, and the like.

As used herein, "alkynyl," employed alone or in combination with other terms, refers to an alkyl group having one or more carbon-carbon triple bonds. In some embodiments, the alkynyl moiety contains 2 to 6 or 2 to 4 carbon atoms. Example alkynyl groups include, but are not limited to, ethynyl, propyn-1-yl, propyn-2-yl, and the like.

As used herein, "halo" or "halogen", employed alone or in combination with other terms, includes fluoro, chloro, bromo, and iodo. In some embodiments, halo is F or Cl. In some embodiments, halo is F.

As used herein, the term "haloalkyl," employed alone or in combination with other terms, refers to an alkyl group having up to the full valency of halogen atom substituents, which may either be the same or different. In some embodiments, the halogen atoms are fluoro atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms. Example haloalkyl groups include CF_3, C_2F_5, CHF_2, CCl_3, $CHCl_2$, C_2Cl_5, and the like.

As used herein, the term "alkoxy," employed alone or in combination with other terms, refers to a group of formula -O-alkyl. In some embodiments, the alkyl group has 1 to

6, 1 to 4, or 1 to 3 carbon atoms. Example alkoxy groups include methoxy, ethoxy, propoxy (e.g., n-propoxy and isopropoxy), t-butoxy, and the like. In some embodiments, alkoxy is methoxy.

As used herein, "haloalkoxy," employed alone or in combination with other terms, refers to a group of formula -O-(haloalkyl). In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms. An example haloalkoxy group is $-OCF_3$.

As used herein, "amino," employed alone or in combination with other terms, refers to NH_2.

As used herein, the term "alkylamino," employed alone or in combination with other terms, refers to a group of formula -NH(alkyl). In some embodiments, the alkylamino group has 1 to 6 or 1 to 4 carbon atoms. Example alkylamino groups include methylamino, ethylamino, propylamino (*e.g.*, n-propylamino and isopropylamino), and the like.

As used herein, the term "dialkylamino," employed alone or in combination with other terms, refers to a group of formula $-N(alkyl)_2$. Example dialkylamino groups include dimethylamino, diethylamino, dipropylamino (*e.g.*, di(n-propyl)amino and di(isopropyl)amino), and the like. In some embodiments, each alkyl group independently has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "alkylthio," employed alone or in combination with other terms, refers to a group of formula -S-alkyl. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "cycloalkyl," employed alone or in combination with other terms, refers to a non-aromatic cyclic hydrocarbon including cyclized alkyl and alkenyl groups. Cycloalkyl groups can include mono- or polycyclic (e.g., having 2, 3, or 4 fused, bridged, or spiro rings) ring systems. Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings (e.g., aryl or heteroaryl rings) fused (i.e., having a bond in common with) to the cycloalkyl ring, for example, benzo derivatives of cyclopentane, cyclohexene, cyclohexane, and the like, or pyrido derivatives of cyclopentane or cyclohexane. Ring-forming carbon atoms of a cycloalkyl group can be optionally substituted by oxo. Cycloalkyl groups also include cycloalkylidenes. The term "cycloalkyl" also includes bridgehead cycloalkyl groups (e.g., non-aromatic cyclic hydrocarbon moieties containing at least one bridgehead carbon, such as admantan-1-yl) and spirocycloalkyl groups (e.g., non-aromatic hydrocarbon moieties containing at least two rings fused at a single carbon atom, such as spiro[2.5]octane and the like). In some embodiments, the cycloalkyl

group has 3 to 10 ring members, or 3 to 7 ring members, or 3 to 6 ring members. In some embodiments, the cycloalkyl group is monocyclic or bicyclic. In some embodiments, the cycloalkyl group is monocyclic. In some embodiments, the cycloalkyl group is a C_{3-7} monocyclic cycloalkyl group. Example cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, tetrahydronaphthalenyl, octahydronaphthalenyl, indanyl, and the like. In some embodiments, the cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

As used herein, the term "heterocycloalkyl," employed alone or in combination with other terms, refers to a non-aromatic ring or ring system, which may optionally contain one or more alkenylene or alkynylene groups as part of the ring structure, which has at least one heteroatom ring member independently selected from nitrogen, sulfur, oxygen, and phosphorus. Heterocycloalkyl groups can include mono- or polycyclic (e.g., having 2, 3 or 4 fused, bridged, or spiro rings) ring systems. In some embodiments, the heterocycloalkyl group is a monocyclic or bicyclic group having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, sulfur and oxygen. Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings (e.g., aryl or heteroaryl rings) fused (i.e., having a bond in common with) to the non-aromatic heterocycloalkyl ring, for example, 1,2,3,4-tetrahydro-quinoline and the like. Heterocycloalkyl groups can also include bridgehead heterocycloalkyl groups (e.g., a heterocycloalkyl moiety containing at least one bridgehead atom, such as azaadmantan-1-yl and the like) and spiroheterocycloalkyl groups (e.g., a heterocycloalkyl moiety containing at least two rings fused at a single atom, such as [1,4-dioxa-8-aza-spiro[4.5]decan-N-yl] and the like). In some embodiments, the heterocycloalkyl group has 3 to 10 ring-forming atoms, 4 to 10 ring-forming atoms, or 3 to 8 ring forming atoms. In some embodiments, the heterocycloalkyl group has 1 to 5 heteroatoms, 1 to 4 heteroatoms, 1 to 3 heteroatoms, or 1 to 2 heteroatoms. The carbon atoms or heteroatoms in the ring(s) of the heterocycloalkyl group can be oxidized to form a carbonyl, an N-oxide, or a sulfonyl group (or other oxidized linkage) or a nitrogen atom can be quaternized. In some embodiments, the heterocycloalkyl portion is a C_{2-7} monocyclic heterocycloalkyl group. In some embodiments, the heterocycloalkyl group is a morpholine ring, pyrrolidine ring, piperazine ring, piperidine ring, dihydropyran ring, tetrahydropyran ring, tetrahyropyridine, azetidine ring, or tetrahydrofuran ring.

As used herein, the term "aryl," employed alone or in combination with other terms, refers to a monocyclic or polycyclic (e.g., having 2 fused rings) aromatic hydrocarbon moiety, such as, but not limited to, phenyl, 1-naphthyl, 2-naphthyl, and the like. In some embodiments, aryl groups have from 6 to 10 carbon atoms or 6 carbon atoms. In some embodiments, the aryl group is a monocyclic or bicyclic group. In some embodiments, the aryl group is phenyl or naphthyl.

As used herein, the term "heteroaryl," employed alone or in combination with other terms, refers to a monocyclic or polycyclic (e.g., having 2 or 3 fused rings) aromatic hydrocarbon moiety, having one or more heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl group is a monocyclic or bicyclic group having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, sulfur and oxygen. Example heteroaryl groups include, but are not limited to, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrryl, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, purinyl, carbazolyl, benzimidazolyl, indolinyl, pyrrolyl, azolyl, quinolinyl, isoquinolinyl, benzisoxazolyl, imidazo[1,2-b]thiazolyl or the like. The carbon atoms or heteroatoms in the ring(s) of the heteroaryl group can be oxidized to form a carbonyl, an N-oxide, or a sulfonyl group (or other oxidized linkage) or a nitrogen atom can be quaternized, provided the aromatic nature of the ring is preserved. In one embodiment the heteroaryl group is a 5 to 10 membered heteroaryl group. In another embodiment the heteroaryl group is a 5 to 6 membered heteroaryl group.

The compounds described herein can be asymmetric (*e.g.*, having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present invention that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically inactive starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms.

Resolution of racemic mixtures of compounds can be carried out by methods known in the art. An example method includes fractional recrystallizaion using a chiral resolving acid which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, for example, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids. Other resolving agents suitable for fractional crystallization methods include stereoisomerically pure forms of methylbenzylamine (*e.g.*, *S* and *R* forms, or diastereomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, N-methylephedrine, cyclohexylethylamine, 1,2-diaminocyclohexane, and the like.

Resolution of racemic mixtures can also be carried out by elution on a column packed with an optically active resolving agent (*e.g.*, dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art.

Compounds of the invention also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone – enol pairs, amide - imidic acid pairs, lactam – lactim pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H-1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

Compounds of the invention also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium.

The term, “compound,” as used herein is meant to include all stereoisomers, geometric iosomers, tautomers, and isotopes of the structures depicted.

All compounds, and pharmaceutically acceptable salts thereof, can be found together with other substances such as water and solvents (e.g., in the form of hydrates and solvates) or can be isolated.

In some embodiments, the compounds of the invention, or salts thereof, are substantially isolated. By “substantially isolated” is meant that the compound is at least

partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched in the compounds of the invention. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compounds of the invention, or salt thereof. Methods for isolating compounds and their salts are routine in the art.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The present invention also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (e.g., methanol, ethanol, iso-propanol, or butanol) or acetonitrile (ACN) are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and *Journal of Pharmaceutical Science*, 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

The following abbreviations may be used herein: AcOH (acetic acid); Ac_2O (acetic anhydride); aq. (aqueous); atm. (atmosphere(s)); Boc (*t*-butoxycarbonyl); br (broad); Cbz (carboxybenzyl); calc. (calculated); d (doublet); dd (doublet of doublets); DCM (dichloromethane); DEAD (diethyl azodicarboxylate); DIAD (*N,N'*-diisopropyl azidodicarboxylate); DIPEA (*N,N*-diisopropylethylamine); DMF (*N,N*-dimethylformamide);

Et (ethyl); EtOAc (ethyl acetate); g (gram(s)); h (hour(s)); HATU (*N*,*N*,*N'*,*N'*-tetramethyl-*O*-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate); HCl (hydrochloric acid); HPLC (high performance liquid chromatography); Hz (hertz); J (coupling constant); LCMS (liquid chromatography – mass spectrometry); m (multiplet); M (molar); *m*CPBA (3-chloroperoxybenzoic acid); $MgSO_4$ (magnesium sulfate); MS (Mass spectrometry); Me (methyl); MeCN (acetonitrile); MeOH (methanol); mg (milligram(s)); min. (minutes(s)); mL (milliliter(s)); mmol (millimole(s)); N (normal); $NaHCO_3$ (sodium bicarbonate); NaOH (sodium hydroxide); Na_2SO_4 (sodium sulfate); NH_4Cl (ammonium chloride); NH_4OH (ammonium hydroxide); nM (nanomolar); NMR (nuclear magnetic resonance spectroscopy); OTf (trifluoromethanesulfonate); Pd (palladium); Ph (phenyl); pM (picomolar); PMB (para-methoxybenzyl), $POCl_3$ (phosphoryl chloride); RP-HPLC (reverse phase high performance liquid chromatography); s (singlet); t (triplet or tertiary); TBS (tert-butyldimethylsilyl); tert (tertiary); tt (triplet of triplets); *t*-Bu (*tert*-butyl); TFA (trifluoroacetic acid); THF (tetrahydrofuran); µg (microgram(s)); µL (microliter(s)); µM (micromolar); wt% (weight percent).

As used herein, the term "cell" is meant to refer to a cell that is *in vitro*, *ex vivo* or *in vivo*. In some embodiments, an *ex vivo* cell can be part of a tissue sample excised from an organism such as a mammal. In some embodiments, an *in vitro* cell can be a cell in a cell culture. In some embodiments, an *in vivo* cell is a cell living in an organism such as a mammal.

As used herein, the term "contacting" refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting" the FGFR4 enzyme with a compound of the invention includes the administration of a compound of the present invention to an individual or patient, such as a human, having FGFR, as well as, for example, introducing a compound of the invention into a sample containing a cellular or purified preparation containing the FGFR4 enzyme.

As used herein, the term "individual" or "patient," used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

As used herein the term "treating" or "treatment" refers to 1) preventing the disease; for example, preventing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease; 2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, arresting further development of the pathology and/or symptomatology), or 3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, reversing the pathology and/or symptomatology).

Synthesis

Compounds of the invention, including salts thereof, can be prepared using known organic synthesis techniques and according to various possible synthetic routes.

The reactions for preparing compounds of the invention can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially nonreactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, e.g., temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

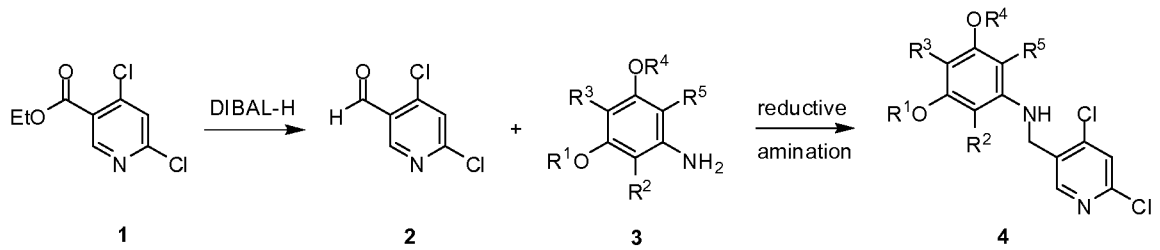
Preparation of compounds of the invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd. Ed., Wiley & Sons, Inc., New York (1999), which is incorporated herein by reference in its entirety.

Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^{1}H or ^{13}C), infrared spectroscopy, spectrophotometry (e.g., UV-visible), or mass spectrometry, or by chromatography such as high performance liquid chromatography (HPLC) or thin layer chromatography.

The expressions, "ambient temperature," "room temperature," and "r.t.", as used herein, are understood in the art, and refer generally to a temperature, *e.g.* a reaction temperature, that is about the temperature of the room in which the reaction is carried out, for example, a temperature from about 20 °C to about 30 °C.

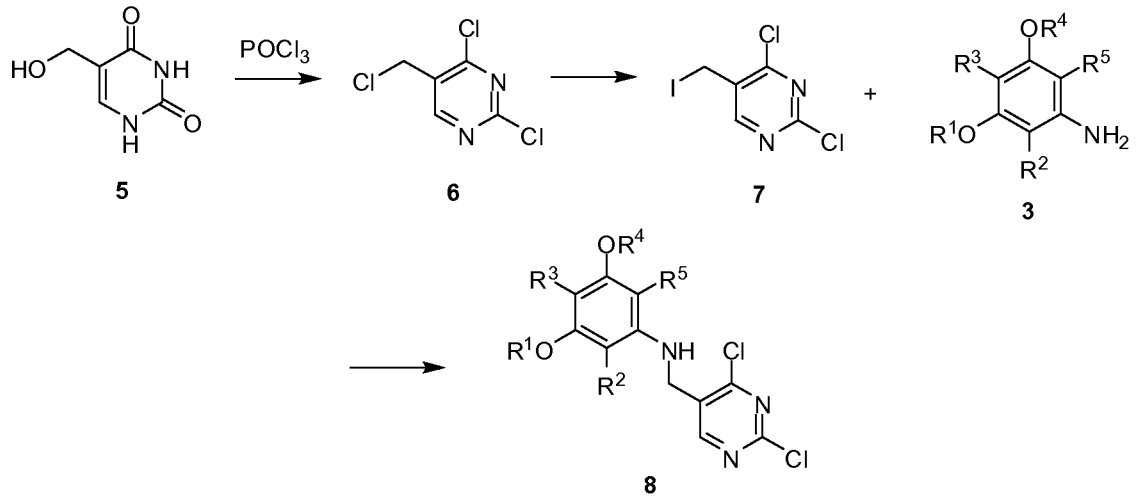
Compounds as disclosed herein can be prepared by one skilled in the art according to preparatory routes known in the literature. Example synthetic methods for preparing compounds of the invention are provided in the Schemes below.

Scheme 1



The synthesis of compound **4** is outlined in **Scheme 1**. Ester **1** can be reduced to the corresponding aldehyde **2** using DIBAL-H. The reductive amination on this aldehyde with aniline **3** can afford dichloropyridine **4.**

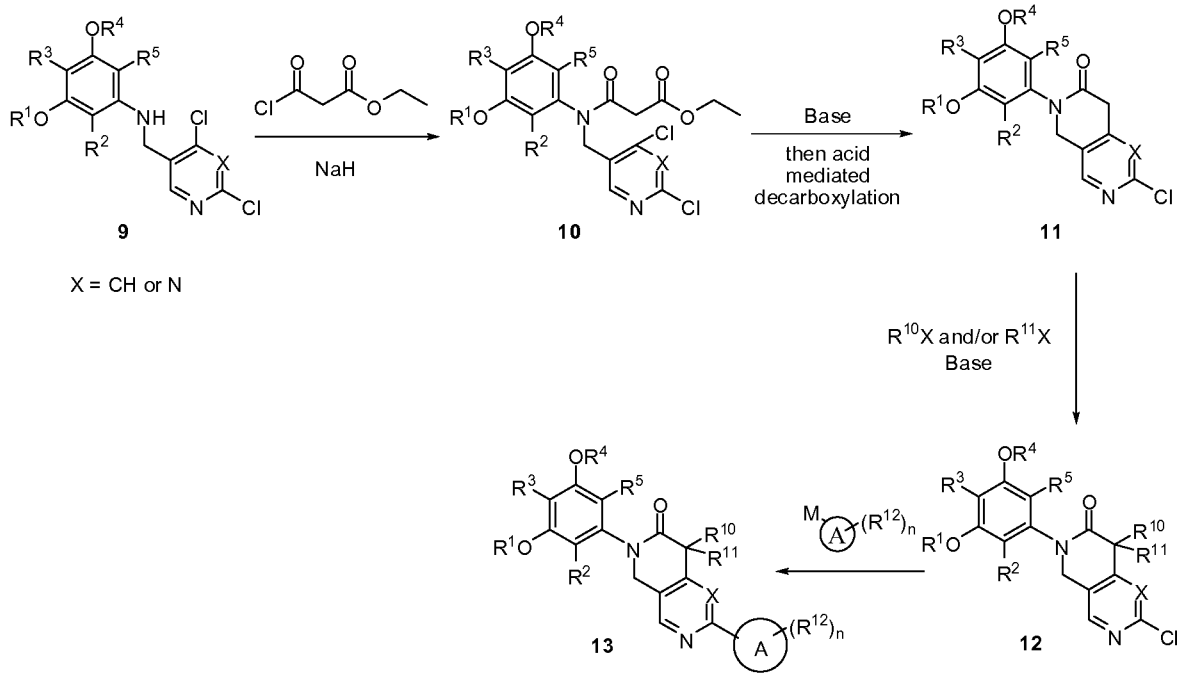
Scheme 2



Dichloropyrimidine **8** can be prepared by the methods described in **Scheme 2.** Treatment of 5-(hydroxymethyl)pyrimidine-2,4(1H,3H)-dione with $POCl_3$ can afford trichloride **6**, which can be converted to iodide **7** using NaI. Compound **7** can be coupled with

aniline **3**, in the presence of a base such as, iPr$_2$NEt, Cs_2CO_3, or NaH, to give dichloropyrimidine **8**.

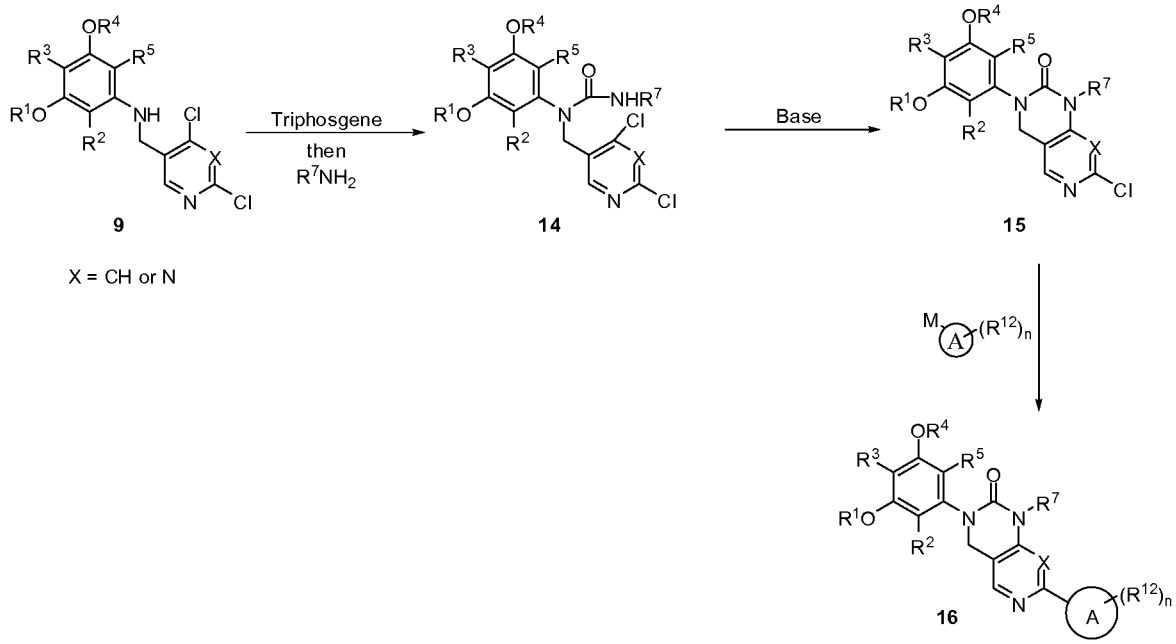
Scheme 3



The synthesis of compound **13** is outlined in **Scheme 3**. Compound **9** can be treated with ethyl 3-chloro-3-oxopropanoate and NaH in THF to provide amide **10**. Lactam **11** can be prepared by the treatment of compounds **10** with a strong base, such as NaH or Cs_2CO_3 in DMF, and followed by an acid, such as HCl, mediated decarboxylation. α-Substituted lactam **12** can be obtained by treating compound **11** with a base, such as NaH or Cs_2CO_3 in DMF or acetonitrile, and followed by the addition of halides $R^{10}X$ and/or $R^{11}X$ (X is halo such as Cl, Br, or I). Chloride **12** can be converted to compound **13**, wherein M is a boronic acid, boronic ester or an appropriately substituted metal (e.g., M is $B(OH)_2$, $Sn(Bu)_3$, or ZnBr), under standard Suzuki conditions {e.g., in the presence of a palladium catalyst, such as, but not limited to, [1,1′-bis(di-cyclohexylphosphino)ferrocene]dichloropalladium(II) and a bicarbonate or carbonate base}, or standard Stille conditions [e.g., in the presence of a palladium catalyst, such as, but not limited to, $Pd(dba)_2$] or standard Negishi conditions [e.g.,

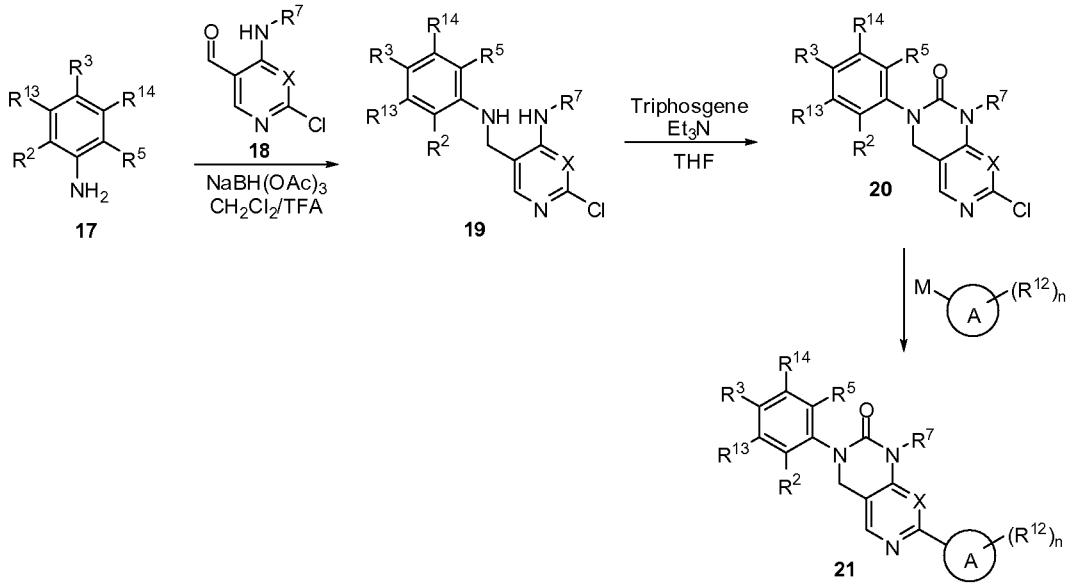
in the presence of a palladium catalyst, such as, but not limited to, tetrakis(triphenylphosphine)palladium(0)].

Scheme 4



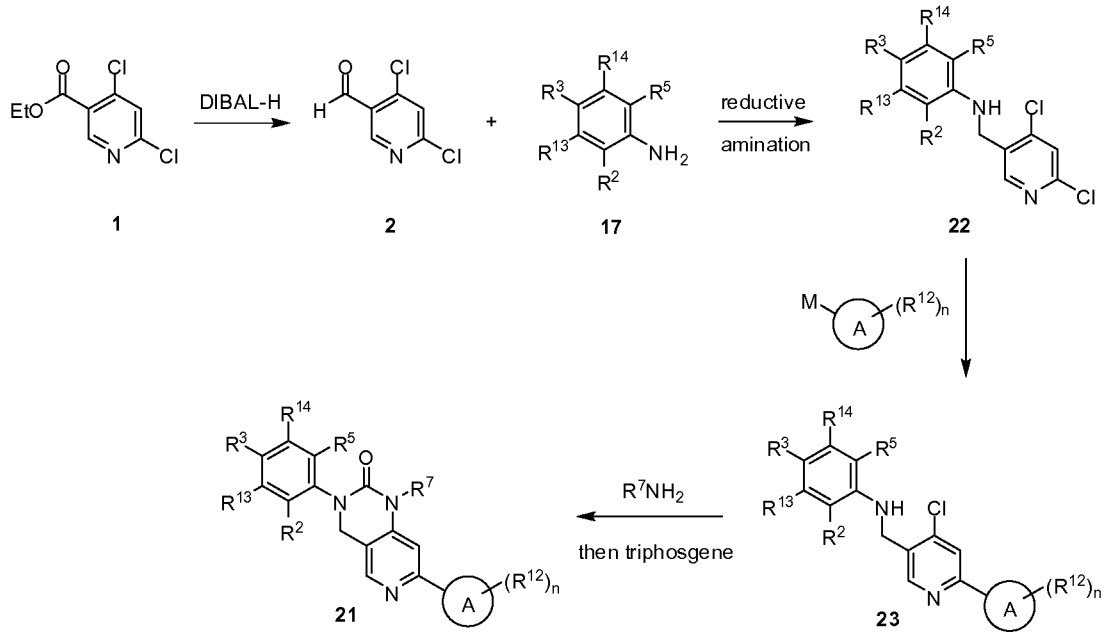
Compound **16** can be synthesized following the procedure shown in **Scheme 4**. Therefore, compound **9** is first treated with triphosgene in the presence of a base such as pyridine, and then with amine R^7NH_2 in the presence of another base (e.g. DIPEA) to afford urea compound **14**. Upon treatment with a proper base (e.g. Cs_2CO_3), cyclization of **14** takes place to generate cyclic urea **15**, which can then be converted to compound **16**, wherein M is a boronic acid, boronic ester or an appropriately substituted metal (e.g., M is $B(OH)_2$, $Sn(Bu)_3$, or ZnBr). The coupling reaction to yield **16** can occur under standard Suzuki conditions {e.g., in the presence of a palladium catalyst, such as, but not limited to, [1,1′-bis(di-cyclohexylphosphino)ferrocene]dichloropalladium(II) and a bicarbonate or carbonate base}, or standard Stille conditions [e.g., in the presence of a palladium catalyst, such as, but not limited to, $Pd(dba)_2$] or standard Negishi conditions [e.g., in the presence of a palladium catalyst, such as, but not limited to, tetrakis(triphenylphosphine)palladium(0)].

Scheme 5



Compound **21** can be prepared according to the synthetic procedures described in Scheme 5. The reductive amination of aldehyde **18** with aniline **17** can afford compound **19.** Compound 1**9** is treated with triphosgene in the presence of a base such as triethylamine to afford urea **20**. Compound **20** can then be converted to compound **21**, wherein M is a boronic acid, boronic ester or an appropriately substituted metal (e.g., M is $B(OH)_2$, $Sn(Bu)_3$, or ZnBr). The coupling reaction to yield **21** can occur under standard Suzuki conditions {e.g., in the presence of a palladium catalyst, such as, but not limited to, [1,1′-bis(di-cyclohexylphosphino)ferrocene]dichloropalladium(II) and a bicarbonate or carbonate base}, or standard Stille conditions [e.g., in the presence of a palladium catalyst, such as, but not limited to, $Pd(dba)_2$] or standard Negishi conditions [e.g., in the presence of a palladium catalyst, such as, but not limited to, tetrakis(triphenylphosphine)palladium(0)].

Scheme 6



Compound **21** can be synthesized using an alternative procedure shown in Scheme 6. Ester **1** can be reduced to the corresponding aldehyde **2** using DIBAL-H. The reductive amination of this aldehyde with aniline **17** can afford compound **22.** Compound **22** is then converted to **23,** wherein M is a boronic acid, boronic ester or an appropriately substituted metal (e.g., M is $B(OH)_2$, $Sn(Bu)_3$, or ZnBr). The coupling reaction to yield **23** can occur under standard Suzuki conditions {e.g., in the presence of a palladium catalyst, such as, but not limited to, [1,1′-bis(di-cyclohexylphosphino)ferrocene]dichloropalladium(II) and a bicarbonate or carbonate base}, or standard Stille conditions [e.g., in the presence of a palladium catalyst, such as, but not limited to, $Pd(dba)_2$] or standard Negishi conditions [e.g., in the presence of a palladium catalyst, such as, but not limited to, tetrakis(triphenylphosphine)palladium(0)]. Compound **23** can undergo Buchwald coupling with amine R^7NH_2 under standard conditions {e.g., in the presence of a palladium catalyst, such as, but not limited to, (2'-aminobiphenyl-2-yl)(chloro)[dicyclohexyl(2',6'-diisopropoxybiphenyl-2-yl)phosphoranyl]palladium and a base, such as, but not limited to,

cesium carbonate or sodium *tert*-butoxide} then cyclized with triphosgene in the presence of a base such as triethylamine to provide compound **21**.

Methods of Use

Compounds of the present disclosure can inhibit the activity of the FGFR enzyme. For example, the compounds of the disclosure can be used to selectivly inhibit the activity of an FGFR3 and/or FGFR4 enzyme in a cell or in an individual or patient in need of inhibition of the enzyme by administering an inhibiting amount of a compound of the disclosure to the cell, individual, or patient.

In some embodiments, the compounds of the disclosure are selective for the enzyme FGFR4 over one or more of FGFR1, FGFR2, and/or FGFR3. In some embodiments, the compounds of the disclosure have selective inhibitory activity for the FGFR4 enzyme over FGFR1, FGFR2, and FGFR3. In some embodiments, the compounds of the disclosure are selective for the enzyme FGFR4 over VEGFR2. In some embodiments, the selectivity is 2-fold or more, 3-fold or more, 5-fold or more, 10-fold or more, 25-fold or more, 50-fold or more, or 100-fold or more.

In some embodiments, the compounds of the disclosure have selective inhibitory activity for the enzyme FGFR3 over one or more of FGFR1 and/or FGFR2 and/or FGFR4. In some embodiments, the compounds of the disclosure are selective for the enzyme FGFR3 over FGFR1 and FGFR2. In certain embodiments, the compounds of the disclosure are selective for the enzyme FGFR3 over FGFR1. In certain embodiments, the compounds of the disclosure are selective for the enzyme FGFR3 over FGFR4. In some embodiments, the compounds of the disclosure are selective for the enzyme FGFR3 over VEGFR2. In some embodiments, the selectivity of the compounds of the present disclosure for FGFR3 over FGFR1 and/or FGFR2 and/or FGFR4 is 2-fold or more, 3-fold or more, 5-fold or more, 10-fold or more, 25-fold or more, 50-fold or more, or 100-fold or more.

As selective FGFR3 and/or FGFR4 inhibitors, the compounds of the disclosure are useful in the treatment of various diseases associated with abnormal expression or activity of the FGFR3 and/or FGFR4 enzyme or FGFR ligands. Compounds which inhibit FGFR will be useful in providing a means of preventing the growth or inducing apoptosis in tumors, particularly by inhibiting angiogenesis. It is therefore anticipated that the compounds will

prove useful in treating or preventing proliferative disorders such as cancers. In particular tumours with activating mutants of receptor tyrosine kinases or upregulation of receptor tyrosine kinases may be particularly sensitive to the inhibitors.

In certain embodiments, the FGFR4, or a mutant thereof, activity is inhibited irreversibly. In certain embodiments, FGFR4, or a mutant thereof, activity is inhibited irreversibly by covalently modifying Cys 552 of FGFR4.

In certain embodiments, the disclosure provides a method for treating a FGFR4-mediated disorder in a patient in need thereof, comprising the step of administering to said patient an effective amount of a compound according to the invention, or a pharmaceutically acceptable composition thereof.

As selective FGFR3 inhibitors, the compounds of the disclosure are useful in the treatment of various diseases associated with abnormal expression or activity of the FGFR3 enzyme or FGFR ligands.

In certain embodiments, the disclosure provides a method for treating a FGFR3-mediated disorder in a patient in need thereof, comprising the step of administering to said patient an effective amount of a compound according to the invention, or a pharmaceutically acceptable composition thereof.

In certain embodiments, compounds of the disclosure are useful in the treatment of cancer. Examplary cancers include bladder cancer, breast cancer, cervical cancer, colorectal cancer, cancer of the small intestine, colon cancer, rectal cancer, cacncer of the anus, endometrial cancer, gastric cancer, head and neck cancer (e.g., cancers of the larynx, hypopharynx, nasopharynx, oropharynx, lips, and mouth), kidney cancer, liver cancer (e.g., hepatocellular carcinoma, cholangiocellular carcinoma), lung cancer (e.g., adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas, parvicellular and non-parvicellular carcinoma, bronchial carcinoma, bronchial adenoma, pleuropulmonary blastoma), ovarian cancer, prostate cancer, testicular cancer, uterine cancer, esophageal cancer, gall bladder cancer, pancreatic cancer (e.g. exocrine pancreatic carcinoma), stomach cancer, thyroid cancer, parathyroid cancer, skin cancer (e.g., squamous cell carcinoma, Kaposi sarcoma, Merkel cell skin cancer), and brain cancer (e.g., astrocytoma, medulloblastoma, ependymoma, neuro-ectodermal tumors, pineal tumors).

Further example cancers include hematopoietic malignancies such as leukemia or lymphoma, multiple myeloma, chronic lymphocytic lymphoma, adult T cell leukemia, B-cell lymphoma, cutaneous T-cell lymphoma, acute myelogenous leukemia, Hodgkin's or non-

Hodgkin's lymphoma, myeloproliferative neoplasms (e.g., polycythemia vera, essential thrombocythemia, and primary myelofibrosis), Waldenstrom's Macroglubulinemia, hairy cell lymphoma, chronic myelogenic lymphoma, acute lymphoblastic lymphoma, AIDS-related lymphomas, and Burkitt's lymphoma.

