

Substituted Spirocyclic-Pyrroloquinazolinones and Spirocyclic-PiperidinoquinazolinonesCross-reference to related applications

[0001] This application claims priority from U.S. Provisional Application No. 63/478,858, filed January 6, 2023, the disclosure of each of which is hereby incorporated by reference in its entirety.

Field

[0002] This disclosure is directed to substituted spirocyclic-pyrroloquinazolinones and spirocyclic-piperidinoquinazolinones, and to such compounds that are useful in the treatment of diseases or disorders associated with PI3K modulation.

Background

[0003] The activity of cells can be regulated by external signals that stimulate or inhibit intracellular events. The process by which stimulatory or inhibitory signals are transmitted into and within a cell to elicit an intracellular response is referred to as signal transduction. Over the past decades, cascades of signal transduction events have been elucidated and found to play a central role in a variety of biological responses. Defects in various components of signal transduction pathways have been found to account for a vast number of diseases, including numerous forms of cancer, inflammatory disorders, metabolic disorders, vascular and neuronal diseases.

[0004] Kinases represent a class of important signaling molecules. Kinases can generally be classified into protein kinases and lipid kinases, and certain kinases exhibit dual specificities. Protein kinases are enzymes that phosphorylate other proteins and/or themselves (i.e., autophosphorylation). Protein kinases can be generally classified into three major groups based upon their substrate utilization: tyrosine kinases which predominantly phosphorylate substrates on tyrosine residues (e.g., erb2, PDGF receptor, EGF receptor, VEGF receptor, src, abl), serine/threonine kinases which predominantly phosphorylate substrates on serine and/or threonine residues (e.g., mTORC1, mTORC2, ATM, ATR, DNA-PK, Akt), and dual-specificity kinases which phosphorylate substrates on tyrosine, serine and/or threonine residues.

[0005] Lipid kinases are enzymes that catalyze the phosphorylation of lipids within cells. These enzymes, and the resulting phosphorylated lipids and lipid-derived biologically active organic molecules, play a role in many different physiological processes, including cell proliferation, migration, adhesion, and differentiation. A particular group of lipid kinases comprises membrane lipid kinases, i.e., kinases that catalyze the phosphorylation of lipids contained in or associated with cell membranes. Examples of such enzymes include

phosphoinositide(s) kinases (such as PI3-Kinases, PI4-Kinases), diacylglycerol kinases, and sphingosine kinases.

[0006] The phosphoinositide 3-kinases (PI3Ks) signaling pathway is one of the most highly mutated systems in human cancers. PI3K signaling is also involved in many other disease states including allergic contact dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, chronic obstructive pulmonary disorder, psoriasis, multiple sclerosis, asthma, disorders related to diabetic complications, and inflammatory complications of the cardiovascular system such as acute coronary syndrome.

[0007] PI3Ks are members of a unique and conserved family of intracellular lipid kinases that phosphorylate the 3' -OH group on phosphatidylinositols or phosphoinositides. The PI3K family comprises 15 kinases with distinct substrate specificities, expression patterns, and modes of regulation. The class I PI3Ks (pi 10a, pi 10b, pi 106, and pi 10g) are typically activated by tyrosine kinases or G-protein coupled receptors to generate PIP3, which engages downstream effectors such as those in the pathways of Akt/PDK1, mTOR, the Tec family kinases, and the Rho family GTPases. The class II and III PI3-Ks play a key role in intracellular trafficking through the synthesis of PI(3)P and PI(3,4)P2.

[0008] The PI3K isoforms have been implicated, for example, in a variety of human cancers and disorders. Mutations in the gene coding for PI3K isoforms or mutations which lead to upregulation of a PI3K isoform are believed to occur in many human cancers. Mutations in the gene coding for a PI3K isoform are point mutations clustered within several hotspots in helical and kinase domains. Because of the high rate of PI3K mutations, targeting of this pathway may provide valuable therapeutic opportunities.

[0009] Genetic alterations in genes in PI3K signaling are believed to be involved in a range of cancers such as endometrial cancer, breast cancer, esophageal squamous-cell cancer, cervical squamous-cell carcinoma, cervical adenocarcinoma, colorectal adenocarcinoma, bladder urothelial carcinoma, glioblastoma, ovarian cancer, non-small-cell lung cancer, esophagogastric cancer, nerve-sheath tumor, head and neck squamous-cell carcinoma, melanoma, esophagogastric adenocarcinoma, soft-tissue sarcoma, prostate cancer, fibrolamellar carcinoma, hepatocellular carcinoma, diffuse glioma, colorectal cancer, pancreatic cancer, cholangiocarcinoma, B-cell lymphoma, mesothelioma, adrenocortical carcinoma, renal non-clear-cell carcinoma, renal clear-cell carcinoma, germ-cell carcinoma, thymic tumor, pheochromocytoma, miscellaneous neuroepithelial tumor, thyroid cancer, leukemia, and encapsulated glioma.

[0010] The alpha (α) isoform of PI3K has been implicated, for example, in a variety of human cancers. Angiogenesis has been shown to selectively require the alpha (α) isoform of

PI3K in the control of endothelial cell migration. Mutations in the gene coding for PI3K α or mutations which lead to upregulation of PI3K α are believed to occur in many human cancers such as lung, stomach, endometrial, ovarian, bladder, breast, colon, brain, prostate, and skin cancers. Mutations in the gene coding for PI3K α are point mutations clustered within several hotspots in helical and kinase domains, such as E542K, E545K, and H1047R. Many of these mutations have been shown to be oncogenic gain-of-function mutations. Because of the high rate of PI3K α mutations, targeting of this pathway may provide valuable therapeutic opportunities. While other PI3K isoforms such as PI3K δ or PI3K γ are expressed primarily in hematopoietic cells, PI3K α , along with PI3K β , is expressed constitutively.

[0011] Due to the central role of PI3K α in regulating organismal glucose homeostasis, PI3K inhibition in patients often gives rise to hyperglycemia and/or hyperinsulinemia. High levels of circulating insulin could potentially be mitogenic and/or antiapoptotic for cancer cells and thus negate the antiproliferative effects of PI3K inhibitors.

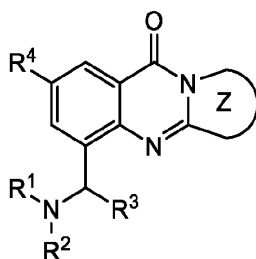
[0012] In the setting of cancer with mutated PI3K α , one way to overcome the problem of compensatory production of insulin and/or glucose upon systemic PI3K α inhibition would be to develop inhibitors with enhanced selectivity for mutant PI3K α over wild-type PI3K α . This would create an increased window for drug dosing to selectively inhibit the pathologic signaling of mutant PI3K α in the cancer cells without affecting the wild-type PI3K α in the host tissues that control systemic metabolism, thus limiting toxicities and permitting higher doses and more complete inhibition of the drug target.

[0013] Existing PI3K α inhibitors are nearly equipotent to wild-type and mutant PI3K α . Mutant selective inhibitors have been elusive due to the PI3K α mutations location far from the active site. As such, inhibitors which target a second, peripheral binding pocket near a known mutation (e.g., H1047R) may provide a route to selective PI3K α inhibition. Thus, targeting a mutated, peripheral binding pocket of PI3K α , may in turn provide a valuable therapeutic target for drug development.

[0014] As such, kinases, for example lipid kinases such as PI3Ks, are prime targets for drug development.

Summary

[0015] In one aspect, the present disclosure provides compounds of formula (I) and pharmaceutically acceptable salts thereof, and prodrugs, solvates, hydrates, isomers, deuterated forms, and tautomers thereof:



(I)

wherein:

R¹ is H, C₁-C₃ alkyl, or C₃-C₆ cycloalkyl;

R² is phenyl or a 5-6 membered heteroaryl group, wherein each phenyl and heteroaryl is optionally substituted with 1-5 R⁷;

each R⁷ is independently C₁-C₄ alkyl; -OR^A, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, -C(O)N(R^B)₂, cyano, halogen or tetrazolyl;

each R^A is independently H, C₁-C₆ alkyl, or C₃-C₆ cycloalkyl;

each R^B is independently H, -OH, C₁-C₆ alkyl, C₁-C₆ alkoxy or C₃-C₆ cycloalkyl;

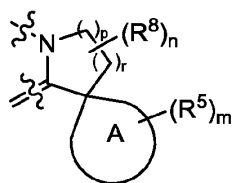
and

R³ is C₁-C₃ alkyl optionally substituted, polysubstituted or persubstituted with fluoro, C₃-C₆ cycloalkyl, C₂-C₃ alkenyl, C₂-C₃ alkynyl, or C₅-C₆ cycloalkenyl;

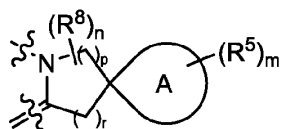
R⁴ is H, C₁-C₃ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkyloxy, C₂-C₃ alkenyl, C₂-C₃ alkynyl, or C₅-C₆ cycloalkenyl, cyano, or halo, wherein each C₁-C₃ alkyl and C₃-C₆ cycloalkyl is optionally substituted with 1-5 halo groups;



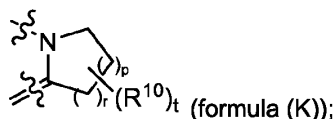
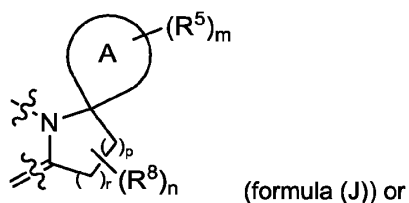
(formula (Z)) represents formula (D), (G), (J) or (K)



(formula (D)),



(formula (G)),



wherein

each ring A is a 3-8 membered carbocyclic ring or 3-7 membered heterocyclic ring,

m is 0, 1, 2, 3, 4 or 5;

p and r are independently 1 or 2, provided that the sum of p and r is 2 or 3;

each R^5 is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halogen, cyano, hydroxy, hydroxy C_1 - C_6 alkyl, amino, mono- or di(C_1 - C_6 alkyl) amino, C_3 - C_6 cycloalkyl, phenyl or 5-6 membered heteroaryl, where each cycloalkyl, phenyl and heteroaryl is optionally substituted with 1-3 of halogen, hydroxy, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, cyano, amino, or mono- or di(C_1 - C_3) alkyl amino;

n is 0, 1 or 2;

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

each R^8 is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, cyano, hydroxy, oxo, halogen, halo(C_1 - C_6)alkyl, hydroxy C_1 - C_6 alkyl, amino, or mono- or di(C_1 - C_6 alkyl) amino; and

each R^{10} is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, cyano, hydroxy, oxo, halogen, halo(C_1 - C_6)alkyl, hydroxy C_1 - C_6 alkyl, amino, or mono- or di(C_1 - C_6 alkyl) amino, R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} or R^{17} wherein

R^{11} is aryl or aryl(C_1 - C_6)alkyl where each aryl is optionally substituted independently with up to 4 of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, cyano, hydroxy, oxo, halogen, halo(C_1 - C_6)alkyl, hydroxy C_1 - C_6 alkyl, amino, or mono- or di(C_1 - C_6 alkyl) amino;

R^{12} is 5-8 membered heteroaryl or 5-8 membered heteroaryl(C_1 - C_6)alkyl where each heteroaryl is optionally substituted independently with up to 4 of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, cyano, hydroxy, oxo, halogen, halo(C_1 - C_6)alkyl, hydroxy C_1 - C_6 alkyl, amino, or mono- or di(C_1 - C_6 alkyl) amino;

R^{13} is aryl(C_1 - C_6)alkoxy, aryl(C_1 - C_6)alkoxy(C_1 - C_6)alkyl, aryl(C_1 - C_6)alkylamino or aryl(C_1 - C_6)alkylamino(C_1 - C_6)alkyl where each aryl is

optionally substituted independently with up to 4 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino;

R¹⁴ is 5-8 membered heteroaryl(C₁-C₆)alkoxy, 5-8 membered heteroaryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, 5-8 membered heteroaryl(C₁-C₆)alkylamino or 5-8 membered heteroaryl(C₁-C₆)alkylamino(C₁-C₆)alkyl where each up to 4 of heteroaryl is optionally substituted independently with C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino;

R¹⁵ is (C₁-C₆)cycloalkyl or (C₁-C₆)cycloalkyl(C₁-C₆)alkyl where each cycloalkyl is optionally substituted independently with up to 4 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino;

R¹⁶ is (C₁-C₆)cycloalkyl(C₁-C₆)alkoxy, (C₁-C₆)cycloalkyl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)cycloalkyl(C₁-C₆)alkylamino or (C₁-C₆)cycloalkyl(C₁-C₆)alkylamino(C₁-C₆)alkyl where each cycloalkyl is optionally substituted independently with up to 4 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino; and

R¹⁷ is 5-8 membered heterocyclyl, 5-8 membered heterocyclyl(C₁-C₆)alkyl, 5-8 membered heterocyclyl(C₁-C₆)alkoxy, 5-8 membered heterocyclyl(C₁-C₆)alkoxy(C₁-C₆)alkyl, 5-8 membered heterocyclyl(C₁-C₆)alkylamino or 5-8 membered heterocyclyl(C₁-C₆)alkylamino(C₁-C₆)alkyl where each 5-8 membered heterocyclyl is optionally substituted independently with up to 4 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino.

[0016] In another aspect, the present disclosure provides for a pharmaceutical composition comprising a compound or salt as otherwise described herein together with a pharmaceutically acceptable carrier, excipient or diluent.

[0017] In another aspect, the present disclosure provides for a method of treating a disease or disorder associated with modulation of phosphoinositide 3-kinase (PI3K), comprising administering to a patient in need thereof a therapeutically effective amount of a

compound of any as otherwise described herein or a pharmaceutical composition as otherwise described herein.

[0018] In another aspect, the present disclosure provides for a method of inhibiting phosphoinositide 3-kinase (PI3K), comprising administering to a patient in need thereof a therapeutically effective amount of a compound as otherwise described herein or a pharmaceutical composition as otherwise described herein.

[0019] In another aspect, the present disclosure provides for a method of treating cancer or a disorder, the method comprising administering to a patient in need thereof a therapeutically effective amount of a compound as otherwise described herein or a pharmaceutical composition as otherwise described herein.

[0020] The compounds disclosed herein selectively bind to H1047R-mutated PI3K α and not to wild-type PI3K α .

[0021] In other aspects, the present disclosure provides intermediates and synthetic methods useful in preparing compounds of formula (I).

[0022] Other aspects and embodiments of the disclosure are evident in view of the detailed description provided herein.

DETAILED DESCRIPTION OF THE INVENTION

[0023] The present invention relates to inhibitors of PI3K α . In particular, the present invention relates to compounds that inhibit PI3K α activity, pharmaceutical compositions comprising a therapeutically effective amount of the compounds, and methods of use therefor.

DEFINITIONS

[0024] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents, patent applications, and publications referred to herein are incorporated by reference to the extent they are consistent with the present disclosure. Terms and ranges have their generally defined definition unless expressly defined otherwise.

[0025] For simplicity, chemical moieties are defined and referred to throughout primarily as univalent chemical moieties (e.g., alkyl, aryl, etc.). Nevertheless, such terms may also be used to convey corresponding multivalent moieties under the appropriate structural circumstances clear to those skilled in the art. For example, while an "alkyl" moiety generally refers to a monovalent radical (e.g. CH₃-CH₂-), in certain circumstances a bivalent linking moiety can be "alkyl," in which case those skilled in the art will understand the alkyl to be a

divalent radical (e.g., $-\text{CH}_2\text{-CH}_2-$), which is equivalent to the term "alkylene." (Similarly, in circumstances in which a divalent moiety is required and is stated as being "aryl," those skilled in the art will understand that the term "aryl" refers to the corresponding divalent moiety, arylene.) All atoms are understood to have their normal number of valences for bond formation (i.e., 4 for carbon, 3 for N, 2 for O, and 2, 4, or 6 for S, depending on the oxidation state of the S).

[0026] The term "amino" refers to $-\text{NH}_2$.

[0027] The term "acetyl" refers to $-\text{C}(\text{O})\text{CH}_3$.

[0028] As herein employed, the term "acyl" refers to an alkylcarbonyl or arylcarbonyl substituent wherein the alkyl and aryl portions are as defined herein.

[0029] The term "alkyl" as employed herein refers to saturated straight and branched chain aliphatic groups having from 1 to 12 carbon atoms. As such, "alkyl" encompasses C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} and C_{12} groups. Alkyl groups may be branched or unbranched. Examples of alkyl groups include, without limitation, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, and hexyl.

[0030] The term "alkenyl" as used herein means an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon double bonds, having from 2 to 12 carbon atoms. As such, "alkenyl" encompasses C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} and C_{12} groups. Examples of alkenyl groups include, without limitation, ethenyl, propenyl, butenyl, pentenyl, and hexenyl.

[0031] The term "alkynyl" as used herein means an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon triple bonds, having from 2 to 12 carbon atoms. As such, "alkynyl" encompasses C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} and C_{12} groups. Examples of alkynyl groups include, without limitation, ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

[0032] An "alkylene," "alkenylene," or "alkynylene" group is an alkyl, alkenyl, or alkynyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups. Examples of alkylene groups include, without limitation, methylene, ethylene, propylene, and butylene. Representative alkenylene groups include, without limitation, ethenylene, propenylene, and butenylene. Representative alkynylene groups include, without limitation, ethynylene, propynylene, and butynylene.

[0033] The term "alkoxy" refers to $-\text{O}(\text{C}_1\text{--}\text{C}_6 \text{ alkyl})$.

[0034] The term "cycloalkyl" as employed herein is a saturated and partially unsaturated cyclic hydrocarbon group having 3 to 12 carbons. As such, "cycloalkyl" includes C_3 , C_4 , C_5 , C_6 ,

C₇, C₈, C₉, C₁₀, C₁₁ and C₁₂ cyclic hydrocarbon groups. Examples of cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

[0035] The term "heteroalkyl" refers to an alkyl group, as defined hereinabove, wherein one or more carbon atoms in the chain are independently replaced O, S, or NR^x, wherein R^x is hydrogen or C₁ – C₃ alkyl. Examples of heteroalkyl groups include methoxymethyl, methoxyethyl and methoxypropyl.

[0036] An "aryl" group is a C₆-C₁₄ aromatic moiety comprising one to three aromatic rings. As such, "aryl" includes C₆, C₁₀, C₁₃, and C₁₄ cyclic hydrocarbon groups. A representative aryl group is a C₆-C₁₀ aryl group. Particular aryl groups include, without limitation, phenyl, naphthyl, anthracenyl, and fluorenyl. An "aryl" group also includes fused multicyclic (e.g., bicyclic) ring systems in which one or more of the fused rings is non-aromatic, provided that at least one ring is aromatic, such as indenyl.

[0037] An "aralkyl" or "arylalkyl" group comprises an aryl group covalently linked to an alkyl group wherein the moiety is linked to another group via the alkyl moiety. An representative aralkyl group is -(C₁-C₈)alkyl(C₆-C₁₀)aryl, including, without limitation, benzyl, phenethyl, and naphthylmethyl. For example, an arC₁-C₃alkyl is an aryl group covalently linked to a C₁-C₃ alkyl.

[0038] A "heterocyclyl" or "heterocyclic" or "heterocycloalkyl" group is a saturated or unsaturated, non-aromatic mono- or bicyclic (fused or spiro) ring structure having from 3 to 12 atoms, (3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 atoms), for example 4 to 8 atoms, wherein one or more ring atoms are independently -C(O)-, N, NR⁴, O, or S, and the remainder of the ring atoms are quaternary or carbonyl carbons. Examples of heterocyclic groups include, without limitation, epoxy, oxiranyl, oxetanyl, azetidiny, aziridiny, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiophenyl, pyrrolidiny, piperidiny, piperaziny, imidazolidiny, thiazolidiny, thiatanyl, dithianyl, trithianyl, azathianyl, oxathianyl, dioxolanyl, oxazolidiny, oxazolidinonyl, decahydroquinoliny, piperidonyl, 4-piperidonyl, thiomorpholiny, dimethyl-morpholiny, and morpholiny. Examples of heterocyclic groups that are spiro ring systems are azaspiro[2.5]octan-6-yl, 5-azaspiro[2.4]heptan-5-yl, 6-azaspiro[3.4]octan-6-yl, 5-oxa-7-azaspiro[3.4]octan-7-yl, 5,5-dimethyl-4-oxa-7-azaspiro[2.5]octan-7-yl, and 7,7-dimethyl-5-azaspiro[2.5]octan-5-yl. Specifically excluded from the scope of this term are compounds having adjacent ring O and/or S atoms. The heterocyclic groups can be attached to a parent group (i.e., the point of attachment) via any ring atom, including one of the heteroatoms or one of the carbon atoms, in the heterocyclic ring group. As chemically required, the heterocyclic ring may be attached to one or more other groups, for instance if operating as a

bridging group. The term "heterocyclyl" also includes fused multicyclic (e.g., bicyclic) ring systems in which one or more of the fused rings is aromatic or non-aromatic, provided that at least one ring is non-aromatic contains an N, O, or S ring atom. Examples of such fused multicyclic ring systems are indolinyl, indolin-2-yl, 2,3-dihydrobenzofuran-2-yl and 2,3,4,5-tetrahydrobenzo[d]oxazol-2-yl. Each of these examples is a 9-membered heterocyclyl.

[0039] As used herein, the term "heteroaryl" refers to a group having 5 to 14 ring atoms, preferably 5, 6, 10, 13 or 14 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to three heteroatoms that are each independently N, O, or S. "Heteroaryl" also includes fused multicyclic (e.g., bicyclic) ring systems in which one or more of the fused rings is non-aromatic, provided that at least one ring is aromatic and at least one ring contains an N, O, or S ring atom. The heteroaryl groups can be attached to a parent group (i.e., the point of attachment) via any ring atom, including one of the heteroatoms or one of the carbon atoms, in the heteroaryl ring group. As chemically required, the heteroaryl may be attached to one or more other groups, for instance if operating as a bridging group.

[0040] Examples of heteroaryl groups include acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzo[d]oxazol-2(3H)-one, 2H-benzo[b][1,4]oxazin-3(4H)-one, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, furanyl, furazanyl, imidazolyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizyl, quinoxalinyl, quinuclidinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

[0041] An "arylene," "heteroarylene," or "heterocyclylene" group is a bivalent aryl, heteroaryl, or heterocyclyl group, respectively, as defined hereinabove, that is positioned between and serves to connect two other chemical groups.

[0042] As employed herein, when a moiety (e.g., cycloalkyl, aryl, heteroaryl, heterocyclyl, urea, etc.) is described as “optionally substituted” without expressly stating the substituents it is meant that the group optionally has multiple non-hydrogen substituents, for example from one to five, or from one to four, or from one to three, or one or two, non-hydrogen substituents.

[0043] The term “halogen” or “halo” as employed herein refers to chlorine, bromine, fluorine, or iodine.

[0044] The term “haloalkyl” refers to an alkyl chain in which one or more hydrogens have been replaced by a halogen. Representative haloalkyls are trifluoromethyl, difluoromethyl, fluorochloromethyl, chloromethyl, and fluoromethyl.

[0045] The term “hydroxyalkyl” refers to -alkylene-OH.

[0046] In formula (I) and other embodiments as indicated, where Ring A is defined as a 3-8 membered carbocyclic ring or 3-7 membered heterocyclic ring, Ring A includes the spiro atom, i.e., the atom the two cyclic groups have in common.

[0047] In embodiments of formula (I) wherein a group, e.g., a -C(O)OR^A or -C(O)N(R^B)₂, is attached to R² at a position alpha or ortho to the point of attachment of R² to the nitrogen atom to which R² is attached, it is understood that structures such as the following are intended



[0048] It is to be understood that each individual atom present in formula (I) and the compounds within formula (I), may be present in the form of any of its naturally occurring isotopes, with the most abundant isotope(s) being preferred. Thus, by way of example, each individual hydrogen atom present in formula (I), or in the formulae depicted hereinafter, may be present as a ¹H, ²H (deuterium; D) or ³H (tritium; T) atom, preferably ¹H. Similarly, by way of example, each individual carbon atom present in formula (I), or in the formulae depicted hereinafter, may be present as a ¹²C, ¹³C or ¹⁴C atom, preferably ¹²C.

[0049] As used herein, “an effective amount” of a compound is an amount that is sufficient to negatively modulate or inhibit the activity of PI3K α .

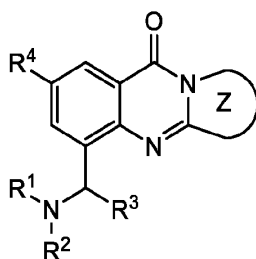
[0050] As used herein, a “therapeutically effective amount” of a compound is an amount that is sufficient to ameliorate or in some manner reduce a symptom or stop or reverse progression of a condition, or negatively modulate or inhibit the activity of PI3K α . Such amount may be administered as a single dosage or may be administered according to a regimen, whereby it is effective.

[0051] As used herein, "treatment" means any manner in which the symptoms or pathology of a condition, disorder or disease in a patient are ameliorated or otherwise beneficially altered.

[0052] As used herein, "amelioration of the symptoms of a particular disorder by administration of a particular compound or pharmaceutical composition" refers to any lessening, whether permanent or temporary, lasting or transient, that can be attributed to or associated with administration of the composition.

COMPOUNDS

[0053] In one aspect, the present disclosure provides compounds of formula (I):



(I)

and pharmaceutically acceptable salts, prodrugs, solvates, hydrates, isomers, deuterated forms, and tautomers thereof, wherein:

R¹ is H, C₁-C₃ alkyl, or C₃-C₆ cycloalkyl;

R² is phenyl or a 5-6 membered heteroaryl group, wherein each phenyl and heteroaryl is optionally substituted with 1-5 R⁷;

each R⁷ is independently C₁-C₄ alkyl; -OR^A, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, -C(O)N(R^B)₂, cyano, halogen or tetrazolyl;

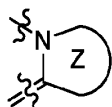
each R^A is independently H, C₁-C₆ alkyl, or C₃-C₆ cycloalkyl;

each R^B is independently H, -OH, C₁-C₆ alkyl, C₁-C₆ alkoxy or C₃-C₆ cycloalkyl;

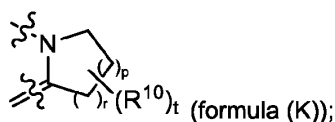
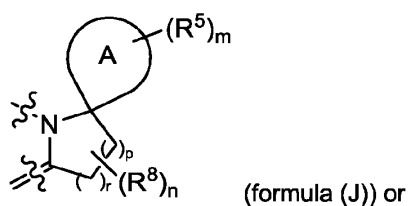
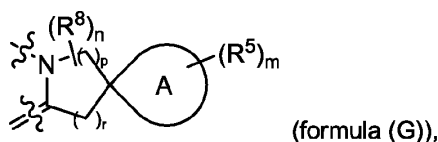
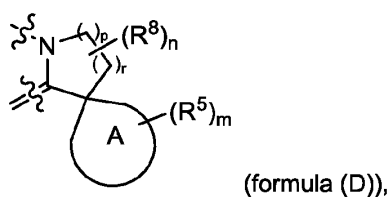
and

R³ is C₁-C₃ alkyl optionally substituted, polysubstituted or persubstituted with fluoro, C₃-C₆ cycloalkyl, C₂-C₃ alkenyl, C₂-C₃ alkynyl, or C₅-C₆ cycloalkenyl;

R⁴ is H, C₁-C₃ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkyloxy, C₂-C₃ alkenyl, C₂-C₃ alkynyl, or C₅-C₆ cycloalkenyl, cyano, or halo, wherein each C₁-C₃ alkyl and C₃-C₆ cycloalkyl is optionally substituted with 1-5 halo groups;



(formula (Z)) represents formula (D), (G), (J) or (K)



wherein

each ring A is a 3-8 membered carbocyclic ring or 3-7 membered heterocyclic ring,

m is 0, 1, 2, 3, 4 or 5;

p and r are independently 1 or 2, provided that the sum of p and r is 2 or 3;

each R⁵ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, cyano, hydroxy, hydroxy C₁-C₆ alkyl, amino, mono- or di(C₁-C₆ alkyl) amino, C₃-C₆ cycloalkyl, phenyl or 5-6 membered heteroaryl, where each cycloalkyl, phenyl and heteroaryl is optionally substituted with 1-3 of halogen, hydroxy, C₁-C₃ alkyl, C₁-C₃ alkoxy, cyano, amino, or mono- or di(C₁-C₃) alkyl amino;

n is 0, 1 or 2;

t is 0, 1, 2, 3 or 4; each R⁸ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino; and

each R¹⁰ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶ or R¹⁷ wherein

R¹¹ is aryl or aryl(C₁-C₆)alkyl where each aryl is optionally substituted independently with up to 4 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano,

- hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino;
- R¹² is 5-8 membered heteroaryl or 5-8 membered heteroaryl(C₁-C₆)alkyl where each heteroaryl is optionally substituted independently with up to 4 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino;
- R¹³ is aryl(C₁-C₆)alkoxy, aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, aryl(C₁-C₆)alkylamino or aryl(C₁-C₆)alkylamino(C₁-C₆)alkyl where each aryl is optionally substituted independently with up to 4 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino;
- R¹⁴ is 5-8 membered heteroaryl(C₁-C₆)alkoxy, 5-8 membered heteroaryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, 5-8 membered heteroaryl(C₁-C₆)alkylamino or 5-8 membered heteroaryl(C₁-C₆)alkylamino(C₁-C₆)alkyl where each up to 4 of heteroaryl is optionally substituted independently with C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino; and
- R¹⁵ is (C₁-C₆)cycloalkyl or (C₁-C₆)cycloalkyl(C₁-C₆)alkyl where each cycloalkyl is optionally substituted independently with up to 4 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino;
- R¹⁶ is (C₁-C₆)cycloalkyl(C₁-C₆)alkoxy, (C₁-C₆)cycloalkyl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)cycloalkyl(C₁-C₆)alkylamino or (C₁-C₆)cycloalkyl(C₁-C₆)alkylamino(C₁-C₆)alkyl where each cycloalkyl is optionally substituted independently with up to 4 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino; and
- R¹⁷ is 5-8 membered heterocyclyl, 5-8 membered heterocyclyl(C₁-C₆)alkyl, 5-8 membered heterocyclyl(C₁-C₆)alkoxy, 5-8 membered heterocyclyl(C₁-C₆)alkoxy(C₁-C₆)alkyl, 5-8 membered heterocyclyl(C₁-C₆)alkylamino or 5-8 membered heterocyclyl(C₁-C₆)alkylamino(C₁-C₆)alkyl where each 5-8 membered heterocyclyl is optionally substituted independently with up to 4 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino.

[0054] In certain embodiments of formula (I) as otherwise described herein, formula (Z) represents formula (D).

[0055] In certain embodiments of formula (I) as otherwise described herein, formula (Z) represents formula (G).

[0056] In certain embodiments of formula (I) as otherwise described herein, formula (Z) represents formula (J).

[0057] In certain embodiments of formula (I) as otherwise described herein, ring A is a 5-7 membered carbocyclic ring.

[0058] In certain embodiments of formula (I) as otherwise described herein, ring A is a 5-7 membered heterocyclic ring.

[0059] In certain embodiments of formula (I) as otherwise described herein, ring A is cyclohexyl or cyclopentyl.

[0060] In certain embodiments of formula (I) as otherwise described herein, ring A is pyranyl or azetidiny.

[0061] In certain embodiments of formula (I) as otherwise described herein, R¹ is H or CH₃.

[0062] In certain embodiments of formula (I) as otherwise described herein, R² is optionally substituted phenyl or optionally substituted pyridinyl.

[0063] In certain embodiments of formula (I) as otherwise described herein, R² is phenyl, pyridinyl, thienyl, thiazolyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, pyrazinyl, pyridazinyl or pyrimidinyl, each of which is optionally substituted with 1-5 R⁷.

[0064] In certain embodiments of formula (I) as otherwise described herein, R² is phenyl or pyridinyl, each of which is optionally substituted with 1-5 R⁷.

[0065] In certain embodiments of formula (I) as otherwise described herein, R² is phenyl or pyridinyl, each of which is optionally substituted with 1-5 R⁷, wherein one R⁷ is -C(O)OR^A or -C(O)N(R^B)₂, wherein the -C(O)OR^A or -C(O)N(R^B)₂ is attached to R² at a position alpha, i.e., ortho, to the point of attachment of R² to the nitrogen atom to which R² is attached.

[0066] In certain embodiments of formula (I) as otherwise described herein, R² is phenyl or pyridinyl, each of which is optionally substituted with 1-5 R⁷, wherein at least one R⁷ is cyano, wherein the at least one cyano is attached to R² at a position alpha to the point of attachment of R² to the nitrogen atom to which R² is attached.

[0067] In certain embodiments of formula (I) as otherwise described herein, R² is phenyl or a 5-7 membered heteroaryl, each of which is substituted with 1, 2, 3 or 4 R⁷ groups.

[0068] In certain embodiments of formula (I) as otherwise described herein, R² is phenyl or a 5-7 membered heteroaryl substituted with 1, 2 or 3 R⁷ groups.

[0069] In certain embodiments of formula (I) as otherwise described herein, R² is phenyl or a 5-7 membered heteroaryl, each of which is substituted with 1, 2, 3 or 4 R⁷ groups, and at least one R⁷ group is -C(O)OR^A.

[0070] In certain embodiments of formula (I) as otherwise described herein, R² is phenyl or a 5-7 membered heteroaryl substituted with 1, 2 or 3 R⁷ groups, and at least one R⁷ group is -C(O)OR^A.

[0071] In certain embodiments of formula (I) as otherwise described herein, R² is substituted with one -C(O)OR^A, wherein the -C(O)OR^A is attached to R² at a position alpha to the point of attachment of R² to the nitrogen atom to which R² is attached.

[0072] In certain embodiments of formula (I) as otherwise described herein, R² is phenyl or a 5-7 membered heteroaryl, each of which is substituted with 1, 2, 3 or 4 R⁷ groups, and at least one R⁷ group is -C(O)OR^A, wherein the -C(O)OR^A is attached to R² at a position alpha to the point of attachment of R² to the nitrogen atom to which R² is attached.

[0073] In certain embodiments of formula (I) as otherwise described herein, R² is phenyl or a 5-7 membered heteroaryl substituted with 1, 2 or 3 R⁷ groups, and at least one R⁷ group is -C(O)OR^A, wherein the -C(O)OR^A is attached to R² at a position alpha to the point of attachment of R² to the nitrogen atom to which R² is attached.

[0074] In certain embodiments of formula (I) as otherwise described herein, R³ is C₁-C₃ alkyl, wherein the alkyl group is unsubstituted, substituted with 1-5 halo groups, or perfluorinated.

[0075] In certain embodiments of formula (I) as otherwise described herein, m is 0, 1, or 2 and each R⁵ is halogen, hydroxy, cyano or amino.

[0076] In certain embodiments of formula (I) as otherwise described herein, R² is phenyl optionally substituted with 1, 2, 3 or 4 R⁷ groups.

[0077] In certain embodiments of formula (I) as otherwise described herein, R² is pyridinyl optionally substituted with 1, 2, 3 or 4 R⁷ groups.

[0078] In certain embodiments of formula (I) as otherwise described herein, R² is thienyl optionally substituted with 1, 2, 3 or 4 R⁷ groups.

[0079] In certain embodiments of formula (I) as otherwise described herein, R² is thiazolyl optionally substituted with 1, 2, 3 or 4 R⁷ groups.

[0080] In certain embodiments of formula (I) as otherwise described herein, R² is oxazolyl optionally substituted with 1, 2, 3 or 4 R⁷ groups.

[0081] In certain embodiments of formula (I) as otherwise described herein, R² is isoxazolyl optionally substituted with 1, 2, 3 or 4 R⁷ groups.

[0082] In certain embodiments of formula (I) as otherwise described herein, R² is imidazolyl optionally substituted with 1, 2, 3 or 4 R⁷ groups.

[0083] In certain embodiments of formula (I) as otherwise described herein, R² is pyrazolyl optionally substituted with 1, 2, 3 or 4 R⁷ groups.

[0084] In certain embodiments of formula (I) as otherwise described herein, R² is pyrazinyl optionally substituted with 1, 2, 3 or 4 R⁷ groups.

[0085] In certain embodiments of formula (I) as otherwise described herein, R² is pyridazinyl optionally substituted with 1, 2, 3 or 4 R⁷ groups.

[0086] In certain embodiments of formula (I) as otherwise described herein, R² is pyrimidinyl optionally substituted with 1, 2, 3 or 4 R⁷ groups.

[0087] In certain embodiments of formula (I) as otherwise described herein, R² is optionally substituted with one -C(O)OR^A.

[0088] In certain embodiments of formula (I) as otherwise described herein, R⁴ is hydrogen, fluoro, chloro, bromo, methyl, methoxy, ethyl, ethoxy, cyclopropyl, trifluoromethyl or cyano.

[0089] In certain embodiments of formula (I) as otherwise described herein, R⁴ is hydrogen, methyl, ethyl or cyano.

[0090] In certain embodiments of formula (I) as otherwise described herein, R⁴ is methoxy.

[0091] In certain embodiments of formula (I) as otherwise described herein, R⁴ is fluoro, chloro, or bromo.

[0092] In certain embodiments of formula (I) as otherwise described herein, R⁴ is hydrogen.

[0093] In certain embodiments of formula (I) as otherwise described herein, R⁴ is fluoro.

[0094] In certain embodiments of formula (I) as otherwise described herein, R⁴ is chloro.

[0095] In certain embodiments of formula (I) as otherwise described herein, R⁴ is bromo.

[0096] In certain embodiments of formula (I) as otherwise described herein, R⁴ is methyl.

[0097] In certain embodiments of formula (I) as otherwise described herein, R⁴ is ethyl.

[0098] In certain embodiments of formula (I) as otherwise described herein, R⁴ is cyano.

[0099] In certain embodiments of formula (I) as otherwise described herein, R⁴ is cyclopropyl.

[00100] In certain embodiments of formula (I) as otherwise described herein, R⁴ is trifluoromethyl.

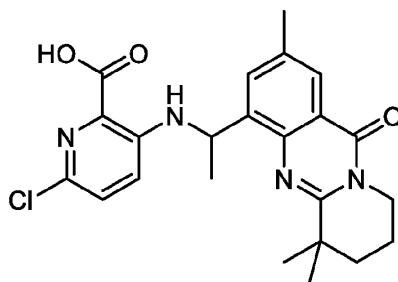
[00101] In certain embodiments of formula (I) as otherwise described herein, m is 0.

[00102] In certain embodiments of formula (I) as otherwise described herein, m is 1 or 2 and each R⁵ is halogen, C₃-C₆ cycloalkyl, phenyl or 5-6 membered heteroaryl, where each cycloalkyl, phenyl and heteroaryl is optionally substituted with 1-3 of halogen, hydroxy, C₁-C₃ alkyl, C₁-C₃ alkoxy, cyano, amino, or mono- or di(C₁-C₃) alkyl amino.

[00103] In certain embodiments of formula (I) as otherwise described herein, m is 1 or 2 and each R⁵ is halogen, C₃-C₆ cycloalkyl, phenyl or 5-6 membered heteroaryl, where each cycloalkyl, phenyl and heteroaryl is optionally substituted with 1 or 2 of halogen, hydroxy, C₁-C₂ alkyl, C₁-C₂ alkoxy, cyano, amino, or mono- or di(C₁-C₂) alkylamino.

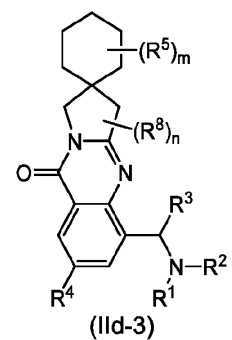
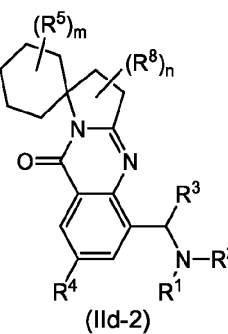
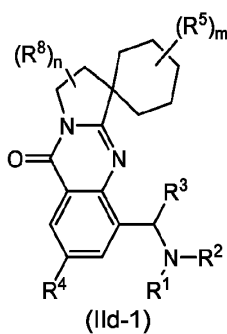
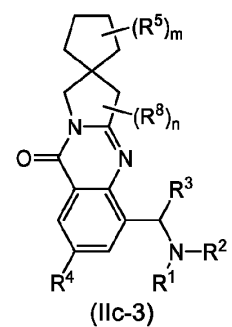
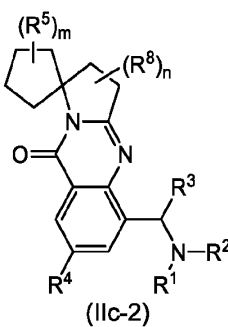
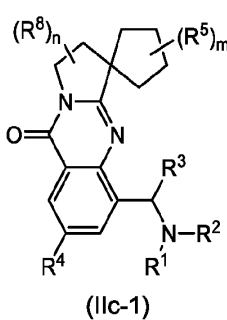
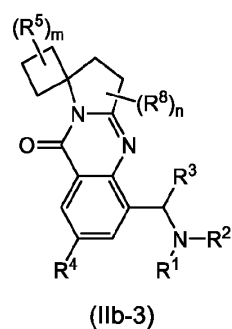
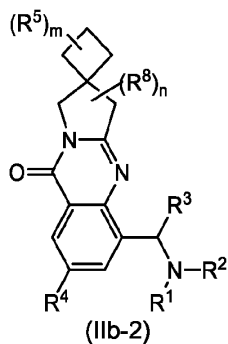
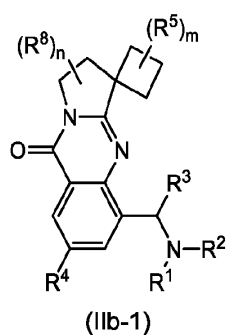
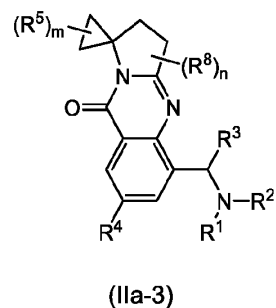
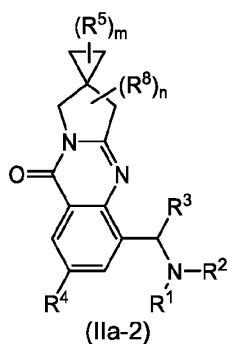
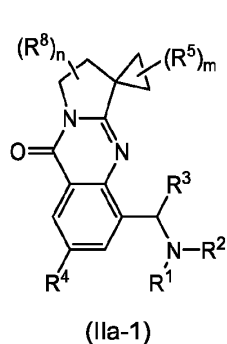
[00104] In certain embodiments of formula (I) as otherwise described herein, R⁸ is hydrogen or C₁-C₆ alkyl.

[00105] In certain embodiments of formula (I) as otherwise described herein, the compound is not a compound of the formula



6-chloro-3-((1-(2,6,6-trimethyl-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-b]quinazolin-4-yl)ethyl)amino)picolinic acid.

[00106] In certain embodiments of formula (I) as otherwise described herein, the compound is of formula (IIa-1), (IIa-2), (IIa-3), (IIb-1), (IIb-2), (IIb-3), (IIc-1), (IIc-2), (IIc-3), (IId-1), (IId-2), or (IId-3):



or a pharmaceutically acceptable salt thereof, wherein:

R¹ is H, C₁-C₃ alkyl, or C₃-C₆ cycloalkyl;

R² is phenyl or pyridinyl, wherein each phenyl and pyridinyl is optionally substituted with 1-5 R⁷;

each R⁷ is independently C₁-C₄ alkyl; -OR^A, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, -C(O)N(R^B)₂, cyano, halogen or tetrazolyl;

each R^A is independently H, C₁-C₆ alkyl, or C₃-C₆ cycloalkyl;

each R^B is independently H, -OH, C₁-C₆ alkyl, C₁-C₆ alkoxy or C₃-C₆ cycloalkyl;

and

R³ is C₁-C₃ alkyl or C₃-C₆ cycloalkyl;

R⁴ is H, C₁-C₃ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, or halo, wherein each C₁-C₃ alkyl is optionally substituted with 1-5 halo groups;

m is 0, 1, 2, 3, 4 or 5;

each R⁵ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, cyano, hydroxy, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino, C₃-C₆ cycloalkyl, phenyl or 5-6 membered heteroaryl, where each cycloalkyl, phenyl and heteroaryl is optionally substituted with 1-3 of halogen, hydroxy, C₁-C₃ alkyl, C₁-C₃ alkoxy, cyano, amino, or mono- or di(C₁-C₃) alkyl amino;

wherein each non-spiro carbon in the ring carrying R⁵ is optionally replaced with a heteroatom which is nitrogen, oxygen, or sulfur;

n is 0, 1 or 2; and

each R⁸ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, halogen, oxo, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino.

[00107] In certain embodiments as otherwise described herein, m is 0, 1, or 2 and each R⁵ is independently halogen, hydroxy, cyano or amino.

[00108] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, n is 0 or 1 and each R⁸ is halogen, hydroxy, cyano or amino.

[00109] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R³ is C₁-C₃ alkyl.

[00110] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R³ is methyl.

[00111] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R⁴ is H, C₁-C₃ alkyl, C₁-C₆ alkoxy, C₃-C₄ cycloalkyl, fluoro, chloro, bromo, cyclopropyl, trifluoromethyl or cyano.

[00112] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R⁴ is hydrogen, methyl, methoxy, ethyl, or cyano.

[00113] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R⁴ is fluoro, chloro, or bromo.

[00114] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R⁴ is hydrogen.

[00115] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R⁴ is methoxy.

[00116] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R⁴ is fluoro.

[00117] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R⁴ is chloro.

[00118] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R⁴ is bromo.

[00119] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R⁴ is methyl.

[00120] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R⁴ is ethyl.

[00121] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R⁴ is cyano.

[00122] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R⁴ is cyclopropyl.

[00123] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R⁴ is trifluoromethyl.

[00124] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R² is phenyl or pyridinyl, each of which is optionally substituted with 1-5 R⁷.

[00125] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R² is phenyl or pyridinyl, each of which is optionally substituted with 1-5 R⁷, wherein one R⁷ is -C(O)OR^A or -C(O)N(R^B)₂, wherein the -C(O)OR^A or -C(O)N(R^B)₂ is attached to R² at a position alpha, i.e., ortho, to the point of attachment of R² to the nitrogen atom to which R² is attached.

[00126] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R² is phenyl or pyridinyl, each of which is optionally substituted with 1-5 R⁷, wherein at least one R⁷ is cyano, wherein the at least one cyano is attached to R² at a position alpha to the point of attachment of R² to the nitrogen atom to which R² is attached.

[00127] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R² is phenyl or a 5-7 membered heteroaryl, each of which is substituted with 1, 2, 3 or 4 R⁷ groups.

[00128] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R² is phenyl or a 5-7 membered heteroaryl substituted with 1, 2 or 3 R⁷ groups.

[00129] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R² is phenyl or a 5-7 membered heteroaryl, each of which is substituted with 1, 2, 3 or 4 R⁷ groups, and at least one R⁷ group is -C(O)OR^A.

[00130] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R² is phenyl or a 5-7 membered heteroaryl substituted with 1, 2 or 3 R⁷ groups, and at least one R⁷ group is -C(O)OR^A.

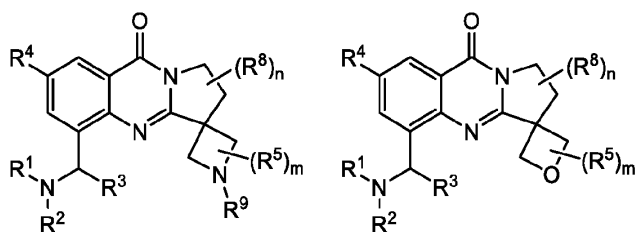
[00131] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R² is substituted with one -C(O)OR^A, wherein the -C(O)OR^A is attached to R² at a position alpha to the point of attachment of R² to the nitrogen atom to which R² is attached.

[00132] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R² is phenyl or a 5-7 membered heteroaryl, each of which is substituted with 1, 2, 3 or 4 R⁷ groups, and at least one R⁷ group is -C(O)OR^A, wherein the -C(O)OR^A is attached to R² at a position alpha to the point of attachment of R² to the nitrogen atom to which R² is attached.

[00133] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R² is phenyl or a 5-7 membered heteroaryl substituted with 1, 2 or 3 R⁷ groups, and at least one R⁷ group is -C(O)OR^A, wherein the -C(O)OR^A is attached to R² at a position alpha to the point of attachment of R² to the nitrogen atom to which R² is attached.

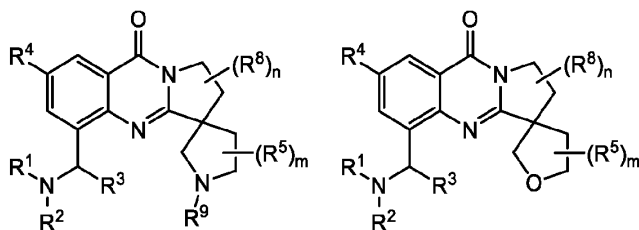
[00134] In certain embodiments of formulae (IIa-1)-(IIId-3) as otherwise described herein, R² is optionally substituted with one -C(O)OR^A.

[00135] Particular embodiments of formulae (IIa-1), (IIa-2), (IIa-3), (IIb-1), (IIb-2), (IIb-3), (IIc-1), (IIc-2), (IIc-3), (IIId-1), (IIId-2), and (IIId-3) in which a non-spiro carbon in the ring carrying R⁵ is replaced with a heteroatom include formula (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IIId-1A) or (IIId-1B):



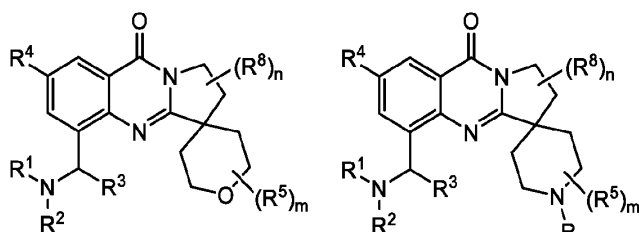
IIb-1A)

(IIb-1B)



(IIc-1A)

(IIc-1B)



(IIId-1A)

(IIId-1B)

or a pharmaceutically acceptable salt thereof, wherein:

R¹ is H, C₁-C₃ alkyl, or C₃-C₆ cycloalkyl;

R² is phenyl or pyridinyl, wherein each phenyl and pyridinyl is optionally substituted with 1-5 R⁷;

each R⁷ is independently C₁-C₄ alkyl; -OR^A, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, -C(O)N(R^B)₂, cyano, halogen or tetrazolyl;

each R^A is independently H, C₁-C₆ alkyl, or C₃-C₆ cycloalkyl;

each R^B is independently H, -OH, C₁-C₆ alkyl, C₁-C₆ alkoxy or C₃-C₆ cycloalkyl;

and

R³ is C₁-C₃ alkyl or C₃-C₆ cycloalkyl;

R⁴ is H, C₁-C₃ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, or halo, wherein each C₁-C₃ alkyl is optionally substituted with 1-5 halo groups;

m is 0 or 1;

each R⁵ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, cyano, hydroxy, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino, C₃-C₆ cycloalkyl, phenyl or 5-6 membered heteroaryl, where each cycloalkyl, phenyl and heteroaryl is optionally substituted with 1-3 of halogen, hydroxy, C₁-C₃ alkyl, C₁-C₃ alkoxy, cyano, amino, or mono- or di(C₁-C₃) alkyl amino;

R⁹ is hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, cyano, hydroxy, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino, C₃-C₆ cycloalkyl, phenyl or 5-6 membered heteroaryl, where each cycloalkyl, phenyl and heteroaryl is optionally substituted with 1-3 of halogen, hydroxy, C₁-C₃ alkyl, C₁-C₃ alkoxy, cyano, amino, or mono- or di(C₁-C₃) alkyl amino;

n is 0, 1 or 2; and

each R⁸ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, halogen, oxo, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino.

[00136] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, n is 0 or 1 and each R⁸ is halogen, hydroxy, cyano or amino.

[00137] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R³ is C₁-C₃ alkyl.

[00138] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R³ is methyl.

[00139] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R⁴ is H, C₁-C₃ alkyl, C₁-C₆ alkoxy, C₃-C₄ cycloalkyl, fluoro, chloro, bromo, cyclopropyl, trifluoromethyl or cyano.

[00140] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R⁴ is hydrogen, methyl, methoxy, ethyl, ethoxy, cyclopropyl, trifluoromethyl or cyano.

[00141] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R⁴ is fluoro, chloro, or bromo.

[00142] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R⁴ is methoxy.

[00143] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R⁴ is hydrogen.

[00144] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R⁴ is fluoro.

[00145] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R⁴ is chloro.

[00146] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R⁴ is bromo.

[00147] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R⁴ is methyl.

[00148] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R⁴ is ethyl.

[00149] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R⁴ is cyano.

[00150] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R⁴ is cyclopropyl.

[00151] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R⁴ is trifluoromethyl.

[00152] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R² is optionally substituted with one -C(O)OR^A.

[00153] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R² is phenyl or pyridinyl, each of which is optionally substituted with 1-5 R⁷.

[00154] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R² is phenyl or pyridinyl, each of which is optionally substituted with 1-5 R⁷, wherein one R⁷ is -C(O)OR^A or -C(O)N(R^B)₂, wherein the -C(O)OR^A or -C(O)N(R^B)₂ is attached to R² at a position alpha, i.e., ortho, to the point of attachment of R² to the nitrogen atom to which R² is attached.

[00155] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R² is phenyl or pyridinyl, each of which is optionally substituted with 1-5 R⁷, wherein at least one R⁷ is cyano, wherein the at least one cyano is attached to R² at a position alpha to the point of attachment of R² to the nitrogen atom to which R² is attached.

[00156] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R² is phenyl or a 5-7 membered heteroaryl, each of which is substituted with 1, 2, 3 or 4 R⁷ groups.

[00157] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R^2 is phenyl or a 5-7 membered heteroaryl substituted with 1, 2 or 3 R^7 groups.

[00158] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R^2 is phenyl or a 5-7 membered heteroaryl, each of which is substituted with 1, 2, 3 or 4 R^7 groups, and at least one R^7 group is $-C(O)OR^A$.

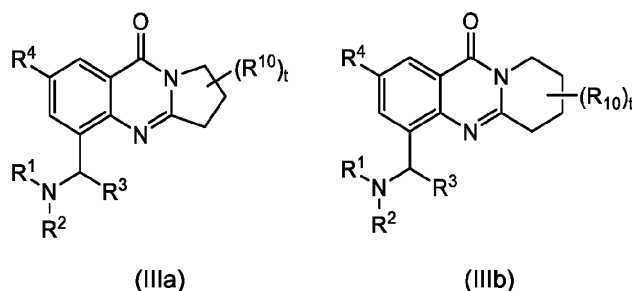
[00159] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R^2 is phenyl or a 5-7 membered heteroaryl substituted with 1, 2 or 3 R^7 groups, and at least one R^7 group is $-C(O)OR^A$.

[00160] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R^2 is substituted with one $-C(O)OR^A$, wherein the $-C(O)OR^A$ is attached to R^2 at a position alpha to the point of attachment of R^2 to the nitrogen atom to which R^2 is attached.

[00161] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R^2 is phenyl or a 5-7 membered heteroaryl, each of which is substituted with 1, 2, 3 or 4 R^7 groups, and at least one R^7 group is $-C(O)OR^A$, wherein the $-C(O)OR^A$ is attached to R^2 at a position alpha to the point of attachment of R^2 to the nitrogen atom to which R^2 is attached.

[00162] In certain embodiments of formulae (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) and (IId-1B) as otherwise described herein, R^2 is phenyl or a 5-7 membered heteroaryl substituted with 1, 2 or 3 R^7 groups, and at least one R^7 group is $-C(O)OR^A$, wherein the $-C(O)OR^A$ is attached to R^2 at a position alpha to the point of attachment of R^2 to the nitrogen atom to which R^2 is attached.

[00163] In certain embodiments of formula (I) as otherwise described herein, the compound is of formula (IIIa) or (IIIb):



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, C_1 - C_3 alkyl, or C_3 - C_6 cycloalkyl;

R² is phenyl or pyridinyl, wherein each phenyl and pyridinyl is optionally substituted with 1-5 R⁷;

each R⁷ is independently C₁-C₄ alkyl; -OR^A, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, -C(O)N(R^B)₂, cyano, halogen or tetrazolyl;

each R^A is independently H, C₁-C₆ alkyl, or C₃-C₆ cycloalkyl;

each R^B is independently H, -OH, C₁-C₆ alkyl, C₁-C₆ alkoxy or C₃-C₆ cycloalkyl;

and

R³ is C₁-C₃ alkyl or C₃-C₆ cycloalkyl; and

R⁴ is H, C₁-C₃ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, or halo, wherein each C₁-C₃ alkyl is optionally substituted with 1-5 halo groups.

[00164] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, each R¹⁰ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino.

[00165] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, t is 1.

[00166] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, t is 2 and both R¹⁰ groups are attached to the same carbon atom.

[00167] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, t is 2 and the R¹⁰ groups are attached to different carbon atoms.

[00168] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, each R¹⁰ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₃)alkyl, hydroxy C₁-C₃ alkyl, amino, or mono- or di(C₁-C₃ alkyl) amino.

[00169] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, each R¹⁰ is independently C₁-C₂ alkyl, C₁-C₂ alkoxy, cyano, hydroxy, halogen, or halo(C₁-C₂)alkyl.

[00170] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, each R¹⁰ is independently C₁-C₂ alkyl, chloro, fluoro, fluoromethyl, difluoromethyl, or trifluoromethyl.

[00171] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, t is 1 and R¹⁰ is C₁-C₂ alkyl, chloro, fluoro, fluoromethyl, difluoromethyl, or trifluoromethyl.

[00172] In certain embodiments of formula (IV) or formula (V) as otherwise described herein, t is 2 and both R^{10} groups are the same and are C_1 - C_2 alkyl, chloro, fluoro, or fluoromethyl.

[00173] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, t is 1 and R^{10} is C_1 - C_2 alkyl, fluoro, fluoromethyl, difluoromethyl, or trifluoromethyl.

[00174] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, t is 1 and R^{10} is C_1 - C_2 alkyl, fluoro or trifluoromethyl.

[00175] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, t is 2 and both R^{10} groups are the same and are methyl, ethyl or fluoro.

[00176] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, t is 2 and both R^{10} groups are the same and are C_1 - C_2 alkyl, fluoro, or fluoromethyl.

[00177] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, t is 1 and R^{10} is R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} or R^{17} .

[00178] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, t is 2 and one R^{10} is C_1 - C_6 alkyl, halogen or halo(C_1 - C_2)alkyl and the other is R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} or R^{17} .

[00179] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, t is 2 and one R^{10} is C_1 - C_2 alkyl, halogen or halo(C_1 - C_2)alkyl and the other is R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} or R^{17} .

[00180] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, t is 2 and one R^{10} is C_1 - C_2 alkyl, chloro, fluoro or halo(C_1 - C_2)alkyl and the other is R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} or R^{17} .

[00181] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, t is 2, both R^{10} groups are attached to the same carbon and one R^{10} is C_1 - C_2 alkyl, chloro, fluoro or halo(C_1 - C_2)alkyl and the other is R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} or R^{17} .

[00182] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, t is 2, the R^{10} groups are attached to different carbon atoms and one R^{10} is C_1 - C_2 alkyl, chloro, fluoro or halo(C_1 - C_2)alkyl and the other is R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} or R^{17} .

[00183] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, t is 1 and R^{10} is R^{11} .

[00184] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, t is 1 and R^{10} is R^{12} .

[00185] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, t is 1 and R¹⁰ is R¹³.

[00186] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, t is 1 and R¹⁰ is R¹⁴.

[00187] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, t is 1 and R¹⁰ is R¹⁵.

[00188] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, t is 1 and R¹⁰ is R¹⁶.

[00189] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, t is 1 and R¹⁰ is R¹⁷.

[00190] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, R¹⁰ is R¹¹ or R¹².

[00191] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, R¹¹ and R¹² are unsubstituted.

[00192] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, R¹¹ and R¹² are substituted with C₁-C₂ alkyl, bromo, chloro, fluoro, fluoromethyl, difluoromethyl, or trifluoromethyl.

[00193] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, wherein t is 2 and one R¹⁰ is C₁-C₆ alkyl, halogen or halo(C₁-C₂)alkyl and the other is R¹¹ wherein R¹¹ is phenyl(C₁-C₆)alkyl and the phenyl is optionally substituted with 1, 2 or 3 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino.

[00194] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, t is 2 and one R¹⁰ is C₁-C₆ alkyl, halogen or halo(C₁-C₂)alkyl and the other is R¹¹ wherein R¹¹ is 5- or 6-membered heteroaryl(C₁-C₆)alkyl and the heteroaryl is optionally substituted with 1, 2 or 3 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino.

[00195] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, the heteroaryl is an optionally substituted pyridyl, thiazolyl, imidazolyl, oxazolyl, or isoxazolyl,

[00196] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, R³ is C₁-C₃ alkyl.

[00197] In certain embodiments of formula (IIIa) or formula (IIIb) as otherwise described herein, R³ is methyl.

[00198] In certain embodiments of formula (IIIa) and formula (IIIb) as otherwise described herein, R⁴ is H, C₁-C₃ alkyl, C₁-C₆ alkoxy, C₃-C₄ cycloalkyl, fluoro, chloro, bromo, cyclopropyl, trifluoromethyl or cyano.

[00199] In certain embodiments of formula (IIIa) and formula (IIIb) as otherwise described herein, R⁴ is hydrogen, methyl, ethyl, ethoxy or cyano.

[00200] In certain embodiments of formula (IIIa) and formula (IIIb) as otherwise described herein, R⁴ is methoxy.

[00201] In certain embodiments of formula (IIIa) and formula (IIIb) as otherwise described herein, R⁴ is fluoro, chloro, or bromo.

[00202] In certain embodiments of formula (IIIa) and formula (IIIb) as otherwise described herein, R⁴ is hydrogen.

[00203] In certain embodiments of formula (IIIa) and formula (IIIb) as otherwise described herein, R⁴ is fluoro.

[00204] In certain embodiments of formula (IIIa) and formula (IIIb) as otherwise described herein, R⁴ is chloro.

[00205] In certain embodiments of formula (IIIa) and formula (IIIb) as otherwise described herein, R⁴ is bromo.

[00206] In certain embodiments of formula (IIIa) and formula (IIIb) as otherwise described herein, R⁴ is methyl.

[00207] In certain embodiments of formula (IIIa) and formula (IIIb) as otherwise described herein, R⁴ is ethyl.

[00208] In certain embodiments of formula (IIIa) and formula (IIIb) as otherwise described herein, R⁴ is cyano.

[00209] In certain embodiments of formula (IIIa) and formula (IIIb) as otherwise described herein, R⁴ is cyclopropyl.

[00210] In certain embodiments of formula (IIIa) and formula (IIIb) as otherwise described herein, R⁴ is trifluoromethyl.

[00211] In certain embodiments of formula (IIIa) and formula (IIIb) as otherwise described herein, R² is phenyl or pyridinyl, each of which is optionally substituted with 1-5 R⁷.

[00212] In certain embodiments of formula (IIIa) and formula (IIIb) as otherwise described herein, R^2 is phenyl or pyridinyl, each of which is optionally substituted with 1-5 R^7 , wherein one R^7 is $-C(O)OR^A$ or $-C(O)N(R^B)_2$, wherein the $-C(O)OR^A$ or $-C(O)N(R^B)_2$ is attached to R^2 at a position alpha, i.e., ortho, to the point of attachment of R^2 to the nitrogen atom to which R^2 is attached.

[00213] In certain embodiments of formula (IIIa) and formula (IIIb) as otherwise described herein, R^2 is phenyl or pyridinyl, each of which is optionally substituted with 1-5 R^7 , wherein at least one R^7 is cyano, wherein the at least one cyano is attached to R^2 at a position alpha to the point of attachment of R^2 to the nitrogen atom to which R^2 is attached.

[00214] In certain embodiments of formula (IIIa) and formula (IIIb) as otherwise described herein, R^2 is phenyl or a 5-7 membered heteroaryl, each of which is substituted with 1, 2, 3 or 4 R^7 groups.

[00215] In certain embodiments of formula (IIIa) and formula (IIIb) as otherwise described herein, R^2 is phenyl or a 5-7 membered heteroaryl substituted with 1, 2 or 3 R^7 groups.

[00216] In certain embodiments of formula (IIIa) and formula (IIIb) as otherwise described herein, R^2 is phenyl or a 5-7 membered heteroaryl, each of which is substituted with 1, 2, 3 or 4 R^7 groups, and at least one R^7 group is $-C(O)OR^A$.

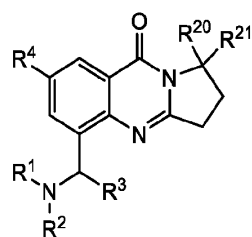
[00217] In certain embodiments of formula (IIIa) and formula (IIIb) as otherwise described herein, R^2 is phenyl or a 5-7 membered heteroaryl substituted with 1, 2 or 3 R^7 groups, and at least one R^7 group is $-C(O)OR^A$.

[00218] In certain embodiments of formula (IIIa) and formula (IIIb) as otherwise described herein, R^2 is substituted with one $-C(O)OR^A$, wherein the $-C(O)OR^A$ is attached to R^2 at a position alpha to the point of attachment of R^2 to the nitrogen atom to which R^2 is attached.

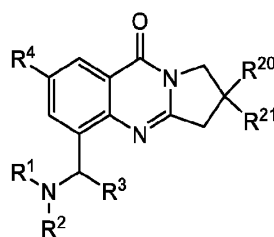
[00219] In certain embodiments of formula (IIIa) and formula (IIIb) as otherwise described herein, R^2 is phenyl or a 5-7 membered heteroaryl, each of which is substituted with 1, 2, 3 or 4 R^7 groups, and at least one R^7 group is $-C(O)OR^A$, wherein the $-C(O)OR^A$ is attached to R^2 at a position alpha to the point of attachment of R^2 to the nitrogen atom to which R^2 is attached.

[00220] In certain embodiments of formula (IIIa) and formula (IIIb) as otherwise described herein, R^2 is phenyl or a 5-7 membered heteroaryl substituted with 1, 2 or 3 R^7 groups, and at least one R^7 group is $-C(O)OR^A$, wherein the $-C(O)OR^A$ is attached to R^2 at a position alpha to the point of attachment of R^2 to the nitrogen atom to which R^2 is attached.

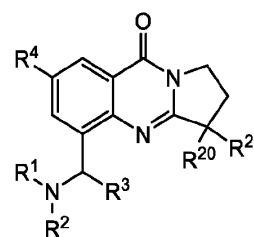
[00221] In certain embodiments, the compound of formula (IIIa) is of formula (IVa), (IVb) or (IVc)



formula (IVa)



formula (IVb).



Formula (IVc)

or a pharmaceutically acceptable salt thereof, wherein:

R¹ is H, C₁-C₃ alkyl, or C₃-C₆ cycloalkyl;

R² is phenyl or pyridinyl, wherein each phenyl and pyridinyl is optionally substituted with 1-5 R⁷;

each R⁷ is independently C₁-C₄ alkyl; -OR^A, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, -C(O)N(R^B)₂, cyano, halogen or tetrazolyl;

each R^A is independently H, C₁-C₆ alkyl, or C₃-C₆ cycloalkyl;

each R^B is independently H, -OH, C₁-C₆ alkyl, C₁-C₆ alkoxy or C₃-C₆ cycloalkyl;

and

R³ is C₁-C₃ alkyl or C₃-C₆ cycloalkyl;

R⁴ is H, C₁-C₃ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, or halo, wherein each C₁-C₃ alkyl is optionally substituted with 1-5 halo groups;

R²⁰ and R²¹ are independently hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino; or

R²⁰ is hydrogen or C₁-C₆ alkyl; and R²¹ is R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶ or R¹⁷ wherein

R¹¹ is aryl or aryl(C₁-C₆)alkyl where each aryl is optionally substituted independently with up to 4 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino;

R¹² is 5-8 membered heteroaryl or 5-8 membered heteroaryl(C₁-C₆)alkyl where each heteroaryl is optionally substituted independently with up to 4 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino;

R¹³ is aryl(C₁-C₆)alkoxy, aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, aryl(C₁-C₆)alkylamino or aryl(C₁-C₆)alkylamino(C₁-C₆)alkyl where each aryl is optionally substituted independently with up to 4 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino;

R¹⁴ is 5-8 membered heteroaryl(C₁-C₆)alkoxy, 5-8 membered heteroaryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, 5-8 membered heteroaryl(C₁-C₆)alkylamino or 5-8 membered heteroaryl(C₁-C₆)alkylamino(C₁-C₆)alkyl where each up to 4 of heteroaryl is optionally substituted independently with C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino;

R¹⁵ is (C₁-C₆)cycloalkyl or (C₁-C₆)cycloalkyl(C₁-C₆)alkyl where each cycloalkyl is optionally substituted independently with up to 4 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino;

R¹⁶ is (C₁-C₆)cycloalkyl(C₁-C₆)alkoxy, (C₁-C₆)cycloalkyl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)cycloalkyl(C₁-C₆)alkylamino or (C₁-C₆)cycloalkyl(C₁-C₆)alkylamino(C₁-C₆)alkyl where each cycloalkyl is optionally substituted independently with up to 4 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino; and

R¹⁷ is 5-8 membered heterocyclyl, 5-8 membered heterocyclyl(C₁-C₆)alkyl, 5-8 membered heterocyclyl(C₁-C₆)alkoxy, 5-8 membered heterocyclyl(C₁-C₆)alkoxy(C₁-C₆)alkyl, 5-8 membered heterocyclyl(C₁-C₆)alkylamino or 5-8 membered heterocyclyl(C₁-C₆)alkylamino(C₁-C₆)alkyl where each 5-8 membered heterocyclyl is optionally substituted independently with up to 4 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino.

[00222] In certain embodiments of formula (IVa), (IVb) and (IVc), R²⁰ and R²¹ are both C₁-C₂ alkyl, fluoro, chloro, or trifluoromethyl.

[00223] In certain embodiments of formula (IVa), (IVb) and (IVc), R²⁰ and R²¹ are both C₁-C₂ alkyl.

[00224] In certain embodiments of formula (IVa), (IVb) and (IVc), R²⁰ and R²¹ are both fluoro.

[00225] In certain embodiments of formula (IVa), (IVb) and (IVc), R²⁰ and R²¹ are both hydrogen.

[00226] In certain embodiments of formula (IVa), (IVb) and (IVc), R²⁰ and R²¹ are both trifluoromethyl.

[00227] In certain embodiments of formula (IVa), (IVb) and (IVc), R²⁰ is hydrogen or methyl and R²¹ is C₁-C₂ alkyl.

[00228] In certain embodiments of formula (IVa), (IVb) and (IVc), R²⁰ is hydrogen or methyl and R²¹ is fluoro.

[00229] In certain embodiments of formula (IVa), (IVb) and (IVc), R²⁰ is hydrogen or methyl and R²¹ is chloro.

[00230] In certain embodiments of formula (IVa), (IVb) and (IVc), R²⁰ is hydrogen and R²¹ is trifluoromethyl.

[00231] In certain embodiments of formula (IVa), (IVb) and (IVc), R²⁰ is hydrogen or methyl and R²¹ is R¹¹.

[00232] In certain embodiments of formula (IVa), (IVb) and (IVc), R²⁰ is hydrogen or methyl and R²¹ is R¹¹ where the R¹¹ aryl is optionally substituted with 1 or 2 of C₁-C₂ alkyl, C₁-C₂ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₂)alkyl, hydroxy C₁-C₂ alkyl, amino, or mono- or di(C₁-C₂ alkyl) amino.

[00233] In certain embodiments of formula (IVa), (IVb) and (IVc), R²⁰ is hydrogen or methyl and R²¹ is R¹².

[00234] In certain embodiments of formula (IVa), (IVb) and (IVc), R²⁰ is hydrogen or methyl and R²¹ is R¹² where the R¹² heteroaryl is optionally substituted with 1 or 2 of C₁-C₂ alkyl, C₁-C₂ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₂)alkyl, hydroxy C₁-C₂ alkyl, amino, or mono- or di(C₁-C₂ alkyl) amino.

[00235] In certain embodiments of formula (IVa), (IVb) and (IVc), as otherwise described herein, R³ is C₁-C₃ alkyl.

[00236] In certain embodiments of formula (IVa), (IVb) and (IVc), as otherwise described herein, R³ is methyl.