Other cancers treatable with the compounds of the disclosure include tumors of the eye, glioblastoma, melanoma, rhabdosarcoma, lymphosarcoma, and osteosarcoma. Compounds of the disclosure can also be useful in the inhibition of tumor metastisis.

In some embodiments, the present disclosure provides a method for treating hepatocellular carcinoma in a patient in need thereof, comprising the step of administering to a patient a compound of Formula (I') or (I) or a compouind as disclosed herein, or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formula (I') or (I) or a compound as disclosed herein.

In some embodiments, the present disclosure provides a method for treating Rhabdomyosarcoma, esophageal cancer, breast cancer, or cancer of a head or neck, in a patient in need thereof, comprising the step of administering to the patient a compound Formula (I') or (I) or a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formula (I') or (I) or a compound as disclosed herein.

In some embodiments, the present disclosure provides a method of treating cancer, wherein the cancer is selected from hepatocellular cancer, breast cancer, bladder cancer, colorectal cancer, melanoma, mesothelioma, lung cancer, prostate cancer, pancreatic cancer, testicular cancer, thyroid cancer, squamous cell carcinoma, glioblastoma, neuroblastoma, uterine cancer, and rhabdosarcoma.

In addition to oncogenic neoplasms, the compounds of the invention are useful in the treatment of skeletal and chondrocyte disorders including, but not limited to, achrondroplasia, hypochondroplasia, dwarfism, thanatophoric dysplasia (TD) (clinical forms TD I and TD II), Apert syndrome, Crouzon syndrome, Jackson-Weiss syndrome, Beare-Stevenson cutis gyrate syndrome, Pfeiffer syndrome, and craniosynostosis syndromes. In some embodiments, the present disclosure provides a method for treating a patient suffering from a skeletal and chondrocyte disorder including, but not limiting to, achrondroplasia, hypochondroplasia, dwarfism, thanatophoric dysplasia (TD) (clinical forms TD I and TD II), Apert syndrome, Crouzon syndrome, Jackson-Weiss syndrome, Beare-Stevenson cutis gyrate syndrome, Pfeiffer syndrome, and craniosynostosis syndromes. The method includes administering to

the patient in need thereof an effective amount of a compound Formula (I') or (I) or a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formula (I') or (I) or a compound as disclosed herein.

The compounds of the invention can also be useful in the treatment of hypophosphatemia disorders including, for example, X-linked hypophosphatemic rickets, autosomal recessive hypophosphatemic rickets, autosomal dominant hypophosphatemic rickets, and tumor-induced osteromalacia. In some embodiments, the present disclosure provides a method for treating a patient suffering from a hypophosphatemia disorder including, but not limiting to, X-linked hypophosphatemic rickets, autosomal recessive hypophosphatemic rickets, autosomal dominant hypophosphatemic rickets, and tumor-induced osteromalacia. The method includes administering to the patient in need thereof an effective amount of a compound Formula (I') or (I) or a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formula (I') or (I) or a compound as disclosed herein.

The compounds of the invention may further be useful in the treatment of fibrotic diseases, such as where a disease symptom or disorder is characterized by fibrosis. Example fibrotic diseases include liver cirrhosis, glomerulonephritis, pulmonary fibrosis, systemic fibrosis, rheumatoid arthritis, and wound healing.

Combination Therapy

One or more additional pharmaceutical agents or treatment methods such as, for example, anti-viral agents, chemotherapeutics or other anti-cancer agents, immune enhancers, immunosuppressants, radiation, anti-tumor and anti-viral vaccines, cytokine therapy (*e.g.*, IL2, GM-CSF, *etc.*), and/or tyrosine kinase inhibitors can be used in combination with the compounds of Formula (I') or (I) or a compound as described herein for treatment of FGFR-associated diseases, disorders or conditions. The agents can be combined with the present compounds in a single dosage form, or the agents can be administered simultaneously or sequentially as separate dosage forms.

Suitable antiviral agents contemplated for use in combination with the compounds of the present disclosure can comprise nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors and other antiviral drugs.

Example suitable NRTIs include zidovudine (AZT); didanosine (ddl); zalcitabine (ddC); stavudine (d4T); lamivudine (3TC); abacavir (1592U89); adefovir dipivoxil [bis(POM)-PMEA]; lobucavir (BMS-180194); BCH-10652; emitricitabine [(-)-FTC]; beta-L-FD4 (also called beta-L-D4C and named beta-L-2', 3'-dicleoxy-5-fluoro-cytidene); DAPD, ((-)-beta-D-2,6,-diamino-purine dioxolane); and lodenosine (FddA). Typical suitable NNRTIs include nevirapine (BI-RG-587); delaviradine (BHAP, U-90152); efavirenz (DMP-266); PNU-142721; AG-1549; MKC-442 (1-(ethoxy-methyl)-5-(1-methylethyl)-6-(phenylmethyl)-(2,4(1H,3H)-pyrimidinedione); and (+)-calanolide A (NSC-675451) and B. Typical suitable protease inhibitors include saquinavir (Ro 31-8959); ritonavir (ABT-538); indinavir (MK-639); nelfnavir (AG-1343); amprenavir (141W94); lasinavir (BMS-234475); DMP-450; BMS-2322623; ABT-378; and AG-1 549. Other antiviral agents include hydroxyurea, ribavirin, IL-2, IL-12, pentafuside and Yissum Project No.11607.

Suitable agents for use in combination with the compounds of the present invention for the treatment of cancer include chemotherapeutic agents, targeted cancer therapies, immunotherapies or radiation therapy. Compounds of this invention may be effective in combination with anti-hormonal agents for treatment of breast cancer and other tumors. Suitable examples are anti-estrogen agents including but not limited to tamoxifen and toremifene, aromatase inhibitors including but not limited to letrozole, anastrozole, and exemestane, adrenocorticosteroids (e.g. prednisone), progestins (e.g. megastrol acetate), and estrogen receptor antagonists (e.g. fulvestrant). Suitable anti-hormone agents used for treatment of prostate and other cancers may also be combined with compounds of the present invention. These include anti-androgens including but not limited to flutamide, bicalutamide, and nilutamide, luteinizing hormone-releasing hormone (LHRH) analogs including leuprolide, goserelin, triptorelin, and histrelin, LHRH antagonists (e.g. degarelix), androgen receptor blockers (e.g. enzalutamide) and agents that inhibit androgen production (e.g. abiraterone).

Compounds of the present invention may be combined with or in sequence with other agents against membrane receptor kinases especially for patients who have developed primary or acquired resistance to the targeted therapy. These therapeutic agents include inhibitors or antibodies against EGFR, Her2, VEGFR, c-Met, Ret, IGFR1, or Flt-3 and against cancer-associated fusion protein kinases such as Bcr-Abl and EML4-Alk. Inhibitors against EGFR include gefitinib and erlotinib, and inhibitors against EGFR/Her2 include but are not limited to dacomitinib, afatinib, lapitinib and neratinib. Antibodies against the EGFR

include but are not limited to cetuximab, panitumumab and necitumumab. Inhibitors of c-Met may be used in combination with FGFR inhibitors. These include onartumzumab, tivantnib, and INC-280. Agents against Abl (or Bcr-Abl) include imatinib, dasatinib, nilotinib, and ponatinib and those against Alk (or EML4-ALK) include crizotinib.

Angiogenesis inhibitors may be efficacious in some tumors in combination with FGFR inhibitors. These include antibodies against VEGF or VEGFR or kinase inhibitors of VEGFR. Antibodies or other therapeutic proteins against VEGF include bevacizumab and aflibercept. Inhibitors of VEGFR kinases and other anti-angiogenesis inhibitors include but are not limited to sunitinib, sorafenib, axitinib, cediranib, pazopanib, regorafenib, brivanib, and vandetanib.

Activation of intracellular signaling pathways is frequent in cancer, and agents targeting components of these pathways have been combined with receptor targeting agents to enhance efficacy and reduce resistance. Examples of agents that may be combined with compounds of the present invention include inhibitors of the PI3K-AKT-mTOR pathway, inhibitors of the Raf-MAPK pathway, inhibitors of JAK-STAT pathway, and inhibitors of protein chaperones and cell cycle progression.

Agents against the PI3 kinase include but are not limited topilaralisib, idelalisib, buparlisib. Inhibitors of mTOR such as rapamycin, sirolimus, temsirolimus, and everolimus may be combined with FGFR inhibitors. Other suitable examples include but are not limited to vemurafenib and dabrafenib (Raf inhibitors) and trametinib, selumetinib and GDC-0973 (MEK inhibitors). Inhibitors of one or more JAKs (e.g., ruxolitinib, baricitinib, tofacitinib), Hsp90 (e.g., tanespimycin), cyclin dependent kinases (e.g., palbociclib), HDACs (e.g., panobinostat), PARP (e.g., olaparib), and proteasomes (e.g., bortezomib, carfilzomib) can also be combined with compounds of the present invention. In some embodiments, the JAK inhibitor is selective for JAK1 over JAK2 and JAK3.

Other suitable agents for use in combination with the compounds of the present invention include chemotherapy combinations such as platinum-based doublets used in lung cancer and other solid tumors (cisplatin or carboplatin plus gemcitabine; cisplatin or carboplatin plus docetaxel; cisplatin or carboplatin plus paclitaxel; cisplatin or carboplatin plus pemetrexed) or gemcitabine plus paclitaxel bound particles (Abraxane®).

Suitable chemotherapeutic or other anti-cancer agents include, for example, alkylating agents (including, without limitation, nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazenes) such as uracil mustard, chlormethine,

cyclophosphamide (Cytoxan™), ifosfamide, melphalan, chlorambucil, pipobroman, triethylene-melamine, triethylenethiophosphoramine, busulfan, carmustine, lomustine, streptozocin, dacarbazine, and temozolomide.

Other suitable agents for use in combination with the compounds of the present invention include: dacarbazine (DTIC), optionally, along with other chemotherapy drugs such as carmustine (BCNU) and cisplatin; the "Dartmouth regimen," which consists of DTIC, BCNU, cisplatin and tamoxifen; a combination of cisplatin, vinblastine, and DTIC; or temozolomide. Compounds according to the invention may also be combined with immunotherapy drugs, including cytokines such as interferon alpha, interleukin 2, and tumor necrosis factor (TNF).

Suitable chemotherapeutic or other anti-cancer agents include, for example, antimetabolites (including, without limitation, folic acid antagonists, pyrimidine analogs, purine analogs and adenosine deaminase inhibitors) such as methotrexate, 5-fluorouracil, floxuridine, cytarabine, 6-mercaptopurine, 6-thioguanine, fludarabine phosphate, pentostatine, and gemcitabine.

Suitable chemotherapeutic or other anti-cancer agents further include, for example, certain natural products and their derivatives (for example, vinca alkaloids, antitumor antibiotics, enzymes, lymphokines and epipodophyllotoxins) such as vinblastine, vincristine, vindesine, bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, ara-C, paclitaxel (TAXOL™), mithramycin, deoxycoformycin, mitomycin-C, L-asparaginase, interferons (especially IFN-a), etoposide, and teniposide.

Other cytotoxic agents include navelbene, CPT-11, anastrazole, letrazole, capecitabine, reloxafine, cyclophosphamide, ifosamide, and droloxafine.

Also suitable are cytotoxic agents such as epidophyllotoxin; an antineoplastic enzyme; a topoisomerase inhibitor; procarbazine; mitoxantrone; platinum coordination complexes such as cis-platin and carboplatin; biological response modifiers; growth inhibitors; antihormonal therapeutic agents; leucovorin; tegafur; and haematopoietic growth factors.

Other anti-cancer agent(s) include antibody therapeutics such as trastuzumab (Herceptin), antibodies to costimulatory molecules such as CTLA-4, 4-1BB and PD-1, or antibodies to cytokines (IL-10, TGF-β, etc.).

Other anti-cancer agents also include those that block immune cell migration such as antagonists to chemokine receptors, including CCR2 and CCR4.

Other anti-cancer agents also include those that augment the immune system such as adjuvants or adoptive T cell transfer.

Anti-cancer vaccines include dendritic cells, synthetic peptides, DNA vaccines and recombinant viruses.

Methods for the safe and effective administration of most of these chemotherapeutic agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (PDR, e.g., 1996 edition, Medical Economics Company, Montvale, NJ), the disclosure of which is incorporated herein by reference as if set forth in its entirety.

Pharmaceutical Formulations and Dosage Forms

When employed as pharmaceuticals, the compounds of the invention can be administered in the form of pharmaceutical compositions which refers to a combination of a compound of the invention, or its pharmaceutically acceptable salt, and at least one pharmaceutically acceptable carrier. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (*e.g.*, by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal), ocular, oral or parenteral. Methods for ocular delivery can include topical administration (eye drops), subconjunctival, periocular or intravitreal injection or introduction by balloon catheter or ophthalmic inserts surgically placed in the conjunctival sac. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal, or intramuscular injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, one or more of the compounds of the invention above in combination with one or more pharmaceutically acceptable carriers. In making the compositions of the invention, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10 % by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, the active compound can be milled to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size can be adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

The Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions can be formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The active compound can be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the

amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid pre-formulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these pre-formulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid pre-formulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of the present invention.

The tablets or pills of the present invention can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the compounds and compositions of the present invention can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

The compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in can be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the

nebulizing device can be attached to a face masks tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions can be administered orally or nasally from devices which deliver the formulation in an appropriate manner

The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient, and the like.

The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of the compounds of the present invention can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound of the invention in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (e.g., hydrophobicity), and the route of administration. For example, the compounds of the invention can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 μg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the

excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

The compounds of the invention can also be formulated in combination with one or more additional active ingredients which can include any pharmaceutical agent such as anti-viral agents, vaccines, antibodies, immune enhancers, immune suppressants, anti-inflammatory agents and the like.

Labeled Compounds and Assay Methods

Another aspect of the present invention relates to fluorescent dye, spin label, heavy metal or radio-labeled compounds of the invention that would be useful not only in imaging but also in assays, both *in vitro* and *in vivo*, for localizing and quantitating the FGFR enzyme in tissue samples, including human, and for identifying FGFR enzyme ligands by inhibition binding of a labeled compound. Accordingly, the present invention includes FGFR enzyme assays that contain such labeled compounds.

The present invention further includes isotopically-labeled compounds of the invention. An "isotopically" or "radio-labeled" compound is a compound of the invention where one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (i.e., naturally occurring). Suitable radionuclides that may be incorporated in compounds of the present invention include but are not limited to ^{2}H (also written as D for deuterium), ^{3}H (also written as T for tritium), ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{18}F, ^{35}S, ^{36}Cl, ^{82}Br, ^{75}Br, ^{76}Br, ^{77}Br, ^{123}I, ^{124}I, ^{125}I and ^{131}I. The radionuclide that is incorporated in the instant radio-labeled compounds will depend on the specific application of that radio-labeled compound. For example, for *in vitro* FGFR enzyme labeling and competition assays, compounds that incorporate ^{3}H, ^{14}C, ^{82}Br, ^{125}I , ^{131}I, or ^{35}S will generally be most useful. For radio-imaging applications ^{11}C, ^{18}F, ^{125}I, ^{123}I, ^{124}I, ^{131}I, ^{75}Br, ^{76}Br or ^{77}Br will generally be most useful.

It is understood that a "radio-labeled " or "labeled compound" is a compound that has incorporated at least one radionuclide. In some embodiments the radionuclide is selected from the group consisting of ^{3}H, ^{14}C, ^{125}I , ^{35}S and ^{82}Br.

Synthetic methods for incorporating radio-isotopes into organic compounds are applicable to compounds of the invention and are well known in the art.

A radio-labeled compound of the invention can be used in a screening assay to identify/evaluate compounds. In general terms, a newly synthesized or identified compound

(i.e., test compound) can be evaluated for its ability to reduce binding of the radio-labeled compound of the invention to the FGFR4 enzyme. Accordingly, the ability of a test compound to compete with the radio-labeled compound for binding to the FGFR4 enzyme directly correlates to its binding affinity.

Kits

The present invention also includes pharmaceutical kits useful, for example, in the treatment or prevention of FGFR-associated diseases or disorders, obesity, diabetes and other diseases referred to herein which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention. Such kits can further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, can also be included in the kit.

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of non-critical parameters which can be changed or modified to yield essentially the same results. The compounds of the Examples were found to be inhibitors of one or more FGFR's as described below.

EXAMPLES

Experimental procedures for compounds of the invention are provided below. Preparatory LC-MS purifications of some of the compounds prepared were performed on Waters mass directed fractionation systems. The basic equipment setup, protocols, and control software for the operation of these systems have been described in detail in the literature. See e.g. "Two-Pump At Column Dilution Configuration for Preparative LC-MS", K. Blom, *J. Combi. Chem.*, 4, 295 (**2002**); "Optimizing Preparative LC-MS Configurations and Methods for Parallel Synthesis Purification", K. Blom, R. Sparks, J. Doughty, G. Everlof, T. Haque, A. Combs, *J. Combi. Chem.*, 5, 670 (**2003**); and "Preparative LC-MS Purification: Improved Compound Specific Method Optimization", K. Blom, B. Glass, R. Sparks, A. Combs, *J. Combi. Chem.*, 6, 874-883 (**2004**). The compounds separated were typically

subjected to analytical liquid chromatography mass spectrometry (LCMS) for purity check under the following conditions: Instrument; Agilent 1100 series, LC/MSD, Column: Waters Sunfire™ C_{18} 5 μm particle size, 2.1 x 5.0 mm, Buffers: mobile phase A: 0.025% TFA in water and mobile phase B: acetonitrile; gradient 2% to 80% of B in 3 minutes with flow rate 2.0 mL/minute.

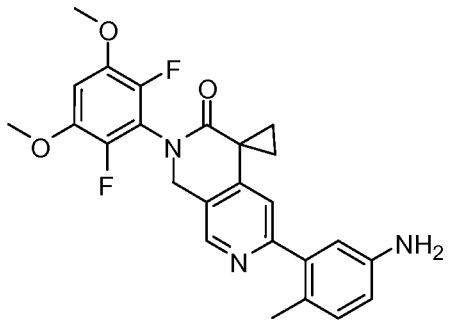
Some of the compounds prepared were also separated on a preparative scale by reverse-phase high performance liquid chromatography (RP-HPLC) with MS detector or flash chromatography (silica gel) as indicated in the Examples. Typical preparative reverse-phase high performance liquid chromatography (RP-HPLC) column conditions are as follows:

pH = 2 purifications: Waters Sunfire™ C_{18} 5 μm particle size, 19 x 100 mm column, eluting with mobile phase A: 0.1% TFA (trifluoroacetic acid) in water and mobile phase B: acetonitrile; the flow rate was 30 mL/minute, the separating gradient was optimized for each compound using the Compound Specific Method Optimization protocol as described in the literature [see "Preparative LCMS Purification: Improved Compound Specific Method Optimization", K. Blom, B. Glass, R. Sparks, A. Combs, *J. Comb. Chem.*, **6**, 874-883 (2004)]. Typically, the flow rate used with the 30 x 100 mm column was 60 mL/minute.

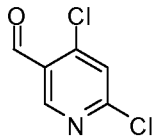
pH = 10 purifications: Waters XBridge C_{18} 5 μm particle size, 19 x 100 mm column, eluting with mobile phase A: 0.15% NH_4OH in water and mobile phase B: acetonitrile; the flow rate was 30 mL/minute, the separating gradient was optimized for each compound using the Compound Specific Method Optimization protocol as described in the literature [See "Preparative LCMS Purification: Improved Compound Specific Method Optimization", K. Blom, B. Glass, R. Sparks, A. Combs, *J. Comb. Chem.*, **6**, 874-883 (2004)]. Typically, the flow rate used with 30 x 100 mm column was 60 mL/minute.

Example 1

6'-(5-amino-2-methylphenyl)-2'-(2,6-difluoro-3,5-dimethoxyphenyl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one

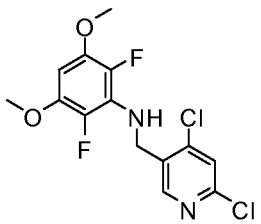


Step 1: 4,6-dichloronicotinaldehyde



To a stirred solution of 2,4-dichloro-5-carbethoxypyridine (10.0 g, 45.4 mmol) in methylene chloride (100.0 mL), diisobutylaluminum hydride in methylene chloride (50.0 mL, 1.0 M, 50.0 mmol) was added dropwise at -78°C. After 2 hours, the reaction was quenched with a saturated solution of Rochelle's salt. After stirring for 12 hours, the aqueous solution was extracted with DCM (3×150 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude aldehyde (7.51 g, 42.9 mmol), which was used directly in the next step without further purification. LC-MS calculated for $C_6H_4Cl_2NO$ $[M+H]^+$ m/z: 176.0; found 176.0.

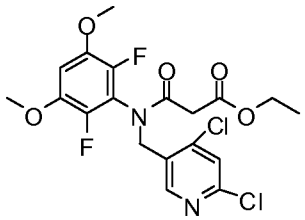
Step 2: N-[(4,6-dichloropyridin-3-yl)methyl]-2,6-difluoro-3,5-dimethoxyaniline



To a stirred solution of 2,6-difluoro-3,5-dimethoxyaniline (9.03 g, 47.7 mmol), sodium triacetoxyborohydride (38.0 g, 180 mmol) in methylene chloride (60 mL) / trifluoroacetic acid (30. mL), 4,6-dichloronicotinaldehyde (8.00 g, 45.5 mmol) was added in small portions at room temperature. After 1 hour, the volatiles were removed *in vacuo* and saturated aqueous $NaHCO_3$ (200 mL) was added. The resulting mixture was extracted with DCM (3×150 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. The residue was purified on silica gel (eluting with 0 to 0-40% EtOAc in hexanes) to afford

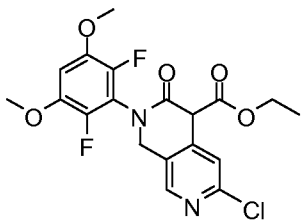
the desired product (15.0 g). LC-MS calculated for $C_{14}H_{13}Cl_2F_2N_2O_2$ $[M+H]^+$ m/z: 349.0; found 349.1.

Step 3: ethyl 3-[[(4,6-dichloropyridin-3-yl)methyl](2,6-difluoro-3,5-dimethoxyphenyl)amino] -3-oxopropanoate



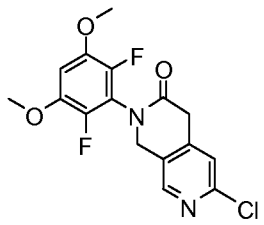
To a stirred solution of *N*-[(4,6-dichloropyridin-3-yl)methyl]-2,6-difluoro-3,5-dimethoxyaniline (3.50 g, 10.0. mmol) in tetrahydrofuran (20 mL), NaH (60% w/w in mineral oil, 421 mg, 10.5 mmol) was added at room temperature. After 10 minutes, ethyl malonyl chloride (1.92 mL, 15.0 mmol) was added dropwise. After another 1 hour, the reaction was quenched with saturated aqueous NH_4Cl, and extracted with DCM (3×100 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. The residue was purified on silica gel (eluting with 0 to 0-35% EtOAc in hexanes) to afford the desired product (4.20 g, 9.1 mmol). LC-MS calculated for $C_{19}H_{19}Cl_2F_2N_2O_5$ $[M+H]^+$ m/z: 463.1; found 463.1.

Step 4: ethyl 6-chloro-2-(2,6-difluoro-3,5-dimethoxyphenyl)-3-oxo-1,2,3,4-tetrahydro-2,7-naphthyridine-4-carboxylate



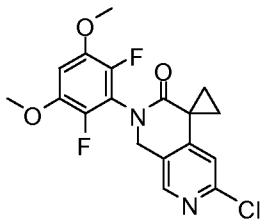
To a stirred solution of ethyl 3-[[(4,6-dichloropyridin-3-yl)methyl](2,6-difluoro-3,5-dimethoxyphenyl)amino]-3-oxopropanoate (1.50 g, 3.24 mmol) in DMF (15. mL) , NaH (60% w/w in mineral oil, 337 mg, 8.42 mmol) was added at room temperature. The resulting mixture was then warmed up to 110°C. After 5 hours, the reaction was cooled to room temperature, and saturated aqueous NH_4Cl (50 mL) was added to form precipitate. After filtration, the solid was dried *in vacuo* to give crude cyclized product (0.95 g, 2.23 mmol). LC-MS calculated for $C_{19}H_{18}ClF_2N_2O_5$ $[M+H]^+$ m/z: 427.1; found 427.0.

Step 5: 6-chloro-2-(2,6-difluoro-3,5-dimethoxyphenyl)-1,2-dihydro-2,7-naphthyridin-3(4H)-one



To a stirred solution of ethyl 6-chloro-2-(2,6-difluoro-3,5-dimethoxyphenyl)-3-oxo-1,2,3,4-tetrahydro-2,7- naphthyridine-4-carboxylate (0.95 g, 2.23 mmol) in 1,4-dioxane (5 mL) hydrogen chloride (4.0 M in dioxane, 2 mL, 8 mmol) was added at room temperature. The resulting mixture was warmed up to 100°C. After 4 hours, the reaction was cooled to ambient temperature, quenched with saturated aqueous $NaHCO_3$, and extracted with DCM (3×100 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. The residue was purified on silica gel (eluting with 0 to 0-30% EtOAc in DCM) to afford the desired product (0.75 g, 2.12 mmol). LC-MS calculated for $C_{16}H_{14}ClF_2N_2O_3$ $[M+H]^+$ m/z: 355.1; found 355.1.

Step 6: 6'-chloro-2'-(2,6-difluoro-3,5-dimethoxyphenyl)-1',2'-dihydro-3'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'-one



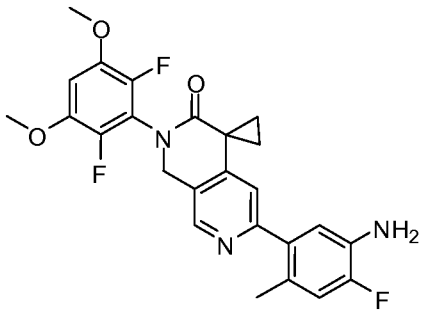
To a stirred solution of 6-chloro-2-(2,6-difluoro-3,5-dimethoxyphenyl)-1,4-dihydro-2,7-naphthyridin-3(2*H*)-one (1.50 g, 4.23 mmol) in DMF (10 mL), cesium carbonate (3.03 g, 9.30 mmol) and 1-bromo-2-chloro-ethane (701 μL, 8.46 mmol) were added sequentially at room temperature. After 5 hours, the reaction was quenched with saturated aqueous NH_4Cl, and extracted with DCM (3×75 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. The residue was purified on silica gel (eluting with 0 to 0-50% EtOAc in hexanes) to afford the desired product (1.20 g, 3.15 mmol). LC-MS calculated for $C_{18}H_{16}ClF_2N_2O_3$ $[M+H]^+$ m/z: 381.1; found 381.1.

Step 7:6'-(5-amino-2-methylphenyl)-2'-(2,6-difluoro-3,5-dimethoxyphenyl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one

A mixture of 6'-chloro-2'-(2,6-difluoro-3,5-dimethoxyphenyl)-1',2'-dihydro-3'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'-one (30.0 mg, 0.0788 mmol), (5-amino-2-methylphenyl)boronic acid (17.8 mg, 0.118 mmol), sodium carbonate (18.4 mg, 0.173 mmol), and [1,1′-bis(di-cyclohexylphosphino)ferrocene]dichloropalladium(II) (3.0 mg, 0.0039 mmol) in *tert*-butyl alcohol (3.0 mL) / water (3.0 mL) was stirred and heated at 90 °C. After 2 hours, the reaction mixture was quenched with saturated aq. NH_4Cl, extracted with methylene chloride. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to dryness under reduced pressure. The crude product was purified on prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product (22 mg) as its TFA salt. LC-MS calculated for $C_{25}H_{24}F_2N_3O_3$ $[M+H]^+$m/z: 452.2; found 452.2.

Example 2

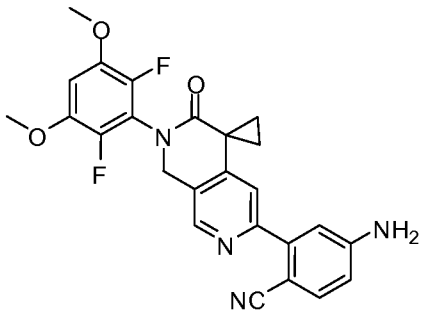
6'-(5-amino-4-fluoro-2-methylphenyl)-2'-(2,6-difluoro-3,5-dimethoxyphenyl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one



This compound was prepared using procedures analogous to those for example 1, step 7, with 2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline replacing (5-amino-2-methylphenyl)boronic acid. LCMS calculated for $C_{25}H_{23}F_3N_3O_3$ $[M+H]^+$ m/z: 470.2; Found: 470.2.

Example 3

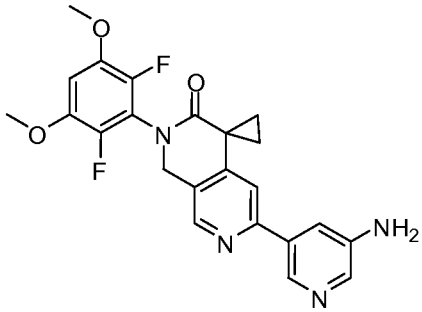
4-amino-2-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)benzonitrile



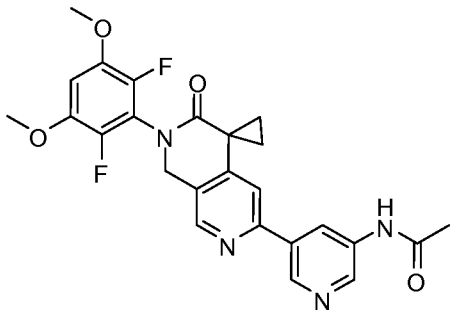
This compound was prepared using procedures analogous to those for example 1, step 7, with 4-amino-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile replacing (5-amino-2-methylphenyl)boronic acid. LCMS calculated for $C_{25}H_{21}F_2N_4O_3$ $[M+H]^+$ m/z: 463.2; Found: 463.2.

Example 4

6'-(5-aminopyridin-3-yl)-2'-(2,6-difluoro-3,5-dimethoxyphenyl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one



Step 1: N-(5-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)pyridin-3-yl)acetamide



This compound was prepared using procedures analogous to those for example 1, step 7, with N-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl]acetamide replacing

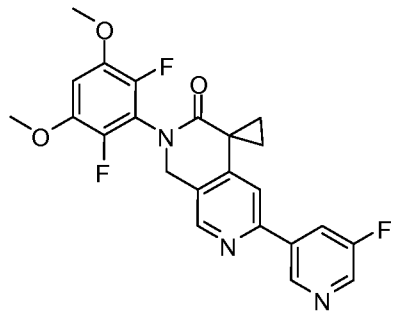
(5-amino-2-methylphenyl)boronic acid. LCMS calculated for $C_{25}H_{23}F_2N_4O_4$ $[M+H]^+$ m/z: 481.2; Found: 481.2.

Step 2: 6'-(5-aminopyridin-3-yl)-2'-(2,6-difluoro-3,5-dimethoxyphenyl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one

To a stirred solution of N-{5-[2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-6'-yl]pyridin-3-yl}acetamide (0.048 g, 0.10 mmol) in ethanol (3.0 mL), potassium hydroxide (2.0 M in water, 0.15 mL, 0.30 mmol) was added at room temperature. The resulting mixture was heated at 60°C overnight. The reaction was quenched with saturated aqueous NH_4Cl and the volatiles were removed under reduced pressure. The residue was dissolved in methylene chloride and was washed with saturated aq. NH_4Cl. The organic layer was dried over Na_2SO_4, filtered, and concentrated to dryness under reduced pressure. The crude product was purified on prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product (26 mg) as its TFA salt LCMS calculated for $C_{23}H_{21}F_2N_4O_3$ $(M+H)^+$ m/z :439.2; Found: 439.2.

Example 5

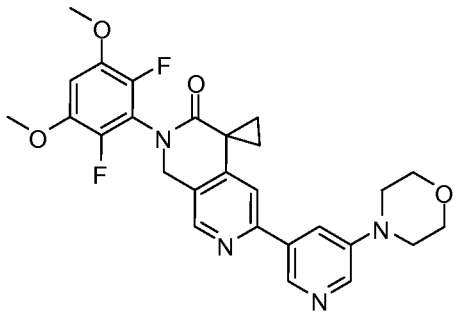
2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(5-fluoropyridin-3-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one



This compound was prepared using procedures analogous to those for example 1, step 7, with (5-fluoropyridin-3-yl)boronic acid replacing (5-amino-2-methylphenyl)boronic acid. LCMS calculated for $C_{23}H_{19}F_3N_3O_3$ $[M+H]^+$ m/z: 442.1; Found: 442.2.

Example 6

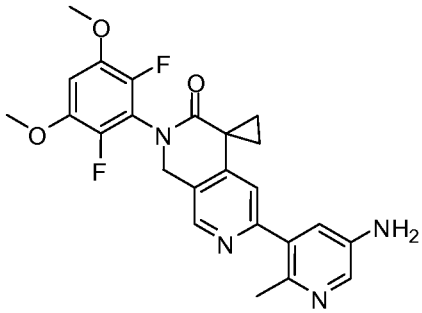
2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(5-morpholinopyridin-3-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one



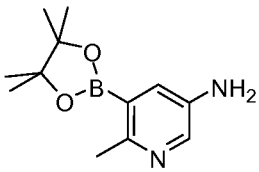
This compound was prepared using procedures analogous to those for example 1, step 7, with 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl]morpholine replacing (5-amino-2-methylphenyl)boronic acid. LCMS calculated for $C_{27}H_{27}F_2N_4O_4$ $[M+H]^+$ m/z: 509.2; Found: 509.2.

Example 7

6'-(5-amino-2-methylpyridin-3-yl)-2'-(2,6-difluoro-3,5-dimethoxyphenyl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one



Step 1: 6-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-amine



A stirred mixture of 5-bromo-6-methylpyridin-3-amine (0.100 g, 0.535 mmol), 4,4,5,5,4',4',5',5'-octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl] (0.136 g, 0.535 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complexed with dichloromethane (1:1) (42 mg, 0.051 mmol), and potassium acetate (0.150 g, 1.53 mmol) in 1,4-dioxane (5.0 mL) was heated at 110°C. After 2 hours, the reaction was quenched with saturated aqueous NH_4Cl, and extracted with DCM (3×30 mL). The organic layers were combined, dried over

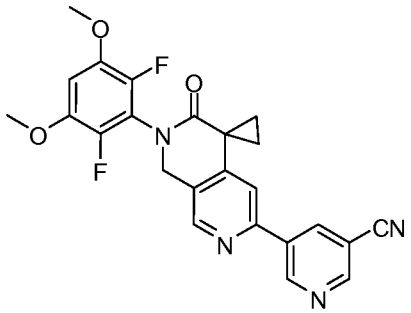
Na_2SO_4, and concentrated. The crude product was used directly in the next step without further purification.