[00237] In certain embodiments of formula (IVa), (IVb) and (IVc), as otherwise described herein, R⁴ is H, C₁-C₃ alkyl, C₁-C₆ alkoxy, C₃-C₄ cycloalkyl, fluoro, chloro, bromo, cyclopropyl, trifluoromethyl or cyano.

[00238] In certain embodiments of formula (IVa), (IVb) and (IVc), as otherwise described herein, R⁴ is hydrogen, methyl, methoxy, ethyl, ethoxy or cyano.

[00239] In certain embodiments of formula (IVa), (IVb) and (IVc), as otherwise described herein, R⁴ is fluoro, chloro, or bromo.

[00240] In certain embodiments of formula (IVa), (IVb) and (IVc), as otherwise described herein, R⁴ is hydrogen.

[00241] In certain embodiments of formula (IVa), (IVb) and (IVc), as otherwise described herein, R⁴ is fluoro.

[00242] In certain embodiments of formula (IVa), (IVb) and (IVc), as otherwise described herein, R⁴ is chloro.

[00243] In certain embodiments of formula (IVa), (IVb) and (IVc), as otherwise described herein, R⁴ is bromo.

[00244] In certain embodiments of formula (IVa), (IVb) and (IVc), as otherwise described herein, R⁴ is methyl.

[00245] In certain embodiments of formula (IVa), (IVb) and (IVc), as otherwise described herein, R⁴ is ethyl.

[00246] In certain embodiments of formula (IVa), (IVb) and (IVc) as otherwise described herein, R⁴ is methoxy.

[00247] In certain embodiments of formula (IVa), (IVb) and (IVc), as otherwise described herein, R⁴ is cyano.

[00248] In certain embodiments of formula (IVa), (IVb) and (IVc), as otherwise described herein, R⁴ is cyclopropyl.

[00249] In certain embodiments of formula (IVa), (IVb) and (IVc), as otherwise described herein, R⁴ is trifluoromethyl.

[00250] In certain embodiments of formula (IVa), (IVb) and (IVc) as otherwise described herein, R² is phenyl or pyridinyl, each of which is optionally substituted with 1-5 R⁷.

[00251] In certain embodiments of formula (IVa), (IVb) and (IVc) as otherwise described herein, R² is phenyl or pyridinyl, each of which is optionally substituted with 1-5 R⁷, wherein one R⁷ is -C(O)OR^A or -C(O)N(R^B)₂, wherein the -C(O)OR^A or -C(O)N(R^B)₂ is attached to R² at a position alpha, i.e., ortho, to the point of attachment of R² to the nitrogen atom to which R² is attached.

[00252] In certain embodiments of formula (IVa), (IVb) and (IVc) as otherwise described herein, R² is phenyl or pyridinyl, each of which is optionally substituted with 1-5 R⁷, wherein at least one R⁷ is cyano, wherein the at least one cyano is attached to R² at a position alpha to the point of attachment of R² to the nitrogen atom to which R² is attached.

[00253] In certain embodiments of formula (IVa), (IVb) and (IVc) as otherwise described herein, R² is phenyl or a 5-7 membered heteroaryl, each of which is substituted with 1, 2, 3 or 4 R⁷ groups.

[00254] In certain embodiments of formula (IVa), (IVb) and (IVc) as otherwise described herein, R² is phenyl or a 5-7 membered heteroaryl substituted with 1, 2 or 3 R⁷ groups.

[00255] In certain embodiments of formula (IVa), (IVb) and (IVc) as otherwise described herein, R^2 is phenyl or a 5-7 membered heteroaryl, each of which is substituted with 1, 2, 3 or 4 R^7 groups, and at least one R^7 group is $-C(O)OR^A$.

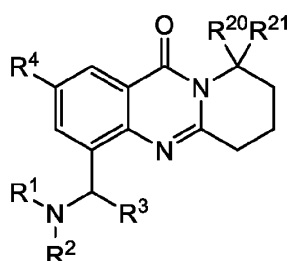
[00256] In certain embodiments of formula (IVa), (IVb) and (IVc) as otherwise described herein, R^2 is phenyl or a 5-7 membered heteroaryl substituted with 1, 2 or 3 R^7 groups, and at least one R^7 group is $-C(O)OR^A$.

[00257] In certain embodiments of formula (IVa), (IVb) and (IVc) as otherwise described herein, R^2 is substituted with one $-C(O)OR^A$, wherein the $-C(O)OR^A$ is attached to R^2 at a position alpha to the point of attachment of R^2 to the nitrogen atom to which R^2 is attached.

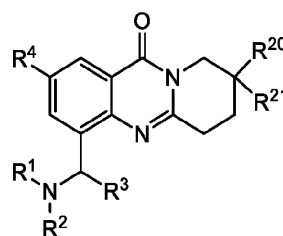
[00258] In certain embodiments of formula (IVa), (IVb) and (IVc) as otherwise described herein, R^2 is phenyl or a 5-7 membered heteroaryl, each of which is substituted with 1, 2, 3 or 4 R^7 groups, and at least one R^7 group is $-C(O)OR^A$, wherein the $-C(O)OR^A$ is attached to R^2 at a position alpha to the point of attachment of R^2 to the nitrogen atom to which R^2 is attached.

[00259] In certain embodiments of formula (IVa), (IVb) and (IVc) as otherwise described herein, R^2 is phenyl or a 5-7 membered heteroaryl substituted with 1, 2 or 3 R^7 groups, and at least one R^7 group is $-C(O)OR^A$, wherein the $-C(O)OR^A$ is attached to R^2 at a position alpha to the point of attachment of R^2 to the nitrogen atom to which R^2 is attached.

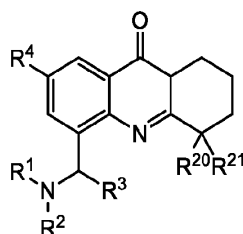
[00260] In certain embodiments, the compound of formula ((IIIb) is of formula (Va), (Vb), (Vc) or (Vd)



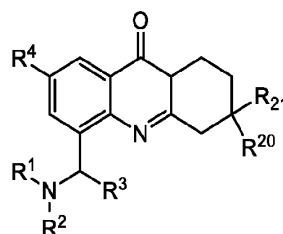
formula (Va)



formula (Vb).



formula (Vc)



formula (Vd)

or a pharmaceutically acceptable salt thereof, wherein:

R¹ is H, C₁-C₃ alkyl, or C₃-C₆ cycloalkyl;

R² is phenyl or pyridinyl, wherein each phenyl and pyridinyl is optionally substituted with 1-5 R⁷;

each R⁷ is independently C₁-C₄ alkyl; -OR^A, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, -C(O)N(R^B)₂, cyano, halogen or tetrazolyl;

each R^A is independently H, C₁-C₆ alkyl, or C₃-C₆ cycloalkyl;

each R^B is independently H, -OH, C₁-C₆ alkyl, C₁-C₆ alkoxy or C₃-C₆ cycloalkyl;

and

R³ is C₁-C₃ alkyl or C₃-C₆ cycloalkyl;

R⁴ is H, C₁-C₃ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, or halo, wherein each C₁-C₃ alkyl is optionally substituted with 1-5 halo groups;

R²⁰ and R²¹ are independently hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino; or

R²⁰ is hydrogen or C₁-C₆ alkyl; and R²¹ is R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶ or R¹⁷ wherein

R¹¹ is aryl or aryl(C₁-C₆)alkyl where each aryl is optionally substituted independently with up to 4 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino;

R¹² is 5-8 membered heteroaryl 5-8 membered heteroaryl(C₁-C₆)alkyl where each heteroaryl is optionally substituted independently with up to 4 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino;

R¹³ is aryl(C₁-C₆)alkoxy, aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, aryl(C₁-C₆)alkylamino or aryl(C₁-C₆)alkylamino(C₁-C₆)alkyl where each aryl is optionally substituted independently with up to 4 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino;

R¹⁴ is 5-8 membered heteroaryl(C₁-C₆)alkoxy, 5-8 membered heteroaryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, 5-8 membered heteroaryl(C₁-C₆)alkylamino or 5-8 membered heteroaryl(C₁-C₆)alkylamino(C₁-C₆)alkyl where each up to 4 of heteroaryl is optionally substituted independently with C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino;

R¹⁵ is (C₁-C₆)cycloalkyl or (C₁-C₆)cycloalkyl(C₁-C₆)alkyl where each cycloalkyl is optionally substituted independently with up to 4 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino;

R¹⁶ is (C₁-C₆)cycloalkyl(C₁-C₆)alkoxy, (C₁-C₆)cycloalkyl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)cycloalkyl(C₁-C₆)alkylamino or (C₁-C₆)cycloalkyl(C₁-C₆)alkylamino(C₁-C₆)alkyl where each cycloalkyl is optionally substituted independently with up to 4 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino; and

R¹⁷ is 5-8 membered heterocyclyl, 5-8 membered heterocyclyl(C₁-C₆)alkyl, 5-8 membered heterocyclyl(C₁-C₆)alkoxy, 5-8 membered heterocyclyl(C₁-C₆)alkoxy(C₁-C₆)alkyl, 5-8 membered heterocyclyl(C₁-C₆)alkylamino or 5-8 membered heterocyclyl(C₁-C₆)alkylamino(C₁-C₆)alkyl where each 5-8 membered heterocyclyl is optionally substituted independently with up to 4 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino.

[00261] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd), R²⁰ and R²¹ are both C₁-C₂ alkyl, fluoro, chloro, or trifluoromethyl.

[00262] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd), R²⁰ and R²¹ are both C₁-C₂ alkyl.

[00263] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd), R²⁰ and R²¹ are both hydrogen.

[00264] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd), R²⁰ and R²¹ are both fluoro.

[00265] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd), R²⁰ and R²¹ are both trifluoromethyl.

[00266] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd), R²⁰ is hydrogen or methyl and R²¹ is C₁-C₂ alkyl.

[00267] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd), R²⁰ is hydrogen or methyl and R²¹ is fluoro.

[00268] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd), R²⁰ is hydrogen or methyl and R²¹ is chloro.

[00269] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd), R²⁰ is hydrogen and R²¹ is trifluoromethyl.

[00270] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd), R²⁰ is hydrogen or methyl and R²¹ is R¹¹.

[00271] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd), R²⁰ is hydrogen or methyl and R²¹ is R¹¹ where the R¹¹ aryl is optionally substituted with 1 or 2 of C₁-C₂ alkyl, C₁-C₂ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₂)alkyl, hydroxy C₁-C₂ alkyl, amino, or mono- or di(C₁-C₂ alkyl) amino.

[00272] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd), R²⁰ is hydrogen or methyl and R²¹ is R¹².

[00273] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd), R²⁰ is hydrogen or methyl and R²¹ is R¹² where the R¹² heteroaryl is optionally substituted with 1 or 2 of C₁-C₂ alkyl, C₁-C₂ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₂)alkyl, hydroxy C₁-C₂ alkyl, amino, or mono- or di(C₁-C₂ alkyl) amino.

[00274] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd), as otherwise described herein, R³ is C₁-C₃ alkyl.

[00275] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd), as otherwise described herein, R³ is methyl.

[00276] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd), as otherwise described herein, R⁴ is H, C₁-C₃ alkyl, C₁-C₆ alkoxy, C₃-C₄ cycloalkyl, fluoro, chloro, bromo or cyano.

[00277] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd), as otherwise described herein, R⁴ is hydrogen, methyl, methoxy, ethyl, ethoxy or cyano.

[00278] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd), as otherwise described herein, R⁴ is fluoro, chloro, or bromo.

[00279] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd), as otherwise described herein, R⁴ is hydrogen.

[00280] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd), as otherwise described herein, R⁴ is fluoro.

[00281] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd), as otherwise described herein, R⁴ is chloro.

[00282] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd), as otherwise described herein, R⁴ is bromo.

[00283] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd), as otherwise described herein, R⁴ is methyl.

[00284] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd), as otherwise described herein, R⁴ is ethyl.

[00285] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd) as otherwise described herein, R⁴ is methoxy.

[00286] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd), as otherwise described herein, R⁴ is cyano.

[00287] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd) as otherwise described herein, R⁴ is cyclopropyl.

[00288] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd) as otherwise described herein, R⁴ is trifluoromethyl.

[00289] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd) as otherwise described herein, R² is phenyl or pyridinyl, each of which is optionally substituted with 1-5 R⁷.

[00290] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd) as otherwise described herein, R² is phenyl or pyridinyl, each of which is optionally substituted with 1-5 R⁷, wherein one R⁷ is -C(O)OR^A or -C(O)N(R^B)₂, wherein the -C(O)OR^A or -C(O)N(R^B)₂ is attached to R² at a position alpha, i.e., ortho, to the point of attachment of R² to the nitrogen atom to which R² is attached.

[00291] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd) as otherwise described herein, R² is phenyl or pyridinyl, each of which is optionally substituted with 1-5 R⁷, wherein at least one R⁷ is cyano, wherein the at least one cyano is attached to R² at a position alpha to the point of attachment of R² to the nitrogen atom to which R² is attached.

[00292] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd) as otherwise described herein, R² is phenyl or a 5-7 membered heteroaryl, each of which is substituted with 1, 2, 3 or 4 R⁷ groups.

[00293] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd) as otherwise described herein, R² is phenyl or a 5-7 membered heteroaryl substituted with 1, 2 or 3 R⁷ groups.

[00294] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd) as otherwise described herein, R² is phenyl or a 5-7 membered heteroaryl, each of which is substituted with 1, 2, 3 or 4 R⁷ groups, and at least one R⁷ group is -C(O)OR^A.

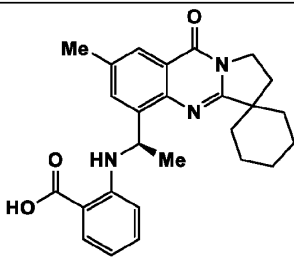
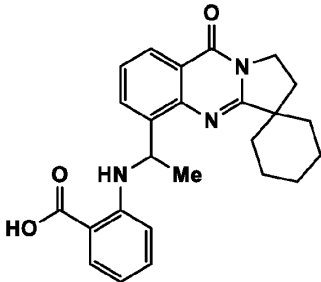
[00295] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd) as otherwise described herein, R^2 is phenyl or a 5-7 membered heteroaryl substituted with 1, 2 or 3 R^7 groups, and at least one R^7 group is $-C(O)OR^A$.

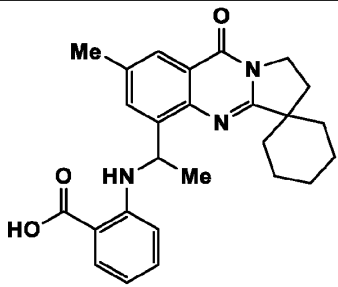
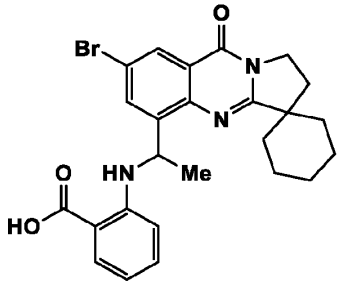
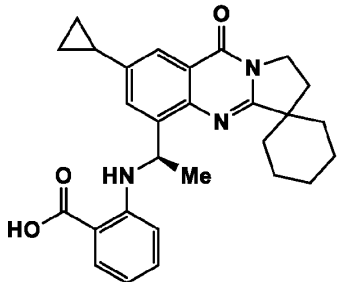
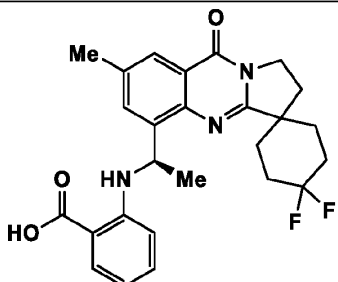
[00296] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd) as otherwise described herein, R^2 is substituted with one $-C(O)OR^A$, wherein the $-C(O)OR^A$ is attached to R^2 at a position alpha to the point of attachment of R^2 to the nitrogen atom to which R^2 is attached.

[00297] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd) as otherwise described herein, R^2 is phenyl or a 5-7 membered heteroaryl, each of which is substituted with 1, 2, 3 or 4 R^7 groups, and at least one R^7 group is $-C(O)OR^A$, wherein the $-C(O)OR^A$ is attached to R^2 at a position alpha to the point of attachment of R^2 to the nitrogen atom to which R^2 is attached.

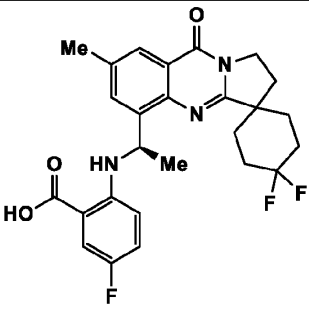
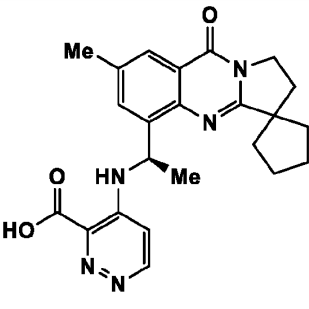
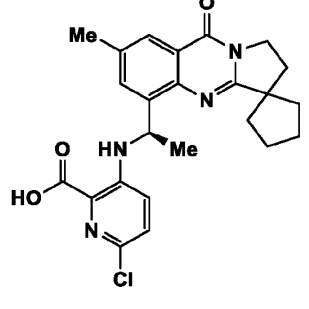
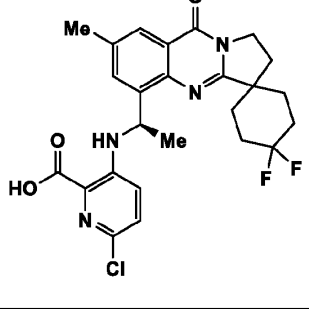
[00298] In certain embodiments of formula (Va), (Vb), (Vc) and (Vd) as otherwise described herein, R^2 is phenyl or a 5-7 membered heteroaryl substituted with 1, 2 or 3 R^7 groups, and at least one R^7 group is $-C(O)OR^A$, wherein the $-C(O)OR^A$ is attached to R^2 at a position alpha to the point of attachment of R^2 to the nitrogen atom to which R^2 is attached.

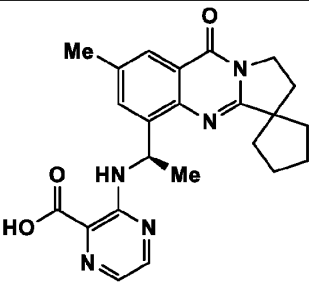
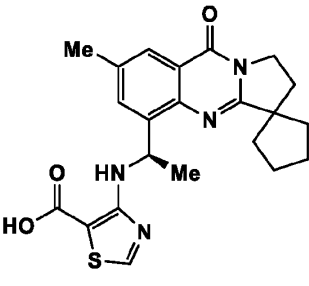
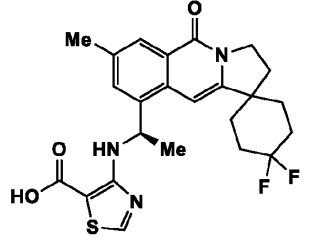
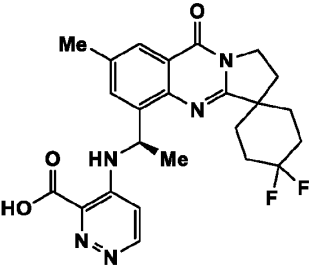
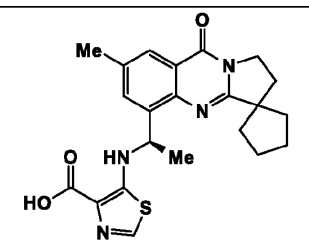
[00299] In one embodiment, the compound of formula (I) is selected from the compounds disclosed in Table 1 below:

No.	Structure	Name
1-1		(R)-2-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-5'-yl)ethyl)amino)benzoic acid;
1-2		2-((1-(9'-oxo-1',2'-dihydro-9'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

1-3		2-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid;
1-4		2-((1-(7'-bromo-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid;
1-5		(<i>R</i>)-2-((1-(7'-cyclopropyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid;
1-6		(<i>R</i>)-2-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

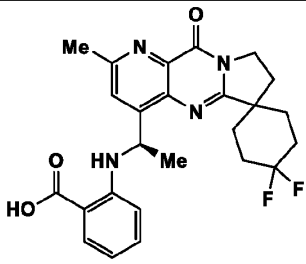
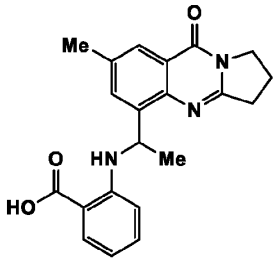
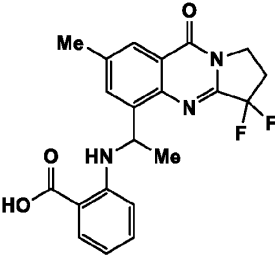
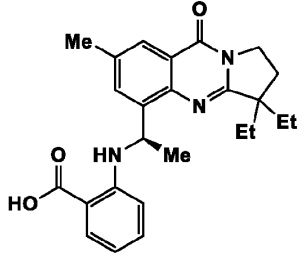
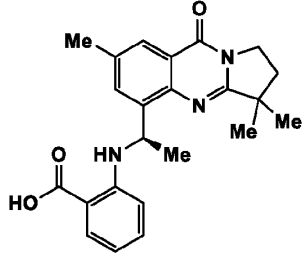
1-7		(<i>R</i>)-2-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclopentane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid;
1-8		(<i>R</i>)-2-((1-(7'-cyano-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclopentane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid;
1-9		(<i>R</i>)-2-((1-(7'-methyl-9'-oxo-1',2,2',3,5,6-hexahydro-9' <i>H</i> -spiro[pyran-4,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid; or
1-10		(<i>R</i>)-5-fluoro-2-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclopentane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid

1-11		(<i>R</i>)-2-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)-5-fluorobenzoic acid
1-12		(<i>R</i>)-4-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclopentane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)pyridazine-3-carboxylic acid
1-13		(<i>R</i>)-6-chloro-3-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclopentane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-14		(<i>R</i>)-6-chloro-3-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid

1-15		(<i>R</i>)-3-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclopentane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)pyrazine-2-carboxylic acid
1-16		(<i>R</i>)-4-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclopentane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)thiazole-5-carboxylic acid
1-17		(<i>R</i>)-4-((1-(4,4-difluoro-7'-methyl-5'-oxo-2',3'-dihydro-5' <i>H</i> -spiro[cyclohexane-1,1'-pyrrolo[1,2- <i>b</i>]isoquinolin]-9'-yl)ethyl)amino)thiazole-5-carboxylic acid
1-18		(<i>R</i>)-4-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)pyridazine-3-carboxylic acid
1-19		(<i>R</i>)-5-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclopentane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)thiazole-4-carboxylic acid

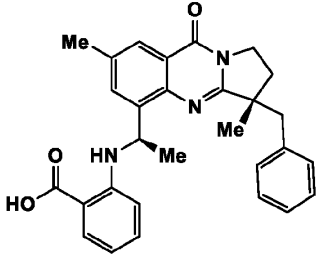
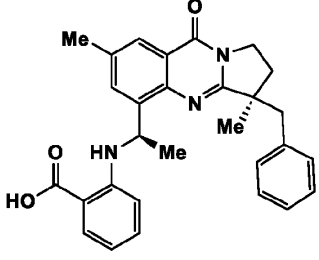
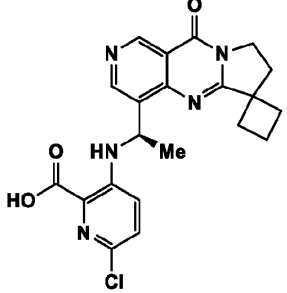
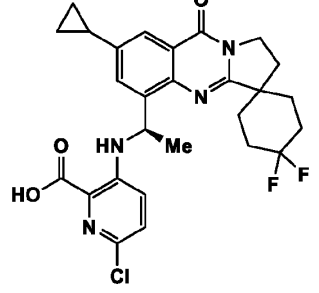
1-20		(<i>R</i>)-5-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)thiazole-4-carboxylic acid
1-21		(<i>R</i>)-3-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)pyrazine-2-carboxylic acid
1-22		(<i>R</i>)-6-chloro-3-((1-(7'-methyl-9'-oxo-1',2,2',3,5,6-hexahydro-9' <i>H</i> -spiro[pyran-4,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-23		(<i>R</i>)-2-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-24		(<i>R</i>)-2-((1-(7'-methyl-9'-oxo-3',9'-dihydro-1' <i>H</i> -spiro[cyclobutane-1,2'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid

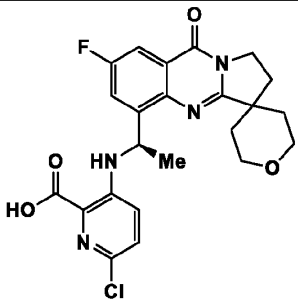
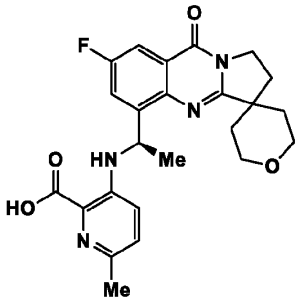
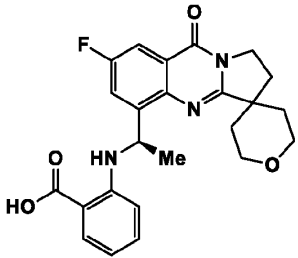
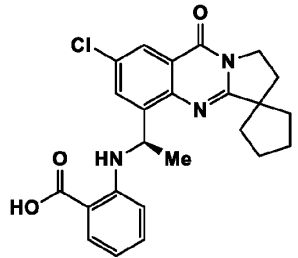
1-25		(<i>R</i>)-2-((1-(7'-methyl-9'-oxo-1-phenyl-1',2'-dihydro-9' <i>H</i> -spiro[azetidine-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-26		(<i>R</i>)-2-((1-(1-(4-cyanophenyl)-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[azetidine-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-27		(<i>R</i>)-2-((1-(1-(4-cyano-2-methylphenyl)-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[azetidine-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-28		(<i>R</i>)-2-((1-(2'-methyl-10'-oxo-7',8'-dihydro-10' <i>H</i> -spiro[cyclopentane-1,6'-pyrido[3,2- <i>d</i>]pyrrolo[1,2- <i>a</i>]pyrimidin]-4'-yl)ethyl)amino)benzoic acid
1-29		(<i>R</i>)-2-((1-(2'-methyl-11'-oxo-8',9'-dihydro-7' <i>H</i> ,11' <i>H</i> -spiro[cyclopentane-1,6'-pyrido[2,1- <i>b</i>]quinazolin]-4'-yl)ethyl)amino)benzoic acid

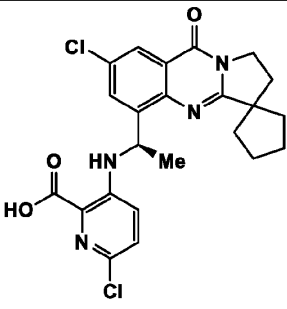
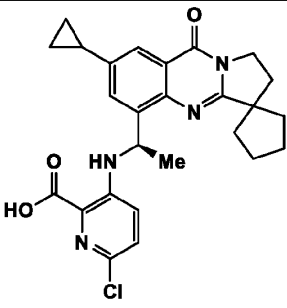
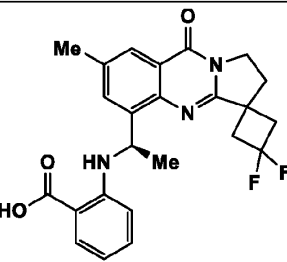
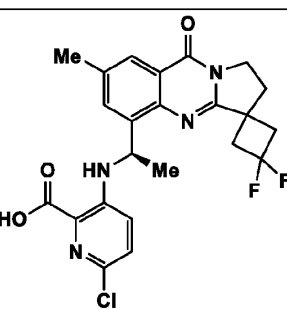
1-30		(R)-2-((1-(4,4-difluoro-2'-methyl-10'-oxo-7',8'-dihydro-10'H-spiro[cyclohexane-1,6'-pyrido[3,2-d]pyrrolo[1,2-a]pyrimidin]-4'-yl)ethyl)amino)benzoic acid
1-31		2-((1-(7-methyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethyl)amino)benzoic acid
1-32		2-((1-(3,3-difluoro-7-methyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethyl)amino)benzoic acid
1-33		(R)-2-((1-(3,3-diethyl-7-methyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethyl)amino)benzoic acid
1-34		(R)-2-((1-(3,3,7-trimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethyl)amino)benzoic acid

1-35		(<i>R</i>)-6-chloro-3-((1-(3,3,7-trimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1- <i>b</i>]quinazolin-5-yl)ethyl)amino)picolinic acid
1-36		(<i>R</i>)-6-chloro-3-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-37		(<i>R</i>)-6-chloro-4-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)pyridazine-3-carboxylic acid
1-38		(<i>R</i>)-2-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclopropane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-39		(<i>R</i>)-3-((1-(3,3,7-trimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1- <i>b</i>]quinazolin-5-yl)ethyl)amino)pyrazine-2-carboxylic acid

1-40		(R)-5-((1-(7'-methyl-9'-oxo-1',2,2',3,5,6-hexahydro-9' <i>H</i> -spiro[pyran-4,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)thiazole-4-carboxylic acid
1-41		(R)-3-((1-(7'-methyl-9'-oxo-1',2,2',3,5,6-hexahydro-9' <i>H</i> -spiro[pyran-4,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)pyrazine-2-carboxylic acid
1-42		(R)-2-((1-(7'-cyclopropyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-43		(R)-6-chloro-3-((1-(7'-cyclopropyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid

1-44 and 1-45	 And 	2-(((<i>R</i>)-1-((<i>S</i>)-3-benzyl-3,7-dimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-<i>b</i>]quinazolin-5-yl)ethyl)amino)benzoic acid And 2-(((<i>R</i>)-1-((<i>R</i>)-3-benzyl-3,7-dimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-<i>b</i>]quinazolin-5-yl)ethyl)amino)benzoic acid
1-46		(<i>R</i>)-6-chloro-3-((1-(10'-oxo-7',8'-dihydro-10'<i>H</i>-spiro[cyclobutane-1,6'-pyrido[4,3-<i>d</i>]pyrrolo[1,2-<i>a</i>]pyrimidin]-4'-yl)ethyl)amino)picolinic acid
1-47		(<i>R</i>)-6-chloro-3-((1-(7'-cyclopropyl-4,4-difluoro-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclohexane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid

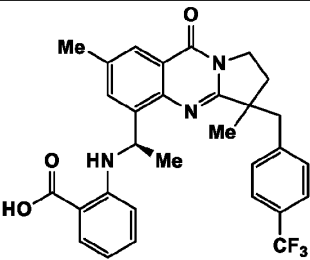
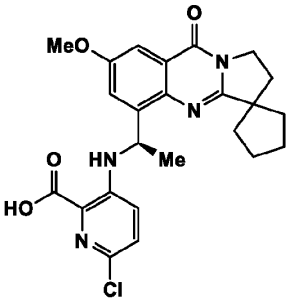
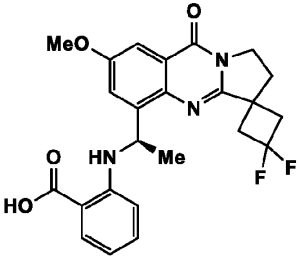
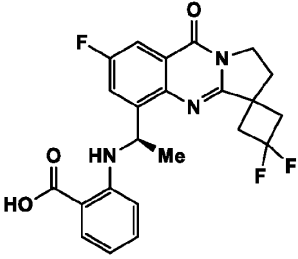
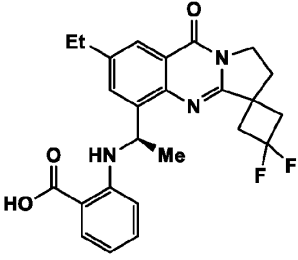
1-48		(<i>R</i>)-6-chloro-3-((1-(7'-fluoro-9'-oxo-1',2,2',3,5,6-hexahydro-9' <i>H</i> -spiro[pyran-4,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-49		(<i>R</i>)-3-((1-(7'-fluoro-9'-oxo-1',2,2',3,5,6-hexahydro-9' <i>H</i> -spiro[pyran-4,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)-6-methylpicolinic acid
1-50		(<i>R</i>)-2-((1-(7'-fluoro-9'-oxo-1',2,2',3,5,6-hexahydro-9' <i>H</i> -spiro[pyran-4,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-51		(<i>R</i>)-2-((1-(7'-chloro-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclopentane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid

1-52		(<i>R</i>)-6-chloro-3-((1-(7'-chloro-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclopentane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-53		(<i>R</i>)-6-chloro-3-((1-(7'-cyclopropyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclopentane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-54		(<i>R</i>)-2-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-55		(<i>R</i>)-6-chloro-3-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid

1-56		(<i>R</i>)-2-((1-(7'-chloro-3,3-difluoro-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-57		(<i>R</i>)-2-((1-(3,3-difluoro-9'-oxo-7'-(trifluoromethyl)-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-58		(<i>R</i>)-6-chloro-3-((1-(3,3-difluoro-9'-oxo-7'-(trifluoromethyl)-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-59 and 1-60	 And 	2-(((<i>R</i>)-1-((<i>S</i>)-2,2-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclopentane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid and 2-(((<i>R</i>)-1-((<i>R</i>)-2,2-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclopentane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid

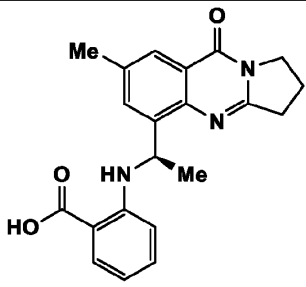
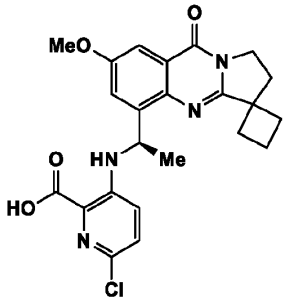
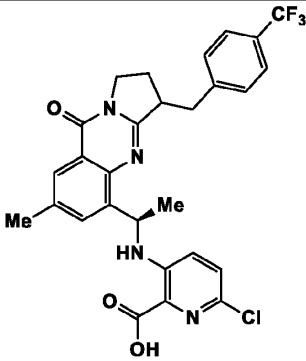
1-61		(<i>R</i>)-2-((1-(7'-ethyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-62		(<i>R</i>)-2-((1-(7'-ethyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclopentane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-63		(<i>R</i>)-6-chloro-3-((1-(7'-ethyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-64 and 1-65	 And 	2-(((<i>R</i>)-1-((<i>S</i>)-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclopentane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid And 2-(((<i>R</i>)-1-((<i>R</i>)-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclopentane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid

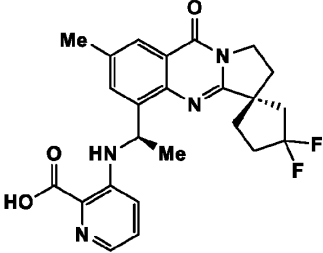
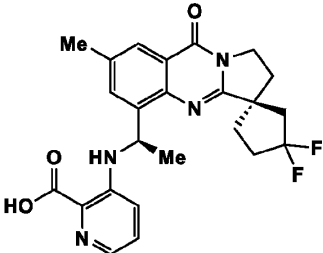
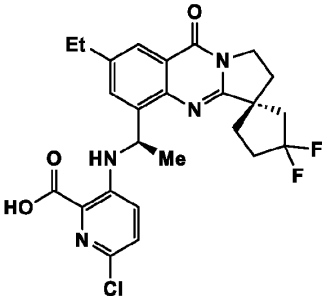
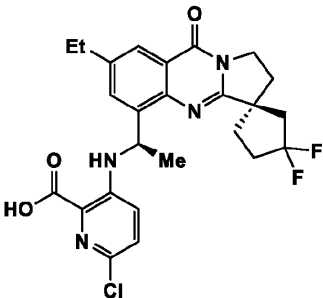
1-66 and 1-67	And	6-chloro-3-(((<i>R</i>)-1-((<i>S</i>)-2,2-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid And 6-chloro-3-(((<i>R</i>)-1-((<i>R</i>)-2,2-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-68		2-(((1<i>R</i>)-1-(3,7-dimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-<i>b</i>]quinazolin-5-yl)ethyl)amino)benzoic acid
1-69		(<i>R</i>)-2-((1-(7'-methoxy-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid

1-70		2-(((1 <i>R</i>)-1-(3,7-dimethyl-9-oxo-3-(4-(trifluoromethyl)benzyl)-1,2,3,9-tetrahydropyrrolo[2,1- <i>b</i>]quinazolin-5-yl)ethyl)amino)benzoic acid
1-71		(<i>R</i>)-6-chloro-3-((1-(7'-methoxy-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclopentane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-72		(<i>R</i>)-2-((1-(3,3-difluoro-7'-methoxy-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-73		(<i>R</i>)-2-((1-(3,3,7'-trifluoro-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-74		(<i>R</i>)-2-((1-(7'-ethyl-3,3-difluoro-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid

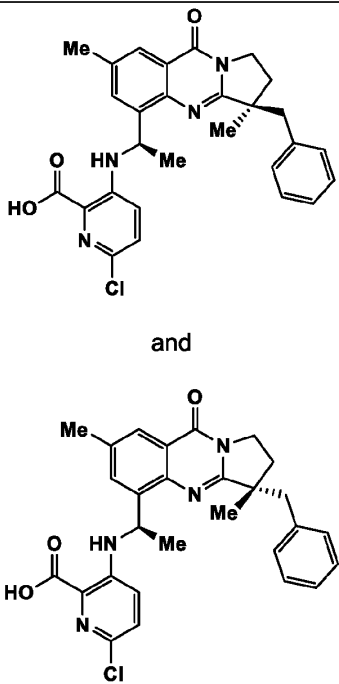
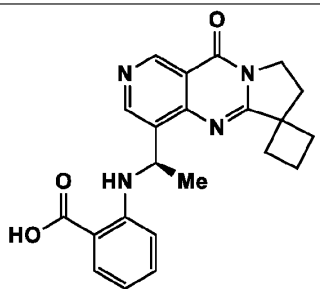
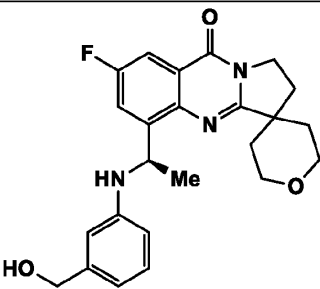
1-75		(<i>R</i>)-6-chloro-3-((1-(3,3-difluoro-7'-methoxy-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-76		(<i>R</i>)-6-chloro-3-((1-(3,3,7'-trifluoro-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-77		(<i>R</i>)-6-chloro-3-((1-(7'-ethyl-3,3-difluoro-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-78		2-(((<i>R</i>)-1-((<i>R</i>)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclopentane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid

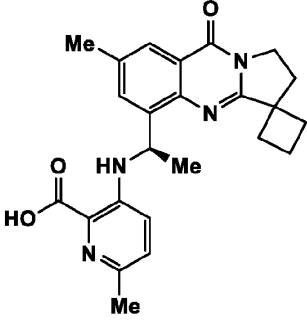
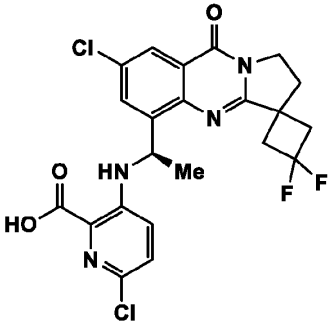
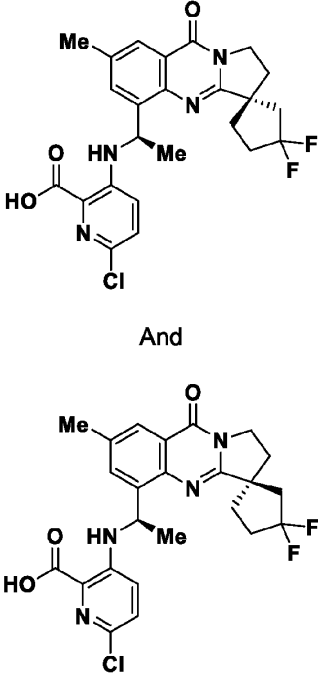
1-79		2-(((<i>R</i>)-1-((<i>S</i>)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclopentane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-80		2-(((<i>R</i>)-1-((<i>R</i>)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-81		2-(((<i>R</i>)-1-((<i>S</i>)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-82		6-chloro-3-(((<i>R</i>)-1-((<i>R</i>)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclopentane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-83		6-chloro-3-(((<i>R</i>)-1-((<i>S</i>)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclopentane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid

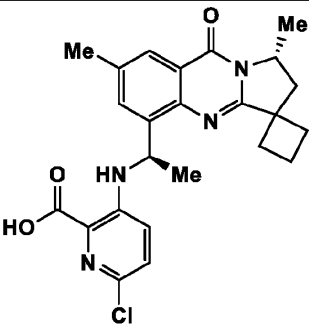
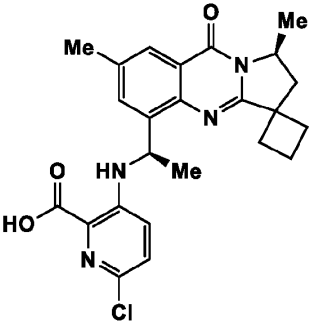
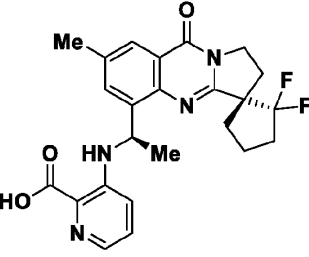
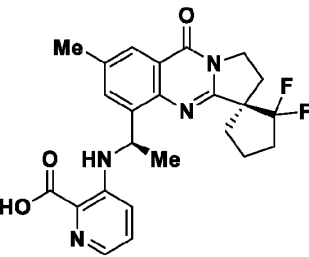
1-84		(<i>R</i>)-2-((1-(7-methyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1- <i>b</i>]quinazolin-5-yl)ethyl)amino)benzoic acid
1-85		(<i>R</i>)-6-chloro-3-((1-(7'-methoxy-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-86		6-chloro-3-(((1 <i>R</i>)-1-(7-methyl-9-oxo-3-(4-(trifluoromethyl)benzyl)-1,2,3,9-tetrahydropyrrolo[2,1- <i>b</i>]quinazolin-5-yl)ethyl)amino)picolinic acid

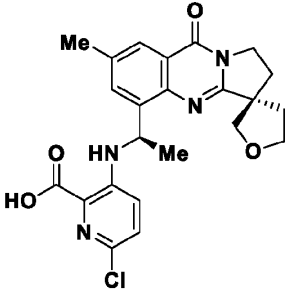
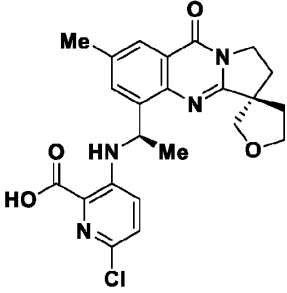
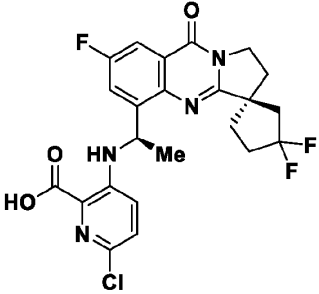
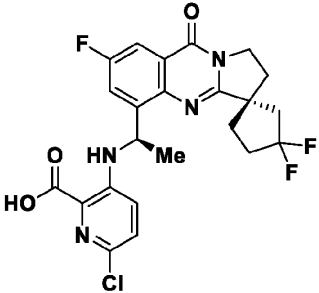
1-87 and 1-88	 And 	3-(((<i>R</i>)-1-((<i>R</i>)-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid And 3-(((<i>R</i>)-1-((<i>S</i>)-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-89 and 1-90	 And 	6-chloro-3-(((<i>R</i>)-1-((<i>R</i>)-7'-ethyl-3,3-difluoro-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid And 6-chloro-3-(((<i>R</i>)-1-((<i>S</i>)-7'-ethyl-3,3-difluoro-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid

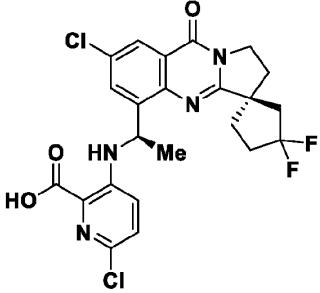
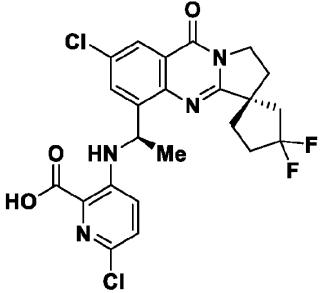
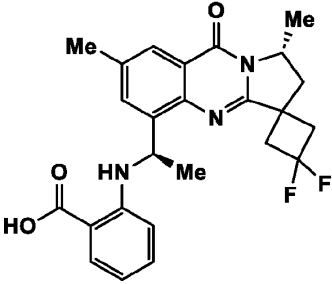
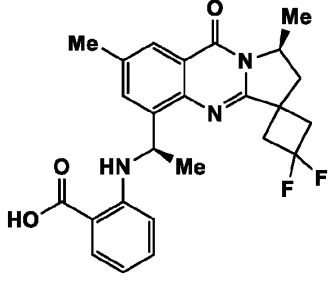
1-91		2-((1-(3,3-difluoro-7-methyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1- <i>b</i>]quinazolin-5-yl)ethyl)amino)benzoic acid
1-92		(<i>R</i>)-3-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)thiophene-2-carboxylic acid
1-93		(<i>R</i>)-2-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)thiophene-3-carboxylic acid
1-94		(<i>R</i>)-3-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)pyrazine-2-carboxylic acid
1-95		(<i>R</i>)-5-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)thiazole-4-carboxylic acid

1-96 and 1-97	 and	3-(((<i>R</i>)-1-((<i>R</i>)-3-benzyl-3,7-dimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-<i>b</i>]quinazolin-5-yl)ethyl)amino)-6-chloropicolinic acid And 3-(((<i>R</i>)-1-((<i>S</i>)-3-benzyl-3,7-dimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1- <i>b</i>]quinazolin-5-yl)ethyl)amino)-6-chloropicolinic acid
1-98		(<i>R</i>)-2-((1-(10'-oxo-7',8'-dihydro-10'<i>H</i>-spiro[cyclobutane-1,6'-pyrido[4,3-<i>d</i>]pyrrolo[1,2-<i>a</i>]pyrimidin]-4'-yl)ethyl)amino)benzoic acid
1-99		(<i>R</i>)-7'-fluoro-5'-(1-((3-(hydroxymethyl)phenyl)amino)ethyl)-1',2,2',3,5,6-hexahydro-9'<i>H</i>-spiro[pyran-4,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-9'-one

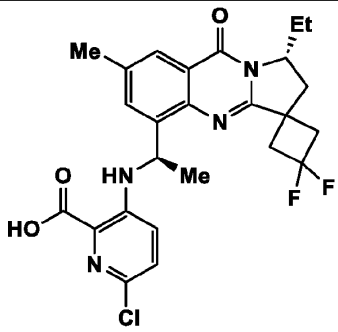
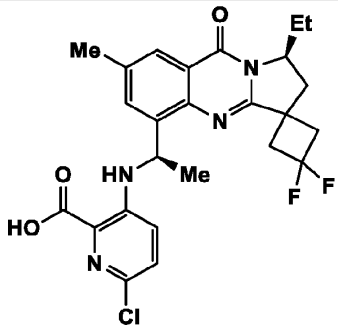
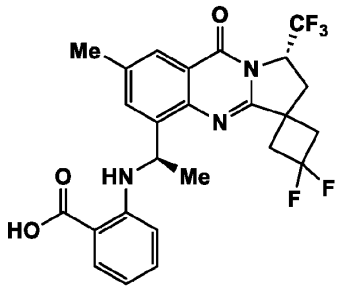
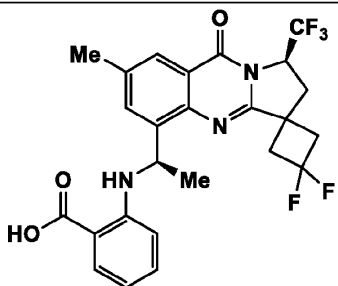
1-100		(R)-6-methyl-3-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-101		(R)-6-chloro-3-((1-(7'-chloro-3,3-difluoro-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-102 and 1-103	 And	6-chloro-3-(((<i>R</i>)-1-(((<i>R</i>)-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid And 6-chloro-3-(((<i>R</i>)-1-(((<i>S</i>)-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid

1-104		6-chloro-3-(((<i>R</i>)-1-((<i>R</i>)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-105		6-chloro-3-(((<i>R</i>)-1-((<i>S</i>)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-106 And 1-107	 And 	6-chloro-3-(((1 <i>R</i>)-1-(2,2-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclopentane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid And 6-chloro-3-(((<i>R</i>)-1-((<i>R</i>)-2,2-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclopentane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid

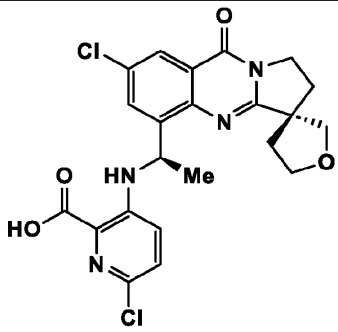
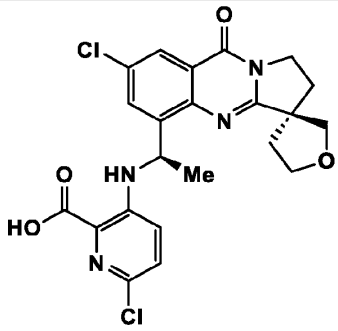
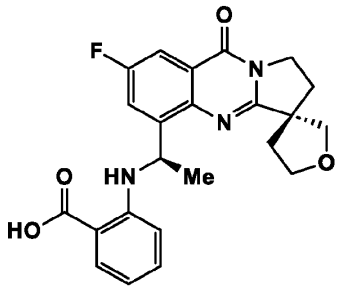
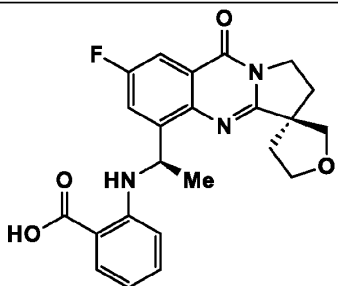
1-108 And 1-109	 And 	6-chloro-3-(((<i>R</i>)-1-((<i>S</i>)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid And 6-chloro-3-(((<i>R</i>)-1-((<i>R</i>)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-110 And 1-111	 And 	6-chloro-3-(((<i>R</i>)-1-((<i>S</i>)-3,3,7'-trifluoro-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid And 6-chloro-3-(((<i>R</i>)-1-((<i>R</i>)-3,3,7'-trifluoro-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid

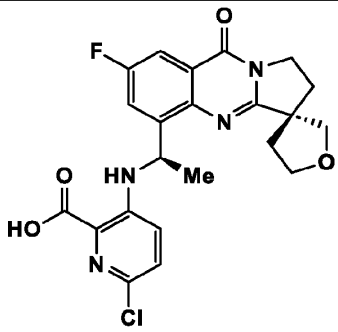
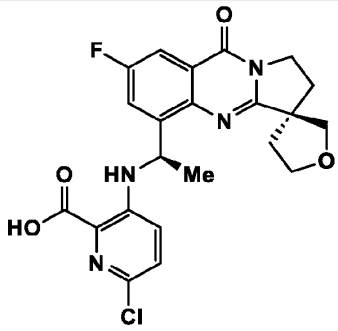
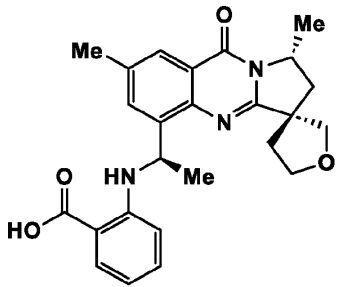
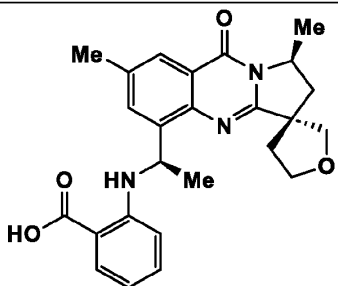
1-112 And 1-113	 And 	6-chloro-3-(((<i>R</i>)-1-((<i>S</i>)-7'-chloro-3,3-difluoro-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid And 6-chloro-3-(((<i>R</i>)-1-((<i>R</i>)-7'-chloro-3,3-difluoro-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-114		2-(((<i>R</i>)-1-((<i>R</i>)-3,3-difluoro-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-115		2-(((<i>R</i>)-1-((<i>S</i>)-3,3-difluoro-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid

1-116		6-chloro-3-(((<i>R</i>)-1-((<i>R</i>)-3,3-difluoro-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-117		6-chloro-3-(((<i>R</i>)-1-((<i>S</i>)-3,3-difluoro-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-118		2-(((<i>R</i>)-1-((<i>R</i>)-1'-ethyl-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-119		2-(((<i>R</i>)-1-((<i>S</i>)-1'-ethyl-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid

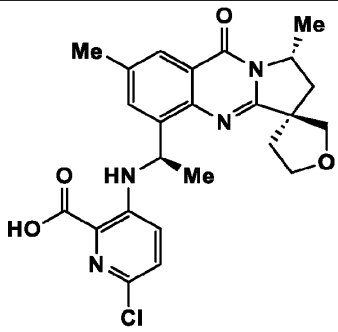
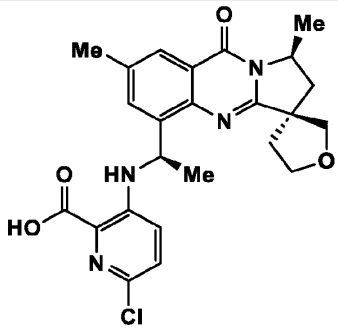
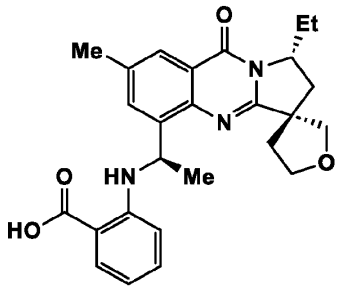
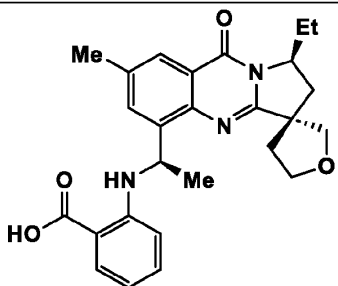
1-120		6-chloro-3-(((<i>R</i>)-1-((<i>R</i>)-1'-ethyl-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-121		6-chloro-3-(((<i>R</i>)-1-((<i>S</i>)-1'-ethyl-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-122		2-(((<i>R</i>)-1-((<i>S</i>)-3,3-difluoro-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-123		2-(((<i>R</i>)-1-((<i>R</i>)-3,3-difluoro-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid

1-124		6-chloro-3-(((<i>R</i>)-1-((<i>S</i>)-3,3-difluoro-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-125		6-chloro-3-(((<i>R</i>)-1-((<i>R</i>)-3,3-difluoro-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-126		2-(((<i>R</i>)-1-((<i>R</i>)-7'-chloro-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-127		2-(((<i>R</i>)-1-((<i>S</i>)-7'-chloro-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid

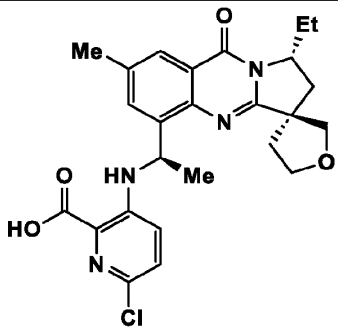
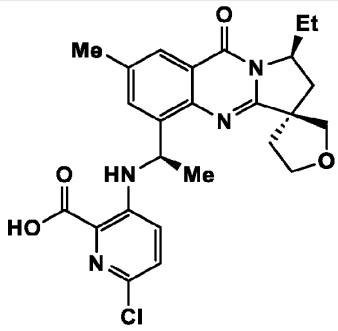
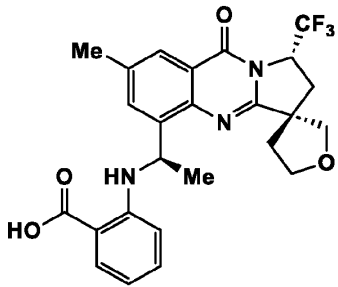
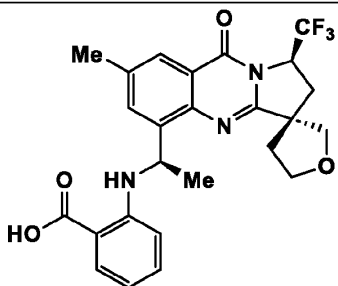
1-128		6-chloro-3-(((<i>R</i>)-1-((<i>R</i>)-7'-chloro-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-129		6-chloro-3-(((<i>R</i>)-1-((<i>S</i>)-7'-chloro-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-130		2-(((<i>R</i>)-1-((<i>R</i>)-7'-fluoro-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-131		2-(((<i>R</i>)-1-((<i>S</i>)-7'-fluoro-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid

1-132		6-chloro-3-(((<i>R</i>)-1-((<i>R</i>)-7'-fluoro-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-133		6-chloro-3-(((<i>R</i>)-1-((<i>S</i>)-7'-fluoro-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-134		2-(((<i>R</i>)-1-((1' <i>R</i> ,3 <i>R</i>)-1',7'-dimethyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-135		2-(((<i>R</i>)-1-((1' <i>S</i> ,3 <i>R</i>)-1',7'-dimethyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid

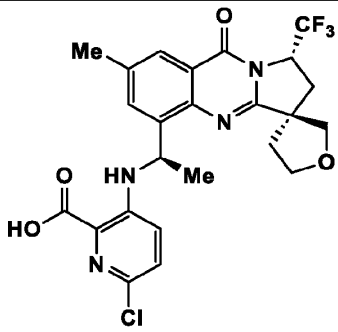
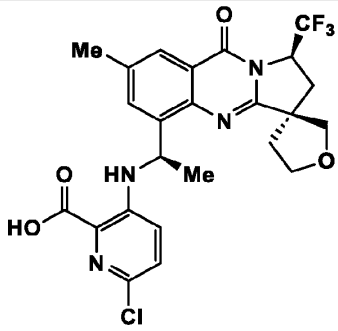
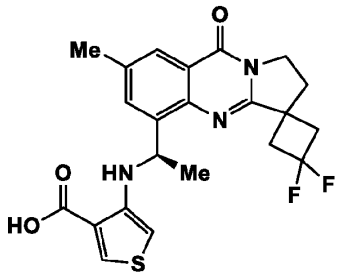
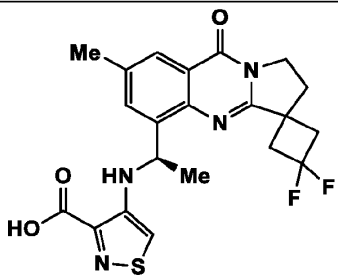
1-136		2-(((<i>R</i>)-1-((1' <i>R</i> ,3 <i>S</i>)-1',7'-dimethyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-137		2-(((<i>R</i>)-1-((1' <i>S</i> ,3 <i>S</i>)-1',7'-dimethyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-138		6-chloro-3-(((<i>R</i>)-1-((1' <i>R</i> ,3 <i>R</i>)-1',7'-dimethyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-139		6-chloro-3-(((<i>R</i>)-1-((1' <i>S</i> ,3 <i>R</i>)-1',7'-dimethyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid

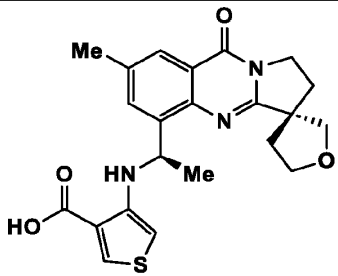
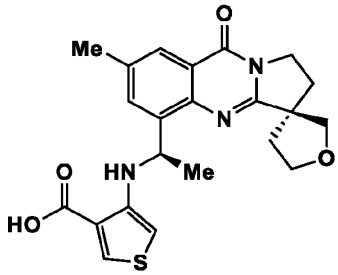
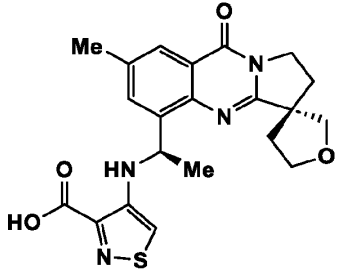
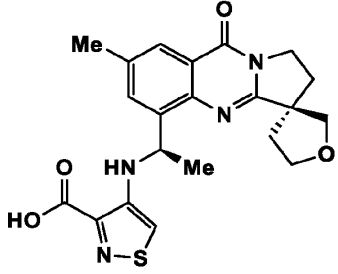
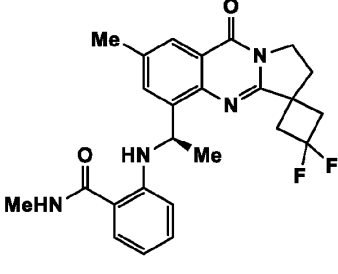
1-140		6-chloro-3-(((<i>R</i>)-1-((1' <i>R</i> ,3 <i>S</i>)-1',7'-dimethyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-141		6-chloro-3-(((<i>R</i>)-1-((1' <i>S</i> ,3 <i>S</i>)-1',7'-dimethyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-142		2-(((<i>R</i>)-1-((1' <i>R</i> ,3 <i>R</i>)-1'-ethyl-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-143		2-(((<i>R</i>)-1-((1' <i>S</i> ,3 <i>R</i>)-1'-ethyl-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid

1-144		2-(((<i>R</i>)-1-(((1' <i>R</i> ,3 <i>S</i>)-1'-ethyl-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-145		2-(((<i>R</i>)-1-(((1' <i>S</i> ,3 <i>S</i>)-1'-ethyl-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-146		6-chloro-3-(((<i>R</i>)-1-(((1' <i>R</i> ,3 <i>R</i>)-1'-ethyl-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-147		6-chloro-3-(((<i>R</i>)-1-(((1' <i>S</i> ,3 <i>R</i>)-1'-ethyl-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid

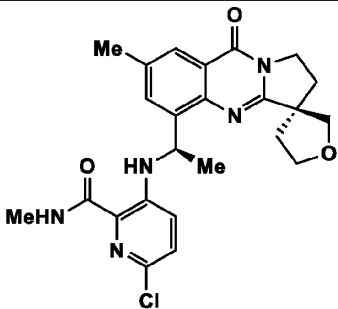
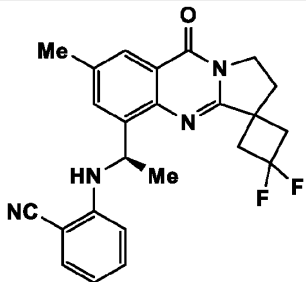
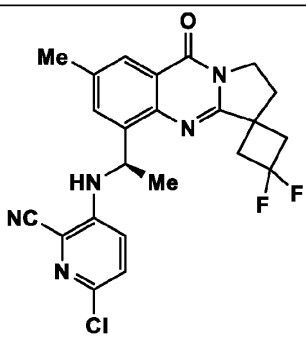
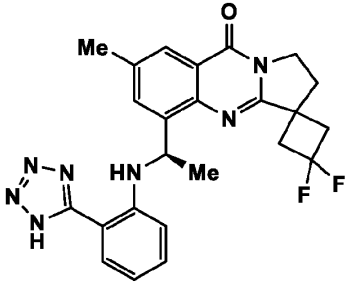
1-148		6-chloro-3-(((<i>R</i>)-1-((1' <i>R</i> ,3 <i>S</i>)-1'-ethyl-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-149		6-chloro-3-(((<i>R</i>)-1-((1' <i>S</i> ,3 <i>S</i>)-1'-ethyl-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-150		2-(((<i>R</i>)-1-((1' <i>S</i> ,3 <i>R</i>)-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-151		2-(((<i>R</i>)-1-((1' <i>R</i> ,3 <i>R</i>)-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid

1-152		2-(((<i>R</i>)-1-((1' <i>S</i> ,3 <i>S</i>)-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-153		2-(((<i>R</i>)-1-((1' <i>R</i> ,3 <i>S</i>)-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-154		6-chloro-3-(((<i>R</i>)-1-((1' <i>S</i> ,3 <i>R</i>)-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-155		6-chloro-3-(((<i>R</i>)-1-((1' <i>R</i> ,3 <i>R</i>)-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid

1-156		6-chloro-3-(((<i>R</i>)-1-((1' <i>S</i> ,3 <i>S</i>)-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-157		6-chloro-3-(((<i>R</i>)-1-((1' <i>R</i> ,3 <i>S</i>)-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-158		(<i>R</i>)-4-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)thiophene-3-carboxylic acid
1-159		(<i>R</i>)-4-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)isothiazole-3-carboxylic acid

1-160		4-(((<i>R</i>)-1-((<i>R</i>)-7-methyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)thiophene-3-carboxylic acid
1-161		4-(((<i>R</i>)-1-((<i>S</i>)-7-methyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)thiophene-3-carboxylic acid
1-162		4-(((<i>R</i>)-1-((<i>R</i>)-7-methyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)isothiazole-3-carboxylic acid
1-163		4-(((<i>R</i>)-1-((<i>S</i>)-7-methyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)isothiazole-3-carboxylic acid
1-164		(<i>R</i>)-2-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)- <i>N</i> -methylbenzamide

1-165		(<i>R</i>)-6-chloro-3-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)- <i>N</i> -methylpicolinamide
1-166		<i>N</i> -methyl-2-(((<i>R</i>)-1-((<i>R</i>)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzamide
1-167		<i>N</i> -methyl-2-(((<i>R</i>)-1-((<i>S</i>)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzamide
1-168		6-chloro- <i>N</i> -methyl-3-(((<i>R</i>)-1-((<i>R</i>)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinamide

1-169		6-chloro- <i>N</i> -methyl-3-(((<i>R</i>)-1-((<i>S</i>)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinamide
1-170		(<i>R</i>)-2-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzonitrile
1-171		(<i>R</i>)-6-chloro-3-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinonitrile
1-172		(<i>R</i>)-5'-(1-((2-(1 <i>H</i> -tetrazol-5-yl)phenyl)amino)ethyl)-3,3-difluoro-7'-methyl-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-9'-one

1-173		(<i>R</i>)-5'-((6-chloro-2-(1H-tetrazol-5-yl)pyridin-3-yl)amino)ethyl)-3,3-difluoro-7'-methyl-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-9'-one
1-174		ethyl (<i>R</i>)-2-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoate
1-175		ethyl (<i>R</i>)-6-chloro-3-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclobutane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinate
1-176		ethyl 2-(((<i>R</i>)-1-((<i>R</i>)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoate

1-177		ethyl 2-(((<i>R</i>)-1-((<i>S</i>)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoate
1-178		ethyl 6-chloro-3-(((<i>R</i>)-1-((<i>R</i>)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinate
1-179		ethyl 6-chloro-3-(((<i>R</i>)-1-((<i>S</i>)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2 <i>H</i> ,9' <i>H</i> -spiro[furan-3,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinate

or a pharmaceutically acceptable salt of one of the foregoing compounds.

PHARMACEUTICAL COMPOSITIONS

[00300] The compounds of Formula I may be formulated into pharmaceutical compositions.

[00301] In another aspect, the invention provides pharmaceutical compositions comprising a PI3K α inhibitor according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent. Compounds of the invention may be formulated by any method well known in the art and may be prepared for administration by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal. In

certain embodiments, compounds of the invention are administered intravenously in a hospital setting. In certain other embodiments, administration may preferably be by the oral route.

[00302] The characteristics of the carrier will depend on the route of administration. As used herein, the term “pharmaceutically acceptable” means a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism, and that does not interfere with the effectiveness of the biological activity of the active ingredient(s). Thus, compositions according to the invention may contain, in addition to the inhibitor, diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The preparation of pharmaceutically acceptable formulations is described in, e.g., Remington’s Pharmaceutical Sciences, 18th Edition, ed. A. Gennaro, Mack Publishing Co., Easton, Pa., 1990.

[00303] As used herein, the term “pharmaceutically acceptable salts” refers to salts that retain the desired biological activity of the above-identified compounds and exhibit minimal or no undesired toxicological effects. Examples of such salts include, but are not limited to acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, and polygalacturonic acid. The compounds can also be administered as pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include the quaternary ammonium salt of the formula $-NR^+Z^-$, wherein R is hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, $-O$ -alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamate, mandelate, benzyloate, and diphenylacetate).

[00304] The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount without causing serious toxic effects in the patient treated. A dose of the active compound for all of the above-mentioned conditions is in the range from about 0.01 to 300 mg/kg, preferably 0.1 to 100 mg/kg per day, more generally 0.5 to about 25 mg per kilogram body weight of the recipient per day. A typical topical dosage will range from 0.01-3% wt/wt in a suitable carrier. The effective dosage range of the pharmaceutically acceptable derivatives can be calculated based on the weight of the parent compound to be delivered. If the derivative exhibits activity in itself, the effective dosage can be estimated as above using the weight of the derivative, or by other means known to those skilled in the art.

[00305] The pharmaceutical compositions comprising compounds of the present invention may be used in the methods described herein.

[00306] METHODS OF USE

[00307] In another aspect, the present disclosure generally relates to methods for treating cancer. These methods comprise administering to a subject in need thereof, a therapeutically effective amount of a PI3K inhibitor (e.g., PI3K α inhibitor or PI3K α H1047R mutant inhibitor).

[00308] In some embodiments, the PI3K inhibitor (e.g., PI3K α inhibitor or PI3K α H1047R mutant inhibitor) is a compound of formula (I) or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof. In particular embodiments, the PI3K inhibitor comprises a compound selected from Table 1.

[00309] In another aspect, the present disclosure provides a compound obtainable by, or obtained by, a method for preparing a compound as described herein (e.g., a method comprising one or more steps described in the Schemes).

[00310] In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, and a pharmaceutically acceptable diluent or carrier.

[00311] In another aspect, the present disclosure provides an intermediate as described herein, being suitable for use in a method for preparing a compound as described herein (e.g., the intermediate is selected from the intermediates described in the Examples).

[00312] In another aspect, the present disclosure provides a method of modulating PI3K (e.g., PI3K α) activity (e.g., in vitro or in vivo), comprising contacting a cell with a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof.

[00313] In particular embodiments, the PI3K-associated with the disease or disorder has a H1047R mutation. For example, in certain embodiments as otherwise described herein, the compounds have a high selectivity for inhibiting H1047R-mutated PI3K α compared to wild-type PI3K α . This unexpected finding suggests that certain compounds may allow targeted inhibition of PI3K α with a novel binding mechanism compared to conventional wild-type PI3K α inhibitors. Without wishing to be bound by theory, the H1047R-mutated PI3K α has a modification distant from the wild-type PI3K α active site. Accordingly, compounds which are selective for H1047R-mutated PI3K α over wild-type PI3K α are not believed to strongly bind at the PI3K α active site, but rather advantageously are believed to target other binding pockets. As the active site of PI3K-type proteins is thought to be better conserved among different

variants, compounds that effectively bind at a position different than the active site may provide high selectivity for PI3K α inhibition over other PI3K proteins, such as PI3K β .

[00314] In another aspect, methods of treating cancer comprising administering to a patient having cancer a therapeutically effective amount of a compound of formula (I), pharmaceutically acceptable salts thereof or pharmaceutical compositions comprising the compound or pharmaceutically acceptable salts thereof are provided.

[00315] The compositions and methods provided herein may be used for the treatment of a wide variety of cancers including tumors such as prostate, breast, brain, skin, cervical carcinomas, testicular carcinomas, etc. More particularly, cancers that may be treated by the compositions and methods of the invention include, but are not limited to tumor types such as astrocytic, breast, cervical, colorectal, endometrial, esophageal, gastric, head and neck, hepatocellular, laryngeal, lung, oral, ovarian, prostate and thyroid carcinomas and sarcomas. More specifically, these compounds can be used to treat: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma,

ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. In certain embodiments, the cancer is diffuse large B-cell lymphoma (DLBCL).

[00316] In one embodiment, the cancer is selected from hepatocellular carcinoma, breast cancer, skin cancer, bladder cancer, liver cancer, pancreatic cancer, and head and neck cancer.