Step 2: 6'-(5-amino-2-methylpyridin-3-yl)-2'-(2,6-difluoro-3,5-dimethoxyphenyl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one

This compound was prepared using procedures analogous to those for example 1, step 7, with 6-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-amine replacing (5-amino-2-methylphenyl)boronic acid. LCMS calculated for $C_{24}H_{23}F_2N_4O_3$ $[M+H]^+$ m/z: 453.2; Found: 453.2.

Example 8

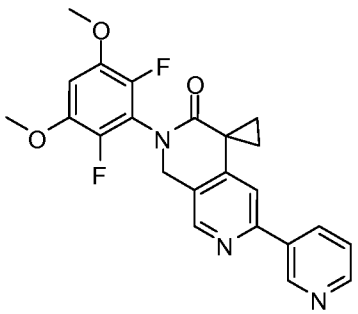
5-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)nicotinonitrile



This compound was prepared using procedures analogous to those for example 7, step 1 to 2, with 5-bromonicotinonitrile replacing 5-bromo-6-methylpyridin-3-amine in step 1. LCMS calculated for $C_{24}H_{19}F_2N_4O_3$ $[M+H]^+$ m/z: 449.1; Found: 449.1.

Example 9

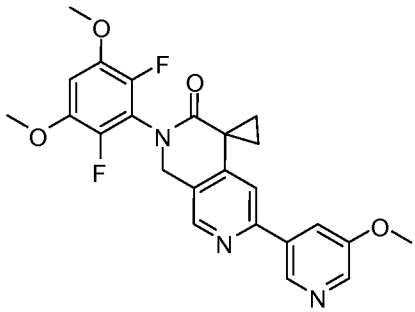
2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(pyridin-3-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one



This compound was prepared using procedures analogous to those for example 1, step 7, with pyridin-3-ylboronic acid replacing (5-amino-2-methylphenyl)boronic acid. LCMS calculated for $C_{23}H_{20}F_2N_3O_3$ $[M+H]^+$ m/z: 424.2; Found: 424.2.

Example 10

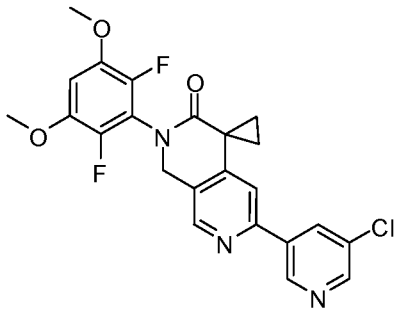
2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(5-methoxypyridin-3-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one



This compound was prepared using procedures analogous to those for example 1, step 7, with 3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine replacing (5-amino-2-methylphenyl)boronic acid. LCMS calculated for $C_{24}H_{22}F_2N_3O_3$ $[M+H]^+$ m/z: 454.2; Found: 454.1.

Example 11

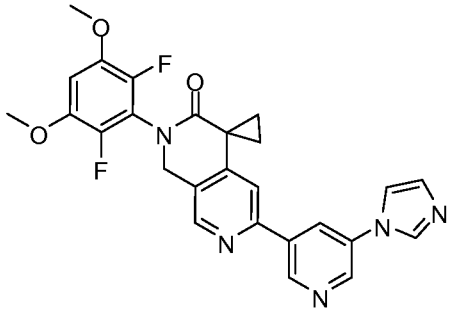
6'-(5-chloropyridin-3-yl)-2'-(2,6-difluoro-3,5-dimethoxyphenyl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one



This compound was prepared using procedures analogous to those for example 1, step 7, with 3-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine replacing (5-amino-2-methylphenyl)boronic acid. LCMS calculated for $C_{23}H_{19}ClF_2N_3O_3$ $[M+H]^+$ m/z: 458.1; Found: 458.1.

Example 12

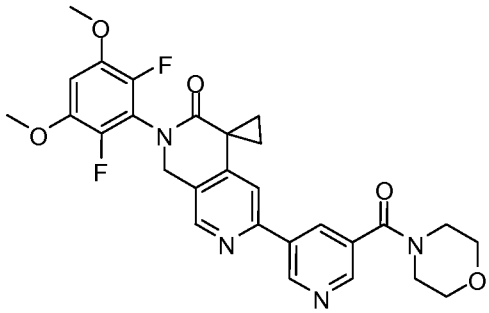
6'-(5-(1H-imidazol-1-yl)pyridin-3-yl)-2'-(2,6-difluoro-3,5-dimethoxyphenyl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one



This compound was prepared using procedures analogous to those for example 1, step 7, with 3-(1H-imidazol-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine replacing (5-amino-2-methylphenyl)boronic acid. LCMS calculated for $C_{26}H_{22}F_2N_5O_3$ $[M+H]^+$ m/z: 490.2; Found: 490.1.

Example 13

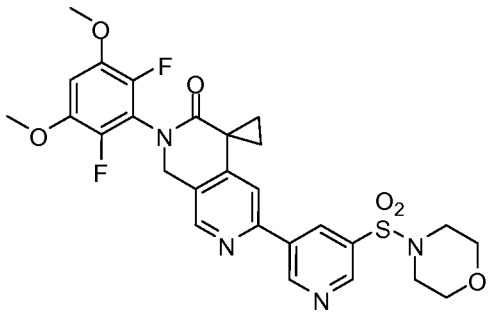
2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(5-(morpholine-4-carbonyl)pyridin-3-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one



This compound was prepared using procedures analogous to those for example 1, step 7, with morpholino(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)methanone replacing (5-amino-2-methylphenyl)boronic acid. LCMS calculated for $C_{28}H_{27}F_2N_4O_5$ $[M+H]^+$ m/z: 537.2; Found: 537.2.

Example 14

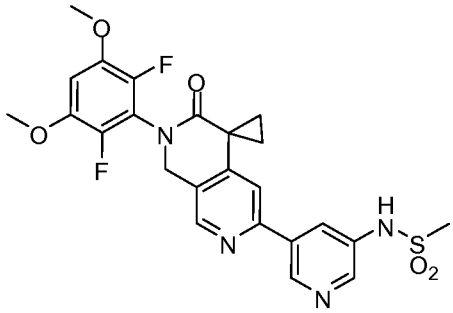
2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(5-(morpholinosulfonyl)pyridin-3-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one



This compound was prepared using procedures analogous to those for example 1, step 7, with 4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-ylsulfonyl)morpholine replacing (5-amino-2-methylphenyl)boronic acid. LCMS calculated for $C_{27}H_{27}F_2N_4O_6S$ $[M+H]^+$ m/z: 573.2; Found: 573.2.

Example 15

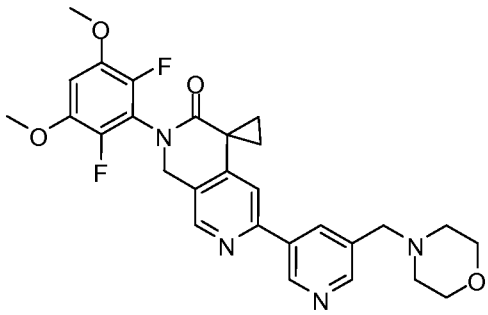
N-(5-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)pyridin-3-yl)methanesulfonamide



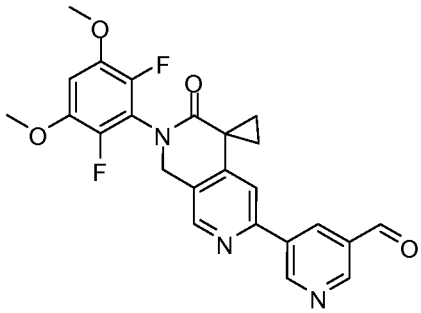
This compound was prepared using procedures analogous to those for example 1, step 7, with N-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)methanesulfonamide replacing (5-amino-2-methylphenyl)boronic acid. LCMS calculated for $C_{24}H_{23}F_2N_4O_5S$ $[M+H]^+$ m/z: 517.1; Found: 517.1.

Example 16

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(5-(morpholinomethyl)pyridin-3-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one



Step 1:5-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)nicotinaldehyde



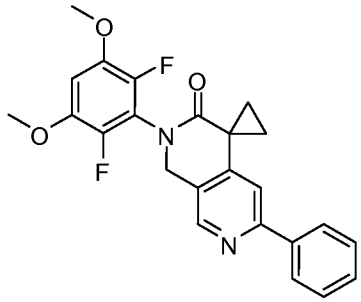
This compound was prepared using procedures analogous to those for example 1, step 7, with N5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinaldehyde replacing (5-amino-2-methylphenyl)boronic acid. LCMS calculated for $C_{24}H_{20}F_2N_3O_4$ $[M+H]^+$ m/z: 452.1; Found: 452.1.

Step 2: 2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(5-(morpholinomethyl)pyridin-3-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one

To a stirred solution of 5-[2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-6'-yl]nicotinaldehyde (20 mg, 0.04 mmol) and morpholine (7.7 µL, 0.088 mmol) in methylene chloride (5.0 mL), acetic acid (0.198 mL, 3.49 mmol) was added at room temperature. After 15 minutes, sodium triacetoxyborohydride (18.7 mg, 0.0884 mmol) was added. After another 1 hour, the volatiles were removed and the residue was purified on prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product (10 mg) as its TFA salt. LCMS calculated for $C_{28}H_{29}F_2N_4O_4$ $(M+H)^+$ m/z :523.2; Found: 523.2.

Example 17

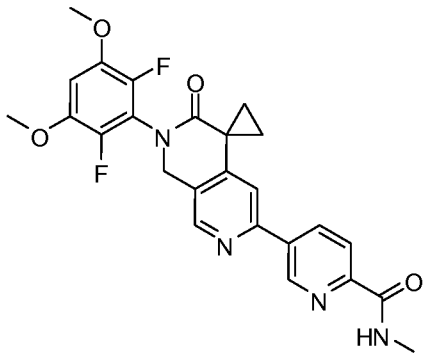
2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-phenyl-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one



This compound was prepared using procedures analogous to those for example 1, step 7, with phenylboronic acid replacing (5-amino-2-methylphenyl)boronic acid. LCMS calculated for $C_{24}H_{21}F_2N_2O_3$ $[M+H]^+$ m/z: 423.2; Found: 423.1.

Example 18

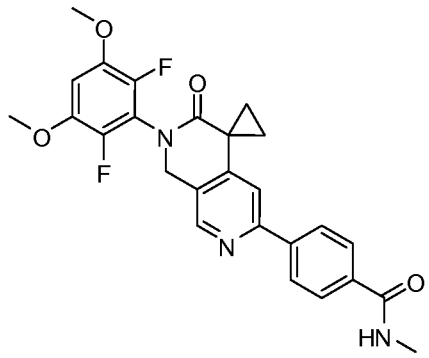
5-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-N-methylpicolinamide



This compound was prepared using procedures analogous to those for example 1, step 7, with N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinamide replacing (5-amino-2-methylphenyl)boronic acid. LCMS calculated for $C_{25}H_{23}F_2N_4O_4$ $[M+H]^+$ m/z: 481.2; Found: 481.1.

Example 19

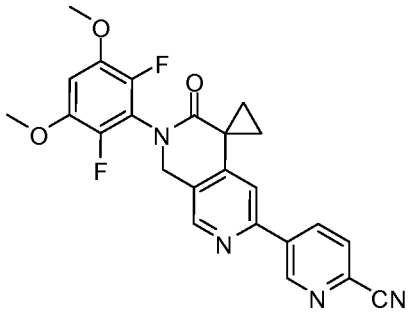
4-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-N-methylbenzamide



This compound was prepared using procedures analogous to those for example 1, step 7, with 4-(methylcarbamoyl)phenylboronic acid replacing (5-amino-2-methylphenyl)boronic acid. LCMS calculated for $C_{26}H_{24}F_2N_3O_4$ $[M+H]^+$ m/z: 480.2; Found: 480.2.

Example 20

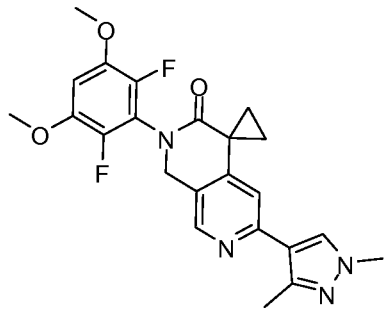
5-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)picolinonitrile



This compound was prepared using procedures analogous to those for example 1, step 7, with 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinonitrile replacing (5-amino-2-methylphenyl)boronic acid. LCMS calculated for $C_{24}H_{19}F_2N_4O_3$ $[M+H]^+$ m/z: 449.1; Found: 449.1.

Example 21

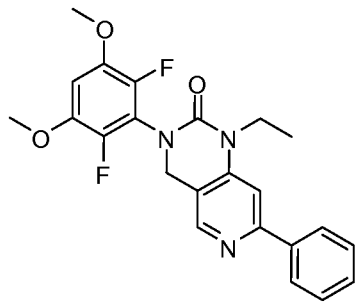
2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1,3-dimethyl-1H-pyrazol-4-yl)-1',2'-dihydro-3'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'-one



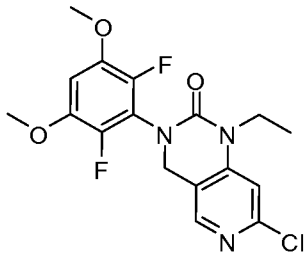
This compound was prepared using procedures analogous to those for example 1, step 7, with 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole replacing (5-amino-2-methylphenyl)boronic acid. LCMS calculated for $C_{23}H_{23}F_2N_4O_3$ $[M+H]^+$ m/z: 441.2; Found: 441.2. ^{1}H NMR (500 MHz, dmso) δ 8.36 (s, 1H), 8.22 (s, 1H), 7.06 (t, *J = 8.0 Hz*, 1H), 7.03 (s, 1H), 4.92 (s, 2H), 3.89 (s, 6H), 3.78 (s, 3H), 2.40 (s, 3H), 1.71-1.73 (m, 2H), 1.55-1.57 (m, 2H).

Example 22

3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-phenyl-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



Step 1: 7-chloro-3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



To a solution of triphosgene (344 mg, 1.16 mmol) in CH_2Cl_2 (12 mL, 190 mmol) at 0 °C was first added pyridine (0.250 mL, 3.09 mmol). The mixture was then stirred at 0 °C for

10 minutes, and added a solution of *N*-[(4,6-dichloropyridin-3-yl)methyl]-2,6-difluoro-3,5-dimethoxy aniline (900 mg, 2.58 mmol) in CH_2Cl_2 (8.0 mL). The reaction mixture was stirred at 0 °C for 1 hour, and added ethylamine in THF (2.0 M, 6.4 mL, 13 mmol), followed by *N*,*N*-diisopropylethylamine (920 µL, 5.3 mmol). The resulting mixture was then warmed to room temperature, stirred overnight, quenched with saturated $NaHCO_3$ (aq) solution, and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude intermediate which was used directly in the next step.

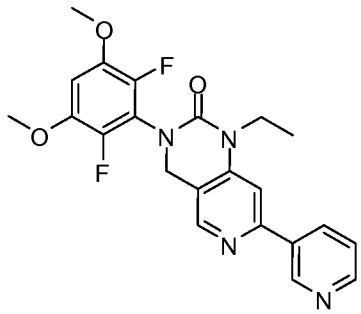
The crude intermediate obtained from previous step was first dissolved in DMF (20 mL), and added Cs_2CO_3 (1.70 g, 5.2 mmol). The reaction mixture was then stirred at 95 °C for 5 hours until completion, cooled to room temperature, quenched with water, and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, and concentrated. The resulting material was purified via column chromatography (25% to 55% EtOAc in hexanes) to give the product as a slightly yellow solid. LC-MS calculated for $C_{17}H_{17}ClF_2N_3O_3$ $[M+H]^+$ m/z: 384.1; found 384.1.

Step 2: 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-phenyl-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one

A mixture of 7-chloro-3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-3,4-dihydropyrido [4,3-d]pyrimidin-2(1H)-one (35.0 mg, 0.0912 mmol), sodium carbonate (19.3 mg, 0.18 mmol), phenylboronic acid (16.7 mg, 0.14 mmol), and Pd-127 (6.9 mg, 0.0091 mmol) in *tert*-butyl alcohol (1.0 mL) and water (1.0 mL) was first degassed with nitrogen, and then stirred and heated at 90 °C for 3 hours. The resulting mixture was cooled to room temperature, diluted with water, and extracted with EtOAc (3 x 1.5 mL). The combined organic layers were dried over Na_2SO_4, and concentrated. The resulting material was purified via pH 2 preparative LC/MS (MeCN/water with TFA) to afford the product as a white solid (TFA salt). LC/MS calculated for $C_{23}H_{22}F_2N_3O_3$ $[M+H]^+$m/z: 426.2; found 426.1.

Example 23

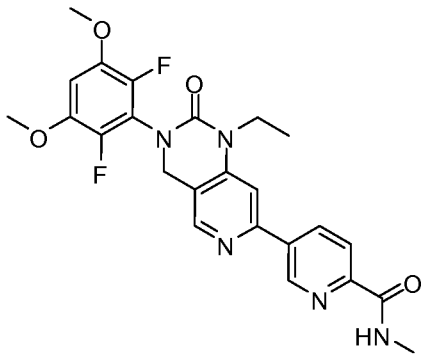
3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(pyridin-3-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



This compound was prepared using procedures analogous to those for example 22, step 2, with 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine replacing phenylboronic acid. LC/MS calculated for $C_{22}H_{21}F_2N_4O_3$ $[M+H]^+$ m/z: 427.2; Found: 427.1.

Example 24

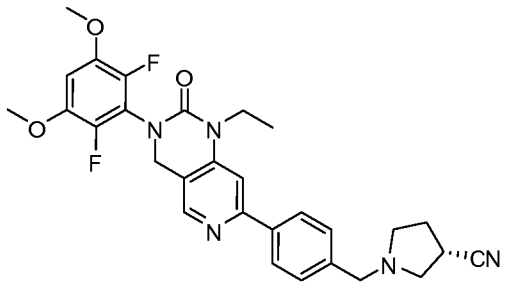
5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)-N-methylpicolinamide



This compound was prepared using procedures analogous to those for example 21, step 2, with N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinamide replacing phenyl boronic acid. LC/MS calculated for $C_{24}H_{24}F_2N_5O_4$ $[M+H]^+$ m/z: 484.2; Found: 484.1.

Example 25

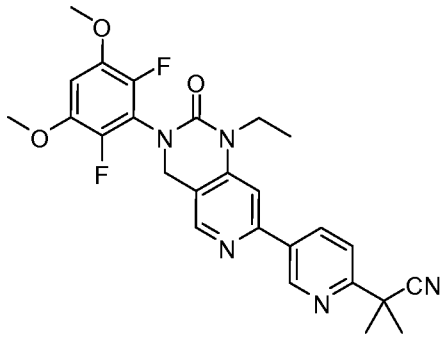
(S)-1-(4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)benzyl)pyrrolidine-3-carbonitrile



This compound was prepared using procedures analogous to those for example 22, step 2, with (S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)pyrrolidine-3-carbonitrile replacing phenyl boronic acid. LC/MS calculated for $C_{29}H_{30}F_2N_5O_3$ $[M+H]^+$ m/z: 534.2; Found: 534.2.

Example 26

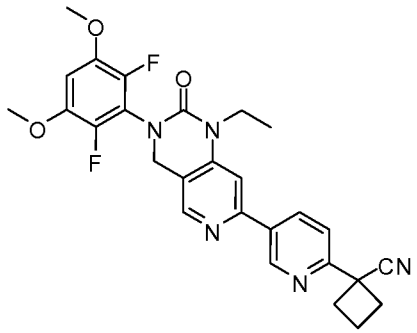
2-(5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)pyridin-2-yl)-2-methylpropanenitrile



This compound was prepared using procedures analogous to those for example 22, step 2, with 2-methyl-2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)propanenitrile replacing phenyl boronic acid. LC/MS calculated for $C_{26}H_{26}F_2N_5O_3$ $[M+H]^+$ m/z: 494.2; Found: 494.2.

Example 27

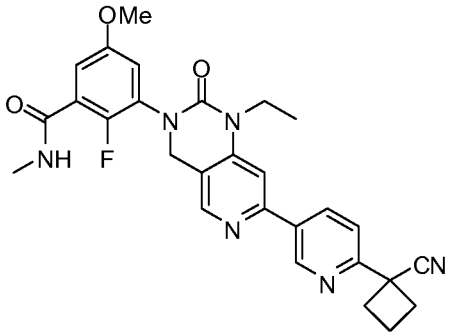
1-(5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)pyridin-2-yl)cyclobutanecarbonitrile



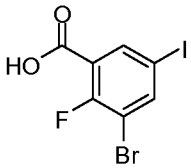
This compound was prepared using procedures analogous to those for example 22, step 2, with 1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)cyclobutanecarbonitrile replacing phenyl boronic acid. LC/MS calculated for $C_{27}H_{26}F_2N_5O_3$ $[M+H]^+$ m/z: 506.2; Found: 506.2. ^{1}H NMR (600 MHz, DMSO) δ 9.34 – 9.32 (m, 1H), 8.55 (dd, J = 8.2, 2.4 Hz, 1H), 8.46 (s, 1H), 7.78 – 7.74 (m, 1H), 7.70 (s, 1H), 7.07 (t, J = 8.1 Hz, 1H), 4.85 (s, 2H), 4.06 (q, J = 6.8 Hz, 2H), 3.91 (s, 6H), 2.87 – 2.80 (m, 2H), 2.79 – 2.73 (m, 2H), 2.35 – 2.26 (m, 1H), 2.13 – 2.05 (m, 1H), 1.23 (t, J = 7.0 Hz, 3H).

Example 28

3-(7-(6-(1-cyanocyclobutyl)pyridin-3-yl)-1-ethyl-2-oxo-1,2-dihydropyrido[4,3-d]pyrimidin-3(4H)-yl)-2-fluoro-5-methoxy-N-methylbenzamide



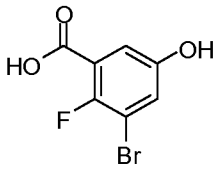
Step 1: 3-bromo-2-fluoro-5-iodobenzoic acid



To a mixture of 3-bromo-2-fluorobenzoic acid (1.50 g, 6.85 mmol) in sulfuric acid (5.0 mL) at 0 °C was added N-iodosuccinimide (1.62 g, 7.19 mmol) portionwise. The resulting mixture was warmed to room temperature, and kept stirring for 3 hours. The reaction mixture was then quenched with cold water, and the precipitate was collected by

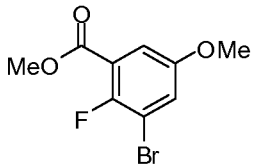
filtration, washed with cold water, and dried under vaccum to give the product as a white solid, which was used directly in the next step (2.36 g, 91%). LC-MS calculated for $C_7H_4BrFIO_2$ $[M+H]^+$ m/z: 344.8; found 344.7.

Step 2: 3-bromo-2-fluoro-5-hydroxybenzoic acid



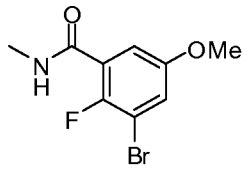
A mixture of 3-bromo-2-fluoro-5-iodobenzoic acid (2.15 g, 6.23 mmol), copper(I) oxide (130 mg, 0.94 mmol), and NaOH (1.25 g, 31.2 mmol) in water (20 mL) was stirred at 100 °C overnight. The reaction mixture was cooled to room temperature and filtered. The filtrate was acidified with 2 M HCl (aq) to ~pH 1, and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, and concentrated to give the product as a yellow solid, which was used directly in the next step (1.41 g, 96%). LC-MS calculated for $C_7H_5BrFO_3$ $[M+H]^+$ m/z: 234.9; found 234.9.

Step 3: methyl 3-bromo-2-fluoro-5-methoxybenzoate



To a solution of 3-bromo-2-fluoro-5-hydroxybenzoic acid (4.88 g, 20.8 mmol) in N,N-dmethylformamide (20 mL) at room temperature was first added K_2CO_3 (8.60 g, 62.3 mmol), followed by MeI (2.84 mL, 45.6 mmol). The reaction mixture was stirred at 80 °C for 1 hour, cooled to room temperature, quenched with water, and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude material was then purified using column chromatography (0% to 30% EtOAc in hexanes) to give the product as a yellow solid (4.87 g, 89%). LC-MS calculated for $C_9H_9BrFO_3$ $[M+H]^+$ m/z: 263.0; found 263.0.

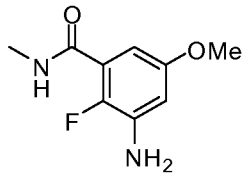
Step 4: 3-bromo-2-fluoro-5-methoxy-N-methylbenzamide



A mixture of methyl 3-bromo-2-fluoro-5-methoxybenzoate (200 mg, 0.76 mmol) in methanol (7.5 mL)/water (2.5 mL) at room temperature was added NaOH (152 mg, 3.80 mmol). The reaction mixture was stirred at room temperature for 2 hours, and 1.0 M HCl in water (4.56 mL, 4.56 mmol) was added. The resulting mixture was extracted with EtOAc, and the combined organic layers were dried over Na_2SO_4, filtered and concentrated to give carboxylic acid intermediate, which was used directly in the next step.

The carboxylic acid obtained from previous step was dissolved in CH_2Cl_2 (7.5 mL), and BOP reagent (404 mg, 0.912 mmol), 2.0 M Methylamine in THF (1.52 mL, 3.04 mmol), and Et_3N (0.424 mL, 3.04 mmol) were added sequentially. The reaction mixture was stirred at room temperature for 3 hours before it was quenched with water, and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified using column chromatography (0% to 50% EtOAc in hexanes) to give the product as a white solid. LC-MS calculated for $C_9H_{10}BrFNO_2$ $[M+H]^+$ m/z: 262.0; found 262.0.

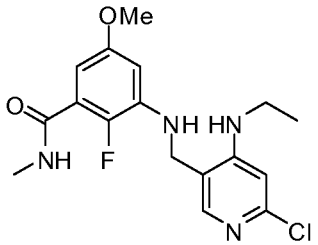
Step 5: 3-amino-2-fluoro-5-methoxy-N-methylbenzamide



A mixture of 3-bromo-2-fluoro-5-methoxy-N-methylbenzamide (205 mg, 0.78 mmol), benzophenone imine (157 μL, 0.94 mmol), (9,9-dimethyl-9H-xanthene-4, 5-diyl)bis(diphenylphosphine) (45 mg, 0.078 mmol), tris(dibenzylideneacetone)dipalladium(0) (36 mg, 0.039 mmol), and Cs_2CO_3 (381 mg, 1.17 mmol) in 1,4-dioxane (3.0 mL) was purged with nitrogen, and stirred at 95°C for 24 hours. The reaction mixture was cooled to room temperature, diluted with water, and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified using column chromatography (25% to 55% EtOAc in hexanes) to give the imine intermediate, which was used directly in the next step.

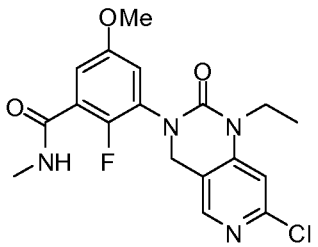
The imine intermediate obtained from previous step was dissolved in THF (3.0 mL), and 1.0 M HCl in water (1.0 mL, 1.0 mmol) was added. The reaction mixture was stirred at room temperature for 1 hour, neutralized with saturated $NaHCO_3$ solution, and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified using column chromatography (0% to 10% MeOH in CH_2Cl_2) to give the product as a yellow solid (132 mg, 85% over two steps). LC-MS calculated for $C_9H_{12}FN_2O_2$ $[M+H]^+$ m/z: 199.1; found 199.1.

Step 6: 3-({[6-chloro-4-(ethylamino)pyridin-3-yl]methyl}amino)-2-fluoro-5-methoxy-N-methylbenzamide



To a solution of 3-amino-2-fluoro-5-methoxy-N-methylbenzamide (132 mg, 0.66 mmol) and 6-chloro-4-(ethylamino)nicotinaldehyde (147 mg, 0.80 mmol) in CH_2Cl_2 (3.0 mL) at room temperature was first added trifluoroacetic acid (1.0 mL). The resulting mixture was stirred at room temperature for 15 minutes. $NaBH(OAc)_3$ (211 mg, 1.00 mmol) was added in four portions over a period of 2 hours. The reaction mixture was then stirred at room temperature for additional 1 hour before it was quenched with saturated $NaHCO_3$ solution, and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude material was purified using column chromatography (0% to 60% EtOAc in hexanes) to give the product as a yellow solid (171 mg, 70%). LC-MS calculated for $C_{17}H_{21}ClFN_4O_2$ $[M+H]^+$ m/z: 367.1; found 367.1.

Step 7: 3-(7-chloro-1-ethyl-2-oxo-1,2-dihydropyrido[4,3-d]pyrimidin-3(4H)-yl)-2-fluoro-5-methoxy-N-methylbenzamide



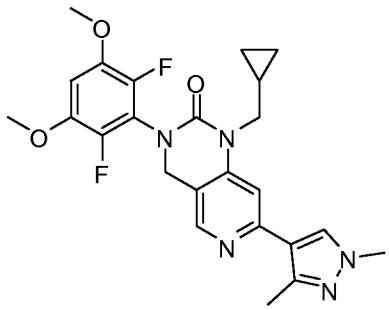
To a solution of 3-({[6-chloro-4-(ethylamino)pyridin-3-yl]methyl}amino)-2-fluoro-5-methoxy-N-methylbenzamide (131 mg, 0.36 mmol) in THF (5.0 mL) at room temperature was added Et_3N (200 μL, 1.4 mmol), followed by triphosgene (85 mg, 0.28 mmol) in THF (1.0 mL). The reaction mixture was stirred at room temperature for 2 hours. 1.0 M NaOH in water (1.4 mL, 1.4 mmol) was then added and the resulting mixture was stirred for another hour before it was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified on column chromatography (0-50% EtOAc in hexanes) to give the product as a colorless oil (137 mg, 98%). LC-MS calculated for $C_{18}H_{19}ClFN_4O_3$ $[M+H]^+$ m/z: 393.1; found 393.1.

Step 8: 3-(7-(6-(1-cyanocyclobutyl)pyridin-3-yl)-1-ethyl-2-oxo-1,2-dihydropyrido[4,3-d]pyrimidin-3(4H)-yl)-2-fluoro-5-methoxy-N-methylbenzamide

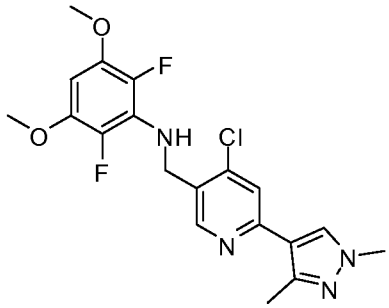
A mixture of 3-(7-chloro-1-ethyl-2-oxo-1,4-dihydropyrido[4,3-d]pyrimidin-3(2H)-yl)-2-fluoro-5-methoxy-N-methylbenzamide (20 mg, 0.051 mmol), [1,1′-bis(di-cyclohexylphosphino)ferrocene]dichloropalladium(II) (7.7 mg, 0.010 mmol), Na_2CO_3 (11 mg, 0.10 mmol), and 1-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]cyclobutanecarbonitrile (22 mg, 0.076 mmol) in water (1.0 mL)/t-BuOH (1.0 mL) was purged with nitrogen, and stirred at 100 °C for 3 hours. The reaction mixture was cooled to room temperature, and extracted with EtOAc. The combined organic layers were concentrated, and purified on prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the product as a white solid (TFA salt). LC-MS calculated for $C_{28}H_{28}FN_6O_3$ $[M+H]^+$ m/z: 515.2; found 515.2. ^{1}H NMR (400 MHz, DMSO) δ 9.34 (d, J = 1.7 Hz, 1H), 8.56 (dd, J = 8.3, 2.3 Hz, 1H), 8.45 (s, 1H), 8.27 (s, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.67 (s, 1H), 7.26 (dd, J = 5.9, 3.2 Hz, 1H), 7.07 (dd, J = 4.9, 3.3 Hz, 1H), 4.87 (s, 3H), 4.05 (q, J = 6.7 Hz, 2H), 3.79 (s, 3H), 2.89 – 2.66 (m, 6H), 2.35 – 2.21 (m, 1H), 2.09 (ddd, J = 20.4, 9.0, 5.4 Hz, 1H), 1.23 (t, J = 6.9 Hz, 3H).

Example 29

1-(cyclopropylmethyl)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one

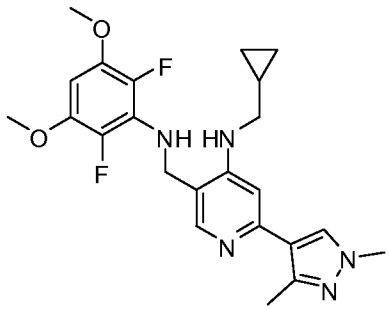


Step 1: N-{[4-chloro-6-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-3-yl]methyl}-2,6-difluoro-3,5-dimethoxyaniline



N-[(4,6-dichloropyridin-3-yl)methyl]-2,6-difluoro-3,5-dimethoxyaniline (1.58 g, 4.52 mmol), 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.00 g, 4.52 mmol) , tetrakis(triphenylphosphine)palladium(0) (520 mg, 0.45 mmol) and potassium carbonate (2.50 g, 18.1 mmol) in a vial were dissolved in a mixture of water (7.1 mL) and 1,4-dioxane (20 mL) The reaction mixture was then stirred at 120 °C overnight. The reaction mixture was quenched with saturated sodium bicarbonate solution and extracted three times with ethyl acetate. The combined extracts were dried over sodium sulfate and concentrated. The residue was purified on silica gel (50-100% ethyl acetate in hexanes) to afford the desired product (1.55 g, 31.6 mmol). LC-MS calculated for $C_{19}H_{19}ClF_2N_4O_2$ $[M+H]^+$ m/z: 409.1, found 409.1.

Step 2: N-(cyclopropylmethyl)-5-((2,6-difluoro-3,5-dimethoxyphenylamino)methyl)-2-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-4-amine



Conditions A:

A solution of N-{[4-chloro-6-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-3-yl]methyl}-2,6-difluoro-3,5-dimethoxyaniline (50.0 mg, 0.122 mmol), (2'-aminobiphenyl-2-yl)(chloro)[dicyclohexyl(2',6'-diisopropoxybiphenyl-2-yl)phosphoranyl]palladium (10 mg, 0.01 mmol), sodium *tert*-butoxide (21 mg, 0.22 mmol), and cyclopropyl methylamine(15.6 μL, 0.183 mmol) in 1,4-dioxane (700 μL) was heated at 90 °C for 2 hours. The reaction mixture was diluted with dichloromethane and filtered through a plug of Celite. The filtrate was concentrated and the residue used directly in the next step. LC-MS calculated for $C_{23}H_{28}F_2N_5O_2$ $[M+H]^+$ m/z: 444.2, found 444.2.

Conditions B:

A solution of N-{[4-chloro-6-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-3-yl]methyl}-2,6-difluoro-3,5-dimethoxyaniline (50.0 mg, 0.122 mmol), (2'-aminobiphenyl-2-yl)(chloro)[dicyclohexyl(2',6'-diisopropoxybiphenyl-2-yl)phosphoranyl]palladium (10 mg, 0.01 mmol), cesium carbonate (71 mg, 0.366 mmol), and cyclopropylmethylamine(15.6 μL, 0.183 mmol) in *tert*-butanol (800 μL) was heated at 100 °C overnight. The reaction mixture was diluted with dichloromethane and filtered through a plug of Celite. The filtrate was concentrated and the residue used directly in the next step.

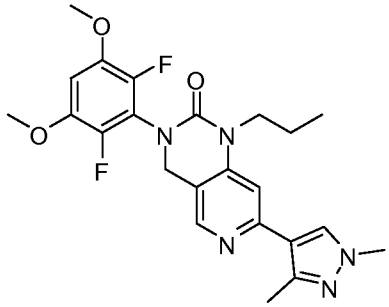
.Step 3: 1-(cyclopropylmethyl)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one

The crude residue from the previous step was dissolved in tetrahydrofuran (1.5 mL). Triethylamine (68.2 μL, 0.489 mmol) was added and the mixture cooled to 0 °C. Triphosgene (36.3 mg, 0.122 mmol) was added in one portion and the reaction mixture stirred at room temperature for 1 hour, then quenched with 1 N NaOH and stirred an additional 1 hour at room temperature. The mixture was diluted with water and extracted with

ethyl acetate three times. The combined organics were dried over sodium sulfate and concentrated. The crude product was purified on prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product (22 mg) as its TFA salt. LC-MS calculated for $C_{24}H_{26}F_2N_5O_3$ $[M+H]^+$ m/z: 470.2, found 470.2.

Example 30

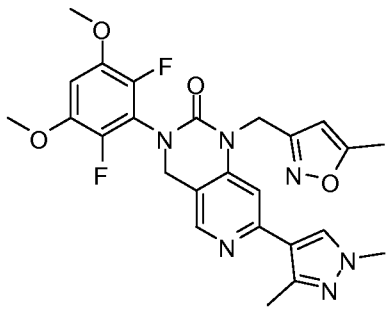
3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-propyl-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



This compound was prepared using procedures analogous to those for example 29, step 2 (Condition A) and step 3, with *n*-propyl amine replacing cyclopropylmethylamine in step 2. LCMS calculated for $C_{23}H_{26}F_2N_5O_3$ $[M+H]^+$ m/z: 458.2; Found: 458.2.

Example 31

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((5-methylisoxazol-3-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one

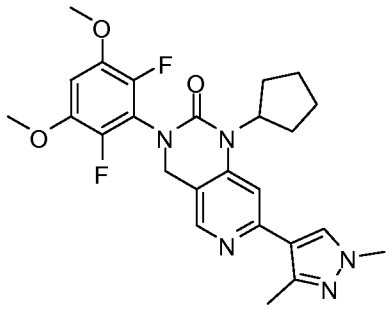


This compound was prepared using procedures analogous to those for example 29, step 2 (Condition B) and step 3, with 1-(5-methylisoxazol-3-yl)methanamine replacing cyclopropylmethylamine in step 2. LCMS calculated for $C_{25}H_{25}F_2N_6O_4$ $[M+H]^+$ m/z: 511.2; Found: 511.1. ^{1}H NMR (500 MHz, DMSO) δ 8.36 (s, 1H), 8.17 (s, 1H), 7.26 (s, 1H), 7.09 (t,

J = 8.2 Hz, 1H), 6.13 (m, 1H), 5.23 (s, 2H), 4.87 (s, 2H), 3.90 (s, 6H), 3.82 (s, 3H), 2.36 (s, 3H), 2.32 (s, 3H).

Example 32

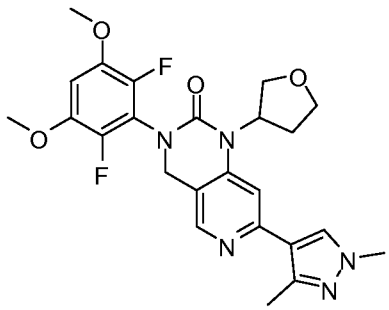
1-cyclopentyl-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



This compound was prepared using procedures analogous to those for example 29, step 2 (Condition A) and step 3, with cyclopentylamine replacing cyclopropylmethylamine in step 2. LCMS calculated for $C_{25}H_{28}F_2N_5O_3$ $[M+H]^+$ m/z: 484.2; Found: 484.2.

Example 33

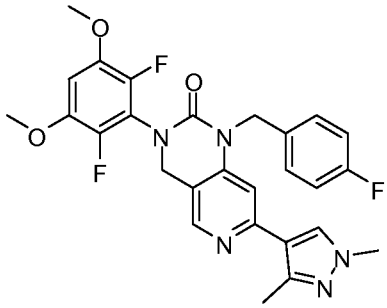
3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(tetrahydrofuran-3-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



This compound was prepared using procedures analogous to those for example 29, step 2 (Condition A) and step 3, with tetrahydrofuran-3-amine (HCl salt) replacing cyclopropylmethylamine in step 2. LCMS calculated for $C_{24}H_{26}F_2N_5O_4$ $[M+H]^+$ m/z: 486.2; Found: 486.2.

Example 34

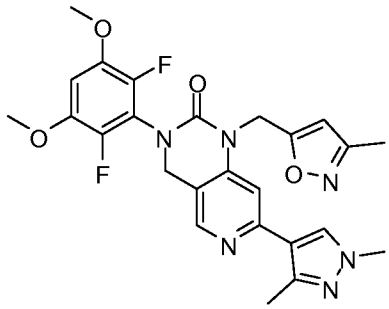
3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(4-fluorobenzyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



This compound was prepared using procedures analogous to those for example 29, step 2 (Condition A) and step 3, with 4-fluorobenzyl amine replacing cyclopropylmethylamine in step 2. LCMS calculated for $C_{27}H_{25}F_3N_5O_3$ $[M+H]^+$ m/z: 524.2; Found: 524.1.

Example 35

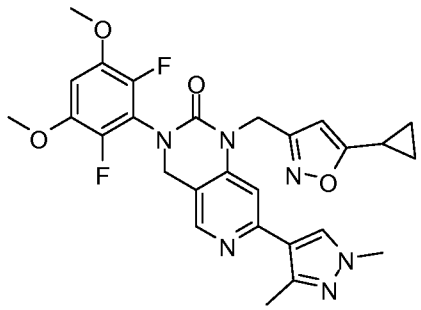
3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((3-methylisoxazol-5-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



This compound was prepared using procedures analogous to those for example 29, step 2 (Condition B) and step 3, with 1-(3-methylisoxazol-5-yl)methanamine replacing cyclopropylmethylamine in step 2. LCMS calculated for $C_{25}H_{25}F_2N_6O_4$ $[M+H]^+$ m/z: 511.2; Found: 511.2.

Example 36

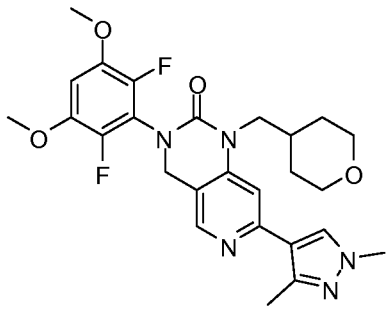
1-((5-cyclopropylisoxazol-3-yl)methyl)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



This compound was prepared using procedures analogous to those for example 29, step 2 (Condition B) and step 3, with 1-(5-cyclopropylisoxazol-3-yl)methanamine replacing cyclopropylmethylamine in step 2. LCMS calculated for $C_{27}H_{27}F_2N_6O_4$ $[M+H]^+$ m/z: 537.2; Found: 537.2.

Example 37

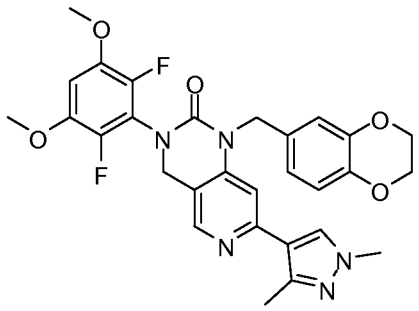
3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



This compound was prepared using procedures analogous to those for example 29, step 2 (Condition A) and step 3, with 1-(tetrahydro-2H-pyran-4-yl)methanamine replacing cyclopropylmethylamine in step 2. LCMS calculated for $C_{26}H_{30}F_2N_5O_4$ $[M+H]^+$ m/z: 514.2; Found: 514.2.

Example 38

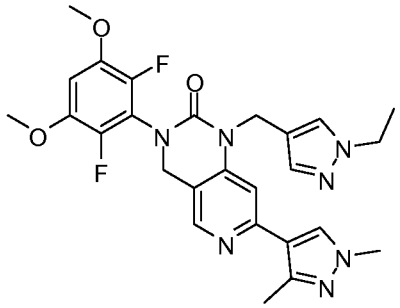
3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



This compound was prepared using procedures analogous to those for example 29, step 2 (Condition B) and step 3, with 1-(3,4-dihydro-2H-chromen-6-yl)methanamine replacing cyclopropylmethylamine in step 2. LCMS calculated for $C_{29}H_{28}F_2N_5O_5$ $[M+H]^+$ m/z: 564.2; Found: 564.2.

Example 39

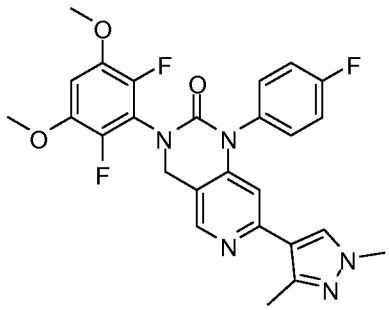
3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((1-ethyl-1H-pyrazol-4-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



This compound was prepared using procedures analogous to those for example 29, step 2 (Condition B) and step 3, with 1-(1-ethyl-1H-pyrazol-4-yl)methanamine replacing cyclopropylmethylamine in step 2. LCMS calculated for $C_{26}H_{28}F_2N_7O_3$ $[M+H]^+$ m/z: 524.2; Found: 524.1. ^{1}H NMR (600 MHz, DMSO) δ 8.39 (s, 1H), 8.25 (s, 1H), 7.73 (s, 1H), 7.45 (s, 1H), 7.32 (s, 1H), 7.11 (t, J = 8.2 Hz, 1H), 5.08 (s, 2H), 4.90 (s, 2H), 4.08 (q, J = 7.2 Hz, 2H), 3.93 (s, 6H), 3.86 (s, 3H), 2.29 (s, 3H), 1.31 (t, J = 7.3 Hz, 3H).

Example 40

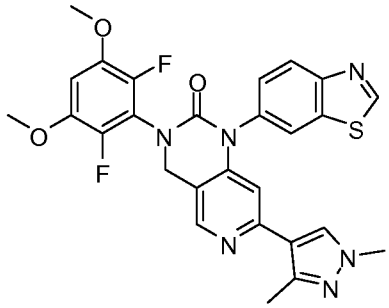
3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(4-fluorophenyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



This compound was prepared using procedures analogous to those for example 29, step 2 (Condition A) and step 3, with 4-fluoro aniline replacing cyclopropylmethylamine in step 2. LCMS calculated for $C_{26}H_{23}F_3N_5O_3$ $[M+H]^+$ m/z: 510.2; Found: 510.1. ^{1}H NMR (600 MHz, DMSO) δ 8.43 (s, 1H), 8.04 (s, 1H), 7.55 – 7.49 (m, 2H), 7.46 – 7.40 (m, 2H), 7.09 (t, J = 8.1 Hz, 1H), 6.28 (s, 1H), 4.99 (s, 2H), 3.91 (s, 6H), 3.77 (s, 3H), 2.11 (s, 3H).

Example 41

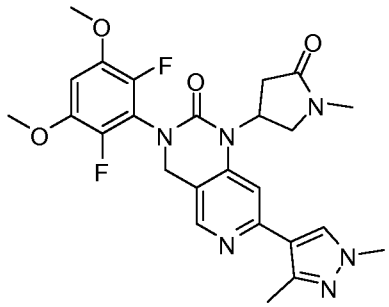
1-(1,3-benzothiazol-6-yl)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



This compound was prepared using procedures analogous to those for example 29, step 2 (Condition B) and step 3, with 1,3-benzothiazol-6-amine replacing cyclopropylmethylamine in step 2. LCMS calculated for $C_{27}H_{23}F_2N_6O_3S$ $[M+H]^+$ m/z: 549.1; Found: 549.1.

Example 42

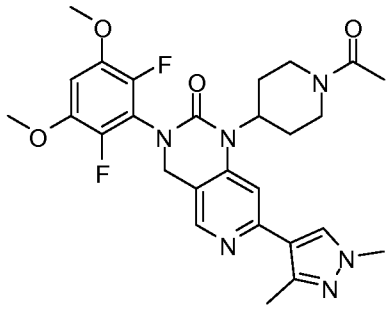
3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(1-methyl-5-oxopyrrolidin-3-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



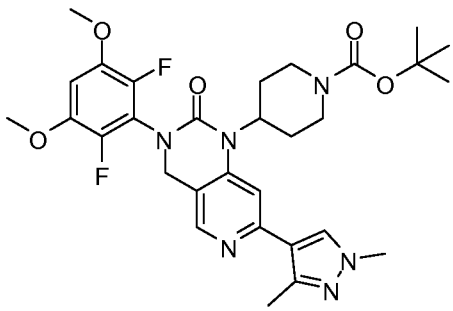
This compound was prepared using procedures analogous to those for example 29, step 2 (Condition B) and step 3, with 4-amino-1-methylpyrrolidin-2-one replacing cyclopropylmethylamine in step 2. LCMS calculated for $C_{25}H_{27}F_2N_6O_4$ $[M+H]^+$ m/z: 513.2; Found: 513.2.

Example 43

1-(1-acetylpiperidin-4-yl)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



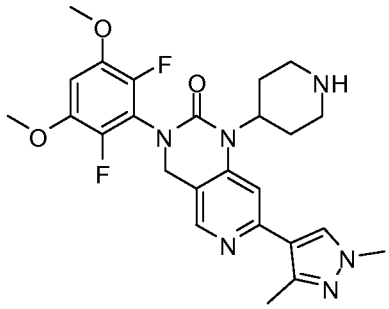
Step 1: tert-butyl 4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)piperidine-1-carboxylate



This compound was prepared using procedures analogous to those for example 29, step 2 (Condition B) and step 3, with 4-amino-1-methylpyrrolidin-2-one replacing

cyclopropylmethylamine in step 2. LCMS calculated for $C_{30}H_{37}F_2N_6O_5$ $[M+H]^+$ m/z: 599.3; Found: 599.2.

Step 2: 3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(piperidin-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



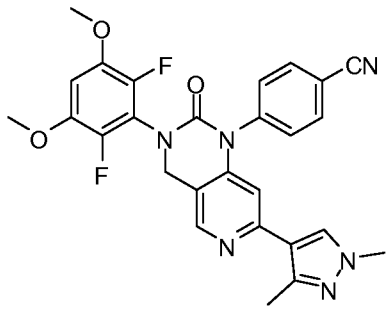
To the crude residue from step 1 was added methanol (1 mL) and 4.0 M HCl in 1,4-dioxane (1 mL). The reaction mixture stirred at room temperature for 1 hour, then concentrated. The crude product was purified on prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product (24 mg) as its bis-TFA salt. LCMS calculated for $C_{25}H_{29}F_2N_6O_3$ $[M+H]^+$ m/z: 499.2; Found: 499.2.

Step 3: 1-(1-acetylpiperidin-4-yl)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one

The product from step 2 (9.8 mg, 0.0135 mmol) was dissolved in methylene chloride (200 μL) and pyridine (5.5 μL, 0.0675 mmol) was added, followed by acetyl chloride (2.9 μL, 0.0405 mmol). The mixture was stirred at room temperature overnight, then purified on prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product (5 mg) as its TFA salt. LCMS calculated for $C_{27}H_{31}F_2N_6O_4$ $[M+H]^+$ m/z: 541.2; Found: 541.2.

Example 44

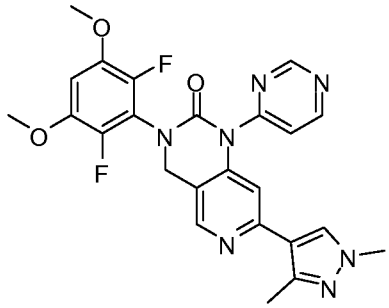
4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)benzonitrile



This compound was prepared using procedures analogous to those for example 29, step 2 (Condition A) and step 3, with 4-aminobenzonitrile replacing cyclopropylmethylamine in step 2. LCMS calculated for $C_{27}H_{23}F_2N_6O_3$ $[M+H]^+$ m/z: 517.2; Found: 517.1. ^{1}H NMR (600 MHz, DMSO) δ 8.45 (s, 1H), 8.09 (d, J = 4.7 Hz, 2H), 8.03 (s, 1H), 7.72 (d, J = 4.7 Hz, 2H), 7.10 (t, J = 8.2 Hz, 1H), 6.29 (s, 1H), 5.00 (s, 2H), 3.91 (s, 6H), 3.77 (s, 3H), 2.14 (s, 3H).

Example 45

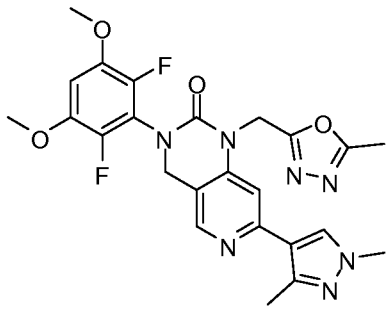
3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-pyrimidin-4-yl-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



This compound was prepared using procedures analogous to those for example 29, step 2 (Condition A) and step 3, with 5-aminopyrimidine replacing cyclopropylmethylamine in step 2. LCMS calculated for $C_{24}H_{22}F_2N_7O_3$ $[M+H]^+$ m/z: 494.2; Found: 494.1. ^{1}H NMR (600 MHz, DMSO) δ 9.32 (d, J = 0.9 Hz, 1H), 9.09 (d, J = 5.4 Hz, 1H), 8.46 (s, 1H), 8.07 (s, 1H), 7.85 (dd, J = 5.3, 1.3 Hz, 1H), 7.10 (t, J = 8.2 Hz, 1H), 6.70 (s, 1H), 4.98 (s, 2H), 3.91 (s, 6H), 3.76 (s, 3H), 2.24 (s, 3H).

Example 46

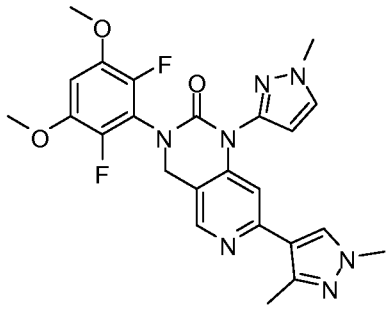
3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



This compound was prepared using procedures analogous to those for example 29, step 2 (Condition B) and step 3, with 1-(5-methyl-1,3,4-oxadiazol-2-yl)methanamine replacing cyclopropylmethylamine in step 2. LCMS calculated for $C_{24}H_{24}F_2N_7O_4$ $[M+H]^+$ m/z: 512.2; Found: 512.2. ^{1}H NMR (600 MHz, DMSO) δ 8.40 (s, 1H), 8.19 (s, 1H), 7.38 (s, 1H), 7.10 (t, J = 8.1 Hz, 1H), 5.45 (s, 2H), 4.89 (s, 2H), 3.90 (s, 6H), 3.83 (s, 3H), 2.48 (s, 3H), 2.36 (s, 3H).

Example 47

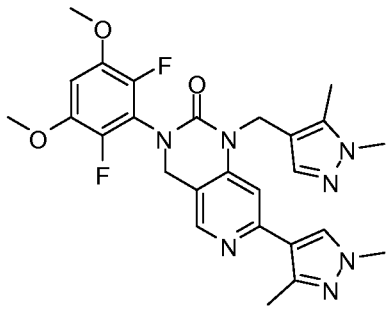
3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



This compound was prepared using procedures analogous to those for example 29, step 2 (Condition B) and step 3, with 1-methyl-1H-pyrazol-4-amine replacing cyclopropylmethylamine in step 2. LCMS calculated for $C_{24}H_{24}F_2N_7O_3$ $[M+H]^+$ m/z: 496.2; Found: 496.2. ^{1}H NMR (600 MHz, DMSO) δ 8.46 (s, 1H), 8.14 (s, 1H), 8.03 (s, 1H), 7.61 (d, J = 0.7 Hz, 1H), 7.10 (t, J = 8.1 Hz, 1H), 6.70 (s, 1H), 4.97 (s, 2H), 3.92 (s, 3H), 3.92 (s, 6H), 3.81 (s, 3H), 2.22 (s, 3H).

Example 48

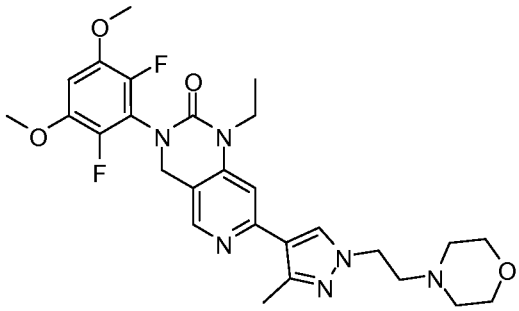
3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



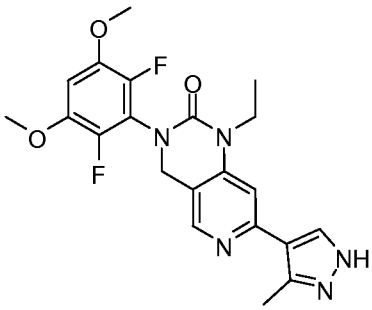
This compound was prepared using procedures analogous to those for example 29, step 2 (Condition B) and step 3, with 1-(1,5-dimethyl-1H-pyrazol-4-yl)methanamine replacing cyclopropylmethylamine in step 2. LCMS calculated for $C_{26}H_{28}F_2N_7O_3$ $[M+H]^+$ m/z: 524.2; Found: 524.2. ^{1}H NMR (600 MHz, DMSO) δ 8.37 (s, 1H), 8.23 (s, 1H), 7.28 (s, 1H), 7.26 (s, 1H), 7.10 (t, J = 8.2 Hz, 1H), 5.08 (s, 2H), 4.86 (s, 2H), 3.92 (s, 6H), 3.85 (s, 3H), 3.68 (s, 3H), 2.28 (s, 3H), 2.25 (s, 3H).

Example 49

3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(3-methyl-1-(2-morpholinoethyl)-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



Step 1: 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(3-methyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



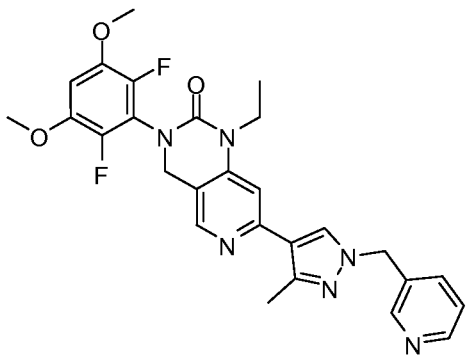
This compound was prepared using procedures analogous to those for example 22, step 2, with 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole replacing phenylboronic acid. LCMS calculated for $C_{21}H_{21}F_2N_5O_3$ $[M+H]^+$ m/z: 430.2; Found: 430.2.

Step 2: 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(3-methyl-1-(2-morpholinoethyl)-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one

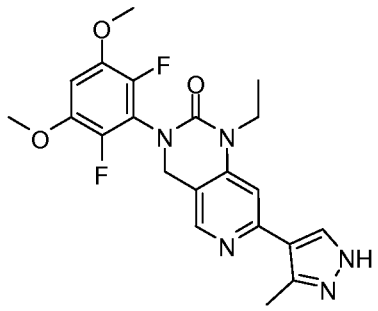
A mixture of 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(3-methyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one (170.0 mg, 0.3959 mmol), cesium carbonate (520.0 mg, 1.6 mmol), and 2-(4-morpholine)ethyl bromide hydrochloride (164.0 mg, 0.712 mmol) in acetonitrile (5.0 mL) was stirred and heated at 90 °C for 12 hours. The resulting mixture was cooled to room temperature, diluted with water, and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, and concentrated. The resulting material was purified via pH 2 preparative LC/MS (MeCN/water with TFA) to afford the product as a white solid (TFA salt). LC/MS calculated for $C_{27}H_{33}F_2N_6O_4$ $[M+H]^+$m/z: 543.2; found 543.2. ^{1}H NMR (500 MHz, dmso) δ 8.42 (s, 1H), 8.36 (s, 1H), 7.23 (s, 1H), 7.07 (t, J = 8.2 Hz, 1H), 4.80 (s, 2H), 4.55 (t, J = 6.6 Hz, 2H), 3.99 (q, J = 7.0 Hz, 2H), 3.89 (s, 6H), 3.64 (t, J = 6.6 Hz, 2H), 2.47 (s, 3H), 1.22 (t, J = 7.0 Hz, 3H). Note: the signals for the 8 protons on the morpholine were very broad and hidden in the baseline.

Example 50

3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(3-methyl-1-(pyridin-3-ylmethyl)-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



Step 1: 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(3-methyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



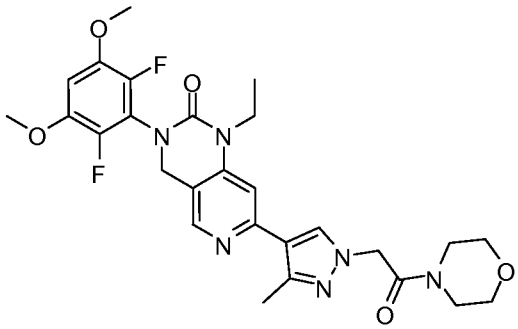
This compound was prepared using procedures analogous to those for example 22, step 2, with 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole replacing phenylboronic acid. LCMS calculated for $C_{21}H_{22}F_2N_5O_3$ $[M+H]^+$ m/z: 430.2; Found: 430.2.

Step 2: 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(3-methyl-1-(pyridin-3-ylmethyl)-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one

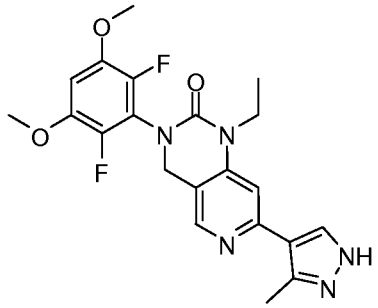
A mixture of 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(3-methyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one (20.0 mg, 0.0466 mmol), cesium carbonate (61.3 mg, 0.1883 mmol), and 3-(bromomethyl)pyridine hydrobromide (21.2 mg, 0.0838 mmol) in acetonitrile (0.6 mL) was stirred and heated at 90 °C for 12 hours. The resulting mixture was cooled to room temperature, diluted with water, and extracted with EtOAc (3 x 2 mL). The combined organic layers were dried over Na_2SO_4, and concentrated. The resulting material was purified via pH 2 preparative LC/MS (MeCN/water with TFA) to afford the product as a white solid (TFA salt). LC/MS calculated for $C_{27}H_{26}F_2N_6O_3$ $[M+H]^+$m/z: 521.2; found 521.2.

Example 51

3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(3-methyl-1-(2-morpholino-2-oxoethyl)-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



Step 1: 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(3-methyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



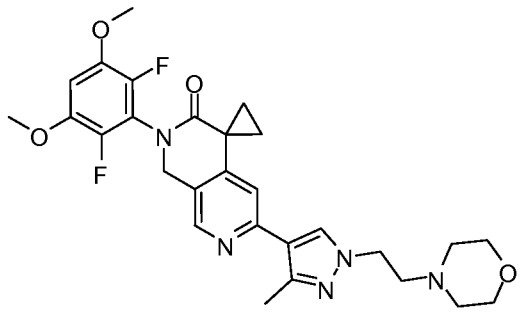
This compound was prepared using procedures analogous to those for example 22, step 2, with 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole replacing phenylboronic acid. LCMS calculated for $C_{21}H_{22}F_2N_5O_3$ $[M+H]^+$ m/z: 430.2; Found: 430.2.

Step 2: 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(3-methyl-1-(2-morpholino-2-oxoethyl)-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one

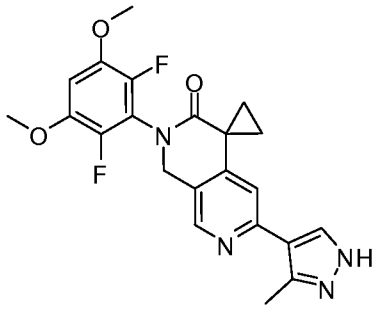
A mixture of 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(3-methyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one (20.0 mg, 0.0466 mmol), cesium carbonate (61.3 mg, 0.1883 mmol), and 2-chloro-1-morpholinoethanone (13.7 mg, 0.0838 mmol) in acetonitrile (0.6 mL) was stirred and heated at 90 °C for 12 hours. The resulting mixture was cooled to room temperature, diluted with water, and extracted with EtOAc (3 x 2 mL). The combined organic layers were dried over Na_2SO_4, and concentrated. The resulting material was purified via pH 2 preparative LC/MS (MeCN/water with TFA) to afford the product as a white solid (TFA salt). LC/MS calculated for $C_{27}H_{31}F_2N_6O_5$ $[M+H]^+$m/z: 557.2; found 557.2.

Example 52

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(3-methyl-1-(2-morpholinoethyl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one



Step 1: 2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(3-methyl-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one



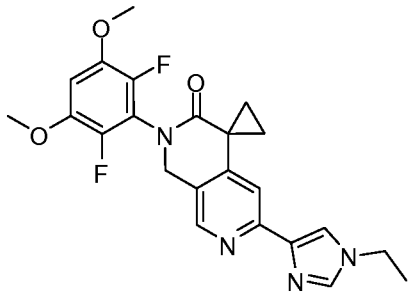
This compound was prepared using procedures analogous to those for example 1, step 7, with 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole replacing (5-amino-2-methylphenyl)boronic acid. LCMS calculated for $C_{22}H_{21}F_2N_4O_3$ $[M+H]^+$ m/z: 427.1; Found: 427.1.

Step 2: 2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(3-methyl-1-(2-morpholinoethyl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one

A mixture of 2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(3-methyl-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one (17.0 mg, 0.0399 mmol), cesium carbonate (40.0 mg, 0.1 mmol), and 2-(4-morpholine)ethyl bromide hydrochloride (23.0 mg, 0.1 mmol) in acetonitrile (0.5 mL) was stirred and heated at 90 °C for 12 hours. The resulting mixture was cooled to room temperature, diluted with water, and extracted with EtOAc (3 x 2 mL). The combined organic layers were dried over Na_2SO_4, and concentrated. The resulting material was purified via pH 2 preparative LC/MS (MeCN/water with TFA) to afford the product as a white solid (TFA salt). LC/MS calculated for $C_{28}H_{31}F_2N_5O_4$ $[M+H]^+$m/z: 540.2; found 540.2. ^{1}H NMR (400 MHz, DMSO) δ 8.41 (s, 1H), 8.36 (s, 1H), 7.14 – 6.98 (m, 2H), 4.94 (s, 2H), 4.49 (t, J = 6.4 Hz, 2H), 3.89 (s, 6H), 3.73 – 3.49 (m, 2H), 2.45 (s, 3H), 1.86 – 1.64 (m, 2H), 1.56 (q, J = 3.9 Hz, 2H).

Example 53

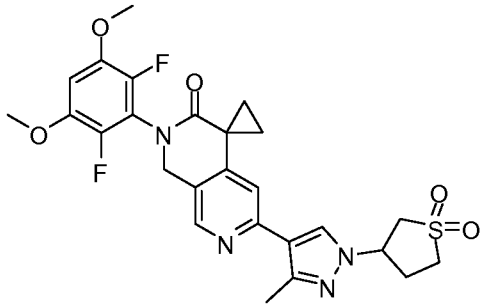
2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1-ethyl-1H-imidazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one



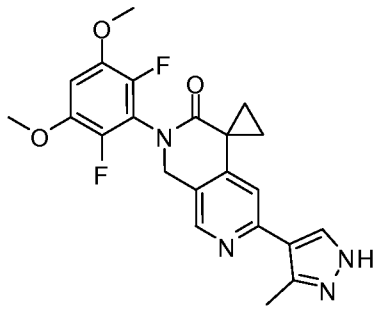
This compound was prepared using procedures analogous to those for example 1, step 7, with 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-imidazole replacing (5-amino-2-methylphenyl)boronic acid. LCMS calculated for $C_{23}H_{23}F_2N_4O_3$ $[M+H]^+$ m/z: 441.2; Found: 441.2.

Example 54

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-[1-(1,1-dioxidotetrahydro-3-thienyl)-3-methyl-1H-pyrazol-4-yl]-1',2'-dihydro-3'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'-one



Step 1: 2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(3-methyl-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one



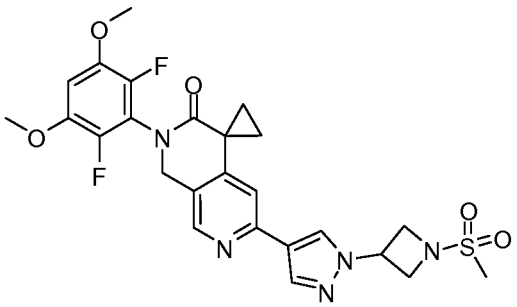
This compound was prepared using procedures analogous to those for example 1, step 7, with 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole replacing (5-amino-2-methylphenyl)boronic acid. LCMS calculated for $C_{22}H_{21}F_2N_4O_3$ $[M+H]^+$ m/z: 427.1; Found: 427.1.