[00317] In another embodiment, the cancer is selected from breast cancer, uterine carcinosarcoma, uterine endometrial carcinoma, colorectal adenocarcinoma, stomach adenocarcinoma, head and neck squamous cell carcinoma, cholangiocarcinoma, esophageal adenocarcinoma, bladder carcinoma, lung squamous cell carcinoma, brain glioma, adrenocortical carcinoma, liver hepatocellular carcinoma, sarcoma, prostate adenocarcinoma, kidney renal cell carcinoma, lung adenocarcinoma, ovarian cystadenocarcinoma, glioblastoma multiforme, melanoma.

[00318] In another embodiment, the cancer is gastric, breast, colorectal, or endometrial cancer.

[00319] In another embodiment, the cancer is gastric cancer.

[00320] In another embodiment, the cancer is breast cancer.

[00321] In another embodiment, the cancer is colorectal cancer.

[00322] In another embodiment, the cancer is endometrial cancer.

[00323] Thus, in certain embodiments, this disclosure provides methods of treating cancer comprising administering a compound of formula (I) a pharmaceutical composition thereof and KRAS inhibitor to a patient in need thereof, wherein the cancer is breast cancer, uterine

carcinosarcoma, uterine endometrial carcinoma, colorectal adenocarcinoma, stomach adenocarcinoma, head and neck squamous cell carcinoma, cholangiocarcinoma, esophageal adenocarcinoma, bladder carcinoma, lung squamous cell carcinoma, brain glioma, adrenocortical carcinoma, liver hepatocellular carcinoma, sarcoma, prostate adenocarcinoma, kidney renal cell carcinoma, lung adenocarcinoma, ovarian cystadenocarcinoma, glioblastoma multiforme, melanoma.

[00324] In other embodiments, this disclosure provides a methods of treating cancer comprising administering a compound of formula (I) a pharmaceutical composition thereof and a mutant selective KRAS inhibitor to a patient in need thereof, wherein the cancer is breast cancer, uterine carcinosarcoma, uterine endometrial carcinoma, colorectal adenocarcinoma, stomach adenocarcinoma, head and neck squamous cell carcinoma, cholangiocarcinoma, esophageal adenocarcinoma, bladder carcinoma, lung squamous cell carcinoma, brain glioma, adrenocortical carcinoma, liver hepatocellular carcinoma, sarcoma, prostate adenocarcinoma, kidney renal cell carcinoma, lung adenocarcinoma, ovarian cystadenocarcinoma, glioblastoma multiforme, melanoma.

[00325] In another embodiment, this disclosure provides a compound of formula (I) a pharmaceutical composition thereof for use in the treatment of cancer in combination with a KRAS inhibitor, wherein the cancer is breast cancer, uterine carcinosarcoma, uterine endometrial carcinoma, colorectal adenocarcinoma, stomach adenocarcinoma, head and neck squamous cell carcinoma, cholangiocarcinoma, esophageal adenocarcinoma, bladder carcinoma, lung squamous cell carcinoma, brain glioma, adrenocortical carcinoma, liver hepatocellular carcinoma, sarcoma, prostate adenocarcinoma, kidney renal cell carcinoma, lung adenocarcinoma, ovarian cystadenocarcinoma, glioblastoma multiforme, melanoma.

[00326] The concentration and route of administration to the patient will vary depending on the cancer to be treated. The compounds, pharmaceutically acceptable salts thereof and pharmaceutical compositions comprising such compounds and salts also may be co-administered with other anti-neoplastic compounds, e.g., chemotherapy, or used in combination with other treatments, such as radiation or surgical intervention, either as an adjuvant prior to surgery or post-operatively.

[00327] The present disclosure provides methods of treating, preventing, or ameliorating a disease or disorder in which PI3K plays a role by administering to a patient in need thereof a therapeutically effective amount of a PI3K inhibitor. The methods of the present disclosure can be used in the treatment of a variety of PI3K-dependent diseases and disorders.

[00328] In some embodiments, the disease or disorder is a cancer (e.g., breast cancer, brain cancers, prostate cancer, endometrial cancer, gastric cancer, leukemia, lymphoma,

sarcoma, colorectal cancer, lung cancer, ovarian cancer, skin cancer, and head and neck cancer). In some embodiments, the disease or disorder associated with PI3K includes, but is not limited to, CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome), PIK3CA-related overgrowth syndrome (PROS), endometrial cancer, breast cancer, esophageal squamous-cell cancer, cervical squamous-cell carcinoma, cervical adenocarcinoma, colorectal adenocarcinoma, bladder urothelial carcinoma, glioblastoma, ovarian cancer, non-small-cell lung cancer, esophagogastric cancer, nerve-sheath tumor, head and neck squamous-cell carcinoma, melanoma, esophagogastric adenocarcinoma, soft-tissue sarcoma, prostate cancer, fibrolamellar carcinoma, hepatocellular carcinoma, diffuse glioma, colorectal cancer, pancreatic cancer, cholangiocarcinoma, B-cell lymphoma, mesothelioma, adrenocortical carcinoma, renal non-clear-cell carcinoma, renal clear-cell carcinoma, germ-cell carcinoma, thymic tumor, pheochromocytoma, miscellaneous neuroepithelial tumor, thyroid cancer, leukemia, and encapsulated glioma.

[00329] The details of the disclosure are set forth in the accompanying description below. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, illustrative methods and materials are now described. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents and publications cited in this specification are incorporated herein by reference in their entireties.

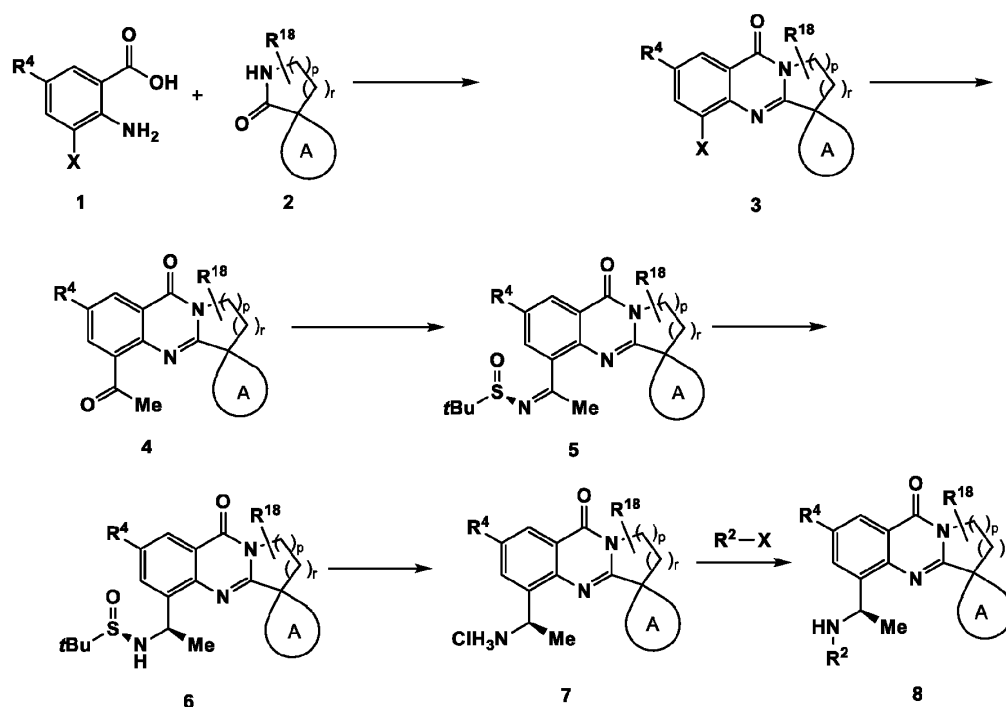
GENERAL REACTION SCHEMES, INTERMEDIATES AND EXAMPLES

[00330] The compounds of the present invention may be prepared using commercially available reagents and intermediates in the synthetic methods and reaction schemes described herein, or may be prepared using other reagents and conventional methods well known to those skilled in the art.

[00331] Where reference is made to “first eluting enantiomer” or “second eluting enantiomer”, unless otherwise specifically indicated, the specific stereochemistry of such enantiomers has not been determined and any stereochemistry depicted in the corresponding compound structures has been arbitrarily assigned.

[00332] For instance, intermediates for preparing compounds and compounds of formula (I) of the present invention may be prepared according to General Reaction Schemes I and II:

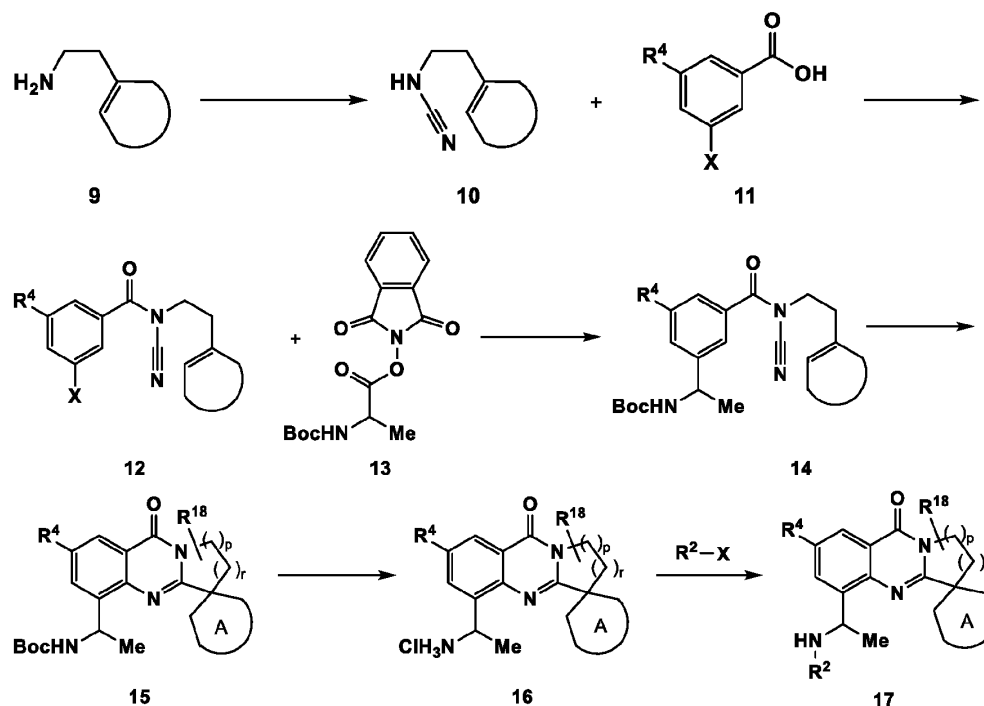
General Reaction Scheme I



wherein R^2 , R^4 , A, p and r are defined as for formula (I) and R^{18} is hydrogen or R^8 as defined for formula (I).

[00333] For General Reaction Scheme I, Compound 8 is an example of formula (I). In this General Reaction Scheme I, Compound 1 is condensed with Compound 2 using a dehydrating agent such as phosphorus oxychloride, to yield Compound 3. Compounds where the spiro center quaternary carbon is at a position other than as shown in Scheme I can be prepared using a different spirocyclic pyrrolidine 2. Compound 3 can then undergo an acylation reaction such as a Heck or Stille coupling using an enol ether coupling partner to form ketone product 4 upon acidic work-up. Compound 4 could then undergo condensation with a chiral sulfinamide, for example Ellman's auxiliary, using a Lewis acid such as titanium (IV) ethoxide to provide imine 5. The reduction of compound 5 to form sulfonamide 6 could be effected using a reductant such as diisobutylaluminum hydride, sodium borohydride, or zirconocene chloride hydride. After acidic deprotection of 6 using, for example, hydrochloric acid in dioxane, amine 7 could be substituted to prepare compound 8 through nucleophilic substitution or metal catalyzed reaction in the presence of an appropriate base.

General Reaction Scheme II



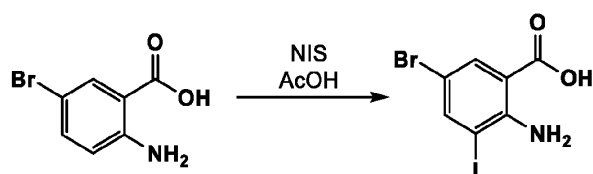
wherein R^2 , R^4 , A, p and r are defined as for formula (I) and R^{18} is hydrogen or R^8 as defined for formula (I).

[00334] For General Reaction Scheme II, Compound 17 is an example of formula (I). In this General Reaction Scheme II, 9 is reacted with a cyanogen bromide in the presence of a suitable base, for example, sodium carbonate, to prepare Compound 10. Compounds where the spiro center quaternary carbon is at a position other than as shown in Scheme II can be prepared using a different starting unsaturated amine 9. Compound 11 can be coupled with compound 10 after a suitable activation of the carboxylic acid, for example, in situ conversion to the acid chloride using oxalyl chloride and dimethylformamide, Ghosez's reagent, or thionyl chloride to prepare compound 12. A transition metal catalyzed cross coupling reaction of the aryl halide on compound 12 with a redox active ester (13) or similar alkyl electrophile can be effected with a suitable reductant, for example, a sacrificial anode or metal powder to yield Compound 14. A cyclization reaction such as an iron catalyzed hydrogen atom transfer radical cyclization can be employed to construct compound 15. An acidic deprotection of the protected amine through the use of hydrochloric acid in dioxane or similar Brønsted acid can produce compound 16. Amine 16 could be substituted to prepare compound 17 through nucleophilic substitution or metal catalyzed reaction in the presence of an appropriate base.

[00335] Substituents shown in Schemes I and II carry the same definitions as set forth above for formula (I) and D represents ring A is a 3-8 membered carbocyclic ring or 4-7 membered heterocyclic ring. The pyrrolidine ring and Rings A and D may be substituted as described for formula (I).

INTERMEDIATE A

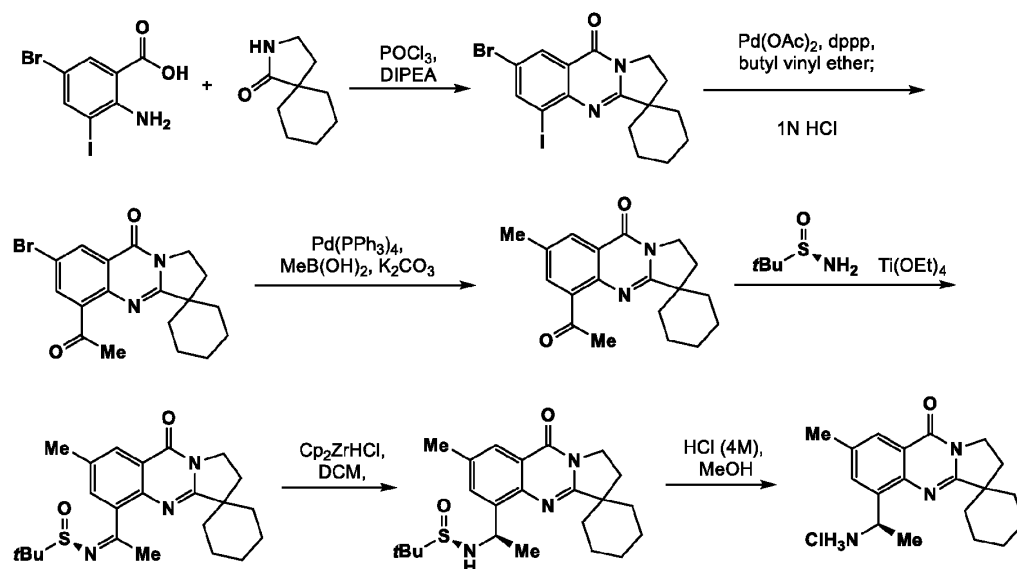
2-amino-5-bromo-3-iodobenzoic acid



[00336] Step A: To a suspension of 2-amino-5-bromobenzoic acid (5.0 g, 1.0 eq., 23 mmol) in acetic acid (23 mL) was added *N*-iodosuccinimide (6.25 g, 1.2 eq., 27.8 mmol). The mixture was stirred at room temperature overnight. The product was concentrated to dryness, dissolved in dichloromethane, and purified via silica gel chromatography to give 2-amino-5-bromo-3-iodobenzoic acid as a light brown solid. LCMS $[M+H]^+ = 343.8$.

[00337] ^1H NMR (500 MHz, DMSO- d_6) δ ppm 6.81 (br s, 2H) 7.86 (d, $J = 2.46$ Hz, 1H) 7.97 (d, $J = 2.46$ Hz, 1H).

INTERMEDIATE B



[00338] Step A: To a flask charged with 2-azaspiro[4.5]decan-1-one (500 mg, 1.0 eq., 3.3 mmol) in 1,2-dichloroethane (12 mL) was added phosphorous oxychloride (650 mg, 395 μ L, 1.3 eq. 4.2 mmol) and diisopropylethylamine (422 mg, 568 μ L, 1.0 eq., 3.3 mmol). The reaction was then heated to 50 °C for one hour. Next, 2-amino-5-bromo-3-iodobenzoic acid (1.12 g, 1 eq., 3.3 mmol) was added as a solid and the reaction was heated to 100 °C. The reaction was stirred overnight before being cooled to room temperature and diluted with water. The aqueous layer was extracted with dichloromethane and the combined organics were washed with brine, dried over magnesium sulfate, and concentrated. The solid was purified by silica gel chromatography to provide 7'-bromo-5'-iodo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-9'-one (780 mg, 1.7 mmol, 52 %) as a yellow solid. LCMS [M+H]⁺ = 461.0.

[00339] Step B: To a vial and a stir bar was added palladium (II) acetate (17 mg, 0.05 eq., 74 μ mol), 1,3-bis(diphenylphosphino)propane (61 mg, 0.10 eq., 15 μ mol) and 7'-bromo-5'-iodo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-9'-one (681 mg, 1.0 eq., 1.48 mmol). The flask was evacuated and backfilled with nitrogen three times. Next, ethylene glycol (3.7 mL), *n*-butyl vinyl ether (960 μ L, 5.0 eq., 7.42 mmol), and *N,N*-Dicyclohexylmethylamine (948 μ L, 3.0 eq., 4.45 mmol) were injected and this solution was sparged with nitrogen. The flask was placed in a heating block, and the mixture was stirred and heated at 115 °C. After full conversion, the reaction was allowed to cool to room temperature and 1N HCl (6 mL) was added to the reaction. The reaction was stirred until the ketone deprotection went to completion (ca. 1h). The aqueous layer was extracted with ethyl acetate three times and the combined organics were washed successively with water and brine, dried over magnesium sulfate, filtered, and concentrated to a residue. This residue was purified via silica gel chromatography to provide 5'-acetyl-7'-bromo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-9'-one (367 mg, 98 μ mol, 66 %) as a yellow solid. LCMS [M+H]⁺ = 433.1.

[00340] Step C: To a vial was added methylboronic acid (57 mg, 2.0 eq., 95 μ mol), 5'-acetyl-7'-bromo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-9'-one (179 mg, 1.0 eq., 477 μ mol), potassium carbonate (132 mg, 2.0 eq., 954 μ mol) and Tetrakis(triphenylphosphine)palladium(0) (55 mg, 0.10 eq., 48 μ mol). The vial was evacuated and backfilled three times with nitrogen. Next, a solution of deoxygenated 1,4-dioxane (1.9 mL) and water (480 μ L) was added and the reaction was heated to 100 °C and stirred overnight. The reaction was cooled to room temperature and quenched with saturated sodium bicarbonate and extracted three times with dichloromethane. The combined organics were washed successively with water, then brine, and dried over magnesium sulfate. After filtration, concentration under reduced pressure and silica gel chromatography 5'-acetyl-7'-methyl-1',2'-

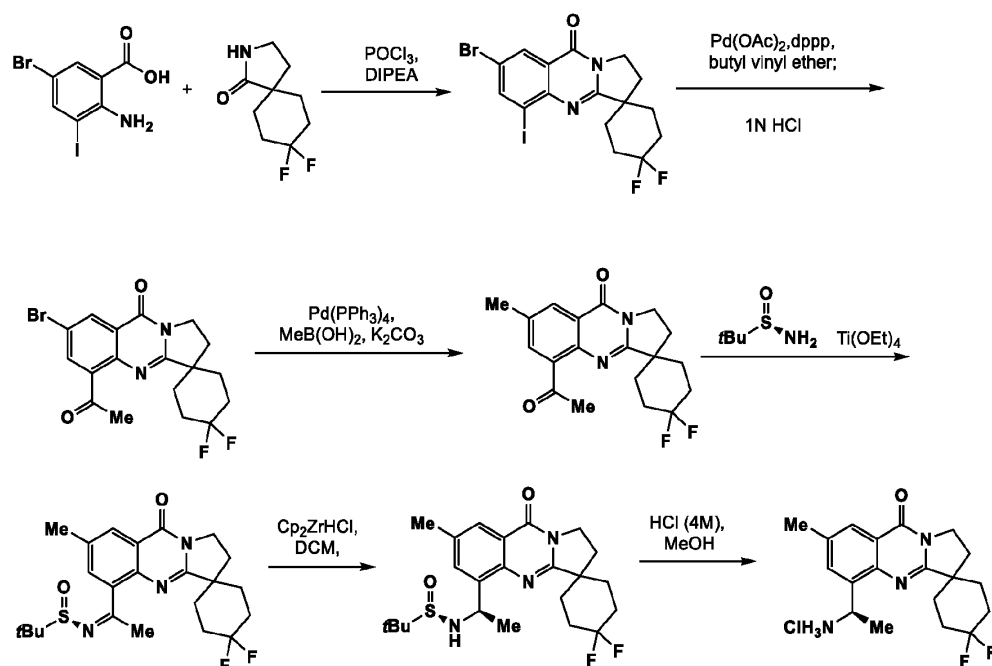
dihydro-9'-H-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-9'-one (65 mg, 0.21 mmol, 44 %) was obtained as a yellow solid. LCMS [M+H]⁺ = 311.2.

[00341] Step D: To a solution of 5'-acetyl-7'-methyl-1',2'-dihydro-9'-H-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-9'-one (84 mg, 1.0 eq., 0.27 mmol) and (*R*)-2-methylpropane-2-sulfinamide (39 mg, 1.2 eq., 0.32 mmol) in tetrahydrofuran (1.1 mL) was added titanium (IV) ethoxide (0.31 g, 0.28 mL, 5 eq., 1.4 mmol). The mixture was stirred at 70 °C for 4 hours then cooled to room temperature. Once at room temperature, a minimal amount of brine was added to form a suspension. The resulting suspension was diluted with ethyl acetate, filtered through a plug of celite, and the filter cake was washed with ethyl acetate several times. The filtrate was concentrated under reduced pressure and the yellow residue was quickly purified via silica gel chromatography (30% to 100% ethyl acetate in heptane) to provide (*R*)-2-methyl-*N*-(1-(7'-methyl-9'-oxo-1',2'-dihydro-9'-H-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-5'-yl)ethylidene)propane-2-sulfinamide (53 mg, 0.13 mmol, 47 %) as a yellow solid.

[00342] Step E: To a solution of (*R*)-2-methyl-*N*-(1-(7'-methyl-9'-oxo-1',2'-dihydro-9'-H-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-5'-yl)ethylidene)propane-2-sulfinamide (53 mg, 1.0 eq., 0.13 mmol) in anhydrous dichloromethane (0.85 mL) at room temperature was added Schwartz's reagent (36 mg, 1.1 eq., 0.14 mmol) as a solid portion wise. The reaction was stirred at this temperature for 15 min before being quenched with ammonium chloride. The aqueous layer was extracted with dichloromethane and the combined organics were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to provide a residue. This solid was purified via silica gel chromatography (0% to 10% methanol in dichloromethane) to provide (*R*)-2-methyl-*N*-((*R*)-1-(7'-methyl-9'-oxo-1',2'-dihydro-9'-H-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-5'-yl)ethyl)propane-2-sulfinamide (47 mg, 0.11 mmol, 88 %) as a white solid. LCMS [M+H]⁺ = 416.2.

[00343] Step F: To a solution of (*R*)-2-methyl-*N*-((*R*)-1-(7'-methyl-9'-oxo-1',2'-dihydro-9'-H-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-5'-yl)ethyl)propane-2-sulfinamide (57 mg, 1.0 eq., 0.14 mmol) in methanol (0.30 mL) at 0 °C was added 86 µL HCl (4M in dioxane). The reaction was monitored for conversion by LCMS and once complete, triturated with diethyl ether to provide (*R*)-5'-(1-aminoethyl)-7'-methyl-1',2'-dihydro-9'-H-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-9'-one, hydrochloride (48 mg) which was used subsequently without further purification. LCMS [M+H]⁺ = 312.2.

INTERMEDIATE C



[00344] Step A: To a flask charged with 8,8-difluoro-2-azaspiro[4.5]decan-1-one (500 mg, 1.0 eq., 2.64 mmol) in 1,2-dichloroethane (9.9 mL) was added phosphorous oxychloride (320 μ L, 1.3 eq., 3.44 mmol) and diisopropylethylamine (460 μ L, 1.0 eq., 2.6 mmol). The reaction was then heated to 50 °C for one hour. Next, 2-amino-5-bromo-3-iodobenzoic acid (904 mg, 1.0 eq., 2.64 mmol) was added as a solid and the reaction was heated to 100 °C. The reaction was stirred overnight before being cooled to room temperature and diluted with water. The aqueous layer was extracted with dichloromethane and the combined organics were washed with brine, dried over magnesium sulfate and concentrated. The solid was purified by silica gel chromatography to provide 7'-bromo-4,4-difluoro-5'-iodo-1',2'-dihydro-9'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-9'-one (759 mg, 1.5 mmol, 58 %) as a yellow solid. LCMS [M+H]⁺ = 496.8.

[00345] ¹H NMR (500 MHz, CDCl₃) δ ppm 1.88 - 1.96 (m, 2H) 1.96 - 2.07 (m, 2H) 2.12 (dt, *J* = 13.7, 4.8 Hz, 2H) 2.15 - 2.19 (m, 2H) 2.70 - 2.86 (m, 2H) 4.10 - 4.16 (m, 2H) 8.35 (*d*, *J* = 2.19 Hz, 1H) 8.39 (*d*, *J* = 2.19 Hz, 1H).

[00346] Step B: To a vial and a stir bar was added palladium (II) acetate (17 mg, 0.05 eq., 77 μ mol), 1,3-bis(diphenylphosphino)propane (63 mg, 0.10 eq., 150 μ mol) and 7'-bromo-4,4-difluoro-5'-iodo-1',2'-dihydro-9'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-9'-one (759

mg, 1.0 eq., 1.53 mmol). The vial evacuated and backfilled with nitrogen three times. Next, ethylene glycol (3.8 mL), *N,N*-Dicyclohexylmethylamine (980 μ L, 3.0 eq., 4.6 mmol), and *n*-butyl vinyl ether (992 μ L, 5.0 eq., 7.66 mmol) was injected and this solution was sparged with nitrogen. The vial was placed in a heating block, and the mixture was stirred and heated at 115 °C. After full conversion, the reaction was allowed to cool to room temperature and 1N HCl (10 mL) was added to the reaction. The reaction was stirred until the ketone deprotection went to completion (ca. 1h). The aqueous layer was extracted with ethyl acetate three times and the combined organics were washed successively with water and brine, dried over magnesium sulfate, filtered, and concentrated to a residue. This residue was purified via silica gel chromatography to provide 5'-acetyl-7'-bromo-4,4-difluoro-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-9'-one (435 mg, 1.1 mmol, 69%) as a yellow solid. LCMS [M+H]⁺ = 467.1, 469.1 (before acidic work-up).

[00347] ¹H NMR (400 MHz, CDCl₃) δ ppm 1.79 - 1.89 (m, 2H) 1.90 - 2.06 (m, 2H) 2.13 - 2.20 (m, 2H) 2.21 - 2.27 (m, 2H) 2.31 - 2.46 (m, 2H) 2.82 (s, 3H) 4.13 - 4.22 (m, 2H) 8.06 (d, *J* = 2.50 Hz, 1H) 8.54 (d, *J* = 2.38 Hz, 1H).

[00348] Step C: To a vial was added methylboronic acid (78 mg, 2.5 eq., 1.3 mmol), 5'-acetyl-7'-bromo-4,4-difluoro-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-9'-one (215 mg, 1.0 eq., 520 μ mol), potassium carbonate (181 mg, 2.5 eq., 1.31 mmol) and tetrakis(triphenylphosphine)palladium(0) (60 mg, 0.10 eq., 52 μ mol). This vial was evacuated and backfilled three times with nitrogen. Next, a solution of deoxygenated 1,4-dioxane (2.1 mL) and water (520 μ L) was added and the reaction was heated to 90 °C and stirred overnight. The reaction was cooled to room temperature and quenched with saturated sodium bicarbonate, extracted three times with dichloromethane. The combined organics were washed successively with water then brine and dried over magnesium sulfate. After filtration, concentration under reduced pressure, and silica gel chromatography 5'-acetyl-4,4-difluoro-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-9'-one (114 mg, 329 μ mol, 63 %) was obtained as a solid pale yellow solid. LCMS [M+H]⁺ = 347.1.

[00349] ¹H NMR (400 MHz, CDCl₃) δ ppm 1.80 - 1.89 (m, 2H) 1.90 - 2.03 (m, 2H) 2.15 - 2.26 (m, 4H) 2.35 - 2.47 (m, 2H) 2.49 (s, 3H) 2.83 (s, 3H) 4.11 - 4.23 (m, 2H) 7.81 (d, *J* = 2.25 Hz, 1H) 8.23 (d, *J* = 1.38 Hz, 1H).

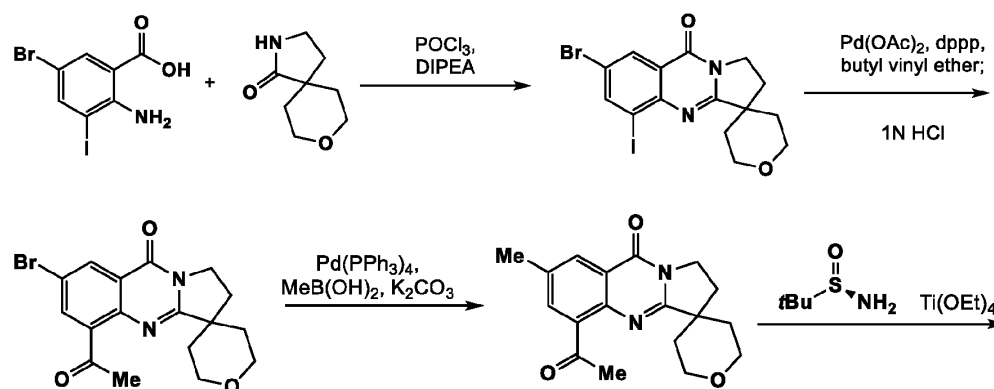
[00350] Step D: To a solution of 5'-acetyl-4,4-difluoro-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-9'-one (114 mg, 1 eq., 329 μ mol) and (*R*)-2-methylpropane-2-sulfinamide (48 mg, 1.2 eq., 400 μ mol) in tetrahydrofuran (1.3 mL) was added titanium (IV) ethoxide (340 μ L, 5.0 eq., 1.7 mmol). The mixture was stirred at 80 °C for 4 hours then cooled to room temperature. Once at room temperature, a minimal amount of

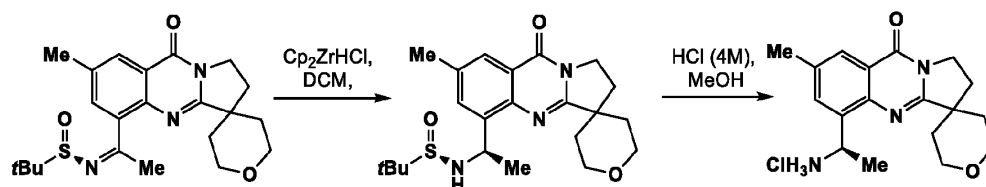
brine was added to form a suspension. The resulting suspension was diluted with ethyl acetate, filtered through a plug of celite, and the filter cake was washed with ethyl acetate several times. The filtrate was concentrated under reduced pressure to provide (*R*)-*N*-(1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)-2-methylpropane-2-sulfonamide (167 mg) as a crude yellow solid which was carried forward without purification.

[00351] Step E: To a solution of (*R*)-*N*-(1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)-2-methylpropane-2-sulfonamide (167 mg, 1.0 eq., 371 μ mol) in anhydrous dichloromethane (2.5 mL) at room temperature was added Schwartz's Reagent (105 mg, 1.10 eq., 409 μ mol) as a solid portion wise. The reaction was stirred at this temperature for 15 min before being quenched with ammonium chloride. The aqueous layer was extracted with dichloromethane and the combined organics were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. This residue was purified via silica gel chromatography (0% to 10% methanol in dichloromethane) to provide (*R*)-*N*-((*R*)-1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)-2-methylpropane-2-sulfonamide (78 mg, 0.17 mmol, 46 % over two steps) as a white solid. LCMS [*M*+*H*]⁺ = 452.2.

[00352] Step F: To a solution of (*R*)-*N*-((*R*)-1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)-2-methylpropane-2-sulfonamide (78 mg, 1.0 eq., 0.17 mmol) in methanol (0.35 mL) at 0 °C was added 0.11 mL HCl (4.0 molar in dioxane). The reaction was stirred at room temperature until complete, then triturated with diethyl ether to provide (*R*)-5'-(1-aminoethyl)-4,4-difluoro-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9-one, hydrochloride as an off-white salt which was used without further purification. LCMS [*M*+*H*]⁺ = 348.2.

INTERMEDIATE D





[00353] Step A: To a flask charged with 8-oxa-2-azaspiro[4.5]decan-1-one (500 mg, 1.0 eq., 3.2 mmol) in 1,2-dichloroethane (12 mL) was added phosphorous oxychloride (390 μ L, 1.3 eq., 4.2 mmol) and diisopropylethylamine (560 μ L, 1.0 eq., 3.2 mmol). The reaction was then heated to 50 °C for one hour. Next, 2-amino-5-bromo-3-iodobenzoic acid (1.1 g, 1.0 eq., 3.2 mmol) added as a solid and the reaction was heated to 100 °C. The reaction was stirred overnight before being cooled to room temperature and diluted with water. The aqueous layer was extracted with dichloromethane and the combined organics were washed with brine, dried over magnesium sulfate and concentrated. The solid was purified by silica gel chromatography to provide 7'-bromo-5'-iodo-1',2,2',3,5,6-hexahydro-9'*H*-spiro[pyran-4,3'-pyrrolo[2,1-b]quinazolin]-9'-one (501 mg, 1.10 mmol, 34%) as a solid. LCMS: [M+H]⁺ = 462.8.

[00354] ¹H NMR (500 MHz, CDCl₃) δ ppm 1.70 - 1.76 (m, 2H), 2.14 - 2.21 (m, 2H) 2.21 - 2.28 (m, 2H) 3.73 (ddd, *J* = 11.64, 7.94, 3.42 Hz, 2H) 4.11 - 4.17 (m, 2H) 4.25 - 4.34 (m, 2H) 8.36 (*d*, *J* = 2.19 Hz, 1H) 8.39 (*d*, *J* = 2.19 Hz, 1H).

[00355] Step B: To a vial and a stir bar was added palladium (II) acetate (12 mg, 0.05 eq., 54 μ mol), 1,3-bis(diphenylphosphino)propane (45 mg, 0.10 eq., 110 μ mol), 7'-bromo-5'-iodo-1',2,2',3,5,6-hexahydro-9'*H*-spiro[pyran-4,3'-pyrrolo[2,1-b]quinazolin]-9'-one (500 mg, 1.0 eq., 1.10 mmol). The flask evacuated and backfilled with nitrogen three times. Next, ethylene glycol (2.7 mL), *N,N*-Dicyclohexylmethylamine (700 μ L, 3.0 eq., 3.3 mmol), and *n*-butyl vinyl ether (700 μ L, 5.0 eq., 5.4 mmol) was injected and this solution was sparged with nitrogen. The vial was placed in a heating block, and the mixture was stirred and heated at 115 °C. After full conversion, the reaction was allowed to cool to room temperature and 1N HCl (9 mL) was added to the reaction. The reaction was stirred until the ketone deprotection went to completion (ca. 1h). The aqueous layer was extracted with ethyl acetate three times and the combined organics were washed successively with water and brine, dried over magnesium sulfate, filtered, and concentrated to a residue. This residue was purified via silica gel chromatography to provide 5'-acetyl-7'-bromo-1',2,2',3,5,6-hexahydro-9'*H*-spiro[pyran-4,3'-pyrrolo[2,1-b]quinazolin]-9'-one (300 mg, 795 μ mol, 73 %) as a red solid. LCMS: [M+H]⁺ = 379.0.

[00356] ¹H NMR (400 MHz, CDCl₃) δ ppm 1.62 (br d, *J* = 13.13 Hz, 2H) 2.17 - 2.28 (m, 2H) 2.33 (br t, *J* = 6.88 Hz, 2H) 2.89 (s, 3H) 3.65 (td, *J* = 11.51, 2.38 Hz, 2H) 4.09 (dt, *J* = 11.79, 3.74 Hz, 2H) 4.18 (br t, *J* = 6.94 Hz, 2H) 8.10 (br s, 1H) 8.54 (*d*, *J* = 2.13 Hz, 1H)

[00357] Step C: To a vial was added methylboronic acid (60 mg, 2.5 eq., 990 μ mol), 5'-acetyl-7'-bromo-1',2,2',3,5,6-hexahydro-9'H-spiro[pyran-4,3'-pyrrolo[2,1-b]quinazolin]-9'-one (150 mg, 1 eq., 398 μ mol), potassium carbonate (137 mg, 2.5 eq., 994 μ mol) and tetrakis(triphenylphosphine)palladium(0) (46 mg, 0.10 eq., 40 μ mol). This vial was evacuated and backfilled three times with nitrogen. Next, a solution of deoxygenated 1,4-dioxane (1.6 mL) and water (400 μ L) was added and the reaction was heated to 90 °C and stirred overnight. The reaction was cooled to room temperature and quenched with saturated sodium bicarbonate, extracted three times with dichloromethane. The combined organics were washed successively with water then brine and dried over magnesium sulfate. After filtration, concentration under reduced pressure and purification using silica gel chromatography 5'-acetyl-7'-methyl-1',2,2',3,5,6-hexahydro-9'H-spiro[pyran-4,3'-pyrrolo[2,1-b]quinazolin]-9'-one (68 mg, 0.22 mmol, 55 %) was obtained as a pale-red solid. LCMS: [M+H]⁺ = 313.2.

[00358] ¹H NMR (400 MHz, CDCl₃) δ ppm 1.62 (br d, *J* = 13.51 Hz, 2H) 1.59 - 1.66 (m, 1H) 2.06 - 2.06 (m, 1H) 2.17 - 2.27 (m, 2H) 2.28 - 2.34 (m, 2H) 2.49 (s, 3H) 2.90 (s, 3H) 3.61 - 3.71 (m, 2H) 4.10 (dt, *J* = 11.91, 3.99 Hz, 2H) 4.14 - 4.19 (m, 2H) 7.85 (d, *J* = 2.00 Hz, 1H) 8.23 (d, *J* = 1.25 Hz, 1H).

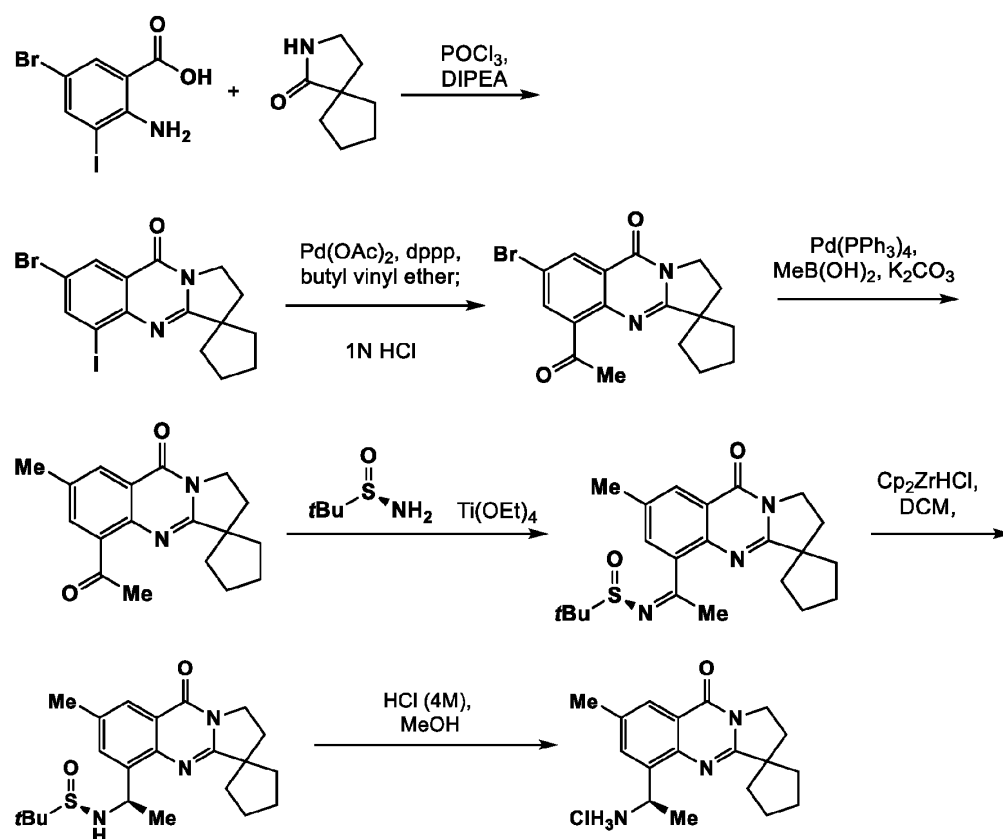
[00359] Step D: To a solution of 5'-acetyl-7'-methyl-1',2,2',3,5,6-hexahydro-9'H-spiro[pyran-4,3'-pyrrolo[2,1-b]quinazolin]-9'-one (68 mg, 1 eq., 0.22 mmol) and (*R*)-2-methylpropane-2-sulfonamide (32 mg, 1.2 eq., 0.26 mmol) in tetrahydrofuran (0.90 mL) was added titanium (IV) ethoxide (0.23 mL, 5.0 eq., 1.1 mmol). The mixture was stirred at 80 °C for 4 hours then cooled to room temperature. Once at room temperature, a minimal amount of brine was added to form a suspension. The resulting suspension was diluted with ethyl acetate, filtered through a plug of celite, and the filter cake was washed with ethyl acetate several times. The filtrate was concentrated under reduced pressure to provide (*R*)-2-methyl-*N*-(1-(7'-methyl-9'-oxo-1',2,2',3,5,6-hexahydro-9'H-spiro[pyran-4,3'-pyrrolo[2,1-b]quinazolin]-5'-yl)ethylidene)propane-2-sulfonamide (97 mg) as a crude yellow solid which was carried forward without further purification.

[00360] Step E: To a solution of (*R*)-2-methyl-*N*-(1-(7'-methyl-9'-oxo-1',2,2',3,5,6-hexahydro-9'H-spiro[pyran-4,3'-pyrrolo[2,1-b]quinazolin]-5'-yl)ethylidene)propane-2-sulfonamide (97 mg, 1 eq., 0.23 mmol) in anhydrous dichloromethane (1.6 mL) at room temperature was added Schwartz's Reagent (66 mg, 1.1 eq., 0.26 mmol) as a solid portion wise. The reaction was stirred at this temperature for 15 min before being quenched with ammonium chloride. The aqueous layer was extracted with dichloromethane and the combined organics were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. This residue was purified via silica gel chromatography (0% to 10% methanol in dichloromethane) to provide (*R*)-2-methyl-*N*-((*R*)-1-(7'-methyl-9'-oxo-1',2,2',3,5,6-

hexahydro-9'-H-spiro[pyran-4,3'-pyrrolo[2,1-b]quinazolin]-5'-yl)ethyl)propane-2-sulfinamide (32 mg, 77 μ mol, 33 % over two steps) as a white solid. LCMS $[M+H]^+ = 418.2$.

[00361] Step F: To a solution of (*R*)-2-methyl-N-((*R*)-1-(7'-methyl-9'-oxo-1',2,2',3,5,6-hexahydro-9'-H-spiro[pyran-4,3'-pyrrolo[2,1-b]quinazolin]-5'-yl)ethyl)propane-2-sulfinamide (33 mg, 1.0 eq., 79 μ mol) in methanol (0.3 mL) at 0 °C was added 49 μ L HCl (4.0 molar in dioxane). The reaction was stirred at room temperature until complete, then triturated with diethyl ether to provide (*R*)-5'-(1-aminoethyl)-7'-methyl-1',2,2',3,5,6-hexahydro-9'-H-spiro[pyran-4,3'-pyrrolo[2,1-b]quinazolin]-9'-one, hydrochloride as a yellow salt which was used without further purification. LCMS $[M+H]^+ = 314.2$.

INTERMEDIATE E



[00362] Step A: To a flask charged with 2-azaspiro[4.4]nonan-1-one (500 mg, 1.0 eq., 3.59 mmol) in 1,2-dichloroethane (14 mL) was added phosphorous oxychloride (435 μ L, 1.3 eq., 4.67 mmol) and diisopropylethylamine (626 μ L, 1.0 eq., 3.59 mmol). The reaction was then heated to 50 °C for one hour. Next, of 2-amino-5-bromo-3-iodobenzoic acid (1.23 g, 1.0 eq.,

3.59 mmol) was added as a solid and the reaction was heated to 100 °C. The reaction was stirred overnight before being cooled to room temperature and diluted with water. The aqueous layer was extracted with dichloromethane and the combined organics were washed with brine, dried over magnesium sulfate and concentrated. The solid was purified by silica gel chromatography to provide 7'-bromo-5'-iodo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (721 mg, 1.62 mmol, 45 %) as a yellow solid. LCMS: [M+H]⁺ = 446.7.

[00363] ¹H NMR (499 MHz, CDCl₃) δ ppm 1.77 - 1.85 (m, 4H) 2.03 - 2.11 (m, 2H) 2.15 - 2.18 (m, 2H) 2.18 - 2.24 (m, 2H) 4.06 - 4.13 (m, 2H) 8.33 (*d*, *J* = 2.19 Hz, 1H) 8.38 (*d*, *J* = 2.19 Hz, 1H).

[00364] Step B: To a vial and a stir bar was added palladium (II) acetate (18 mg, 0.05 eq., 81 μmol), 1,3-bis(diphenylphosphino)propane (67 mg, 0.10 eq., 160 μmol), 7'-bromo-5'-iodo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (721 mg, 1.0 eq., 1.62 mmol). The vial was evacuated and backfilled with nitrogen three times. Next, ethylene glycol (4.05 mL), *N,N*-Dicyclohexylmethylamine (1.00 mL, 3.0 eq., 4.9 mmol), and *n*-butyl vinyl ether (1.1 mL, 5.0 eq., 8.1 mmol) were injected and this solution was sparged with nitrogen. The vial was placed in a heating block, and the mixture was stirred and heated at 115 °C. After full conversion, the reaction was allowed to cool to room temperature and 1N HCl (9 mL) was added to the reaction. The reaction was stirred until the ketone deprotection went to completion (ca. 1h). The aqueous layer was extracted with ethyl acetate three times and the combined organics were washed successively with water and brine, dried over magnesium sulfate, filtered, and concentrated to a residue. This residue was purified via silica gel chromatography to provide 5'-acetyl-7'-bromo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (449 mg, 1.24 mmol, 77 %) as a yellow solid. LCMS: [M+H]⁺ = 419.1 (before acidic workup).

[00365] ¹H NMR (400 MHz, CDCl₃) δ ppm 1.78 - 1.88 (m, 4H) 1.91 - 2.03 (m, 2H) 2.14 (br dd, *J* = 4.88, 2.13 Hz, 2H) 2.16 - 2.21 (m, 2H) 2.86 (s, 2H) 4.04 - 4.21 (m, 2H) 8.09 (*d*, *J* = 2.50 Hz, 1H) 8.54 (*d*, *J* = 2.50 Hz, 1H).

[00366] Step C: To a vial was added methylboronic acid (62 mg, 2.5 eq., 1.00 mmol), 5'-acetyl-7'-bromo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (150 mg, 1.0 eq., 415 μmol), potassium carbonate (143 mg, 2.5 eq., 1.04 mmol) and tetrakis(triphenylphosphine)palladium(0) (48 mg, 0.10 eq., 42 μmol). This vial was evacuated and backfilled three times with nitrogen. Next, a solution of deoxygenated 1,4-dioxane (1.7 mL) and water (420 μL) was added and the reaction was heated to 90 °C and stirred overnight. The reaction was cooled to room temperature and quenched with saturated sodium bicarbonate

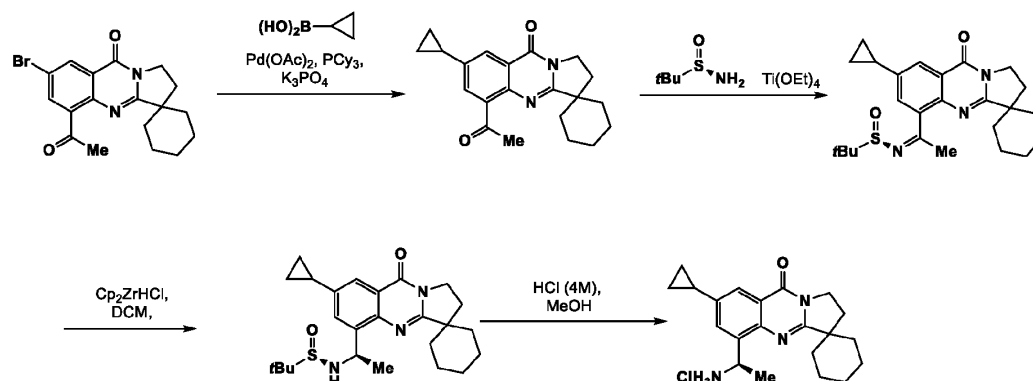
and extracted three times with dichloromethane. The combined organics were washed successively with water then brine and dried over magnesium sulfate. After filtration, concentration under reduced pressure and purification on silica gel chromatography, 5'-acetyl-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (65 mg, 0.22 mmol, 53 %) was obtained as a pale-yellow solid. LCMS: [M+H]⁺ = 297.2.

[00367] Step D: To a solution of 5'-acetyl-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (87 mg, 1.0 eq., 0.29 mmol) and (*R*)-2-methylpropane-2-sulfonamide (43 mg, 1.2 eq., 0.35 mmol) in tetrahydrofuran (1.2 mL) was added titanium (IV) ethoxide (0.33 g, 0.31 mL, 5.0 eq., 1.5 mmol). The mixture was stirred at 80 °C for 4 hours then cooled to room temperature. Once at room temperature, a minimal amount of brine was added to form a suspension. The resulting suspension was diluted with ethyl acetate, filtered through a plug of celite, and the filter cake was washed with ethyl acetate several times. The filtrate was concentrated under reduced pressure and the yellow residue was quickly purified via silica gel chromatography (30% to 100% ethyl acetate in heptane) to provide (*R*)-2-methyl-*N*-(1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)propane-2-sulfonamide (57 mg, 0.14 mmol, 49 %) as a yellow solid.

[00368] Step E: To a solution of (*R*)-2-methyl-*N*-(1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)propane-2-sulfonamide (57 mg, 1 eq., 0.14 mmol) in anhydrous dichloromethane (0.95 mL) at room temperature was added Schwartz's Reagent (40 mg, 1.1 eq., 0.16 mmol) as a solid portion wise. The reaction was stirred at this temperature for 15 min before being quenched with ammonium chloride. The aqueous layer was extracted with dichloromethane and the combined organics were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. This residue was purified via silica gel chromatography (0% to 10% methanol in dichloromethane) to provide (*R*)-2-methyl-*N*-((*R*)-1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)propane-2-sulfonamide (57 mg, 0.14 mmol, 99 %) as a white solid. LCMS [M+H]⁺ = 402.2.

[00369] Step F: To a solution of (*R*)-2-methyl-*N*-((*R*)-1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)propane-2-sulfonamide (47 mg, 1.0 eq., 0.12 mmol) in methanol (0.2 mL) at 0 °C was added 73 µL HCl (4.0 molar in dioxane). The reaction was stirred at room temperature until complete, then triturated with diethyl ether to provide (*R*)-5'-(1-aminoethyl)-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one, hydrochloride as an off-white salt. LCMS [M+H]⁺ = 298.2.

INTERMEDIATE F



[00370] Step A: The aryl bromide starting material was prepared identically to that in Intermediate B. A procedure adapted from Wallace, D.J. and Chen C.-Y. *Tetrahedron Letters* 43, 2002, 6987-6990 was used to effect the desired Suzuki reaction. To a vial was added cyclopropylboronic acid (44 mg, 1.3 eq., 510 μ mol), 5'-acetyl-7'-bromo-1',2'-dihydro-9'-H-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-9-one (147 mg, 1.0 eq., 392 μ mol), palladium(II) acetate (4 mg, .05 eq., 20 μ mol), tripotassium phosphate (291 mg, 3.5 eq., 1.37 mmol) and tricyclohexylphosphine (11.0 mg, 0.1 eq., 39.2 μ mol) which was evacuated and backfilled three times with nitrogen. Next, a solution of deoxygenated toluene (1.9 mL) and water (90 μ L) was added, and the reaction was heated to 100 °C and stirred overnight. The reaction was quenched with saturated sodium bicarbonate, extracted three times with dichloromethane. The combined organics were washed successively with water then brine and dried over magnesium sulfate. After filtration, concentration under reduced pressure, and silica gel chromatography, 5'-acetyl-7'-cyclopropyl-1',2'-dihydro-9'-H-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-9-one (92 mg, 0.27 mmol, 70%) was obtained as a white solid. LCMS $[M+H]^+ = 337.2$.

[00371] ^1H NMR (400 MHz, CDCl_3) δ ppm 0.76 - 0.84 (m, 2H) 1.01 - 1.10 (m, 2H) 1.35 - 1.50 (m, 3H) 1.66 (m, 2H) 1.71 - 1.78 (m, 1H) 1.79 - 1.92 (m, 4H) 1.98 - 2.08 (m, 1H) 2.10 - 2.10 (m, 1H) 2.16 - 2.22 (m, 2H) 2.90 (s, 3H) 4.07 - 4.15 (m, 2H) 7.75 (d, $J = 2.25$ Hz, 1H) 8.09 (d, $J = 2.38$ Hz, 1H).

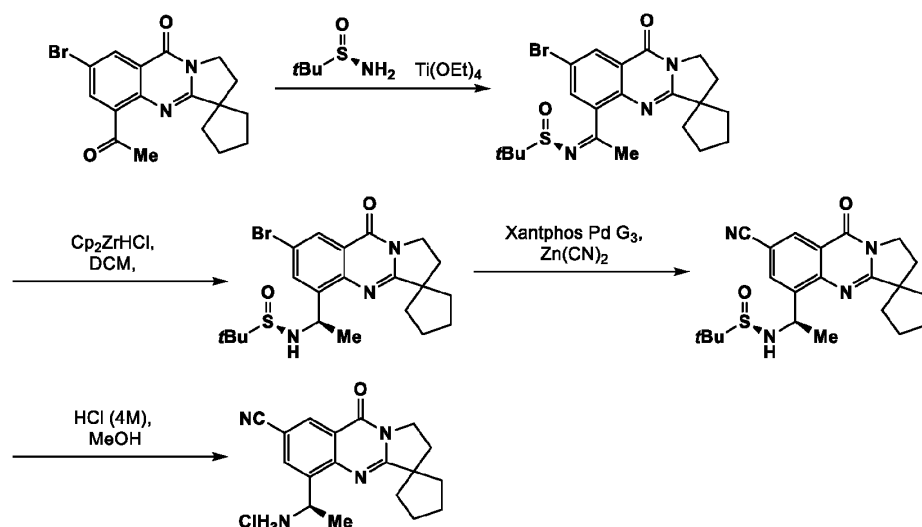
[00372] Step B: To a solution of 5'-acetyl-7'-cyclopropyl-1',2'-dihydro-9'-H-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-9-one (92 mg, 1 eq., 0.27 mmol) and (R)-2-methylpropane-2-sulfonamide (40 mg, 1.2 eq., 0.33 mmol) in tetrahydrofuran (1.1 mL) was added titanium (IV) ethoxide (0.31 g, 0.28 mL, 5 eq., 1.4 mmol). The mixture was stirred at 80 °C for 4 hours then cooled to room temperature. Once at room temperature, a minimal amount of brine was added to form a suspension. The resulting suspension was diluted with ethyl acetate, filtered through a plug of celite, and the filter cake was washed with ethyl acetate

several times. The filtrate was concentrated under reduced pressure to provide (*R*)-*N*-(1-(7'-cyclopropyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)-2-methylpropane-2-sulfonamide (138 mg) as a crude yellow solid which was used without further purification.

[00373] Step C: To a solution of (*R*)-*N*-(1-(7'-cyclopropyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)-2-methylpropane-2-sulfonamide (138 mg, 1 eq., 314 μ mol) in anhydrous dichloromethane (2.1 mL) at room temperature was added Schwartz's Reagent (89 mg, 1.1 eq., 350 μ mol) as a solid portion wise. The reaction was stirred at this temperature for 15 min before being quenched with ammonium chloride. The aqueous layer was extracted with dichloromethane and the combined organics were washed with brine, dried over magnesium sulfate and concentrated under reduced. This residue was purified via silica gel chromatography (0% to 10% methanol in dichloromethane) to provide (*R*)-*N*-((*R*)-1-(7'-cyclopropyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)-2-methylpropane-2-sulfonamide (60 mg, 0.14 mmol, 43 %) as a white solid. LCMS [M+H]⁺ = 442.3.

[00374] Step D: To a solution of (*R*)-*N*-((*R*)-1-(7'-cyclopropyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)-2-methylpropane-2-sulfonamide (60 mg, 1.0 eq., 0.14 mmol) in methanol (0.3 mL) at 0 °C was added 85 μ L HCl (4.0 M in dioxane). The reaction was stirred at room temperature until complete, then triturated with diethyl ether to provide (*R*)-5'-(1-aminoethyl)-7'-cyclopropyl-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one, hydrochloride (45 mg, 0.12 mmol, 89 %) as an off-white salt which was used without further purification. LCMS [M+H]⁺ = 338.3.

INTERMEDIATE G



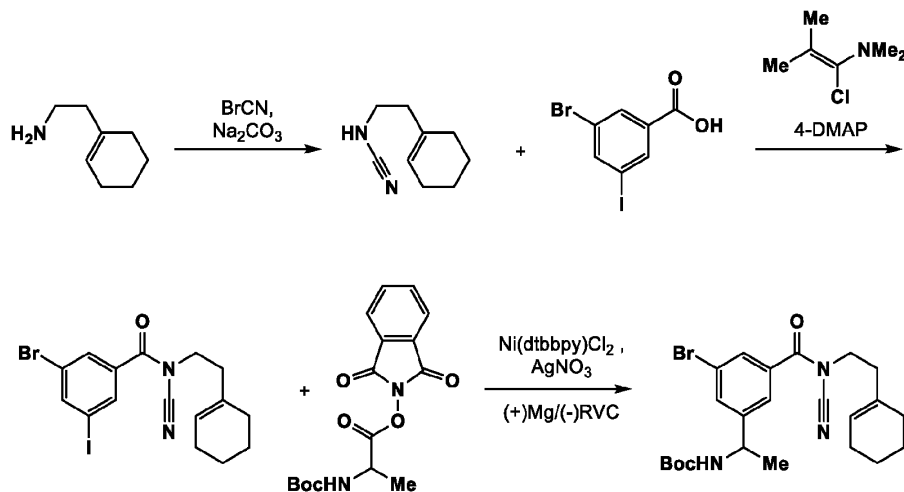
[00375] Step A: To a solution of 5'-acetyl-7'-bromo-1',2'-dihydro-9'-H-spiro[cyclopentane-1,3'-pyrrolo[2,1-b]quinazolin]-9'-one (296 mg, 1.0 eq., 819 μmol) and (*R*)-2-methylpropane-2-sulfonamide (119 mg, 1.2 eq., 983 μmol) in tetrahydrofuran (2.05 mL) was added titanium (IV) ethoxide (850 μL , 5.0 eq., 4.1 mmol). The mixture was stirred at 80 °C for 3 hours then cooled to room temperature. Once at room temperature, a minimal amount of brine was added to form a suspension. The resulting suspension was diluted with ethyl acetate, filtered through a plug of celite, and the filter cake was washed with ethyl acetate several times. The filtrate was concentrated under reduced pressure and the yellow residue was quickly purified via silica gel chromatography (30% to 100% ethyl acetate in heptane) to provide (*R*)-N-(1-(7'-bromo-9'-oxo-1',2'-dihydro-9'-H-spiro[cyclopentane-1,3'-pyrrolo[2,1-b]quinazolin]-5'-yl)ethylidene)-2-methylpropane-2-sulfonamide (280 mg, 600 μmol , 74%) as a yellow solid.

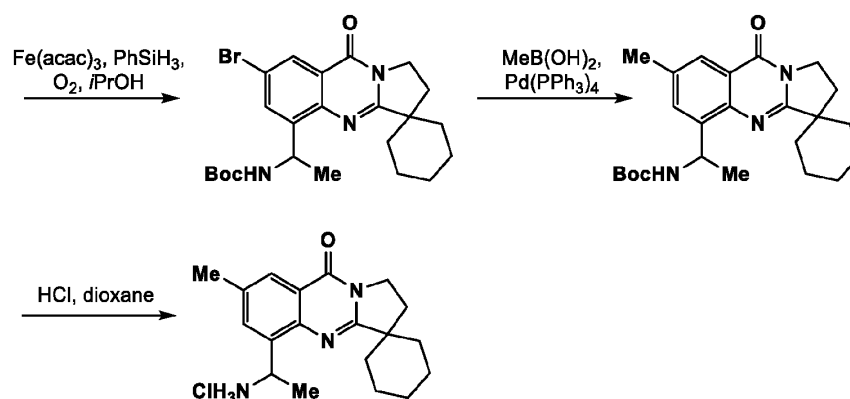
[00376] Step B: To a solution of (*R*)-N-(1-(7'-bromo-9'-oxo-1',2'-dihydro-9'-H-spiro[cyclopentane-1,3'-pyrrolo[2,1-b]quinazolin]-5'-yl)ethylidene)-2-methylpropane-2-sulfonamide (280 mg, 1.0 eq., 600 μmol) in anhydrous dichloromethane (4.0 mL) at room temperature was added Schwartz's Reagent (171 mg, 1.1 eq., 663 μmol) as a solid portion wise. The reaction was stirred at this temperature for 15 min before being quenched with ammonium chloride. The aqueous layer was extracted with dichloromethane and the combined organics were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to provide a residue. This residue was purified via silica gel chromatography (0% to 10% methanol in dichloromethane) to provide (*R*)-N-((*R*)-1-(7'-bromo-9'-oxo-1',2'-dihydro-9'-H-spiro[cyclopentane-1,3'-pyrrolo[2,1-b]quinazolin]-5'-yl)ethyl)-2-methylpropane-2-sulfonamide (249 mg, 530 μmol , 89 %) as a white solid. LCMS: $[\text{M}+\text{H}]^+ = 468.1$.

[00377] Step C: To a flask under nitrogen containing zinc cyanide (6 mg, 3.0 μ L, 0.55 eq., 5 μ mol), (*R*)-*N*-((*R*)-1-(7'-bromo-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)-2-methylpropane-2-sulfinamide (40 mg, 1.0 eq., 86 μ mol) and XantPhos Pd G3 (4.0 mg, 0.05 eq., 4.0 μ mol) was added dimethylacetamide (0.9 mL) and the reaction was heated to 100 °C for 12 hour. The reaction was quenched with 1M sodium carbonate and extracted with ethyl acetate. The combined organics were washed with water, then brine, then dried over magnesium sulfate, filtered and concentrated via rotary evaporation. The product was purified via silica gel chromatography to provide (*R*)-*N*-((*R*)-1-(7'-cyano-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)-2-methylpropane-2-sulfinamide (18 mg, 44 μ mol, 51 %) as a yellow solid. LCMS: $[M+H]^+ = 413.2$.

[00378] Step D: To a solution of (*R*)-*N*-((*R*)-1-(7'-cyano-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)-2-methylpropane-2-sulfinamide (18 mg, 1 eq., 44 μ mol) in methanol (0.2 mL) at 0 °C was added 16 μ L HCl (4.0 molar in dioxane). The reaction was stirred at room temperature until complete, then triturated with diethyl ether to provide (*R*)-5'-(1-aminoethyl)-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazoline]-7'-carbonitrile, hydrochloride as an off-white salt which was used without further purification. LCMS $[M+H]^+ = 309.1$.

INTERMEDIATE H





[00379] Step A: Procedure adapted from Turner et al. *Chemistry – A European Journal*, 2020, 26, 3026-3029. To cyanogen bromide (3.00 g, 1.77 mL, 1.0 eq., 28.3 mmol) and sodium carbonate (4.50 g, 1.5 eq., 42.5 mmol) in a flask at 0 °C was added diethyl ether (30 mL). Then a solution of 2-(1-Cyclohexenyl)ethylamine (3.55 g, 3.94 mL, 1.0 eq., 28.3 mmol) in tetrahydrofuran (30 mL) was added slowly. The reaction was allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was then filtered over celite, the solids washed with ethyl acetate and the organics dried in vacuo to yield *N*-(2-(cyclohex-1-en-1-yl)ethyl)cyanamide (2.47 g, 16.4 mmol, 58. %) which was purified via silica gel chromatography (ethyl acetate/heptane 0% to 40%). The product was visualized via TLC staining with iodine.

[00380] ^1H NMR (400 MHz, CDCl_3) δ ppm 1.52 - 1.59 (m, 2H) 1.60 - 1.69 (m, 2H) 1.90 (br d, J = 1.25 Hz, 2H) 1.97 - 2.06 (m, 2H) 2.22 (t, J = 6.57 Hz, 2H) 3.12 - 3.21 (m, 2H) 3.32 (br s, 1H) 5.53 (br s, 1H).

[00381] Step B: To a suspension of 3-bromo-5-iodobenzoic acid (4.35 g, 2.0 eq., 13.3 mmol) in dichloromethane (10 mL) was added Ghosez's reagent (1.78 g, 1.76 mL, 2.0 eq., 13.3 mmol). The mixture was stirred 15 minutes at room temperature until the solution became clear and was then added to a stirring solution of *N*-(2-(cyclohex-1-en-1-yl)ethyl)cyanamide (1.00 g, 1.0 eq., 6.66 mmol), 4-(dimethylamino)pyridine (81.3 mg, 0.10 eq., 666 μmol), and pyridine (2.63 g, 2.69 mL, 5.0 eq., 33.3 mmol) in dichloromethane (20 mL). The reaction was stirred until complete conversion (ca. 1h). The reaction was diluted with dichloromethane, washed with a saturated solution of sodium bicarbonate, brine, and dried over magnesium sulfate. The organics were filtered and concentrated and the desired product was purified via silica gel chromatography to provide 3-bromo-*N*-cyano-*N*-(2-(cyclohex-1-en-1-yl)ethyl)-5-iodobenzamide. LCMS: $[\text{M} + \text{H}_2\text{O} + \text{Na}]^+ = 500.9$.

[00382] ^1H NMR (400 MHz, CDCl_3) δ ppm 1.55 - 1.71 (m, 4H) 1.93 - 2.11 (m, 4H) 2.40 (t, J = 6.75 Hz, 2H) 3.83 (t, J = 6.82 Hz, 2H) 5.61 (br s, 1H) 7.81 (t, J = 1.50 Hz, 1H) 7.96 (d, J = 1.25 Hz, 1H) 8.06 (d, J = 1.50 Hz, 1H).

[00383] Step C: Procedure adapted from Harwood et al. *Science*, 2022, 745-752. To a 5 mL electrasyn vial and stir bar was added 4,4'-Di-tert-butyl-2,2'-dipyridyl (81 mg, 0.2 eq., 300 μmol), Nickel chloride hexahydrate (71 mg, 0.2 eq., 300 μmol), 1,3-dioxoisindolin-2-yl (tert-butoxycarbonyl)alaninate (627 mg, 1.25 eq., 1.88 mmol), silver nitrate (76 mg, 0.30 eq., 450 μmol), and 3-bromo-*N*-cyano-*N*-(2-(cyclohex-1-en-1-yl)ethyl)-5-iodobenzamide (689 mg, 1.0 eq., 1.50 mmol). The vial was then fitted with a standard electrasyn cap bearing a magnesium anode and RVC (100 ppi) cathode. The vial was then evacuated and backfilled three times with nitrogen before anhydrous, deoxygenated dimethylformamide (4.0 mL) was added. The vial was placed on an electrasyn 2.0 set to the following parameters: 1.50 mmol, 2.3 F/mol, 45 mA. Once complete, the reaction was evaluated by LCMS and quenched with 1N HCl. The organics were extracted with ethyl acetate, washed successively with water and brine, dried over magnesium sulfate, concentrated and tert-butyl (1-(3-bromo-5-(cyano(2-(cyclohex-1-en-1-yl)ethyl)carbamoyl)phenyl)ethyl)carbamate (421 mg, 880 μmol , 59 %) was purified via silica gel chromatography (0% to 45% ethyl acetate in heptane) to provide a white solid. LCMS $[\text{M} + \text{H}]^+ = 422.0$.

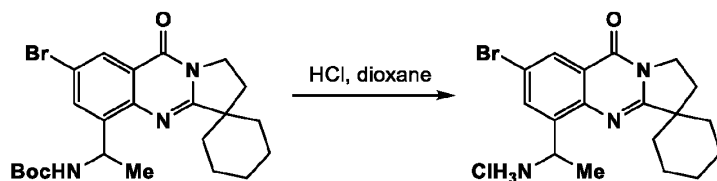
[00384] Step D: Procedure adapted from Turner et al. *Chemistry – A European Journal*, 2020, 26, 3026-3029. To a vial was added tert-butyl (1-(3-bromo-5-(cyano(2-(cyclohex-1-en-1-yl)ethyl)carbamoyl)phenyl)ethyl)carbamate (606 mg, 1.0 eq., 1.27 mmol) and Iron(III) acetylacetonate (45 mg, 0.1 eq., 130 μmol), to this was added a solution of phenylsilane (145 mg, 166 μL , 1.05 eq., 1.34 mmol) in isopropanol (5.09 mL). The reaction was then stirred open to air, at 50 °C. Once complete, the reaction was cooled to room temperature and concentrated under reduced pressure. The crude regioisomers were separated via silica gel chromatography (0% to 60% ethyl acetate in heptane) to provide tert-butyl (1-(7'-bromo-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)carbamate (219 mg, 561 μmol , 36 %) as a white solid and the undesired regioisomer tert-butyl (1-(5'-bromo-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-7'-yl)ethyl)carbamate (186 mg, 390 μmol , 31 %) in a 1.17:1 ratio. LCMS $[\text{M} + \text{H}]^+ = 478.1$.

[00385] Step E: To a vial was added methylboronic acid (38 mg, 2.0 eq., 630 μmol), tert-butyl (1-(7'-bromo-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)carbamate (150 mg, 1.0 eq., 315 μmol), potassium carbonate (87 mg, 2.0 eq., 630 μmol) and tetrakis(triphenylphosphine)palladium(0) (36 mg, 0.1 eq., 32 μmol) which was evacuated and backfilled three times with nitrogen. Next, a solution of degassed 1,4-dioxane (1.3 mL) and water (320 μL) was added, and the reaction was heated to 90 °C and stirred

overnight. After cooling to room temperature, the reaction was quenched with saturated sodium bicarbonate and extracted three times with dichloromethane. The combined organics were washed successively with water then brine and dried over magnesium sulfate. After filtration, concentration under reduced pressure and silica gel chromatography, tert-butyl (1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)carbamate (65 mg, 0.16 mmol, 50 %) was obtained as a white solid. LCMS $[M+H]^+ = 412.2$.

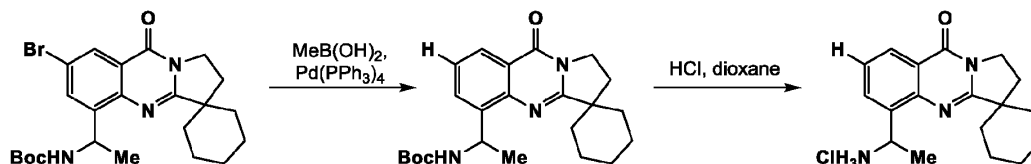
[00386] Step F: To a vial containing tert-butyl (1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)carbamate (67 mg, 1.0 eq., 0.16 mmol) was added 0.50 mL HCl (4 M in dioxane). The reaction stirred at room temperature until completion (3h), then triturated with diethyl ether and the solid was washed three times with diethyl ether to provide 5'-(1-aminoethyl)-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one, hydrochloride as a white salt which was used without further purification in the subsequent steps. LCMS $[M+H]^+ = 312.2$.

INTERMEDIATE I



[00387] Step A: To a vial containing tert-butyl (1-(7'-bromo-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)carbamate (50 mg, 1.0 eq., 0.10 mmol) was added (0.5 mL) HCl (4.0 molar in dioxane). The reaction was stirred at room temperature until completion (3h), then triturated with diethyl ether and the solid was washed three times with diethyl ether to provide 5'-(1-aminoethyl)-7'-bromo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one, hydrochloride (34 mg, 98 μ mol, 93 %) as a white salt. LCMS $[M+H]^+ = 377.95$.

INTERMEDIATE J

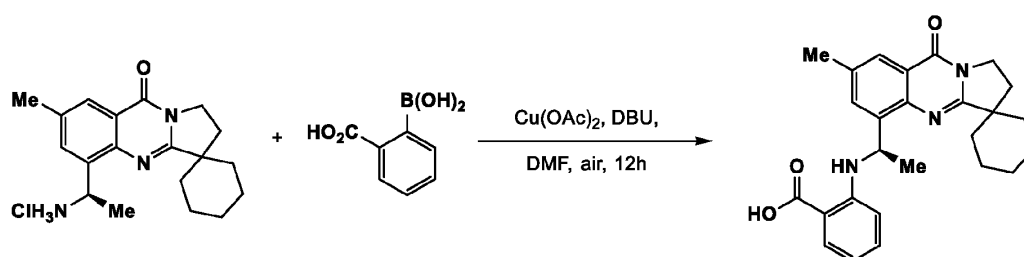


[00388] Step A: The reaction of for Intermediate H, Step E also produced tert-butyl (1-(9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)carbamate (7.0 mg, 18 μ mol, 5.6 %) as a minor product. LCMS $[M+H]^+ = 398.3$.

[00389] Step B: To a vial containing tert-butyl (1-(9'-oxo-1',2'-dihydro-9'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-5'-yl)ethyl)carbamate (8.0 mg, 1 eq., 20 μ mol) was added (0.3 mL) HCl (4.0 molar in dioxane). The reaction was stirred at room temperature until completion (3h) then triturated with diethyl ether and the solid was washed three times with diethyl ether to provide 5'-(1-aminoethyl)-1',2'-dihydro-9'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-9'-one, hydrochloride (7mg, 20 μ mol, quant.) as a white salt. LCMS $[M+H]^+ = 298.1$.

EXAMPLE 1-1

(*R*)-2-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-5'-yl)ethyl)amino)benzoic acid



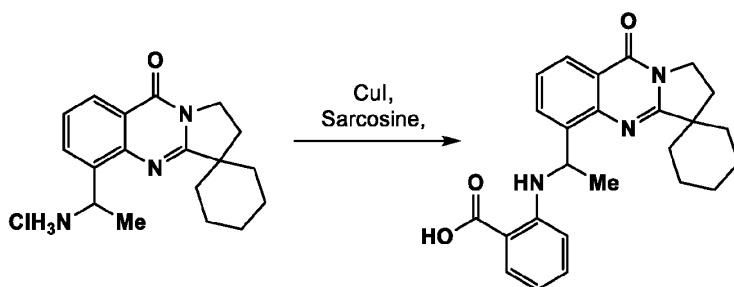
[00390] To a vial and stir bar was added (*R*)-5'-(1-aminoethyl)-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-9'-one, hydrochloride (48 mg, 1 eq., 0.14 mmol), 2-carboxyphenylboronic acid (69 mg, 3.0 eq., 0.41 mmol) and copper (II) acetate (38 mg, 1.5 eq., 0.21 mmol) as solids. Next, the vial was sealed with a septum cap and dimethylformamide (0.69 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.10 mL, 5.0 eq., 0.69 mmol) were added successively. A vent needle was punctured through the septum to expose the reaction to ambient atmosphere and the reaction was stirred at room temperature for 12 hours. The reaction was quenched with aqueous ammonium chloride and diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate three times and the combined organics were washed successively with saturated ammonium chloride and brine before being dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The reaction residue was purified via silica gel chromatography (0% to 75% ethyl acetate in heptane) to provide (*R*)-2-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-5'-yl)ethyl)amino)benzoic acid (8.0 mg, 19 μ mol, 13 %) as a white solid. LCMS $[M+H]^+ = 432.2$.

[00391] ^1H NMR (400 MHz, CDCl_3) δ ppm 1.41 - 1.56 (m, 3H) 1.60 - 1.76 (m, 6H) 1.84 - 1.99 (m, 4H) 2.19 (t, $J = 7.19$ Hz, 2H) 2.40 (s, 3H) 4.12 (t, $J = 7.19$ Hz, 2H) 5.61 - 5.75 (m,

1H) 6.53 (br d, $J = 8.50$ Hz, 1H) 6.58 (br t, $J = 7.13$ Hz, 1H) 7.13 - 7.21 (m, 1H) 7.57 (br s, 1H) 7.96 (d, $J = 1.50$ Hz, 1H) 7.98 (s, 1H).

EXAMPLE 1-2

2-((1-(9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid

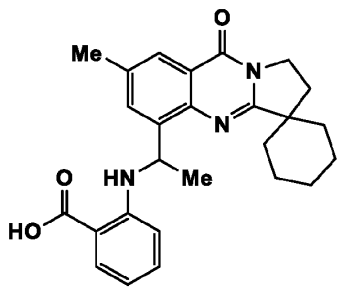
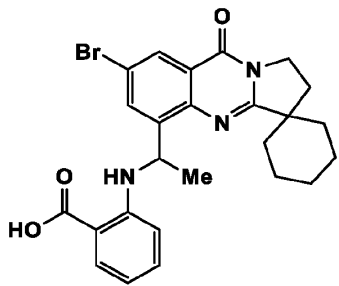
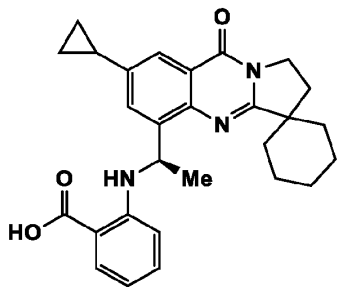


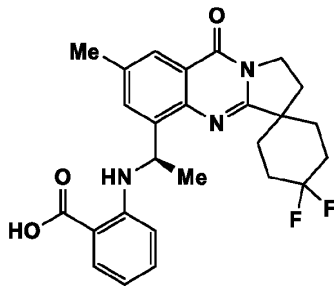
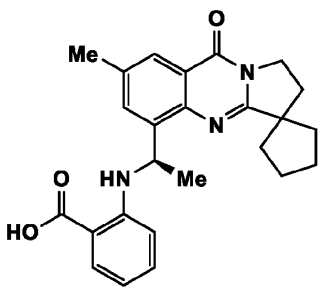
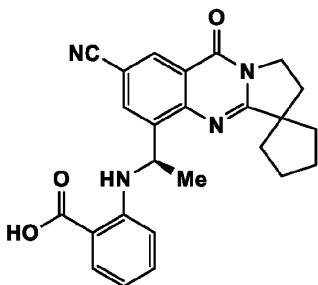
[00392] To a vial containing 2-iodobenzoic acid (9 mg, 1.5 eq., 40 μ mol), sarcosine (1 mg, 0.6 eq., 10 μ mol) potassium carbonate (10 mg, 3.0 eq., 70 μ mol) and copper (I) iodide (1 mg, 0.3 eq., 7 μ mol) and 5'-(1-aminoethyl)-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9-one (7 mg, 1.0 eq., 20 μ mol) under nitrogen was added dimethyl sulfoxide (0.5 mL). The reaction was stirred for 5 minutes before being heated to 40 °C for 18 hours. The reaction was cooled and quenched with saturated ammonium chloride and extracted with ethyl acetate. The combined organics were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified via preparative TLC to provide 2-((1-(9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid (2 mg, 4 μ mol, 15%). LCMS $[M+H]^+ = 418.2$.

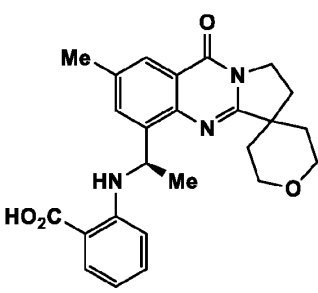
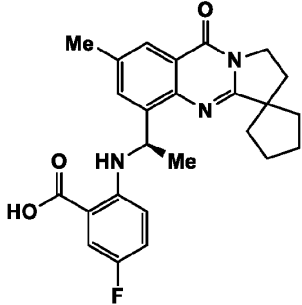
[00393] ^1H NMR (400 MHz, CDCl_3) δ ppm 1.46 - 1.53 (m, 3H) 1.66 (d, $J = 6.75$ Hz, 4H) 1.67 - 1.75 (m, 3H) 1.85 - 2.02 (m, 4H) 2.20 (t, $J = 7.38$ Hz, 2H) 4.13 (t, $J = 7.32$ Hz, 2H) 6.46 (d, $J = 8.63$ Hz, 1H) 6.53 (t, $J = 7.50$ Hz, 1H) 7.15 (td, $J = 7.85, 1.69$ Hz, 1H) 7.33 (t, $J = 7.75$ Hz, 1H) 7.68 - 7.76 (m, 1H) 7.92 (dd, $J = 7.94, 1.56$ Hz, 1H) 8.17 (dd, $J = 7.88, 1.38$ Hz, 1H).

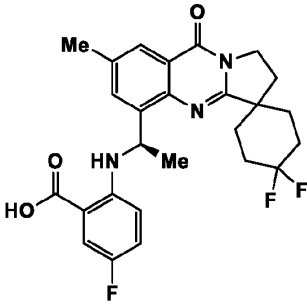
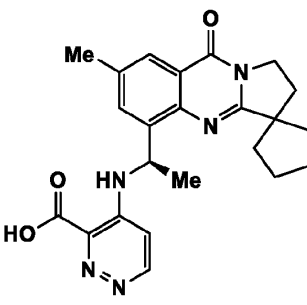
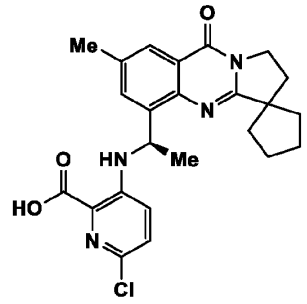
[00394] Examples 1-3 to 1-90

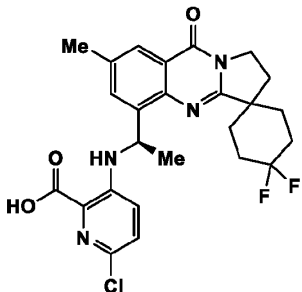
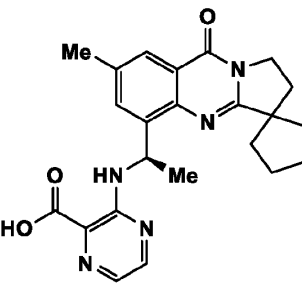
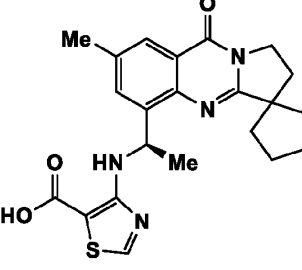
[00395] The following compounds are prepared essentially according to the procedures set forth in the above and below schemes and examples.

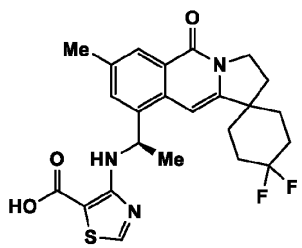
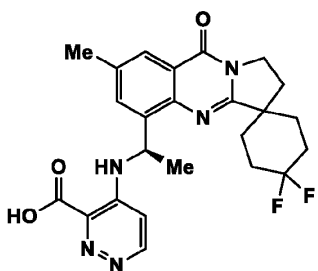
Ex. #	Structure	Spectral Data
1-3	 2-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-5'-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ ppm 1.49 (m, 3 H) 1.64 (d, <i>J</i> = 6.75 Hz, 3 H) 1.66 - 1.72 (m, 3 H) 1.85 - 2.02 (m, 4 H) 2.19 (t, <i>J</i> = 7.19 Hz, 2 H) 2.39 (s, 3 H) 4.12 (t, <i>J</i> = 7.25 Hz, 2 H) 5.65 (q, <i>J</i> = 6.84 Hz, 1 H) 6.49 (d, <i>J</i> = 8.63 Hz, 1 H) 6.54 (t, <i>J</i> = 7.50 Hz, 1 H) 7.16 (ddd, <i>J</i> = 8.54, 7.10, 1.63 Hz, 1 H) 7.53 (d, <i>J</i> = 1.88 Hz, 1 H) 7.93 - 7.98 (m, 2 H). LCMS [M+H] ⁺ = 432.2.
1-4	 2-((1-(7'-bromo-9'-oxo-1',2'-dihydro-9'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-5'-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ ppm 1.53-1.49 (m, 3H) 1.65 (d, <i>J</i> = 6.63 Hz, 3H) 1.67 - 1.74 (m, 3H) 1.84 - 2.03 (m, 4H) 2.21 (t, <i>J</i> = 7.25 Hz, 2H) 4.13 (t, <i>J</i> = 7.25 Hz, 2H) 5.62 (q, <i>J</i> = 6.67 Hz, 1H) 6.41 (d, <i>J</i> = 8.50 Hz, 1H) 6.54 - 6.62 (m, 1H) 7.18 (ddd, <i>J</i> = 8.54, 7.10, 1.63 Hz, 1 H) 7.80 (d, <i>J</i> = 2.38 Hz, 1H) 7.98 (dd, <i>J</i> = 8.00, 1.50 Hz, 1H) 8.06 - 8.25 (br s, 1H) 8.30 (d, <i>J</i> = 2.38 Hz, 1H). LCMS [M+H] ⁺ = 496.2.
1-5		¹ H NMR (400 MHz, CDCl ₃) δ ppm 0.66 - 0.82 (m, 2H) 0.98 (br d, <i>J</i> = 8.13 Hz, 2H) 1.47 (m, 3H) 1.58 - 1.67 (d, 3H) 1.71 (m, 3H) 1.82 - 1.98 (m, 5H) 2.17 (t, <i>J</i> = 7.19 Hz, 2H) 4.09 (t, <i>J</i> = 7.07 Hz, 2H) 5.61 - 5.78 (m, 1H) 6.49 - 6.59 (m, 1H) 6.59 - 6.72 (m, 1H) 7.11 - 7.21 (m, 1H) 7.57 (br s,

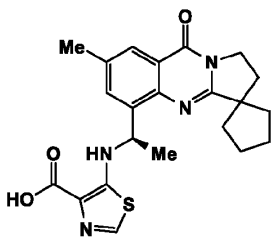
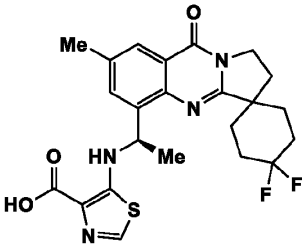
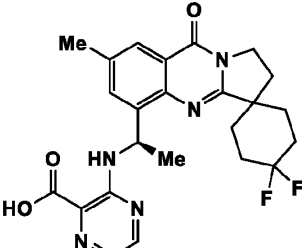
	(<i>R</i>)-2-((1-(7'-cyclopropyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	¹ H) 7.79 (s, 1H) 7.96 (dd, <i>J</i> = 7.94, 1.44 Hz, 1H). LCMS [<i>M</i> + <i>H</i>] ⁺ = 458.2.
1-6	 (<i>R</i>)-2-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclohexane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ ppm 1.64 (d, <i>J</i> = 6.75 Hz, 3H) 1.90 (dtd, <i>J</i> = 13.43, 8.95, 8.95, 4.44 Hz, 2H) 1.97 - 2.10 (m, 2H) 2.21 (br t, <i>J</i> = 6.63 Hz, 4H) 2.41 (s, 3H) 2.44 - 2.72 (m, 2H) 4.09 - 4.24 (m, 2H) 5.57 (q, <i>J</i> = 6.63 Hz, 1H) 6.40 (d, <i>J</i> = 8.63 Hz, 1H) 6.57 (t, <i>J</i> = 7.57 Hz, 1H) 7.12 - 7.21 (m, 1H) 7.58 (d, <i>J</i> = 1.25 Hz, 1H) 7.98 (td, <i>J</i> = 3.88, 1.63 Hz, 2H). LCMS [<i>M</i> + <i>H</i>] ⁺ = 468.2.
1-7	 (<i>R</i>)-2-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 8.01 - 7.91 (m, 2H), 7.62 (br s, 1H), 7.22 - 7.13 (m, 1H), 6.71 - 6.60 (m, 1H), 6.59 - 6.51 (m, 1H), 5.69 (br d, <i>J</i> = 3.4 Hz, 1H), 4.11 (t, <i>J</i> = 6.9 Hz, 2H), 2.42 (s, 3H), 2.22-2.11 (m, 4H), 2.06-1.93 (m, 2H), 1.88-1.76 (m, 4H), 1.75-1.65 (m, 3H). LCMS [<i>M</i> + <i>H</i>] ⁺ = 418.2.
1-8		¹ H NMR (400 MHz, CDCl ₃) δ ppm 1.65 (d, <i>J</i> = 6.63 Hz, 3H) 1.80 - 1.91 (m, 4H) 1.97 - 2.07 (m, 2H) 2.27 - 2.15 (m, 4H) 4.15 (t, <i>J</i> = 6.94 Hz, 2H) 5.52 - 5.63 (m, 1H) 6.32 (br d, <i>J</i> = 7.75 Hz, 1H) 6.62 (br t, <i>J</i> = 6.88 Hz, 1H) 7.11 - 7.21 (m, 1H) 7.91 (s,

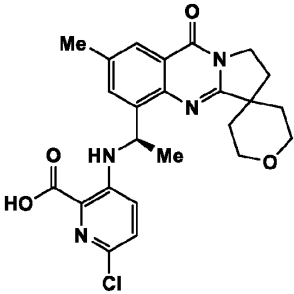
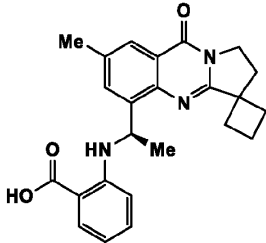
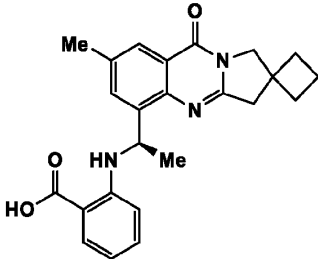
	(<i>R</i>)-2-((1-(7'-cyano-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	¹H) 7.97 (dd, <i>J</i> = 8.13, 1.38 Hz, 1H) 8.49 (d, <i>J</i> = 1.88 Hz, 1H). LCMS [M+H]⁺ = 429.2.
1-9	 (<i>R</i>)-2-((1-(7'-methyl-9'-oxo-1',2,2',3,5,6-hexahydro-9'<i>H</i>-spiro[pyran-4,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	¹H NMR (400 MHz, CD₃OD) δ = 7.86-7.91 (m, 2H), 7.55-7.58 (m, 3H), 7.08 (t, <i>J</i> = 7.8 Hz, 1H), 6.48 (t, <i>J</i> = 7.6 Hz, 1H), 6.37 (d, <i>J</i> = 8.6 Hz, 1H), 5.59 (q, <i>J</i> = 6.6 Hz, 1H), 4.11-4.21 (m, 4H), 3.74 (br t, <i>J</i> = 10.3 Hz, 2H), 3.48 (s, 1H), 2.37 (s, 3H), 2.19-2.35 (m, 4H), 1.74 (br t, <i>J</i> = 11.9 Hz, 2H), 1.60 (d, <i>J</i> = 6.6 Hz, 3H). LCMS [M+H]⁺ = 434.5.
1-10	 (<i>R</i>)-5-fluoro-2-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	¹H NMR (400 MHz, CDCl₃) δ = 7.99 (s, 1H), 7.63-7.66 (m, 1H), 7.57 (br s, 1H), 6.90-6.96 (m, 1H), 6.51 (br s, 1H), 5.60 (br s, 1H), 4.12 (t, <i>J</i> = 6.9 Hz, 2H), 2.41 (s, 3H), 2.10-2.24 (m, 5H), 2.00 (br s, 3H), 1.75-1.88 (m, 5H), 1.62-1.73 (m, 4H), 1.25 (s, 1H). LCMS: [M+H]⁺ = 436.4.

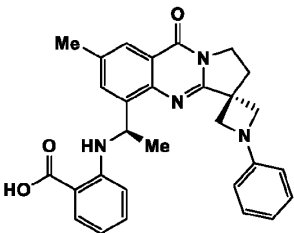
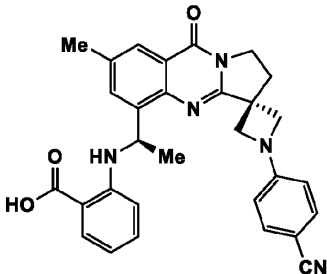
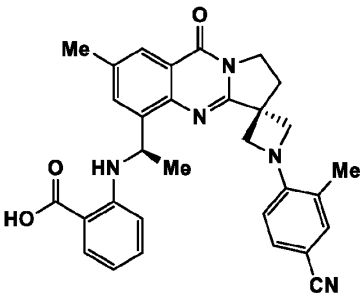
1-11	 (<i>R</i>)-2-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclohexane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)-5-fluorobenzoic acid	¹ H NMR (400 MHz, CD ₃ OD,) δ = 7.77 (s, 1H), 7.58 (s, 1H), 7.45 (dd, <i>J</i> = 3.1, 10.1 Hz, 1H), 6.59 (dt, <i>J</i> = 3.1, 8.5 Hz, 1H), 6.14 (dd, <i>J</i> = 4.4, 9.1 Hz, 1H), 5.45 (q, <i>J</i> = 6.6 Hz, 1H), 4.06 (t, <i>J</i> = 7.1 Hz, 2H), 2.56 - 2.32 (m, 2H), 2.27 (s, 3H), 2.21 - 2.08 (m, 4H), 1.95 (dt, <i>J</i> = 5.6, 13.3 Hz, 2H), 1.88 - 1.78 (m, 2H), 1.46 (d, <i>J</i> = 6.6 Hz, 3H). LCMS [<i>M</i> + <i>H</i>] ⁺ = 486.20.
1-12	 (<i>R</i>)-4-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)pyridazine-3-carboxylic acid	
1-13	 (<i>R</i>)-6-chloro-3-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)pyridazine-3-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 10.34-10.89 (m, 1H), 8.28 (br d, <i>J</i> = 6.6 Hz, 1H), 7.99 (s, 1H), 7.47 (s, 1H), 7.09 (d, <i>J</i> = 8.9 Hz, 1H), 6.97 (d, <i>J</i> = 8.9 Hz, 1H), 5.55-5.62 (m, 1H), 4.07-4.17 (m, 2H), 2.40 (s, 3H), 2.18 (br t, <i>J</i> = 6.9 Hz, 4H), 2.01 (br s, 2H), 1.83 (br d, <i>J</i> = 3.1 Hz, 4H), 1.60-1.70 (m, 4H). LCMS: [<i>M</i> + <i>H</i>] ⁺ = 453.4.

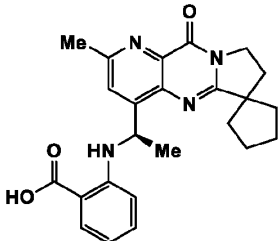
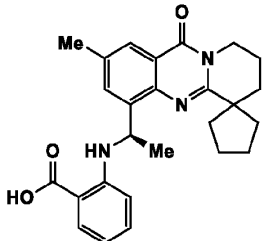
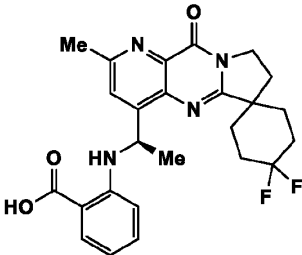
	1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid	
1-14	 (<i>R</i>)-6-chloro-3-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclohexane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid	LCMS [M+H] ⁺ = 503.05.
1-15	 (<i>R</i>)-3-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)pyrazine-2-carboxylic acid	¹ H NMR (400 MHz, CD ₃ OD) δ = 8.22-8.24 (m, 1H), 7.91 (s, 1H), 7.76 (s, 1H), 7.60 (s, 1H), 5.95 (q, <i>J</i> = 7.0 Hz, 1H), 4.05-4.16 (m, 2H), 2.44 (s, 3H), 2.14-2.34 (m, 4H), 1.94-2.08 (m, 2H), 1.78-1.90 (m, 4H), 1.72 (d, <i>J</i> = 7.0 Hz, 3H). LCMS [M+H] ⁺ = 420.1.
1-16		

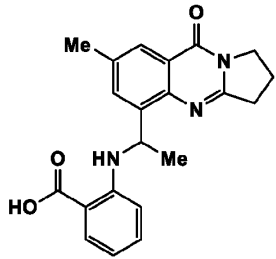
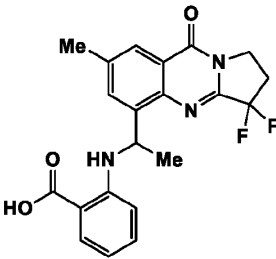
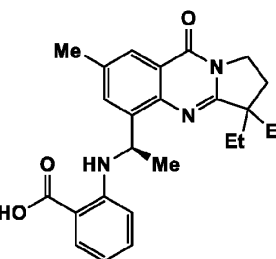
	(<i>R</i>)-4-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)thiazole-5-carboxylic acid	
1-17	 (<i>R</i>)-4-((1-(4,4-difluoro-7'-methyl-5'-oxo-2',3'-dihydro-5'<i>H</i>-spiro[cyclohexane-1,1'-pyrrolo[1,2-<i>b</i>]isoquinolin]-9'-yl)ethyl)amino)thiazole-5-carboxylic acid	
1-18	 (<i>R</i>)-4-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclohexane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)pyridazine-3-carboxylic acid	

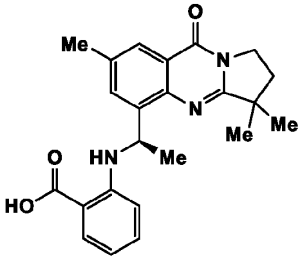
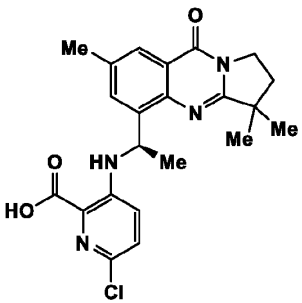
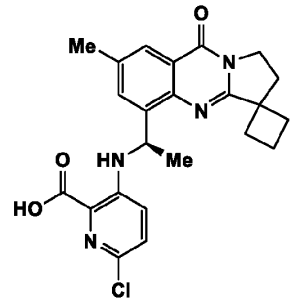
1-19	 (<i>R</i>)-5-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)thiazole-4-carboxylic acid	
1-20	 (<i>R</i>)-5-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclohexane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)thiazole-4-carboxylic acid	¹ H NMR (400 MHz, CD ₃ OD) δ = 7.98 (s, 1H), 7.89 (s, 1H), 7.67 (s, 1H), 5.24-5.37 (m, 1H), 4.12-4.24 (m, 2H), 2.47 (s, 3H) 2.34-2.54 (m, 2H), 2.30 (t, <i>J</i> = 7.1 Hz, 3H), 2.14-2.25 (m, 1H), 1.97-2.13 (m, 2H), 1.87-1.96 (m, 2H), 1.75 (br d, <i>J</i> = 6.9 Hz, 3H). LCMS [M+H] ⁺ = 475.2.
1-21	 (<i>R</i>)-3-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclohexane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)pyrazine-2-carboxylic acid	¹ H NMR (400 MHz, CD ₃ OD) δ = 8.19 (s, 1H), 7.94 (s, 1H), 7.78 (s, 1H), 7.65 (s, 1H), 6.06 (q, <i>J</i> = 6.9 Hz, 1H), 4.08-4.26 (m, 2H), 2.48-2.60 (m, 1H), 2.45 (s, 3H), 2.24-2.42 (m, 4H), 2.16 (ddd, <i>J</i> = 13.5, 9.3, 4.0 Hz, 1H), 1.97-2.10 (m, 2H), 1.83-1.97 (m, 2H), 1.72 (d, <i>J</i> = 6.9 Hz, 3H). LCMS [M+H] ⁺ = 470.4.

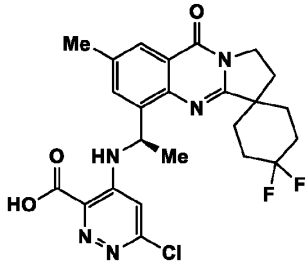
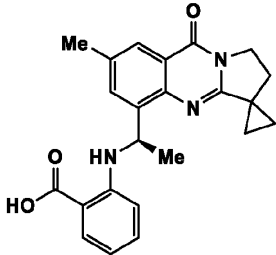
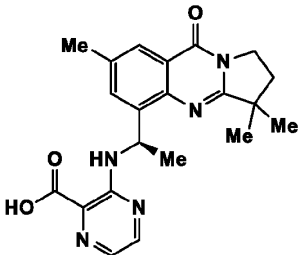
1-22	 (<i>R</i>)-6-chloro-3-((1-(7'-methyl-9'-oxo-1',2,2',3,5,6-hexahydro-9'<i>H</i>-spiro[pyran-4,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid	¹ H NMR (400 MHz, CD ₃ OD) δ = 7.93 (s, 1H), 7.61 (s, 1H), 7.20 (d, <i>J</i> = 9.0 Hz, 1H), 7.08 (d, <i>J</i> = 9.0 Hz, 1H), 5.61 (q, <i>J</i> = 6.6 Hz, 1H), 4.07-4.20 (m, 4H), 3.73 (br t, <i>J</i> = 10.6 Hz, 2H), 2.42 (s, 3H), 2.32-2.41 (m, 2H), 2.16-2.29 (m, 2H), 1.71-1.77 (m, 2H), 1.70 (d, <i>J</i> = 6.6 Hz, 3H). LCMS [M+H] ⁺ = 469.5.
1-23	 (<i>R</i>)-2-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 7.94-8.03 (m, 2H), 7.66 (br s, 1H), 7.20 (t, <i>J</i> = 7.9 Hz, 1H), 6.56-6.74 (m, 2H), 5.75-5.85 (m, 1H), 4.06 (t, <i>J</i> = 7.0 Hz, 2H), 2.52-2.73 (m, 2H), 2.43 (s, 3H), 2.38 (t, <i>J</i> = 7.1 Hz, 2H), 2.07-2.29 (m, 4H), 1.72-1.82 (m, 3H). LCMS [M+H] ⁺ = 404.2.
1-24	 (<i>R</i>)-2-((1-(7'-methyl-9'-oxo-3',9'-dihydro-1'<i>H</i>-spiro[cyclobutane-1,2'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 8.01 - 7.95 (m, 2H), 7.54 (d, <i>J</i> = 1.5 Hz, 1H), 7.22 - 7.14 (m, 1H), 6.55 (t, <i>J</i> = 7.5 Hz, 1H), 6.45 (d, <i>J</i> = 8.5 Hz, 1H), 5.57 (q, <i>J</i> = 6.7 Hz, 1H), 4.19 (s, 2H), 3.27 (s, 2H), 2.39 (s, 3H), 2.24-2.15 (m, 4H), 2.09 - 1.96 (m, 2H), 1.63 (d, <i>J</i> = 6.6 Hz, 3H). LCMS [M+H] ⁺ = 404.1.

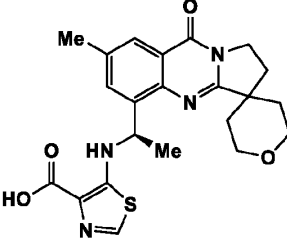
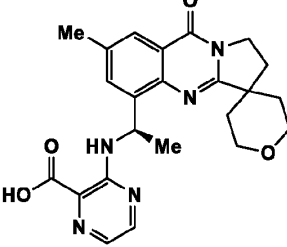
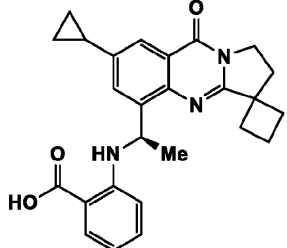
1-25	 (<i>R</i>)-2-((1-(7'-methyl-9'-oxo-1-phenyl-1',2'-dihydro-9'<i>H</i>-spiro[azetidine-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	
1-26	 (<i>R</i>)-2-((1-(1-(4-cyanophenyl)-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[azetidine-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	
1-27	 (<i>R</i>)-2-((1-(1-(4-cyano-2-methylphenyl)-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[azetidine-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	

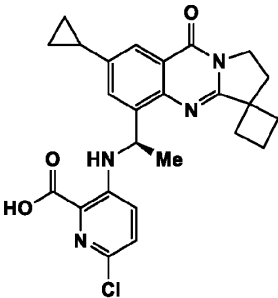
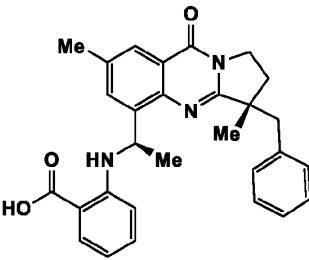
	<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	
1-28	 (<i>R</i>)-2-((1-(2'-methyl-10'-oxo-7',8'-dihydro-10'H-spiro[cyclopentane-1,6'-pyrido[3,2-<i>d</i>]pyrrolo[1,2-<i>a</i>]pyrimidin]-4'-yl)ethyl)amino)benzoic acid	
1-29	 (<i>R</i>)-2-((1-(2'-methyl-11'-oxo-8',9'-dihydro-7'<i>H</i>,11'<i>H</i>-spiro[cyclopentane-1,6'-pyrido[2,1-<i>b</i>]quinazolin]-4'-yl)ethyl)amino)benzoic acid	
1-30	 (<i>R</i>)-2-((1-(4,4-difluoro-2'-methyl-10'-oxo-7',8'-dihydro-10'<i>H</i>-spiro[cyclohexane-1,6'-pyrido[3,2-	

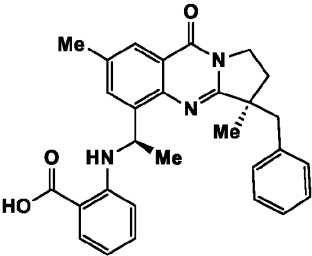
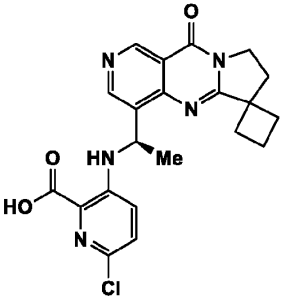
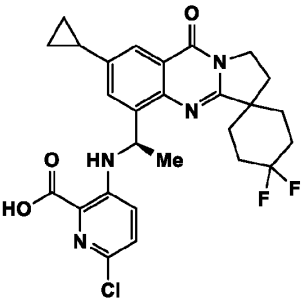
	<i>d</i>]pyrrolo[1,2- <i>a</i>]pyrimidin]-4'-yl)ethyl)amino)benzoic acid	
1-31	 2-((1-(7-methyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-<i>b</i>]quinazolin-5-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 8.00 - 7.93 (m, 2H), 7.55 (d, <i>J</i> = 1.8 Hz, 1H), 7.20 - 7.13 (m, 1H), 6.55 (t, <i>J</i> = 7.6 Hz, 1H), 6.45 (d, <i>J</i> = 8.6 Hz, 1H), 5.60 (q, <i>J</i> = 6.6 Hz, 1H), 4.23 (t, <i>J</i> = 7.3 Hz, 2H), 3.26 (t, <i>J</i> = 7.9 Hz, 2H), 2.39 (s, 3H), 2.32 (quin, <i>J</i> = 7.6 Hz, 2H), 1.62 (d, <i>J</i> = 6.6 Hz, 3H). LCMS [M+H] ⁺ = 365.1.
1-32	 2-((1-(3,3-difluoro-7-methyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-<i>b</i>]quinazolin-5-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CD ₃ OD) δ = 8.18 (br d, <i>J</i> = 8.4 Hz, 1H), 7.88 (d, <i>J</i> = 8.0 Hz, 1H), 7.84 (d, <i>J</i> = 7.6 Hz, 1H), 7.59 - 7.48 (m, 1H), 7.06 (br t, <i>J</i> = 7.6 Hz, 1H), 6.49 (br t, <i>J</i> = 7.3 Hz, 1H), 6.36 (br d, <i>J</i> = 8.8 Hz, 1H), 5.80 - 5.63 (m, 1H), 4.26 (br t, <i>J</i> = 6.4 Hz, 2H), 2.98 - 2.83 (m, 2H), 1.63 (br d, <i>J</i> = 6.4 Hz, 3H). LCMS [M+H] ⁺ = 386.1.
1-33	 (<i>R</i>)-2-((1-(3,3-diethyl-7-methyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-<i>b</i>]quinazolin-5-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 8.02 - 7.94 (m, 2H), 7.55 (d, <i>J</i> = 1.4 Hz, 1H), 7.15 (t, <i>J</i> = 7.9 Hz, 1H), 6.54 (t, <i>J</i> = 7.5 Hz, 1H), 6.47 (d, <i>J</i> = 8.6 Hz, 1H), 5.67 (q, <i>J</i> = 6.8 Hz, 1H), 4.12 (t, <i>J</i> = 7.3 Hz, 2H), 2.40 (s, 3H), 2.14 (t, <i>J</i> = 7.4 Hz, 2H), 1.91 - 1.80 (m, 4H), 1.63 (d, <i>J</i> = 6.8 Hz, 3H), 1.03 - 0.90 (m, 6H). LCMS [M+H] ⁺ = 420.2.

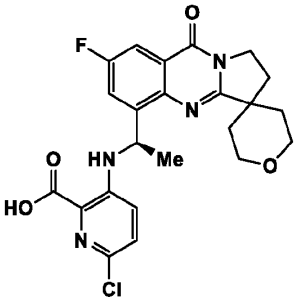
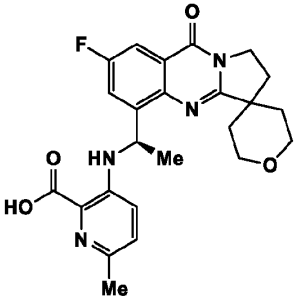
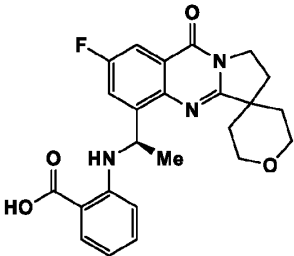
1-34	 (<i>R</i>)-2-((1-(3,3,7-trimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-<i>b</i>]quinazolin-5-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 7.95-8.00 (m, 2H), 7.58 (br s, 1H), 7.18 (t, <i>J</i> = 7.8 Hz, 1H), 6.51-6.64 (m, 2H), 5.62-5.71 (m, 1H), 4.05-4.19 (m, 2H), 2.41 (s, 3H), 2.13 (t, <i>J</i> = 7.1 Hz, 2H), 1.68 (br d, <i>J</i> = 6.3 Hz, 3H), 1.44 (d, <i>J</i> = 7.5 Hz, 7H). LCMS [M+H] ⁺ = 392.2.
1-35	 (<i>R</i>)-6-chloro-3-((1-(3,3,7-trimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-<i>b</i>]quinazolin-5-yl)ethyl)amino)picolinic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 8.24-8.42 (m, 1H), 8.00 (s, 1H), 7.49 (s, 1H), 7.10 (d, <i>J</i> = 8.9 Hz, 1H), 7.04 (d, <i>J</i> = 9.0 Hz, 1H), 5.62 (q, <i>J</i> = 7.4 Hz, 1H), 4.04-4.22 (m, 2H), 2.41 (s, 3H), 2.14 (t, <i>J</i> = 7.1 Hz, 2H), 1.66 (d, <i>J</i> = 6.8 Hz, 3H), 1.46 (d, <i>J</i> = 5.9 Hz, 6H). LCMS [M+H] ⁺ = 427.4.
1-36	 (<i>R</i>)-6-chloro-3-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'H-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 8.31-8.38 (m, 1H), 7.99 (s, 1H), 7.49 (d, <i>J</i> = 1.5 Hz, 1H), 7.09-7.13 (m, 1H), 7.02-7.05 (m, 1H), 5.69 (quin, <i>J</i> = 6.8 Hz, 1H), 4.04-4.12 (m, 2H), 2.59-2.74 (m, 2H), 2.41 (s, 4H), 2.07-2.30 (m, 4H), 1.67-1.74 (m, 3H). LCMS [M+H] ⁺ = 439.4.

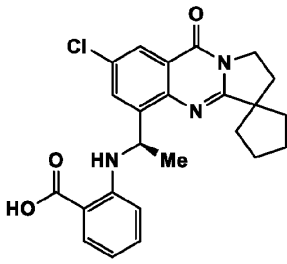
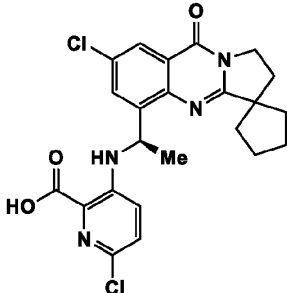
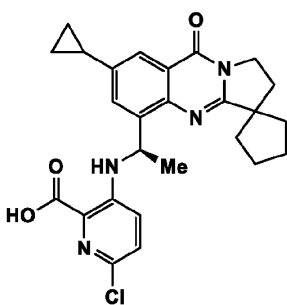
1-37	 (<i>R</i>)-6-chloro-4-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclohexane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)pyridazine-3-carboxylic acid	¹ H NMR (400 MHz, CD ₃ OD) δ = 10.01 (br d, <i>J</i> = 5.5 Hz, 1H), 7.99 (s, 1H), 7.68 (s, 1H), 6.68 (br s, 1H), 5.72 - 5.55 (m, 1H), 4.23 - 4.12 (m, 2H), 2.45 (s, 3H), 2.42 - 2.17 (m, 6H), 2.13 - 1.99 (m, 2H), 1.92 (s, 2H), 1.69 (br d, <i>J</i> = 6.5 Hz, 3H). LCMS [<i>M</i> + <i>H</i>] ⁺ = 504.1.
1-38	 (<i>R</i>)-2-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopropane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 7.93-7.99 (m, 2H), 7.57 (s, 1H), 7.21 (t, <i>J</i> = 7.8 Hz, 1H), 6.66 (br t, <i>J</i> = 7.8 Hz, 1H), 6.53 (br d, <i>J</i> = 8.5 Hz, 1H), 5.52 (q, <i>J</i> = 6.6 Hz, 1H), 4.28 (br t, <i>J</i> = 7.6 Hz, 2H), 2.40 (s, 3H), 2.35 (br t, <i>J</i> = 7.5 Hz, 2H), 1.64 (br d, <i>J</i> = 6.6 Hz, 3H), 1.35-1.54 (m, 2H), 1.09-1.17 (m, 2H). LCMS [<i>M</i> + <i>H</i>] ⁺ = 390.2.
1-39	 (<i>R</i>)-3-((1-(3,3,7-trimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-<i>b</i>]quinazolin-5-yl)ethyl)amino)pyrazine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 8.31 (d, <i>J</i> = 1.8 Hz, 1H), 8.00 (s, 1H), 7.70 (d, <i>J</i> = 1.8 Hz, 1H), 7.56 (s, 1H), 5.87 (q, <i>J</i> = 6.9 Hz, 1H), 4.18-4.27 (m, 1H), 4.07-4.16 (m, 1H), 2.45 (s, 3H), 2.10-2.20 (m, 2H), 1.76 (d, <i>J</i> = 6.9 Hz, 3H), 1.51 (s, 6H). LCMS [<i>M</i> + <i>H</i>] ⁺ = 394.2.

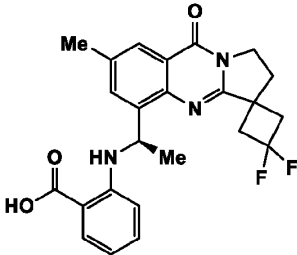
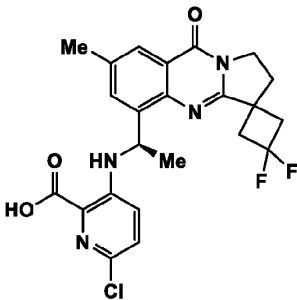
1-40	 (<i>R</i>)-5-((1-(7'-methyl-9'-oxo-1',2,2',3,5,6-hexahydro-9'<i>H</i>-spiro[pyran-4,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)thiazole-4-carboxylic acid	¹ H NMR (400 MHz, CD ₃ OD) δ = 7.96 (s, 1H), 7.92 (s, 1H), 7.64 (s, 1H), 5.22 (q, <i>J</i> = 6.6 Hz, 1H), 4.13-4.18 (m, 2H), 4.03-4.13 (m, 2H), 3.67-3.79 (m, 2H), 2.46 (s, 3H), 2.29-2.42 (m, 3H), 2.18-2.28 (m, 1H), 1.77 (d, <i>J</i> = 6.6 Hz, 3H), 1.71 (br d, <i>J</i> = 13.6 Hz, 2H). LCMS [M+H] ⁺ = 441.1.
1-41	 (<i>R</i>)-3-((1-(7'-methyl-9'-oxo-1',2,2',3,5,6-hexahydro-9'<i>H</i>-spiro[pyran-4,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)pyrazine-2-carboxylic acid	¹ H NMR (400 MHz, CD ₃ OD) δ = 8.21-8.24 (m, 1H), 7.92 (s, 1H), 7.74-7.79 (m, 1H), 7.63 (s, 1H), 6.03 (d, <i>J</i> = 6.9 Hz, 1H), 4.11-4.20 (m, 3H), 4.02-4.09 (m, 1H), 3.66-3.79 (m, 2H), 3.34-3.36 (m, 1H), 2.44 (s, 3H), 2.29-2.41 (m, 3H), 2.17-2.26 (m, 1H), 1.73-1.77 (m, 3H), 1.65-1.73 (m, 2H). LCMS [M+H] ⁺ = 436.1.
1-42	 (<i>R</i>)-2-((1-(7'-cyclopropyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 7.97 (d, <i>J</i> = 7.9 Hz, 1H), 7.80 (s, 1H), 7.58 (br s, 1H), 7.20 (t, <i>J</i> = 7.9 Hz, 1H), 6.68 - 6.56 (m, 2H), 5.83 - 5.69 (m, 1H), 4.06 (t, <i>J</i> = 7.0 Hz, 2H), 2.71 - 2.54 (m, 2H), 2.38 (t, <i>J</i> = 7.0 Hz, 2H), 2.30 - 2.06 (m, 4H), 2.03 - 1.90 (m, 1H), 1.75 (br s, 3H), 1.06 - 1.00 (m, 1H).

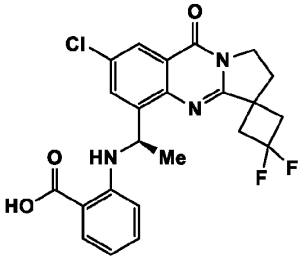
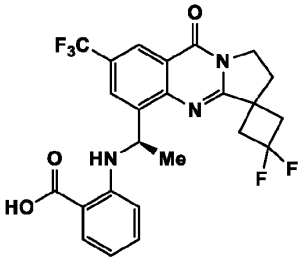
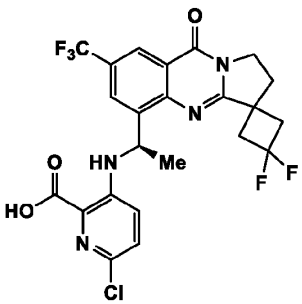
	pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	0.91 (m, 2H), 0.84 - 0.67 (m, 2H). LCMS [M+H] ⁺ = 430.2.
1-43	 (<i>R</i>)-6-chloro-3-((1-(7'-cyclopropyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 8.35 (br d, <i>J</i> = 6.5 Hz, 1H), 7.78 (s, 1H), 7.46 (s, 1H), 7.15 - 6.99 (m, 2H), 5.67 (quin, <i>J</i> = 6.5 Hz, 1H), 4.10 - 4.04 (m, 2H), 2.73 - 2.59 (m, 2H), 2.40 (t, <i>J</i> = 6.9 Hz, 2H), 2.29 - 2.09 (m, 5H), 1.98 - 1.87 (m, 1H), 1.70 (d, <i>J</i> = 6.6 Hz, 3H), 1.07 - 0.96 (m, 2H), 0.78 - 0.63 (m, 2H). LCMS [M+H] ⁺ = 465.2.
1-44 and 1-45	 2-(((<i>R</i>)-1-(((<i>S</i>)-3-benzyl-3,7-dimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-<i>b</i>]quinazolin-5-yl)ethyl)amino)benzoic acid And	Compound derived from Intermediate L-1: ¹H NMR (400 MHz, CD₃OD) δ = 7.89 - 7.82 (m, 2H), 7.64 (s, 1H), 7.21 - 7.07 (m, 4H), 7.02-7.00 (m, 2H), 6.56 - 6.45 (m, 2H), 5.64 (q, <i>J</i> = 6.8 Hz, 1H), 3.95-3.89 (m, 1H), 3.26 (d, <i>J</i> = 13.1 Hz, 1H), 3.23 - 3.14 (m, 1H), 2.98 (d, <i>J</i> = 13.1 Hz, 1H), 2.47 - 2.38 (m, 4H), 2.13-2.04 (m, 1H), 1.70 (d, <i>J</i> = 6.8 Hz, 3H), 1.58 (s, 3H). LCMS [M+H]⁺ = 468.2. Compound resulting from Intermediate L-2: ¹H NMR (400 MHz, CD₃OD) δ = 7.92 - 7.84 (m, 2H), 7.64 (s, 1H), 7.21 - 7.11 (m, 4H), 7.10 - 7.05 (m, 2H), 6.60 (d, <i>J</i> = 8.5 Hz, 1H), 6.51 (t, <i>J</i> = 7.5 Hz, 1H), 5.73 (q, <i>J</i> = 6.7 Hz, 1H), 3.96 - 3.86

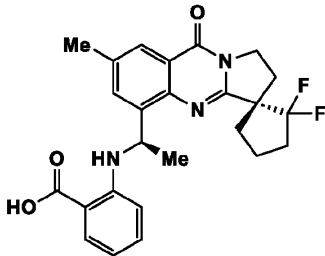
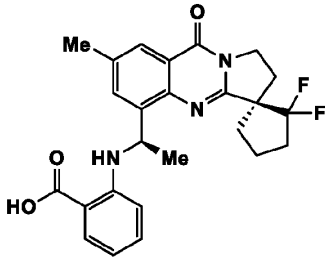
	 2-(((<i>R</i>)-1-((<i>R</i>)-3-benzyl-3,7-dimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-<i>b</i>]quinazolin-5-yl)ethyl)amino)benzoic acid	(m, 1H), 3.29 - 3.20 (m, 2H), 3.01 (d, $J = 13.1$ Hz, 1H), 2.46 - 2.35 (m, 4H), 2.13 - 2.04 (m, 1H), 1.65 (d, $J = 6.6$ Hz, 3H), 1.55 (s, 3H). LCMS $[M+H]^+ = 468.2$.
1-46	 (<i>R</i>)-6-chloro-3-(((1-(10'-oxo-7',8'-dihydro-10'<i>H</i>-spiro[cyclobutane-1,6'-pyrido[4,3-<i>d</i>]pyrrolo[1,2-<i>a</i>]pyrimidin]-4'-yl)ethyl)amino)picolinic acid	^1H NMR (400 MHz, CDCl_3) $\delta = 9.41$ (s, 1H), 8.75 (s, 1H), 8.52 (br d, $J = 6.6$ Hz, 1H), 7.17 (d, $J = 8.8$ Hz, 1H), 6.98 (br d, $J = 8.8$ Hz, 1H), 5.41 (quin, $J = 6.4$ Hz, 1H), 4.21 - 4.03 (m, 2H), 2.81 - 2.64 (m, 2H), 2.53 - 2.41 (m, 2H), 2.35 - 2.12 (m, 5H), 1.82 (d, $J = 6.6$ Hz, 3H). LCMS $[M+H]^+ = 426.1$.
1-47	 (<i>R</i>)-6-chloro-3-(((1-(7'-cyclopropyl-4,4-difluoro-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclohexane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin-5-yl)ethyl)amino)picolinic acid	^1H NMR (400 MHz, CDCl_3) $\delta = 8.28$ (br d, $J = 6.4$ Hz, 1H), 7.79 (d, $J = 1.8$ Hz, 1H), 7.48 (d, $J = 1.9$ Hz, 1H), 7.11 (d, $J = 9.0$ Hz, 1H), 6.88 (d, $J = 9.0$ Hz, 1H), 5.52 (quin, $J = 6.7$ Hz, 1H), 4.16 (t, $J = 7.1$ Hz, 2H), 2.59 - 2.39 (m, 2H), 2.28 - 2.12 (m, 4H), 2.08 - 1.83 (m, 1H), 2.08 - 1.81 (m, 5H), 1.65 (d, $J = 6.6$ Hz, 3H), 1.07 - 0.95 (m, 2H), 0.77 - 0.64 (m, 2H). LCMS $[M+H]^+ = 539.1$.

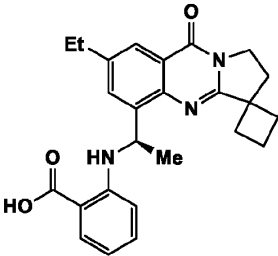
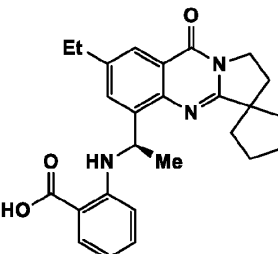
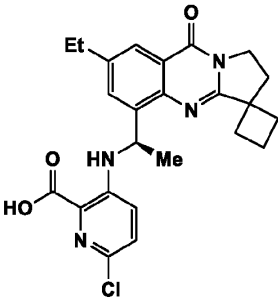
	<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid	
1-48	 (<i>R</i>)-6-chloro-3-((1-(7'-fluoro-9'-oxo-1',2,2',3,5,6-hexahydro-9'<i>H</i>-spiro[pyran-4,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid	¹ H NMR (400 MHz, CD ₃ OD) δ = 7.76 (dd, <i>J</i> = 2.9, 8.3 Hz, 1H), 7.55 (dd, <i>J</i> = 3.0, 9.1 Hz, 1H), 7.26 - 7.18 (m, 1H), 7.07 - 7.01 (m, 1H), 5.63 (q, <i>J</i> = 6.9 Hz, 1H), 4.18 (t, <i>J</i> = 7.2 Hz, 2H), 4.14 - 4.06 (m, 2H), 3.77 - 3.68 (m, 2H), 2.38 (dt, <i>J</i> = 1.5, 7.3 Hz, 2H), 2.28 - 2.16 (m, 2H), 1.78 - 1.68 (m, 5H). LCMS [M+H] ⁺ = 473.1.
1-49	 (<i>R</i>)-3-((1-(7'-fluoro-9'-oxo-1',2,2',3,5,6-hexahydro-9'<i>H</i>-spiro[pyran-4,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)-6-methylpicolinic acid	¹ H NMR (400 MHz, CD ₃ OD) δ = 7.75 (dd, <i>J</i> = 3.0, 8.4 Hz, 1H), 7.57 (dd, <i>J</i> = 2.9, 9.2 Hz, 1H), 7.34-7.25 (m, 2H), 5.72 (q, <i>J</i> = 7.2 Hz, 1H), 4.18 (t, <i>J</i> = 7.3 Hz, 2H), 4.13 - 4.05 (m, 2H), 3.77 - 3.68 (m, 2H), 2.51 (s, 3H), 2.42 - 2.35 (m, 2H), 2.28 - 2.11 (m, 2H), 1.80 - 1.68 (m, 5H). LCMS [M+H] ⁺ = 453.2.
1-50	 (<i>R</i>)-3-((1-(7'-fluoro-9'-oxo-1',2,2',3,5,6-hexahydro-9'<i>H</i>-spiro[pyran-4,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid	¹ H NMR (400 MHz, CD ₃ OD) δ = 7.90 (dd, <i>J</i> = 1.6, 8.0 Hz, 1H), 7.71 (dd, <i>J</i> = 3.0, 8.4 Hz, 1H), 7.49 (dd, <i>J</i> = 3.0, 9.3 Hz, 1H), 7.11 (ddd, <i>J</i> = 1.7, 7.0, 8.5 Hz, 1H), 6.56 - 6.49 (m, 1H), 6.39 (d, <i>J</i> = 8.4 Hz, 1H), 5.65 (q, <i>J</i> = 6.6 Hz, 1H), 4.21 - 4.10 (m, 4H), 3.79 - 3.70 (m, 2H), 2.40 - 2.33 (m, 2H),

	(<i>R</i>)-2-((1-(7'-fluoro-9'-oxo-1',2,2',3,5,6-hexahydro-9' <i>H</i> -spiro[pyran-4,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	2.29 - 2.18 (m, 2H), 1.82 - 1.72 (m, 2H), 1.66 (d, <i>J</i> = 6.6 Hz, 3H). LCMS [M+H] ⁺ = 438.2.
1-51	 (<i>R</i>)-2-((1-(7'-chloro-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CD ₃ OD) δ = 8.03 (d, <i>J</i> = 2.5 Hz, 1H), 7.90 (dd, <i>J</i> = 1.6, 8.0 Hz, 1H), 7.65 (d, <i>J</i> = 2.5 Hz, 1H), 7.11 (ddd, <i>J</i> = 1.6, 7.1, 8.6 Hz, 1H), 6.56 - 6.48 (m, 1H), 6.38 (d, <i>J</i> = 8.4 Hz, 1H), 5.59 (q, <i>J</i> = 6.6 Hz, 1H), 4.13 (dt, <i>J</i> = 0.9, 7.1 Hz, 2H), 2.28 - 2.19 (m, 4H), 2.08 - 2.00 (m, 2H), 1.96 - 1.84 (m, 4H), 1.62 (d, <i>J</i> = 6.8 Hz, 3H). LCMS [M+H] ⁺ = 438.1.
1-52	 (<i>R</i>)-6-chloro-3-((1-(7'-chloro-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid	¹ H NMR (400 MHz, CD ₃ OD) δ = 8.07 (d, <i>J</i> = 2.5 Hz, 1H), 7.71 (d, <i>J</i> = 2.4 Hz, 1H), 7.23 (d, <i>J</i> = 8.9 Hz, 1H), 7.06 (d, <i>J</i> = 9.0 Hz, 1H), 5.55 (q, <i>J</i> = 6.8 Hz, 1H), 4.13 (dt, <i>J</i> = 2.4, 7.1 Hz, 2H), 2.27 - 2.18 (m, 4H), 2.06 - 1.97 (m, 2H), 1.95 - 1.83 (m, 4H), 1.70 (d, <i>J</i> = 6.6 Hz, 3H). LCMS [M+H] ⁺ = 473.1.
1-53		¹ H NMR (400 MHz, CD ₃ OD) δ = 7.77 (d, <i>J</i> = 2.1 Hz, 1H), 7.51 (d, <i>J</i> = 2.0 Hz, 1H), 7.20 (d, <i>J</i> = 8.9 Hz, 1H), 7.08 (d, <i>J</i> = 9.1 Hz, 1H), 5.55 (q, <i>J</i> = 6.6 Hz, 1H), 4.11 (dt, <i>J</i> = 2.6, 7.0 Hz, 2H), 2.25 - 2.17 (m, 4H), 2.05 - 1.96 (m, 3H), 1.93 - 1.82 (m, 4H), 1.68 (d, <i>J</i> = 6.6 Hz, 3H), 1.04 - 0.99

	(<i>R</i>)-6-chloro-3-((1-(7'-cyclopropyl-9'-oxo-1',2'-dihydro-9' <i>H</i> -spiro[cyclopentane-1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid	(m, 2H), 0.75 - 0.62 (m, 2H). LCMS [M+H] ⁺ = 479.2.
1-54	 (<i>R</i>)-2-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 7.99 (s, 1H), 7.97 (dd, <i>J</i> = 1.5, 8.0 Hz, 1H), 7.63 (br s, 1H), 7.24 - 7.16 (m, 1H), 6.68 - 6.59 (m, 1H), 6.55 (br d, <i>J</i> = 8.1 Hz, 1H), 5.65 (q, <i>J</i> = 6.6 Hz, 1H), 4.16 (t, <i>J</i> = 7.0 Hz, 2H), 3.38 - 3.17 (m, 2H), 2.76 (tdd, <i>J</i> = 4.3, 9.2, 13.9 Hz, 2H), 2.51 (t, <i>J</i> = 6.9 Hz, 2H), 2.42 (s, 3H), 1.69 (br d, <i>J</i> = 6.8 Hz, 3H). ¹⁹ F NMR (377 MHz, CDCl ₃) δ = -85.00, -85.51, -95.88, -96.41. LCMS [M+H] ⁺ = 440.2.
1-55	 (<i>R</i>)-6-chloro-3-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 8.34 (br d, <i>J</i> = 6.6 Hz, 1H), 8.01 (d, <i>J</i> = 1.1 Hz, 1H), 7.52 (d, <i>J</i> = 2.0 Hz, 1H), 7.12 (d, <i>J</i> = 8.9 Hz, 1H), 6.97 (d, <i>J</i> = 9.0 Hz, 1H), 5.60 (quin, <i>J</i> = 6.8 Hz, 1H), 4.23 - 4.08 (m, 2H), 3.43 - 3.28 (m, 1H), 3.26 - 3.10 (m, 1H), 2.86 - 2.70 (m, 2H), 2.53 (t, <i>J</i> = 7.0 Hz, 2H), 2.42 (s, 3H), 1.68 (d, <i>J</i> = 6.8 Hz, 3H). ¹⁹ F NMR (377 MHz, CDCl ₃) δ = -85.39, -85.91, -95.25, -95.77. LCMS [M+H] ⁺ = 475.2.

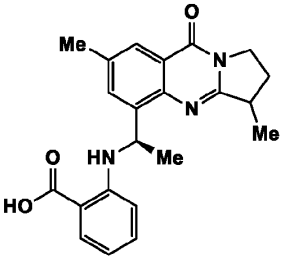
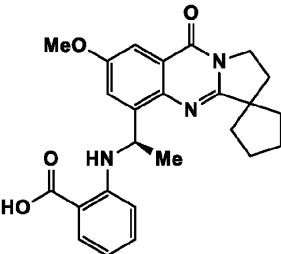
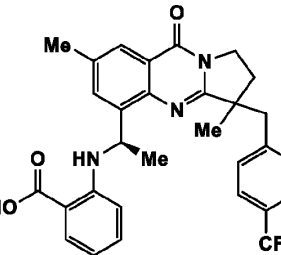
1-56	 (<i>R</i>)-2-((1-(7'-chloro-3,3-difluoro-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 8.16 (<i>d</i> , <i>J</i> = 2.4 Hz, 1H), 8.00 (<i>dd</i> , <i>J</i> = 1.6, 8.1 Hz, 1H), 7.73 (<i>d</i> , <i>J</i> = 1.9 Hz, 1H), 7.24 - 7.17 (<i>m</i> , 1H), 6.62 (<i>br t</i> , <i>J</i> = 7.4 Hz, 1H), 6.42 (<i>br d</i> , <i>J</i> = 8.0 Hz, 1H), 5.61 (<i>q</i> , <i>J</i> = 6.5 Hz, 1H), 4.18 (<i>t</i> , <i>J</i> = 7.0 Hz, 2H), 3.37 - 3.20 (<i>m</i> , 2H), 2.86 - 2.70 (<i>m</i> , 2H), 2.55 (<i>t</i> , <i>J</i> = 7.0 Hz, 2H), 1.68 (<i>d</i> , <i>J</i> = 6.8 Hz, 3H). ¹⁹ F NMR (377 MHz, CDCl ₃) δ = -85.13, -85.65, -95.71, -96.23. LCMS [<i>M</i> + <i>H</i>] ⁺ = 460.1.
1-57	 (<i>R</i>)-2-((1-(3,3-difluoro-9'-oxo-7'-(trifluoromethyl)-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 8.50 (<i>s</i> , 1H), 8.00 (<i>m</i> , 2H), 7.23 (<i>br t</i> , <i>J</i> = 7.4 Hz, 1H), 6.66 (<i>br s</i> , 1H), 6.56 - 6.37 (<i>br s</i> , 1H), 5.66 (<i>m</i> , 1H), 4.20 (<i>t</i> , <i>J</i> = 7.0 Hz, 2H), 3.42 - 3.21 (<i>m</i> , 2H), 2.87 - 2.74 (<i>m</i> , 2H), 2.57 (<i>t</i> , <i>J</i> = 7.0 Hz, 2H), 1.72 (<i>d</i> , <i>J</i> = 6.6 Hz, 3H). ¹⁹ F NMR (377 MHz, CDCl ₃) δ = -62.23, -85.21, -85.73 (<i>m</i>), -95.54, -96.06. LCMS [<i>M</i> + <i>H</i>] ⁺ = 494.2.
1-58	 (<i>R</i>)-6-chloro-3-((1-(3,3-difluoro-9'-oxo-7'-(trifluoromethyl)-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 8.51 (<i>d</i> , <i>J</i> = 1.1 Hz, 1H), 8.42 (<i>br d</i> , <i>J</i> = 6.4 Hz, 1H), 7.89 (<i>d</i> , <i>J</i> = 2.0 Hz, 1H), 7.16 (<i>d</i> , <i>J</i> = 9.0 Hz, 1H), 6.90 (<i>d</i> , <i>J</i> = 9.0 Hz, 1H), 5.56 (<i>quin</i> , <i>J</i> = 6.7 Hz, 1H), 4.27 - 4.15 (<i>m</i> , 2H), 3.45 - 3.31 (<i>m</i> , 1H), 3.28 - 3.13 (<i>m</i> , 1H), 2.91 - 2.74 (<i>m</i> , 2H), 2.57 (<i>t</i> , <i>J</i> = 7.1 Hz, 2H), 1.73 (<i>d</i> , <i>J</i> = 6.6 Hz, 3H). ¹⁹ F NMR (377 MHz, CDCl ₃) δ = -62.28, -85.58, -86.10, -94.91, -95.43. LCMS [<i>M</i> + <i>H</i>] ⁺ = 508.2.

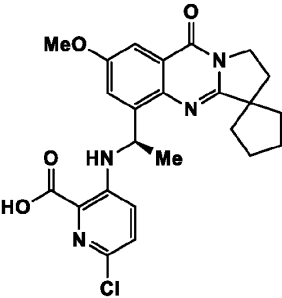
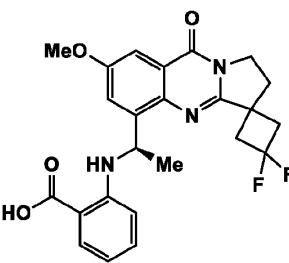
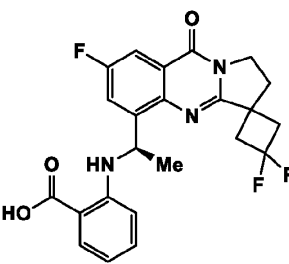
	<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid	= 529.1.
1-59 and 1-60	 2-(((<i>R</i>)-1-((<i>S</i>)-2,2-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid And  2-(((<i>R</i>)-1-((<i>R</i>)-2,2-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	Compound derived Intermediate O-1: ¹H NMR (400 MHz, CD₃OD) δ = 7.94 (<i>d</i>, <i>J</i> = 1.2 Hz, 1H), 7.91 (<i>dd</i>, <i>J</i> = 1.6, 8.0 Hz, 1H), 7.63 (<i>d</i>, <i>J</i> = 2.0 Hz, 1H), 7.18 - 7.03 (<i>m</i>, 1H), 6.55 - 6.47 (<i>m</i>, 1H), 6.39 (<i>d</i>, <i>J</i> = 8.4 Hz, 1H), 5.63 (<i>q</i>, <i>J</i> = 6.8 Hz, 1H), 4.31 - 4.17 (<i>m</i>, 1H), 4.15 - 4.03 (<i>m</i>, 1H), 2.85 - 2.65 (<i>m</i>, 2H), 2.62 - 2.49 (<i>m</i>, 1H), 2.41 (<i>s</i>, 3H), 2.38 - 2.22 (<i>m</i>, 3H), 2.19 - 2.07 (<i>m</i>, 1H), 2.06 - 1.92 (<i>m</i>, 1H), 1.62 (<i>d</i>, <i>J</i> = 6.8 Hz, 3H). ¹⁹F NMR (377 MHz, CD₃OD) δ = -100.27, -100.88, -111.67, -112.28. LCMS [M+1]⁺ = 454.2. Compound derived from Intermediate O-2: ¹H NMR (400 MHz, CD₃OD) δ = 7.94 (<i>d</i>, <i>J</i> = 1.2 Hz, 1H), 7.89 (<i>dd</i>, <i>J</i> = 1.6, 8.0 Hz, 1H), 7.65 (<i>d</i>, <i>J</i> = 2.0 Hz, 1H), 7.18 - 7.03 (<i>m</i>, 1H), 6.55 - 6.39 (<i>m</i>, 2H), 5.61 (<i>q</i>, <i>J</i> = 6.8 Hz, 1H), 4.27 - 4.17 (<i>m</i>, 1H), 4.15 - 4.02 (<i>m</i>, 1H), 2.86 - 2.68 (<i>m</i>, 2H), 2.66 - 2.54 (<i>m</i>, 1H), 2.43 (<i>s</i>, 3H), 2.39 - 2.22 (<i>m</i>, 3H), 2.17 - 2.06 (<i>m</i>, 1H), 2.05 - 1.90 (<i>m</i>, 1H), 1.65 (<i>d</i>, <i>J</i> = 6.8 Hz, 3H). ¹⁹F NMR (377 MHz, CD₃OD) δ = -100.80, -100.40, -111.22, -111.83. LCMS [M+1]⁺ = 454.2.

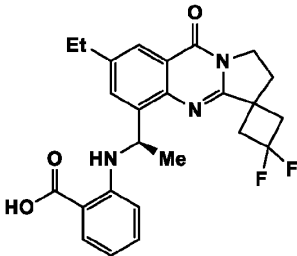
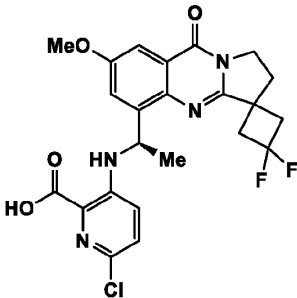
1-61	 (<i>R</i>)-2-((1-(7'-ethyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 8.02-8.05 (m, 1H), 7.97 (dd, <i>J</i> = 8.0, 1.5 Hz, 1H), 7.75 (br s, 1H), 7.19-7.25 (m, 1H), 6.77 (br t, <i>J</i> = 7.5 Hz, 1H), 6.70 (br d, <i>J</i> = 8.1 Hz, 1H), 5.80-5.88 (m, 1H), 4.06 (t, <i>J</i> = 7.0 Hz, 2H), 2.70-2.79 (m, 2H), 2.50-2.69 (m, 2H), 2.37 (t, <i>J</i> = 6.9 Hz, 2H), 2.09-2.25 (m, 4H), 1.83 (br d, <i>J</i> = 6.4 Hz, 3H), 1.25 (t, <i>J</i> = 7.6 Hz, 3H). LCMS [M+H] ⁺ = 418.2.
1-62	 (<i>R</i>)-2-((1-(7'-ethyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 8.01 (d, <i>J</i> = 1.9 Hz, 1H), 7.94-7.98 (m, 1H), 7.59 (s, 1H), 7.19 (td, <i>J</i> = 7.8, 1.6 Hz, 1H), 6.62 (t, <i>J</i> = 7.4 Hz, 1H), 6.54 (d, <i>J</i> = 8.5 Hz, 1H), 5.64 (q, <i>J</i> = 6.8 Hz, 1H), 4.14 (t, <i>J</i> = 7.0 Hz, 3H), 2.70 (q, <i>J</i> = 7.6 Hz, 2H), 2.18 (br t, <i>J</i> = 7.0 Hz, 4H), 1.95-2.07 (m, 2H), 1.82 (br d, <i>J</i> = 3.0 Hz, 4H), 1.68 (d, <i>J</i> = 6.6 Hz, 3H), 1.21 (t, <i>J</i> = 7.6 Hz, 3H). LCMS [M+H] ⁺ = 432.2.
1-63	 (<i>R</i>)-6-chloro-3-((1-(7'-ethyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 8.02 (d, <i>J</i> = 2.0 Hz, 1H), 7.55 (d, <i>J</i> = 2.0 Hz, 1H), 7.09-7.13 (m, 1H), 6.98-7.05 (m, 1H), 5.68 (q, <i>J</i> = 6.6 Hz, 1H), 4.12 (td, <i>J</i> = 7.0, 1.9 Hz, 2H), 2.60-2.75 (m, 4H), 2.43 (t, <i>J</i> = 7.1 Hz, 2H), 2.08-2.30 (m, 4H), 1.72 (d, <i>J</i> = 6.8 Hz, 3H), 1.22 (t, <i>J</i> = 7.6 Hz, 3H). LCMS [M+H] ⁺ = 453.1.