Step 2: 2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-[1-(1,1-dioxidotetrahydro-3-thienyl)-3-methyl-1H-pyrazol-4-yl]-1',2'-dihydro-3'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'-one

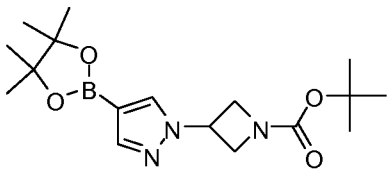
A mixture of 2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(3-methyl-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one (20.0 mg, 0.0469 mmol), cesium carbonate (40.0 mg, 0.1 mmol), and 3-Bromotetrahydrothiophene 1,1-dioxide (23.0 mg, 0.12 mmol) in acetonitrile (0.6 mL) was stirred and heated at 90 °C for 12 hours. The resulting mixture was cooled to room temperature, diluted with water, and extracted with EtOAc (3 x 2 mL). The combined organic layers were dried over Na_2SO_4, and concentrated. The resulting material was purified via pH 2 preparative LC/MS (MeCN/water with TFA) to afford the product as a white solid (TFA salt). LC/MS calculated for $C_{26}H_{27}F_2N_4O_5S$ $[M+H]^+$m/z: 545.2; found 545.2.

Example 55

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1-(1-(methylsulfonyl)azetidin-3-yl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one

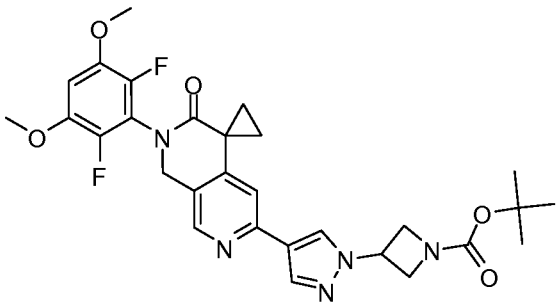


Step 1: tert-butyl 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)azetidine-1-carboxylate



A mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (19.4 mg, 0.10 mmol), cesium carbonate (49.0 mg, 0.15 mmol), and tert-butyl 3-iodoazetidine-1-carboxylate (31.0 mg, 0.11 mmol) in acetonitrile (0.5 mL) was stirred and heated at 90 °C for 12 hours. The resulting mixture was cooled to room temperature, and the reaction was quenched with saturated aqueous NH_4Cl, and extracted with DCM (3×2 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. The crude product was used directly in the next step without further purification.

Step 2: tert-butyl 3-(4-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-1H-pyrazol-1-yl)azetidine-1-carboxylate



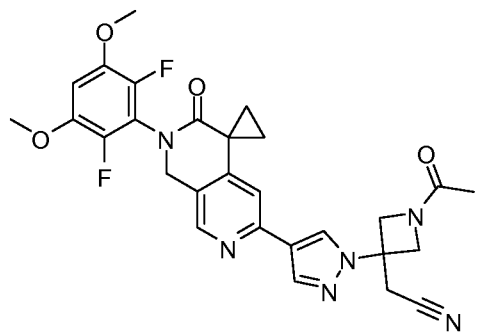
This compound was prepared using procedures analogous to those for example 1, step 7, with tert-butyl 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)azetidine-1-carboxylate replacing (5-amino-2-methylphenyl)boronic acid. The crude product was used directly in the next step without further purification.

Step 3: 2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1-(1-(methylsulfonyl)azetidin-3-yl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one

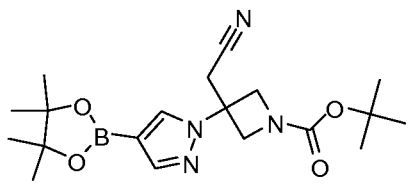
tert-Butyl 3-(4-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-1H-pyrazol-1-yl)azetidine-1-carboxylate was dissolved in hydrogen chloride solution, 4.0 M in dioxane (1 mL), and the resulting mixture was stirred at room temperature for 1 hour. The crude reaction mixture was concentrated, and then dissolved in DCM (0.6 mL). After cooling to 0 °C, triethylamine (0.023 mL, 0.16 mmol) and methanesulfonyl chloride (0.010 mL, 0.129 mmol) were added slowly into the reaction mixture. The resulting solution was stirred at room temperature for 1 hour. The reaction was quenched with aq. $NaHCO_3$, (2 mL) and extracted with EtOAc (3 x 2 mL). The combined organic layers were dried over Na_2SO_4, and concentrated. The resulting material was purified via pH 2 preparative LC/MS (MeCN/water with TFA) to afford the product as a white solid (TFA salt). LC/MS calculated for $C_{25}H_{26}F_2N_4O_5S$ $[M+H]^+$m/z: 545.2; found 545.2.

Example 56

2-(1-acetyl-3-(4-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-1H-pyrazol-1-yl)azetidin-3-yl)acetonitrile

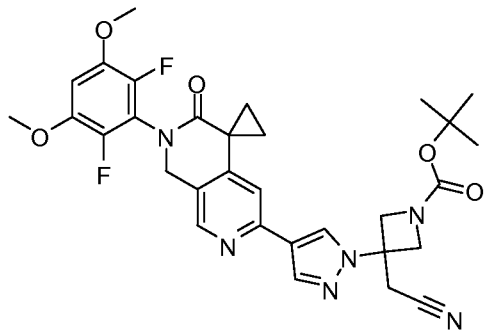


Step 1: tert-butyl 3-(cyanomethyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)azetidine-1-carboxylate



A mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (19.4 mg, 0.10 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.0313 mL, 0.209 mmol), and tert-butyl 3-(cyanomethylene)azetidine-1-carboxylate (19.4 mg, 0.10 mmol) in acetonitrile (0.5 mL) was stirred at room temperature for 12 hours. The resulting mixture was quenched with saturated aqueous NH_4Cl, and extracted with DCM (3×2 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. The crude product was used directly in the next step without further purification.

Step 2: tert-butyl 3-(cyanomethyl)-3-(4-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-1H-pyrazol-1-yl)azetidine-1-carboxylate



This compound was prepared using procedures analogous to those for example 1, step 7, with tert-butyl 3-(cyanomethyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)azetidine-1-carboxylate replacing (5-amino-2-methylphenyl)boronic acid. The crude product was used directly in the next step without further purification.

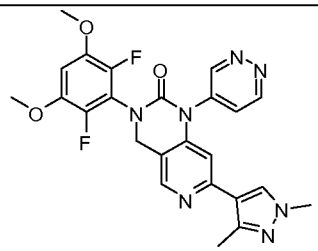
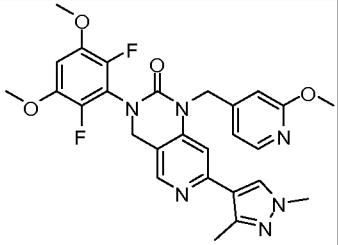
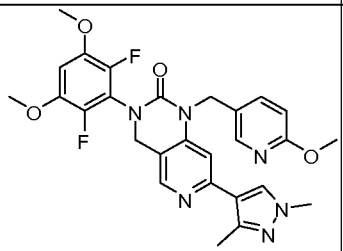
Step 3: 2-(1-acetyl-3-(4-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-1H-pyrazol-1-yl)azetidin-3-yl)acetonitrile

tert-Butyl 3-(cyanomethyl)-3-(4-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-1H-pyrazol-1-yl)azetidine-1-carboxylate was dissolved in hydrogen chloride solution, 4.0 M in dioxane (1 mL), and the resulting mixture was stirred at room temperature for 1 hour. The crude reaction mixture was concentrated, and then dissolved in DCM (0.6 mL). After cooling to 0 °C, triethylamine (0.015 mL, 0.11 mmol) and acetyl chloride (0.010 mL, 0.140 mmol) were added slowly into the reaction mixture. The resulting solution was stirred at room temperature for 1 hour. The reaction was quenched with aq. $NaHCO_3$, (2 mL) and extracted with EtOAc (3 x 2 mL). The

combined organic layers were dried over Na_2SO_4, and concentrated. The resulting material was purified via pH 2 preparative LC/MS (MeCN/water with TFA) to afford the product as a white solid (TFA salt). LC/MS calculated for $C_{28}H_{27}F_2N_6O_4$ $[M+H]^+$m/z: 549.2; found 549.2.

Table 5. The compounds in **Table 5** were prepared in an analogous fashion to **Example 29** using the appropriate amine building block and using method A or B in *Step 2* as noted below.

Table 5.

Example	Method	Name/^{1}H NMR	Structure	LCMS $(M+H)^+$
57	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(pyridazin-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one: ^{1}H NMR (600 MHz, DMSO) δ 9.48 (dd, *J* = 5.5, 1.1 Hz, 1H), 9.42 (dd, *J* = 2.6, 1.1 Hz, 1H), 8.46 (s, 1H), 8.06 (s, 1H), 7.99 (dd, *J* = 5.6, 2.6 Hz, 1H), 7.09 (t, *J* = 8.1 Hz, 1H), 6.47 (s, 1H), 4.99 (s, 2H), 3.90 (s, 6H), 3.73 (s, 3H), 2.20 (s, 3H).		494.2
58	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((2-methoxypyridin-4-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		537.2
59	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((6-methoxypyridin-3-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one: ^{1}H NMR (600 MHz, DMSO) δ 8.37 (s, 1H), 8.21 – 8.16 (m, 2H), 7.65 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.16 – 7.07 (m, 2H), 6.84 (d, *J* = 8.9 Hz, 1H), 5.23 (s, 2H), 4.93 (s, 2H), 3.92		537.2

		(s, 6H), 3.82 (s, 3H), 3.81 (s, 3H), 2.17 (s, 3H).		
60	**A**	3-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)benzonitrile		517.2
61	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(pyrimidin-5-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		494.2
62	**B**	4-((3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)methyl)-N-methylbenzamide		563.2
63	**A**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(isoquinolin-7-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		543.2
64	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((5-ethylisoxazol-3-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		525.2
65	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(pyrimidin-4-ylmethyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		508.2

66	**A**	5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)-2-fluorobenzonitrile		535.2
67	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((5-ethyl-1,3,4-oxadiazol-2-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		526.2
68	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((2-methylpyridin-4-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		521.2
69	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(pyridin-4-ylmethyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one: ^{1}H NMR (600 MHz, DMSO) δ 8.74 (d, *J* = 6.4 Hz, 2H), 8.39 (s, 1H), 8.11 (s, 1H), 7.63 (d, *J* = 6.0 Hz, 2H), 7.09 (t, *J* = 8.1 Hz, 1H), 6.96 (s, 1H), 5.43 (s, 2H), 4.96 (s, 2H), 3.91 (s, 6H), 3.78 (s, 3H), 2.14 (s, 3H).		507.2
70	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(pyrazin-2-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		494.2
71	**A**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(1-(methylsulfonyl)piperidin-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		577.2

72	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((1-methyl-1H-pyrazol-4-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		510.2
73	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-(3,4-difluorobenzyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		542.2
74	**B**	5-((3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)methyl)picolinonitrile		532.2
75	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(2-methylbenzo[d]oxazol-6-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		547.2
76	**A**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-methyl-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		430.2
77	**A**	1-(4-(1H-pyrazol-1-yl)phenyl)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		558.2

78	**A**	3-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)-5-fluorobenzonitrile		535.2
79	**B**	6-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)nicotinonitrile		518.2
80	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(oxazol-5-ylmethyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		497.2
81	**A**	4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)-2-methoxybenzonitrile		547.2
82	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((5-methyloxazol-2-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		511.2
83	**A**	1-cyclopropyl-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		456.2

84	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(pyrimidin-5-ylmethyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		508.2
85	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(pyrazin-2-ylmethyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		508.2
86	**A**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(pyridin-3-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		493.2
87	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(6-methylpyrazin-2-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		508.2
88	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(pyridazin-3-ylmethyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		508.2
89	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(3-(1-methyl-1H-1,2,3-triazol-5-yl)phenyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		573.2

90	**A**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-isopropyl-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		458.2
91	**B**	1-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)cyclopropanecarbonitrile		481.2
92	**A**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(pyridin-2-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		493.2
93	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((5-isopropylisoxazol-3-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		539.2
94	**A**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(pyridin-2-ylmethyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		507.2
95	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((2-methylthiazol-4-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		527.2

96	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((1-methyl-5-oxopyrrolidin-3-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		527.2
97	**A**	2-(4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)phenyl)acetonitrile		531.2
98	**A**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(4-(methylsulfonyl)phenyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		570.2
99	**A**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(3-fluorophenyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		510.2
100	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(1-methyl-1H-pyrazol-3-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		496.2
101	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((1,3-dimethyl-1H-pyrazol-4-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		524.2

102	**A**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-(3,4-difluorophenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		528.2
103	**A**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-(3,5-difluorophenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		528.2
104	**A**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(4-methoxyphenyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		522.2
105	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(pyrimidin-2-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		494.2
106	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(5-ethylpyrazin-2-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		522.2
107	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(5-methylpyrazin-2-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		508.2

108	**A**	(R)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((tetrahydrofuran-3-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		500.2
109	**A**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(3-methoxyphenyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		522.2
110	**A**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(2-fluorophenyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		510.2
111	**A**	3-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)-N-methylbenzenesulfonamide		585.2
112	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(5-methoxypyrazin-2-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		524.2
113	**A**	4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)-N,N-dimethylbenzamide		563.2

114	**A**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(2-(1-methyl-1H-pyrazol-4-yl)ethyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		524.2
115	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		574.2
116	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((2-ethoxypyridin-4-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		551.2
117	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((1-methyl-2-oxo-1,2-dihydropyridin-4-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		537.2
118	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		561.2
119	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(2-oxoindolin-5-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		547.2

120	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(2-methyl-3-oxoisoindolin-5-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		561.2
121	**B**	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((2-methylpyrimidin-4-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		522.2

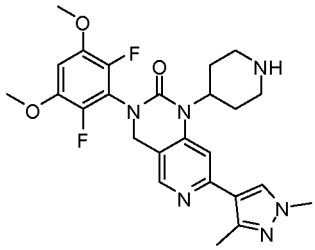
Example 122

Methyl 4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)piperidine-1-carboxylate

Step 1. Preparation of tert-butyl 4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)piperidine-1-carboxylate

This compound was prepared using procedures analogous to those for *Example 29, Step 2* (Condition B) and *Step 3*, with *tert*-butyl 4-aminopiperidine-1-carboxylate replacing 4-aminomethyl pyridine in *Step 2*. LCMS calculated for $C_{30}H_{37}F_2N_6O_5$ $[M+H]^+$ m/z: 599.1; Found: 599.1.

Step 2: 3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(piperidin-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



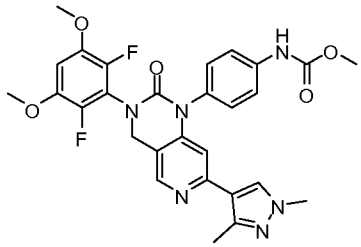
To the crude residue from *Step 1* above was added methanol (1 mL) and 4.0 M HCl 1,4-dioxane (1 mL) and the reaction mixture stirred at room temperature for 1h, then concentrated. The crude product was purified on prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product (24 mg) as its bis-TFA salt. LCMS calculated for $C_{25}H_{29}F_2N_6O_3$ $[M+H]^+$ m/z: 499.2; Found: 499.1.

Step 3. Preparation of methyl 4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)piperidine-1-carboxylate

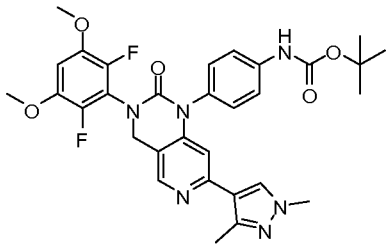
To a solution of 3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-piperidin-4-yl-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one (7.00 mg, 0.0140 mmol) in tetrahydrofuran (500 µL) was added N,N-diisopropylethylamine (9.78 µL, 0.0562 mmol) and methyl chloroformate (1.63 µL, 0.0211 mmol). The reaction mixture was stirred overnight then diluted with methanol and purified directly by reverse phase HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired product as the corresponding TFA salt. LCMS calculated for $C_{27}H_{31}F_2N_6O_5$ $[M+H]^+$ m/z: 557.2, found 557.2.

Example 123

Methyl 4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)phenylcarbamate.

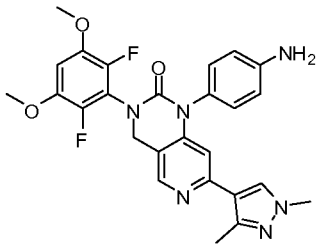


Step 1. tert-butyl 4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)phenylcarbamate



This compound was prepared using procedures analogous to those for *Example 29, Step 2* (Condition B) and *Step 3*, with tert-butyl 4-aminophenylcarbamate replacing 4-aminomethyl pyridine in *Step 2*. LCMS calculated for $C_{31}H_{33}F_2N_6O_5$ $[M+H]^+$ m/z: 607.2; Found: 607.2

Step 2. Preparation of 1-(4-aminophenyl)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one.



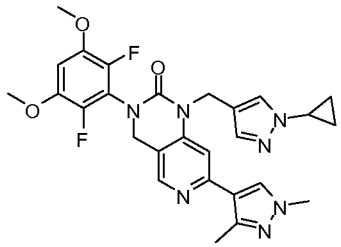
To the crude residue from *Step 1* above was added methanol (1 mL) and 4.0 M HCl 1,4-dioxane (1 mL) and the reaction mixture stirred at room temperature for 1h, then concentrated. The crude product was purified by column chromatography (0-10% methanol in dichloromethane). LCMS calculated for $C_{26}H_{25}F_2N_6O_3$ $[M+H]^+$ m/z: 507.2; Found: 507.2.

Step 3. Preparation of methyl 4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)phenylcarbamate.

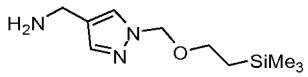
To a solution of 1-(4-aminophenyl)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one (7.00 mg, 0.0140 mmol) in tetrahydrofuran (500 µL) was added N,N-diisopropylethylamine (9.78 µL, 0.0562 mmol) and methyl chloroformate (1.63 µL, 0.0211 mmol). The reaction mixture was stirred overnight, then diluted with methanol and purified directly by reverse phase HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired product as the corresponding TFA salt. LC-MS calculated for $C_{28}H_{27}F_2N_6O_5$ $[M+H]^+$ m/z: 565.2, found 565.2.

Example 124

1-((1-cyclopropyl-1H-pyrazol-4-yl)methyl)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



Step 1. Preparation of (1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)methanamine



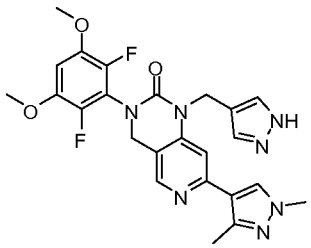
To a solution of ethyl 1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxylate (500 mg, 2 mmol) in tetrahydrofuran (2 mL) was added 2.0 M lithium tetrahydroaluminate in tetrahydrofuran (1.11 mL, 2.22 mmol) and the mixture stirred at room temperature for 2h, then quenched by the addition of 20 μL water, 20 μL of a 15% aqueous NaOH solution, then an additional 60 μL of water. After stirring an additional 1h, the reaction mixture was filtered through a plug of Celite and concentrated.

To the above residue in methylene chloride (10 mL) was added triethylamine (644 μL, 4.62 mmol) and the mixture cooled to 0 degrees. Methanesulfonyl chloride (143 μL, 1.85 mmol) was added dropwise and the mixture stirred at room temperature 30 min, then recooled to 0 degrees and quenched by the careful addition of 2 mL of water. The mixture was washed with brine and the aqueous layer extracted with additional methylene chloride. The combined organics were dried over sodium sulfate and concentrated.

The residue was dissolved in N,N-dimethylformamide (10 mL) and sodium azide (180 mg, 2.77 mmol) was added. The mixture was stirred overnight at room temperature, then quenched at 0 degrees by the addition of 1.5 mL of water. The mixture was diluted with diethyl ether and the layers separated. The organic layer was then washed with water and brine, then dried over sodium sulfate and concentrated.

The residue was dissolved in 1,4-Dioxane (1.5 mL) and resin bound triphenylphosphine (924 mg, 2.77 mmol) was added. The mixture was stirred for 1h, then a 4:1 mixture of dioxane:water (1.5 mL total) was added and the mixture was stirred at room temperature overnight. The resin was removed by filtration and the filtrate concentrated to yield the desired compound, which was used without further purification in the next step. LC-MS calculated for $C_{10}H_{22}N_3OSi$ $[M+H]^+$ m/z: 228.2, found 228.2.

Step 2. Preparation of 1-((1H-pyrazol-4-yl)methyl)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



To a mixture of N-{[4-chloro-6-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-3-yl]methyl}-2,6-difluoro-3,5-dimethoxyaniline (50 mg, 0.1 mmol), 1-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-4-yl)methanamine (41.7 mg, 0.183 mmol), (2'-aminobiphenyl-2-yl)(chloro)[dicyclohexyl(2',6'-diisopropoxybiphenyl-2-yl)phosphoranyl]palladium (9.5 mg, 0.012 mmol) and cesium carbonate (120 mg, 0.367 mmol) was added tert-butyl alcohol (2 mL) and the reaction vessel evacuated and back filled with nitrogen three times. The mixture was then stirred at 100 degrees overnight, at which point LCMS showed complete conversion. The reaction mixture was diluted with dichloromethane and filtered through a pad of Celite. The filtrate was concentrated.

The residue was dissolved in tetrahydrofuran (2.2 mL) and triethylamine (68.2 μL, 0.489 mmol) was added. After cooling to 0 degrees, triphosgene (36.3 mg, 0.122 mmol) was added in one portion and the reaction mixture allowed to stir at room temperature for 1h, then quenched by the addition of 1N NaOH and stirred for an additional 1h. The mixture was then extracted with ethyl acetate and the organic layer dried over sodium sulfate and concentrated.

The residue was dissolved in trifluoroacetic acid (1.0 mL) and stirred at room temperature for 1h. LCMS analysis showed complete conversion to the desired product. The mixture was concentrated, then purified by column chromatography (50-100% ethyl acetate in hexanes) to provide the desired product as a brown powder. LC-MS calculated for $C_{24}H_{24}F_2N_7O_3$ $[M+H]^+$ m/z: 496.2, found 496.2.

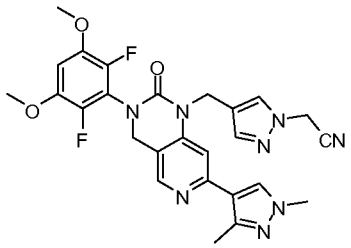
Step 3. Preparation of 1-((1-cyclopropyl-1H-pyrazol-4-yl)methyl)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-on.

A mixture of 3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(1H-pyrazol-4-ylmethyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one (10 mg, 0.02

mmol), cyclopropylboronic acid (6.93 mg, 0.0807 mmol), sodium carbonate (8.56 mg, 0.0807 mmol), copper(II) diacetate (7.33 mg, 0.0404 mmol) and 2,2'-bipyridine (6.30 mg, 0.0404 mmol) was dissolved in 1,2-dichloroethane (200 μL) and the mixture was heated at 95 degrees overnight. The mixture was diluted with methanol and purified directly by reverse phase HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired product as a white solid. LC-MS calculated for $C_{27}H_{28}F_2N_7O_3$ $[M+H]^+$ m/z: 536.2, found 536.2.

Example 125

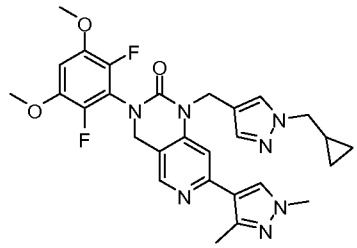
2-(4-((3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)methyl)-1H-pyrazol-1-yl)acetonitrile



To a solution of 3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(1H-pyrazol-4-ylmethyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one (*Example 124, Step 2*; 17 mg, 0.034 mmol) in N,N-dimethylformamide (500 μL) at 0 degrees was added sodium hydride (4.12 mg, 0.172 mmol) and the mixture stirred at 0 degrees for 10 minutes. Bromoacetonitrile (23.9 μL, 0.343 mmol) was then added and the reaction mixture stirred for 1h at room temperature. The reaction mixture was then diluted with methanol and purified directly by reverse phase HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired product as the corresponding TFA salt. LC-MS calculated for $C_{26}H_{25}F_2N_8O_3$ $[M+H]^+$ m/z: 535.2, found 535.2.

Example 126

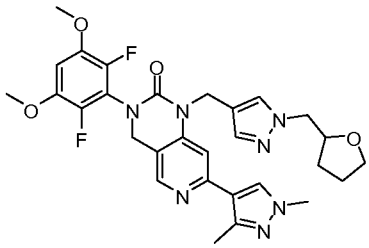
1-((1-(cyclopropylmethyl)-1H-pyrazol-4-yl)methyl)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



This compound was prepared using procedures analogous to those for *Example 125*, with cyclopropylmethyl bromide replacing bromoacetonitrile. LCMS calculated for $C_{28}H_{30}F_2N_7O_3$ $[M+H]^+$ m/z: 550.2; Found: 550.2.

Example 127

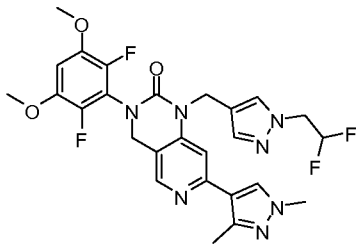
3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((1-((tetrahydrofuran-2-yl)methyl)-1H-pyrazol-4-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



This compound was prepared using procedures analogous to those for *Example 125*, with 2-(bromomethyl)tetrahydrofuran replacing bromoacetonitrile. LCMS calculated for $C_{29}H_{32}F_2N_7O_4$ $[M+H]^+$ m/z: 580.2; Found: 580.2.

Example 128

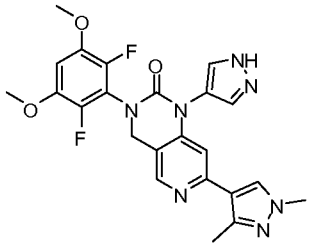
3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-((1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)methyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



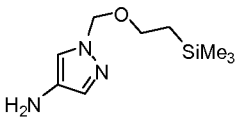
This compound was prepared using procedures analogous to those for *Example 125*, with 2-bromo-1,1-difluoroethane replacing bromoacetonitrile. LCMS calculated for $C_{26}H_{26}F_4N_7O_3$ $[M+H]^+$ m/z: 560.2; Found: 560.2.

Example 129

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



Step 1. Preparation of 1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-amine



To a 0 degree solution of 4-nitro-1H-pyrazole (250 mg, 2.2 mmol) in tetrahydrofuran (10 mL) was added sodium hydride (60wt% in mineral oil, 63.7 mg, 2.65 mmol) and the reaction mixture stirred for 10 minutes at this temperature. [β-(Trimethylsilyl)ethoxy]methyl chloride (430 μL, 2.43 mmol) was then added dropwise and the reaction mixture stirred for an additional 1h at room temperature. The reaction mixture was quenched with brine and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated. The residue was purified by column chromatography (10-80% ethyl acetate in hexanes) to provide the intermediate protected nitro pyrazole.

The residue was dissolved in ethyl acetate (2.5 mL) and 10% palladium on carbon (240 mg, 0.11 mmol) was added. The reaction vessel was evacuated and backfilled with hydrogen gas (1 atm) and the reaction mixture stirred for 2h at room temperature. The mixture was filtered through a pad of Celite and concentrated. The residue was used without further purification in the next step. LCMS calculated for $C_9H_{20}N_3OSi$ $[M+H]^+$ m/z: 214.1; Found: 214.2.

Step 2. Preparation of 3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one.

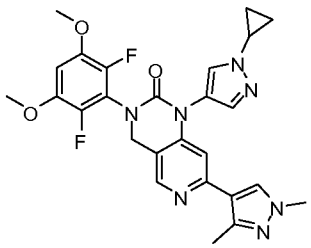
To a mixture of N-{[4-chloro-6-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-3-yl]methyl}-2,6-difluoro-3,5-dimethoxyaniline (50 mg, 0.1 mmol), 1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-4-amine (39.1 mg, 0.183 mmol), RuPhos Pd G2 (9.5 mg, 0.012 mmol) and

cesium carbonate (120 mg, 0.367 mmol) was added tert-butyl alcohol (2 mL) and the reaction vessel evacuated and back filled with nitrogen three times. The mixture was then stirred at 100 degrees overnight,. The reaction mixture was diluted with dichloromethane and filtered through a pad of Celite. The filtrate was concentrated.

The residue was dissolved in tetrahydrofuran (2.2 mL) and triethylamine (68.2 µL, 0.489 mmol) was added. After cooling to 0 degrees, triphosgene (36.3 mg, 0.122 mmol) was added in one portion and the reaction mixture allowed to stir at room temperature for 1h, then quenched by the addition of 1N NaOH and stirred for an additional 1h. The mixture was then extracted with ethyl acetate and the organic layer dried over sodium sulfate and concentrated. The residue was purified by column chromatography (0-15% methanol in dichloromethane) to provide the desired product as a light brown solid. This solid was further purified by reverse phase HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired product as the corresponding TFA salt. LCMS calculated for $C_{23}H_{22}F_2N_7O_3$ $[M+H]^+$ m/z: 482.2; Found: 482.2.

Example 130

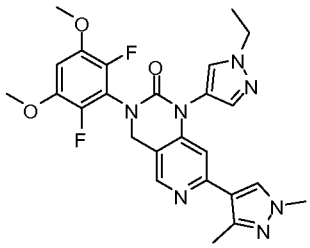
1-(1-cyclopropyl-1H-pyrazol-4-yl)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



This compound was prepared using procedures analogous to those for *Example 124, Step 3* with the product of *Example 129* serving as the starting material. LCMS calculated for $C_{26}H_{26}F_2N_7O_3$ $[M+H]^+$ m/z: 522.2; Found: 522.2.

Example 131

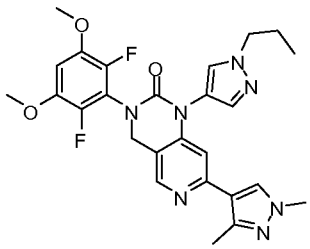
3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(1-ethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



This compound was prepared using procedures analogous to those for *Example 125* with *3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one (Example 129)* replacing *3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(1H-pyrazol-4-ylmethyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one* and *ethyl iodide* replacing *bromoacetonitrile*. LCMS calculated for $C_{25}H_{26}F_2N_7O_3$ $[M+H]^+$ m/z: 510.2; Found: 510.2.

Example 132

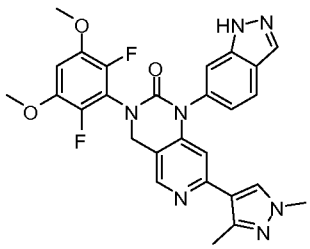
3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(1-propyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



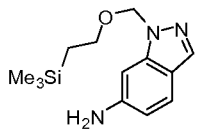
This compound was prepared using procedures analogous to those for *Example 131* with propyl iodide replacing ethyl iodide. LCMS calculated for $C_{26}H_{28}F_2N_7O_3$ $[M+H]^+$ m/z: 524.2; Found: 524.2.

Example 133

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(1H-indazol-6-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



Step 1. Preparation of 1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-amine.



To a solution of 5-nitroindazole (250 mg, 1.5 mmol) in tetrahydrofuran (10 mL) at 0 degrees was added sodium hydride (60% suspension in mineral oil, 67 mg, 1.7 mmol) and the mixture stirred for 10 minutes at 0 degrees.[β-(Trimethylsilyl)ethoxy]methyl chloride (320 μL, 1.8 mmol) was then added dropwise and the reaction mixture warmed to room temperature and stirred for 1h, at which point LCMS confirmed complete conversion. The reaction mixture was quenched with water and diluted with ethyl acetate. The layers were separated and the aqueous layer extracted with additional ethyl acetate. The combined organics were dried over sodium sulfate and concentrated. The residue was purified by column (0-35% ethyl acetate in hexanes) to provide the desired intermediate.

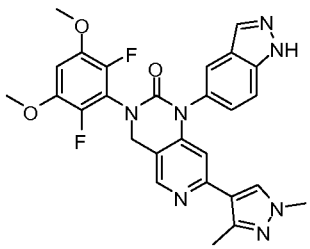
The residue from above was dissolved in ethyl acetate (10 mL) and 10% palladium on carbon (0.16 g, 0.15 mmol) was added. The reaction was then placed under balloon pressure of hydrogen and stirred overnight then filtered and concentrated to provide the desired product, which was purified by column chromatography (0-20% methanol in dichloromethane). LCMS calculated for $C_{13}H_{22}N_3OSi$ $[M+H]^+$ m/z: 264.2; Found: 264.2.

Step 2. Preparation of 3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(1H-indazol-6-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one.

This compound was prepared using procedures analogous to those for *Example 29, Step 2* (Condition B) and *Step 3*, with the product from *Step 1* replacing cyclopropylmethylamine in *Step 2*. LCMS calculated for $C_{27}H_{24}F_2N_7O_3$ $[M+H]^+$ m/z: 532.2; Found: 532.2.

Example 134

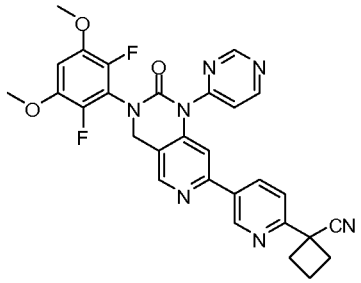
3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(1H-indazol-5-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



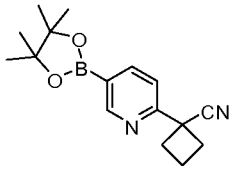
This compound was prepared using procedures analogous to those for *Example 133* with 4-nitroimidazole replacing 5-nitroimidazole. LCMS calculated for $C_{27}H_{24}F_2N_7O_3$ $[M+H]^+$ m/z: 532.2; Found: 532.2.

Example 135

1-(5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-2-oxo-1-(pyrimidin-4-yl)-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)pyridin-2-yl)cyclobutanecarbonitrile

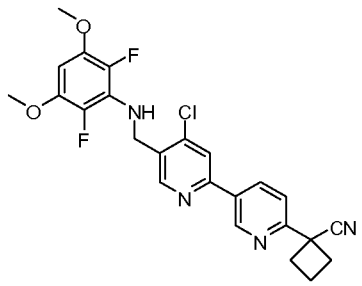


Step 1. Preparation of 1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)cyclobutanecarbonitrile.



A mixture of 1-(6-bromopyridin-3-yl)cyclobutanecarbonitrile (500 mg, 2 mmol), 4,4,5,5,4',4',5',5'-octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl] (802 mg, 3.16 mmol), potassium acetate (621 mg, 6.33 mmol), and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (II) (92 mg, 0.13 mmol) in 1,4-dioxane (8 mL) was first purged with nitrogen gas, and then stirred at 90 °C overnight. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate, filtered through a pad of celite, and concentrated. The crude material was then purified via column chromatography (0% to 30% EtOAc in hexanes) to give the product as a yellow solid. LCMS calculated for $C_{10}H_{12}BN_2O_2$ [M+H for boronic acid]$^+$ m/z: 203.1; Found: 203.1.

Step 2. Preparation of 1-(4-chloro-5-((2,6-difluoro-3,5-dimethoxyphenylamino)methyl)-2,3'-bipyridin-6'-yl)cyclobutanecarbonitrile.