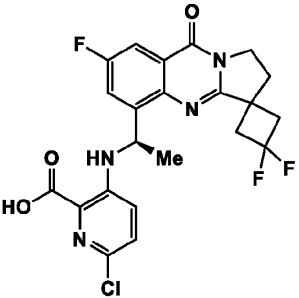
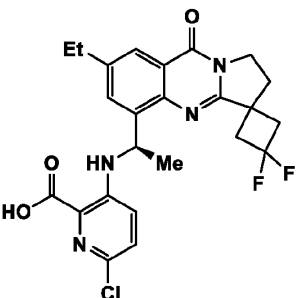
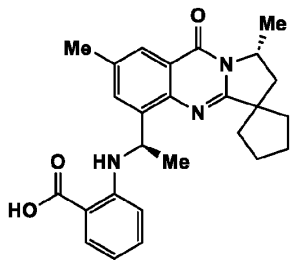
1-64 and 1-65	2-(((<i>R</i>)-1-((<i>S</i>)-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid And 2-(((<i>R</i>)-1-((<i>R</i>)-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	Compound derived from Intermediate N-1: ¹H NMR (400 MHz, CD₃OD) δ = 8.45 (s, 1H), 7.92 - 7.88 (m, 1H), 7.86 (dd, <i>J</i> = 1.6, 8.0 Hz, 1H), 7.61 (<i>d</i>, <i>J</i> = 2.0 Hz, 1H), 7.05 (ddd, <i>J</i> = 1.6, 7.2, 8.8 Hz, 1H), 6.50 - 6.44 (m, 1H), 6.43 (<i>d</i>, <i>J</i> = 8.4 Hz, 1H), 5.62 (q, <i>J</i> = 6.8 Hz, 1H), 4.27 - 3.97 (m, 2H), 2.88 (m, 1H), 2.68 - 2.50 (m, 1H), 2.49 - 2.39 (m, 2H), 2.39 (s, 3H), 2.38 - 2.27 (m, 3H), 2.21 - 2.07 (m, 1H), 1.61 (<i>d</i>, <i>J</i> = 6.8 Hz, 3H). ¹⁹F NMR (377 MHz, CD₃OD) δ = -88.11, -88.72, -93.54, -94.15. LCMS [<i>M</i>+1]⁺ = 454.3. Compound derived from Intermediate N-2: ¹H NMR (400 MHz, CD₃OD) δ = 7.90 (<i>d</i>, <i>J</i> = 1.2 Hz, 1H), 7.87 (dd, <i>J</i> = 1.6, 8.0 Hz, 1H), 7.60 (<i>d</i>, <i>J</i> = 2.0 Hz, 1H), 7.08 (ddd, <i>J</i> = 1.6, 7.2, 8.4 Hz, 1H), 6.51 (t, <i>J</i> = 7.2, 1H), 6.43 (<i>d</i>, <i>J</i> = 8.4 Hz, 1H), 5.62 (q, <i>J</i> = 6.8 Hz, 1H), 4.24 - 4.03 (m, 2H), 2.88 (m, 1H), 2.65 - 2.49 (m, 1H), 2.47 - 2.41 (m, 1H), 2.39 (s, 3H), 2.38 - 2.23 (m, 4H), 2.19 - 2.10 (m, 1H), 1.62 (<i>d</i>, <i>J</i> = 6.8 Hz, 3H). ¹⁹F NMR (377 MHz, CD₃OD) δ = -88.34, -88.95, -93.57, -94.18. LCMS [<i>M</i>+1]⁺ = 454.3.
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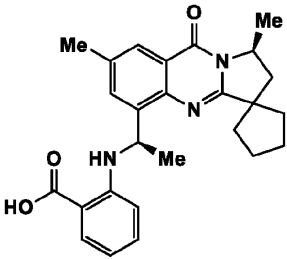
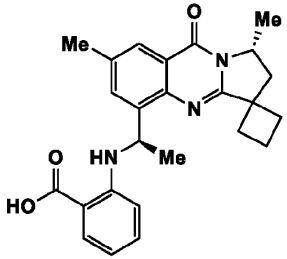
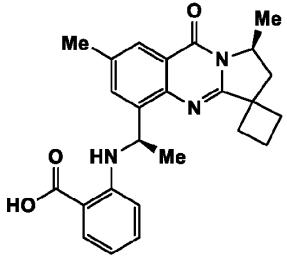
1-66 and 1-67	6-chloro-3-(((<i>R</i>)-1-((<i>S</i>)-2,2-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid And 6-chloro-3-(((<i>R</i>)-1-((<i>R</i>)-2,2-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid	Compound derived from Intermediate O-1: ¹H NMR (400 MHz, CD₃OD) δ = 7.95 (s, 1H), 7.65 (<i>d</i>, <i>J</i> = 1.6 Hz, 1H), 7.18 - 7.13 (m, 1H), 7.11 - 7.05 (m, 1H), 5.55 (<i>q</i>, <i>J</i> = 6.8 Hz, 1H), 4.24 - 4.14 (m, 1H), 4.07 (<i>td</i>, <i>J</i> = 8.0, 12.0 Hz, 1H), 2.80 - 2.72 (m, 1H), 2.71 - 2.54 (m, 2H), 2.43 (s, 3H), 2.39 - 2.20 (m, 3H), 2.14 - 2.03 (m, 1H), 2.03 - 1.90 (m, 1H), 1.69 (<i>d</i>, <i>J</i> = 6.8 Hz, 3H). LCMS [<i>M</i>+23]⁺ = 511.1. Compound derived from Intermediate O-2: ¹H NMR (400 MHz, CD₃OD) δ = 7.95 (s, 1H), 7.62 (s, 1H), 7.16 (br <i>d</i>, <i>J</i> = 8.4 Hz, 1H), 6.93 (br <i>d</i>, <i>J</i> = 8.4 Hz, 1H), 5.60 (<i>q</i>, <i>J</i> = 6.4 Hz, 1H), 4.25 - 4.17 (m, 1H), 4.11 - 4.05 (m, 1H), 2.82 - 2.73 (m, 1H), 2.72 - 2.59 (m, 1H), 2.59 - 2.50 (m, 1H), 2.41 (s, 3H), 2.35 - 2.21 (m, 3H), 2.15 - 2.04 (m, 1H), 2.03 - 1.89 (m, 1H), 1.65 (<i>d</i>, <i>J</i> = 6.8 Hz, 3H). ¹⁹F NMR (377 MHz, CD₃OD) δ = -100.7, -101.3, -110.9, -111.5. LCMS [<i>M</i>+1]⁺ = 489.0.
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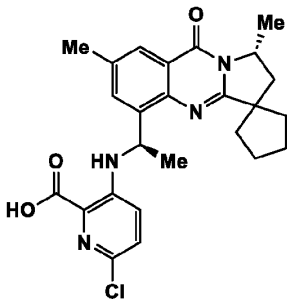
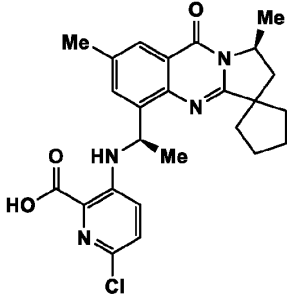
1-68	 2-(((1<i>R</i>)-1-(3,7-dimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-<i>b</i>]quinazolin-5-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CD ₃ OD) δ = 7.75-7.81 (m, 2H), 7.45-7.51 (m, 1H), 6.95-7.03 (m, 1H), 6.36-6.44 (m, 1H), 6.28 (d, <i>J</i> = 8.4 Hz, 1H), 5.54 (q, <i>J</i> = 6.6 Hz, 1H), 4.13-4.21 (m, 1H), 3.86-3.95 (m, 1H), 3.27-3.36 (m, 1H), 2.39-2.50 (m, 1H), 2.27-2.30 (m, 3H), 1.75-1.87 (m, 1H), 1.51 (d, <i>J</i> = 6.6 Hz, 3H), 1.41 (d, <i>J</i> = 7.0 Hz, 3H). LCMS [M+H] ⁺ = 378.1.
1-69	 (<i>R</i>)-2-((1-(7'-methoxy-9'-oxo-1',2'-dihydro-9'-<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 7.95 (d, <i>J</i> = 8.0 Hz, 1H), 7.55 (d, <i>J</i> = 3.0 Hz, 1H), 7.34 (d, <i>J</i> = 2.9 Hz, 1H), 7.14-7.21 (m, 1H), 6.57 (t, <i>J</i> = 7.4 Hz, 1H), 6.44 (d, <i>J</i> = 8.5 Hz, 1H), 5.58 (q, <i>J</i> = 6.5 Hz, 1H), 4.16 (t, <i>J</i> = 7.1 Hz, 2H), 3.85 (s, 3H), 2.20 (br t, <i>J</i> = 7.1 Hz, 4H), 1.96-2.09 (m, 2H), 1.78-1.90 (m, 4H), 1.64 (d, <i>J</i> = 6.8 Hz, 3H). LCMS [M+H] ⁺ = 434.2.
1-70	 2-(((1<i>R</i>)-1-(3,7-dimethyl-9-oxo-3-(4-(trifluoromethyl)benzyl))-1,2,3,9-tetrahydropyrrolo[2,1-<i>b</i>]quinazolin-5-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CD ₃ OD) δ = 7.83-7.93 (m, 2H), 7.63-7.67 (m, 1H), 7.44-7.54 (m, 2H), 7.24-7.38 (m, 2H), 7.08-7.20 (m, 1H), 6.46-6.62 (m, 2H), 5.51-5.71 (m, 1H), 3.91-4.07 (m, 1H), 3.44-3.63 (m, 1H), 3.11-3.28 (m, 2H), 2.40-2.44 (m, 4H), 2.03-2.16 (m, 1H), 1.65 (d, <i>J</i> = 6.6 Hz, 3H), 1.57 (s, 1H), 1.52 (s, 2H), 1.25-1.44 (m, 2H). ¹⁹ F NMR (377 MHz, CD ₃ OD) δ: -63.91. LCMS [M+H] ⁺ = 390.2.

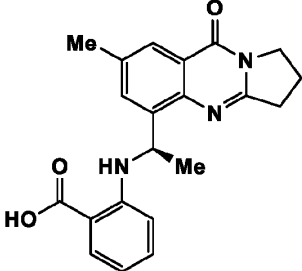
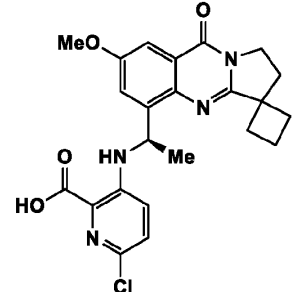
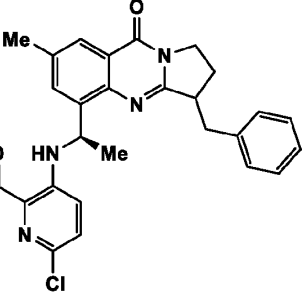
1-71	 (<i>R</i>)-6-chloro-3-((1-(7'-methoxy-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 8.11-8.39 (m, 1H), 7.50-7.62 (m, 1H), 7.28 (d, <i>J</i> = 3.0 Hz, 1H), 7.09 (d, <i>J</i> = 8.9 Hz, 1H), 6.90 (d, <i>J</i> = 9.1 Hz, 1H), 5.54 (q, <i>J</i> = 6.6 Hz, 1H), 4.16 (td, <i>J</i> = 7.1, 2.4 Hz, 2H), 3.85 (s, 3H), 2.20 (t, <i>J</i> = 7.1 Hz, 3H), 1.94-2.17 (m, 3H), 1.78-1.93 (m, 4H), 1.66 (d, <i>J</i> = 6.6 Hz, 3H). LCMS [M+H] ⁺ = 469.4.
1-72	 (<i>R</i>)-2-((1-(3,3-difluoro-7'-methoxy-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 7.96 (dd, <i>J</i> = 1.5, 8.0 Hz, 1H), 7.58 (d, <i>J</i> = 3.0 Hz, 1H), 7.46 (br s, 1H), 7.22 (br t, <i>J</i> = 7.4 Hz, 1H), 6.75 - 6.63 (m, 1H), 6.58 (br dd, <i>J</i> = 2.8, 6.3 Hz, 1H), 5.70 - 5.59 (m, 1H), 4.16 (t, <i>J</i> = 6.9 Hz, 2H), 3.87 (s, 3H), 3.37 - 3.15 (m, 2H), 2.83 - 2.67 (m, 2H), 2.52 (t, <i>J</i> = 6.9 Hz, 2H), 1.71 (br d, <i>J</i> = 6.6 Hz, 3H). ¹⁹ F NMR (377 MHz, CDCl ₃) δ = -85.01, -85.52, -95.93, -96.44. [M+H] ⁺ = 456.2.
1-73	 (<i>R</i>)-2-((1-(3,3,7'-trifluoro-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 7.99 (dd, <i>J</i> = 1.3, 7.9 Hz, 1H), 7.82 (dd, <i>J</i> = 2.9, 8.1 Hz, 1H), 7.55 (br d, <i>J</i> = 7.1 Hz, 1H), 7.21 (m, 1H), 6.66 (m, 1H), 6.55 - 6.40 (m, 1H), 5.65 (m, 1H), 4.17 (t, <i>J</i> = 6.9 Hz, 2H), 3.36 - 3.19 (m, 2H), 2.78 (m, 2H), 2.54 (t, <i>J</i> = 6.9 Hz, 2H), 1.70 (d, <i>J</i> = 6.6 Hz, 3H). ¹⁹ F NMR (377 MHz, CDCl ₃) δ = -85.15, -85.67, -95.73, -96.23, -

	pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	111.81. LCMS [M+H] ⁺ = 444.2.
1-74	 (<i>R</i>)-2-((1-(7'-ethyl-3,3-difluoro-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	¹H NMR (400 MHz, CDCl₃) δ = 8.02 (<i>d</i>, <i>J</i> = 1.9 Hz, 1H), 7.97 (<i>dd</i>, <i>J</i> = 1.5, 8.0 Hz, 1H), 7.65 (<i>br s</i>, 1H), 7.24 - 7.17 (<i>m</i>, 1H), 6.63 (<i>m</i>, 1H), 6.57 (<i>br d</i>, <i>J</i> = 7.1 Hz, 1H), 5.65 (<i>q</i>, <i>J</i> = 6.3 Hz, 1H), 4.15 (<i>t</i>, <i>J</i> = 6.9 Hz, 2H), 3.39 - 3.14 (<i>m</i>, 2H), 2.84 - 2.65 (<i>m</i>, 4H), 2.51 (<i>t</i>, <i>J</i> = 6.9 Hz, 2H), 1.72 (<i>br d</i>, <i>J</i> = 6.5 Hz, 3H), 1.23 (<i>t</i>, <i>J</i> = 7.6 Hz, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ = -85.00, -85.52, -95.86, -96.41. LCMS [M+H]⁺ = 454.2.
1-75	 (<i>R</i>)-6-chloro-3-((1-(3,3-difluoro-7'-methoxy-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid	¹H NMR (400 MHz, CDCl₃) δ = 8.33 (<i>br d</i>, <i>J</i> = 6.6 Hz, 1H), 7.58 (<i>d</i>, <i>J</i> = 3.0 Hz, 1H), 7.30 (<i>d</i>, <i>J</i> = 2.9 Hz, 1H), 7.12 (<i>d</i>, <i>J</i> = 9.0 Hz, 1H), 6.92 (<i>d</i>, <i>J</i> = 9.0 Hz, 1H), 5.55 (<i>quin</i>, <i>J</i> = 6.8 Hz, 1H), 4.17 (<i>dt</i>, <i>J</i> = 1.8, 7.0 Hz, 2H), 3.86 (<i>s</i>, 3H), 3.40 - 3.26 (<i>m</i>, 1H), 3.25 - 3.11 (<i>m</i>, 1H), 2.86 - 2.71 (<i>m</i>, 2H), 2.53 (<i>t</i>, <i>J</i> = 7.0 Hz, 2H), 1.69 (<i>d</i>, <i>J</i> = 6.8 Hz, 3H). ¹⁹F NMR (377 MHz, CDCl₃,) δ = -85.36, -85.88, -95.42, -95.94. LCMS [M+H]⁺ = 491.2.

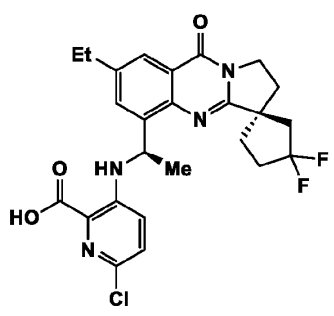
1-76	 (<i>R</i>)-6-chloro-3-((1-(3,3,7'-trifluoro-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 8.34 (br d, <i>J</i> = 6.9 Hz, 1H), 7.84 (dd, <i>J</i> = 3.0, 8.1 Hz, 1H), 7.44 (dd, <i>J</i> = 2.9, 8.8 Hz, 1H), 7.14 (<i>d</i> , <i>J</i> = 8.9 Hz, 1H), 6.87 (<i>d</i> , <i>J</i> = 9.0 Hz, 1H), 5.58 (quin, <i>J</i> = 6.7 Hz, 1H), 4.18 (dt, <i>J</i> = 1.1, 7.0 Hz, 2H), 3.40 - 3.26 (m, 1H), 3.26 - 3.13 (m, 1H), 2.87 - 2.74 (m, 2H), 2.55 (t, <i>J</i> = 7.0 Hz, 2H), 1.70 (<i>d</i> , <i>J</i> = 6.8 Hz, 3H). ¹⁹ F NMR (377 MHz, CDCl ₃) δ = -85.51, -86.03, -95.11, -95.64, -111.30. LCMS [M+H] ⁺ = 479.2.
1-77	 (<i>R</i>)-6-chloro-3-((1-(7'-ethyl-3,3-difluoro-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 8.36 (br d, <i>J</i> = 7.0 Hz, 1H), 8.04 (<i>d</i> , <i>J</i> = 2.0 Hz, 1H), 7.54 (<i>d</i> , <i>J</i> = 1.9 Hz, 1H), 7.12 (<i>d</i> , <i>J</i> = 9.0 Hz, 1H), 6.98 (<i>d</i> , <i>J</i> = 9.0 Hz, 1H), 5.59 (quin, <i>J</i> = 6.7 Hz, 1H), 4.16 (dt, <i>J</i> = 2.8, 7.0 Hz, 2H), 3.45 - 3.28 (m, 1H), 3.26 - 3.09 (m, 1H), 2.84 - 2.75 (m, 2H), 2.71 (q, <i>J</i> = 7.7 Hz, 2H), 2.53 (t, <i>J</i> = 7.0 Hz, 2H), 1.69 (<i>d</i> , <i>J</i> = 6.8 Hz, 3H), 1.23 (t, <i>J</i> = 7.6 Hz, 3H). ¹⁹ F NMR (377 MHz, CDCl ₃) δ = -85.40, -85.92, -95.23, -95.75. LCMS [M+H] ⁺ = 489.3.
1-78	 2-(((<i>R</i>)-1-((<i>R</i>)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 8.00 - 7.95 (m, 2H), 7.57 (br s, 1H), 7.19 (ddd, <i>J</i> = 1.6, 7.1, 8.5 Hz, 1H), 6.61 (m, 1H), 6.54 (br d, <i>J</i> = 8.4 Hz, 1H), 5.63 (m, 1H), 4.78 - 4.64 (m, 1H), 2.43 - 2.35 (m, 4H), 2.33 - 2.15 (m, 2H), 2.08 - 1.98 (m, 2H), 1.94 - 1.72 (m, 5H), 1.68 (br d, <i>J</i> = 5.9 Hz, 3H),

	1,3'-pyrrolo[2,1- <i>b</i>]quinazolin-5'-yl)ethyl)amino)benzoic acid	1.60 (<i>d</i> , <i>J</i> = 6.5 Hz, 3H). LCMS [M+H] ⁺ = 432.3.
1-79	 2-(((<i>R</i>)-1-((<i>S</i>)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin-5'-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 7.98 - 7.93 (m, 2H), 7.56 (br s, 1H), 7.22 - 7.12 (m, 1H), 6.57 (m, 1H), 6.52 (br d, <i>J</i> = 8.4 Hz, 1H), 5.65 (q, <i>J</i> = 6.4 Hz, 1H), 4.78 - 4.65 (m, 1H), 2.46 - 2.35 (m, 4H), 2.31 - 2.17 (m, 2H), 2.10 - 1.96 (m, 2H), 1.94 - 1.71 (m, 5H), 1.65 (br d, <i>J</i> = 6.0 Hz, 3H), 1.59 (<i>d</i> , <i>J</i> = 6.5 Hz, 3H). LCMS [M+H] ⁺ = 432.3.
1-80	 2-(((<i>R</i>)-1-((<i>R</i>)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin-5'-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 7.97 (m, 2H), 7.60 (br s, 1H), 7.24 - 7.17 (m, 1H), 6.62 (m, 2H), 5.75 (m, 1H), 4.71 (m, 1H), 2.89 - 2.75 (m, 1H), 2.57 (br s, 1H), 2.47 - 2.38 (m, 4H), 2.38 - 2.27 (m, 2H), 2.23 - 2.04 (m, 3H), 1.73 (br d, <i>J</i> = 5.3 Hz, 3H), 1.50 (<i>d</i> , <i>J</i> = 6.5 Hz, 3H). LCMS [M+H] ⁺ = 418.3.
1-81	 2-(((<i>R</i>)-1-((<i>S</i>)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin-5'-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 7.99 - 7.93 (m, 2H), 7.61 (br s, 1H), 7.23 - 7.14 (m, 1H), 6.59 (m, 2H), 5.85 - 5.70 (m, 1H), 4.78 - 4.65 (m, 1H), 2.85 - 2.71 (m, 1H), 2.66 - 2.54 (m, 1H), 2.45 (dd, <i>J</i> = 8.5, 13.1 Hz, 1H), 2.41 (s, 3H), 2.36 - 2.26 (m, 2H), 2.22 - 2.05 (m, 3H), 1.74 (br d, <i>J</i> = 5.9 Hz, 3H), 1.48 (<i>d</i> , <i>J</i> = 6.5 Hz, 3H). LCMS [M+H] ⁺ = 418.3.

	1,3'-pyrrolo[2,1- <i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid	
1-82	 6-chloro-3-(((<i>R</i>)-1-((<i>R</i>)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 8.26 (br s, 1H), 7.98 (<i>d</i> , <i>J</i> = 1.1 Hz, 1H), 7.46 (<i>d</i> , <i>J</i> = 1.9 Hz, 1H), 7.11 (<i>d</i> , <i>J</i> = 9.0 Hz, 1H), 6.98 (<i>d</i> , <i>J</i> = 9.0 Hz, 1H), 5.59 (q, <i>J</i> = 6.1 Hz, 1H), 4.80 - 4.65 (m, 1H), 2.44 - 2.37 (m, 4H), 2.35 - 2.26 (m, 1H), 2.25 - 2.16 (m, 1H), 2.08 - 1.98 (m, 2H), 1.91 (br dd, <i>J</i> = 3.4, 13.0 Hz, 2H), 1.88 - 1.72 (m, 3H), 1.65 (<i>d</i> , <i>J</i> = 6.8 Hz, 3H), 1.61 (<i>d</i> , <i>J</i> = 6.6 Hz, 3H). LCMS [M+H] ⁺ = 467.4.
1-83	 6-chloro-3-(((<i>R</i>)-1-((<i>S</i>)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 8.40 - 8.15 (m, 1H), 7.98 (<i>d</i> , <i>J</i> = 1.0 Hz, 1H), 7.47 (<i>d</i> , <i>J</i> = 2.0 Hz, 1H), 7.11 - 7.07 (m, 1H), 7.02 - 6.98 (m, 1H), 5.62 (q, <i>J</i> = 6.7 Hz, 1H), 4.79 - 4.68 (m, 1H), 2.44 - 2.37 (m, 4H), 2.32 - 2.20 (m, 2H), 2.09 - 1.97 (m, 2H), 1.95 - 1.87 (m, 2H), 1.87 - 1.73 (m, 3H), 1.64 (<i>d</i> , <i>J</i> = 6.8 Hz, 3H), 1.60 (<i>d</i> , <i>J</i> = 6.5 Hz, 3H). LCMS [M+H] ⁺ = 467.4.

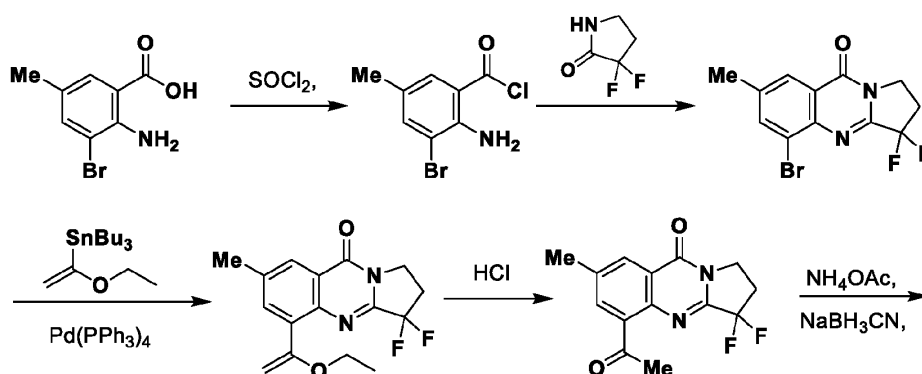
1-84	 (<i>R</i>)-2-((1-(7-methyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-<i>b</i>]quinazolin-5-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CD ₃ OD) δ = 7.77-7.81 (m, 2H), 7.49 (d, <i>J</i> = 2.0 Hz, 1H), 6.97-7.02 (m, 1H), 6.39-6.44 (m, 1H), 6.29 (d, <i>J</i> = 8.5 Hz, 1H), 5.47 (q, <i>J</i> = 6.5 Hz, 1H), 4.11 (t, <i>J</i> = 7.3 Hz, 2H), 3.13-3.19 (m, 2H), 2.28 (s, 3H), 2.18-2.27 (m, 2H), 1.48 (d, <i>J</i> = 6.6 Hz, 3H). LCMS [<i>M</i> + <i>H</i>] ⁺ = 364.2.
1-85	 (<i>R</i>)-6-chloro-3-((1-(7'-methoxy-9'-oxo-1',2'-dihydro-9'-<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid	¹ H NMR (400 MHz, CDCl ₃) δ = 8.33 (br s, 1H), 7.56 (d, <i>J</i> = 2.9 Hz, 1H), 7.29 (d, <i>J</i> = 2.9 Hz, 1H), 7.11 (d, <i>J</i> = 8.9 Hz, 1H), 6.97 (d, <i>J</i> = 9.0 Hz, 1H), 5.63 (m, 1H), 4.06-4.14 (m, 2H), 3.86 (s, 3H), 2.60-2.73 (m, 2H), 2.42 (t, <i>J</i> = 7.1 Hz, 2H), 2.13-2.28 (m, 5H), 1.72 (d, <i>J</i> = 6.8 Hz, 3H). LCMS [<i>M</i> + <i>H</i>] ⁺ = 455.3.
1-86	 6-chloro-3-(((1<i>R</i>)-1-(7-methyl-9-oxo-3-(4-(trifluoromethyl)benzyl)-1,2,3,9-tetrahydropyrrolo[2,1-<i>b</i>]quinazolin-5-yl)ethyl)amino)picolinic acid	LCMS [<i>M</i> + <i>H</i>] ⁺ = 557.2.

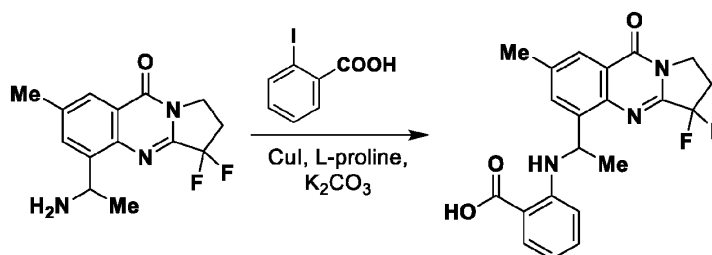
1-87 and 1-88	3-(((<i>R</i>)-1-((<i>R</i>)-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid And 3-(((<i>R</i>)-1-((<i>S</i>)-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid	Compound derived Intermediate N-1: ¹H NMR (400 MHz, CD₃OD) δ = 7.95 (s, 1H), 7.76 (<i>d</i>, <i>J</i> = 4.8 Hz, 1H), 7.68 (<i>d</i>, <i>J</i> = 1.2 Hz, 1H), 7.51 - 7.45 (m, 1H), 7.43 - 7.37 (m, 1H), 5.70 (q, <i>J</i> = 6.8 Hz, 1H), 4.23 - 4.11 (m, 2H), 2.93 - 2.80 (m, 1H), 2.66 - 2.55 (m, 1H), 2.48 - 2.35 (m, 8H), 2.18 - 2.10 (m, 1H), 1.71 (<i>d</i>, <i>J</i> = 6.4 Hz, 3H). ¹⁹F NMR (377 MHz, CD₃OD) δ = -88.1, -88.7, -93.1, -93.7. LCMS [<i>M</i>+<i>H</i>]⁺ = 455.4. Compound derived Intermediate N-2: ¹H NMR (400 MHz, CD₃OD) δ = 7.95 (s, 1H), 7.76 (<i>d</i>, <i>J</i> = 4.4 Hz, 1H), 7.67 (<i>d</i>, <i>J</i> = 1.2 Hz, 1H), 7.50 - 7.42 (m, 1H), 7.36 (<i>d</i>, <i>J</i> = 8.4 Hz, 1H), 5.70 (q, <i>J</i> = 6.8 Hz, 1H), 4.25 - 4.09 (m, 2H), 2.98 - 2.85 (m, 1H), 2.55 - 2.32 (m, 9H), 2.21 - 2.13 (m, 1H), 1.70 (<i>d</i>, <i>J</i> = 6.8 Hz, 3H). ¹⁹F NMR (377 MHz, CD₃OD) δ = -88.5, -89.1, -93.3, -93.9. LCMS [<i>M</i>+<i>H</i>]⁺ = 455.3.
1-89 and 1-90	6-chloro-3-(((<i>R</i>)-1-((<i>R</i>)-7'-ethyl-3,3-difluoro-9'-oxo-1',2'-dihydro-9'<i>H</i>-	Compound derived from the first eluting diastereomer of reduction: ¹H NMR (400 MHz, CDCl₃) δ = 8.37 (br <i>d</i>, <i>J</i> = 6.8 Hz, 1H), 8.04 (<i>d</i>, <i>J</i> = 2.0 Hz, 1H), 7.53 (<i>d</i>, <i>J</i> = 2.0 Hz, 1H), 7.13 (<i>d</i>, <i>J</i> = 8.8 Hz, 1H), 6.94 (<i>d</i>, <i>J</i> = 8.8 Hz, 1H), 5.53 (quin, <i>J</i> = 6.8 Hz, 1H), 4.27 - 4.18 (m, 1H), 4.16 - 4.07 (m, 1H), 2.95 - 2.79 (m, 1H), 2.71 (q, <i>J</i> = 7.6 Hz, 2H), 2.68 - 2.53 (m, 1H),

	spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid And  6-chloro-3-(((<i>R</i>)-1-((<i>S</i>)-7-ethyl-3,3-difluoro-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclopentane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid	2.44 - 2.28 (m, 5H), 2.14 - 2.01 (m, 1H), 1.68 (<i>d</i>, <i>J</i> = 6.8 Hz, 3H), 1.23 (t, <i>J</i> = 7.6 Hz, 3H). LCMS [<i>M</i>+<i>H</i>]⁺ = 503.3. Compound derived from the second eluting diastereomer of reduction: ¹H NMR (400 MHz, CDCl₃) δ = 8.33 (br d, <i>J</i> = 6.8 Hz, 1H), 8.04 (<i>d</i>, <i>J</i> = 2.0 Hz, 1H), 7.53 (<i>d</i>, <i>J</i> = 2.0 Hz, 1H), 7.11 (<i>d</i>, <i>J</i> = 9.2 Hz, 1H), 6.93 (<i>d</i>, <i>J</i> = 8.8 Hz, 1H), 5.55 (quin, <i>J</i> = 6.8 Hz, 1H), 4.26 - 4.17 (m, 1H), 4.17 - 4.07 (m, 1H), 2.99 - 2.81 (m, 1H), 2.71 (q, <i>J</i> = 7.6 Hz, 2H), 2.64 - 2.47 (m, 1H), 2.43 - 2.26 (m, 5H), 2.14 - 2.00 (m, 1H), 1.68 (<i>d</i>, <i>J</i> = 6.8 Hz, 3H), 1.22 (t, <i>J</i> = 7.6 Hz, 3H). LCMS [<i>M</i>+<i>H</i>]⁺ = 503.2.
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EXAMPLE 1-91

2-((1-(3,3-difluoro-7-methyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-5-yl)ethyl)amino)benzoic acid





[00396] Step A: A mixture of 2-amino-3-bromo-5-methylbenzoic acid (10.0 g, 43.5 mmol, 1.00 eq.) in toluene (50.0 mL) was added thionyl chloride (25.9 g, 217 mmol, 15.8 mL, 5.00 eq.) dropwise at 25 °C, then the reaction mixture was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 100 °C for 3 hrs under nitrogen atmosphere. After completion, the reaction mixture was concentrated under reduced pressure to remove solvent to afford 2-amino-3-bromo-5-methylbenzoyl chloride (10.5 g, 97% yield) as brown oil used into the next step without further purification.

[00397] Step B: To a solution of 3,3-difluoropyrrolidin-2-one (400 mg, 3.30 mmol, 1.00 eq.) in chloroform (10.0 mL) was added a solution of 2-amino-3-bromo-5-methylbenzoyl chloride (1.50 g, 6.04 mmol, 1.83 eq.) in chloroform (5.00 mL) dropwise, then mixture was degassed and purged with nitrogen for 3 times and stirred at 25 °C for 16 hours under nitrogen atmosphere. After completion, the reaction mixture was quenched by adding sodium hydroxide (2 M, 20.0 mL) aqueous solution at 25 °C, then the resulting solution was extracted with DCM (10.0 mL × 2). The combined organic layers were washed with brine (20.0 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 5-bromo-3,3-difluoro-7-methyl-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (250 mg, 22% yield, 90% purity) as a yellow solid. LCMS $[M+3]^+ = 317.3$.

[00398] Step C: A mixture of 5-bromo-3,3-difluoro-7-methyl-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (250 mg, 793 μmol, 1.00 eq.), tributyl(1-ethoxyvinyl)stannane (287 mg, 793 μmol, 268 μL, 1.00 eq.) and tetrakis(triphenylphosphine)palladium (0) (91.7 mg, 79.3 μmol, 0.10 eq.) in dioxane (5.00 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 100 °C for 16 hours under nitrogen atmosphere. After completion, the reaction mixture was cooled to 25 °C, quenched by adding potassium fluoride saturated aqueous solution (20.0 mL) at 20 °C, and then filtered, the filtrate was extracted with ethyl acetate (10.0 mL × 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product 5-(1-ethoxyvinyl)-3,3-difluoro-7-methyl-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (200 mg, 82% yield) as yellow oil which was used in next step directly.

[00399] Step D: A mixture of 5-(1-ethoxyvinyl)-3,3-difluoro-7-methyl-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (200 mg, 653 μmol , 1.00 *eq.*) and hydrochloric acid (4 M, 2.00 mL, 12.3 *eq.*) in tetrahydrofuran (2.00 mL) was stirred at 25 °C for 2 hours. After completion, The reaction mixture was partitioned between water (10.0 mL) and dichloromethane (10.0 mL $\times$ 2). The organic phase was separated, washed with brine (20.0 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate=10/1 to dichloromethane/methanol = 1/0) to afford 5-acetyl-3,3-difluoro-7-methyl-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (220 mg, 97% yield, 80% purity) as a yellow solid.

[00400] ^1H NMR (400 MHz, CDCl_3) δ = 8.29 (br s, 1H), 7.95 (br s, 1H), 4.26 (br s, 2H), 2.91 (br s, 3H), 2.87 - 2.75 (m, 2H), 2.54 (br s, 3H).

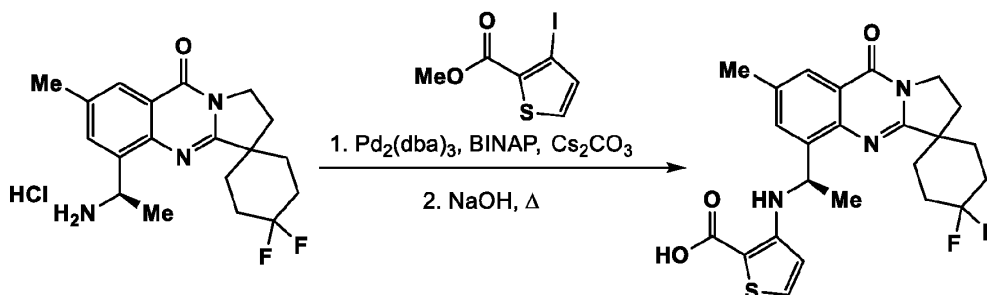
[00401] Step E: A yellow solution of 5-acetyl-3,3-difluoro-7-methyl-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (110 mg, 395 μmol , 1.00 *eq.*) and ammonium acetate (305 mg, 3.95 mmol, 10.0 *eq.*) in ethanol (5.00 mL) was stirred at 70 °C for 1 hours. Then sodium cyanoborohydride (49.7 mg, 791 μmol , 2.00 *eq.*) was added to the mixture. The reaction mixture was stirred at 70 °C for another 1 hour. After completion, the reaction mixture was cooled to 25 °C, diluted with dichloromethane (30.0 mL), then the organic solution was washed with water (30.0 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to give a residue, the residue was purified by prep-TLC (dichloromethane/methanol=10/1) to afford 5-(1-aminoethyl)-3,3-difluoro-7-methyl-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (17.0 mg, 15.4% yield) as a pale yellow solid. LCMS $[\text{M}+\text{H}]^+ = 280.4$.

[00402] Step F: A blue suspension of 2-iodobenzoic acid (18.9 mg, 76.1 μmol , 1.25 *eq.*), 5-(1-aminoethyl)-3,3-difluoro-7-methyl-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (17.0 mg, 60.9 μmol , 1.00 *eq.*), cuprous iodide (2.32 mg, 12.2 μmol , 0.20 *eq.*), L-proline (2.80 mg, 24.35 μmol , 0.4 *eq.*) and potassium carbonate (12.6 mg, 91.3 μmol , 1.50 *eq.*) in dimethyl sulfoxide (2.00 mL) was degassed and purged with nitrogen for 3 times and stirred at 100 °C under nitrogen for 2 hours. After completion, the reaction mixture cooled to 25 °C and filtered, the filtrate was added acetic acid (2.00 mL) and directly concentrated in vacuum to give a residue. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate=3/1 to 1/1, 4 g silica gel column) to give 2-((1-(3,3-difluoro-7-methyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-5-yl)ethyl)amino)benzoic acid (8.00 mg, 19.2 μmol , 32% yield, 96% purity) as a pale yellow solid. LCMS $[\text{M}+3]^+ = 400.1$.

[00403] ^1H NMR (400 MHz, CD_3OD) δ = 7.98 (s, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.68 (s, 1H), 7.07 (t, J = 7.2 Hz, 1H), 6.49 (t, J = 7.6 Hz, 1H), 6.36 (d, J = 8.4 Hz, 1H), 5.67 (q, J = 6.4 Hz, 1H), 4.24 (br t, J = 7.2 Hz, 2H), 2.98 - 2.81 (m, 2H), 2.42 (s, 3H), 1.61 (d, J = 6.8 Hz, 3H).

EXAMPLE 1-92

(*R*)-3-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)thiophene-2-carboxylic acid



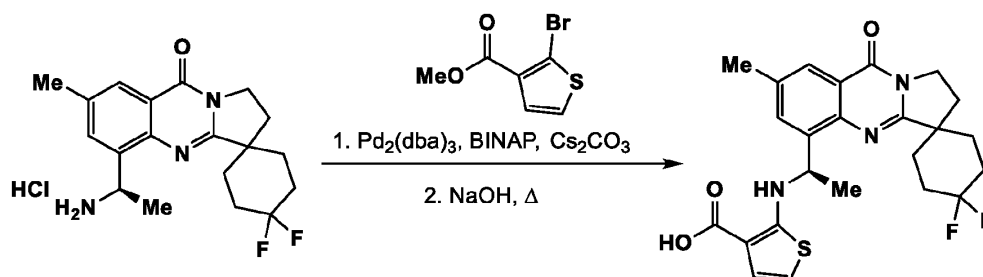
[00404] Step A: Procedure adapted from *Tetrahedron Letters*, **2000**, 7731. To (*R*)-5'-(1-aminoethyl)-4,4-difluoro-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one, HCl (10 mg, 1.0 eq., 26 μmol), methyl 3-iodothiophene-2-carboxylate (10 mg, 1.50 eq., 39 μmol), cesium carbonate (29 mg, 3.4 eq., 89 μmol), tris(dibenzylideneacetone) dipalladium(0) (1.2 mg, 0.05 eq., 1.3 μmol) and ($\pm$)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (1.6 mg, 0.10 eq., 2.6 μmol) under nitrogen was added toluene (0.26 mL) and the reaction was stirred at 100°C for 20 h. After cooling to room temperature, the reaction mixture was pre-absorbed onto silica and purified by flash chromatography to yield methyl (*R*)-3-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)thiophene-2-carboxylate (9.5 mg, 19 μmol , 75 % yield). LCMS $[\text{M}+\text{H}]^+ = 488.3$.

[00405] Step B: To a vial containing methyl (*R*)-3-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)thiophene-2-carboxylate (12 mg, 1 eq., 25 μmol) in tetrahydrofuran (98 μL), methanol (98 μL), and Water (49 μL) at room temperature was added sodium hydroxide (3.9 mg, 4 eq, 98 μmol) as a solid in a single portion. The reaction was allowed to stir for 24h before being quenched to $\sim \text{pH} = 5$ using 1N hydrochloric acid. The aqueous layer was extracted three times with ethyl acetate and the combined organics were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated to provide a residue which was purified via silica gel chromatography to yield (*R*)-3-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)thiophene-2-carboxylic acid as a tan solid. LCMS $[\text{M}+\text{H}]^+ = 474.1$.

[00406] ^1H NMR (400 MHz, CDCl_3) δ = 7.99 (s, 1H), 7.55 (s, 1H), 7.25 (d, J = 5.6 Hz, 1H), 6.38 (d, J = 5.4 Hz, 1H), 5.59 - 5.47 (m, 1H), 4.16 (t, J = 7.1 Hz, 2H), 2.61 - 2.46 (m, 2H), 2.44 (s, 3H), 2.30 - 2.13 (m, 4H), 2.10 - 1.92 (m, 2H), 1.92 - 1.82 (m, 2H), 1.63 (d, J = 6.6 Hz, 3H).

EXAMPLE 1-93

(*R*)-2-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)thiophene-3-carboxylic acid



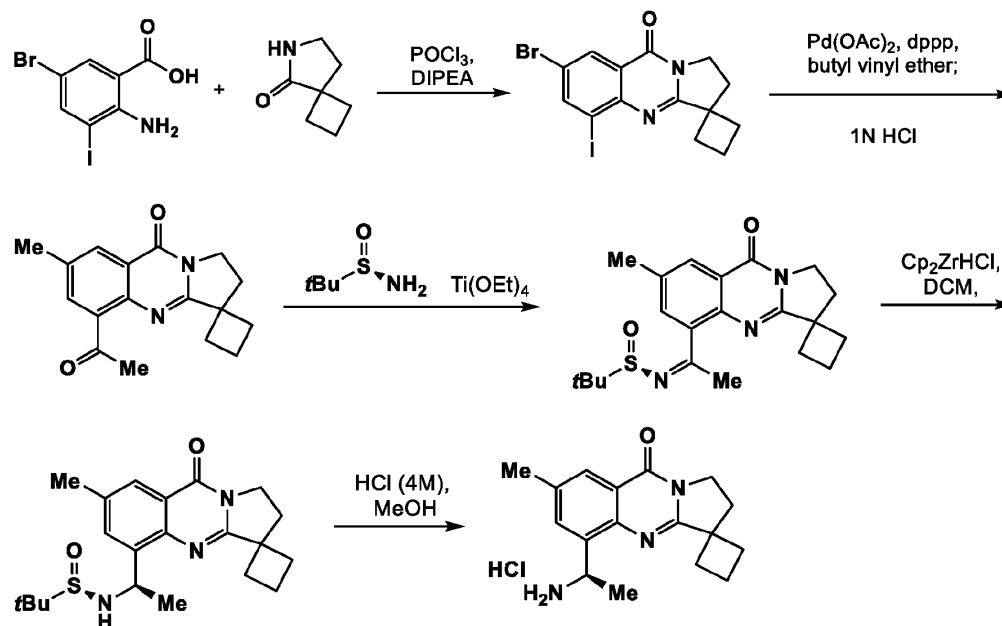
[00407] Step A: Procedure adapted from *Tetrahedron Letters*, **2000**, 7731. To (*R*)-5'-(1-aminoethyl)-4,4-difluoro-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one, HCl (10 mg, 1.0 eq., 26 μmol), methyl 2-bromothiophene-3-carboxylate (8.6 mg, 1.50 eq., 39 μmol), cesium carbonate (29 mg, 3.4 eq., 89 μmol), tris(dibenzylideneacetone) dipalladium(0) (1.2 mg, 0.05 eq., 1.3 μmol) and ($\pm$)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (1.6 mg, 0.10 eq., 2.6 μmol) under nitrogen was added toluene (0.26 mL) and the reaction was stirred at 100°C for 20 h. After cooling to room temperature, the reaction mixture was pre-absorbed onto silica and purified by flash chromatography to yield methyl (*R*)-2-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)thiophene-3-carboxylate (10 mg, 21 μmol , 79 % yield). LCMS $[\text{M}+\text{H}]^+ = 488.3$.

[00408] Step B: To a vial containing methyl methyl (*R*)-2-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)thiophene-3-carboxylate (10.08 mg, 1 eq., 20.67 μmol) in tetrahydrofuran (82.70 μL), methanol (82.70 μL), and water (41.35 μL) at room temperature was added sodium hydroxide (3.308 mg, 4 eq., 82.70 μmol) as a solid in a single portion. The reaction was allowed to stir for 36h before being quenched to $\sim \text{pH} = 5$ using 1N hydrochloric acid. The aqueous layer was extracted three times with ethyl acetate and the combined organics were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated to provide a residue which was purified via silica gel chromatography to yield (*R*)-2-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)thiophene-3-carboxylic acid as a tan solid. LCMS $[\text{M}+\text{H}]^+ = 474.2$.

[00409] ^1H NMR (400 MHz, CDCl_3) δ = 8.01 (s, 1H), 7.54 (s, 1H), 7.02 (d, J = 5.6 Hz, 1H), 6.10 (d, J = 5.8 Hz, 1H), 5.34 - 5.22 (m, 1H), 4.15 (t, J = 6.9 Hz, 2H), 2.65 - 2.47 (m, 2H), 2.45 (s, 3H), 2.31 - 2.14 (m, 4H), 2.09 - 1.93 (m, 2H), 1.91 - 1.80 (m, 2H), 1.70 (d, J = 6.8 Hz, 3H).

Intermediate K

(*R*)-5'-(1-aminoethyl)-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one, hydrochloride



[0001] Step A: To a flask charged with 6-azaspiro[3.4]octan-5-one (485 mg, 1.0 eq., 3.9 mmol) in 1,2-dichloroethane (19 mL) was added phosphorous oxychloride (772 mg, 469 μL , 1.3 eq. 5.0 mmol) and diisopropylethylamine (501 mg, 675 μL , 1.0 eq., 3.9 mmol). The reaction was then heated to 50 $^{\circ}\text{C}$ for one hour. Next, 2-amino-5-bromo-3-iodobenzoic acid (891 mg, 1 eq., 3.9 mmol) was added as a solid and the reaction was heated to 100 $^{\circ}\text{C}$. The reaction was stirred overnight before being cooled to room temperature and diluted with water. The aqueous layer was extracted with dichloromethane and the combined organics were washed with brine, dried over magnesium sulfate, and concentrated. The solid was purified by silica gel chromatography to provide 5'-bromo-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (495 mg, 1.6 mmol, 40 % yield) as a yellow solid. LCMS $[\text{M}+\text{H}]^+ = 319.0$.

[0002] Step B: To a vial and a stir bar was added palladium (II) acetate (17 mg, 0.05 eq., 78 μmol), 1,3-bis(diphenylphosphino)propane (64 mg, 0.10 eq., 155 μmol) and 5'-bromo-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (495 mg, 1.0

eq., 1.55 mmol). The flask was evacuated and backfilled with nitrogen three times. Next, ethylene glycol (3.9 mL), *n*-butyl vinyl ether (777 μ L, 5.0 eq., 7.75 mmol), and *N,N*-dicyclohexylmethylamine (909 μ L, 3.0 eq., 4.65 mmol) were injected and this solution was sparged with nitrogen. The flask was placed in a heating block, and the mixture was stirred and heated at 115 °C. After full conversion, the reaction was allowed to cool to room temperature and 1N HCl (8 mL) was added to the reaction. The reaction was stirred until the ketone deprotection went to completion (ca. 1h). The aqueous layer was extracted with ethyl acetate three times and the combined organics were washed successively with water and brine, dried over magnesium sulfate, filtered, and concentrated to a residue. This residue was purified via silica gel chromatography to provide 5'-acetyl-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (283 mg, 1.00 mmol, 65 % yield) as a yellow solid. LCMS $[M+H]^+ = 283.1$.

[0003] Step C: 5'-acetyl-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (239 mg, 1.0 eq., 846 μ mol) and (*R*)-2-methylpropane-2-sulfinamide (123 mg, 1.2 eq., 1.02 mmol) in tetrahydrofuran (2.1 mL) was added titanium (IV) ethoxide (965 mg, 881 μ L, 5 eq., 4.23 mmol). The mixture was stirred at 80 °C for 4 hours then cooled to room temperature. Once at room temperature, a minimal amount of brine was added to form a suspension. The resulting suspension was diluted with ethyl acetate, filtered through a plug of celite, and the filter cake was washed with ethyl acetate several times. The filtrate was concentrated under reduced pressure and the yellow residue was quickly purified via silica gel chromatography (30% to 100% ethyl acetate in heptane) to provide (*R*)-2-methyl-*N*-(1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)propane-2-sulfinamide (179 mg, 464 μ mol, 55 % yield) as a yellow solid.

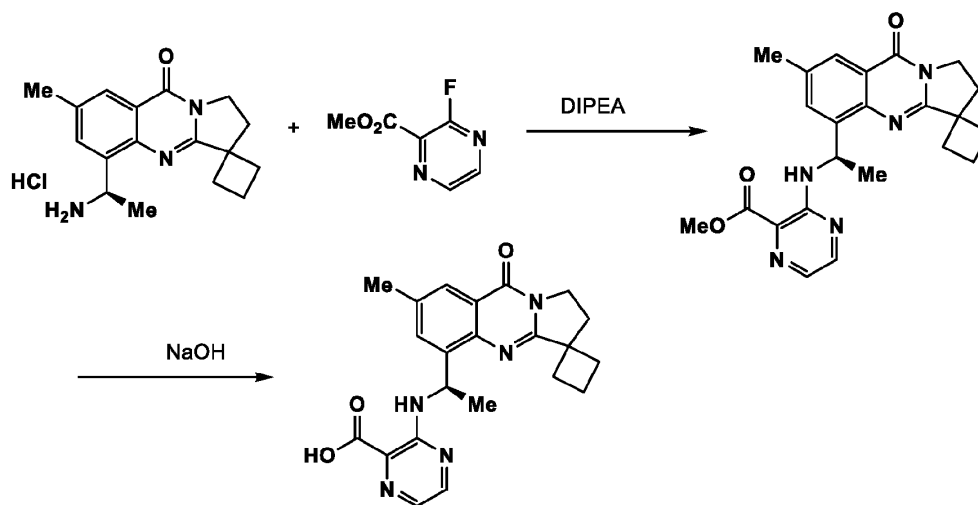
[0004] Step D: To a solution of (*R*)-2-methyl-*N*-(1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)propane-2-sulfinamide (179 mg, 1.0 eq., 464 μ mol) in anhydrous dichloromethane (3.10 mL) at room temperature was added Schwartz's reagent (132 mg, 1.1 eq., 511 μ L) as a solid portion wise. The reaction was stirred at this temperature for 15 min before being quenched with ammonium chloride. The aqueous layer was extracted with dichloromethane and the combined organics were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to provide a residue. This solid was purified via silica gel chromatography (0% to 10% methanol in dichloromethane) to provide (*R*)-2-methyl-*N*-((*R*)-1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)propane-2-sulfinamide (119 mg, 307 μ mol, 66 % yield) as a white solid. LCMS $[M+H]^+ = 388.2$.

[0005] Step E: To a solution of (*R*)-2-methyl-*N*-((*R*)-1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)propane-2-sulfinamide (119 mg,

1.0 eq., 307 μmol) in methanol (614 μL) at 0 °C was added 192 μL HCl (4M in dioxane). The reaction was monitored for conversion by LCMS and once complete, triturated with diethyl ether to provide (*R*)-5'-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one,hydrochloride (89 mg) which was used subsequently without further purification. LCMS $[\text{M}+\text{H}]^+ = 284.1$.

EXAMPLE 1-94

(*R*)-3-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)pyrazine-2-carboxylic acid



[00410] Step A: A mixture of starting material (*R*)-5'-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one, hydrochloride (20 mg, 1 eq., 63 μmol) and methyl 3-bromopyrazine-2-carboxylate (20 mg, 1.5 eq., 94 μmol), and diisopropylethylamine in isopropanol (500 μL) was heated to 90 °C for 21h. After full conversion by LCMS the reaction was concentrated, and the crude material was purified by prep-HPLC (Shimadzu Prep-HPLC; Column: Phenomenex Gemini® 5uM NX-C18 110 Å; 150 x 30 mm; gradient: 5% acetonitrile (0.035% TFA)/95% water (0.05% TFA) to 95% acetonitrile (0.035% TFA)/5% water (0.05% TFA)) to give methyl (*R*)-3-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)pyrazine-2-carboxylate (12 mg, 29 μmol , 46 % yield). LCMS $[\text{M}+\text{H}]^+ = 420.4$.

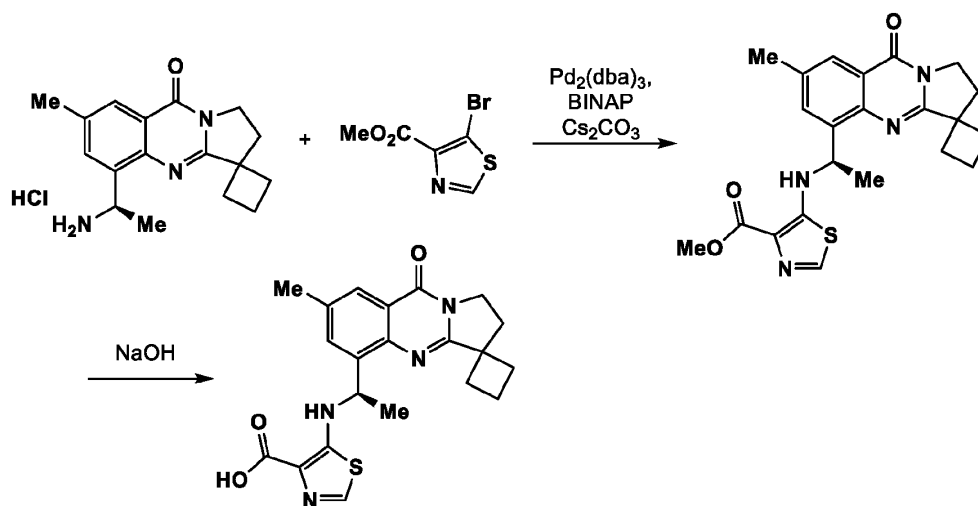
[00411] Step B: To a vial was added methyl (*R*)-3-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)pyrazine-2-carboxylate (12 mg, 1 eq., 29 μmol) in methanol (0.15 mL) and tetrahydrofuran (0.15 mL). The solution was stirred for 10 minutes before adding sodium hydroxide (5.7 mg, 5eq., 0.14 mmol) and water (0.7 mL). The reaction was allowed stir for four hours at room temperature. The reaction was

concentrated, 1M HCl was added until the solution was ~ pH = 4. The solution was stirred until precipitation occurred and the solid was filtered and washed with water, then dried under vacuum to provide (*R*)-3-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)pyrazine-2-carboxylic acid (5.0 mg, 12 μ mol, 43 % yield) as a yellow solid. LCMS $[M+H]^+ = 406.2$.

[00412] ^1H NMR (400 MHz, CDCl_3) δ = 9.12-9.22 (m, 1H), 8.30 (s, 1H), 7.99 (s, 1H), 7.68 (s, 1H), 7.54 (s, 1H), 5.93-6.05 (m, 1H), 3.98-4.15 (m, 2H), 2.86-2.93 (m, 1H), 2.70-2.80 (m, 1H), 2.44 (s, 4H), 2.06-2.36 (m, 5H), 1.82 (br d, J = 6.6 Hz, 4H).

EXAMPLE 1-95

(*R*)-5-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)thiazole-4-carboxylic acid



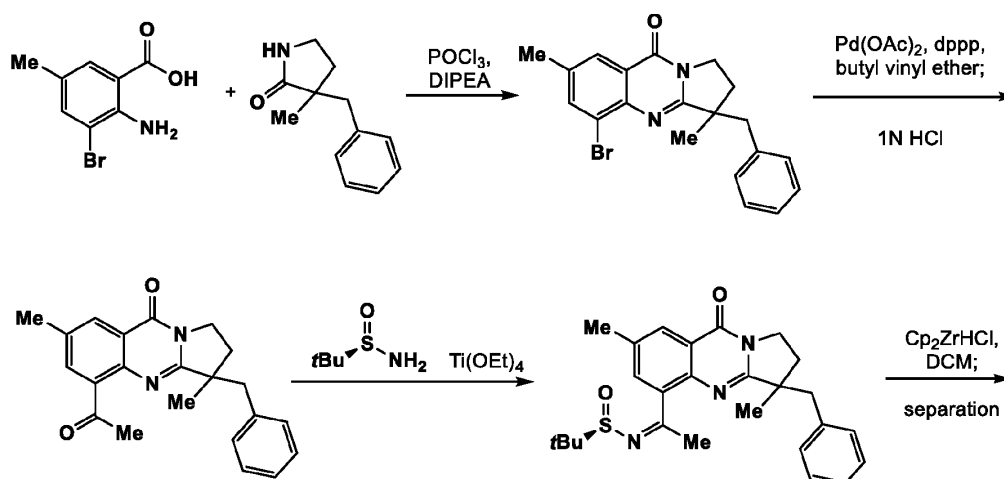
[00413] Step A: To a vial and stir bar was added), tris(dibenzylideneacetone) dipalladium(0) (2.9 mg, 0.05 eq., 3.1 μ mol), ($\pm$)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (3.9 mg, 0.10 eq., 6.3 μ mol), (*R*)-5'-((1-aminoethyl)-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one hydrochloride (20 mg, 1 eq., 63 μ mol), methyl 5-bromothiazole-4-carboxylate (21 mg, 1.5 eq., 94 μ mol) and cesium carbonate (71 mg, 3.5 eq., 0.22 mmol). The vial was sealed with a Teflon screw cap and the vial was evacuated backfilled three times with nitrogen. Next, anhydrous, deoxygenated toluene (0.26 mL) was added, and the reaction was stirred at room temperature until the dark red color transformed to a yellow/orange (ca. 15 minutes). The reaction was subsequently heated to 100 °C overnight. The reaction was cooled to room temperature, diluted with water and dichloromethane and the aqueous layer was extracted three times with dichloromethane. The combined organics were washed with brine, dried over magnesium sulfate, filtered and

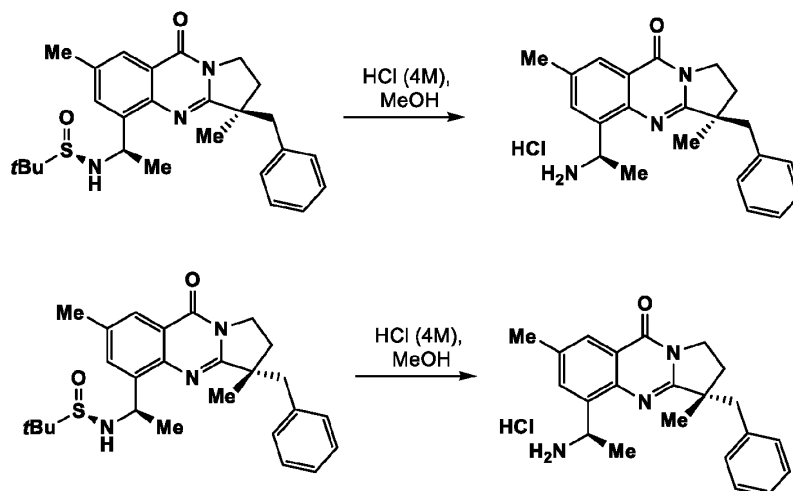
concentrated to a residue which was purified by prep-HPLC (Shimadzu Prep-HPLC; Column: Phenomenex Gemini® 5uM NX-C18 110 Å; 150 x 30 mm; gradient: 5% acetonitrile (0.035% TFA)/95% water (0.05% TFA) to 95% acetonitrile (0.035% TFA)/5% water (0.05% TFA)) to provide methyl (*R*)-5-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)thiazole-4-carboxylate (10 mg, 24 μmol, 38 % yield). LCMS $[M+H]^+ = 425.5$.

[00414] Step B: To a vial was added methyl (*R*)-5-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)thiazole-4-carboxylate (9.0 mg, 1 eq., 21 μmol) and methanol (0.10 mL) and tetrahydrofuran (0.10 mL). The solution stirred for 10 minutes before adding sodium hydroxide (4.2 mg, 5 eq., 0.11 mmol) and water (0.12 mL). The reaction was allowed to stir for four hours at room temperature. The reaction was concentrated, 1M HCl was added until solution was ~ pH = 4. The reaction was stirred until precipitation occurred and the solids were filtered and washed with water and dried under vacuum to provide (*R*)-5-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)thiazole-4-carboxylic acid was a yellow fluffy solid. LCMS $[M+H]^+ = 411.2$.

[00415] ^1H NMR (400 MHz, CDCl_3) δ = 8.14-8.28 (m, 1H), 8.02 (s, 1H), 7.71 (s, 1H), 7.48 (s, 1H), 5.11-5.19 (m, 1H), 4.06 (td, J = 6.8, 2.0 Hz, 2H), 2.72-2.82 (m, 1H), 2.61-2.72 (m, 1H), 2.45 (s, 3H), 2.39 (br d, J = 4.5 Hz, 2H), 2.06-2.31 (m, 5H), 1.80 (d, J = 6.8 Hz, 3H).

[00416] Intermediate L-1 and L-2





[00417] Step A: To a flask charged with 3-benzyl-3-methylpyrrolidin-2-one (1 g, 1.0 eq., 5.3 mmol) in 1,2-dichloroethane (26 mL) was added phosphorous oxychloride (1.05 g, 640 μ L, 1.3 eq. 6.9 mmol) and diisopropylethylamine (683 mg, 920 μ L, 1.0 eq., 5.3 mmol). The reaction was then heated to 50 °C for one hour. Next, 2-amino-3-bromo-5-methylbenzoic acid (1.22 g, 1 eq., 5.3 mmol) was added as a solid and the reaction was heated to 100 °C. The reaction was stirred overnight before being cooled to room temperature and diluted with water. The aqueous layer was extracted with dichloromethane and the combined organics were washed with brine, dried over sodium sulfate, and concentrated. The solid was purified by silica gel chromatography to provide 3-benzyl-5-bromo-3,7-dimethyl-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (780 mg, 2.0 mmol, 38 % yield) as a yellow solid. LCMS $[M+H]^+$ = 382.9.

[00418] ^1H NMR (400 MHz, CDCl_3) δ = 8.02 (s, 1H), 7.88 (s, 1H), 7.23 - 7.17 (m, 3H), 7.13 - 7.07 (m, 2H), 3.95-3.87 (m, 1H), 3.54-3.44 (m, 1H), 3.29 (*d*, J = 13.3 Hz, 1H), 2.95 (*d*, J = 13.4 Hz, 1H), 2.46 (s, 3H), 2.36 - 2.27 (m, 1H), 1.99 - 1.90 (m, 1H), 1.50 (s, 3H).

[00419] Step B: To a vial and a stir bar was added palladium (II) acetate (22.8 mg, 0.05 eq., 102 μ mol), 1,3-bis(diphenylphosphino)propane (83.9 mg, 0.10 eq., 204 μ mol) and 3-benzyl-5-bromo-3,7-dimethyl-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (780 mg, 1.0 eq., 2.04 mmol). The flask was evacuated and backfilled with nitrogen three times. Next, ethylene glycol (8.1 mL), *n*-butyl vinyl ether (1.84 mL, 7.0 eq., 14.2 mmol), and *N,N*-dicyclohexylmethylamine (1.30 μ L, 3.0 eq., 6.11 mmol) were injected and this solution was sparged with nitrogen. The flask was placed in a heating block, and the mixture was stirred and heated at 115 °C. After full conversion, the reaction was allowed to cool to room temperature and 1N HCl (6 mL) was added to the reaction. The reaction was stirred until the ketone deprotection went to completion (ca. 1h). The aqueous layer was extracted with ethyl acetate three times and the combined

organics were washed successively with water and brine, dried over sodium sulfate, filtered, and concentrated to a residue. This residue was purified via silica gel chromatography to provide 5-acetyl-3-benzyl-3,7-dimethyl-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (430 mg, 2.04 mmol, 61 % yield) as a yellow solid. LCMS [M+H]⁺ = 347.4.

[00420] ¹H NMR (400 MHz, CDCl₃) δ = 8.22 (s, 1H), 7.89 (s, 1H), 7.23 - 7.15 (m, 3H), 7.04 - 6.97 (m, 2H), 4.01 - 3.90 (m, 1H), 3.50 - 3.40 (m, 1H), 3.18 (*d*, *J* = 13.3 Hz, 1H), 2.97 - 2.88 (m, 4H), 2.50 (s, 3H), 2.38 - 2.26 (m, 1H), 2.05 - 1.93 (m, 1H), 1.49 (s, 3H).

[00421] Step C: To a solution of 5-acetyl-3-benzyl-3,7-dimethyl-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (430 mg, 1.0 eq., 1.24 mmol) and (*R*)-2-methylpropane-2-sulfonamide (181 mg, 1.2 eq., 1.49 mmol) in tetrahydrofuran (3.1 mL) was added titanium (IV) ethoxide (1.42 g, 1.29 mL, 5 eq., 6.21 mmol). The mixture was stirred at 80 °C for 4 hours then cooled to room temperature. Once at room temperature, a minimal amount of brine was added to form a suspension. The resulting suspension was diluted with ethyl acetate, filtered through a plug of celite, and the filter cake was washed with ethyl acetate several times. The filtrate was concentrated under reduced pressure and the yellow residue was quickly purified via silica gel chromatography (0% to 80% ethyl acetate in heptane) to provide (*R*)-*N*-(1-(3-benzyl-3,7-dimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-5-yl)ethylidene)-2-methylpropane-2-sulfonamide (290 mg, 645 μmol, 52 % yield) as a yellow solid.

[00422] Step D: To a solution of (*R*)-*N*-(1-(3-benzyl-3,7-dimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-5-yl)ethylidene)-2-methylpropane-2-sulfonamide (290 mg, 1.0 eq., 645 μmol) in anhydrous dichloromethane (4.30 mL) at room temperature was added Schwartz's reagent (216 mg, 1.3 eq., 839 μmol) as a solid portion wise. The reaction was stirred at this temperature for 15 min before being quenched with ammonium chloride. The aqueous layer was extracted with dichloromethane and the combined organics were washed with brine, dried over sodium sulfate and concentrated under reduced pressure to provide a residue. This solid was purified via silica gel chromatography (0% to 5% methanol in dichloromethane) to provide separated diastereomers.

[00423] Step E: To a solution of the first eluting isomer (87 mg, 1.0 eq., 0.19 mmol) in methanol (0.96 mL) was added 120 μL HCl (4M in dioxane). The reaction was monitored for conversion by LCMS and once complete, triturated with diethyl ether to provide Intermediate L-1 (71 mg) which was used subsequently without further purification. LCMS [M+H]⁺ = 348.2 .

[00424] ¹H NMR (400 MHz, CDCl₃) δ = 8.99 (br s, 2H), 8.07 (s, 1H), 7.57 (s, 1H), 7.23 (m, 3H), 7.02 - 6.98 (m, 2H), 4.96 - 4.87 (m, 1H), 4.08 - 3.97 (m, 1H), 3.54 - 3.44 (m, 1H), 3.09 (br *d*, *J* = 13.6 Hz, 1H), 2.98 (*d*, *J* = 13.6 Hz, 1H), 2.47 (s, 3H), 2.39 - 2.28 (m, 1H), 2.06 - 1.96 (m, 1H), 1.92 (br *d*, *J* = 6.3 Hz, 3H), 1.51 (s, 3H).

[00425] Step E': To a solution of the second eluting isomer (87 mg, 1.0 eq., 0.19 mmol) in methanol (0.96 mL) was added 120 μ L HCl (4M in dioxane). The reaction was monitored for conversion by LCMS and once complete, triturated with diethyl ether to provide Intermediate L-2 (74 mg) which was used subsequently without further purification. LCMS $[M+H]^+ = 348.2$.

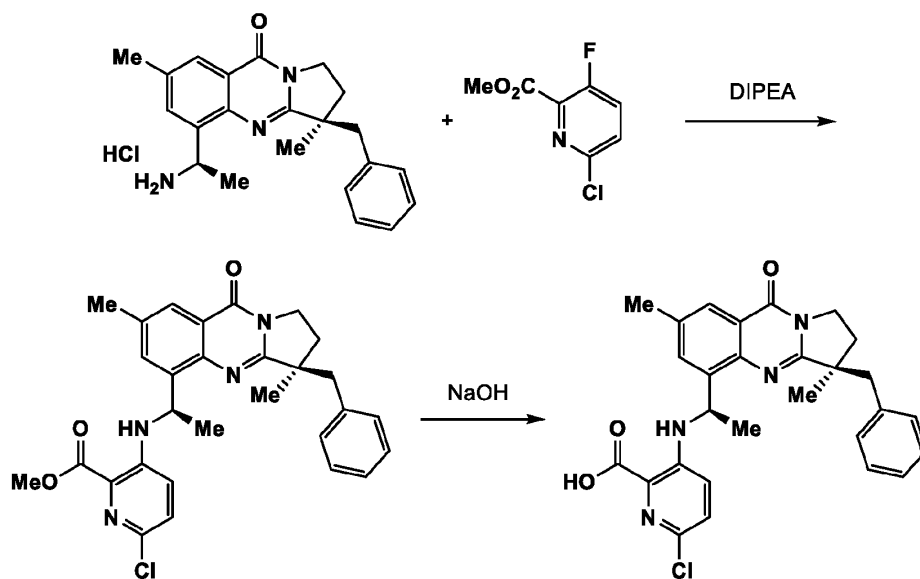
[00426] ^1H NMR (400 MHz, CDCl_3) δ = 8.92 (br s, 2H), 8.06 (s, 1H), 7.57 (s, 1H), 7.27 - 7.22 (m, 3H), 7.04 - 6.95 (m, 2H), 5.00 - 4.89 (m, 1H), 4.07-4.00 (m, 1H), 3.60 - 3.47 (m, 1H), 3.09 (*d*, *J* = 13.4 Hz, 1H), 2.95 (*d*, *J* = 13.4 Hz, 1H), 2.46 (s, 3H), 2.39 - 2.29 (m, 1H), 2.04 - 1.97 (m, 1H), 1.90 (*d*, *J* = 6.8 Hz, 3H), 1.51 (s, 3H).

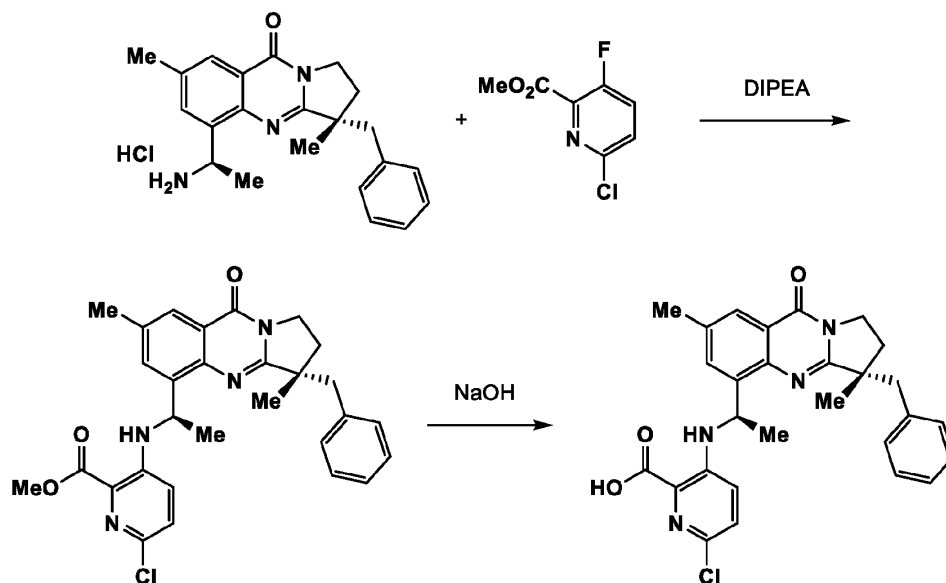
EXAMPLE 1-96 and EXAMPLE 1-97

3-(((*R*)-1-((*R*)-3-benzyl-3,7-dimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-5-yl)ethyl)amino)-6-chloropicolinic acid

And

3-(((*R*)-1-((*S*)-3-benzyl-3,7-dimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-5-yl)ethyl)amino)-6-chloropicolinic acid





[00427] Step A: To a vial was added L-1 (46 mg, 1 eq., 0.12 mmol), methyl 6-chloro-3-fluoropicolinate (38 mg, 1.65 eq., 0.20 mmol) and dimethylformamide (0.66 mL). Lastly, diisopropylethylamine (0.12 mL, 5.5 eq., 0.66 mmol) was added and the vial was sealed and stirred at 100 °C for 12 hours. The mixture was diluted with ethyl acetate and washed with water. The aqueous layer was extracted with ethyl acetate twice more. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified via prep HPLC (Gemini 150x30mm column, 5-95% 0.035% acetonitrile/trifluoroacetic acid mixture in 0.05% water/trifluoroacetic acid mixture) then lyophilized to afford the methyl picolinate product as a trifluoroacetic acid salt (28 mg, 44 μ mol, 37 % yield) and as a white solid. LCMS $[M+H]^+ = 517.2$.

[00428] ^1H NMR (400 MHz, CD_3OD) δ = 7.91 (s, 1H), 7.66 (s, 1H), 7.28 - 7.21 (m, 2H), 7.21 - 7.14 (m, 3H), 7.09 - 7.02 (m, 2H), 5.60 (q, J = 6.7 Hz, 1H), 3.96 - 3.88 (m, 4H), 3.40 - 3.34 (m, 1H), 3.18 - 3.11 (m, 1H), 3.07 - 2.99 (m, 1H), 2.44 (s, 3H) 2.43 - 2.35 (m, 1H), 2.09 - 2.01 (m, 1H), 1.73 (d, J = 6.6 Hz, 3H), 1.51 (s, 3H).

[00429] Step B: To a vial containing the methyl picolinate (26 mg, 1 eq., 41 μ mol) in methanol (0.2 mL) and tetrahydrofuran (0.2 mL) was added 2M lithium hydroxide (0.13 mL, 6.5 eq., 0.27 mmol). The reaction stirred for 1 hour. The methanol and lithium hydroxide was stripped off via rotary evaporator. The residue was brought up in dichloromethane and washed with water. The solution was brought to pH5 with 1N hydrochloric acid. The aqueous layer was extracted with dichloromethane twice more before being washed with brine, dried over sodium sulfate, and concentrated. The residue was brought up in water, frozen and lyophilized to afford EXAMPLE 1-96 (19 mg, 37 μ mol, 90 % yield) as a white solid. LCMS $[M+H]^+ = 503.2$.

[00430] ^1H NMR (400 MHz, CD_3OD) δ = 7.90 (s, 1H), 7.66 (s, 1H), 7.22 - 7.14 (m, 5H), 7.09 - 7.03 (m, 2H), 5.62 (q, J = 6.5 Hz, 1H), 3.97 - 3.85 (m, 1H), 3.40 - 3.33 (m, 1H), 3.17 (d, J = 13.3 Hz, 1H), 3.02 (d, J = 13.3 Hz, 1H), 2.43 (s, 3H), 2.42 - 2.35 (m, 1H), 2.10 - 2.01 (m, 1H), 1.70 (d, J = 6.8 Hz, 3H), 1.52 (s, 3H).

[00431] Step C: To a vial was added Intermediate L-2 (49 mg, 1.0 eq., 0.13 mmol), methyl 6-chloro-3-fluoropicolinate (40 mg, 1.65 eq., 0.21 mmol) and dimethylformamide (0.71 mL). Lastly, diisopropylethylamine (0.12 mL, 5.5 eq., 0.70 mmol) was added and the vial was sealed and stirred at 100 °C for 12 hours. The mixture was diluted with ethyl acetate and washed with water. The aqueous layer was extracted with ethyl acetate twice more. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified via prep HPLC (Gemini 150x30mm column, 5-95% 0.035% acetonitrile/trifluoroacetic acid mixture in 0.05% water/trifluoroacetic acid mixture) then lyophilized to afford the methyl picolinate product as a trifluoroacetic acid salt (23 mg, 36 μmol , 29 % yield) and as a white solid. LCMS $[\text{M}+\text{H}]^+ = 517.2$.

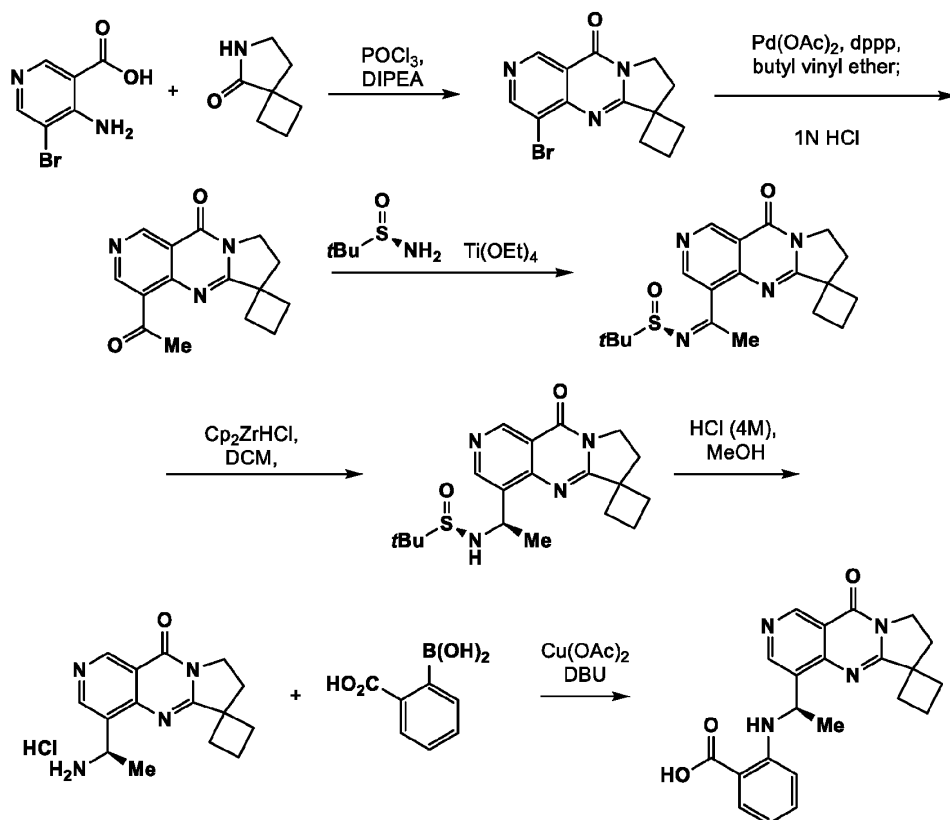
[00432] ^1H NMR (400 MHz, CD_3OD) δ = 7.90 (s, 1H), 7.68 (s, 1H), 7.22 (s, 2H), 7.20 - 7.07 (m, 3H), 6.97 (d, J = 7.4 Hz, 2H), 5.50 (q, J = 6.8 Hz, 1H), 3.94-3.88 (m, 1H), 3.84 (s, 3H), 3.28 (m, 1H), 3.21 - 3.13 (m, 1H), 2.98 (d, J = 13.1 Hz, 1H), 2.46 - 2.37 (m, 4H), 2.12-2.04 (m, 1H), 1.78 (d, J = 6.8 Hz, 3H), 1.57 (s, 3H).

[00433] To a vial containing the methyl picolinate (21 mg, 1.0 eq., 33 μmol) in methanol (0.2 mL) and tetrahydrofuran (0.2 mL) was added 2M lithium hydroxide (0.10 mL, 6 eq., 0.20 mmol). The reaction stirred for 1 hour. The methanol and lithium hydroxide was stripped off via rotary evaporator. The residue was brought up in dichloromethane and washed with water. The solution was brought to pH5 with 1N hydrochloric acid. The aqueous layer was extracted with dichloromethane twice more before being washed with brine, dried over sodium sulfate, and concentrated. The residue was brought up in water, frozen and lyophilized to afford EXAMPLE 1-97 (17 mg, 37 μmol , 100%) as a white solid. LCMS $[\text{M}+\text{H}]^+ = 503.1$.

[00434] ^1H NMR (400 MHz, CD_3OD) δ = 7.89 (s, 1H), 7.68 (s, 1H), 7.20 - 7.08 (m, 5H), 6.98 (d, J = 7.4 Hz, 2H), 5.57 (q, J = 6.3 Hz, 1H), 3.97 - 3.86 (m, 1H), 3.25 (d, J = 13.1 Hz, 1H), 3.22 - 3.12 (m, 1H), 2.97 (d, J = 13.1 Hz, 1H), 2.47 - 2.38 (m, 4H), 2.12 - 2.05 (m, 1H), 1.74 (d, J = 6.6 Hz, 3H), 1.56 (s, 3H).

EXAMPLE 1-98

(*R*)-2-((1-(10'-oxo-7',8'-dihydro-10'*H*-spiro[cyclobutane-1,6'-pyrido[4,3-*d*]pyrrolo[1,2-*a*]pyrimidin]-4'-yl)ethyl)amino)benzoic acid



[00435] Step A: To a flask charged with 6-azaspiro[3.4]octan-5-one (500 mg, 1.0 eq., 3.99 mmol) in 1,2-dichloroethane (20.0 mL) was added phosphorous oxychloride (735 mg, 447 μ L, 1.2 eq., 4.79 mmol) and diisopropylethylamine (516 mg, 696 μ L, 1.0 eq., 3.99 mmol). The reaction was then heated to 50 °C for 1 hour. Next, 4-amino-5-bromonicotinic acid (867 mg, 1.0 eq., 3.99 mmol) was added as a solid, the flask was fitted with a reflux condenser and the reaction was heated to 100 °C. The reaction was stirred overnight before being cooled to room temperature and diluted with water. The aqueous layer was extracted with dichloromethane and the combined organics were washed with brine, dried over magnesium sulfate, and concentrated. The solid was purified by silica gel chromatography to provide 4'-bromo-7',8'-dihydro-10'*H*-spiro[cyclobutane-1,6'-pyrido[4,3-*d*]pyrrolo[1,2-*a*]pyrimidin]-10'-one (228 mg, 745 μ mol, 19 % yield) as a yellow solid.

[00436] ^1H NMR (400 MHz, CDCl_3) δ (ppm) = 9.38 (s, 1H), 8.98 (s, 1H), 4.11 (t, J = 7.1 Hz, 2H), 2.80 - 2.66 (m, 2H), 2.44 (t, J = 7.0 Hz, 2H), 2.37 - 2.27 (m, 1H), 2.26 - 2.08 (m, 3H).

[00437] Step B: To a vial and a stir bar was added palladium (II) acetate (3.67 mg, 0.05 eq., 16.3 μ mol), 1,3-bis(diphenylphosphino)propane (13.5 mg, 0.10 eq., 32.7 μ mol) and 4'-bromo-7',8'-dihydro-10'*H*-spiro[cyclobutane-1,6'-pyrido[4,3-*d*]pyrrolo[1,2-*a*]pyrimidin]-10'-one (100

mg, 1.0 eq., 327 μmol). The vial evacuated and backfilled with nitrogen three times. Next, Ethylene glycol (817 μL), *N,N*-dicyclohexylmethylamine (191 mg, 209 μL , 3.0 eq., 980 μmol), and *n*-butylvinylether (164 mg, 211 μL , 5.0 eq., 1.63 mmol) was injected and this solution was sparged with nitrogen. The vial was placed in a heating block, and the mixture was stirred and heated to 115 °C. After full conversion, the reaction was allowed to cool to room temperature and 1N HCl (2 mL; ~3 volumes relative to ethylene glycol) was added to the reaction. The reaction was stirred until the ketone deprotection went to completion (ca. 1h). The aqueous layer was extracted with ethyl acetate three times and the combined organics were washed successively with water and brine, dried over magnesium sulfate, filtered, and concentrated to a residue. This residue was purified via silica gel chromatography to provide 4'-acetyl-7',8'-dihydro-10'*H*-spiro[cyclobutane-1,6'-pyrido[4,3-*d*]pyrrolo[1,2-*a*]pyrimidin]-10'-one (89 mg, 0.33 mmol, 100 % yield) as a yellow solid. LCMS $[\text{M}+\text{H}]^+ = 270.1$.

[00438] Step C: To a solution of 4'-acetyl-7',8'-dihydro-10'*H*-spiro[cyclobutane-1,6'-pyrido[4,3-*d*]pyrrolo[1,2-*a*]pyrimidin]-10'-one (89 mg, 1.0 eq., 0.33 mmol) and (*R*)-2-methylpropane-2-sulfinamide (48 mg, 1.2 eq., 0.40 mmol) in tetrahydrofuran (0.83 mL) was added titanium (IV) ethoxide (0.38 g, 0.34 mL, 5.0 eq., 1.7 mmol) in a sealed tube. The sealed tube was placed in a heating block at 80 °C for 4 hours then cooled to room temperature. Once at room temperature, a minimal amount of brine was added to form a suspension. The resulting suspension was diluted with ethyl acetate, filtered through a plug of celite, and the filter cake was washed with ethyl acetate several times. The filtrate was concentrated under reduced pressure to a crude yellow solid which was quickly purified via silica gel chromatography to provide (*R*)-2-methyl-*N*-(1-(10'-oxo-7',8'-dihydro-10'*H*-spiro[cyclobutane-1,6'-pyrido[4,3-*d*]pyrrolo[1,2-*a*]pyrimidin]-4'-yl)ethylidene)propane-2-sulfinamide (90 mg, 0.24 mmol, 73 % yield).

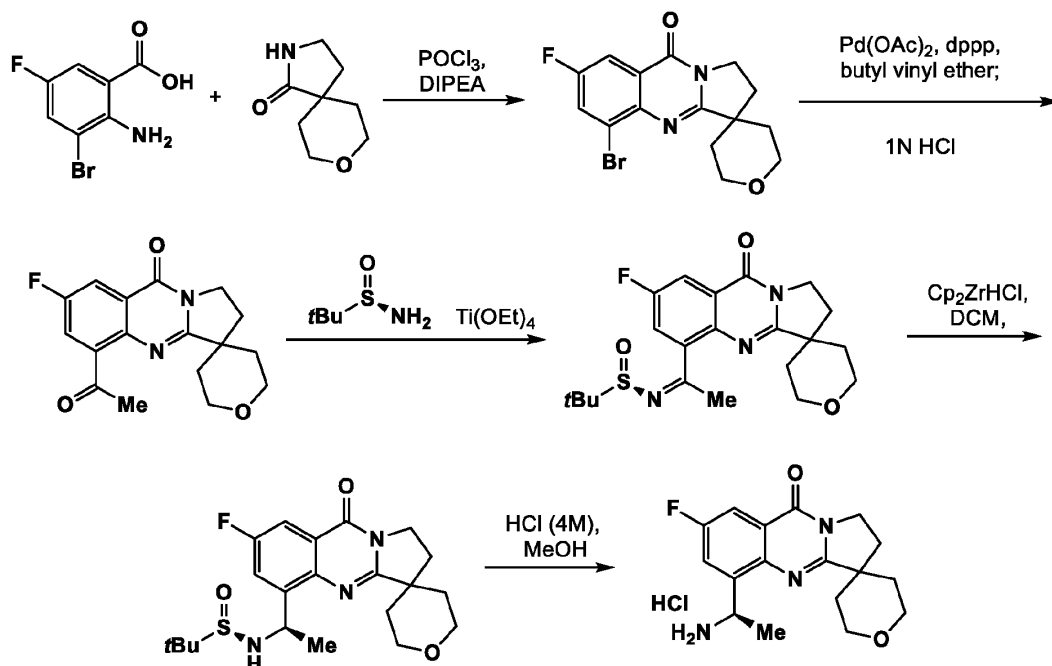
[00439] Step D: To a solution of (*R*)-2-methyl-*N*-(1-(10'-oxo-7',8'-dihydro-10'*H*-spiro[cyclobutane-1,6'-pyrido[4,3-*d*]pyrrolo[1,2-*a*]pyrimidin]-4'-yl)ethylidene)propane-2-sulfinamide (89 mg, 1.0 eq., 0.24 mmol) in anhydrous dichloromethane (1.2 mL) at room temperature was added Schwartz's reagent (68 mg, 1.1 eq., 0.26 mmol) as a solid portion wise (*note: a minimal amount of bubbling was observed*). The reaction was stirred at this temperature for 15 min before being quenched with ammonium chloride. The aqueous layer was extracted with dichloromethane and the combined organics were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. This residue was purified via silica gel chromatography (0% to 10% methanol in dichloromethane) to provide (*R*)-2-methyl-*N*-((*R*)-1-(10'-oxo-7',8'-dihydro-10'*H*-spiro[cyclobutane-1,6'-pyrido[4,3-*d*]pyrrolo[1,2-*a*]pyrimidin]-4'-yl)ethyl)propane-2-sulfinamide (30 mg, 80 μmol , 34 % yield) as a white solid. LCMS $[\text{M}+\text{H}]^+ = 375.2$.

[00440] Step E: To a solution of (*R*)-2-methyl-*N*-((*R*)-1-(10'-oxo-7',8'-dihydro-10'*H*-spiro[cyclobutane-1,6'-pyrido[4,3-*d*]pyrrolo[1,2-*a*]pyrimidin]-4'-yl)ethyl)propane-2-sulfonamide (30 mg, 1.0 eq., 80 μmol) in methanol (0.27 mL) at 0 °C was added HCl (4 molar in dioxane) (4.4 mg, 30 μL, 4.0 molar, 1.5 eq., 0.12 mmol). The reaction was stirred at room temperature until complete, then triturated with diethyl ether to provide (*R*)-4'-(1-aminoethyl)-7',8'-dihydro-10'*H*-spiro[cyclobutane-1,6'-pyrido[4,3-*d*]pyrrolo[1,2-*a*]pyrimidin]-10'-one, HCl as an off-white salt which was used without further purification. LCMS [M+H]⁺ = 271.2.

[00441] Step F: To a vial and stir bar was added (*R*)-4'-(1-aminoethyl)-7',8'-dihydro-10'*H*-spiro[cyclobutane-1,6'-pyrido[4,3-*d*]pyrrolo[1,2-*a*]pyrimidin]-10'-one, HCl (15 mg, 1.0 eq., 49 μmol), 2-boronobenzoic acid (24 mg, 3.0 eq., 0.15 mmol) and copper (II) acetate (13 mg, 1.5 eq., 73 μmol) as solids. Next, the vial was sealed with a septum cap and dimethylformamide (0.24 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (37 mg, 37 μL, 5.0 eq., 0.24 mmol) were added successively. A vent needle was punctured through the septum to expose the reaction to ambient atmosphere and the reaction was stirred at room temperature for 12 hours. The reaction was quenched with aqueous ammonium chloride and diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate three times and the combined organics were washed successively with saturated ammonium chloride and brine before being dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The reaction residue was purified via silica gel chromatography (0% to 75% ethyl acetate in heptane) to provide (*R*)-2-((1-(10'-oxo-7',8'-dihydro-10'*H*-spiro[cyclobutane-1,6'-pyrido[4,3-*d*]pyrrolo[1,2-*a*]pyrimidin]-4'-yl)ethyl)amino)benzoic acid as a white solid. LCMS [M+H]⁺ = 391.1.

[00442] ¹H NMR (400 MHz, CDCl₃) δ = 9.37 (s, 1H), 8.99 (s, 1H), 8.72 - 8.54 (br s, 1H), 8.03 - 7.90 (m, 1H), 7.21 - 7.12 (m, 1H), 6.67 - 6.48 (m, 2H), 5.70 (m, 1H), 4.15 - 4.06 (m, 2H), 2.82 - 2.66 (m, 2H), 2.45 (br t, *J* = 6.8 Hz, 2H), 2.37 - 2.08 (m, 4H), 1.75 (br d, *J* = 6.5 Hz, 3H).

Intermediate M



[00443] Step A: To a flask charged with 8-oxa-2-azaspiro[4.5]decan-1-one (1.0 g, 1.0 eq., 6.4 mmol) in 1,2-dichloroethane (32 mL) was added phosphorous oxychloride (1.3 g, 0.78 mL, 1.3 eq. 8.4 mmol) and diisopropylethylamine (0.83 g, 1.1 mL, 1.0 eq., 6.4 mmol). The reaction was then heated to 50 °C for one hour. Next, 2-amino-3-bromo-5-fluorobenzoic acid (1.5 g, 1 eq., 6.4 mmol) was added as a solid and the reaction was heated to 100 °C. The reaction was stirred overnight before being cooled to room temperature and diluted with water. The aqueous layer was extracted with dichloromethane and the combined organics were washed with brine, dried over sodium sulfate, and concentrated. The solid was purified by silica gel chromatography to provide 5'-bromo-7'-fluoro-1',2,2',3,5,6-hexahydro-9'H-spiro[pyran-4,3'-pyrrolo[2,1-b]quinazolin]-9'-one (960 mg, 2.7 mmol, 42 % yield) as a yellow solid. LCMS $[\text{M}+\text{H}]^+ = 353.0$.

[00444] ^1H NMR (400 MHz, CD_3OD) δ = 7.97 – 7.92 (m, 1H), 7.87 (dd, J = 2.4, 8.3 Hz, 1H), 4.24 - 4.11 (m, 4H), 3.78 - 3.68 (m, 2H), 2.33 (t, J = 7.2 Hz, 2H), 2.22 - 2.10 (m, 2H), 1.78-1.72 (m, 2H).

[00445] Step B: To a vial and a stir bar was added palladium (II) acetate (30.2 mg, 0.05 eq., 134 μmol), 1,3-bis(diphenylphosphino)propane (111 mg, 0.10 eq., 269 μmol) and 5'-bromo-7'-fluoro-1',2,2',3,5,6-hexahydro-9'H-spiro[pyran-4,3'-pyrrolo[2,1-b]quinazolin]-9'-one (950 mg, 1.0 eq., 2.69 mmol). The flask was evacuated and backfilled with nitrogen three times. Next,

ethylene glycol (10.8 mL), *n*-butyl vinyl ether (1.74 mL, 5.0 eq., 13.4 mmol), and *N,N*-dicyclohexylmethylamine (1.72 mL, 3.0 eq., 8.07 mmol) were injected and this solution was sparged with nitrogen. The flask was placed in a heating block, and the mixture was stirred and heated at 115 °C. After full conversion, the reaction was allowed to cool to room temperature and 1N HCl (30 mL) was added to the reaction. The reaction was stirred until the ketone deprotection went to completion (ca. 1h). The aqueous layer was brought to pH = 5 with 2M lithium hydroxide and extracted with ethyl acetate three times. The combined organics were washed successively with water and brine, dried over sodium sulfate, filtered, and concentrated to a residue. This residue was purified via silica gel chromatography to provide 5'-acetyl-7'-fluoro-1',2,2',3,5,6-hexahydro-9'*H*-spiro[pyran-4,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (680 mg, 2.15 mmol, 80 % yield) as a yellow solid. LCMS [M+H]⁺ = 317.1.

[00446] ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.98 (dd, *J* = 3.0, 8.1 Hz, 1H), 7.78 (dd, *J* = 2.9, 8.7 Hz, 1H), 4.09 (t, *J* = 7.1 Hz, 2H), 3.94-3.87 (m, 2H), 3.56 (br t, *J* = 11.1 Hz, 2H), 2.81 (s, 3H), 2.29 (t, *J* = 7.1 Hz, 2H), 2.03 - 1.92 (m, 2H), 1.70 - 1.62 (m, 2H).

[00447] Step C: To a solution of 5'-acetyl-7'-fluoro-1',2,2',3,5,6-hexahydro-9'*H*-spiro[pyran-4,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (675 mg, 1.0 eq., 2.13 mmol) and (*R*)-2-methylpropane-2-sulfinamide (310 mg, 1.2 eq., 2.56 mmol) in tetrahydrofuran (7.11 mL) was added titanium (IV) ethoxide (2.43 g, 2.22 mL, 5 eq., 10.7 mmol). The mixture was stirred at 80 °C for 4 hours then cooled to room temperature. Once at room temperature, a minimal amount of brine was added to form a suspension. The resulting suspension was diluted with ethyl acetate, filtered through a plug of celite, and the filter cake was washed with ethyl acetate several times. The filtrate was concentrated under reduced pressure and the yellow residue was quickly purified via silica gel chromatography (0% to 10% methanol in dichloromethane) to provide (*R*)-*N*-(1-(7'-fluoro-9'-oxo-1',2,2',3,5,6-hexahydro-9'*H*-spiro[pyran-4,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)-2-methylpropane-2-sulfinamide (895 mg, 2.13 mmol, 100 % yield) as a yellow oil.

[00448] Step D: To a solution of (*R*)-*N*-(1-(7'-fluoro-9'-oxo-1',2,2',3,5,6-hexahydro-9'*H*-spiro[pyran-4,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)-2-methylpropane-2-sulfinamide (895 mg, 1.0 eq., 2.13 mmol) in anhydrous dichloromethane (14.2 mL) at room temperature was added Schwartz's reagent (688 mg, 1.25 eq., 2.67 mmol) as a solid portion wise. The reaction was stirred at this temperature for 15 min before being quenched with ammonium chloride. The aqueous layer was extracted with dichloromethane and the combined organics were washed with brine, dried over sodium sulfate and concentrated under reduced pressure to provide a residue. This solid was purified via silica gel chromatography (0% to 10% methanol in dichloromethane) to provide (*R*)-*N*-((*R*)-1-(7'-fluoro-9'-oxo-1',2,2',3,5,6-hexahydro-9'*H*-

spiro[pyran-4,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)-2-methylpropane-2-sulfinamide (380 mg, 0.90 mmol, 42 % yield) as a clear oil. LCMS $[M+H]^+ = 422.2$

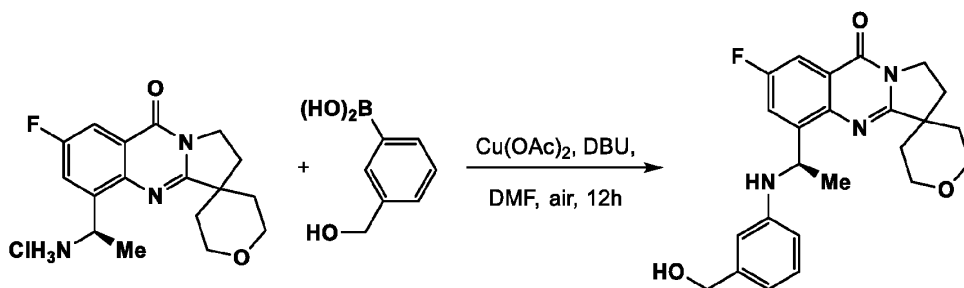
[00449] ^1H NMR (400 MHz, CD_3OD) $\delta = 7.76$ (dd, $J = 2.8, 8.3$ Hz, 1H), 7.68 (dd, $J = 2.6, 9.2$ Hz, 1H), 5.28 (q, $J = 7.1$ Hz, 1H), 4.17 (t, $J = 7.2$ Hz, 2H), 4.13 - 4.02 (m, 2H), 3.72 (br t, $J = 10.7$ Hz, 2H), 2.37 (t, $J = 7.2$ Hz, 2H), 2.24 - 2.10 (m, 2H), 1.73 (br d, $J = 13.1$ Hz, 2H), 1.62 (d, $J = 6.9$ Hz, 3H), 1.24 (s, 9H).

[00450] Step E: To a solution of (*R*)-*N*-((*R*)-1-(7'-fluoro-9'-oxo-1',2,2',3,5,6-hexahydro-9'*H*-spiro[pyran-4,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)-2-methylpropane-2-sulfinamide (380 mg, 1.0 eq., 0.90 mmol) in methanol (3.61 mL) was added 1.13 mL of HCl (4M in dioxane). The reaction was monitored for conversion by LCMS and once complete, concentrated, then triturated with diethyl ether to provide (*R*)-5'-(1-aminoethyl)-7'-fluoro-1',2,2',3,5,6-hexahydro-9'*H*-spiro[pyran-4,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one, hydrochloride (220 mg) as an off white solid which was used subsequently without further purification. LCMS $[M+H]^+ = 318.1$.

[00451] ^1H NMR (400 MHz, CD_3OD) $\delta = 7.92$ (dd, $J = 2.3, 8.3$ Hz, 1H), 7.73 (dd, $J = 2.2, 8.9$ Hz, 1H), 5.31 (q, $J = 6.8$ Hz, 1H), 4.19 (t, $J = 7.2$ Hz, 2H), 4.09 - 4.00 (m, 2H), 3.72 (br t, $J = 11.5$ Hz, 2H), 2.41 (t, $J = 7.3$ Hz, 2H), 2.28 - 2.14 (m, 2H), 1.77 (d, $J = 6.9$ Hz, 3H), 1.71 (br d, $J = 13.5$ Hz, 2H).

EXAMPLE 1-99

(*R*)-7'-fluoro-5'-(1-((3-(hydroxymethyl)phenyl)amino)ethyl)-1',2,2',3,5,6-hexahydro-9'*H*-spiro[pyran-4,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one



[00452] Step A: To a vial and stir bar was added (*R*)-5'-(1-aminoethyl)-7'-fluoro-1',2,2',3,5,6-hexahydro-9'*H*-spiro[pyran-4,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one, hydrochloride (40 mg, 1 eq., 0.11 mmol), 3-(hydroxymethyl)phenylboronic acid (17 mg, 1.0 eq., 0.11 mmol) and copper (II) acetate (31 mg, 1.5 eq., 0.17 mmol) as solids. Next, the vial was sealed with a septum cap and dimethylformamide (0.57 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.08 mL, 5.0 eq., 0.57 mmol) were added successively. A vent needle was punctured through the septum to expose the reaction to ambient atmosphere and the reaction was stirred at room temperature

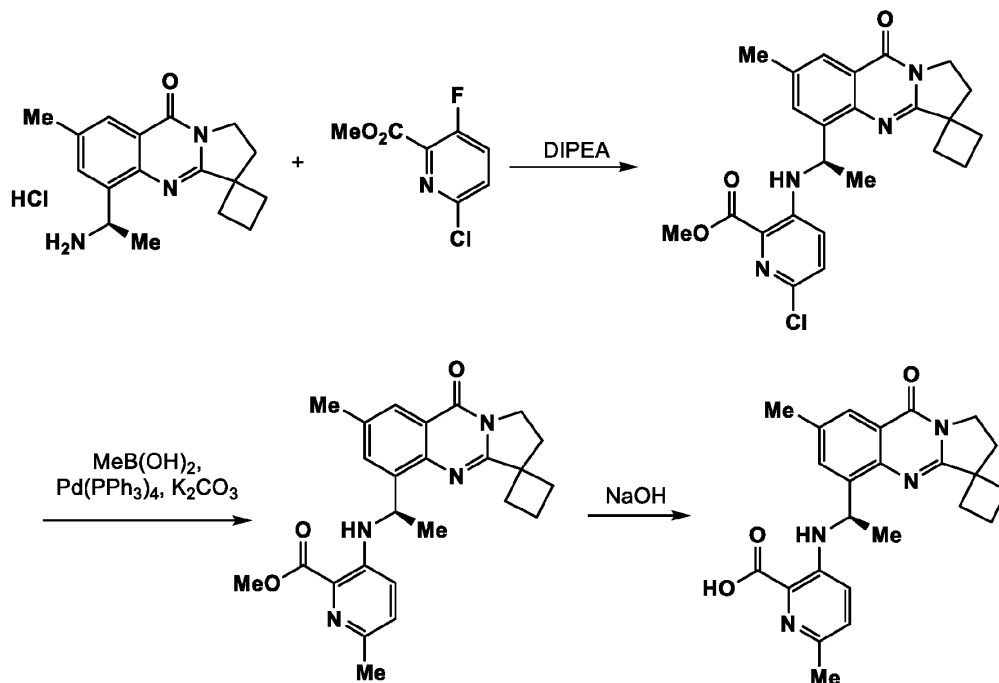
for 12 hours. The reaction was quenched with aqueous ammonium chloride and diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate three times and the combined organics were washed successively with saturated ammonium chloride and brine before being dried over sodium sulfate, filtered, and concentrated under reduced pressure. The reaction residue was purified via reverse phase prep HPLC (5% to 95% 0.035% acetonitrile/trifluoroacetic acid in 0.05% water/trifluoroacetic acid) and lyophilized to provide (*R*)-7'-fluoro-5'--(1-((3-(hydroxymethyl)phenyl)amino)ethyl)-1',2,2',3,5,6-hexahydro-9'*H*-spiro[pyran-4,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one, trifluoroacetic acid (17.7 mg, 33 μ mol, 29 % yield) as a white solid. LCMS $[M+H]^+ = 424.2$.

[00453] ^1H NMR (400 MHz, CD_3OD) δ = 7.72 (dd, J = 3.0, 8.4 Hz, 1H), 7.62 (dd, J = 3.0, 9.4 Hz, 1H), 7.04 (t, J = 7.8 Hz, 1H), 6.75 (s, 1H), 6.71 (d, J = 7.6 Hz, 1H), 6.57 (dd, J = 1.5, 8.0 Hz, 1H), 5.60 (q, J = 6.8 Hz, 1H), 4.43 (s, 2H), 4.21 - 4.09 (m, 4H), 3.79 - 3.69 (m, 2H), 2.42 - 2.35 (m, 2H), 2.27-2.17 (m, 2H), 1.81-1.73 (m, 2H), 1.62 (d, J = 6.8 Hz, 3H)

^{19}F NMR (377 MHz, CD_3OD) δ = -77.23, -115.26.

EXAMPLE 1-100

(*R*)-6-methyl-3-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid



[00454] Step A: A mixture of (*R*)-5'-(1-aminoethyl)-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one hydrochloride (148 mg, 1 eq., 463 μ mol), methyl 6-chloro-3-fluoropicolinate (132 mg, 1.5 eq., 694 μ mol), and diisopropylethylamine (299 mg, 403 μ L, 5 eq., 2.31 mmol) in dimethylformamide (2.31 mL) was stirred at 100 °C for 21h. The mixture was diluted with water and extracted with ethyl acetate. The combined organics were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography to give the product methyl (*R*)-6-chloro-3-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinate (130 mg, 287 μ mol, 62 % yield). LCMS [M+H]⁺ = 453.2.

[00455] Step B: To a vial was added methylboronic acid (28 mg, 2.5 eq., 0.47 mmol), methyl (*R*)-6-chloro-3-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinate (85 mg, 1 eq., 0.19 mmol), potassium carbonate (65 mg, 2.5 eq., 0.47 mmol) and tetrakis(triphenylphosphine)palladium(0) (22 mg, 0.1 eq., 19 μ mol). The vial was evacuated and backfilled three times with nitrogen. Next, a solution of deoxygenated 1,4-Dioxane (0.75 mL) and Water (0.19 mL) was added, and the reaction was heated to 100 °C and stirred overnight. The reaction was quenched with saturated sodium bicarbonate, extracted three times with dichloromethane. The combined organics were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography to give the product methyl (*R*)-6-methyl-3-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinate (35 mg, 81 μ mol, 43 % yield). LCMS[M+H]⁺ = 433.2.

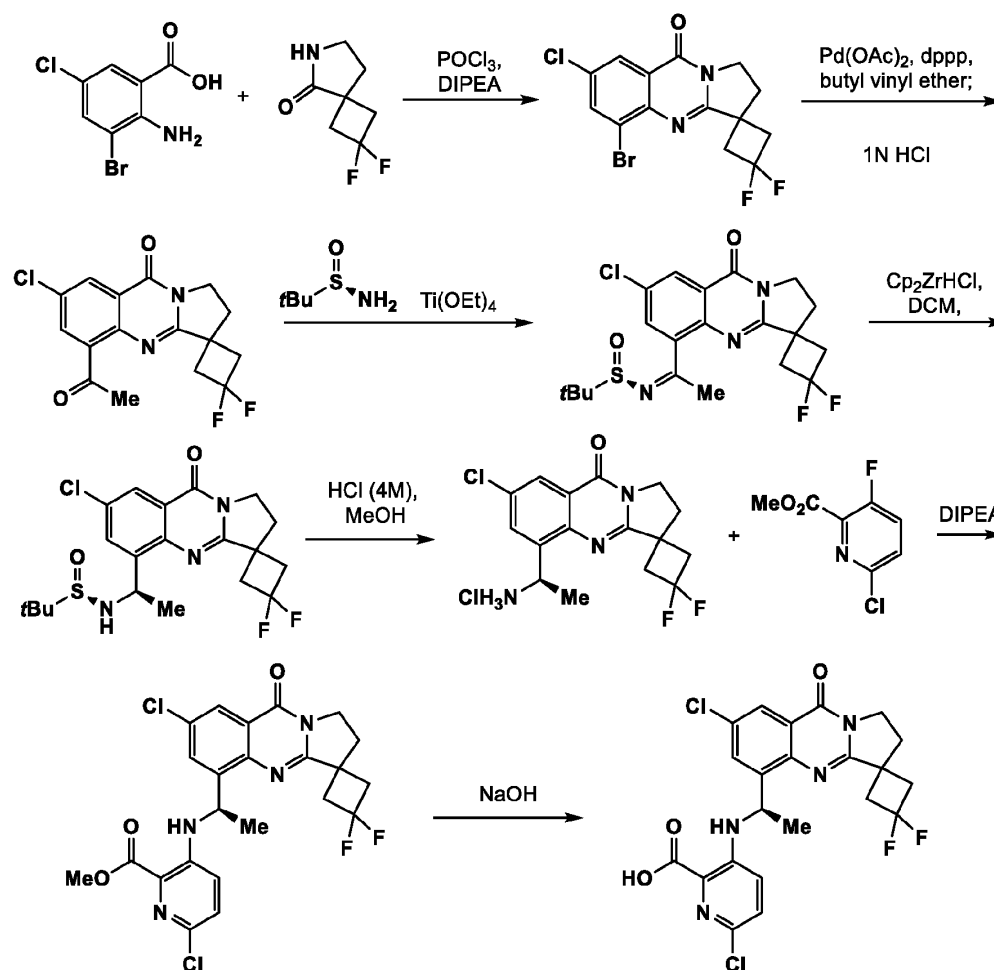
[00456] Step C: To a vial was added methyl (*R*)-6-methyl-3-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinate (18 mg, 1 eq., 42 μ mol) followed by methanol (0.10 mL) and tetrahydrofuran (0.10 mL). The solution stirred for 10 minutes before adding sodium hydroxide (8.3 mg, 5 eq., 0.21 mmol) and water (0.5 mL). The reaction was allowed to stir for four hours at room temperature. Then the reaction was concentrated under vacuum to a more concentrated solution and 1M HCl was added until solution was ~ pH = 4. The solution was directly purified by prep-HPLC (Shimadzu Prep-HPLC; Column: Phenomenex Gemini® 5uM NX-C18 110 Å; 150 x 30 mm; gradient: 5% acetonitrile (0.035% TFA)/95% water (0.05% TFA) to 95% acetonitrile (0.035% TFA)/5% water (0.05% TFA)) to provide (*R*)-6-methyl-3-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid. LCMS [M+H]⁺ = 419.2.

[00457] ¹H NMR (400 MHz, CDCl₃) δ = 7.99 (s, 1H), 7.97 (br s, 1H), 7.54 (d, *J* = 1.6 Hz, 1H), 7.29 (d, *J* = 9.0 Hz, 1H), 7.11-7.18 (m, 1H), 5.70-5.79 (m, 1H), 4.09 (t, *J* = 6.9 Hz, 2H),

2.73 (s, 1H), 2.60-2.71 (m, 2H), 2.57 (s, 2H), 2.36-2.46 (m, 5H), 2.10-2.29 (m, 5H), 1.67-1.74 (m, 3H).

EXAMPLE 1-101

(*R*)-6-chloro-3-((1-(7'-chloro-3,3-difluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid



[00458] Step A: To a flask charged with 2,2-difluoro-6-azaspiro[3.4]octan-5-one (1.000 g, 1.0 eq., 6.205 mmol) in 1,2-dichloroethane (31.03 mL) was added phosphorous oxychloride (1.142 g, 694.0 μL , 1.2 eq., 7.446 mmol) and diisopropylethylamine (802.0 mg, 1.08 mL, 1.0 eq., 6.205 mmol). The reaction was then stirred at 19 °C for 1 hour. Next, 2-amino-3-bromo-5-chlorobenzoic acid (1.554 g, 1.0 eq., 6.205 mmol) was added as a solid, the flask was fitted with a reflux condenser and the reaction was heated to 100 °C. The reaction was stirred overnight before being cooled to room temperature and diluted with water. The aqueous layer

was extracted with dichloromethane and the combined organics were washed with brine, dried over magnesium sulfate, and concentrated. The solid was purified by silica gel chromatography to provide 5'-bromo-7'-chloro-3,3-difluoro-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (976 mg, 2.60 mmol, 42 % yield) as a yellow solid. LCMS $[M+H]^+ = 376.9$.

[00459] Step B: To a vial and a stir bar was added palladium (II) acetate (35.06 mg, 0.05 *eq.*, 156.2 μ mol), 1,3-bis(diphenylphosphino)propane (128.8 mg, 0.10 *eq.*, 312.3 μ mol) and 5'-bromo-7'-chloro-3,3-difluoro-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (1.173 g, 1.0 *eq.*, 3.123 mmol). The vial evacuated and backfilled with nitrogen three times. Next, Ethylene glycol (7.808 mL), *N,N*-dicyclohexylmethylamine (1.830 g, 2.00 mL, 3.0 *eq.*, 9.369 mmol), and *n*-butylvinylether (1.564 g, 2.02 mL, 5.0 *eq.*, 15.62 mmol) was injected. The vial was placed in a heating block, and the mixture was stirred and heated to 115 °C. After full conversion, the reaction was allowed to cool to room temperature and 1N HCl (2 mL; ~3 volumes relative to ethylene glycol) was added to the reaction. The reaction was stirred until the ketone deprotection went to completion (ca. 1h). The aqueous layer was extracted with ethyl acetate three times and the combined organics were washed successively with water and brine, dried over magnesium sulfate, filtered, and concentrated to a residue. This residue was purified via silica gel chromatography to provide 5'-acetyl-7'-chloro-3,3-difluoro-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (868 mg, 2.56 mmol, 82 % yield) as a yellow solid. LCMS $[M+H]^+ = 339.0$.

[00460] Step C: To a solution of 5'-acetyl-7'-chloro-3,3-difluoro-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (868 mg, 1.0 *eq.*, 2.56 mmol) and (*R*)-2-methylpropane-2-sulfinamide (373 mg, 1.2 *eq.*, 3.07 mmol) in tetrahydrofuran (6.41 mL) was added titanium (IV) ethoxide (2.92 g, 2.67 mL, 5.0 *eq.*, 12.8 mmol) in a sealed tube. The sealed tube was placed in a heating block at 80 °C for 12 hours then cooled to room temperature. Once at room temperature, a minimal amount of brine was added to form a suspension. The resulting suspension was diluted with ethyl acetate, filtered through a plug of celite, and the filter cake was washed with ethyl acetate several times. The filtrate was concentrated under reduced pressure to a crude yellow solid which was quickly purified via silica gel chromatography to provide (*R*)-*N*-(1-(7'-chloro-3,3-difluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)-2-methylpropane-2-sulfinamide (1.027 g, 2.324 mmol, 91 % yield).

[00461] Step D: To a solution of (*R*)-*N*-(1-(7'-chloro-3,3-difluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)-2-methylpropane-2-sulfinamide (1.027 g, 1.0 *eq.*, 2.324 mmol) in anhydrous dichloromethane (15.49 mL) at room temperature was added Schwartz's reagent (779.1 mg, 1.3 *eq.*, 3.021 mmol) as a solid portion

wise (*note: a minimal amount of bubbling was observed*). The reaction was stirred at this temperature for 1 hour before being quenched with aqueous ammonium chloride. The aqueous layer was extracted with dichloromethane and the combined organics were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. This residue was purified via silica gel chromatography (0% to 10% methanol in dichloromethane) to provide (*R*)-*N*-((*R*)-1-(7'-chloro-3,3-difluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)-2-methylpropane-2-sulfinamide (818 mg, 1.84 mmol, 79 % yield) as a white solid. LCMS $[M+H]^+ = 444.3$.

[00462] Step E: To a solution of (*R*)-*N*-((*R*)-1-(7'-chloro-3,3-difluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)-2-methylpropane-2-sulfinamide (818 mg, 1.0 eq., 1.84 mmol) in methanol (7.37 mL) was added HCl (4 molar in dioxane) (101 mg, 691 μ L, 4.0 molar, 1.5 eq., 2.76 mmol). The reaction was stirred at room temperature until complete, then triturated with diethyl ether to provide (*R*)-5'-(1-aminoethyl)-7'-chloro-3,3-difluoro-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one, HCl (601 mg, 1.60 mmol, 87 % yield) as an off-white salt which was used without further purification. LCMS $[M+H]^+ = 340.1$.

[00463] Step F: A mixture of (*R*)-5'-(1-aminoethyl)-7'-chloro-3,3-difluoro-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one, HCl (606 mg, 1.0 eq., 1.61 mmol), methyl 6-chloro-3-fluoropicolinate (458 mg, 1.5 eq., 2.42 mmol), and diisopropylethylamine (1.04 g, 1.39 mL, 5.00 eq., 8.05 mmol) in dimethylsulfoxide (8.05 mL) was stirred at 100 °C for 12h. The mixture was diluted with water and extracted with ethyl acetate. The combined organics were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography (0% to 70% ethyl acetate in heptane) to give the methyl (*R*)-6-chloro-3-((1-(7'-chloro-3,3-difluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinate (699 mg, 1.37 mmol, 85 % yield). LCMS $[M+H]^+ = 509.1$.

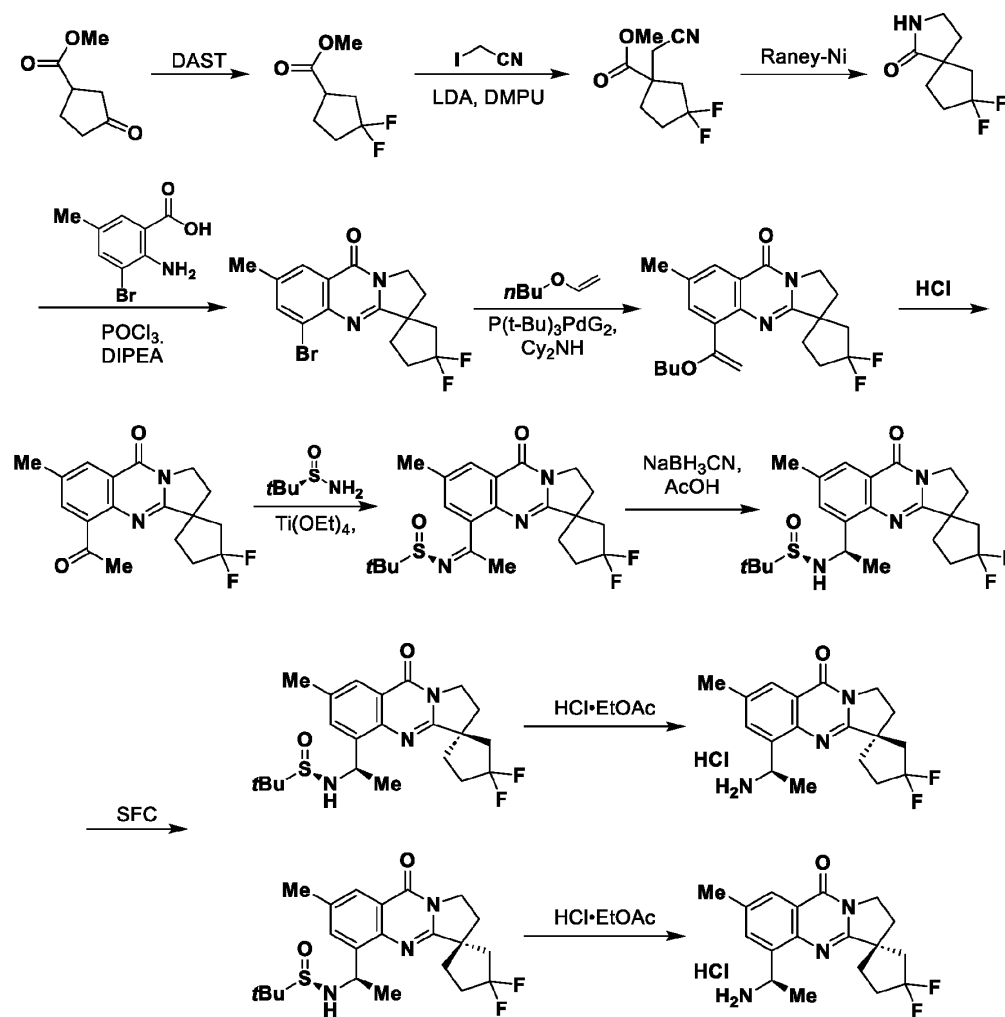
[00464] Step G: To a vial and stir bar charged with methyl (*R*)-6-chloro-3-((1-(7'-chloro-3,3-difluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinate (674 mg, 1 eq., 1.32 mmol) was added tetrahydrofuran (2.12 mL), methanol (2.12 mL), water (1.06 mL) followed by solid sodium hydroxide (159 mg, 3 eq., 3.97 mmol). The reaction was allowed to stir for one hour at room temperature before 1N HCl was added and the reaction diluted with ethyl acetate and brine. The aqueous layer was extracted three times and the combined organics were washed with brine, then dried over magnesium sulfate, filtered, and concentrated to a residue which was purified by silica gel chromatography (0% to 100% ethyl acetate in heptane) to provide (*R*)-6-chloro-3-((1-(7'-chloro-3,3-difluoro-9'-

oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid (662 mg, 1.34 mmol, 100 % yield). LCMS $[M+H]^+ = 495.1$.

[00465] ^1H NMR (400 MHz, CDCl_3) δ ppm = 8.35 (br d, $J = 6.5$ Hz, 1H), 8.18 (*d*, $J = 2.4$ Hz, 1H), 7.65 (*d*, $J = 2.4$ Hz, 1H), 7.15 (*d*, $J = 9.0$ Hz, 1H), 6.89 (*d*, $J = 8.9$ Hz, 1H), 5.54 (quin, $J = 6.6$ Hz, 1H), 4.17 (dt, $J = 1.4, 7.0$ Hz, 2H), 3.42 - 3.27 (m, 1H), 3.25 - 3.11 (m, 1H), 2.88 - 2.72 (m, 2H), 2.55 (t, $J = 7.0$ Hz, 2H), 1.69 (*d*, $J = 6.8$ Hz, 3H).

[00466] ^{19}F NMR (377 MHz, CDCl_3) δ ppm = -85.5, -86.0, -95.1, -95.6.

Intermediate N-1 and N-2



[00467] Step A: A mixture of methyl 3-oxocyclopentanecarboxylate (50.0 g, 351 mmol, 1.00 eq.) in (Diethylamino)sulfur trifluoride (150 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 25 °C for 12 hours under nitrogen atmosphere. After

completion of the reaction, the reaction mixture was quenched by addition into saturated sodium bicarbonate aqueous solution (1.00 L) and extracted with ethyl acetate (500 mL $\times$ 2). The combined organic layer was washed with brine (1.00 L), dried over anhydrous sodium sulfate, then the mixture was filtered and the filtrate was concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=10/1 to 4/1) to give methyl 3,3-difluorocyclopentanecarboxylate (27.3 g, 158 mmol, 45% yield) as a yellow oil.

[00468] ¹H NMR (400 MHz, CDCl₃) δ = 3.68 (s, 3H), 3.07 - 2.91 (m, 1H), 2.45 - 2.28 (m, 2H), 2.24 - 2.00 (m, 4H).

[00469] ¹⁹F NMR (377 MHz, CDCl₃) δ = -90.8, -91.4, -93.8, -94.4.

[00470] Step B: A solution of methyl 3,3-difluorocyclopentanecarboxylate (27.3 g, 158 mmol, 1.00 eq.) in anhydrous tetrahydrofuran (500 mL) was cooled to -78 °C. Then lithium diisopropylamine (2 M, 86.9 mL, 1.10 eq.) was added dropwise under nitrogen. The reaction was stirred at -78 °C for 1.5 hour. Then a solution of 2-iodoacetonitrile (31.7 g, 190 mmol, 1.20 eq.) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (10.1 g, 79.0 mmol, 9.52 mL, 0.50 eq.) in tetrahydrofuran (20.0 mL) was added dropwise while keeping the inner temperature at -78 °C. The reaction was then warmed up to 25 °C and stirred for 16 hours. After completion, the reaction was quenched with hydrochloric acid (1 N, 300 mL) at 0 °C under nitrogen atmosphere. The resulting aqueous solution was extracted with ethyl acetate (500 mL $\times$ 2). The combined organic phase was washed with brine (1.00 L), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=10/1 to 3/1) to give methyl 1-(cyanomethyl)-3,3-difluoro-cyclopentanecarboxylate (14.5 g, 71.4 mmol, 45% yield) as a yellow oil.

[00471] ¹H NMR (400 MHz, CDCl₃) δ = 3.80 (s, 3H), 2.83 - 2.71 (m, 3H), 2.43 - 2.34 (m, 1H), 2.31 - 2.15 (m, 3H), 1.98 - 1.87 (m, 1H).

[00472] Step C: To a solution of Raney-Ni (6.11 g, 71.4 mmol, 1.00 eq.) in methanol (200 mL) was added methyl 1-(cyanomethyl)-3,3-difluoro-cyclopentanecarboxylate (14.5 g, 71.4 mmol, 1.00 eq.) under nitrogen atmosphere. The flask was evacuated and backfilled with hydrogen 3 times. The reaction mixture was stirred under hydrogen (15 psi.) at 25 °C for 6 hours. After completion of the reaction, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=10/1 to 0/1) to give 7,7-difluoro-2-azaspiro[4.4]nonan-1-one (5 g, 28.5 mmol, 40.0% yield) as a yellow solid.

[00473] ¹H NMR (400 MHz, CDCl₃) δ = 6.85 (br s, 1H), 3.43 - 3.18 (m, 2H), 2.63 - 2.47 (m, 1H), 2.43 - 2.27 (m, 1H), 2.25 - 2.13 (m, 4H), 2.10 - 1.97 (m, 1H), 1.86 - 1.71 (m, 1H).

[00474] Step D: To a flask charged with 7,7-difluoro-2-azaspiro[4.4]nonan-1-one (5 g, 28.5 mmol, 1.00 eq.) in 1,2-dichloroethane (100 mL) was added phosphorus oxychloride (5.69 g, 37.1 mmol, 3.46 mL, 1.30 eq.) and diisopropylethylamine (3.69 g, 28.5 mmol, 4.97 mL, 1.00 eq.). The reaction was then heated to 50 °C for 1 hour. Next, the reaction was heated to 85 °C and 2-amino-3-bromo-5-methyl-benzoic acid (7.22 g, 31.4 mmol, 1.10 eq.) was added as a solid. The reaction was stirred at 85 °C for 12 hours. After completion of the reaction, the reaction was cooled to 25 °C and diluted with water (30.0 mL). The aqueous layer was extracted with dichloromethane (50.0 mL × 2) and the combined organics were washed with brine (100 mL), dried over sodium sulfate, and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=1/0 to 0/1) to give 5'-bromo-3,3-difluoro-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (8.1 g, 13.6 mmol, 48% yield, 62% purity) as a yellow solid. LCMS [M+H]⁺ = 369.0.

[00475] Step E: A mixture of 5'-bromo-3,3-difluoro-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (8.10 g, 13.6 mmol, 1.00 eq.), 1-vinyloxybutane (4.08 g, 40.74 mmol, 5.24 mL, 3 eq), Methanesulfonato (di-tert-butyl) methylphosphino (2'-amino-1,1'-biphenyl-2-yl) palladium(II) (696 mg, 1.36 mmol, 0.10 eq.) and dicyclohexylamine (2.95 g, 16.3 mmol, 3.25 mL, 1.20 eq.) in dioxane (50.0 mL) was evacuated and backfilled with nitrogen 3 times, then the mixture was stirred at 100 °C for 1 hour under nitrogen atmosphere. After completion of the reaction, the mixture was cooled to 25 °C, diluted with ethyl acetate (100 mL) and then filtered, the filtrate was concentrated under reduced pressure to give 5'-(1-butoxyvinyl)-3,3-difluoro-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (8 g, crude) as a yellow oil and used into the next step without further purification. LCMS [M+H]⁺ = 389.2.

[00476] Step F: To a solution of 5'-(1-butoxyvinyl)-3,3-difluoro-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (8.00 g, 20.6 mmol, 1.00 eq.) in tetrahydrofuran (80.0 mL) was added hydrochloric acid (4 M, 51.5 mL, 10.0 eq.). The mixture was stirred at 45 °C for 1 hour. After completion of the reaction, the reaction was cooled to 25 °C and quenched with saturated sodium bicarbonate aqueous solution (200 mL). The resulting mixture was extracted with ethyl acetate (100 mL × 2). The combined organic phase was washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=1/0 to 1/1) to give 5'-acetyl-3,3-difluoro-7'-methyl-1',2'-dihydro-

9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (1.80 g, 3.20 mmol, 16% yield, 59% purity) as a yellow oil. LCMS $[M+H]^+ = 333.0$.

[00477] Step G: To a solution of 5'-acetyl-3,3-difluoro-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (1.80 g, 3.20 mmol, 1.00 eq.) and (*R*)-2-methylpropane-2-sulfinamide (582 mg, 4.80 mmol, 1.50 eq.) in 2-methyltetrahydrofuran (20.0 mL) was added titanium (IV) ethoxide (2.19 g, 9.60 mmol, 1.99 mL, 3.00 eq.). The mixture was stirred at 90 °C for 12 hours. After completion of the reaction, the reaction was quenched with water (2.00 mL) and diluted with ethyl acetate (100 mL), then filtered and the filtrate was concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=10/1 to 0/1) to give (*R*)-*N*-(1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)-2-methylpropane-2-sulfinamide (1.20 g, 2.61 mmol, 81% yield, 95% purity) as a yellow oil. LCMS $[M+H]^+ = 436.2$.

[00478] Step H: To a solution of (*R*)-*N*-(1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)-2-methylpropane-2-sulfinamide (1.20 g, 2.61 mmol, 1.00 eq.) in dichloromethane (10.0 mL) and methanol (10.0 mL) was added sodium cyanoborohydride (409 mg, 6.52 mmol, 2.50 eq.) and acetic acid (157 mg, 2.61 mmol, 149 μL, 1.00 eq.). The mixture was stirred at 25 °C for 12 hours. After completion of the reaction, the reaction was quenched with saturated ammonium chloride solution (20.0 mL). The resulting mixture was extracted with dichloromethane (20.0 mL × 2). The combined organic phase was washed with water (40.0 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=1/0 to 0/1) to give (*R*)-*N*-((1*R*)-1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)-2-methylpropane-2-sulfinamide (870 mg, 1.88 mmol, 72% yield, 94% purity) as a yellow solid. LCMS $[M+H]^+ = 438.1$.

[00479] ¹H NMR (400 MHz, CDCl₃) δ = 8.00 (*d*, *J* = 0.8 Hz, 1H), 7.47 (*d*, *J* = 2.0 Hz, 1H), 5.01 (*dd*, *J* = 8.4, 15.6 Hz, 1H), 4.90 - 4.75 (*m*, 1H), 4.21 (*m*, 1H), 4.03 (*m*, 1H), 2.96 - 2.73 (*m*, 1H), 2.64 - 2.49 (*m*, 1H), 2.46 (*s*, 3H), 2.38 - 2.26 (*m*, 5H), 2.09 - 2.05 (*m*, 1H), 1.63 (*d*, *J* = 6.8 Hz, 3H), 1.22 (*d*, *J* = 3.2 Hz, 9H).

[00480] Step I: (*R*)-*N*-((1*R*)-1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)-2-methylpropane-2-sulfinamide was separated by SFC (condition: column: REGIS (*R,R*)WHELK-O1 (250mm × 25mm, 10 μm); mobile phase: [CO₂ - MeOH (0.1% NH₃·H₂O)]; B%: 65%, isocratic elution mode). The desired fractions of peak one were collected and concentrated in vacuum to give the first eluting isomer

(340 mg, 757 μ mol, 40% yield, 97% purity) as a yellow solid. The desired fractions of peak two were collected and concentrated under vacuum to give the second eluting isomer (400 mg, 913 μ mol, 49% yield, 99.9% purity).

[00481] Step J : To a solution of the first eluting isomer (340 mg, 777 μ mol, 1.00 eq.) in ethyl acetate (2.00 mL) was added hydrochloric acid / ethyl acetate (2 M, 1.55 mL, 4.00 eq.). The mixture was stirred at 25 °C for 30 minutes. After completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was triturated with petroleum ether / ethyl acetate =10/1 (20.0 mL) at 25 °C for 1 hour. Then filtered and the filter cake was dried in vacuum to give Intermediate N-1 (250 mg, 675 μ mol, 87% yield, 99.9% purity) as a yellow hydrochloride salt. LCMS $[M+H]^+ = 334.1$.

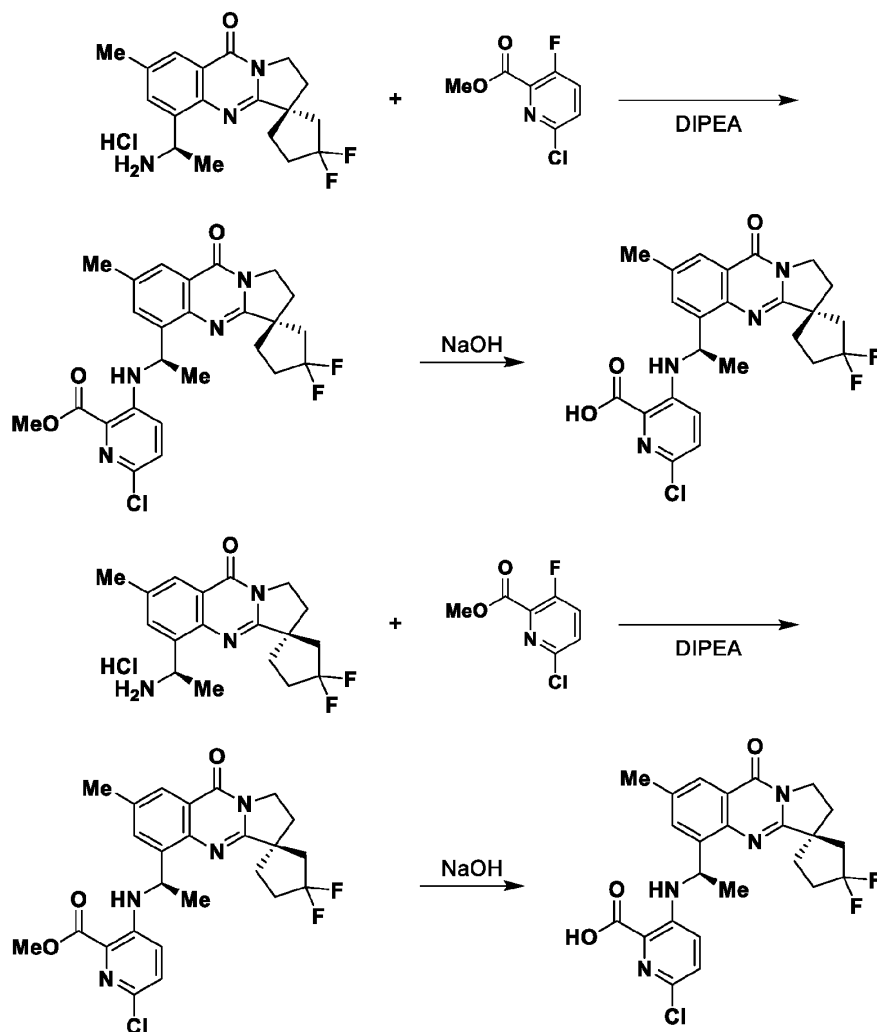
[00482] Step K: To a solution of the second eluting isomer (400 mg, 914 μ mol, 1.00 eq.) in ethyl acetate (2.00 mL) was added hydrochloric acid / ethyl acetate (2 M, 1.83 mL, 4.00 eq.). The mixture was stirred at 25 °C for 30 minutes. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was triturated with petroleum ether/ ethyl acetate =10/1 (20.0 mL) at 25 °C for 1 hour. Then filtered and the filter cake was dried in vacuum to give Intermediate N-1 (330 mg, 890 μ mol, 97% yield, 99.7% purity) as a yellow hydrochloride salt. LCMS $[M+H]^+ = 334.1$.

EXAMPLES 1-102 and 1-103

6-chloro-3-(((*R*)-1-((*R*)-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid

And

6-chloro-3-(((*R*)-1-((*S*)-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid



[00483] Step A: Intermediate N-2 (100 mg, 270 μmol , 1.00 eq.) in dimethylformamide (1.00 mL) was added diisopropylethylamine (105 mg, 810 μmol , 141 μL , 3.00 eq.) and methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (56.3 mg, 297 μmol , 1.10 eq.). The mixture was stirred at 100 $^{\circ}\text{C}$ for 12 hours. After completion of the reaction, the mixture was cooled to 25 $^{\circ}\text{C}$, diluted with water (10.0 mL) and extracted with ethyl acetate (10.0 mL $\times$ 3). The combined organic phase was washed with brine (30.0 mL $\times$ 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the methyl picolinate product (116 mg, 176 μmol , 66% yield, 77% purity) as a yellow solid and used into the next step without further purification. LCMS $[\text{M}+\text{H}]^{+} = 503.2$.

[00484] Step B: To a solution of the methyl picolinate product (50.0 mg, 76.1 μmol , 1.00 eq.) in methanol (0.20 mL) and tetrahydrofuran (0.20 mL) was added sodium hydroxide (2 M,

145 μ L, 4.00 eq.). The mixture was stirred at 25 °C for 1 hour. After completion of the reaction, the mixture was adjusted to ~ pH = 4 with hydrochloric acid (1 M) aqueous solution. Then the solution was extracted with ethyl acetate (10.0 mL $\times$ 2), and the combined organic layer was washed with brine (20.0 mL), dried over anhydrous sodium sulfate. And filtered. The filtrate was concentrated under vacuum to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 $\times$ 25mm $\times$ 10 μ m; mobile phase: [water (formic acid) - acetonitrile]; gradient: 55% - 85% acetonitrile over 9 min) to give EXAMPLE 1-102 (12.5 mg, 25.5 μ mol, 34% yield, 99.9% purity) as a white solid. LCMS [M+H]⁺ = 489.3.

[00485] ¹H NMR (400 MHz, CD₃OD) δ = 7.93 (s, 1H), 7.61 (*d*, *J* = 1.6 Hz, 1H), 7.19 (*d*, *J* = 9.2 Hz, 1H), 7.07 (*d*, *J* = 9.2 Hz, 1H), 5.58 (q, *J* = 6.8 Hz, 1H), 4.22 - 4.15 (m, 1H), 4.14 - 4.05 (m, 1H), 2.89 (m, 1H), 2.62 - 2.42 (m, 2H), 2.42 (s, 3H), 2.39 - 2.29 (m, 4H), 2.20 - 2.05 (m, 1H), 1.68 (*d*, *J* = 6.8 Hz, 3H).

[00486] ¹⁹F NMR (377 MHz, CD₃OD) δ = -88.4, -89.0, -93.5, -94.1.

[00487] Step C: To a solution of Intermediate N-1 (100 mg, 270 μ mol, 1.00 eq.) in DMF (1.00 mL) was added DIEA (105 mg, 810 μ mol, 141 μ L, 3.00 eq.) and methyl 6-chloro-3-fluoropyridine-2-carboxylate (56.3 mg, 297 μ mol, 1.10 eq.). The mixture was stirred at 100 °C for 12 hours. After completion of the reaction, the mixture was cooled to 25 °C, diluted with water (10.0 mL) and exacted with ethyl acetate (10.0 mL $\times$ 3). The combined organic phase was washed with brine (30.0 mL $\times$ 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the methyl picolinate product (100 mg, 145 μ mol, 54% yield, 73% purity) as a yellow solid and used into the next step without further purification. LCMS [M+H]⁺ = 503.2.

[00488] Step D: To a solution of the methyl picolinate product (50.0 mg, 72.6 μ mol, 1.00 eq.) in methanol (0.20 mL) and tetrahydrofuran (0.20 mL) was added sodium hydroxide (2 M, 145 μ L, 4.00 eq.). The mixture was stirred at 25 °C for 1 hour. After completion of the reaction, the mixture was adjusted to ~ pH = 4 with hydrochloric acid (1 M). Then the solution was extracted with ethyl acetate (10.0 mL $\times$ 2), and the combined organic layer was washed with brine (20.0 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum to give a residue. The residue was purified by *prep*-HPLC (FA condition; column: Phenomenex luna C18 150 $\times$ 25mm $\times$ 10 μ m; mobile phase: [water (formic acid) - acetonitrile]; gradient: 55% - 85% acetonitrile over 9 min) to give EXAMPLE 1-103 (8.01 mg, 16.4 μ mol, 23% yield, 99.9% purity) as an off-white solid. LCMS [M+H]⁺ = 489.3.

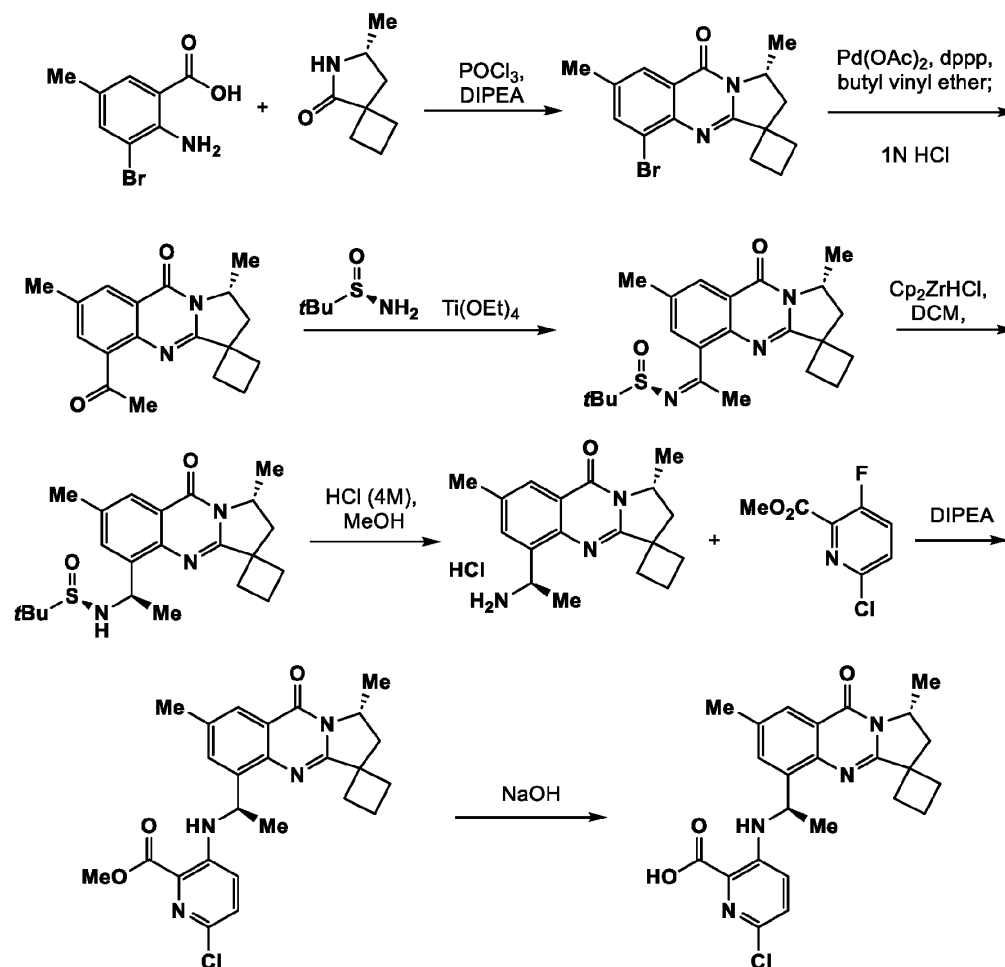
[00489] ¹H NMR (400 MHz, CD₃OD) δ = 7.93 (s, 1H), 7.62 (s, 1H), 7.22 (*d*, *J* = 8.8 Hz 1H), 7.06 (*d*, *J* = 9.2 Hz 1H), 5.56 (q, *J* = 6.8 Hz, 1H), 4.24 - 4.14 (m, 1H), 4.14 - 4.04 (m, 1H), 2.86

(m, 1H), 2.67 - 2.50 (m, 1H), 2.49 - 2.42 (m, 1H), 2.42 (s, 3H), 2.38 - 2.31 (m, 4H), 2.19 - 2.06 (m, 1H), 1.68 (d, $J = 6.8$ Hz, 3H).