A mixture of N-[(4,6-dichloropyridin-3-yl)methyl]-2,6-difluoro-3,5-dimethoxyaniline (400 mg, 1 mmol), 1-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]cyclobutanecarbonitrile (330 mg, 1.2 mmol), tetrakis(triphenylphosphine)palladium(0) (120 mg, 0.10 mmol) and potassium carbonate (580 mg, 4.2 mmol) was dissolved in a mixture of 1,4-dioxane (5 mL) and water (1 mL). The reaction flask was evacuated and back filled with nitrogen, then heated to 120 degrees for 2h, at which point LCMS showed nearly complete conversion. The reaction mixture was quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated. The residue was purified by column chromatography (0-30% ethyl acetate in hexanes) to provide the desired product as a pale yellow solid. LCMS calculated for $C_{24}H_{22}ClF_2N_4O_2$ $[M+H]^+$ m/z: 471.1; Found: 471.1.

Step 3. Preparation of 1-(5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-2-oxo-1-(pyrimidin-4-yl)-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)pyridin-2-yl)cyclobutanecarbonitrile.

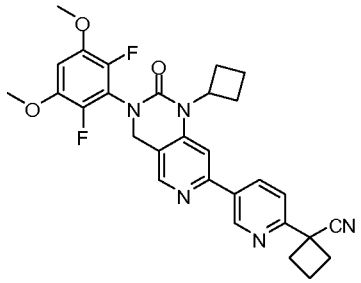
A mixture of 1-(4-chloro-5-{[(2,6-difluoro-3,5-dimethoxyphenyl)amino]methyl}-2,3'-bipyridin-6'-yl)cyclobutanecarbonitrile (30.0 mg, 0.0637 mmol), pyrimidin-4-amine (9.09 mg, 0.0956 mmol), RuPhos Pd G2 (4.9 mg, 0.0064 mmol) and cesium carbonate (62.3 mg, 0.191 mmol) was dissolved in tert-butyl alcohol (0.6 mL) and the reaction flask was evacuated and backfilled with nitrogen three times. The reaction was then stirred at 95 degrees overnight. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate, then diluted with ethyl acetate. The layers were separated and the aqueous layer extracted with additional ethyl acetate. The combined organics were dried over sodium sulfate and concentrated.

The residue was dissolved in tetrahydrofuran (0.75 mL) and triethylamine (25.8 mg, 0.255 mmol) was added. After cooling to 0 degrees, triphosgene (18.9 mg, 0.0637 mmol) was added and the mixture stirred at room temperature for 1h, then diluted with methanol and purified using reverse phase HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired

product as the corresponding TFA salt. LCMS calculated for $C_{29}H_{24}F_2N_7O_3$ $[M+H]^+$ m/z: 556.2; Found: 556.2.

Example 136

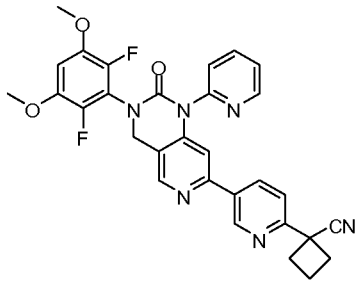
1-(5-(1-cyclobutyl-3-(2,6-difluoro-3,5-dimethoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)pyridin-2-yl)cyclobutanecarbonitrile



This compound was prepared using procedures analogous to those for *Example 135, Step 3* with cyclobutylamine replacing pyrimidin-4-amine. LCMS calculated for $C_{29}H_{28}F_2N_5O_3$ $[M+H]^+$ m/z: 532.2; Found: 532.2.

Example 137

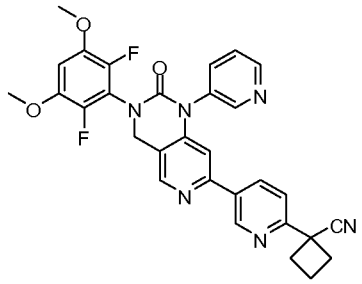
1-(5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-2-oxo-1-(pyridin-2-yl)-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)pyridin-2-yl)cyclobutanecarbonitrile



This compound was prepared using procedures analogous to those for *Example 135, Step 3* with 2-aminopyridine replacing pyrimidin-4-amine. LCMS calculated for $C_{30}H_{25}F_2N_6O_3$ $[M+H]^+$ m/z: 555.2; Found: 555.2.

Example 138

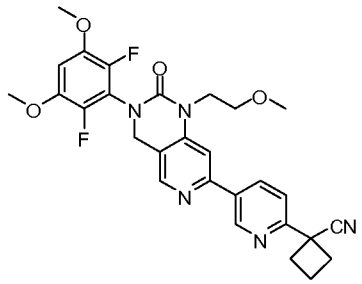
1-(5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-2-oxo-1-(pyridin-3-yl)-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)pyridin-2-yl)cyclobutanecarbonitrile



This compound was prepared using procedures analogous to those for *Example 135, Step 3* with 3-aminopyridine replacing pyrimidin-4-amine. LCMS calculated for $C_{30}H_{25}F_2N_6O_3$ $[M+H]^+$ m/z: 555.2; Found: 555.2.

Example 139

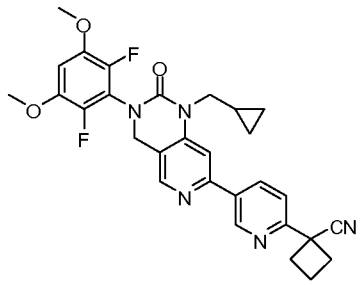
1-(5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-(2-methoxyethyl)-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)pyridin-2-yl)cyclobutanecarbonitrile



This compound was prepared using procedures analogous to those for *Example 135, Step 3* with 2-methoxy ethylamine replacing pyrimidin-4-amine. LCMS calculated for $C_{28}H_{28}F_2N_5O_4$ $[M+H]^+$ m/z: 536.2; Found: 536.2.

Example 140

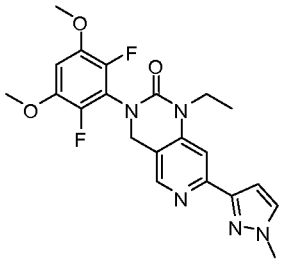
1-(5-(1-(cyclopropylmethyl)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)pyridin-2-yl)cyclobutanecarbonitrile



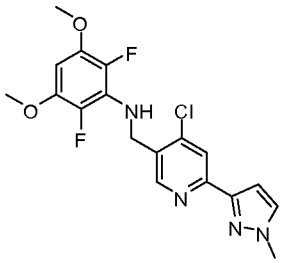
This compound was prepared using procedures analogous to those for *Example 135, Step 3* with cyclopropylmethyl amine replacing pyrimidin-4-amine. LCMS calculated for $C_{29}H_{28}F_2N_5O_3$ $[M+H]^+$ m/z: 532.2; Found: 532.2.

Example 141

3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(1-methyl-1H-pyrazol-3-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



Step 1. Preparation of N-((4-chloro-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)methyl)-2,6-difluoro-3,5-dimethoxyanilin.



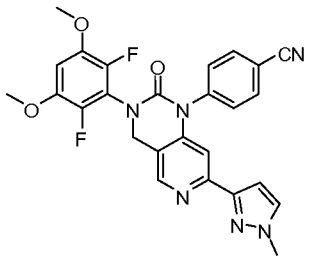
This compound was prepared using procedures analogous to those for *Example 135, Step 2* with 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole replacing 1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)cyclobutanecarbonitrile. LCMS calculated for $C_{18}H_{18}ClF_2N_4O_2$ $[M+H]^+$ m/z: 395.1; Found: 395.1.

Step 2. Preparation of 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(1-methyl-1H-pyrazol-3-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one.

This compound was prepared using procedures analogous to those for *Example 135, Step 3* with *N-((4-chloro-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)methyl)-2,6-difluoro-3,5-dimethoxyanilin (Step 1)* replacing *1-(4-chloro-5-((2,6-difluoro-3,5-dimethoxyphenylamino)methyl)-2,3'-bipyridin-6'-yl)cyclobutanecarbonitrile* and ethylamine replacing pyrimidin-4-amine. LCMS calculated for $C_{21}H_{22}F_2N_5O_3$ $[M+H]^+$ m/z: 430.2; Found: 430.2.

Example 142

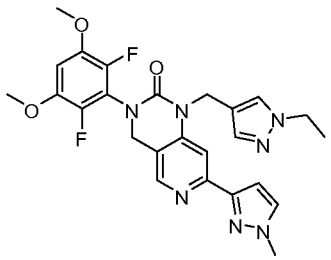
4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1-methyl-1H-pyrazol-3-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)benzonitrile



This compound was prepared using procedures analogous to those for *Example 141, Step 2* with 4-amino benzonitrile replacing ethylamine. LCMS calculated for $C_{26}H_{21}F_2N_6O_3$ $[M+H]^+$ m/z: 503.2; Found: 503.2.

Example 143

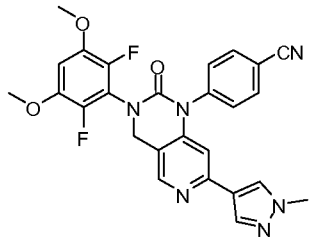
3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-((1-ethyl-1H-pyrazol-4-yl)methyl)-7-(1-methyl-1H-pyrazol-3-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



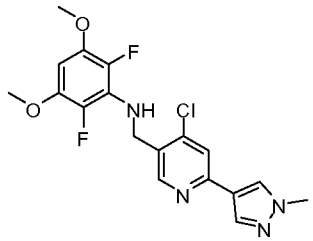
This compound was prepared using procedures analogous to those for *Example 141, Step 2* with (1-ethyl-1H-pyrazol-4-yl)methanamine replacing ethylamine. LCMS calculated for $C_{25}H_{26}F_2N_7O_3$ $[M+H]^+$ m/z: 510.2; Found: 510.2.

Example 144

4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1-methyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)benzonitrile



Step 1. Preparation of N-((4-chloro-6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,6-difluoro-3,5-dimethoxyanilin.



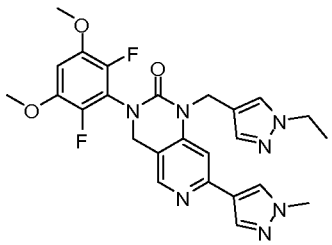
This compound was prepared using procedures analogous to those for *Example 135, Step 2* with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole replacing 1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)cyclobutanecarbonitrile. LCMS calculated for $C_{18}H_{18}ClF_2N_4O_2$ $[M+H]^+$ m/z: 395.1; Found: 395.1.

Step 2. Preparation of 4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1-methyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)benzonitrile.

This compound was prepared using procedures analogous to those for *Example 135, Step 3* with 4-amino benzonitrile replacing pyrimidin-4-amine. LCMS calculated for $C_{26}H_{21}F_2N_6O_3$ $[M+H]^+$ m/z: 503.2; Found: 503.2.

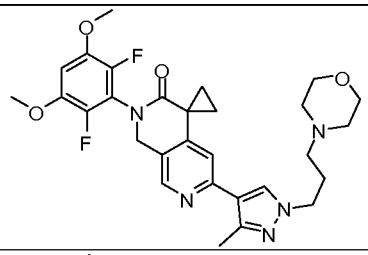
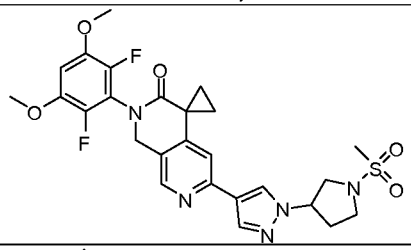
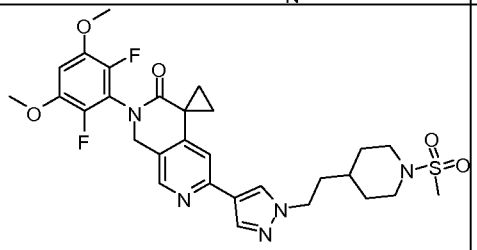
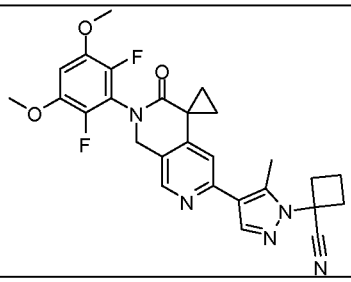
Example 145

3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-((1-ethyl-1H-pyrazol-4-yl)methyl)-7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one

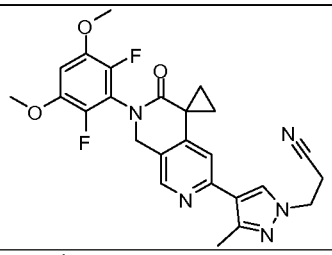
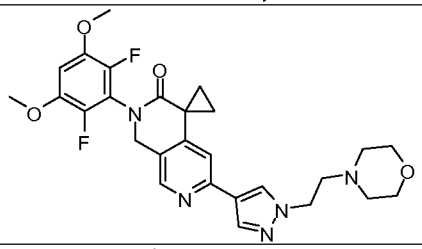
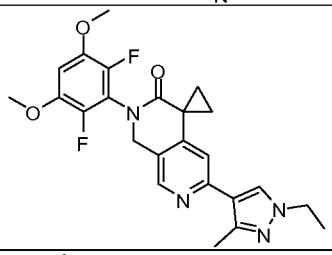
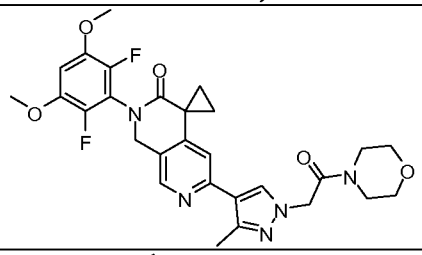
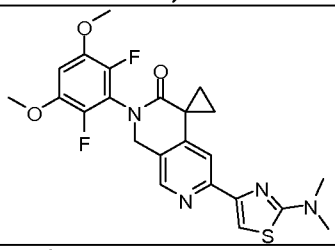
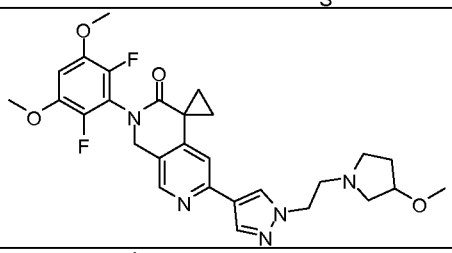
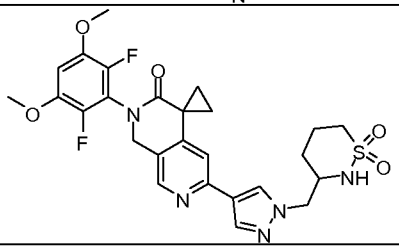


This compound was prepared using procedures analogous to those for *Example 144, Step 2* with (1-ethyl-1H-pyrazol-4-yl)methanamine replacing 4-amino benzonitrile. LCMS calculated for $C_{25}H_{26}F_2N_7O_3$ $[M+H]^+$ m/z: 510.2; Found: 510.2.

Table 6. The compounds in **Table 6** were prepared in accordance with the synthetic protocols set forth in **Scheme 3** and **Example 1**, using the appropriate starting materials

Example	Name	Structure	LCMS (M+H)+
146	2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(3-methyl-1-(3-morpholinopropyl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one		554.1
147	2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1-(1-(methylsulfonyl)pyrrolidin-3-yl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one		560.1
148	2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1-(2-(1-(methylsulfonyl)piperidin-4-yl)ethyl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one		602.3
149	1-(4-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-5-methyl-1H-pyrazol-1-yl)cyclobutanecarbonitrile		506.2

150	6'-(1-(1-acetylpyrrolidin-3-yl)-1H-pyrazol-4-yl)-2'-(2,6-difluoro-3,5-dimethoxyphenyl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one		524.2
151	2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1-(3-morpholinopropyl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one		540.1
152	2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1-(2-(4-methoxypiperidin-1-yl)ethyl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one		554.2
153	2-(4-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-3-methyl-1H-pyrazol-1-yl)acetonitrile		466.2
154	2-(3-(4-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-3-methyl-1H-pyrazol-1-yl)pyrrolidin-1-yl)acetonitrile		535.1
155	2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(3-methyl-1-(pyridin-3-ylmethyl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one		518.1

156	3-(4-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-3-methyl-1H-pyrazol-1-yl)propanenitrile		480.1
157	2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one		526.2
158	2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1-ethyl-3-methyl-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one		455.1
159	2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(3-methyl-1-(2-morpholino-2-oxoethyl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one		554.2
160	2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(2-(dimethylamino)thiazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one		473.1
161	2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1-(2-(3-methoxypyrrolidin-1-yl)ethyl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one		540.2
162	2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-{1-[(1,1-dioxido-1,2-thiazinan-3-yl)methyl]-1H-pyrazol-4-yl}-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one		560.1

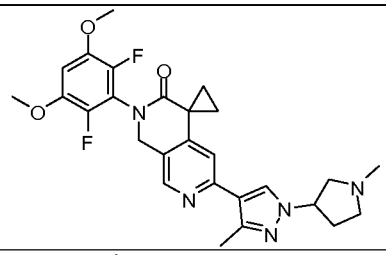
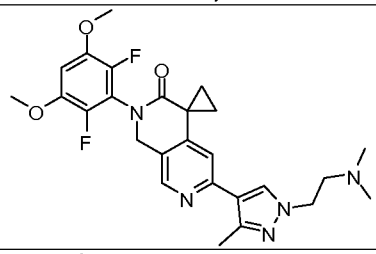
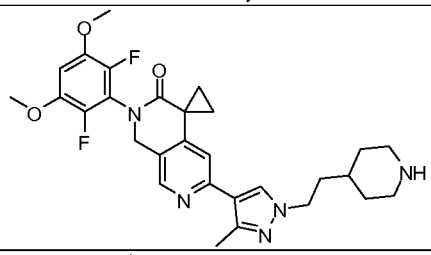
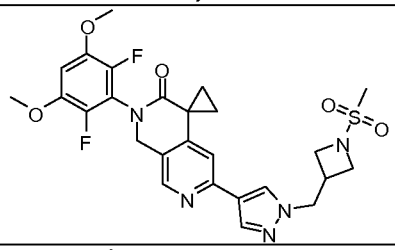
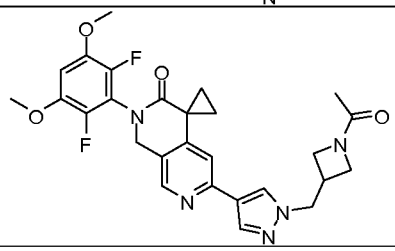
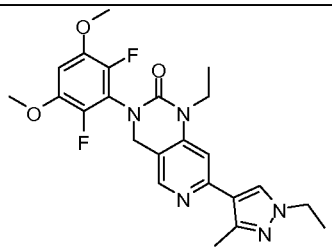
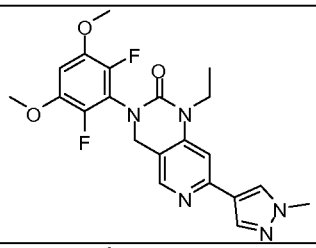
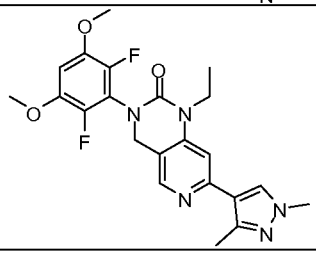
163	2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(3-methyl-1-(1-methylpyrrolidin-3-yl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one		510.2
164	2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1-(2-(dimethylamino)ethyl)-3-methyl-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one		498.4
165	2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(3-methyl-1-(2-(piperidin-4-yl)ethyl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one		538.2
166	2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1-((1-(methylsulfonyl)azetidin-3-yl)methyl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one		560.1
167	6'-(1-((1-acetylazetidin-3-yl)methyl)-1H-pyrazol-4-yl)-2'-(2,6-difluoro-3,5-dimethoxyphenyl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one		524.2

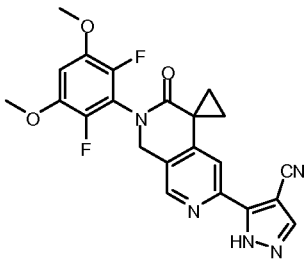
Table 7. The compounds in **Table 7** were prepared in accordance with the synthetic protocols set forth in **Scheme 4** and **Example 22**, using the appropriate starting materials

Example	**Name/^{1}H NMR**	**Structure**	**LCMS (M+H)+**

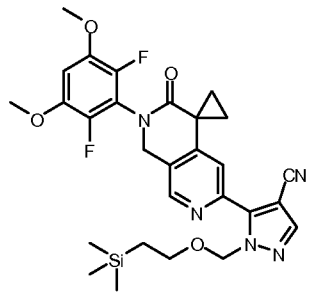
168	3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(1-ethyl-3-methyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one: ^{1}H NMR (500 MHz, dmso) δ 8.38 (s, 1H), 8.36 (s, 1H), 7.31 (s, 1H), 7.09 (t, *J* = 8.2 Hz, 1H), 4.83 (s, 2H), 4.14 (q, *J* = 7.3 Hz, 2H), 4.02 (q, *J* = 6.9 Hz, 2H), 3.91 (s, 6H), 2.45 (s, 3H), 1.41 (t, *J* = 7.0 Hz, 3H), 1.23 (t, *J* = 7.0 Hz, 3H).		458.2
169	3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		430.2
170	3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-ethyl-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one		444.2

Example 171

5-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-1H-pyrazole-4-carbonitrile



Step 1: 5-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carbonitrile



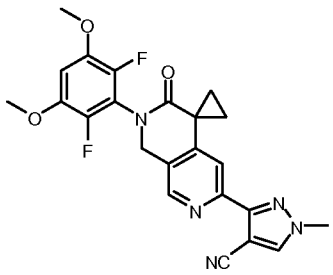
6'-chloro-2'-(2,6-difluoro-3,5-dimethoxyphenyl)-1',2'-dihydro-3'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'-one (0.507 g, 1.33 mmol), 1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (0.342 g, 1.53 mmol), palladium acetate (29.9 mg, 0.133 mmol), trimethylacetic Acid (34.0 mg, 0.333 mmol), potassium carbonate (0.552 g, 4.00 mmol) and di-1-adamantyl(butyl)phosphine (71.6 mg, 0.200 mmol) were mixed in *N,N*-dimethylformamide (2.67 mL) and 1,4-dioxane (2.67 mL). The mixture was heated at 130 °C for 1.5 h. The crude was diluted with DCM, and filtered through Celite. The filtrate was concentrated. The residue was purified by chromatography on silica gel (35-60% EtOAc/Hex) to give the desired coupling product 760 mg (not 100% pure). Rf = 0.41 (50% EtOAc/Hex). LC/MS calculated for $C_{28}H_{32}F_2N_5O_4Si$ $[M+H]^+$ m/z: 568.2; found: 568.2.

Step 2: 5-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-1H-pyrazole-4-carbonitrile

Trifluoroacetic acid (0.464 mL, 6.02 mmol) was added to the solution of 5-[2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-6'-yl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (171 mg, 0.301 mmol) in DCM. The mixture was stirred at room temperature for 15 h. The resulting mixture was concentrated, and NH_4OH in MeOH was added. The mixture was stirred at room temperature for 30 min. The crude was diluted with water and extracted with DCM. The organic phase was concentrated. The residue was purified by chromatography on silica gel (4-10% MeOH/DCM) to give the product 49.0 mg. LC/MS calculated for $C_{22}H_{18}F_2N_5O_3$ $[M+H]^+$ m/z: 438.1; found: 438.2.

Example 172

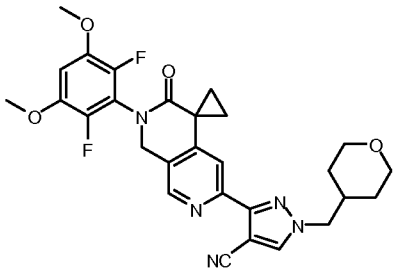
3-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-1-methyl-1H-pyrazole-4-carbonitrile



Cesium Carbonate (13.1 mg, 0.0402 mmol) was added to the solution of 5-[2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-6'-yl]-1H-pyrazole-4-carbonitrile (*Example 171*: 8.8 mg, 0.020 mmol) in *N,N*-dimethylformamide (150 µL), followed by methyl iodide (7.14 mg, 0.0503 mmol). The mixture was stirred at room temperature overnight. The crude was diluted with DCM and filtered. The filtrate was concentrated. The residue was diluted with MeOH and purified via pH 2 preparative LC/MS (MeCN/water with TFA) to afford the product as a white solid (TFA salt). LC/MS calculated for $C_{23}H_{20}F_2N_5O_3$ $[M+H]^+$ m/z: 452.2; found: 452.2.

Example 173

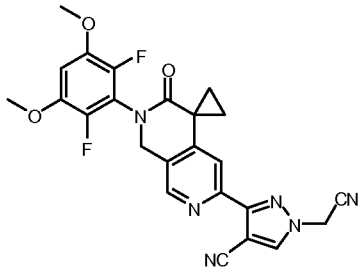
3-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-pyrazole-4-carbonitrile



Cesium Carbonate (10.4 mg, 0.0320 mmol) was added to the solution of 5-[2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-6'-yl]-1H-pyrazole-4-carbonitrile (*Example 171*: 7.0 mg, 0.016 mmol) and 4-(bromomethyl)tetrahydro-2*H*-pyran (7.16 mg, 0.0400 mmol) in *N,N*-dimethylformamide (120 µL). The mixture was stirred at room temperature overnight. The crude was diluted with DCM and filtered. The filtrate was concentrated. The residue was diluted with MeOH and purified via pH 2 preparative LC/MS (MeCN/water with TFA) to afford the product as a white solid (TFA salt). LC/MS calculated for $C_{28}H_{28}F_2N_5O_4$ $[M+H]^+$ m/z: 536.2; found: 536.1.

Example 174

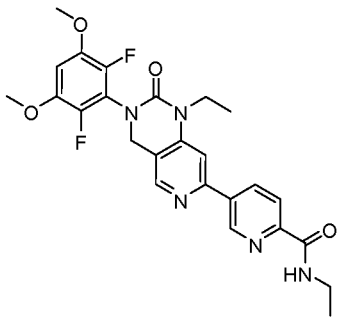
1-(cyanomethyl)-3-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-1H-pyrazole-4-carbonitrile



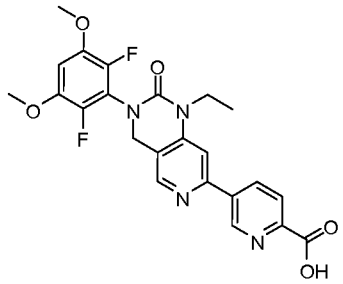
Cesium Carbonate (10.4 mg, 0.0320 mmol) was added to the solution of 5-[2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-6'-yl]-1H-pyrazole-4-carbonitrile (*Example 171*: 7.0 mg, 0.016 mmol) and bromoacetonitrile (4.80 mg, 0.0400 mmol) in *N,N*-dimethylformamide (120 µL). The mixture was stirred at 40 °C for 2 h. The crude was diluted with DCM and filtered. The filtrate was concentrated. The residue was diluted with MeOH and purified via pH 2 preparative LC/MS (MeCN/water with TFA) to afford the product as a white solid (TFA salt). LC/MS calculated for $C_{24}H_{19}F_2N_6O_3$ $[M+H]^+$ m/z: 477.1; found: 477.2.

Example 175

5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)-N-ethylpicolinamide



Step 1: 5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)picolinic acid



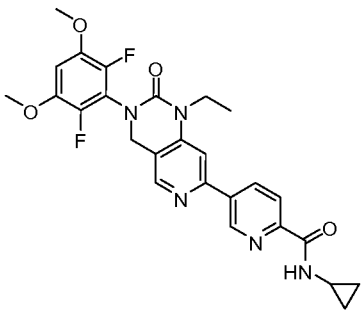
This compound was prepared using procedures analogous to those for *Example 22, Step 2*, with 6-(methoxycarbonyl)pyridin-3-ylboronic acid replacing phenyl boronic acid. LC/MS calculated for $C_{23}H_{21}F_2N_4O_5$ $[M+H]^+$ m/z: 471.1; Found: 471.2.

Step 2: 5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)-N-ethylpicolinamide

To a mixture of 5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)picolinic acid (10 mg, 0.021 mmol) from previous step, Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (11 mg, 0.025 mmol), and Et_3N (15 µL, 0.11 mmol) in DMF (1.5 mL) at rt was added $EtNH_2$ (2.0 M in THF, 53 µL, 0.11 mmol). The reaction mixture was stirred at rt overnight, diluted with MeOH, and directly purified via pH 2 preparative LC/MS (MeCN/water with TFA) to give the desired product as a white solid (TFA salt). LC/MS calculated for $C_{25}H_{26}F_2N_5O_4$ $[M+H]^+$ m/z: 498.2; Found: 498.2. ^{1}H NMR (600 MHz, DMSO) δ 9.32 (dd, J = 2.2, 0.7 Hz, 1H), 8.87 (t, J = 6.0 Hz, 1H), 8.67 (dd, J = 8.2, 2.2 Hz, 1H), 8.46 (s, 1H), 8.15 (dd, J = 8.2, 0.7 Hz, 1H), 7.72 (s, 1H), 7.07 (t, J = 8.1 Hz, 1H), 4.84 (s, 2H), 4.07 (q, J = 7.0 Hz, 2H), 3.90 (s, 6H), 3.42 – 3.32 (m, 2H), 1.23 (t, J = 7.0 Hz, 3H), 1.15 (t, J = 7.2 Hz, 3H).

Example 176

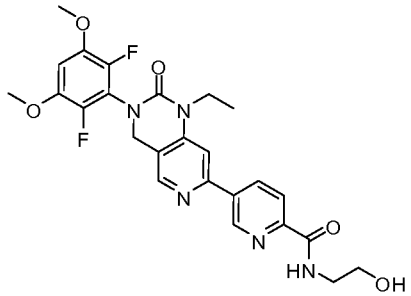
N-cyclopropyl-5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)picolinamide



This compound was prepared using procedures analogous to those for *Example 175, Step 2*, with cyclopropylamine replacing $EtNH_2$ (2.0 M in THF). LC/MS calculated for $C_{26}H_{26}F_2N_5O_4$ $[M+H]^+$ m/z: 510.2; Found: 510.2.

Example 177

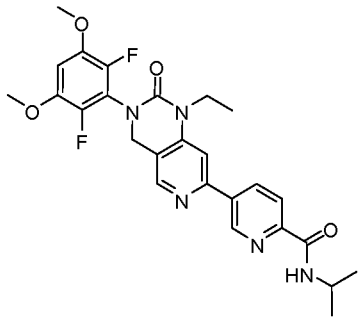
5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)-N-(2-hydroxyethyl)picolinamide



This compound was prepared using procedures analogous to those for *Example 175, Step 2*, with ethanolamine replacing $EtNH_2$ (2.0 M in THF). LC/MS calculated for $C_{25}H_{26}F_2N_5O_5$ $[M+H]^+$ m/z: 514.2; Found: 514.2.

Example 178

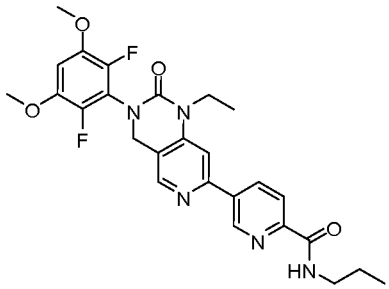
5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)-N-isopropylpicolinamide



This compound was prepared using procedures analogous to those for *Example 175, Step 2*, with 2-propanamine replacing $EtNH_2$ (2.0 M in THF). LC/MS calculated for $C_{26}H_{28}F_2N_5O_4$ $[M+H]^+$ m/z: 512.2; Found: 512.2.

Example 179

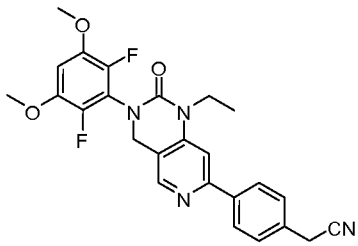
5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)-N-propylpicolinamide



This compound was prepared using procedures analogous to those for *Example 175, Step 2*, with 1-propanamine replacing $EtNH_2$ (2.0 M in THF). LC/MS calculated for $C_{26}H_{28}F_2N_5O_4$ $[M+H]^+$ m/z: 512.2; Found: 512.2.

Example 180

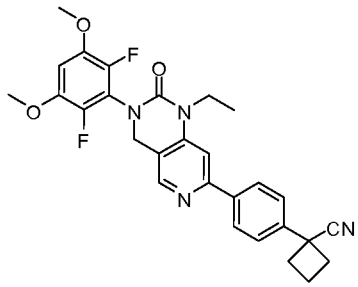
2-(4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)phenyl)acetonitrile



This compound was prepared using procedures analogous to those for *Example 22, step 2*, with 4-(cyanomethyl)phenylboronic acid replacing phenyl boronic acid. LC/MS calculated for $C_{25}H_{23}F_2N_4O_3$ $[M+H]^+$ m/z: 465.2; Found: 465.1.

Example 181

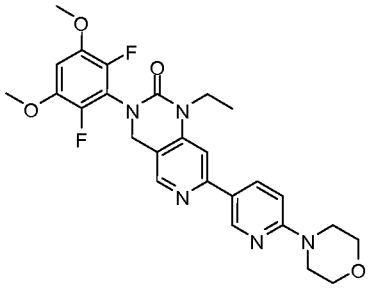
1-(4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)phenyl)cyclobutanecarbonitrile



This compound was prepared using procedures analogous to those for *Example 22, Step 2*, with 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclobutanecarbonitrile replacing phenyl boronic acid. LC/MS calculated for $C_{28}H_{27}F_2N_4O_3$ $[M+H]^+$ m/z: 505.2; Found: 505.2.

Example 182

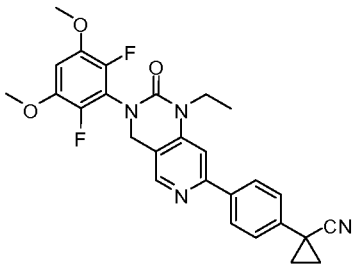
3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(6-morpholinopyridin-3-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one



This compound was prepared using procedures analogous to those for *Example 22, Step 2*, with 4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine replacing phenyl boronic acid. LC/MS calculated for $C_{26}H_{28}F_2N_5O_4$ $[M+H]^+$ m/z: 512.2; Found: 512.2.