[00490] ^{19}F NMR (377 MHz, CD_3OD) $\delta = -88.0, -88.6, -93.4, -94.0$.

EXAMPLE 1-104

6-chloro-3-(((*R*)-1-((*R*)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'-*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid



[00491] Step A: To a vial charged with (*R*)-7-methyl-6-azaspiro[3.4]octan-5-one (500 mg, 1.0 *eq.*, 3.59 mmol) in 1,2-dichloroethane (18.0 mL) was added phosphorous oxychloride (716 mg, 435 μL , 1.3 *eq.*, 4.67 mmol) and diisopropylethylamine (464 mg, 626 μL , 1.0 *eq.*, 3.59 mmol). The reaction was stirred at room temperature for 1 hour. Next, 2-amino-3-bromo-5-methylbenzoic acid (826 mg, 1.0 *eq.*, 3.59 mmol) was added as a solid and the reaction was heated to 100 $^{\circ}\text{C}$. The reaction was stirred overnight before being cooled to room temperature

and diluted with water. The aqueous layer was extracted with dichloromethane and the combined organics were washed with brine, dried over magnesium sulfate, and concentrated. The solid was purified by silica gel chromatography to provide (*R*)-5'-bromo-1',7'-dimethyl-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (682 mg, 2.05 mmol, 36 % yield) as a yellow solid.

[00492] ¹H NMR (400 MHz, CDCl₃) δ ppm = 8.03 (*d*, *J* = 1.0 Hz, 1H), 7.84 (*d*, *J* = 1.9 Hz, 1H), 4.61-4.76 (m, 1H), 2.78-2.89 (m, 1H), 2.59-2.71 (m, 1H), 2.45 (s, 3H), 2.39-2.44 (m, 1H), 2.25-2.39 (m, 2H), 2.18 (dd, *J* = 13.1, 2.2 Hz, 1H), 2.01-2.15 (m, 2H), 1.47 (*d*, *J* = 6.5 Hz, 3H).

[00493] Step B: To a vial and a stir bar was added palladium (II) acetate (23.0 mg, 0.05 *eq.*, 102 μmol), 1,3-bis(diphenylphosphino)propane (84.4 mg, 0.10 *eq.*, 205 μmol) and (*R*)-5'-bromo-1',7'-dimethyl-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (682 mg, 1.0 *eq.*, 2.05 mmol). The vial evacuated and backfilled with nitrogen three times. Next, Ethylene glycol (3.41 mL), *N,N*-dicyclohexylmethylamine (1.20 g, 1.31 mL, 3.0 *eq.*, 6.14 mmol), and *n*-butylvinylether (1.02 g, 1.32 mL, 5.0 *eq.*, 10.2 mmol) was. The vial was placed in a heating block, and the mixture was stirred and heated to 115 °C. After full conversion, the reaction was allowed to cool to room temperature and 1N HCl (2 mL; ~3 volumes relative to ethylene glycol) was added to the reaction. The reaction was stirred until the ketone deprotection went to completion (ca. 1h). The aqueous layer was extracted with ethyl acetate three times and the combined organics were washed successively with water and brine, dried over magnesium sulfate, filtered, and concentrated to a residue. This residue was purified via silica gel chromatography to provide (*R*)-5'-acetyl-1',7'-dimethyl-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (508 mg, 1.71 mmol, 84 % yield) as a yellow solid.

[00494] ¹H NMR (400 MHz, CDCl₃) δ ppm = 8.23 (*d*, *J* = 1.4 Hz, 1H), 7.87 (*d*, *J* = 2.1 Hz, 1H), 4.65-4.79 (m, 1H), 2.98 (s, 3H), 2.68-2.80 (m, 1H), 2.54-2.66 (m, 1H), 2.49 (s, 3H), 2.45 (dd, *J* = 13.1, 8.4 Hz, 1H), 2.24-2.39 (m, 2H), 2.03-2.23 (m, 3H), 1.48 (*d*, *J* = 6.5 Hz, 3H).

[00495] Step C: To a solution of (*R*)-5'-acetyl-1',7'-dimethyl-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (508 mg, 1.0 *eq.*, 1.71 mmol) and (*R*)-2-methylpropane-2-sulfinamide (249 mg, 1.2 *eq.*, 2.06 mmol) in tetrahydrofuran (2.86 mL) was added titanium (IV) ethoxide (1.95 g, 1.78 mL, 5.0 *eq.*, 8.57 mmol) in a sealed tube. The sealed tube was placed in a heating block at 80 °C for 12 hours then cooled to room temperature. Once at room temperature, a minimal amount of brine was added to form a suspension. The resulting suspension was diluted with ethyl acetate, filtered through a plug of celite, and the filter cake was washed with ethyl acetate several times. The filtrate was concentrated under reduced pressure to a crude yellow solid which was quickly purified via silica gel

chromatography to provide (*R*)-*N*-((*R*)-1-((*R*)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)-2-methylpropane-2-sulfonamide (494 mg, 1.24 mmol, 72 % yield).

[00496] Step D: To a solution of (*R*)-*N*-((*Z*)-1-((*R*)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)-2-methylpropane-2-sulfonamide (494 mg, 1.0 *eq.*, 1.24 mmol) in anhydrous dichloromethane (6.18 mL) at room temperature was added Schwartz's reagent (414 mg, 1.3 *eq.*, 1.61 mmol) as a solid portion wise (*note: a minimal amount of bubbling was observed*). The reaction was stirred at this temperature for 1 hour before being quenched with aqueous ammonium chloride. The aqueous layer was extracted with dichloromethane and the combined organics were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. This residue was purified via silica gel chromatography (0% to 10% methanol in dichloromethane) to provide (*R*)-*N*-((*R*)-1-((*R*)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)-2-methylpropane-2-sulfonamide (373 mg, 929 μ mol, 75 % yield) as a white solid. LCMS [M+H]⁺ = 402.3.

[00497] Step E: To a solution of (*R*)-*N*-((*R*)-1-((*R*)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)-2-methylpropane-2-sulfonamide (373 mg, 1.0 *eq.*, 929 μ mol) in methanol (1.86 mL) was added HCl (4 molar in dioxane) (50.8 mg, 348 μ L, 4.0 molar, 1.5 *eq.*, 1.39 mmol). The reaction was stirred at room temperature until complete, then triturated with diethyl ether to provide (*R*)-5'-((*R*)-1-aminoethyl)-1',7'-dimethyl-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one, HCl (286 mg, 857 μ mol, 92 % yield) as an off-white salt which was used without further purification. LCMS [M+H]⁺ = 298.2.

[00498] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm = 8.39 (br s, 3H), 7.97 (s, 1H), 7.81 (*d*, *J* = 1.8 Hz, 1H), 5.28 (dt, *J* = 12.2, 6.2 Hz, 1H), 4.55-4.72 (m, 1H), 2.62-2.75 (m, 1H), 2.54 (m, 1H), 2.48 (s, 3H), 2.41-2.46 (m, 1H), 2.29-2.39 (m, 1H), 2.03-2.26 (m, 4H), 1.64 (*d*, *J* = 6.9 Hz, 3H), 1.38 (*d*, *J* = 6.5 Hz, 3H).

[00499] Step F: A mixture of (*R*)-5'-((*R*)-1-aminoethyl)-1',7'-dimethyl-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one, hydrochloride (15 mg, 1.0 *eq.*, 45 μ mol), methyl 6-chloro-3-fluoropicolinate (13 mg, 1.5 *eq.*, 67 μ mol), and diisopropylethylamine (29 mg, 39 μ L, 5.00 *eq.*, 0.22 mmol) in dimethyl sulfoxide (0.22 mL) was stirred at 100 °C for 12h. The mixture was diluted with water and extracted with ethyl acetate. The combined organics were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography (0% to 70% ethyl acetate in heptane) to give the methyl 6-chloro-3-(((*R*)-1-((*R*)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-

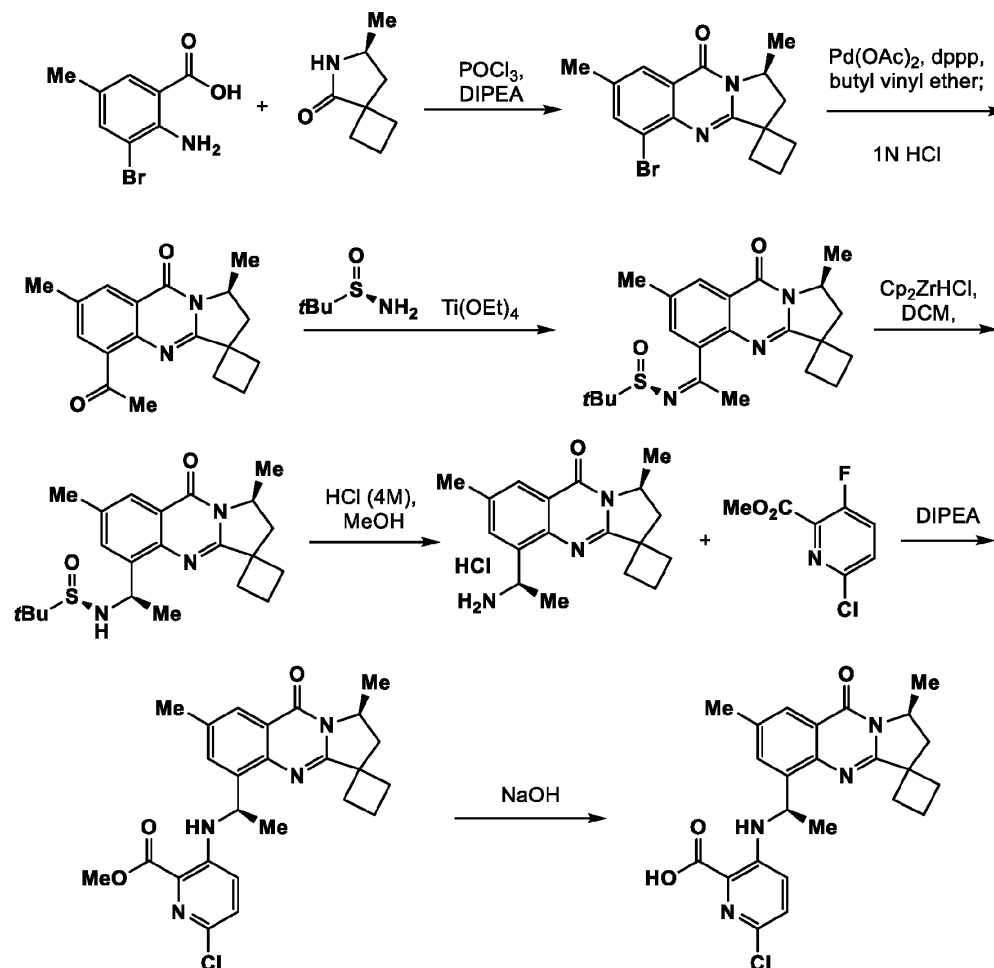
spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinate (12 mg, 26 μ mol, 57 % yield). LCMS $[M+H]^+ = 467.4$.

[00500] Step G: To a vial and stir bar charged with methyl 6-chloro-3-(((*R*)-1-((*R*)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinate (12 mg, 1 *eq.*, 26 μ mol) was added tetrahydrofuran (0.10 mL), methanol (0.10 mL), water (51 μ L) followed by solid sodium hydroxide (4.1 mg, 4 *eq.*, 0.10 mmol). The reaction was allowed to stir for one hour at room temperature before 1N hydrochloric acid was added and the reaction diluted with ethyl acetate and brine. The aqueous layer was extracted three times and the combined organics were washed with brine, then dried over magnesium sulfate, filtered, and concentrated to a residue which was purified by silica gel chromatography (0% to 100% ethyl acetate in heptane) to provide 6-chloro-3-(((*R*)-1-((*R*)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid (9.7 mg, 21 μ mol, 83 % yield). LCMS $[M+H]^+ = 453.4$.

[00501] ^1H NMR (400 MHz, CDCl_3) δ ppm = 7.99 (*d*, $J = 1.1$ Hz, 1H), 7.49 (*d*, $J = 1.9$ Hz, 1H), 7.12-7.16 (*m*, 1H), 7.08-7.11 (*m*, 1H), 5.74 (*q*, $J = 6.2$ Hz, 1H), 4.67-4.81 (*m*, 1H), 2.79-2.92 (*m*, 1H), 2.53-2.65 (*m*, 1H), 2.46 (*dd*, $J = 13.1, 8.4$ Hz, 1H), 2.41 (*s*, 3H), 2.26-2.39 (*m*, 2H), 2.22 (*dd*, $J = 13.1, 1.9$ Hz, 1H), 2.09-2.19 (*m*, 2H), 1.70 (*d*, $J = 6.6$ Hz, 3H), 1.51 (*d*, $J = 6.5$ Hz, 3H).

EXAMPLE 1-105

6-chloro-3-(((*R*)-1-((*S*)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid



[00502] Step A: To a vial charged with (*S*)-7-methyl-6-azaspiro[3.4]octan-5-one (500 mg, 1.0 *eq.*, 3.59 mmol) in 1,2-dichloroethane (18.0 mL) was added phosphorous oxychloride (716 mg, 435 μ L, 1.3 *eq.*, 4.67 mmol) and diisopropylethylamine (464 mg, 626 μ L, 1.0 *eq.*, 3.59 mmol). The reaction was stirred at room temperature for 1 hour. Next, 2-amino-3-bromo-5-methylbenzoic acid (826 mg, 1.0 *eq.*, 3.59 mmol) was added as a solid and the reaction was heated to 100 °C. The reaction was stirred overnight before being cooled to room temperature and diluted with water. The aqueous layer was extracted with dichloromethane and the combined organics were washed with brine, dried over magnesium sulfate, and concentrated. The solid was purified by silica gel chromatography to provide (*S*)-5'-bromo-1',7'-dimethyl-1',2'-

dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (702 mg, 2.11 mmol, 59 % yield) as a yellow solid.

[00503] ¹H NMR (400 MHz, CDCl₃) δ ppm = 8.03 (*d*, *J* = 0.9 Hz, 1H), 7.84 (*d*, *J* = 1.8 Hz, 1H), 4.64-4.74 (m, 1H), 2.78-2.89 (m, 1H), 2.59-2.70 (m, 1H), 2.45 (s, 3H), 2.39-2.44 (m, 1H), 2.25-2.39 (m, 2H), 2.18 (dd, *J* = 13.1, 2.2 Hz, 1H), 2.02-2.15 (m, 2H), 1.47 (*d*, *J* = 6.6 Hz, 3H).

[00504] Step B: To a vial and a stir bar was added palladium (II) acetate (23.6 mg, 0.05 *eq.*, 105 μmol), 1,3-bis(diphenylphosphino)propane (86.9 mg, 0.10 *eq.*, 211 μmol) and (S)-5'-bromo-1',7'-dimethyl-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (702 mg, 1.0 *eq.*, 2.11 mmol). The vial evacuated and backfilled with nitrogen three times. Next, Ethylene glycol (3.51 mL), *N,N*-dicyclohexylmethylamine (1.23 g, 1.35 mL, 3.0 *eq.*, 6.32 mmol), and *n*-butylvinylether (1.06 g, 1.36 mL, 5.0 *eq.*, 10.5 mmol) was injected. The vial was placed in a heating block, and the mixture was stirred and heated to 115 °C. After full conversion, the reaction was allowed to cool to room temperature and 1N HCl (2 mL; ~3 volumes relative to ethylene glycol) was added to the reaction. The reaction was stirred until the ketone deprotection went to completion (ca. 1h). The aqueous layer was extracted with ethyl acetate three times and the combined organics were washed successively with water and brine, dried over magnesium sulfate, filtered, and concentrated to a residue. This residue was purified via silica gel chromatography to provide (S)-5'-acetyl-1',7'-dimethyl-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (527 mg, 1.78 mmol, 84 % yield) as a yellow solid.

[00505] ¹H NMR (400 MHz, CDCl₃) δ ppm = 8.23 (*d*, *J* = 1.4 Hz, 1H), 7.87 (*d*, *J* = 2.0 Hz, 1H), 4.64-4.78 (m, 1H), 2.98 (s, 3H), 2.70-2.79 (m, 1H), 2.53-2.62 (m, 1H), 2.49 (s, 3H), 2.44 (dd, *J* = 13.1, 8.4 Hz, 1H), 2.25-2.39 (m, 2H), 2.14-2.23 (m, 2H), 2.03-2.13 (m, 1H), 1.48 (*d*, *J* = 6.6 Hz, 3H).

[00506] Step C: To a solution of (S)-5'-acetyl-1',7'-dimethyl-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (527 mg, 1.0 *eq.*, 1.78 mmol) and (*R*)-2-methylpropane-2-sulfinamide (259 mg, 1.2 *eq.*, 2.13 mmol) in tetrahydrofuran (2.96 mL) was added titanium (IV) ethoxide (2.03 g, 1.85 mL, 5.0 *eq.*, 8.89 mmol) in a sealed tube. The sealed tube was placed in a heating block at 80 °C for 12 hours then cooled to room temperature. Once at room temperature, a minimal amount of brine was added to form a suspension. The resulting suspension was diluted with ethyl acetate, filtered through a plug of celite, and the filter cake was washed with ethyl acetate several times. The filtrate was concentrated under reduced pressure to a crude yellow solid which was quickly purified via silica gel chromatography to provide (*R*)-*N*-(1-((*S*)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-

spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)-2-methylpropane-2-sulfonamide (467 mg, 1.17 mmol, 66 % yield).

[00507] Step D: To a solution of (*R*)-*N*-(1-((*S*)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)-2-methylpropane-2-sulfonamide (467 mg, 1.0 eq., 1.17 mmol) in anhydrous dichloromethane (5.84 mL) at room temperature was added Schwartz's reagent (392 mg, 1.3 eq., 1.52 mmol) as a solid portion wise (*note: a minimal amount of bubbling was observed*). The reaction was stirred at this temperature for 1 hour before being quenched with aqueous ammonium chloride. The aqueous layer was extracted with dichloromethane and the combined organics were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. This residue was purified via silica gel chromatography (0% to 10% methanol in dichloromethane) to provide (*R*)-*N*-((*R*)-1-((*S*)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)-2-methylpropane-2-sulfonamide (345 mg, 859 μ mol, 74 % yield) as a white solid. LCMS $[M+H]^+ = 402.2$.

[00508] Step E: To a solution of (*R*)-*N*-((*R*)-1-((*S*)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)-2-methylpropane-2-sulfonamide (345 mg, 1.0 eq., 859 μ mol) in methanol (1.72 mL) was added HCl (4 molar in dioxane) (47.0 mg, 322 μ L, 4.0 molar, 1.5 eq., 1.29 mmol). The reaction was stirred at room temperature until complete, then triturated with diethyl ether to provide (*S*)-5'-((*R*)-1-aminoethyl)-1',7'-dimethyl-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one, HCl (237 mg, 710 μ mol, 83 % yield) as an off-white salt which was used without further purification. LCMS $[M+H]^+ = 298.2$.

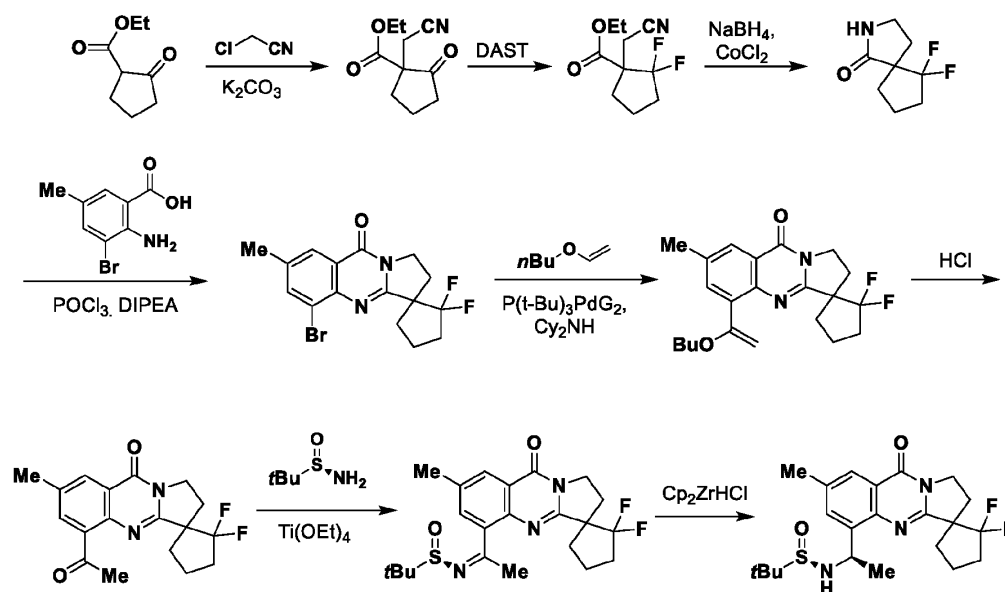
[00509] ^1H NMR (400 MHz, DMSO- d_6) δ ppm = 8.41 (br s, 3H), 7.97 (s, 1H), 7.81 (*d*, $J = 1.8$ Hz, 1H), 5.26 (br *d*, $J = 6.0$ Hz, 1H), 4.56-4.71 (m, 1H), 2.63-2.75 (m, 1H), 2.52-2.55 (m, 1H), 2.48 (s, 3H), 2.41-2.46 (m, 1H), 2.29-2.38 (m, 1H), 2.23 (dd, $J = 13.1, 2.1$ Hz, 1H), 2.01-2.19 (m, 3H), 1.64 (*d*, $J = 6.9$ Hz, 3H), 1.38 (*d*, $J = 6.6$ Hz, 3H).

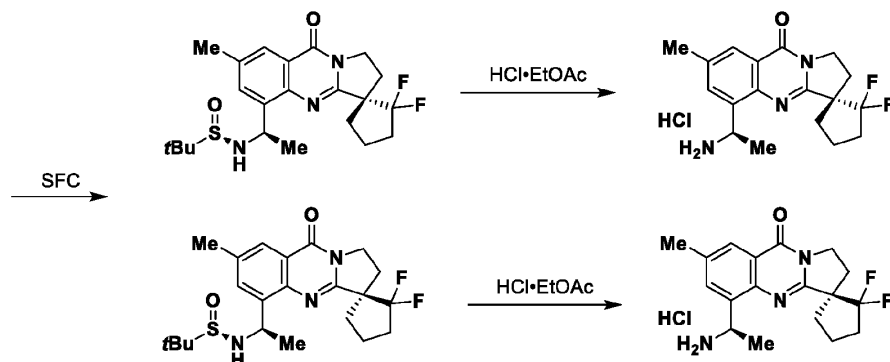
[00510] Step F: A mixture of (*S*)-5'-((*R*)-1-aminoethyl)-1',7'-dimethyl-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one, HCl (15 mg, 1.0 eq., 45 μ mol), methyl 6-chloro-3-fluoropicolinate (13 mg, 1.5 eq., 67 μ mol), and diisopropylethylamine (29 mg, 39 μ L, 5.0 eq., 0.22 mmol) in DMSO (0.30 mL) was stirred at 100 $^{\circ}\text{C}$ for 6h. The mixture was diluted with water and extracted with ethyl acetate. The combined organics were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography (0% to 70% ethyl acetate in heptane) to give the methyl 6-chloro-3-(((*R*)-1-((*S*)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinate (12 mg, 26 μ mol, 57 % yield). LCMS $[M+H]^+ = 467.4$.

[00511] Step G: To a vial and stir bar charged with methyl 6-chloro-3-(((*R*)-1-((*S*)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinate (12 mg, 1 eq., 26 μ mol) was added tetrahydrofuran (0.10 mL), methanol (0.10 mL), water (51 μ L) followed by solid sodium hydroxide (4.1 mg, 4 eq., 0.10 mmol). The reaction was allowed to stir for one hour at room temperature before 1N HCl was added, and the reaction was diluted with ethyl acetate and brine. The aqueous layer was extracted three times and the combined organics were washed with brine, then dried over magnesium sulfate, filtered, and concentrated to a residue which was purified silica gel chromatography (0% to 100% ethyl acetate in heptane) to provide 6-chloro-3-(((*R*)-1-((*S*)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid (10 mg, 22 μ mol, 86 % yield). LCMS $[M+H]^+ = 453.4$.

[00512] ^1H NMR (400 MHz, CDCl_3) δ ppm = 8.33 (br s, 1H), 7.98 (*d*, $J = 1.0$ Hz, 1H), 7.49 (*d*, $J = 2.0$ Hz, 1H), 7.08-7.13 (m, 1H), 7.01-7.06 (m, 1H), 5.64-5.77 (m, 1H), 4.67-4.78 (m, 1H), 2.74-2.84 (m, 1H), 2.56-2.68 (m, 1H), 2.47 (dd, $J = 13.1, 8.4$ Hz, 1H), 2.40 (s, 3H), 2.26-2.38 (m, 2H), 2.21 (dd, $J = 13.1, 2.1$ Hz, 1H), 2.07-2.25 (m, 2H), 1.71 (*d*, $J = 6.8$ Hz, 3H), 1.49 (*d*, $J = 6.5$ Hz, 3H).

Intermediate O-1 and O-2





[00513] Step A: To a solution of ethyl 2-oxocyclopentanecarboxylate (5.00 g, 32.0 mmol, 4.74 mL, 1.00 *eq.*) and 2-chloroacetonitrile (4.83 g, 64.0 mmol, 4.05 mL, 2.00 *eq.*) in acetonitrile (50.0 mL) was added potassium carbonate (13.2 g, 96.0 mmol, 3.00 *eq.*). The mixture was stirred at 60 °C for 12 hours. Upon completion, the reaction mixture was cooled to 25 °C, then the mixture was diluted with water (100 mL) and extracted with ethyl acetate (100 mL × 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate / Petroleum ether gradient @ 40 mL/min) to give ethyl 1-(cyanomethyl)-2-oxocyclopentane-1-carboxylate (3.20 g, 16.3 mmol, 51% yield) as clear oil.

[00514] ¹H NMR (400 MHz, CDCl₃) δ = 4.27 - 4.20 (m, 2H), 2.94 (*d*, *J* = 17.2 Hz, 1H), 2.76 (*d*, *J* = 16.8 Hz, 1H), 2.69 - 2.52 (m, 2H), 2.48 - 2.33 (m, 1H), 2.30 - 2.17 (m, 2H), 2.16 - 2.08 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 3H).

[00515] Step B: To a solution of ethyl 1-(cyanomethyl)-2-oxocyclopentane-1-carboxylate (3.20 g, 16.3 mmol, 1.00 *eq.*) in (Diethylamino)sulfur trifluoride (5.00 mL) was stirred at 25 °C for 16 hours. Upon completion the reaction mixture was quenched by drop-wise to water (100 mL) at 25 °C and extracted with ethyl acetate (100 mL × 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether, gradient @ 40 mL/min) to give ethyl 1-(cyanomethyl)-2,2-difluorocyclopentane-1-carboxylate (2.50 g, 11.5 mmol, 70% yield) as clear oil.

[00516] ¹H NMR (400 MHz, CDCl₃) δ = 4.38 - 4.23 (m, 2H), 3.08 - 2.66 (m, 2H), 2.66 - 2.59 (m, 1H), 2.57 - 2.07 (m, 3H), 2.07 - 1.80 (m, 2H), 1.39 - 1.30 (m, 3H).

[00517] ¹⁹F NMR (377 MHz, CDCl₃) δ = -101.60, -102.01, -102.63, -131.67.

[00518] Step C: To a solution of ethyl 1-(cyanomethyl)-2,2-difluorocyclopentane-1-carboxylate (2.20 g, 10.1 mmol, 1.00 eq.) and cobalt (II) chloride (657 mg, 5.06 mmol, 0.50 eq.) in tetrahydrofuran (30.0 mL) and water (15.0 mL) was added sodium borohydride (3.07 g, 81.0 mmol, 8.00 eq.) at 0 °C. The mixture was stirred at 0 °C for 16 hours. Upon completion the reaction mixture was quenched by water (100 mL) and extracted with ethyl acetate (100 mL × 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether, gradient @ 40 mL/min) to give 6,6-difluoro-2-azaspiro[4.4]nonan-1-one (900 mg, 3.88 mmol, 38% yield) as yellow oil.

[00519] ¹H NMR (400 MHz, CDCl₃) δ = 6.23 (br s, 1H), 3.42 - 3.36 (m, 1H), 3.36 - 3.26 (m, 1H), 2.69 - 2.59 (m, 1H), 2.58 - 2.40 (m, 1H), 2.32 - 1.99 (m, 4H), 1.89 - 1.72 (m, 2H).

[00520] Step D: To a solution of 6,6-difluoro-2-azaspiro[4.4]nonan-1-one (678 mg, 3.87 mmol, 0.99 eq) in 1,2-dichloroethane (10.0 mL) was added phosphorus oxychloride (899 mg, 5.87 mmol, 546 µL, 1.50 eq.) and diisopropylethylamine (1.01 g, 7.82 mmol, 1.36 mL, 2.00 eq.), the reaction mixture was stirred at 50 °C for 1 hr. Then, 2-amino-3-bromo-5-methylbenzoic acid (900 mg, 3.91 mmol, 1.00 eq.) was added at 50 °C. The mixture was stirred at 85 °C for 16 hours. Upon completion the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (100 mL × 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give 5'-bromo-2,2-difluoro-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (800 mg, 2.17 mmol, 55% yield) as a white solid. LCMS [M+3]⁺ = 371.0.

[00521] Step E: To a solution of give 5'-bromo-2,2-difluoro-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (600 mg, 1.63 mmol, 1.00 eq.) and 1-vinylxybutane (325 mg, 3.25 mmol, 417 µL, 2.00 eq.) in dioxane (5.00 mL) was added (*t*-Bu)₂PMe-Pd-G3 (83.2 mg, 162 µmol, 0.10 eq.) and dicyclohexylamine (324. mg, 1.79 mmol, 356 µL, 1.10 eq.). The mixture was stirred at 90 °C for 6 hours under nitrogen atmosphere. Upon completion the reaction mixture was cooled to 25 °C, filtered, and concentrated under reduced pressure to give 5'-(1-butoxyvinyl)-2,2-difluoro-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (600 mg, crude) as a yellow solid. LCMS [M+1]⁺ = 389.2.

[00522] Step F: To a solution of give 5'-(1-butoxyvinyl)-2,2-difluoro-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (600 mg, 1.54 mmol, 1.00 eq.) in tetrahydrofuran (5.00 mL) was added HCl (4.00 M, 1.93 mL, 5.00 eq.). The mixture was stirred at 25 °C for 1 hours. Upon completion the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (100 mL × 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 5'-acetyl-2,2-difluoro-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (500 mg, 1.50 mmol, 97% yield) as a yellow solid. LCMS [M+1]⁺ = 333.1.

[00523] Step G: To a solution of 5'-acetyl-2,2-difluoro-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (340 mg, 1.02 mmol, 1.00 eq.) and (*R*)-2-methylpropane-2-sulfinamide (247 mg, 2.05 mmol, 2.00 eq.) in tetrahydrofuran (3.00 mL) was added titanium (IV) ethoxide (700 mg, 3.07 mmol, 636 µL, 3.00 eq.) and 1,2-dimethoxyethane (101 mg, 1.13 mmol, 116 µL, 1.10 eq.). The mixture was stirred at 70 °C for 2 hours. Upon completion the reaction mixture was diluted with water (1.00 mL) and ethyl acetate (50.0 mL) and stirred for 5 minutes. The resulting mixture was filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give (*R*)-*N*-(1-(2,2-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)-2-methylpropane-2-sulfinamide (310 mg, 711.78 µmol, 70% yield) as a white solid. LCMS [M+1]⁺ = 436.2.

[00524] Step H: To a solution of (*R*)-*N*-(1-(2,2-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)-2-methylpropane-2-sulfinamide (300 mg, 688 µmol, 1.00 eq.) in dichloromethane (3.00 mL) was added Schwartz's reagent (675 mg, 3.44 mmol, 5.00 eq.). The mixture was stirred at 25 °C for 2 hours. Upon completion the reaction mixture was quenched with adding water (1.00 mL), filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give (*R*)-*N*-((1*R*)-1-(2,2-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)-2-methylpropane-2-sulfinamide (220 mg, 502 µmol, 73% yield) as a yellow solid. LCMS [M+1]⁺ = 438.1.

[00525] Step I: (*R*)-*N*-((1*R*)-1-(2,2-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)-2-methylpropane-2-sulfinamide (220 mg, 502 µmol, 1.00 eq.) was separated by SFC (column: DAICEL CHIRALPAK

IG(250mm*50mm,10um); mobile phase: [carbon dioxide-ethanol (neutral)]; Gradient: 27% ethanol, isocratic elution mode). The desired fractions of the first peak were collected and concentrated to give the first eluting isomer (50.0 mg, 114 μ mol, 25.0% yield) as a white solid. The desired fractions of the second peak were collected and concentrated to give the second eluting isomer (80.0 mg, 183 μ mol, 40% yield) as a white solid.

[00526] Step J : To a solution of the first eluting isomer (20.0 mg, 45.7 μ mol, 1.00 eq.) in a solution of HCl in ethyl acetate (2M, 1.00 mL) was stirred at 25 °C for 2 hours. Upon completion the reaction mixture was concentrated under reduced pressure to give a residue, then the residue was added saturated sodium bicarbonate aqueous solution (10.0 mL) to adjust PH>7 and the resulting aqueous solution was extracted with dichloromethane (10.0 mL $\times$ 3). The combined organic layers were washed with brine (10.0 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give Intermediate O-1 (15.0 mg, 44.9 μ mol, 98% yield) as a white solid. LCMS $[M+1]^+ = 334.2$.

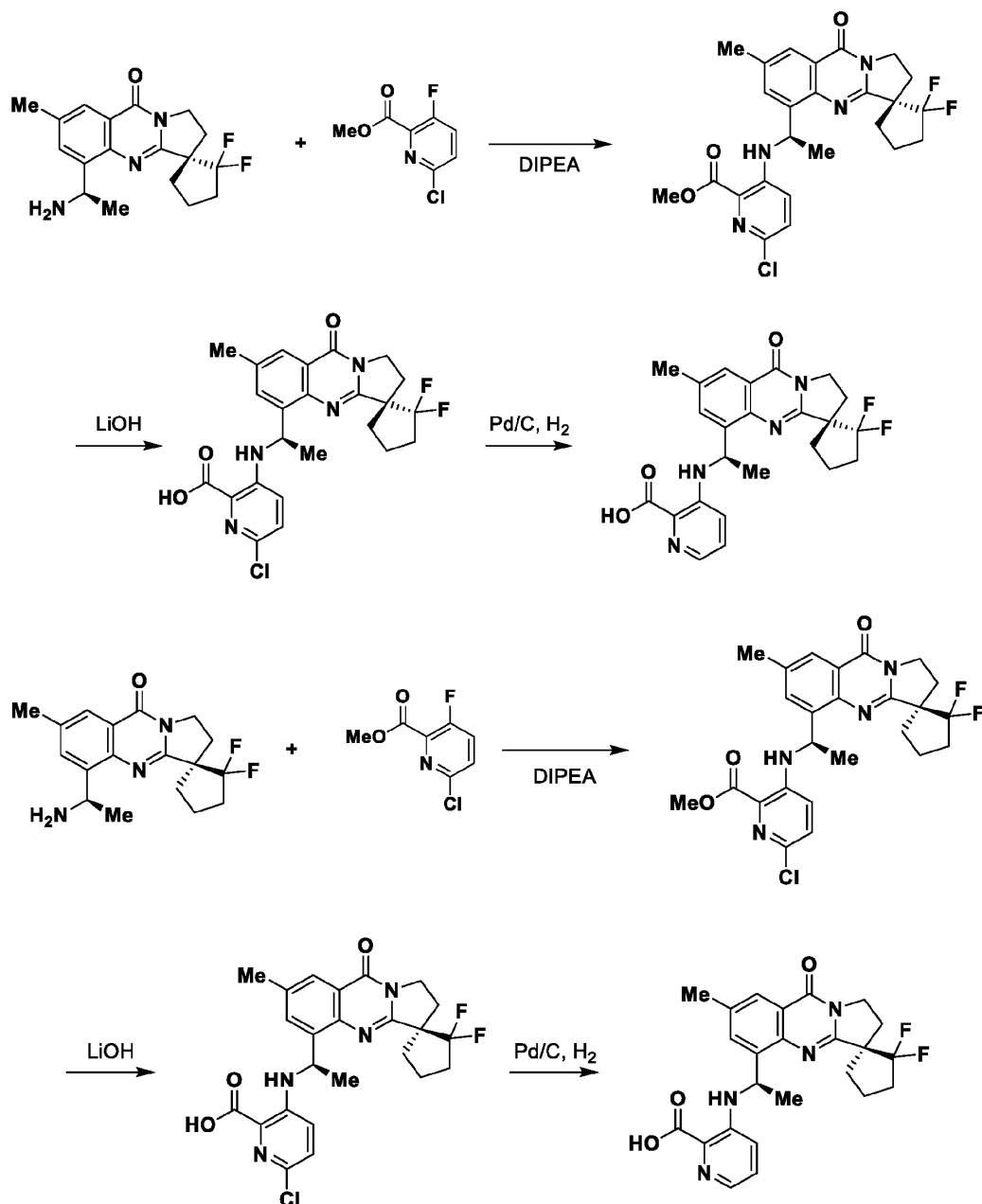
[00527] Step K: A solution of the second eluting isomer (50.0 mg, 114 μ mol, 1.00 eq.) in a solution of HCl in ethyl acetate (2M, 1.00 mL) was stirred at 25 °C for 2 hours. Upon completion the reaction mixture was concentrated under reduced pressure to give a residue, then the residue was added saturated sodium bicarbonate aqueous solution (10.0 mL) to adjust PH>7 and the resulting aqueous solution was extracted with dichloromethane (10.0 mL $\times$ 3). The combined organic layers were washed with brine (10.0 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give Intermediate O-2 (35.0 mg, 104 μ mol, 92% yield) as a white solid. LCMS $[M+1]^+ = 334.2$.

EXAMPLES 1-106 and 1-107

6-chloro-3-(((1*R*)-1-(2,2-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid

And

6-chloro-3-(((*R*)-1-((*R*)-2,2-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid



[00528] Step A: To a solution of Intermediate O-1 (72.0 mg, 216 μ mol, 1.00 *eq.*) and methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (81.9 mg, 432 μ mol, 2.00 *eq.*) in dimethylformamide (1.00 mL) was added diisopropylethylamine (83.7 mg, 648 μ mol, 113 μ L, 3.00 *eq.*). The mixture was stirred at 100 °C for 16 hours. After completion of the reaction, the reaction was cooled to 25 °C. The reaction mixture was diluted with addition water (10.0 mL) and ethyl acetate (5.00 mL). The aqueous phase was extracted with ethyl acetate (10.0 mL $\times$ 2). The combined organic

phase was washed with brine (10.0 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give a residue. The residue was purified by prep-TLC (silicon dioxide, petroleum ether: ethyl acetate = 1:1) to give the methyl picolinate (50.0 mg, 99.4 μ mol, 46% yield) as colorless oil. LCMS $[M+1]^+ = 503.1$.

[00529] Step B: To a solution of the methyl picolinate (50.0 mg, 99.4 μ mol, 1.00 eq.) in tetrahydrofuran (0.50 mL) and methanol (0.50 mL) was added lithium hydroxide (2.00 M, 357 μ L, 7.18 eq.). The mixture was stirred at 25 °C for 2 hours. After completion of the reaction, the reaction mixture was added hydrochloric acid (2.00 M, 1.00 mL) to adjust to pH < 6, and then extracted with dichloromethane (10.0 mL $\times$ 2). The combined organic layers were washed with brine (10.00 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (formic acid condition column: YMC-Actus Triart C18 150 $\times$ 30 mm $\times$ 7 μ m; mobile phase: [water (formic acid)-acetonitrile]; gradient: 60%-90% acetonitrile over 10 min) to give EXAMPLE 1-66 (30.0 mg, 61.3 μ mol, 62% yield, 99.9% purity) as a white solid. LCMS $[M+23]^+ = 511.1$.

[00530] Step C: To a solution of EXAMPLE 1-66 (15.0 mg, 30.7 μ mol, 1.00 eq.) in methanol (1.00 mL) was added palladium on carbon (50.0 mg, 47.0 μ mol, 10 wt%, 1.53 eq.) under nitrogen atmosphere. The suspension was evacuated and backfilled with hydrogen 3 times. The mixture was stirred at 25 °C for 30 minutes under hydrogen (15 psi). The reaction mixture was diluted by addition methanol (10.0 mL), filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (YMC-Actus Triart C18 150 $\times$ 30 mm $\times$ 7 μ m; mobile phase: [water (formic acid)-acetonitrile]; gradient: 35%-65% acetonitrile over 10 min) to give EXAMPLE 1-106. LCMS $[M+1]^+ = 455.2$.

[00531] ^1H NMR (400 MHz, CD_3OD) δ = 7.96 (s, 1H), 7.78 - 7.66 (m, 2H), 7.45 - 7.30 (m, 2H), 5.66 (q, J = 6.4 Hz, 1H), 4.25 - 4.16 (m, 1H), 4.08 (td, J = 8.0, 12.0 Hz, 1H), 2.81 - 2.72 (m, 1H), 2.71 - 2.57 (m, 2H), 2.42 (s, 3H), 2.38 - 2.21 (m, 3H), 2.15 - 2.04 (m, 1H), 2.03 - 1.90 (m, 1H), 1.71 (d, J = 6.8 Hz, 3H).

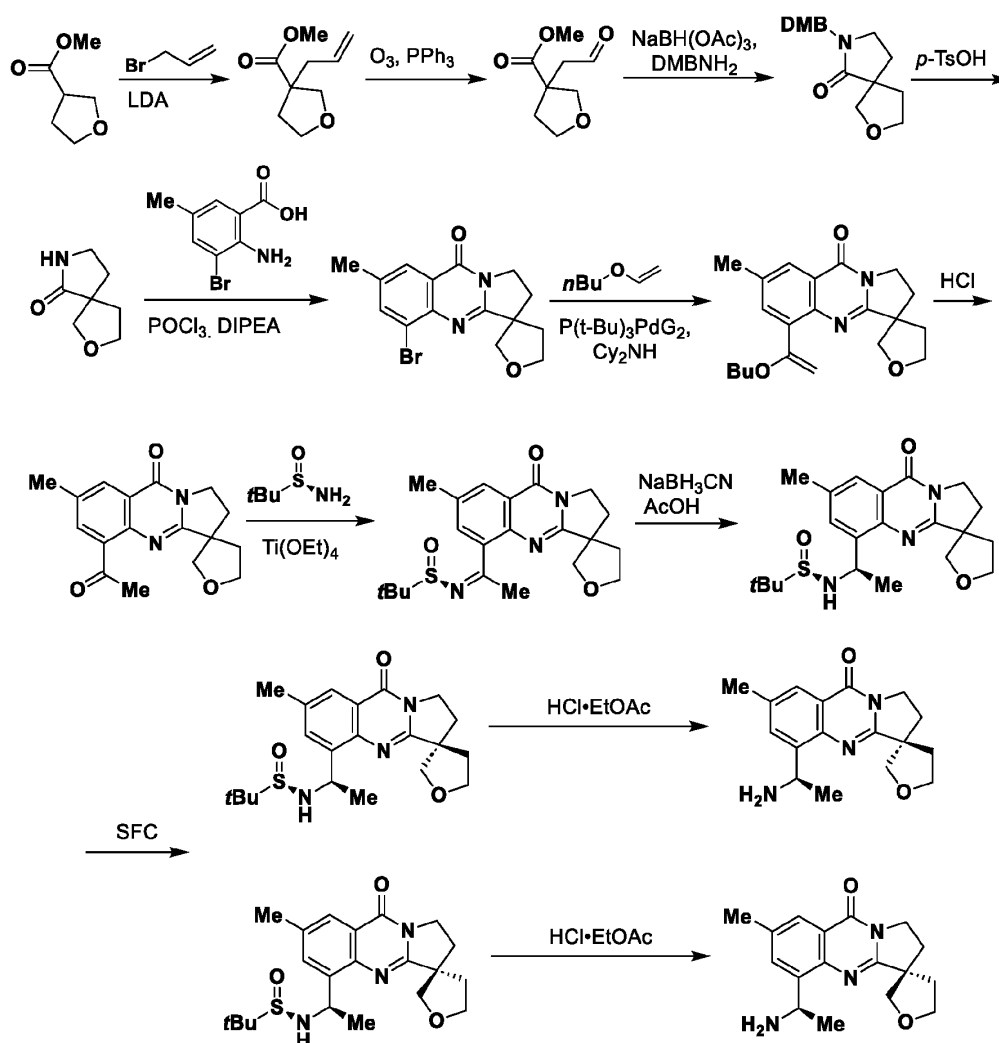
[00532] Step D: To a solution of Intermediate O-2 (70.0 mg, 210 μ mol, 1.00 eq.) methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (79.6 mg, 420 μ mol, 2.00 eq.) in dimethylformamide (1.00 mL) was added diisopropylethylamine (81.4 mg, 630 μ mol, 110 μ L, 3.00 eq.). The mixture was stirred at 100 °C for 16 hours. The reaction was cooled to 25 °C, diluted with water (10.0 mL) and ethyl acetate (5.00 mL). The solution was extracted with ethyl acetate (10.0 mL $\times$ 2). The combined organic layers were washed with brine (10.0 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give a residue. The residue was purified by prep-TLC (silicon dioxide, petroleum ether: ethyl acetate = 1:1) to the methyl picolinate (50.0 mg, 92.5 μ mol, 44% yield, 93% purity) as a colorless oil. LCMS $[M+1]^+ = 503.3$.

[00533] Step E: To a solution of the methyl picolinate (50.0 mg, 99.4 μmol , 1.00 eq.) in tetrahydrofuran (0.50 mL) and methanol (0.50 mL) was added lithium hydroxide (2.00 M, 400 μL , 8.05 eq.). The mixture was stirred at 25 °C for 1 hour. After completion, the reaction mixture was added hydrochloric acid (2.00 M) to adjust pH < 6, and then extracted with ethyl acetate (10.0 mL $\times$ 2). The combined organic layers were washed with brine (10.0 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: YMC-Actus Triart C18 150 $\times$ 30mm $\times$ 7 μm ; mobile phase: [water (formic acid) - acetonitrile]; gradient: 60%-90% B over 10 min) to give EXAMPLE 1-67 (25.0 mg, 51.1 μmol , 51.4% yield) as a yellow solid. LCMS $[\text{M}+1]^+ = 489.0$.

[00534] Step F: To a solution of EXAMPLE 1-67 (80.0 mg, 164 μmol , 1.00 eq.) in methanol (1.00 mL) was added palladium on carbon (17.4 mg, 16.4 μmol , 10 wt%, 0.10 eq.) under nitrogen atmosphere. The suspension was degassed and purged with hydrogen for 3 times. The mixture was stirred under hydrogen (15 Psi) at 25 °C for 0.5 hour. After completion, the reaction mixture was diluted with methanol (10 mL), filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (FA condition column: Phenomenex luna C18 150 $\times$ 25mm $\times$ 10 μm ; mobile phase: [water (FA) - ACN]; gradient: 32% - 62% B over 9 min) to give EXAMPLE 1-107 (10.4 mg, 22.9 μmol , 14% yield, 99.8% purity) as an off-white solid. LCMS $[\text{M}+1]^+ = 455.2$.

[00535] ^1H NMR (400 MHz, CD_3OD) δ = 7.95 (s, 1H), 7.75 (br d, J = 4.8 Hz, 1H), 7.66 (d, J = 1.6 Hz, 1H), 7.48 (dd, J = 4.8, 8.8 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 5.68 (q, J = 6.4 Hz, 1H), 4.25 – 4.19(m, 1H), 4.10 – 4.03(m, 1H), 2.81 - 2.73 (m, 1H), 2.73 - 2.52 (m, 2H), 2.41 (s, 3H), 2.38 - 2.21 (m, 3H), 2.00 – 1.93 (m, 1H), 2.00 - 1.97 (m, 1H), 1.68 (d, J = 6.8 Hz, 3H).

Intermediate P-1 and P-2



[00536] Step A: A solution of methyl tetrahydrofuran-3-carboxylate (8.30 g, 63.78 mmol, 1.00 *eq.*) and allyl bromide (8.49 g, 70.2 mmol, 1.10 *eq.*) in anhydrous tetrahydrofuran (125 mL) was cooled to -78 °C. Then lithium diisopropylamine (2 M, 38.3 mL, 1.20 *eq.*) was added dropwise. The reaction was stirred at -78 °C for 2 hours. The reaction was quenched with hydrochloric acid (1 N, 200 mL) at 0 °C under nitrogen atmosphere. The obtained mixture was extracted with ethyl acetate (100 mL × 2). The combined organic phase was washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=1/0 to 10/1) to give methyl 3-allyltetrahydrofuran-3-carboxylate (7.00 g, 41 mmol, 65% yield) as a yellow oil.

[00537] ^1H NMR (400 MHz, CDCl_3) δ = 5.70 - 5.62 (m, 1H), 5.07 - 5.02 (m, 2H), 4.02 (d, J = 8.8 Hz, 1H), 3.87 - 3.79 (m, 2H), 3.68 (s, 3H), 3.60 (d, J = 8.8 Hz, 1H), 2.50 - 2.45 (m, 1H), 2.41 - 2.35 (m, 2H), 1.86 - 1.80 (m, 1H).

[00538] Step B: A solution of methyl 3-allyltetrahydrofuran-3-carboxylate (7.00 g, 41.1 mmol, 1.00 eq.) in dichloromethane (50.0 mL) and methanol (50.0 mL) at -78 °C was saturated with ozone until a blue color persisted. The solution was then purged with nitrogen until disappearance of the blue coloration and triphenylphosphine (11.9 g, 45.2 mmol, 1.10 eq.) was added to the mixture at 25 °C. The solution was left to warm up to 25 °C and stirred for 12 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ ethyl acetate=1/0 to 1/1) to give methyl 3-(2-oxoethyl)tetrahydrofuran-3-carboxylate (4.80 g, 27.9 mmol, 68% yield) as a yellow oil.

[00539] ^1H NMR (400 MHz, CDCl_3) δ = 9.71 (s, 1H), 4.12 - 4.09 (m, 1H), 3.95 - 3.84 (m, 2H), 3.70 (s, 3H), 3.64 (d, J = 9.2 Hz, 1H), 2.91 (s, 2H), 2.51 - 2.43 (m, 1H), 1.92 - 1.74 (m, 1H).

[00540] Step C: To a solution of methyl 3-(2-oxoethyl)tetrahydrofuran-3-carboxylate (4.60 g, 26.7 mmol, 1.00 eq.) in tetrahydrofuran (80.0 mL) was added 2,4-dimethoxybenzylamine (4.91 g, 29.4 mmol, 4.42 mL, 1.10 eq.) followed by sodium triacetoxyborohydride (11.3 g, 53.4 mmol, 2.00 eq.). The mixture was stirred at 25 °C for 2 hours. The reaction was quenched with hydrochloric acid (2 N, 50.0 mL) and then diluted with water (100 mL). The mixture was extracted with ethyl acetate (100 mL $\times$ 2). The combined organic phase was washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give 7-(3,4-dimethylbenzyl)-2-oxa-7-azaspiro[4.4]nonan-6-one (5.30 g, 16.4 mmol, 62% yield, 90% purity) as a yellow oil. LCMS $[\text{M}+1]^+$ = 292.1.

[00541] ^1H NMR (400 MHz, CDCl_3) δ = 7.14 - 7.07 (m, 1H), 6.52 - 6.43 (m, 2H), 4.54 - 4.34 (m, 2H), 4.00 (dt, J = 5.2, 8.4 Hz, 1H), 3.88 (d, J = 8.4 Hz, 1H), 3.80 (s, 6H), 3.68 - 3.66 (m, 1H), 3.23 - 3.11 (m, 2H), 2.42 - 2.31 (m, 2H), 2.10 - 2.01 (m, 1H), 1.98 - 1.90 (m, 1H), 1.83 - 1.72 (m, 1H).

[00542] Step D: To a solution of 7-(3,4-dimethylbenzyl)-2-oxa-7-azaspiro[4.4]nonan-6-one (5.30 g, 16.4 mmol, 1.00 eq.) in toluene (50.0 mL) was added *p*-toluenesulfonic acid (4.69 g, 24.6 mmol, 1.50 eq.). The mixture was stirred at 110 °C for 1 hour. The mixture was cooled to 25 °C and poured into water (100 mL). The mixture was adjusted to ~ pH = 9 with solid sodium carbonate, then the solution was extracted with ethyl acetate (100 mL $\times$ 3), and the combined organic layers were discarded. The aqueous phase was collected, filtered, and the filtrate was concentrated under vacuum to give a white solid. The crude product was triturated with

dichloromethane (200 mL), then filtered and concentrated under reduced pressure to give 2-oxa-7-azaspiro[4.4]nonan-6-one (950 mg, 4.06 mmol, 25% yield, 60% purity) as a white solid. LCMS $[M+1]^+ = 142.0$.

[00543] ^1H NMR (400 MHz, CDCl_3) δ = 6.72 (br s, 1H), 3.99 (dt, J = 5.2, 8.4 Hz, 1H), 3.94 - 3.85 (m, 2H), 3.72 (d, J = 8.4 Hz, 1H), 3.50 - 3.26 (m, 2H), 2.34 (td, J = 8.0, 12.4 Hz, 1H), 2.27 - 2.17 (m, 1H), 2.16 - 2.06 (m, 1H), 1.86 - 1.79 (m, 1H).

[00544] Step E: To a flask charged with 2-oxa-7-azaspiro[4.4]nonan-6-one (850 mg, 3.63 mmol, 1.00 eq.) in dichloroethane (15.0 mL) was added phosphorus oxychloride (724 mg, 4.72 mmol, 440 μL , 1.30 eq.) and diisopropylethylamine (469 mg, 3.63 mmol, 632 μL , 1.00 eq.). The reaction was then heated to 50 °C for 1 hour. Next, the reaction was heated to 85 °C and 2-amino-3-bromo-5-methyl-benzoic acid (919 mg, 3.99 mmol, 1.10 eq.) was added to the mixture as a solid. The reaction was stirred at 85 °C for 12 hours. The reaction was cooled to 25 °C and diluted with warm water (20.0 mL). The aqueous layer was extracted with dichloromethane (20.0 mL) and the combined organics were washed with brine, dried over anhydrous sodium sulfate, and concentrated under vacuum to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate=1/0 to 1/1) to give 5'-bromo-7'-methyl-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (418 mg, 1.18 mmol, 33% yield, 95% purity) as a yellow solid. LCMS $[M+3]^+ = 337.0$.

[00545] ^1H NMR (400 MHz, CDCl_3) δ = 8.04 (d, J = 1.2 Hz, 1H), 7.85 (d, J = 1.6 Hz, 1H), 4.28 - 4.21 (m, 1H), 4.20 - 4.05 (m, 4H), 3.95 (d, J = 8.4 Hz, 1H), 2.72 - 2.57 (m, 1H), 2.46 (s, 3H), 2.43 - 2.34 (m, 1H), 2.32 - 2.22 (m, 1H), 2.15 - 2.05 (m, 1H).

[00546] Step F: A mixture of 5'-bromo-7'-methyl-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (418 mg, 1.18 mmol, 1.00 eq.), 1-vinyloxybutane (237 mg, 2.37 mmol, 304 μL , 2.00 eq.), (*t*-Bu) $_2\text{PMe-Pd-G3}$ (60.6 mg, 118 μmol , 0.10 eq.), dicyclohexylamine (257 mg, 1.42 mmol, 283 μL , 1.20 eq.) in dioxane (4.00 mL) was evacuated and backfilled with nitrogen 3 times, and then the mixture was stirred at 100 °C for 1 hour under nitrogen atmosphere. The reaction mixture was filtered at 25 °C and concentrated under reduced pressure to give 5'-(1-butoxyvinyl)-7'-methyl-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (510 mg, crude) as a yellow oil and used into the next step without further purification. LCMS $[M+1]^+ = 355.2$.

[00547] Step G: To a solution of 5'-(1-butoxyvinyl)-7'-methyl-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (510 mg, 1.44 mmol, 1.00 eq.) in tetrahydrofuran (5.00 mL) was added hydrochloric acid (4 M, 1.44 mL, 4.00 eq.). The mixture was stirred at 25 °C for 0.5 hour. Then, the mixture was poured into saturated sodium bicarbonate solution (30.0 mL) and extracted with ethyl acetate (20.0 mL $\times$ 2). The combined

organic layer was washed with brine (50.0 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ ethyl acetate = 1/0 to 1/3) to give 5'-acetyl-7'-methyl-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (350 mg, 1.11 mmol, 77% yield, 95% purity) as a yellow oil. LCMS [M+1]⁺ = 299.1.

[00548] Step H: To a solution of 5'-acetyl-7'-methyl-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (300 mg, 951 μmol, 1.00 eq.) and (*R*)-2-methylpropane-2-sulfonamide (173 mg, 1.43 mmol, 1.50 eq.) in 2-methyltetrahydrofuran (5.00 mL) was added titanium (IV) ethoxide (651 mg, 2.85 mmol, 592 μL, 3.00 eq.). The mixture was stirred at 80 °C for 12 hours. The reaction was quenched with water (0.60 mL), then diluted with ethyl acetate (20.0 mL), filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ ethyl acetate=1/0 to 0/1) to give (*R*)-2-methyl-*N*-(1-(7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)propane-2-sulfonamide (336 mg, 485 μmol, 51% yield, 58% purity) as a yellow oil. [M+1]⁺ = 402.2.

[00549] Step I: To a solution of (*R*)-2-methyl-*N*-(1-(7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)propane-2-sulfonamide (336 mg, 485 μmol, 1.00 eq.) in dichloromethane (3.00 mL) and methanol (3.00 mL) was added sodium cyanoborohydride (61.0 mg, 970. μmol, 2.00 eq.) and acetic acid (2.91 mg, 48.5 μmol, 2.78 μL, 0.10 eq.). The mixture was stirred at 25 °C for 1 hour. The reaction was quenched with saturated sodium bicarbonate solution (50 mL). The obtained solution was extracted with dichloromethane (30.0 mL × 3). The combined organic phase was washed with brine (50.0 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ ethyl acetate=1/0 to 0/1) to give (*R*)-2-methyl-*N*-((1*R*)-1-(7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)propane-2-sulfonamide (150 mg, 368 μmol, 76% yield, 99% purity) as a yellow solid. LCMS [M+1]⁺ = 404.2.

[00550] Step J: (*R*)-2-methyl-*N*-[(1*R*)-1-(7-methyl-9-oxo-spiro[1,2-dihydropyrrolo[2,1-*b*]quinazoline-3,3'-tetrahydrofuran]-5-yl)ethyl]propane-2-sulfonamide (150 mg, 368 μmol, 76% yield, 99% purity) was further separated by SFC (condition: column: DAICEL CHIRALCEL OX (250 mm × 30 mm, 10 μm); mobile phase: [CO₂ – EtOH (0.1% NH₃•H₂O)]; Gradient EtOH (0.1% NH₃•H₂O), 50%, isocratic elution mode). The desired fractions of the first peak were collected and concentrated under vacuum to give the first eluting isomer (50.0 mg, 115 μmol, 31% yield, 93% purity) as an off-white solid. The desired fractions of the second peak were collected and concentrated under vacuum to give the second eluting isomer (50.0 mg, 123 μmol, 34% yield, 99.5% purity) as an off-white solid.

[00551] Step K: To a solution of the second eluting isomer (50.0 mg, 115 μ mol, 1.00 eq.) in ethyl acetate (1.00 mL) was added hydrochloric acid in ethyl acetate (2 M, 229 μ L, 4.00 eq.). The mixture was stirred at 25 °C for 30 minutes. The mixture was diluted with water (10.0 mL) and the mixture was adjusted to ~ pH = 8 with saturated sodium bicarbonate solution. Then the solution was extracted with dichloromethane/ methane=10/ 1 (10 mL $\times$ 3, and the combined organic layer was dried over anhydrous sodium sulfate. The mixture was filtered, and concentrated to give Intermediate P-2 (30.0 mg, 100 μ mol, 87% yield, 99.9% purity) as a yellow oil. LCMS $[M+1]^+ = 300.1$.

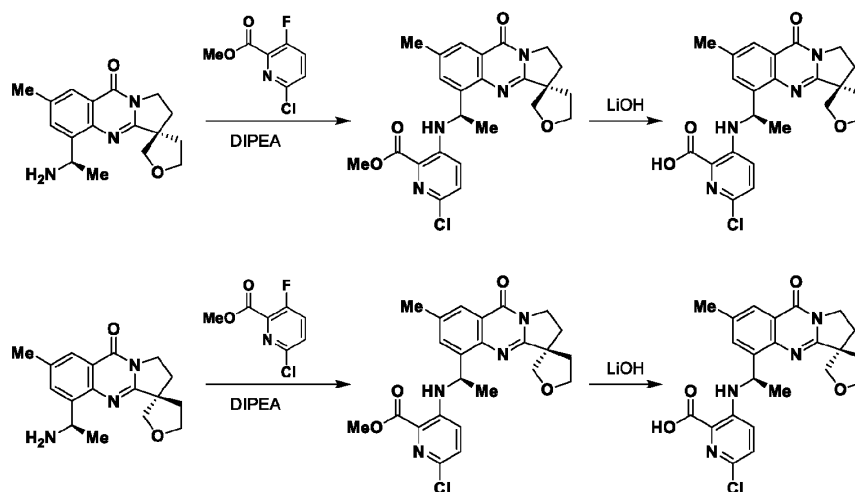
[00552] Step L: To a solution of the first eluting isomer (50.0 mg, 123 μ mol, 1.00 eq.) in ethyl acetate (1.00 mL) was added hydrochloric acid in ethyl acetate (2 M, 246 μ L, 4.00 eq.). The mixture was stirred at 25 °C for 30 minutes. The mixture was diluted with water (10.0 mL) and the mixture was adjusted to ~ pH = 8 with saturated sodium bicarbonate solution. Then the solution was extracted with dichloromethane/ methane = 10/1 (10 mL $\times$ 3) and the combined organic layer was dried over anhydrous sodium sulfate. The mixture was filtered and the filtrate was concentrated to give Intermediate P-1 (35.0 mg, 117 μ mol, 95% yield) as a yellow oil. LCMS $[M+1]^+ = 300.1$.

EXAMPLE 1-108 and 1-109

6-chloro-3-(((*R*)-1-((*S*)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid

And

6-chloro-3-(((*R*)-1-((*R*)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid



[00553] Step A: To a solution of Intermediate P-2 (35.0 mg, 117 μmol , 1.00 *eq.*) and methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (26.6 mg, 140 μmol , 1.20 *eq.*) in dimethyl formamide (1.00 mL) was added diisopropylethylamine (30.2 mg, 234 μmol , 40.7 μL , 2.00 *eq.*). The mixture was stirred at 100 °C for 12 hours. The mixture was diluted with water (10.0 mL) at 25 °C and extracted with ethyl acetate (10.0 mL $\times$ 3). The combined organic phase was washed with brine (30.0 mL $\times$ 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (SiO_2 , petroleum ether/ ethyl acetate = 1/ 1) to give the methyl picolinate (29.0 mg, 60.2 μmol , 52% yield, 97% purity) as an off-white solid. LCMS $[\text{M}+1]^+ = 469.2$.

[00554] Step B: To a solution of the methyl picolinate (29.0 mg, 60.0 μmol , 1.00 *eq.*) in tetrahydrofuran (0.50 mL) and methanol (0.50 mL) was added lithium hydroxide (aq.) (2 M, 60.2 μL , 2.00 *eq.*). The mixture was stirred at 40 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Phenomenex luna C18 250 $\times$ 50 mm $\times$ 15 μm ; mobile phase: [water (formic acid) – acetonitrile]; gradient: 42% -72% acetonitrile over 9 min) to give EXAMPLE 1-108, (15.3 mg, 33.6 μmol , 56% yield, 99.9% purity) as a white solid. LCMS $[\text{M}+1]^+ = 455.2$.

[00555] ^1H NMR (400 MHz, CD_3OD) δ = 7.93 (s, 1H), 7.62 (*d*, *J* = 1.6 Hz, 1H), 7.25 - 7.16 (m, 1H), 7.13 - 7.08 (m, 1H), 5.56 (q, *J* = 6.8 Hz, 1H), 4.24 - 4.11 (m, 4H), 4.09 - 4.01 (m, 1H), 3.97 (*d*, *J* = 8.8 Hz, 1H), 2.57 (td, *J* = 7.6, 12.4 Hz, 1H), 2.42 (s, 3H), 2.41 - 2.29 (m, 2H), 2.25 - 2.16 (m, 1H), 1.67 (*d*, *J* = 6.8 Hz, 3H).

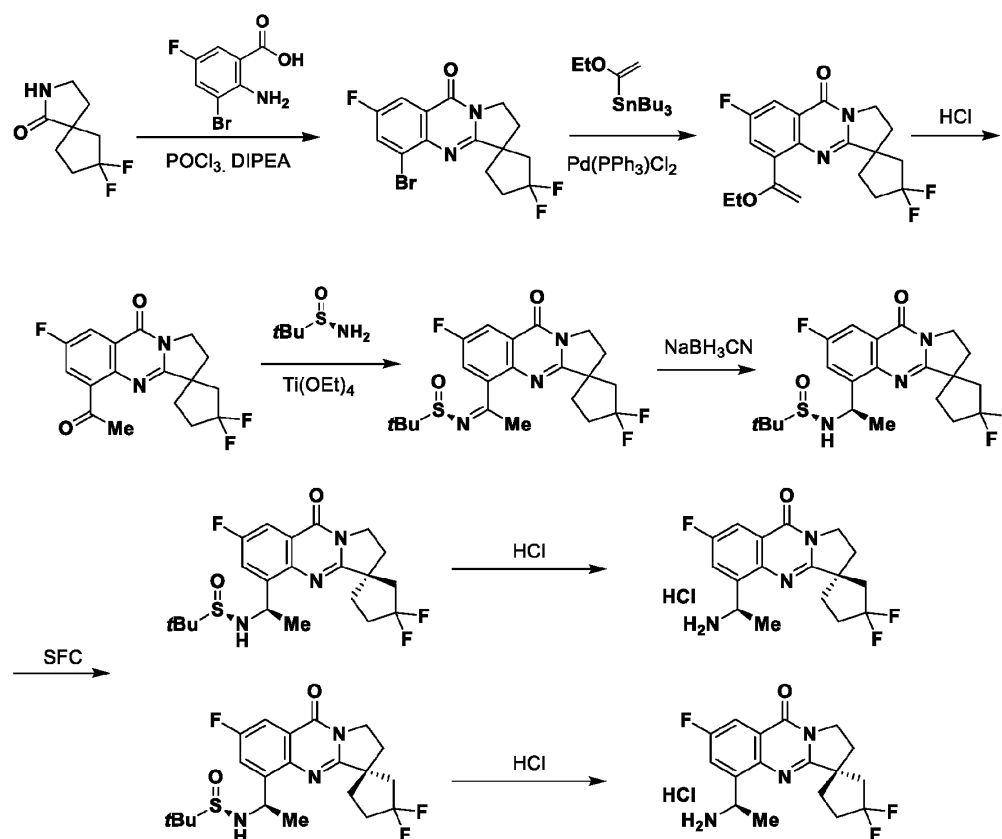
[00556] Step C: To a solution of Intermediate P-1 (30.0 mg, 100 μmol , 1.00 *eq.*) and methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (22.8 mg, 1208 μmol , 1.20 *eq.*) in dimethyl formamide (1.00 mL) was added diisopropylethylamine (25.9 mg, 201 μmol , 34.9 μL , 2.00 *eq.*). The mixture was stirred at 100 °C for 12 hours. The mixture was diluted with water (10.0 mL) at 25 °C and extracted with ethyl acetate (10.0 mL $\times$ 3). The combined organic phase was washed with brine (30.0 mL $\times$ 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (SiO_2 , petroleum ether/ ethyl acetate = 1/ 1) to give the methyl picolinate (20.0 mg, 39.5 μmol , 40% yield, 93% purity) as an off-white solid. LCMS $[\text{M}+1]^+ = 469.2$.

[00557] Step D: To a solution of the methyl picolinate (20.0 mg, 39.5 μmol , 1.00 *eq.*) in tetrahydrofuran (0.50 mL) and methanol (0.50 mL) was added lithium hydroxide (2 M, 39.5 μL , 2.00 *eq.*). The mixture was stirred at 40 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Phenomenex luna C18 250 $\times$ 50 mm $\times$ 15 μm ; mobile phase: [water (formic acid) - acetonitrile];

gradient: 42% -72% acetonitrile over 9 min) to give EXAMPLE 1-109 (6.75 mg, 14.8 μ mol, 37% yield, 99.5% purity) as a yellow solid. LCMS $[M+1]^+ = 455.2$.

[00558] ^1H NMR (400 MHz, CD_3OD) δ = 7.93 (*d*, *J* = 1.2 Hz, 1H), 7.62 (*d*, *J* = 1.6 Hz, 1H), 7.22 - 7.17 (m, 1H), 7.16 - 7.11 (m, 1H), 5.58 (q, *J* = 6.8 Hz, 1H), 4.23 (dt, *J* = 5.6, 8.4 Hz, 1H), 4.19 - 4.12 (m, 3H), 4.07 (q, *J* = 7.2 Hz, 1H), 3.97 (*d*, *J* = 8.4 Hz, 1H), 2.62 (td, *J* = 7.6, 12.4 Hz, 1H), 2.42 (s, 3H), 2.41 - 2.35 (m, 2H), 2.23 - 2.12 (m, 1H), 1.67 (*d*, *J* = 6.8 Hz, 3H).

Intermediate Q-1 and Q-2



[00559] Step A: To a solution of 7,7-difluoro-2-azaspiro[4.4]nonan-1-one (2.40 g, 13.7 mmol, 1.34 eq.) in 1,2-dichloroethane (24.0 mL) was added diisopropylethylamine (3.98 g, 30.8 mmol, 5.36 mL, 3.00 eq.) and phosphorus oxychloride (3.14 g, 20.5 mmol, 1.91 mL, 2.00 eq.). The mixture was stirred at 50 °C for 1 hour, then 2-amino-3-bromo-5-fluorobenzoic acid (2.40 g, 10.3 mmol, 1.00 eq.) was added and the reaction was heated to 80 °C for 15 minutes. After completion of the reaction, the reaction was cooled to 25 °C and water (100 mL) was added slowly and stirred at 25 °C for 1 hr. The aqueous layer was extracted with dichloromethane (100 mL) and the combined organics were washed with saturated sodium

bicarbonate solution (60.0 mL × 2), dried over sodium sulfate, and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=10/1 to 3/1) to give 5'-bromo-3,3,7'-trifluoro-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (1.35 g, 3.62 mmol, 35% yield) as a yellow solid. LCMS [M+3]⁺ = 374.9.