Example 183

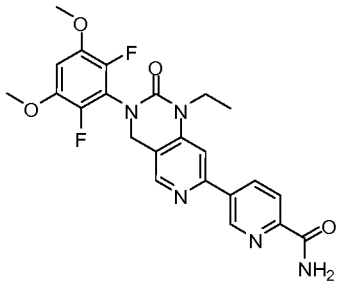
1-(4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)phenyl)cyclopropanecarbonitrile



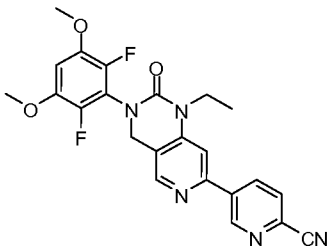
This compound was prepared using procedures analogous to those for *Example 22, Step 2*, with 4-(1-cyanocyclopropyl)phenylboronic acid replacing phenyl boronic acid. LC/MS calculated for $C_{27}H_{25}F_2N_4O_3$ $[M+H]^+$ m/z: 491.2; Found: 491.2.

Example 184

5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)picolinamide



Step 1: 5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)picolinonitrile



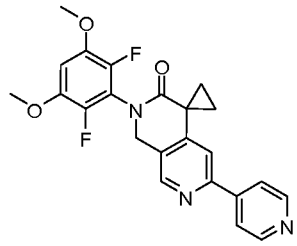
This compound was prepared using procedures analogous to those for *Example 22, Step 2*, with 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinonitrile replacing phenyl boronic acid. LC/MS calculated for $C_{23}H_{20}F_2N_5O_3$ $[M+H]^+$ m/z: 452.2; Found: 452.1.

Step 2: 5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)picolinamide

A mixture of *5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)picolinonitrile* (94 mg, 0.21 mmol) in NaOH solution (1.0 M in H_2O) (1.20 mL) and ethanol (3.6 mL) was stirred at 80 °C overnight. The reaction mixture was cooled to rt, quenched with HCl solution (12.0 M in H_2O, 120 μL), and concentrated. The crude material was then purified via pH 2 preparative LC/MS (MeCN/water with TFA) to give the desired product as a white solid (TFA salt). LC/MS calculated for $C_{23}H_{22}F_2N_5O_4$ $[M+H]^+$ m/z: 470.2; Found: 470.1.

Example 185

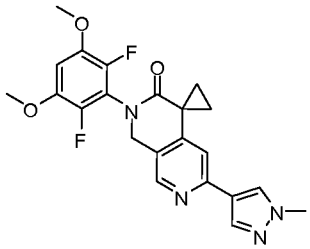
2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(pyridin-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one



This compound was prepared using procedures analogous to those for *Example 1, Step 7*, with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine replacing (5-amino-2-methylphenyl)boronic acid. LC/MS calculated for $C_{23}H_{20}F_2N_3O_3$ $[M+H]^+$ m/z: 424.1; Found: 424.2.

Example 186

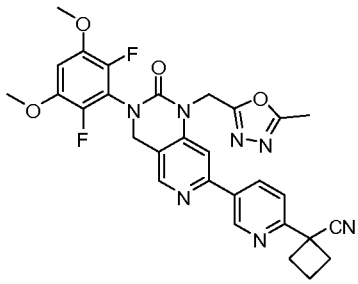
2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1-methyl-1H-pyrazol-4-yl)-1',2'-dihydro-3'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'-one



This compound was prepared using procedures analogous to those for *Example 1, Step 7*, with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole replacing (5-amino-2-methylphenyl)boronic acid. LC/MS calculated for $C_{22}H_{21}F_2N_4O_3$ $[M+H]^+$ m/z: 427.2; Found: 427.1.

Example 187

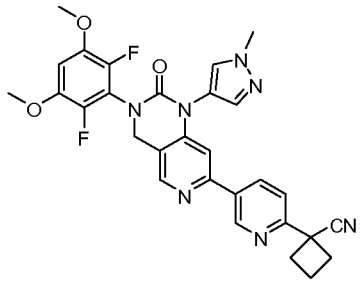
1-(5-{3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl}pyridin-2-yl)cyclobutanecarbonitrile



This compound was prepared using procedures analogous to those for *Example 135, Step 3* with 1-(5-methyl-1,3,4-oxadiazol-2-yl)methanamine replacing pyrimidin-4-amine. LCMS calculated for $C_{29}H_{26}F_2N_7O_4$ $[M+H]^+$ m/z: 574.2; Found: 574.2.

Example 188

1-{5-[3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-(1-methyl-1H-pyrazol-4-yl)-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl]pyridin-2-yl}cyclobutanecarbonitrile



This compound was prepared using procedures analogous to those for *Example 135, Step 3* with 1-methyl-1H-pyrazol-4-amine replacing pyrimidin-4-amine. LCMS calculated for $C_{29}H_{26}F_2N_7O_3$ $[M+H]^+$ m/z: 558.2; Found: 558.1.

Example A

FGFR Enzymatic Assay

The inhibitor potency of the exemplified compounds was measured in an enzyme assay that measures peptide phosphorylation using FRET measurements to detect product formation. Inhibitors were serially diluted in DMSO and a volume of 0.5 μL was transferred to the wells of a 384-well plate. For FGFR3, a 10 μL volume of FGFR3 enzyme (Millipore) diluted in assay buffer (50 mM HEPES, 10 mM $MgCl_2$, 1 mM EGTA, 0.01% Tween-20, 5 mM DTT, pH 7.5) was added to the plate and pre-incubated for a time between 5-10 minutes and up to 4 hours. Appropriate controls (enzyme blank and enzyme with no inhibitor) were included on the plate. The assay was initiated by the addition of a 10 μL solution containing biotinylated EQEDEPEGDYFEWLE peptide substrate (SEQ ID NO: 1) and ATP (final concentrations of 500 nM and 140 μM respectively) in assay buffer to the wells. The plate was incubated at 25 °C for 1 hr. The reactions were ended with the addition of 10 μL/well of quench solution (50 mM Tris, 150 mM NaCl, 0.5 mg/mL BSA, pH 7.8; 30 mM EDTA with Perkin Elmer Lance Reagents at 3.75 nM Eu-antibody PY20 and 180 nM APC-Streptavidin).

The plate was allowed to equilibrate for ~1 hr before scanning the wells on a PheraStar plate reader (BMG Labtech).

FGFR1, FGFR2, and FGFR4 are measured under equivalent conditions with the following changes in enzyme and ATP concentrations: FGFR1, 0.02 nM and 210 uM respectively, FGFR2, 0.01 nM and 100 uM, respectively, and FGFR4, 0.04 nM and 600 uM respectively. The enzymes were purchased from Millipore or Invitrogen.

GraphPad prism3 was used to analyze the data. The IC_{50} values were derived by fitting the data to the equation for a sigmoidal dose-response with a variable slope. Y=Bottom + (Top-Bottom)/(1+10^((LogIC_{50}-X)*HillSlope)) where X is the logarithm of concentration and Y is the response. Compounds having an IC_{50} of 1 μM or less are considered active.

The compounds of the invention were found to be selective inhibitors of FGFR3 and/or FGFR4 according to the FGFR Enzymatic Assays. Compouds of Formula (I') and (I) and all the compounds as described herein have been tested and exhibit an IC_{50} of less than 1 μM.

Table 1 provides IC_{50} data for compounds of the invention assayed in the FGFR Enzymatic Assay after dilution in assay buffer, added to the plate and pre-incubated for 4 hours. The symbol: "+" indicates an IC_{50} less than 10 nM; "++" indicates an IC_{50} greater than or equal to 10 nM but less than 30 nM; "+++" indicates an IC_{50} greater than or equal to 30 nM but less than 200 nM; and "++++" indicates an IC_{50} greater than or equal to 200 nM. Table 2 provides IC_{50} ratios showing FGFR4 selectivity. Table 2A provides IC_{50} ratios showing FGFR3 selectivity of the compounds.

Table 1

Example No.	FGFR1 IC50 (nM)	FGFR2 IC50 (nM)	FGFR3 IC50 (nM)	FGFR4 IC50 (nM)
1	++++	++++	++++	+++
2	++++	++++	++++	+++
3	++++	++++	++++	++
4	+++	+++	+++	+
5	+++	++	++	+
6	++++	++++	+++	+
7	++++	++++	++++	+++
8	++++	++++	+++	++
9	+++	+++	++	++
10	+++	++	++	+
11	++++	++++	++++	++
12	++++	+++	+++	+

13	++++	+++	+++	+
14	++++	+++	+++	+
15	+++	+++	+++	+
16	++++	+++	+++	+
17	++++	+++	++	++
18	++	+	+	++
19	++	+	+	+
20	+++	++	++	++
21	++	+	+	++
22	+++	++	++	++
23	+++	+	+	+
24	++	+	+	++
25	++	+	+	++
26	++	+	+	++
27	++	+	+	++
28	++++	+++	+++	++++
29	++	+	+	++
30	++	+	+	++
31	++	+	+	++
32	++	+	+	++
33	+++	+	+	+++
34	+++	++	+	+++
35	++	+	+	++
36	++	+	+	++
37	++	+	+	+++
38	+++	++	+	+++
39	++	+	+	+
40	+++	+	+	+++
41	+++	++	++	+++
42	++++	+++	+++	++++
43	++++	+++	++	+++
44	+++	++	+	+++
45	+++	++	+	+++
46	++	+	+	++
47	+++	+	+	+++
48	++	+	+	++
49	+++	+	+	+++
50	+++	++	++	++
51	++++	+++	+++	++++
52	+++	++	+	++
53	++	+	+	++
54	+++	+	+	++
55	++	+	+	+
56	++++	+++	+++	+++
57	++++	+++	++	+++
58	+++	+	+	++
59	+++	++	++	+++

60	+++	++	+	+++
61	++++	+++	++	++++
62	+++	++	+	+++
63	+++	++	+	+++
64	+++	++	+	+++
65	+++	+	+	+++
66	++++	+++	++	+++
67	+++	+	+	+++
68	+++	++	+	+++
69	+++	++	+	+++
70	+++	++	++	+++
71	+++	+++	++	+++
72	+	+	+	+
73	+++	++	++	+++
74	+++	+++	++	+++
75	+++	+++	++	+++
76	+++	+++	++	+++
77	++	+	+	+++
78	+++	++	+	+++
79	+++	+	+	+++
80	+++	++	+	+++
81	+++	++	++	++++
82	+++	+	+	+++
83	+++	+++	++	++++
84	+++	+	+	+++
85	+++	++	+	+++
86	+++	++	++	+++
87	+++	+	+	+++
88	+	+	+	+
89	++	+	+	+++
90	+++	++	+	+++
91	+++	+	+	+++
92	+++	++	++	+++
93	+++	+	+	+++
94	+	+	+	++
95	++	+	+	+++
96	+++	++	++	+++
97	+++	+	+	+++
98	+++	++	++	+++
99	+++	+	+	+++
100	+++	++	++	+++
101	+	+	+	++
102	+++	++	++	+++
103	+++	++	++	+++
104	++	+	+	+++
105	+++	++	++	+++
106	+++	+++	++	+++

107	+++	++	++	+++
108	+++	++	++	+++
109	++	+	+	+++
110	++	+	+	+++
111	++	+	+	+++
112	+++	+	+	+++
113	+++	+	++	+++
114	+++	++	++	+++
115	+++	+	+	+++
122	+++	++	++	+++
123	+++	+	+	++
124	+	+	+	+
125	+++	+	++	+++
129	++	+	+	+++
130	+++	++	++	+++
131	+++	++	++	++++
132	+++	++	++	+++
133	++	+	+	+++
134	++	+	+	+++
135	+++	+	+	+++
146	+++	++	+	+++
147	++	+	+	+
148	+++	++	+	++
149	+++	+	+	+++
150	+	+	+	+
151	+	+	+	+
152	++	+	+	++
153	+++	++	+	++
154	+++	++	++	+++
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157	++	+	+	+
158	+++	+	+	++
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160	++	+	+	++
161	++	+	+	++
162	++	+	+	+
163	+++	+	+	+++
164	+++	++	++	+++
165	++	+	+	++
166	++	+	+	++
167	+	+	+	++
168	++	+	+	++
169	+	+	+	++
170	++	+	+	++
171	+++	+++	+++	+
172	++++	++++	++++	++

173	++++	++++	++++	++
174	++++	++++	++++	++
175	+++	+	+	+++
176	++	+	+	++
177	++	+	+	++
178	++	+	+	++
179	++	+	+	++
180	+++	+	+	++
181	+++	+	+	+++
182	++	+	+	++
183	++	+	+	+++
184	++	+	+	++
185	++	+	+	++
186	+	+	+	+
187	+++	+	+	+++
188	+++	++	++	+++

Table 2

Example No.	**FGFR1/ FGFR4**	**FGFR2/ FGFR4**	**FGFR3/ FGFR4**
1	>25	>25	>25
2	>10	>10	>10
3	>25	>25	>10
4	>25	>10	>10
5	>10	>5	>1
6	>100	>100	>25
7	>50	>25	>25
8	>50	>10	>10
9	>10	>1	>1
10	>25	>25	>10
11	>25	>25	>10
12	>50	>25	>10
13	>50	>25	>10
14	>50	>10	>1
15	>50	>25	>10
16	>50	>25	>10
171	>10	>10	>10
172	>50	>25	>10
173	>100	>100	>50
174	>100	>10	>25

Table 2A

Example No.	FGFR1/ FGFR3	FGFR4/ FGFR3
4	>1	

5	>3	
6	>3	
7	>1	
8	>5	
9	>3	
10	>1	
11	>1	
12	>3	
13	>3	
14	>5	
15	>3	
16	>1	
17	>10	
18	>5	
19	>5	
20	>5	
21	>5	
22	>5	
23	>5	
24	>5	
25	>5	>5
26	>5	>5
27	>10	>10
28	>10	>25
29	>1	>5
30	>1	>5
31	>5	>10
32	>1	>5
33	>5	>5
34	>5	>10
35	>5	>10
36	>5	>10
37	>1	>10
38	>5	>5
39	>10	>10
40	>10	>10
41	>1	>5
42	>5	>1
43	>10	>5
44	>10	>10
45	>10	>10
46	>10	>10
47	>10	>10
48	>10	>10
49	>5	>1
50	>1	>1
51	>1	>1

52	>10	>1
53	>5	>5
54	>5	>1
55	>10	>5
56	>5	>1
57	>10	>10
58	>10	>10
59	>10	>10
60	>10	>5
61	>10	>5
62	>10	>5
63	>10	>5
z64	>10	>10
65	>5	>10
66	>5	>5
67	>5	>10
68	>5	>5
69	>5	>5
70	>5	>5
71	>5	>3
72	>5	>10
73	>5	>10
74	>5	>5
75	>5	>3
76	>5	>5
77	>5	>10
78	>5	>3
79	>5	>3
80	>5	>10
81	>5	>10
82	>5	>5
83	>5	>5
84	>5	>5
85	>5	>10
86	>5	>10
87	>5	>10
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92	>5	>10
93	>5	>5
94	>5	>10
95	>5	>10
96	>5	>5
97	>5	>10
98	>5	>10

99	>5	>5
100	>5	>5
101	>5	>10
102	>3	>10
103	>3	>5
104	>3	>5
105	>3	>5
106	>3	>5
107	>3	>10
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111	>3	>5
112	>3	>5
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114	>3	>5
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125	>5	>5
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157	>5	>3
158	>5	>3
159	>5	>3
160	>5	>5
161	>5	>3
162	>5	> 1
163	>3	>3
164	>3	>3

165	>3	>3
166	>3	>3
167	>3	>3
168	>5	>3
169	>3	>5
170	>3	>5
175	>10	>5
176	>10	>5
177	>5	>10
178	>5	>5
179	>5	>10
180	>5	>5
181	>5	>10
182	>5	>5
183	>3	>10
184	> 5	>5
185	>3	>3
186	>5	>5
187	>10	>10
188	>5	>5

Table 3 provides IC_{50} data for compounds of the invention assayed in the FGFR Enzymatic Assay after dilution in assay buffer, added to the plate and pre-incubated for 5 to 10 minutes. The symbol: "+" indicates an IC_{50} less than 10 nM; "++" indicates an IC_{50} greater than or equal to 10 nM but less than 30 nM; "+++" indicates an IC_{50} greater than or equal to 30 nM but less than 200 nM; and "++++" indicates an IC_{50} greater than or equal to 200 nM. Table 4 provides ratios of IC_{50} data, showing FGFR4 selectivity.

Table 3

Example No.	FGFR1 IC50 (nM)	FGFR2 IC50 (nM)	FGFR3 IC50 (nM)	FGFR4 IC50 (nM)
1	++++	++++	++++	+++
2	++++	++++	++++	+++
3	++++	++++	++++	++
4	+++	++	++	+
5	+++	++	++	+
6	++++	++++	+++	+
7	++++	++++	++++	+++
8	++++	++++	+++	++
9	+++	++	+++	++
10	+++	++	++	+
11	++++	++++	+++	++
12	++++	+++	+++	+

13	++++	+++	+++	+
14	++++	+++	++	+
15	+++	+++	+++	+
16	++++	+++	+++	+
57	+++	+++	++	++++
58	++	+	+	++
59	+++	++	++	+++
69	+++	+	+	+++
116	++	+	+	++
117	+++	++	++	+++
118	+++	++	++	+++
119	++	+	+	++
120	+++	++	++	+++
121	++	+	+	+++
126	++	+	+	+++
127	+++	++	++	+++
128	+	+	+	++
136	+++	++	++	+++
137	+++	++	++	+++
138	+++	++	++	+++
139	+++	+	+	+++
140	+++	+	++	+++
141	+++	++	+	+++
142	+++	+++	++	+++
143	+++	++	+	+++
144	+++	++	++	+++
145	+	+	+	++
168	++	+	+	++
169	+	+	+	++
170	++	+	+	++
175	++	+	+	++
186	+	+	+	+
187	++	+	+	+++

Table 4

Example No.	FGFR1/ FGFR4	FGFR2/ FGFR4	FGFR3/ FGFR4
1	>25	>25	>50
2	>10	>10	>10
3	>25	>25	>25
4	>10	>10	>5
5	>10	>5	>4
6	>100	>100	>50
7	>25	>10	>10
8	>50	>10	>10
9	>5	>1	>1

10	>25	>10	>10
11	>50	>20	>25
12	>50	>25	>20
13	>50	>20	>10
14	>25	>5	>5
15	>50	>25	>10
16	>25	>10	>10

Example B

FGFR4 Cellular and In Vivo Assays

The FGFR4 inhibitory activity of the example compounds in cells, tissues, and/or animals can be demonstrated according to one or more assays or models described in the art such as, for example, in French et al. "Targeting FGFR4 Inihibits Hepatocellular Carcinoma in Preclinical Mouse Models," PLoS ONE, May 2012, Vol. 7, Issue 5, e36713, which is incorporated herein by reference in its entirety.

Example C

Cell-Based FGFR Phosphorylation Assays

The inhibitory effect of compounds on FGFR phosphorylation in relevant cell lines (Ba/F3-FGFR3, KMS-11, RT112, KatoIII, H-1581 cancer cell lines and HUVEC cell line) can be assessed using immunoassays specific for FGFR phosphorylation. Cells are starved in media with reduced serum (0.5%) and no FGF1 for 4 to 18 h depending upon the cell line then treated with various concentrations of individual inhibitors for 1-4 hours. For some cell lines, such as Ba/F3-FGFR3 and KMS-11, cells are stimulated with Heparin (20 μg/mL) and FGF1 (10 ng/mL) for 10 min. Whole cell protein extracts are prepared by incubation in lysis buffer with protease and phosphatase inhibitors [50 mM HEPES (pH 7.5), 150 mM NaCl, 1.5 mM $MgCl_2$, 10% Glycerol, 1% Triton X-100, 1 mM sodium orthovanadate, 1 mM sodium fluoride, aprotinin (2 μg/mL), leupeptin (2 μg/mL), pepstatin A (2 μg/mL), and phenylmethylsulfonyl fluoride (1 mM)] at 4°C. Protein extracts are cleared of cellular debris by centrifugation at 14,000 x g for 10 minutes and quantified using the BCA (bicinchoninic acid) microplate assay reagent (Thermo Scientific).

Phosphorylation of FGFR receptor in protein extracts was determined using immunoassays including western blotting, enzyme-linked immunoassay (ELISA) or bead-based immunoassays (Luminex). For detection of phosphorylated FGFR2, a commercial ELISA kit DuoSet IC Human Phospho-FGF R2α ELISA assay (R&D Systems, Minneapolis,

MN) can be used. For the assay KatoIII cells are plated in 0.2% FBS supplemented Iscove's medium (50,000 cells / well/ per 100 μL) into 96-well flat-bottom tissue culture treated plates (Corning, Corning, NY), in the presence or absence of a concentration range of test compounds and incubated for 4 hours at 37 °C, 5% CO_2. The assay is stopped with addition of 200 μL of cold PBS and centrifugation. The washed cells are lysed in Cell Lysis Buffer (Cell Signaling, #9803) with Protease Inhibitor (Calbiochem, #535140) and PMSF (Sigma, #P7626) for 30 min on wet ice. Cell lysates were frozen at -80 °C before testing an aliquot with the DuoSet IC Human Phospho-FGF R2α ELISA assay kit. GraphPad prism3 was used to analyze the data. The IC_{50} values were derived by fitting the data to the equation for a sigmoidal dose-response with a variable slope.

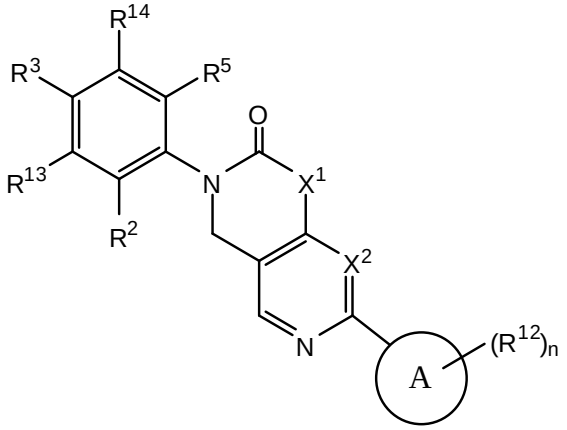
For detection of phosphorylated FGFR3, a bead based immunoassay was developed. An anti-human FGFR3 mouse mAb (R&D Systems, cat#MAB7661) was conjugated to Luminex MAGplex microspheres, bead region 20 and used as the capture antibody. RT-112 cells were seeded into multi-well tissue culture plates and cultured until 70% confluence. Cells were washed with PBS and starved in RPMI + 0.5% FBS for 18 hr. The cells were treated with 10 μL of 10X concentrations of serially diluted compounds for 1 hr at 37 °C, 5% CO_2 prior to stimulation with 10 ng/mL human FGF1 and 20 μg/mL Heparin for 10 min. Cells were washed with cold PBS and lysed with Cell Extraction Buffer (Invitrogen) and centrifuged. Clarified supernatants were frozen at -80 °C until analysis.

For the assay, cell lysates are diluted 1:10 in Assay Diluent and incubated with capture antibody-bound beads in a 96-well filter plate for 2 hours at room temperature on a plate shaker. Plates are washed three times using a vacuum manifold and incubated with anti-phospho-FGF R1-4 (Y653/Y654) rabbit polyclonal antibody (R&D Systems cat# AF3285) for 1 hour at RT with shaking. Plates are washed three times. The diluted reporter antibody, goat anti-rabbit-RPE conjugated antibody (Invitrogen Cat. # LHB0002) is added and incubated for 30 minutes with shaking. Plates are washed three times. The beads are suspended in wash buffer with shaking at room temperature for 5 minutes and then read on a Luminex 200 instrument set to count 50 events per sample, gate settings 7500-13500. Data is expressed as mean fluorescence intensity (MFI). MFI from compound treated samples are divided by MFI values from DMSO controls to determine the percent inhibition, and the IC_{50} values are calculated using the GraphPad Prism software. Compounds having an IC_{50} of 1 μM or less are considered active.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference, including all patent, patent applications, and publications, cited in the present application is incorporated herein by reference in its entirety.

What is claimed is:

1. A combination of a compound and an additional therapeutic agent for use in treating cancer, wherein the compound has Formula (I'):



,

or a pharmaceutically acceptable salt thereof, wherein:

ring A is a C_{6-10} aryl or 5- to 10-membered heteroaryl having carbon and 1 to 4 heteroatoms as ring members selected from O, N, and S, wherein the N and S are each optionally oxidized;

each R^{12} is independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^a, SR^a, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NR^aR^a, NR^aOR^a, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- are each optionally substituted with 1, 2, 3, or 4 independently selected R^b substituents;

or two adjacent R^{12} substituents on ring A taken together with the atoms to which they are attached form a fused 5- or 6-membered cycloalkyl ring, 5 to 6-membered heterocycloalkyl ring, phenyl or 5 to 6-membered heteroaryl ring, wherein the heterocycloalkyl or heteroaryl has 1-2 heteroatoms as ring members selected from O, N, and S;

each R^a is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^a are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^d substituents;

or any two R^a substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

each R^b is independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$, and $S(O)_2NR^cR^c$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^b are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^f substituents;

each R^c is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^c are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^f substituents;

or any two R^c substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

each R^d is independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, CN, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$;

each R^f is independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, CN, OR^g, SR^g, $C(O)R^g$, $C(O)NR^gR^g$, $C(O)OR^g$, $OC(O)R^g$, $OC(O)NR^gR^g$, NR^gR^g, $NR^gC(O)R^g$, $NR^gC(O)NR^gR^g$, $NR^gC(O)OR^g$, $C(=NR^g)NR^gR^g$, $NR^gC(=NR^g)NR^gR^g$, $S(O)R^g$, $S(O)NR^gR^g$, $S(O)_2R^g$, $NR^gS(O)_2R^g$, $NR^gS(O)_2NR^gR^g$, and $S(O)_2NR^gR^g$;

each R^h is independently selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{1-6} haloalkyl, halo, CN, OR^i, SR^i, $C(O)R^i$, $C(O)NR^iR^i$, $C(O)OR^i$, $OC(O)R^i$, $OC(O)NR^iR^i$, NR^iR^i, $NR^iC(O)R^i$, $NR^iC(O)NR^iR^i$, $NR^iC(O)OR^i$, $C(=NR^i)NR^iR^i$, $NR^iC(=NR^i)NR^iR^i$, $S(O)R^i$, $S(O)NR^iR^i$, $S(O)_2R^i$, $NR^iS(O)_2R^i$, $NR^iS(O)_2NR^iR^i$, and $S(O)_2NR^iR^i$, wherein said C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, and 5-6 membered heteroaryl of R^h are optionally substituted by 1, 2, or 3 independently selected R^j substituents;

each R^j is independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, CN, OR^k, SR^k, $C(O)R^k$, $C(O)NR^kR^k$, $C(O)OR^k$, $OC(O)R^k$, $OC(O)NR^kR^k$, NR^kR^k, $NR^kC(O)R^k$, $NR^kC(O)NR^kR^k$, $NR^kC(O)OR^i$, $C(=NR^k)NR^kR^k$, $NR^kC(=NR^k)NR^kR^k$, $S(O)R^k$, $S(O)NR^kR^k$, $S(O)_2R^k$, $NR^kS(O)_2R^k$, $NR^kS(O)_2NR^kR^k$, and $S(O)_2NR^kR^k$;

each R^e, R^g, R^i or R^k is independently selected from H, C_{1-4} alkyl, C_{6-10}aryl, C_{1-4} haloalkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, wherein the C_{1-4} alkyl, C_{6-10}aryl, C_{2-4} alkenyl or C_{2-4} alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

or any two R^e substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^g substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^i substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

X^1 is $-CR^{10}R^{11}-$ or $–NR^7-$

X^2 is N or CR^6;

R^{13} is H, CN, $NR^{c4}R^{d4}$, OR^1 or -C(O)NHR^e, wherein R^1 is C_{1-3} alkyl or C_{1-3} haloalkyl;

R^2 and R^5 are halogen;

R^3 is H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, CN, or C_{1-3} alkoxy;

R^{14} is H, CN, $NR^{c4}R^{d4}$, OR^4 or -C(O)NHR^g, wherein R^4 is C_{1-3} alkyl or C_{1-3} haloalkyl;

R^6 is selected from H, halo, CN, OR^{a4}, SR^{a4}, C(O)$NR^{c4}R^{d4}$, OC(O)$NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)OR^{a4}, NR^{c4}C(O)$NR^{c4}R^{d4}$, NR^{c4}S(O)R^{b4}, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, S(O)$R^{b4}$, S(O)$NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $S(O)_2NR^{c4}R^{d4}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl groups of R^6 are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10A};

R^7 is selected from H, C(O)$NR^{c4}R^{d4}$, S(O)R^{b4}, S(O)$NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $S(O)_2NR^{c4}R^{d4}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, 5- to 10-membered heteroaryl having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, 4- to 10-membered heterocycloalkyl having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5- to 10-membered heteroaryl, 4-7 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- groups of R^7 are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10A}; or two R^{10A} substituents attached to the adjacent ring atoms of the aryl or heteroaryl ring of R^7, taken together with the atoms to which they are attached, form a fused C_{5-6} cycloalkyl ring or a fused 5- to 6-membered heterocycloalkyl ring having 1-2 heteroatoms as ring members independently selected from O, N and S, wherein the nitrogen and sulfur atoms are each optionally oxidized and the fused C_{5-6} cycloalkyl ring or fused 5 to 6-membered heterocycloalkyl is optionally substituted with 1 or 2 independently selected R^{19} groups;

R^{10} and R^{11} are each independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, a 5-10 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-10

membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl groups of R^{10} and R^{11} are each optionally substituted with 1, 2, or 3, R^{10A};

alternatively, R^{10} and R^{11} together with the carbon atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl group or a 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl group; wherein said 3-, 4-, 5-, 6-, or 7-membered cycloalkyl group and 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl group are each optionally substituted with 1, 2, 3 or 4 R^{10A};

each R^{10A} is independently selected from halo, CN, NO_2, OR^{a4}, SR^{a4}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $S(O)_2NR^{c4}R^{d4}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl group of R^{10A} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{19};

each R^{a4}, R^{b4}, R^{c4}, and R^{d4} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl group of R^{a4}, R^{b4}, R^{c4}, and R^{d4} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{19};

alternatively, R^{c4} and R^{d4} together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group which is optionally substituted with 1, 2 or 3 substituents independently selected from R^{19};

each R^{e4} is independently H or C_{1-4} alkyl;

each R^{19} is independently selected from halo, CN, NO_2, OR^{a9}, SR^{a9}, $C(O)R^{b9}$, $C(O)NR^{c9}R^{d9}$, $C(O)OR^{a9}$, $OC(O)R^{b9}$, $OC(O)NR^{c9}R^{d9}$, $NR^{c9}R^{d9}$, $NR^{c9}C(O)R^{b9}$,

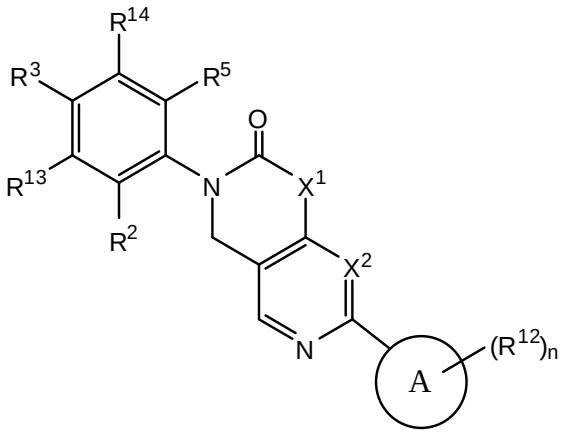
$NR^{c9}C(O)OR^{a9}$, $NR^{c9}C(O)NR^{c9}R^{d9}$, $NR^{c9}S(O)R^{b9}$, $NR^{c9}S(O)_2R^{b9}$, $NR^{c9}S(O)_2NR^{c9}R^{d9}$, $S(O)R^{b9}$, $S(O)NR^{c9}R^{d9}$, $S(O)_2R^{b9}$, $S(O)_2NR^{c9}R^{d9}$, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6}cycloalkyl, 4- to 6-membered heterocycloalkyl and C_{1-4} haloalkyl, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6}cycloalkyl, 4- to 6-membered heterocycloalkyl and C_{1-4} haloalkyl of R^{19} are each further optionally substituted with 1 or 2 R^{20} substituents independently selected from H, halo, CN, NO_2, OR^q, SR^q, $C(O)R^q$, $C(O)NR^qR^q$, $C(O)OR^q$, $OC(O)R^q$, $OC(O)NR^qR^q$, NR^qR^q, $NR^qC(O)R^q$, $NR^qC(O)OR^q$, $NR^qC(O)NR^qR^q$, $NR^qS(O)R^q$, $NR^qS(O)_2R^q$, $NR^qS(O)_2NR^qR^q$, $S(O)R^q$, $S(O)NR^qR^q$, $S(O)_2R^q$, $S(O)_2NR^qR^q$, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl and C_{1-4} haloalkyl, wherein each R^q is independently H or C_{1-4}alkyl;

each R^{a9}, R^{c9}, and R^{d9} is independently selected from H and C_{1-4} alkyl;

each R^{b9} is independently C_{1-4} alkyl; and

the subscript n is 0, 1, 2 or 3.

2. A compound for use in treating cancer, wherein the compound is administered in combination with an additional therapeutic agent, and wherein the compound has Formula (I'):



or a pharmaceutically acceptable salt thereof, wherein:

ring A is a C_{6-10} aryl or 5- to 10-membered heteroaryl having carbon and 1 to 4 heteroatoms as ring members selected from O, N, and S, wherein the N and S are each optionally oxidized;

each R^{12} is independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^a, SR^a,

$C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NR^aR^a, NR^aOR^a, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- are each optionally substituted with 1, 2, 3, or 4 independently selected R^b substituents;

or two adjacent R^{12} substituents on ring A taken together with the atoms to which they are attached form a fused 5- or 6-membered cycloalkyl ring, 5 to 6-membered heterocycloalkyl ring, phenyl or 5 to 6-membered heteroaryl ring, wherein the heterocycloalkyl or heteroaryl has 1-2 heteroatoms as ring members selected from O, N, and S;

each R^a is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^a are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^d substituents;

or any two R^a substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

each R^b is independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$, and $S(O)_2NR^cR^c$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^b are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^f substituents;

each R^c is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^c are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^f substituents;

or any two R^c substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

each R^d is independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, CN, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$;

each R^f is independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, CN, OR^g, SR^g, $C(O)R^g$, $C(O)NR^gR^g$, $C(O)OR^g$, $OC(O)R^g$, $OC(O)NR^gR^g$, NR^gR^g, $NR^gC(O)R^g$, $NR^gC(O)NR^gR^g$, $NR^gC(O)OR^g$, $C(=NR^g)NR^gR^g$, $NR^gC(=NR^g)NR^gR^g$, $S(O)R^g$, $S(O)NR^gR^g$, $S(O)_2R^g$, $NR^gS(O)_2R^g$, $NR^gS(O)_2NR^gR^g$, and $S(O)_2NR^gR^g$;

each R^h is independently selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{1-6} haloalkyl, halo, CN, OR^i, SR^i, $C(O)R^i$, $C(O)NR^iR^i$, $C(O)OR^i$, $OC(O)R^i$, $OC(O)NR^iR^i$, NR^iR^i, $NR^iC(O)R^i$, $NR^iC(O)NR^iR^i$, $NR^iC(O)OR^i$, $C(=NR^i)NR^iR^i$, $NR^iC(=NR^i)NR^iR^i$, $S(O)R^i$, $S(O)NR^iR^i$, $S(O)_2R^i$, $NR^iS(O)_2R^i$, $NR^iS(O)_2NR^iR^i$, and $S(O)_2NR^iR^i$, wherein said C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, and 5-6 membered heteroaryl of R^h are optionally substituted by 1, 2, or 3 independently selected R^j substituents;

each R^j is independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, CN, OR^k, SR^k, $C(O)R^k$, $C(O)NR^kR^k$, $C(O)OR^k$, $OC(O)R^k$, $OC(O)NR^kR^k$, NR^kR^k, $NR^kC(O)R^k$, $NR^kC(O)NR^kR^k$, $NR^kC(O)OR^i$, $C(=NR^k)NR^kR^k$, $NR^kC(=NR^k)NR^kR^k$, $S(O)R^k$, $S(O)NR^kR^k$, $S(O)_2R^k$, $NR^kS(O)_2R^k$, $NR^kS(O)_2NR^kR^k$, and $S(O)_2NR^kR^k$;

each R^e, R^g, R^i or R^k is independently selected from H, C_{1-4} alkyl, C_{6-10}aryl, C_{1-4} haloalkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, wherein the C_{1-4} alkyl, C_{6-10}aryl, C_{2-4} alkenyl or C_{2-4} alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH,

CN, amino, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

or any two R^e substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^g substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^i substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

X^1 is $-CR^{10}R^{11}-$ or $-NR^7-$

X^2 is N or CR^6;

R^{13} is H, CN, $NR^{c4}R^{d4}$, OR^1 or $-C(O)NHR^e$, wherein R^1 is C_{1-3} alkyl or C_{1-3} haloalkyl;

R^2 and R^5 are halogen;

R^3 is H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, CN, or C_{1-3} alkoxy;

R^{14} is H, CN, $NR^{c4}R^{d4}$, OR^4 or $-C(O)NHR^g$, wherein R^4 is C_{1-3} alkyl or C_{1-3} haloalkyl;

R^6 is selected from H, halo, CN, OR^{a4}, SR^{a4}, $C(O)NR^{c4}R^{d4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $S(O)_2NR^{c4}R^{d4}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl groups of R^6 are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10A};

R^7 is selected from H, $C(O)NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $S(O)_2NR^{c4}R^{d4}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, 5- to 10-membered heteroaryl having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, 4- to 10-membered heterocycloalkyl having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5- to 10-membered heteroaryl, 4-7 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10}

cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- groups of R^7 are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10A}; or two R^{10A} substituents attached to the adjacent ring atoms of the aryl or heteroaryl ring of R^7, taken together with the atoms to which they are attached, form a fused C_{5-6} cycloalkyl ring or a fused 5- to 6-membered heterocycloalkyl ring having 1-2 heteroatoms as ring members independently selected from O, N and S, wherein the nitrogen and sulfur atoms are each optionally oxidized and the fused C_{5-6} cycloalkyl ring or fused 5 to 6-membered heterocycloalkyl is optionally substituted with 1 or 2 independently selected R^{19} groups;

R^{10} and R^{11} are each independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, a 5-10 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-10 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl groups of R^{10} and R^{11} are each optionally substituted with 1, 2, or 3, R^{10A};

alternatively, R^{10} and R^{11} together with the carbon atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl group or a 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl group; wherein said 3-, 4-, 5-, 6-, or 7-membered cycloalkyl group and 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl group are each optionally substituted with 1, 2, 3 or 4 R^{10A};

each R^{10A} is independently selected from halo, CN, NO_2, OR^{a4}, SR^{a4}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $S(O)_2NR^{c4}R^{d4}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl group of R^{10A} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{19};

each R^{a4}, R^{b4}, R^{c4}, and R^{d4} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl moiety

having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl group of R^{a4}, R^{b4}, R^{c4}, and R^{d4} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{19};

alternatively, R^{c4} and R^{d4} together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group which is optionally substituted with 1, 2 or 3 substituents independently selected from R^{19};

each R^{e4} is independently H or C_{1-4} alkyl;

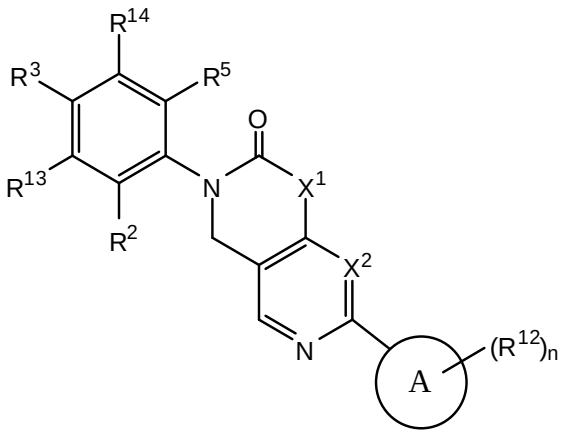
each R^{19} is independently selected from halo, CN, NO_2, OR^{a9}, SR^{a9}, $C(O)R^{b9}$, $C(O)NR^{c9}R^{d9}$, $C(O)OR^{a9}$, $OC(O)R^{b9}$, $OC(O)NR^{c9}R^{d9}$, $NR^{c9}R^{d9}$, $NR^{c9}C(O)R^{b9}$, $NR^{c9}C(O)OR^{a9}$, $NR^{c9}C(O)NR^{c9}R^{d9}$, $NR^{c9}S(O)R^{b9}$, $NR^{c9}S(O)_2R^{b9}$, $NR^{c9}S(O)_2NR^{c9}R^{d9}$, $S(O)R^{b9}$, $S(O)NR^{c9}R^{d9}$, $S(O)_2R^{b9}$, $S(O)_2NR^{c9}R^{d9}$, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6}cycloalkyl, 4- to 6-membered heterocycloalkyl and C_{1-4} haloalkyl, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6}cycloalkyl, 4- to 6-membered heterocycloalkyl and C_{1-4} haloalkyl of R^{19} are each further optionally substituted with 1 or 2 R^{20} substituents independently selected from H, halo, CN, NO_2, OR^q, SR^q, $C(O)R^q$, $C(O)NR^qR^q$, $C(O)OR^q$, $OC(O)R^q$, $OC(O)NR^qR^q$, NR^qR^q, $NR^qC(O)R^q$, $NR^qC(O)OR^q$, $NR^qC(O)NR^qR^q$, $NR^qS(O)R^q$, $NR^qS(O)_2R^q$, $NR^qS(O)_2NR^qR^q$, $S(O)R^q$, $S(O)NR^qR^q$, $S(O)_2R^q$, $S(O)_2NR^qR^q$, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl and C_{1-4} haloalkyl, wherein each R^q is independently H or C_{1-4}alkyl;

each R^{a9}, R^{c9}, and R^{d9} is independently selected from H and C_{1-4} alkyl;

each R^{b9} is independently C_{1-4} alkyl; and

the subscript n is 0, 1, 2 or 3.

3. An additional therapeutic agent for use in treating cancer, wherein the additional therapeutic agent is administered in combination with a compound, and wherein the compound has Formula (I'):



or a pharmaceutically acceptable salt thereof, wherein:

ring A is a C_{6-10} aryl or 5- to 10-membered heteroaryl having carbon and 1 to 4 heteroatoms as ring members selected from O, N, and S, wherein the N and S are each optionally oxidized;

each R^{12} is independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^a, SR^a, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NR^aR^a, NR^aOR^a, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- are each optionally substituted with 1, 2, 3, or 4 independently selected R^b substituents;

or two adjacent R^{12} substituents on ring A taken together with the atoms to which they are attached form a fused 5- or 6-membered cycloalkyl ring, 5 to 6-membered heterocycloalkyl ring, phenyl or 5 to 6-membered heteroaryl ring, wherein the heterocycloalkyl or heteroaryl has 1-2 heteroatoms as ring members selected from O, N, and S;

each R^a is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10}

cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^a are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^d substituents;

or any two R^a substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

each R^b is independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$, and $S(O)_2NR^cR^c$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^b are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^f substituents;

each R^c is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^c are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^f substituents;

or any two R^c substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

each R^d is independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, CN, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$;

each R^f is independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, CN, OR^g, SR^g, $C(O)R^g$, $C(O)NR^gR^g$, $C(O)OR^g$, $OC(O)R^g$, $OC(O)NR^gR^g$, NR^gR^g, $NR^gC(O)R^g$,

$NR^gC(O)NR^gR^g$, $NR^gC(O)OR^g$, $C(=NR^g)NR^gR^g$, $NR^gC(=NR^g)NR^gR^g$, $S(O)R^g$, $S(O)NR^gR^g$, $S(O)_2R^g$, $NR^gS(O)_2R^g$, $NR^gS(O)_2NR^gR^g$, and $S(O)_2NR^gR^g$;

each R^h is independently selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{1-6} haloalkyl, halo, CN, OR^i, SR^i, $C(O)R^i$, $C(O)NR^iR^i$, $C(O)OR^i$, $OC(O)R^i$, $OC(O)NR^iR^i$, NR^iR^i, $NR^iC(O)R^i$, $NR^iC(O)NR^iR^i$, $NR^iC(O)OR^i$, $C(=NR^i)NR^iR^i$, $NR^iC(=NR^i)NR^iR^i$, $S(O)R^i$, $S(O)NR^iR^i$, $S(O)_2R^i$, $NR^iS(O)_2R^i$, $NR^iS(O)_2NR^iR^i$, and $S(O)_2NR^iR^i$, wherein said C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, and 5-6 membered heteroaryl of R^h are optionally substituted by 1, 2, or 3 independently selected R^j substituents;

each R^j is independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, CN, OR^k, SR^k, $C(O)R^k$, $C(O)NR^kR^k$, $C(O)OR^k$, $OC(O)R^k$, $OC(O)NR^kR^k$, NR^kR^k, $NR^kC(O)R^k$, $NR^kC(O)NR^kR^k$, $NR^kC(O)OR^i$, $C(=NR^k)NR^kR^k$, $NR^kC(=NR^k)NR^kR^k$, $S(O)R^k$, $S(O)NR^kR^k$, $S(O)_2R^k$, $NR^kS(O)_2R^k$, $NR^kS(O)_2NR^kR^k$, and $S(O)_2NR^kR^k$;

each R^e, R^g, R^i or R^k is independently selected from H, C_{1-4} alkyl, C_{6-10}aryl, C_{1-4} haloalkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, wherein the C_{1-4} alkyl, C_{6-10}aryl, C_{2-4} alkenyl or C_{2-4} alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

or any two R^e substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^g substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^i substituents attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

X^1 is $-CR^{10}R^{11}-$ or $–NR^7-$

X^2 is N or CR^6;

R^{13} is H, CN, $NR^{c4}R^{d4}$, OR^1 or $-C(O)NHR^e$, wherein R^1 is C_{1-3} alkyl or C_{1-3} haloalkyl;

R^2 and R^5 are halogen;

R^3 is H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, CN, or C_{1-3} alkoxy;

R^{14} is H, CN, $NR^{c4}R^{d4}$, OR^4 or $-C(O)NHR^g$, wherein R^4 is C_{1-3} alkyl or C_{1-3} haloalkyl;

R^6 is selected from H, halo, CN, OR^{a4}, SR^{a4}, $C(O)NR^{c4}R^{d4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $S(O)_2NR^{c4}R^{d4}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl groups of R^6 are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10A};

R^7 is selected from H, $C(O)NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $S(O)_2NR^{c4}R^{d4}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, 5- to 10-membered heteroaryl having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, 4- to 10-membered heterocycloalkyl having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5- to 10-membered heteroaryl, 4-7 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- groups of R^7 are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10A}; or two R^{10A} substituents attached to the adjacent ring atoms of the aryl or heteroaryl ring of R^7, taken together with the atoms to which they are attached, form a fused C_{5-6} cycloalkyl ring or a fused 5- to 6-membered heterocycloalkyl ring having 1-2 heteroatoms as ring members independently selected from O, N and S, wherein the nitrogen and sulfur atoms are each optionally oxidized and the fused C_{5-6} cycloalkyl ring or fused 5 to 6-membered heterocycloalkyl is optionally substituted with 1 or 2 independently selected R^{19} groups;

R^{10} and R^{11} are each independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, a 5-10 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-10 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl groups of R^{10} and R^{11} are each optionally substituted with 1, 2, or 3, R^{10A};

alternatively, R^{10} and R^{11} together with the carbon atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl group or a 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl group; wherein said 3-, 4-, 5-, 6-, or 7-membered cycloalkyl group and 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl group are each optionally substituted with 1, 2, 3 or 4 R^{10A};

each R^{10A} is independently selected from halo, CN, NO_2, OR^{a4}, SR^{a4}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $S(O)_2NR^{c4}R^{d4}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl group of R^{10A} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{19};

each R^{a4}, R^{b4}, R^{c4}, and R^{d4} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl group of R^{a4}, R^{b4}, R^{c4}, and R^{d4} are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{19};

alternatively, R^{c4} and R^{d4} together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group which is optionally substituted with 1, 2 or 3 substituents independently selected from R^{19};

each R^{e4} is independently H or C_{1-4} alkyl;

each R^{19} is independently selected from halo, CN, NO_2, OR^{a9}, SR^{a9}, $C(O)R^{b9}$, $C(O)NR^{c9}R^{d9}$, $C(O)OR^{a9}$, $OC(O)R^{b9}$, $OC(O)NR^{c9}R^{d9}$, $NR^{c9}R^{d9}$, $NR^{c9}C(O)R^{b9}$, $NR^{c9}C(O)OR^{a9}$, $NR^{c9}C(O)NR^{c9}R^{d9}$, $NR^{c9}S(O)R^{b9}$, $NR^{c9}S(O)_2R^{b9}$, $NR^{c9}S(O)_2NR^{c9}R^{d9}$, $S(O)R^{b9}$, $S(O)NR^{c9}R^{d9}$, $S(O)_2R^{b9}$, $S(O)_2NR^{c9}R^{d9}$, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6}cycloalkyl, 4- to 6-membered heterocycloalkyl and C_{1-4} haloalkyl, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6}cycloalkyl, 4- to 6-membered heterocycloalkyl and C_{1-4} haloalkyl

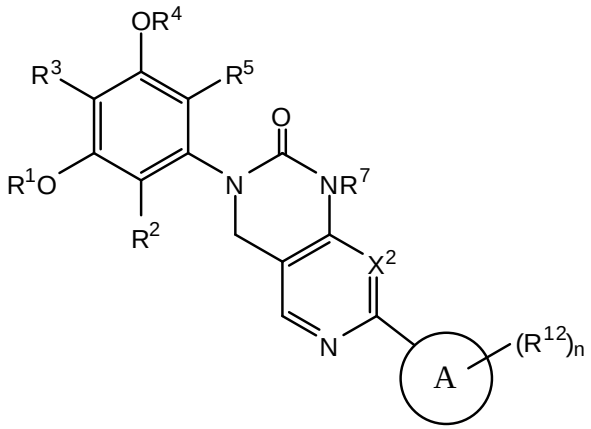
of R^{19} are each further optionally substituted with 1 or 2 R^{20} substituents independently selected from H, halo, CN, NO_2, OR^q, SR^q, $C(O)R^q$, $C(O)NR^qR^q$, $C(O)OR^q$, $OC(O)R^q$, $OC(O)NR^qR^q$, NR^qR^q, $NR^qC(O)R^q$, $NR^qC(O)OR^q$, $NR^qC(O)NR^qR^q$, $NR^qS(O)R^q$, $NR^qS(O)_2R^q$, $NR^qS(O)_2NR^qR^q$, $S(O)R^q$, $S(O)NR^qR^q$, $S(O)_2R^q$, $S(O)_2NR^qR^q$, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl and C_{1-4} haloalkyl, wherein each R^q is independently H or C_{1-4}alkyl;

each R^{a9}, R^{c9}, and R^{d9} is independently selected from H and C_{1-4} alkyl;

each R^{b9} is independently C_{1-4} alkyl; and

the subscript n is 0, 1, 2 or 3.

4. The combination of a compound and an additional therapeutic agent of claim 1, the compound for use according to claim 2, or the additional therapeutic agent for use according to claim 3, wherein the compound has Formula (Ib):



(Ib)

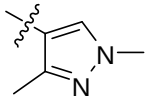
or a pharmaceutically acceptable salt thereof.

5. The combination of a compound and an additional therapeutic agent of claim 1 or 4, the compound for use according to claim 2 or 4, or the additional therapeutic agent for use according to claim 3 or 4, wherein:

(a) ring A is 5-membered heteroaryl; or

(b) ring A is a 5-membered heteroaryl selected from pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, thiophenyl, thiazolyl, isoxazolyl, isothiazolyl, and furanyl; or

(c) ring A is 4-pyrazolyl; or

(d) ring A is  .

6. The combination of a compound and an additional therapeutic agent of any one of claims 1, 4, and 5, the compound for use according to any one of claims 2, 4 and 5, or the additional therapeutic agent for use according to any one of claims 3-5, wherein R^2 and R^5 are F.

7. The combination of a compound and an additional therapeutic agent of any one of claims 1 and 4-6, the compound for use according to any one of claims 2 and 4-6, or the additional therapeutic agent for use according to any one of claims 3-6, wherein:

(a) R^1 and R^4 are each C_{1-3} alkyl; or

(b) R^1 and R^4 are each methyl.

8. The combination of a compound and an additional therapeutic agent of any one of claims 1 and 4-7, the compound for use according to any one of claims 2 and 4-7, or the additional therapeutic agent for use according to any one of claims 3-7, wherein:

(a) X^2 is N or CH; or

(b) X^2 is CH.

9. The combination of a compound and an additional therapeutic agent of any one of claims 1 and 4-8, the compound for use according to any one of claims 2 and 4-8, or the additional therapeutic agent for use according to any one of claims 3-8, wherein:

(a) each R^{12} is independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OR^a, SR^a, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NR^aR^a, NR^aOR^a, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-

, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- are each optionally substituted with 1, 2 or 3 R^b substituents; or

(b) each R^{12} is independently selected from $–NH_2$, -NHOH, -NHOR^a, -NHR^a, -NHC(O)R^a, -NHC(O)NHR^a, -NHS(O)$_2$R^a, -C(O)R^a, -S(O)$_2$R^a, C_{1-6} alkyl, C_{1-6}alkoxy, C_{1-6} haloalkyl, C_{1-4} haloalkoxy, halo, CN, C_{3-6} cycloalkyl, phenyl-C_{1-4}alkyl, 5-6 membered heteroaryl, 5- to 6-membered heteroaryl-C_{1-4}alkyl, 4- to 6-membered heterocycloalkyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl-C_{1-4}alkyl, 5-6 membered heteroaryl, 5- to 6-membered heteroaryl-C_{1-4}alkyl, 4 to 6-membered heterocycloalkyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- is optionally substituted with from 1-3 R^b; and C_{1-6} alkoxy or C_{1-4} haloalkoxy is optionally substituted by 1-3 R^d; or

(c) each R^{12} is independently selected from F, Cl, CN, CH_3, CH_2CH_3, NH_2, OCH_3, -C(O)NH(C_{1-4} alkyl), NHC(O)CH_3, NHS(O)$_2$$CH_3$, NHS(O)$_2$R^a, C(O)R^a, -$CH_2$C(O)R^a, -$CH_2CH_2$R^a, morpholinosulfonyl, imidazolyl, 4-morpholinyl, (3-cyanopyrrolidin-1-yl)methyl, 2-cyanoprop-2-yl, 1-cyanocyclobutyl, 1-cyanocyclopropyl, benzyl, pyridylmethyl, 1,1-dioxothiolan-3-yl, 1-methylsulfonylazetidin-3-yl, 1-acetyl-3-(cyanomethyl)azetidin-3-yl, and -CH_2-(4-morpholinyl), wherein R^a is 4-morpholinyl; or

(d) each R^{12} is independently NH_2, CH_3, F, CN, 1-piperidinyl, 1-piperazinyl, or 4-morpholinyl.

10. The combination of a compound and an additional therapeutic agent of any one of claims 1 and 4-9, the compound for use according to any one of claims 2 and 4-9, or the additional therapeutic agent for use according to any one of claims 3-9, wherein:

(a) R^7 is C_{1-6} alkyl, phenyl, benzyl, C_{3-6} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, 4- to 10-membered heterocycloalkyl, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, 5- to 10-membered heteroaryl, or (5- to 10-membered heteroaryl)-C_{1-4} alkyl-, each of which is optionally substituted with 1, 2, or 3 independently selected R^{10A} substituents; or two R^{10A} substituents attached to the adjacent ring atoms of the aryl or heteroaryl ring of R^7 are optionally taken together with the atoms to which they are attached form a fused C_{5-6} cycloalkyl ring or a fused 5 to 6-membered heterocycloalkyl ring having 1-2 heteroatoms as ring members independently selected from O, N and S, wherein the nitrogen and sulfur atoms are each optionally oxidized and the fused C_{5-6} cycloalkyl ring or fused 5 to 6-membered heterocycloalkyl is optionally substituted with 1 or 2 independently selected R^{19} groups; or

(b) R^7 is C_{1-6} alkyl, cyclopropylmethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-fluorobenzyl, tetrahydrofuran-3-yl, (3-methylisoxazol-5-yl)methyl, (tetrahydro-2H-pyran-4-yl)methyl, (5-cyclopropylisoxazol-3-yl)methyl, 5-methylisoxazol-3-yl)methyl, 4-fluorophenyl, (1-ethylpyrazol-4-yl)methyl, benzothiazol-6-yl, 1-methyl-5-oxopyrrolidin-3-yl, 1-acetylpiperidin-4-yl, 2,3-dihydro-1,4-benzodioxin-6-ylmethyl, 1-t-butoxycarbonylpiperidin-4-yl, 4-cyanophenyl, 4-pyrimidinyl, 2-pyrimidinyl, 5-pyrimidinyl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, (1,5-dimethylpyrazol-4-yl)methyl, or (5-methyl-1,3,4-oxadiazol-2-yl)methyl; or

(c) R^7 is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, a 5-6 membered heteroaryl having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S, and a 4-7 membered heterocycloalkyl moiety having carbon and 1, 2, or 3 heteroatoms independently selected from N, O and S; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl groups of R^7 are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10A}.

11. The combination of a compound and an additional therapeutic agent of any one of claims 1 and 4-10, the compound for use according to any one of claims 2 and 4-10, or the additional therapeutic agent for use according to any one of claims 3-10, wherein subscript n is 0, 1 or 2.

12. The combination of a compound and an additional therapeutic agent of claim 1, the compound for use according to claim 2, or the additional therapeutic agent for use according to claim 3, wherein the compound is:

(a) selected from:

6'-(5-amino-2-methylphenyl)-2'-(2,6-difluoro-3,5-dimethoxyphenyl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

6'-(5-amino-4-fluoro-2-methylphenyl)-2'-(2,6-difluoro-3,5-dimethoxyphenyl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

4-amino-2-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)benzonitrile;

6'-(5-aminopyridin-3-yl)-2'-(2,6-difluoro-3,5-dimethoxyphenyl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(5-fluoropyridin-3-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(5-morpholinopyridin-3-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

6'-(5-amino-2-methylpyridin-3-yl)-2'-(2,6-difluoro-3,5-dimethoxyphenyl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

5-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)nicotinonitrile;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(pyridin-3-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(5-methoxypyridin-3-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

6'-(5-chloropyridin-3-yl)-2'-(2,6-difluoro-3,5-dimethoxyphenyl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

6'-(5-(1H-imidazol-1-yl)pyridin-3-yl)-2'-(2,6-difluoro-3,5-dimethoxyphenyl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(5-(morpholine-4-carbonyl)pyridin-3-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(5-(morpholinosulfonyl)pyridin-3-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

N-(5-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)pyridin-3-yl)methanesulfonamide; and

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(5-(morpholinomethyl)pyridin-3-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one,

or a pharmaceutically acceptable salt thereof; or

(b) selected from:

3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(pyridin-3-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)-N-methylpicolinamide;

(S)-1-(4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)benzyl)pyrrolidine-3-carbonitrile;

2-(5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)pyridin-2-yl)-2-methylpropanenitrile;

1-(5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)pyridin-2-yl)cyclobutanecarbonitrile;

1-(cyclopropylmethyl)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-propyl-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((5-methylisoxazol-3-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

1-cyclopentyl-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(tetrahydrofuran-3-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(4-fluorobenzyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((3-methylisoxazol-5-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

1-((5-cyclopropylisoxazol-3-yl)methyl)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((1-ethyl-1H-pyrazol-4-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(4-fluorophenyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

1-(1,3-benzothiazol-6-yl)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(1-methyl-5-oxopyrrolidin-3-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

1-(1-acetylpiperidin-4-yl)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)benzonitrile;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-pyrimidin-4-yl-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(3-methyl-1-(2-morpholinoethyl)-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(3-methyl-1-(pyridin-3-ylmethyl)-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(3-methyl-1-(2-morpholino-2-oxoethyl)-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(3-methyl-1-(2-morpholinoethyl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1-ethyl-1H-imidazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-[1-(1,1-dioxidotetrahydro-3-thienyl)-3-methyl-1H-pyrazol-4-yl]-1',2'-dihydro-3'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'-one;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1-(1-(methylsulfonyl)azetidin-3-yl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one; and

2-(1-acetyl-3-(4-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-1H-pyrazol-1-yl)azetidin-3-yl)acetonitrile;

or a pharmaceutically acceptable salt thereof; or

(c) selected from:

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(pyridazin-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((2-methoxypyridin-4-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((6-methoxypyridin-3-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)benzonitrile;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(pyrimidin-5-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

4-((3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)methyl)-N-methylbenzamide;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(isoquinolin-7-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((5-ethylisoxazol-3-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(pyrimidin-4-ylmethyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)-2-fluorobenzonitrile;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((5-ethyl-1,3,4-oxadiazol-2-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((2-methylpyridin-4-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(pyridin-4-ylmethyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(pyrazin-2-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(1-(methylsulfonyl)piperidin-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((1-methyl-1H-pyrazol-4-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-(3,4-difluorobenzyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

5-((3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)methyl)picolinonitrile;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(2-methylbenzo[d]oxazol-6-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-methyl-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

1-(4-(1H-pyrazol-1-yl)phenyl)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)-5-fluorobenzonitrile;

6-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)nicotinonitrile;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(oxazol-5-ylmethyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)-2-methoxybenzonitrile;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((5-methyloxazol-2-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

1-cyclopropyl-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(pyrimidin-5-ylmethyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(pyrazin-2-ylmethyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(pyridin-3-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(6-methylpyrazin-2-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(pyridazin-3-ylmethyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(3-(1-methyl-1H-1,2,3-triazol-5-yl)phenyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-isopropyl-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

1-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)cyclopropanecarbonitrile;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(pyridin-2-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((5-isopropylisoxazol-3-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(pyridin-2-ylmethyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((2-methylthiazol-4-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((1-methyl-5-oxopyrrolidin-3-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

2-(4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)phenyl)acetonitrile;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(4-(methylsulfonyl)phenyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(3-fluorophenyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(1-methyl-1H-pyrazol-3-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((1,3-dimethyl-1H-pyrazol-4-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-(3,4-difluorophenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-(3,5-difluorophenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(4-methoxyphenyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(pyrimidin-2-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(5-ethylpyrazin-2-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(5-methylpyrazin-2-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

(R)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((tetrahydrofuran-3-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(3-methoxyphenyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(2-fluorophenyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)-N-methylbenzenesulfonamide;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(5-methoxypyrazin-2-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)-N,N-dimethylbenzamide;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(2-(1-methyl-1H-pyrazol-4-yl)ethyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((2-ethoxypyridin-4-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((1-methyl-2-oxo-1,2-dihydropyridin-4-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(2-oxoindolin-5-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(2-methyl-3-oxoisoindolin-5-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((2-methylpyrimidin-4-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

Methyl 4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)piperidine-1-carboxylate;

Methyl 4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)phenylcarbamate;

1-((1-cyclopropyl-1H-pyrazol-4-yl)methyl)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

2-(4-((3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)methyl)-1H-pyrazol-1-yl)acetonitrile;

1-((1-(cyclopropylmethyl)-1H-pyrazol-4-yl)methyl)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((1-((tetrahydrofuran-2-yl)methyl)-1H-pyrazol-4-yl)methyl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-((1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)methyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

1-(1-cyclopropyl-1H-pyrazol-4-yl)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(1-ethyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(1-propyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(1H-indazol-6-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(1H-indazol-5-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

1-(5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-2-oxo-1-(pyrimidin-4-yl)-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)pyridin-2-yl)cyclobutanecarbonitrile;

1-(5-(1-cyclobutyl-3-(2,6-difluoro-3,5-dimethoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)pyridin-2-yl)cyclobutanecarbonitrile;

1-(5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-2-oxo-1-(pyridin-2-yl)-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)pyridin-2-yl)cyclobutanecarbonitrile;

1-(5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-2-oxo-1-(pyridin-3-yl)-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)pyridin-2-yl)cyclobutanecarbonitrile;

1-(5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-(2-methoxyethyl)-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)pyridin-2-yl)cyclobutanecarbonitrile;

1-(5-(1-(cyclopropylmethyl)-3-(2,6-difluoro-3,5-dimethoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)pyridin-2-yl)cyclobutanecarbonitrile;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(1-methyl-1H-pyrazol-3-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1-methyl-1H-pyrazol-3-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)benzonitrile;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-((1-ethyl-1H-pyrazol-4-yl)methyl)-7-(1-methyl-1H-pyrazol-3-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1-methyl-1H-pyrazol-4-yl)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)benzonitrile;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-((1-ethyl-1H-pyrazol-4-yl)methyl)-7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(3-methyl-1-(3-morpholinopropyl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1-(1-(methylsulfonyl)pyrrolidin-3-yl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1-(2-(1-(methylsulfonyl)piperidin-4-yl)ethyl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

1-(4-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-5-methyl-1H-pyrazol-1-yl)cyclobutanecarbonitrile;

6'-(1-(1-acetylpyrrolidin-3-yl)-1H-pyrazol-4-yl)-2'-(2,6-difluoro-3,5-dimethoxyphenyl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1-(3-morpholinopropyl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1-(2-(4-methoxypiperidin-1-yl)ethyl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

2-(4-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-3-methyl-1H-pyrazol-1-yl)acetonitrile;

2-(3-(4-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-3-methyl-1H-pyrazol-1-yl)pyrrolidin-1-yl)acetonitrile;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(3-methyl-1-(pyridin-3-ylmethyl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

3-(4-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-3-methyl-1H-pyrazol-1-yl)propanenitrile;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1-ethyl-3-methyl-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(3-methyl-1-(2-morpholino-2-oxoethyl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(2-(dimethylamino)thiazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1-(2-(3-methoxypyrrolidin-1-yl)ethyl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-{1-[(1,1-dioxido-1,2-thiazinan-3-yl)methyl]-1H-pyrazol-4-yl}-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(3-methyl-1-(1-methylpyrrolidin-3-yl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1-(2-(dimethylamino)ethyl)-3-methyl-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(3-methyl-1-(2-(piperidin-4-yl)ethyl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1-((1-(methylsulfonyl)azetidin-3-yl)methyl)-1H-pyrazol-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

6'-(1-((1-acetylazetidin-3-yl)methyl)-1H-pyrazol-4-yl)-2'-(2,6-difluoro-3,5-dimethoxyphenyl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(1-ethyl-3-methyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-ethyl-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

5-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-1H-pyrazole-4-carbonitrile;

3-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-1-methyl-1H-pyrazole-4-carbonitrile;

3-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-pyrazole-4-carbonitrile;

1-(cyanomethyl)-3-(2'-(2,6-difluoro-3,5-dimethoxyphenyl)-3'-oxo-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridine]-6'-yl)-1H-pyrazole-4-carbonitrile;

5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)-N-ethylpicolinamide;

N-cyclopropyl-5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)picolinamide;

5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)-N-(2-hydroxyethyl)picolinamide;

5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)-N-isopropylpicolinamide;

5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)-N-propylpicolinamide;

2-(4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)phenyl)acetonitrile;

1-(4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)phenyl)cyclobutanecarbonitrile;

3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(6-morpholinopyridin-3-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one;

1-(4-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)phenyl)cyclopropanecarbonitrile;

5-(3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)picolinamide;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(pyridin-4-yl)-1'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'(2'H)-one;

2'-(2,6-difluoro-3,5-dimethoxyphenyl)-6'-(1-methyl-1H-pyrazol-4-yl)-1',2'-dihydro-3'H-spiro[cyclopropane-1,4'-[2,7]naphthyridin]-3'-one;

1-(5-{3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl}pyridin-2-yl)cyclobutanecarbonitrile; and

1-{5-[3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-(1-methyl-1H-pyrazol-4-yl)-2-oxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl]pyridin-2-yl}cyclobutanecarbonitrile;

or a pharmaceutically acceptable salt thereof.

13. The combination of a compound and an additional therapeutic agent of claim 1, the compound for use according to claim 2, or the additional therapeutic agent for use according to claim 3, wherein the compound is 3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(pyridazin-4-yl)-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one, or a pharmaceutically acceptable salt thereof.

14. The combination of a compound and an additional therapeutic agent of claim 1, the compound for use according to claim 2, or the additional therapeutic agent for use according to claim 3, wherein the compound is 3-(2,6-difluoro-3,5-dimethoxyphenyl)-7-(1,3-dimethyl-1H-pyrazol-4-yl)-1-pyrimidin-4-yl-3,4-dihydropyrido[4,3-d]pyrimidin-2(1H)-one, or a pharmaceutically acceptable salt thereof.

15. The combination of a compound and an additional therapeutic agent of claim 1, the compound for use according to claim 2, or the additional therapeutic agent for use according to claim 3, wherein said additional therapeutic agent is selected from sorafenib, imatinib, docetaxel, paclitaxel, cisplatin, capecitabine, bortezomib, gemcitabine, erlotinib, abiraterone,

prednisone, enzalutamide, fulvestrant, exemestane, anastrozole, letrozole, palbociclib, carboplatin, olaparib, selumetinib, ruxolitinib, and trastuzumab.

16. The combination of a compound and an additional therapeutic agent of claim 1, the compound for use according to claim 2, or the additional therapeutic agent for use according to claim 3, wherein said cancer is selected from kidney cancer, gastric cancer, esophageal cancer, multiple myeloma, pancreatic cancer, lung cancer, prostate cancer, breast cancer, bladder cancer, liver cancer, polycythemia vera, essential thrombocythemia, primary myelofibrosis, head and neck cancer, ovarian cancer, and glioblastoma.