[00560] ¹H NMR (400 MHz, CDCl₃) δ = 7.92 (dd, *J* = 2.8, 8.0 Hz, 1H), 7.79 (dd, *J* = 2.8, 8.0 Hz, 1H), 4.33 - 4.15 (m, 1H), 4.14 - 4.04 (m, 1H), 3.05 - 2.80 (m, 1H), 2.75 - 2.50 (m, 1H), 2.45 - 2.26 (m, 5H), 2.11 - 2.01 (m, 1H).

[00561] ¹⁹F NMR (377 MHz, CDCl₃) δ = -87.254, -88.862 -93.638 -94.246, -111.958

[00562] Step B: A mixture of 5'-bromo-3,3,7'-trifluoro-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (1.50 g, 4.02 mmol, 1.00 eq.), tributyl(1-ethoxyvinyl)stannane (1.67 g, 4.62 mmol, 1.56 mL, 1.15 eq.), and bis(triphenylphosphine)palladium(II) dichloride (282 mg, 402 μmol, 0.10 eq.) in dioxane (36.0 mL) was evacuated and backfilled with nitrogen 3 times, and then the mixture was stirred at 100 °C for 4 hours under a nitrogen atmosphere. Upon completion, the reaction mixture was cooled to 25 °C and quenched by the addition potassium fluoride (aq.) 50.0 mL and stirred for 1 hour. The mixture was filtered and extracted with ethyl acetate (40.0 mL × 2). The combined organic layers were washed with water (30.0 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 5'-(1-ethoxyvinyl)-3,3,7'-trifluoro-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (1.90 g, 4.02 mmol, 99.9% yield, 77% purity) as a yellow solid which was used directly. LCMS [M+1]⁺ = 365.3.

[00563] Step C: To a solution of give 5'-(1-ethoxyvinyl)-3,3,7'-trifluoro-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (1.8 g, 3.80 mmol, 1.00 eq.) in tetrahydrofuran (20 mL) was added hydrochloric acid (1 M in water, 7.61 mL, 2.00 eq.). The mixture was stirred at 25 °C for 2.5 hours. Upon completion, saturated sodium bicarbonate solution (30.0 mL) was added to the solution to adjust to ~ pH = 7, then the solution was stirred at 25°C for 5 minutes. The solution was extracted with ethyl acetate (80.0 mL × 2), and the combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=10/1 to 2/1) to give 5'-acetyl-3,3,7'-trifluoro-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (1.07 g, 3.18 mmol, 84% yield) as a yellow solid. LCMS [M+1]⁺ = 337.1.

[00564] ¹H NMR (400 MHz, CDCl₃) δ = 8.08 (dd, *J* = 3.2, 8.0 Hz, 1H), 7.78 (dd, *J* = 3.0, 8.4 Hz, 1H), 4.34 - 4.18 (m, 1H), 4.17 - 4.05 (m, 1H), 2.98 - 2.74 (m, 4H), 2.62 - 2.43 (m, 1H), 2.43 - 2.26 (m, 5H), 2.15 - 2.01 (m, 1H).

[00565] ^{19}F NMR (377 MHz, CDCl_3) δ = -87.5, -88.1 -93.2, -93.8, -112.4.

[00566] Step D: To a mixture of 5'-acetyl-3,3,7'-trifluoro-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (1.07 g, 3.18 mmol, 1.00 *eq.*) and (*R*)-2-methylpropane-2-sulfinamide (1.54 g, 12.7 mmol, 4.00 *eq.*) in 2-methyltetrahydrofuran (20.0 mL) was added titanium (IV) ethoxide (2.90 g, 12.7 mmol, 2.64 mL, 4.0 *eq.*). The reaction was stirred at 80°C for 24 hours. Upon completion, the mixture was cooled to 25 °C, and water (0.80 mL) was added followed by ethyl acetate (80.0 mL). The mixture was stirred for 30 minutes, then the mixture was filtered, the cake was washed with ethyl acetate (80.0 mL × 3) and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate = 10/1 to 2/1) to give (*R*)-2-methyl-*N*-(1-(3,3,7'-trifluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)propane-2-sulfinamide (1.34 g, 3.05 mmol, 96% yield) as a yellow oil. LCMS $[\text{M}+1]^+ = 440.1$.

[00567] Step E: To a solution of (*R*)-2-methyl-*N*-(1-(3,3,7'-trifluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)propane-2-sulfinamide (1.26 g, 2.87 mmol, 1.00 *eq.*), acetic acid (866 mg, 14.4 mmol, 826 μL , 5.03 *eq.*) in dichloromethane (10.0 mL) and methanol (10.0 mL) was added sodium cyanoborohydride (721 mg, 11.5 mmol, 4.00 *eq.*) portion wise. The mixture was stirred at 0 °C for 1 hour. After completion, brine (10.0 mL) was added to the reaction mixture, then the mixture was extracted with a 10:1 mixture solvent of dichloromethane: methanol for (66 mL × 3), combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 × 40mm × 15 μm ; mobile phase: [water(formic acid)-acetonitrile]; gradient: 45%-75% acetonitrile over 15 min) to give (*R*)-2-methyl-*N*-((1*R*)-1-(3,3,7'-trifluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)propane-2-sulfinamide (921 mg, 2.03 mmol, 71% yield, 97% purity) as an off-white solid. LCMS $[\text{M}+1]^+ = 442.2$.

[00568] Step F: (*R*)-2-methyl-*N*-((1*R*)-1-(3,3,7'-trifluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)propane-2-sulfinamide purified by SFC separation (column: DAICEL CHIRALPAK AD(250mm × 30mm, 10 μm); mobile phase: [carbon dioxide-isopropanol (0.1% ammonium hydroxide)]; Gradient 20% isopropanol (0.1% ammonium hydroxide), isocratic elution mode). The desired fractions of the first peak were collected and concentrated to provide the eluting isomer (408 mg, 902 μmol , 46% yield, 98% purity) as a white solid. The desired fractions of the second peak were collected and concentrated to provide the second eluting isomer (444 mg, 996 μmol , 50% yield, 99% purity) as a white solid. SFC conditions: Column: (S,S)Whelk-O1 50 × 4.6mm I.D., 3 μm . Gradient

elution: isopropanol+acetonitrile (0.05% diethylamine) from 20% to 60% in carbon dioxide, Flow rate: 3 mL/min; Detector: PDA; Column Temp: 35 °C; Back Pressure: 100 Bar.

[00569] Step G: To a solution of the first eluting isomer (150 mg, 332 μ mol, 1.00 eq.) in ethyl acetate (1.50 mL) was added a solution of hydrochloric acid in ethyl acetate (2 M, 390 μ L, 2.35 eq.). The mixture was stirred at 0 °C for 1.5 hrs. The reaction mixture was allowed to warm and was directly concentrated at 25°C to give Intermediate Q-1 (120 mg, 321 μ mol, 97% yield, hydrochloride salt) as a white solid which was used directly. LCMS $[M+1]^+ = 338.2$.

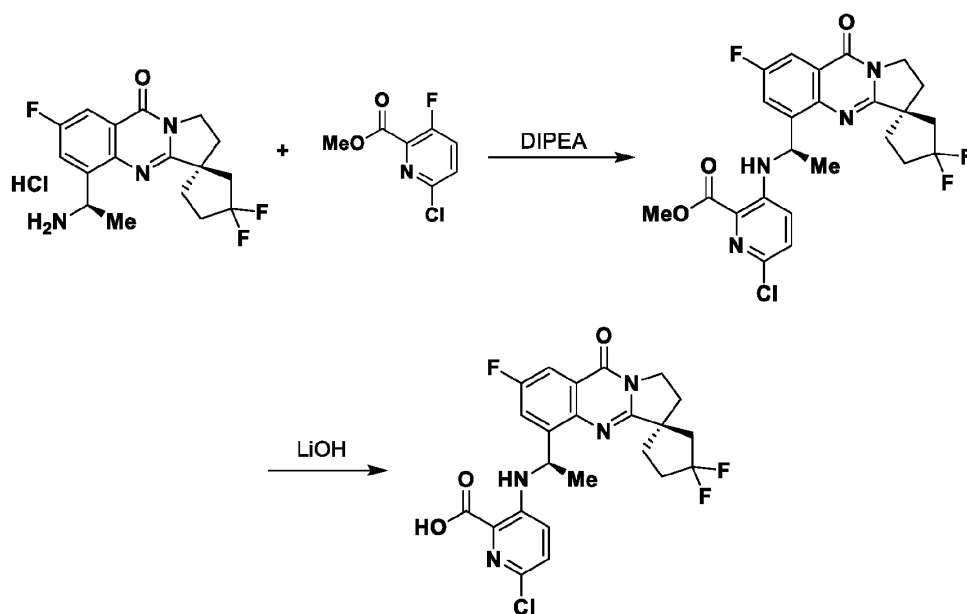
[00570] Step H: To a solution of the second eluting isomer (150 mg, 336 μ mol, 1.00 eq.) in ethyl acetate (1.5 mL) was added a solution of hydrochloric acid in ethyl acetate (2 M, 396 μ L, 2.35 eq.). The mixture was stirred at 0 °C for 1.5 hours. After completion of the reaction, the reaction mixture was allowed to warm and was directly concentrated at 25 °C to give Intermediate Q-2 (120 mg, 321 μ mol, 96% yield, hydrochloride salt) as a white solid which was used directly. LCMS $[M+1]^+ = 338.2$.

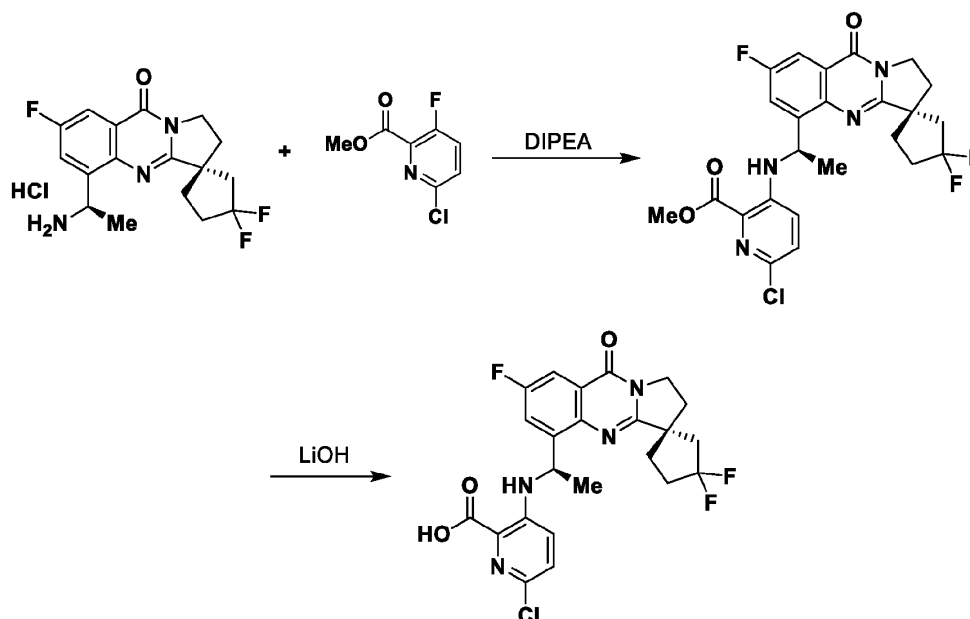
EXAMPLE 1-110 and 1-111

6-chloro-3-(((*R*)-1-((*S*)-3,3,7'-trifluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid

And

6-chloro-3-(((*R*)-1-((*R*)-3,3,7'-trifluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid





[00571] Step A: A mixture of Intermediate Q-1 (120 mg, 321 μ mol, 1.00 *eq.*, hydrochloride salt), methyl 6-chloro-3-fluoropicolinate (169 mg, 802 μ mol, 2.50 *eq.*) and diisopropylethylamine (290 mg, 2.24 mmol, 391 μ L, 6.99 *eq.*) in dimethylformamide (1.50 mL) was stirred at 80 °C for 12 hours. After completion, the reaction mixture was cooled to 25 °C and purified by prep-HPLC (column: Phenomenex luna C18 150 $\times$ 25mm $\times$ 10 μ m; mobile phase: [water(formic acid)-acetonitrile]; gradient:55%-85% acetonitrile over 1 min) to give the methyl picolinate product (93.0 mg, 183 μ mol, 57% yield) as a white solid. LCMS $[M+1]^+$ = 507.1.

[00572] Step B: To a solution of the methyl picolinate (93.0 mg, 183 μ mol, 1.00 *eq.*) in tetrahydrofuran (1.00 mL) and methanol (1.00 mL) was added lithium hydroxide (2 M in water, 183 μ L, 2.00 *eq.*). The mixture was stirred at 25 °C for 2 hours. After completion, formic acid was added to adjust the reaction to $\sim$ pH = 7, and then purified by prep-HPLC (column: Phenomenex luna C18 150 $\times$ 25mm $\times$ 10 μ m; mobile phase: [water(formic acid)-acetonitrile];gradient:53%-83% acetonitrile over 15 min) to give EXAMPLE 1-110 (61.5 mg, 122 μ mol, 67% yield, 98% purity) as a white solid. LCMS $[M+1]^+$ = 493.1.

[00573] ^1H NMR (400 MHz, CD_3OD) δ = 7.75 (dd, J = 2.8, 8.4 Hz, 1H), 7.56 (dd, J = 2.8, 8.8 Hz, 1H), 7.20 (*d*, J = 8.8 Hz, 1H), 7.05 (*d*, J = 8.8 Hz, 1H), 5.58 (q, J = 6.8 Hz, 1H), 4.28 - 4.16 (m, 1H), 4.16 - 4.05 (m, 1H), 2.87 (td, J = 14.8, 19.6 Hz, 1H), 2.68 - 2.50 (m, 1H), 2.48 - 2.27 (m, 5H), 2.19 - 2.08 (m, 1H), 1.69 (*d*, J = 6.8 Hz, 3H).

[00574] ^{19}F NMR (377 MHz, CD_3OD) δ = -88.024, -88.632, -93.364, -93.978, -114.807.

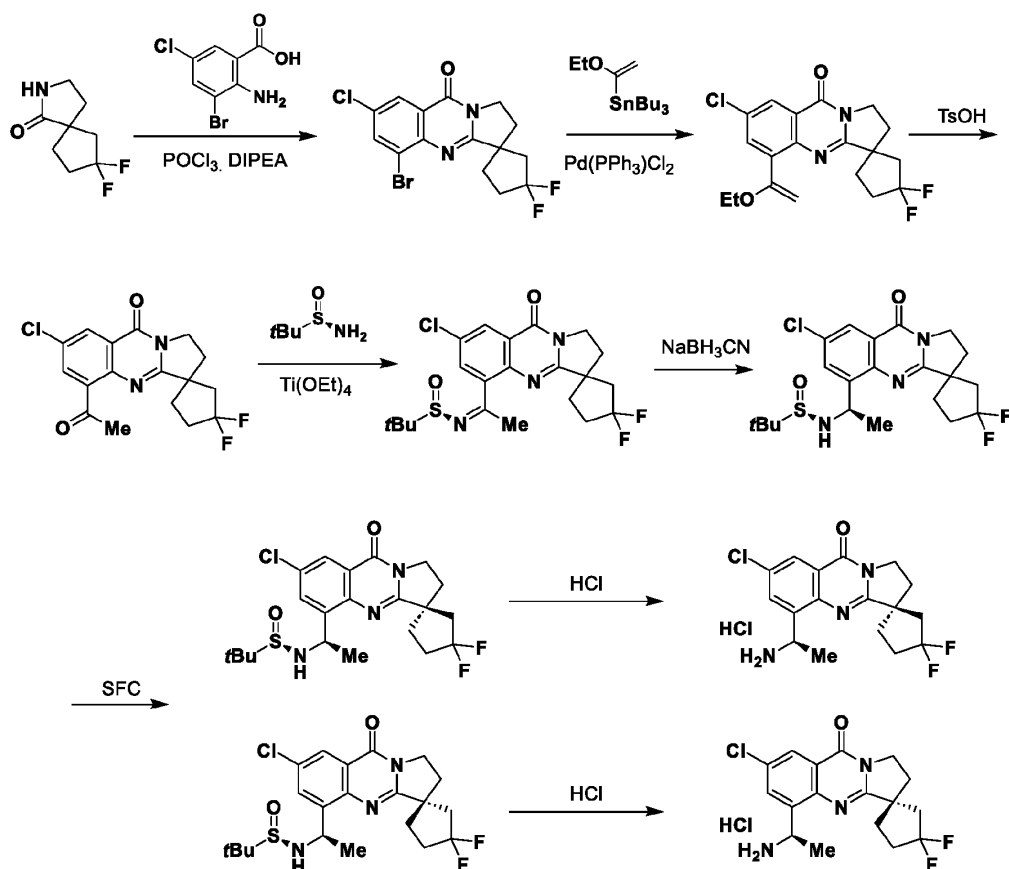
[00575] Step C: A mixture of Intermediate Q-2 (120 mg, 321 μmol , 1.00 *eq.*, hydrochloride salt), methyl 6-chloro-3-fluoropicolinate (169 mg, 802 μmol , 2.50 *eq.*), diisopropylethylamine (290 mg, 2.25 mmol, 391 μL , 7.00 *eq.*) in dimethylformamide (1.00 mL) was stirred at 90 °C for 12 hours. After completion, the reaction mixture was cooled to 25 °C and purified by prep-HPLC (column: Welch Xtimate C18 150 $\times$ 25mm $\times$ 5 μm ; mobile phase: [water(formic acid)-acetonitrile]; gradient: 60%-80% acetonitrile over 10 min) to give the methyl picolinate product (78.0 mg, 154 μmol , 48% yield) as a white solid. LCMS $[\text{M}+1]^+ = 507.0$.

[00576] Step D: To a solution the methyl picolinate (78.0 mg, 154 μmol , 1.00 *eq.*) in methanol (1.00 mL) and tetrahydrofuran (1.00 mL) was added lithium hydroxide (2 M in water, 300 μL , 3.90 *eq.*). The mixture was stirred at 25 °C for 1.5 hour. After completion, formic acid was added to adjust the reaction to $\sim \text{pH} = 7$, and then purified by prep-HPLC (column: Welch Xtimate C18 150 $\times$ 25mm $\times$ 5 μm ; mobile phase: [water(formic acid)-acetonitrile]; gradient: 55%-75% acetonitrile over 10 min) to give EXAMPLE 1-111 (37.9 mg, 76.7 μmol , 50% yield, 99.8% purity) as an off-white solid. LCMS $[\text{M}+1]^+ = 493.1$.

[00577] ^1H NMR (400 MHz, CD_3OD) $\delta = 7.74$ (br dd, $J = 2.8, 8.4$ Hz, 1H), 7.54 (dd, $J = 2.8, 8.8$ Hz, 1H), 7.21 (*d*, $J = 8.8$ Hz, 1H), 7.04 (*d*, $J = 8.8$ Hz, 1H), 5.59 (q, $J = 6.8$ Hz, 1H), 4.24 - 4.15 (m, 1H), 4.15 - 4.06 (m, 1H), 2.98 - 2.81 (m, 1H), 2.63 - 2.48 (m, 1H), 2.47 - 2.27 (m, 5H), 2.21 - 2.10 (m, 1H), 1.70 (*d*, $J = 6.8$ Hz, 3H).

[00578] ^{19}F NMR (377 MHz, CD_3OD) $\delta = -88.4, -89.0, -93.4, -94.0, -114.8$.

Intermediate R-1 and R-1



[00579] Step A: To a solution of 7,7-difluoro-2-azaspiro[4.4]nonan-1-one (600 mg, 3.43 mmol, 1.00 eq.) in 1,2-dichloroethane (6.00 mL) was added diisopropylethylamine (1.33 g, 10.3 mmol, 1.79 mL, 3.00 eq.) and phosphorous oxychloride (1.05 g, 6.85 mmol, 639 μ L, 2.00 eq.). The mixture was stirred at 50 °C for 1 hour. Next, the reaction was heated to 80 °C and 2-amino-3-bromo-5-chloro-benzoic acid (858 mg, 3.43 mmol, 1.00 eq.) was added to the above mixture as a solid. The reaction was stirred at 80 °C for 30 minutes. After completion of the reaction, the reaction mixture was cooled to 25 °C and added to water (40.0 mL), the obtained aqueous solution extracted with dichloromethane (40.0 mL $\times$ 3). The combined organic layers were washed with brine (120 mL $\times$ 3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether, gradient @ 36 mL/min) to 5'-bromo-7'-chloro-3,3-difluoro-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (350 mg, 898 μ mol, 26% yield) as a yellow solid. LCMS $[M+1]^+ = 391.0$.

[00580] ^1H NMR (400 MHz, CDCl_3) δ = 8.22 (*d*, J = 2.0 Hz, 1H), 7.99 (*d*, J = 2.4 Hz, 1H), 4.28 - 4.02 (m, 2H), 3.03 - 2.82 (m, 1H), 2.72 - 2.51 (m, 1H), 2.45 - 2.25 (m, 5H), 2.13 - 1.99 (m, 1H)

[00581] Step B: A mixture of 5'-bromo-7'-chloro-3,3-difluoro-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (1.50 g, 3.85 mmol, 1.00 eq.), tributyl(1-ethoxyvinyl)tin (2.01 g, 5.57 mmol, 1.88 mL, 1.45 eq.), bis(triphenylphosphine)palladium(II) chloride (270 mg, 385 μmol , 0.10 eq.) in dioxane (15.0 mL) was evacuated and backfilled with nitrogen 3 times, and then the mixture was stirred at 100 °C for 2 hours under nitrogen atmosphere. After completion, the mixture was cooled to 25 °C and poured into saturated aqueous potassium fluoride solution (60.0 mL) and stirred for 1 hour. The aqueous phase was extracted with dichloromethane (60.0 mL $\times$ 3), the combined organic phase was washed with brine (180.0 mL $\times$ 3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 7'-chloro-5'-(1-ethoxyvinyl)-3,3-difluoro-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (1.40 g, crude) as a yellow oil. LCMS $[\text{M}+1]^+ = 381.1$.

[00582] Step C: To a solution of 7'-chloro-5'-(1-ethoxyvinyl)-3,3-difluoro-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (1.40 g, 3.68 mmol, 1.00 eq.) in acetone (14.0 mL) was added 4-toluenesulfonic acid monohydrate (699 mg, 3.68 mmol, 1.00 eq.). The mixture was stirred at 25 °C for 1 hour. After completion, the reaction mixture was concentrated under reduced pressure to give a residue. Then the residue was dissolved in dichloromethane (80.0 mL), washed with saturated sodium bicarbonate aqueous solution (80.0 mL $\times$ 3) and brine (80.0 mL $\times$ 2), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~70% Ethyl acetate/Petroleum ether, gradient @ 60 mL/min) to give 5'-acetyl-7'-chloro-3,3-difluoro-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (1.10 g, 3.12 mmol, 85% yield) as a yellow solid. LCMS $[\text{M}+1]^+ = 353.1$.

[00583] Step D: To a solution of 5'-acetyl-7'-chloro-3,3-difluoro-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (1.00 g, 2.83 mmol, 1.00 eq.) in 2-methyltetrahydrofuran (11.0 mL) was added (*R*)-2-methylpropane-2-sulfinamide (1.03 g, 8.50 mmol, 3.00 eq.) and titanium (IV) ethoxide (2.39 g, 10.5 mmol, 2.17 mL, 3.70 eq.). The mixture was stirred at 80 °C for 12 hours. After completion, the reaction mixture was cooled to 25 °C, water (0.80 mL) and dichloromethane (30 mL) were added, and the reaction was stirred for 30 minutes. Then, the mixture was filtered and the filter cake was washed with dichloromethane (50.0 mL $\times$ 3). The combined organics were concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g

SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether, gradient @ 60 mL/min) to give (*R*)-*N*-(1-(7'-chloro-3,3-difluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)-2-methylpropane-2-sulfonamide (1.20 g, 2.63 mmol, 93% yield) as a yellow solid. LCMS $[M+1]^+ = 456.1$.

[00584] Step E: To a solution of (*R*)-*N*-(1-(7'-chloro-3,3-difluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethylidene)-2-methylpropane-2-sulfonamide (1.00 g, 2.19 mmol, 1.00 eq.) in dichloromethane (5.00 mL) and methanol (5.00 mL) was added acetic acid (1.32 g, 21.9 mmol, 1.26 mL, 10.0 eq.) and sodium cyanoborohydride (413 mg, 6.58 mmol, 3.00 eq.). The mixture was stirred at 0 °C for 2 hours. After completion, the reaction mixture was adjusted to ~ pH = 7 with saturated sodium bicarbonate aqueous solution and then diluted with dichloromethane (45.0 mL). The organic phase was separated, washed with brine (40.0 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 (250 × 70mm, 10 μm); mobile phase: [water(formic acid)-acetonitrile]; gradient: 45%-75% acetonitrile over 20 min) to give (*R*)-*N*-((1*R*)-1-(7'-chloro-3,3-difluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)-2-methylpropane-2-sulfonamide (900 mg, 1.89 mmol, 86% yield, 96% purity) as a yellow solid. LCMS $[M+1]^+ = 458.2$.

[00585] ¹H NMR (400 MHz, CDCl₃) δ = 8.16 (*d*, *J* = 2.8 Hz, 1H), 7.61 (*d*, *J* = 2.4 Hz, 1H), 5.00 - 4.93 (*m*, 1H), 4.24 - 4.14 (*m*, 1H), 4.13 - 4.04 (*m*, 1H), 2.95 - 2.73 (*m*, 1H), 2.63 - 2.44 (*m*, 1H), 2.42 - 2.24 (*m*, 5H), 2.11 - 2.06 (*m*, 1H), 1.63 (*dd*, *J* = 1.6, 6.4 Hz, 3H), 1.22 (*d*, *J* = 3.6 Hz, 9H).

[00586] Step F: (*R*)-*N*-((1*R*)-1-(7'-chloro-3,3-difluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)-2-methylpropane-2-sulfonamide (900 mg, 1.89 mmol) was purified by SFC separation (column: REGIS(S,S)WHELK-O1(250mm × 25mm, 10μm); isocratic elution acetonitrile/isopropanol (0.1% ammonium hydroxide) 50% in carbon dioxide) and the desired fractions of the first peak were collected and concentrated to provide the first eluting isomer (400 mg, 873 μmol, 46% yield, 99.9% purity) as a yellow solid. The isocratic elution was continued and the desired fractions of the second peak were collected to provide the second eluting isomer (420 mg, 824 μmol, 44% yield, 90% purity) as a yellow solid.

[00587] Step G: To a solution of the first eluting isomer (150 mg, 327 μmol, 1.00 eq.) in ethyl acetate (1.50 mL) was added hydrochloric acid in ethyl acetate (2.00 M, 1.50 mL, 9.16 eq.). The mixture was stirred at 25 °C for 30 minutes. After completion, the reaction mixture was

concentrated under reduced pressure to give Intermediate R-1 (120 mg, 307 μmol , 94% yield, HCl) as a yellow solid. LCMS $[M+1]^+ = 354.1$.

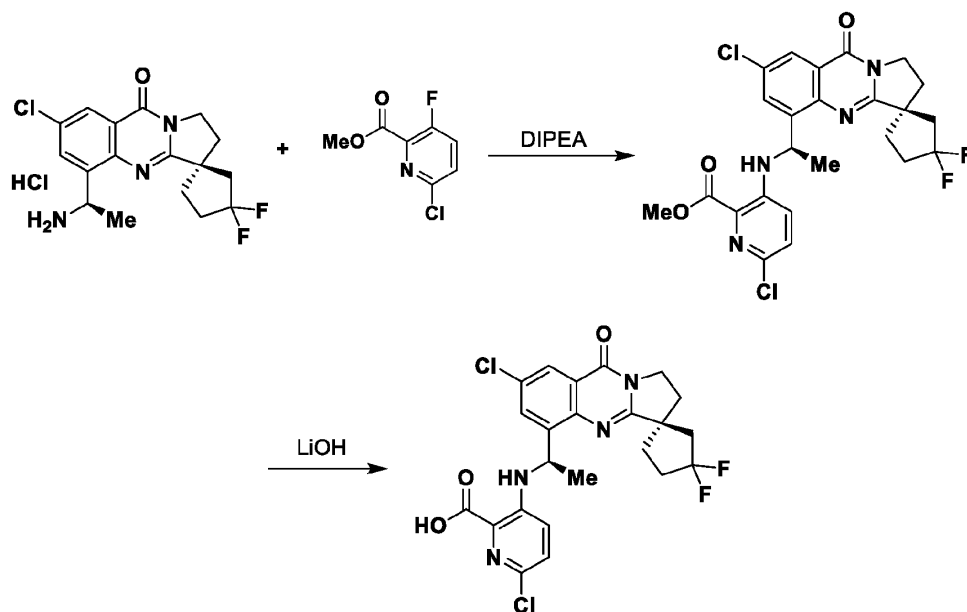
[00588] Step H: To a solution of the second eluting isomer (150 mg, 294 μmol , 1.00 eq.) in ethyl acetate (1.50 mL) was added hydrochloric acid in ethyl acetate (2.00 M, 1.47 mL, 10.0 eq.). The mixture was stirred at 25 °C for 30 minutes. After completion, the reaction mixture was concentrated under reduced pressure to give Intermediate R-2 (100 mg, 256 μmol , 87% yield, HCl) as a white solid. LCMS $[M+1]^+ = 354.2$.

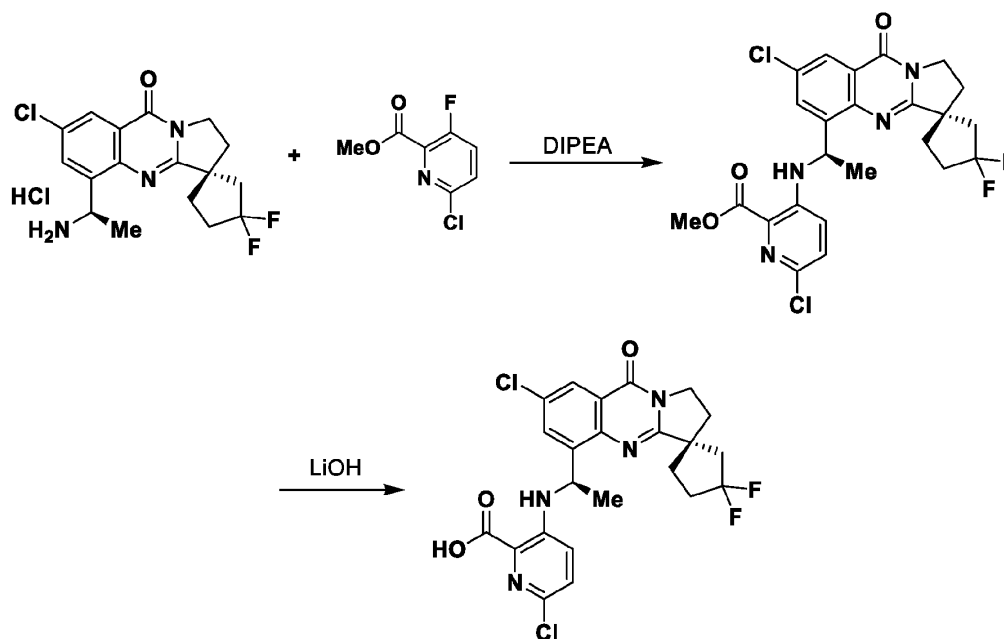
EXAMPLE 1-112 and 1-113

6-chloro-3-(((*R*)-1-((*S*)-7'-chloro-3,3-difluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid

And

6-chloro-3-(((*R*)-1-((*R*)-7'-chloro-3,3-difluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid





[00589] Step A: To a solution of Intermediate R-1 (120 mg, 307 μmol , 1.00 *eq.*, HCl) in *N,N*-dimethylformamide (1.00 mL) was added methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (146 mg, 769 μmol , 2.50 *eq.*) and diisopropylethylamine (119 mg, 922 μmol , 161 μL , 3.00 *eq.*). The mixture was stirred at 90 °C for 12 hours. After completion, the mixture was cooled to 25 °C and partitioned between ethyl acetate (30.0 mL) and water (30.0 mL). The organic phase was separated, washed with brine (30.0 mL $\times$ 3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 18 mL/min) to the methyl picolinate product (80.0 mg, 153 μmol , 50% yield) as a yellow solid. LCMS $[\text{M}+23]^+ = 545.2$.

[00590] Step B: To a solution of the methyl picolinate (80.0 mg, 153 μmol , 1.00 *eq.*) in tetrahydrofuran (0.50 mL) and methanol (0.50 mL) was added lithium hydroxide (2.00 M, 153 μL , 2.00 *eq.*). The mixture was stirred at 25 °C for 2 hours. After completion, the reaction mixture was adjusted to pH = 7.0 with formic acid and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: YMC-Actus Triart C18 150 $\times$ 30mm $\times$ 7 μm ; mobile phase: [water(formic acid)-acetonitrile]; gradient: 55%-85% acetonitrile over 10 min) to give EXAMPLE 1-112 (35.1 mg, 68.8 μmol , 45% yield, 99.9% purity) as an off-white solid. LCMS $[\text{M}+1]^+ = 509.1.7$

[00591] ^1H NMR (400 MHz, CDCl_3) δ = 11.21 - 10.05 (m, 1H), 8.36 (br d, J = 6.4 Hz, 1H), 8.18 (d, J = 2.4 Hz, 1H), 7.64 (d, J = 2.4 Hz, 1H), 7.15 (d, J = 8.8 Hz, 1H), 6.86 (d, J = 8.8

Hz, 1H), 5.49 (quin, $J = 6.8$ Hz, 1H), 4.28 - 4.18 (m, 1H), 4.17 - 4.07 (m, 1H), 2.93 - 2.77 (m, 1H), 2.70 - 2.53 (m, 1H), 2.45 - 2.30 (m, 5H), 2.10 (br dd, $J = 6.8, 12.0$ Hz, 1H), 1.68 (d, $J = 6.8$ Hz, 3H).

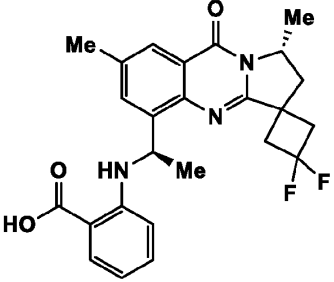
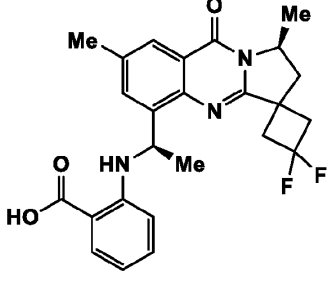
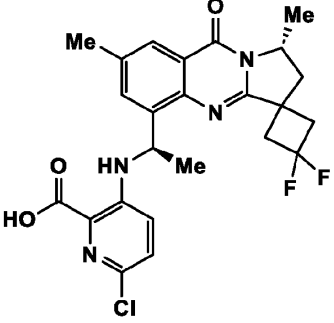
[00592] Step C: To a solution of Intermediate R-2 (100 mg, 256 μ mol, 1.00 eq., HCl) in *N,N*-dimethylformamide (1.00 mL) was added methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (121 mg, 641 μ mol, 2.50 eq.) and diisopropylethylamine (99.4 mg, 769 μ mol, 134 μ L, 3.00 eq.). The mixture was stirred at 90 °C for 12 hours. After completion, the mixture was cooled to 25 °C and partitioned between ethyl acetate (30.0 mL) and water (30.0 mL). The organic phase was separated, washed with brine (30.0 mL $\times$ 3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 18 mL/min) to give the methyl picolinate product (70.0 mg, 134 μ mol, 52% yield) as a yellow solid. LCMS $[M+1]^+ = 523.1$.

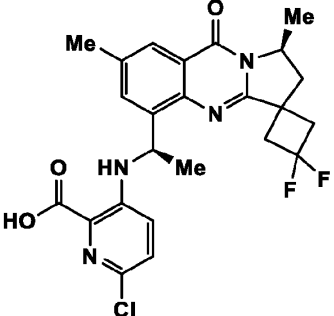
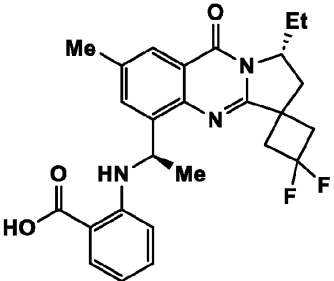
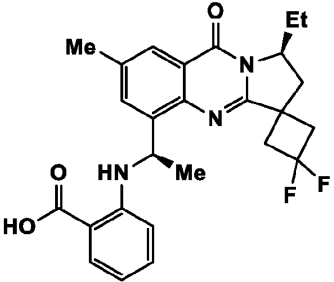
[00593] Step D: To a the methyl picolinate (70.0 mg, 134 μ mol, 1.00 eq.) in tetrahydrofuran (0.50 mL) and methanol (0.50 mL) was added lithium hydroxide (2.00 M, 134 μ L, 2.00 eq.). The mixture was stirred at 25 °C for 2 hours. The reaction mixture was adjusted to ~ pH = 7.0 with formic acid and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: YMC-Actus Triart C18 150 $\times$ 30mm $\times$ 7 μ m; mobile phase: [water(formic acid)-acetonitrile]; gradient: 55%-85% acetonitrile over 10 min) to give EXAMPLE 1-113 (23.7 mg, 46.5 μ mol, 35% yield, 99.9% purity) as an off-white solid. LCMS $[M+1]^+ = 509.1$.

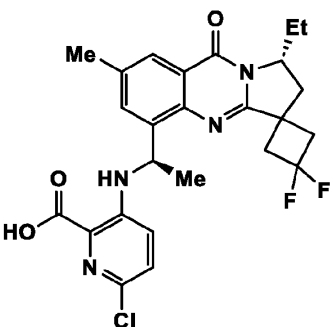
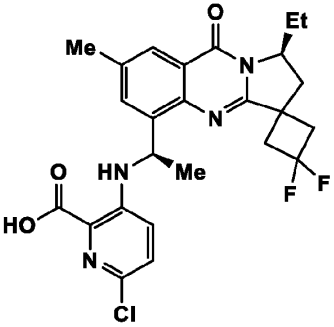
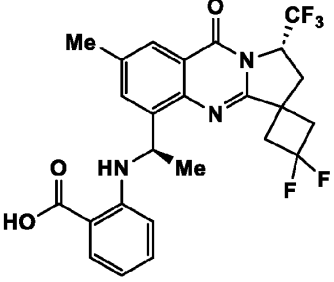
[00594] ^1H NMR (400 MHz, CDCl_3) $\delta = 11.30 - 9.92$ (m, 1H), 8.32 (br d, $J = 6.0$ Hz, 1H), 8.17 (d, $J = 2.4$ Hz, 1H), 7.64 (d, $J = 2.4$ Hz, 1H), 7.14 (d, $J = 8.8$ Hz, 1H), 6.84 (d, $J = 8.8$ Hz, 1H), 5.50 (quin, $J = 6.8$ Hz, 1H), 4.27 - 4.18 (m, 1H), 4.17 - 4.08 (m, 1H), 2.97 - 2.79 (m, 1H), 2.64 - 2.48 (m, 1H), 2.44 - 2.29 (m, 5H), 2.16 - 2.06 (m, 1H), 1.68 (d, $J = 6.8$ Hz, 3H).

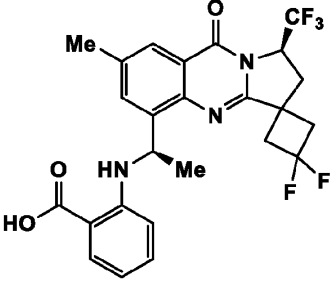
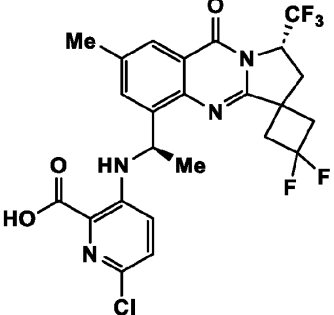
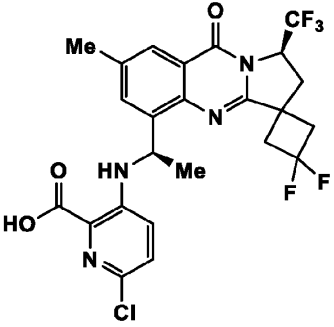
[00595] Examples 1-114 to 1-179

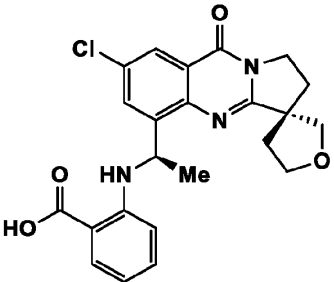
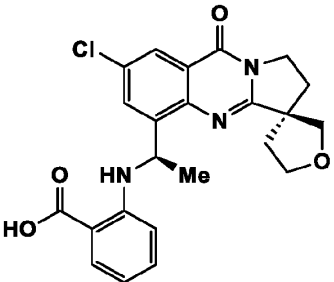
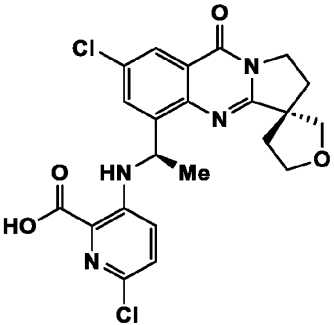
[00596] The following compounds are prepared essentially according to the procedures set forth in the above schemes and examples.

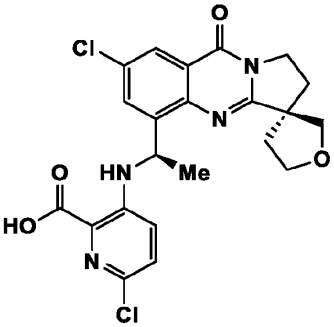
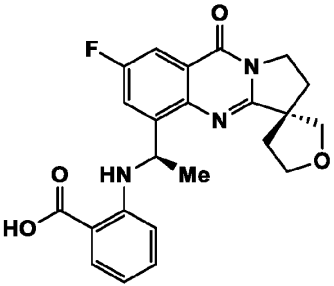
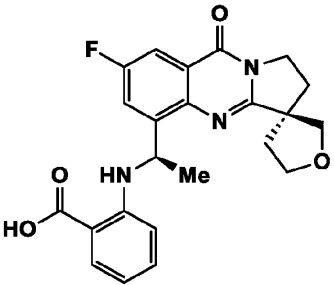
Ex. #	Structure
1-114	 2-(((<i>R</i>)-1-((<i>R</i>)-3,3-difluoro-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-115	 2-(((<i>R</i>)-1-((<i>S</i>)-3,3-difluoro-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-116	 6-chloro-3-(((<i>R</i>)-1-((<i>R</i>)-3,3-difluoro-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid

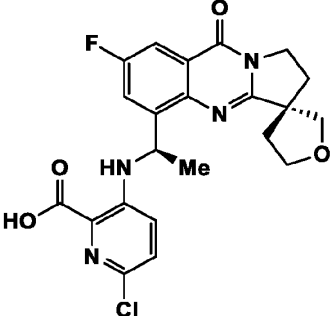
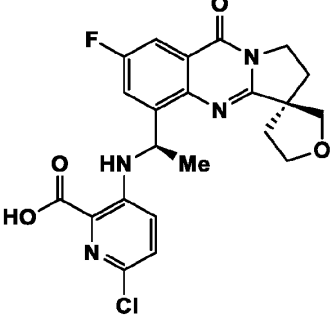
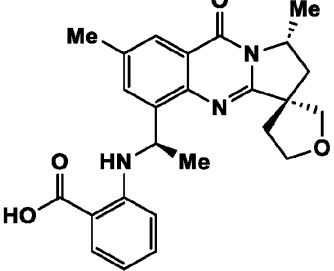
1-117	 6-chloro-3-(((<i>R</i>)-1-((<i>S</i>)-3,3-difluoro-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-118	 2-(((<i>R</i>)-1-((<i>R</i>)-1'-ethyl-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-119	 2-((@-1-((<i>S'</i>-1'-ethyl-3,3-difluor'-7'-methy'-9'-ox'-1',2'-dihydr'-9'<i>H</i>-spi211yclobuteneane-',3'-pyrrolo[2,1-<i>b</i>]quinazolin'-5'-yl)ethyl)amino)benzoic acid

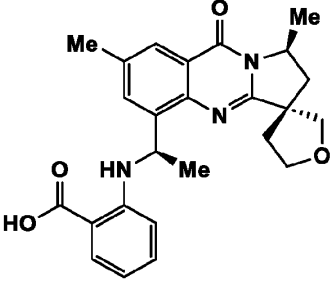
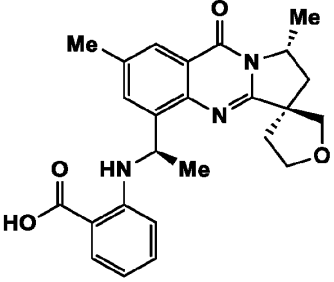
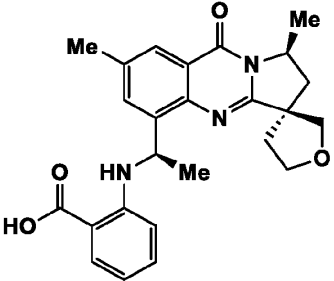
1-120	 6-chloro-3-(((<i>R</i>)-1-((<i>R</i>)-1'-ethyl-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-121	 6-chloro-3-(((<i>R</i>)-1-((<i>S</i>)-1'-ethyl-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-122	 2-(((<i>R</i>)-1-((<i>S</i>)-3,3-difluoro-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid

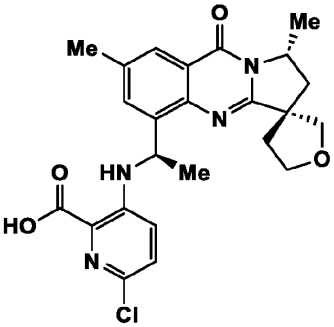
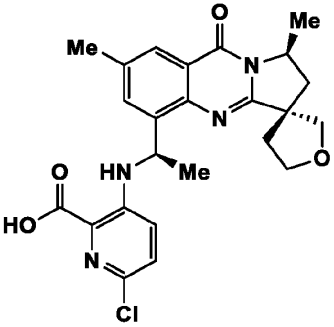
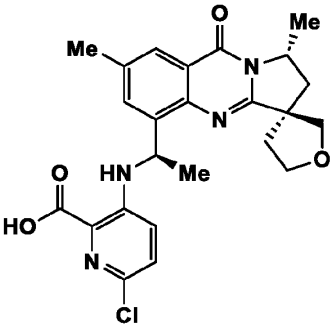
1-123	 2-(((<i>R</i>)-1-((<i>R</i>)-3,3-difluoro-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-124	 6-chloro-3-(((<i>R</i>)-1-((<i>S</i>)-3,3-difluoro-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-125	 6-chloro-3-(((<i>R</i>)-1-((<i>R</i>)-3,3-difluoro-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid

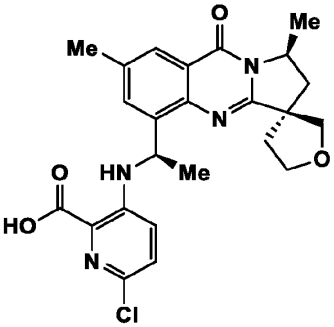
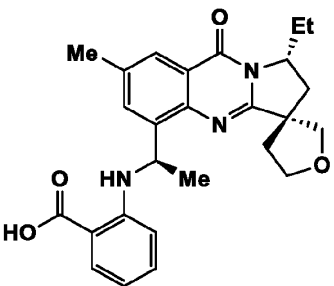
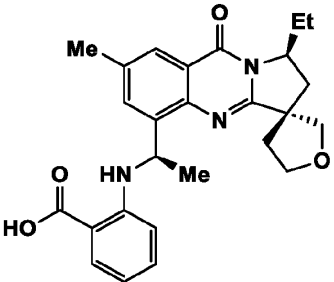
1-126	 2-(((<i>R</i>)-1-((<i>R</i>)-7'-chloro-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-127	 2-(((<i>R</i>)-1-((<i>S</i>)-7'-chloro-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-128	 6-chloro-3-(((<i>R</i>)-1-((<i>R</i>)-7'-chloro-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid

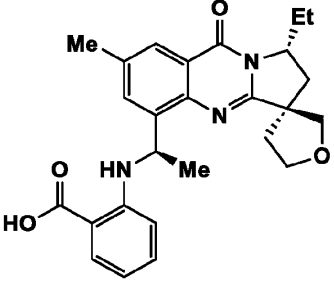
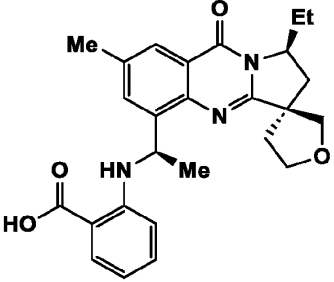
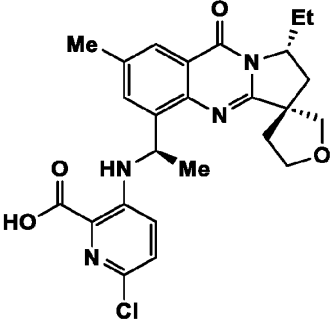
1-129	 6-chloro-3-(((<i>R</i>)-1-((<i>S</i>)-7'-chloro-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-130	 2-(((<i>R</i>)-1-((<i>R</i>)-7'-fluoro-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-131	 2-(((<i>R</i>)-1-((<i>S</i>)-7'-fluoro-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid

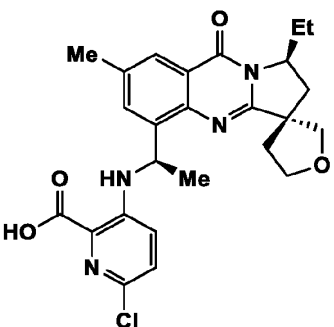
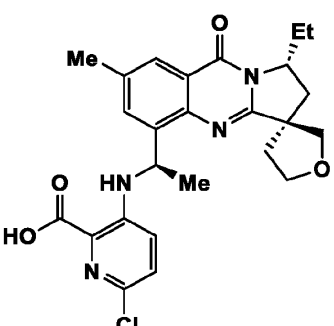
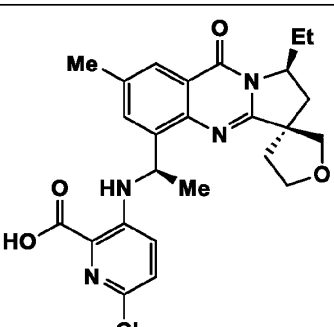
1-132	 6-chloro-3-(((<i>R</i>)-1-((<i>R</i>)-7'-fluoro-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-133	 6-chloro-3-(((<i>R</i>)-1-((<i>S</i>)-7'-fluoro-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-134	 2-(((<i>R</i>)-1-((1'<i>R</i>,3<i>R</i>)-1',7'-dimethyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid

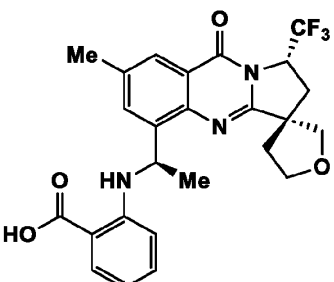
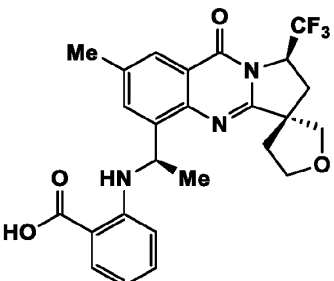
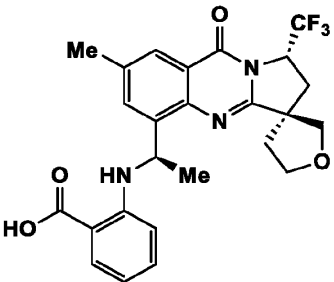
1-135	 2-(((<i>R</i>)-1-((1'<i>S</i>,3<i>R</i>)-1',7'-dimethyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-136	 2-(((<i>R</i>)-1-((1'<i>R</i>,3<i>S</i>)-1',7'-dimethyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-137	 2-(((<i>R</i>)-1-((1'<i>S</i>,3<i>S</i>)-1',7'-dimethyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid

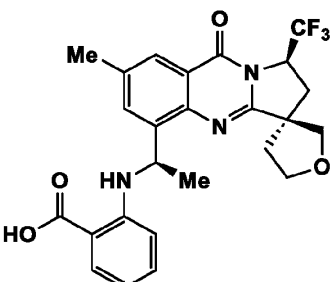
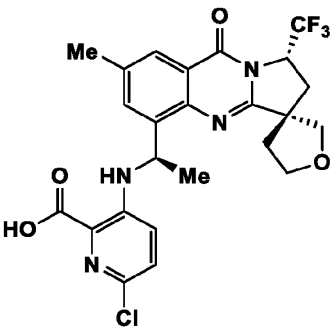
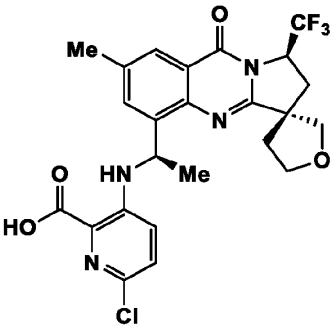
1-138	 6-chloro-3-(((<i>R</i>)-1-((1'<i>R</i>,3<i>R</i>)-1',7'-dimethyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-139	 6-chloro-3-(((<i>R</i>)-1-((1'<i>S</i>,3<i>R</i>)-1',7'-dimethyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-140	 6-chloro-3-(((<i>R</i>)-1-((1'<i>R</i>,3<i>S</i>)-1',7'-dimethyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid

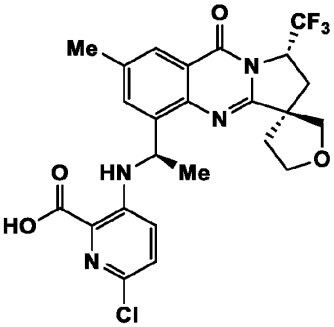
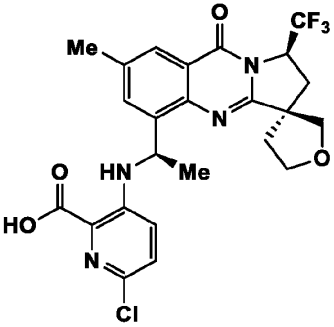
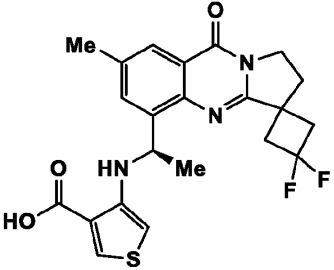
1-141	 6-chloro-3-(((<i>R</i>)-1-((1'<i>S</i>,3<i>S</i>)-1',7'-dimethyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-142	 2-(((<i>R</i>)-1-((1'<i>R</i>,3<i>R</i>)-1'-ethyl-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-143	 2-(((<i>R</i>)-1-((1'<i>S</i>,3<i>R</i>)-1'-ethyl-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid

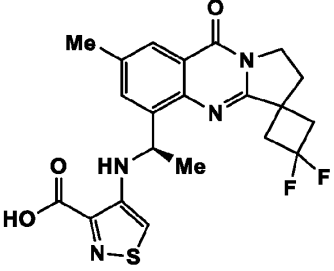
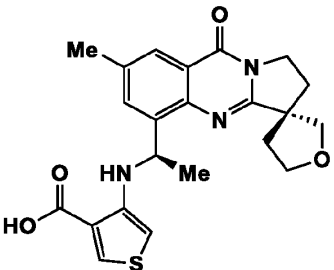
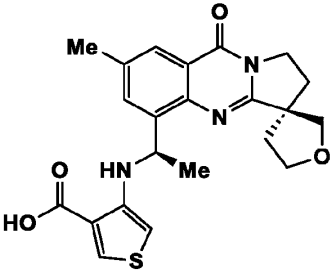
1-144	 2-(((<i>R</i>)-1-((1'<i>R</i>,3<i>S</i>)-1'-ethyl-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-145	 2-(((<i>R</i>)-1-((1'<i>S</i>,3<i>S</i>)-1'-ethyl-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-146	 6-chloro-3-(((<i>R</i>)-1-((1'<i>R</i>,3<i>R</i>)-1'-ethyl-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid

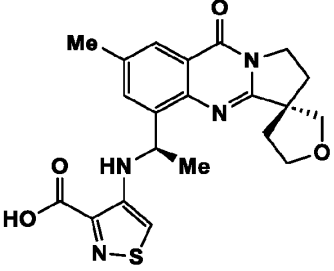
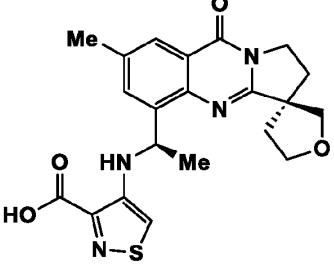
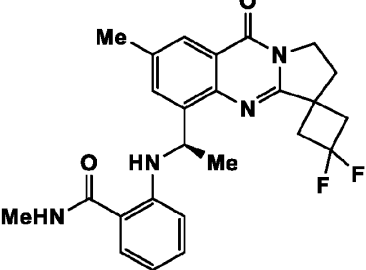
1-147	 6-chloro-3-(((<i>R</i>)-1-((1'<i>S</i>,3<i>R</i>)-1'-ethyl-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-148	 6-chloro-3-(((<i>R</i>)-1-((1'<i>R</i>,3<i>S</i>)-1'-ethyl-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-149	 6-chloro-3-(((<i>R</i>)-1-((1'<i>S</i>,3<i>S</i>)-1'-ethyl-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid

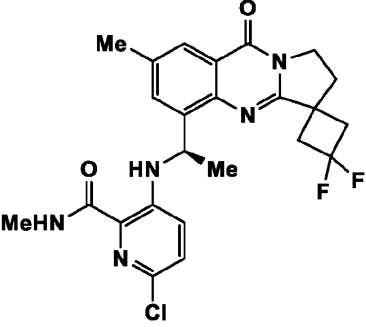
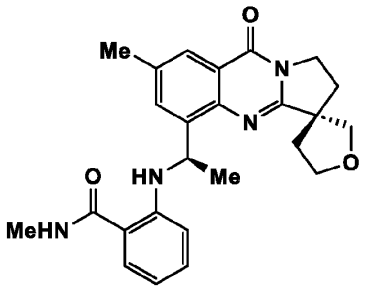
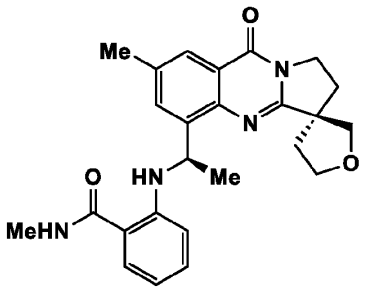
1-150	 2-(((<i>R</i>)-1-((1'<i>S</i>,3<i>R</i>)-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-151	 2-(((<i>R</i>)-1-((1'<i>R</i>,3<i>R</i>)-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-152	 2-(((<i>R</i>)-1-((1'<i>S</i>,3<i>S</i>)-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid

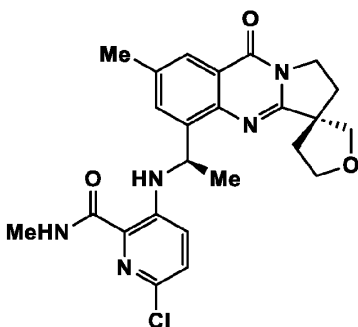
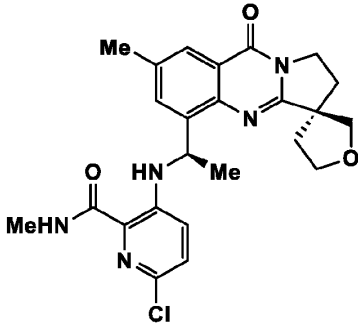
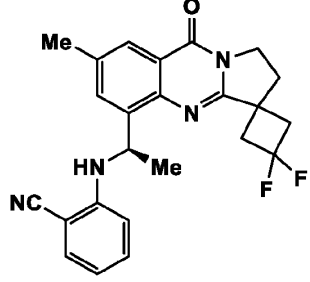
1-153	 2-(((<i>R</i>)-1-((1'<i>R</i>,3<i>S</i>)-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoic acid
1-154	 6-chloro-3-(((<i>R</i>)-1-((1'<i>S</i>,3<i>R</i>)-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-155	 6-chloro-3-(((<i>R</i>)-1-((1'<i>R</i>,3<i>R</i>)-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid

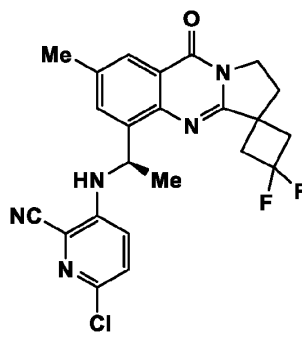
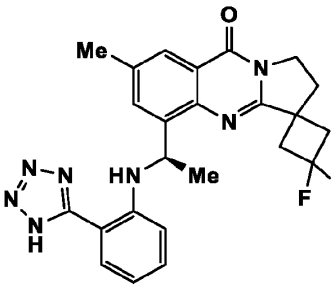
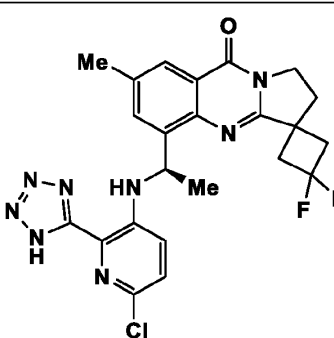
1-156	 6-chloro-3-(((<i>R</i>)-1-((1'<i>S</i>,3<i>S</i>)-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-157	 6-chloro-3-(((<i>R</i>)-1-((1'<i>R</i>,3<i>S</i>)-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinic acid
1-158	 (<i>R</i>)-4-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)thiophene-3-carboxylic acid

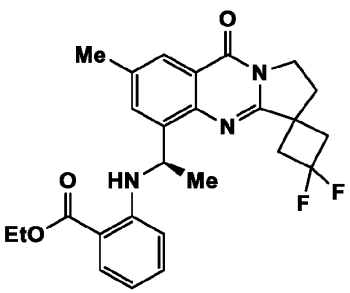
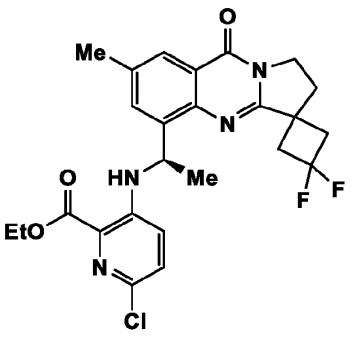
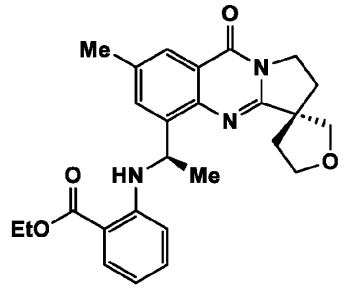
1-159	 (<i>R</i>)-4-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)isothiazole-3-carboxylic acid
1-160	 4-(((<i>R</i>)-1-((<i>R</i>)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)thiophene-3-carboxylic acid
1-161	 4-(((<i>R</i>)-1-((<i>S</i>)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)thiophene-3-carboxylic acid

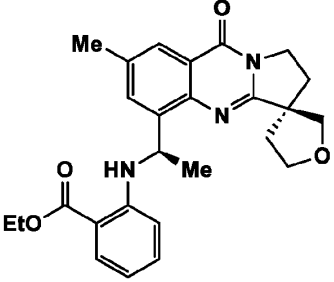
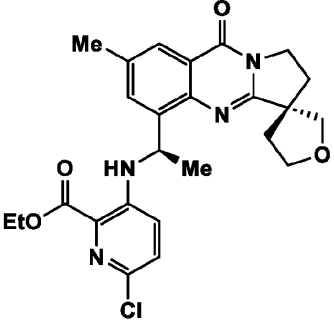
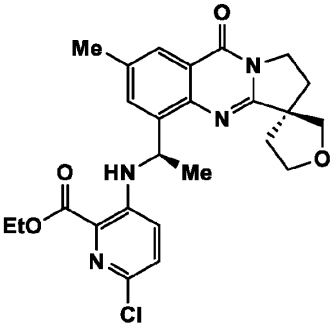
1-162	 4-(((<i>R</i>)-1-((<i>R</i>)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)isothiazole-3-carboxylic acid
1-163	 4-(((<i>R</i>)-1-((<i>S</i>)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)isothiazole-3-carboxylic acid
1-164	 (<i>R</i>)-2-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)-<i>N</i>-methylbenzamide

1-165	 <i>(R)</i>-6-chloro-3-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)-<i>N</i>-methylpicolinamide
1-166	 <i>N</i>-methyl-2-(((<i>R</i>)-1-((<i>R</i>)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzamide
1-167	 <i>N</i>-methyl-2-(((<i>R</i>)-1-((<i>S</i>)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzamide

1-168	 6-chloro-<i>N</i>-methyl-3-(((<i>R</i>)-1-((<i>R</i>)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinamide
1-169	 6-chloro-<i>N</i>-methyl-3-(((<i>R</i>)-1-((<i>S</i>)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinamide
1-170	 (<i>R</i>)-2-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzonitrile

1-171	 (R)-6-chloro-3-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'H-spiro[cyclobutane-1,3'-pyrrolo[2,1-b]quinazolin]-5'-yl)ethyl)amino)picolinonitrile
1-172	 (R)-5'-(1-((2-(1H-tetrazol-5-yl)phenyl)amino)ethyl)-3,3-difluoro-7'-methyl-1',2'-dihydro-9'H-spiro[cyclobutane-1,3'-pyrrolo[2,1-b]quinazolin]-9'-one
1-173	 (R)-5'-(1-((6-chloro-2-(1H-tetrazol-5-yl)pyridin-3-yl)amino)ethyl)-3,3-difluoro-7'-methyl-1',2'-dihydro-9'H-spiro[cyclobutane-1,3'-pyrrolo[2,1-b]quinazolin]-9'-one

1-174	 ethyl (<i>R</i>)-2-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoate
1-175	 ethyl (<i>R</i>)-6-chloro-3-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'<i>H</i>-spiro[cyclobutane-1,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinate
1-176	 ethyl 2-(((<i>R</i>)-1-((<i>R</i>)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoate

1-177	 ethyl 2-(((<i>R</i>)-1-((<i>S</i>)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)benzoate
1-178	 ethyl 6-chloro-3-(((<i>R</i>)-1-((<i>R</i>)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinate
1-179	 ethyl 6-chloro-3-(((<i>R</i>)-1-((<i>S</i>)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2<i>H</i>,9'<i>H</i>-spiro[furan-3,3'-pyrrolo[2,1-<i>b</i>]quinazolin]-5'-yl)ethyl)amino)picolinate

EXAMPLE A

[00597] This Example illustrates that representative compounds of the present invention inhibit the formation of phospho-AKT (pAKT) in a cell.

[00598] The ability of a compound of formula (I) to inhibit the formation of pAKT was measured using alphaLISA Surefire Ultra AKT 1/2/3 (pS473) Assay Kit (#ALSU-PAKT-B50K) was obtained from Perkin Elmer (Waltham, MA).

[00599] To prepare assay plates for pAKT alphaLISA assays, cells were trypsinized, resuspended in fresh media, and viable cells were counted utilizing trypan blue exclusion. Prior to seeding, cells were washed with PBS and resuspended in HBSS (Gibco, #14025092). T47D (12,000/w), SKBR3 (12,000/w), or MKN1 (24,000/w) cells were seeded at 12 μ l per well in a solid white flat bottom 384 cell culture plate (Perkin Elmer #6007680).

[00600] Immediately after seeding, cells were dosed using an Echo Liquid Handler (Beckman Coulter) with compounds at a 10.4 μ M starting concentration and serially diluted (1:4) for a total of 10 concentrations. 14 vehicle (DMSO) and 14 positive control (Alpelisib @ 3.125 μ M) wells were included on each assay plate. Cells were incubated with the compounds (solubilized in DMSO) for approximately 1 hour or 24 hours at 37 °C. After 1 hour of treatment, cells were lysed with 3 μ l of the 5x lysis buffer (provided and incubated at room temperature for 15 min on a microtiter plate shaker). Once cells were sufficiently lysed, 7.5 μ l of the acceptor bead mix (made using the manufacturers recommended dilutions) was added to each well and left on the microtiter plate shaker for 1 min prior to incubating plates at room temperature for 1 hour, in the absence of light. After 1 hour of incubation with the acceptor bead mix, 7.5 μ l of the donor bead mix (made using the manufacturers recommended dilutions) was added to each well and left on the microtiter plate shaker for 1 min prior to incubating plates at room temperature overnight in the absence of light. Plates were then imaged the following day using a CLARIOstar microplate reader (BMG Labtech, Germany).

[00601] Percent of control values were calculated by subtracting the average signal from the positive control (alpelisib) treated wells from all treated wells (including DMSO control wells) and then divided by the average signal from the vehicle DMSO treated control wells. Percent of vehicle control values were plotted as log(inhibitor) vs. response – Variable slope (four parameters) for curve fitting and IC₅₀ values were determined using XLfit.

[00602] The results are shown in Tables below. Key: N.D. = not determined

Table A

Inhibition of pAKT in T47D (PI3K α H1047R mutant) cells by
representative compounds of formula (I)

Example #	T47D pAKT (H1047R mutant) IC ₅₀ (nM)	Example #	T47D pAKT (H1047R mutant) IC ₅₀ (nM)
1-1	22.3	1-45	9.9
1-2	25.8	1-47	12.4
1-3	24.3	1-48	6
1-4	56.5	1-49	721
1-5	37.2	1-50	60.8
1-6	5.69	1-51	2.6
1-7	6.63	1-52	1.0
1-8	31.7	1-53	2.9
1-9	52.4	1-54	3.4
1-10	3.5	1-55	1.7
1-11	4.4	1-56	7.3
1-13	1.6	1-57	13.9
1-14	9.0	1-58	16.1
1-15	641	1-59	7.4
1-20	603	1-60	16.1
1-21	211	1-61	16.6
1-22	3.2	1-62	13.6
1-23	6.9	1-63	2
1-24	110	1-64	20.6
1-32	>10000	1-65	4.8
1-33	33	1-66	1.6
1-34	14	1-67	4.2
1-35	2.5	1-68	55.7
1-36	2.7	1-69	37.5
1-37	2636	1-70	5.6
1-39	1339	1-71	1.7
1-40	939	1-72	42.3
1-41	461	1-73	15.3
1-42	13.8	1-74	6.4
1-43	2.2	1-75	1.9
1-44	50.2	1-76	0.5
1-77	3.3	1-96	5.5
1-78	18.7	1-97	1.3
1-79	14.8	1-99	2202

Example #	T47D pAKT (H1047R mutant) IC ₅₀ (nM)	Example #	T47D pAKT (H1047R mutant) IC ₅₀ (nM)
1-80	8.2	1-100	113
1-81	10.1	1-101	3.0
1-82	2.3	1-102	3.0
1-83	3.8	1-103	3.3
1-84	703	1-104	1.4
1-87	91.5	1-105	1.5
1-88	88.1	1-106	136
1-89	8.4	1-107	324
1-90	9.3	1-108	3.4
1-91	2011	1-109	4.5
1-92	>10000	1-110	3.7
1-93	360	1-111	4.1
1-94	221	1-112	5.1
1-95	71	1-113	5.6

Table B

Inhibition of pAKT in MKN1 (PI3K α E545K mutant) cells by
representative compounds of formula (I)

Example #	MKN1 (E545K) pAKT IC ₅₀ (nM)
1-2	3814
1-3	2196
1-4	2004.4

Table C

Inhibition of pAKT in SKBR3 (PI3K α wild type) cells by
representative compounds of formula (I)

Example #	SKBR3 (WT) pAKT IC ₅₀ (nM)
1-1	>10000
1-2	>10000
1-3	>10000
1-4	4932
1-5	>10000
1-6	>10000
1-7	>10000
1-8	>10000

EXAMPLE B

[00603] This Example illustrates that exemplary compounds of the present invention decrease the viability of cells.

[00604] The ability of a compound of formula (I) to decrease the viability of cells was measured using CellTiter-Glo 2.0 (CTG) Luminescent Cell Viability Assay (#G9241) obtained from Promega (Madison, WI).

[00605] To prepare assay plates for viability assays, cells were trypsinized, resuspended in fresh media, and viable cells were counted utilizing trypan blue exclusion. T47D, SKBR3, or MKN1 cells were seeded at 1000 cells in 30 μ l per well in a solid white flat bottom 384 cell culture plate (Perkin Elmer #6007680) and incubated at 37 °C overnight.

[00606] Assay day 1, cells were dosed using an Echo Liquid Handler (Beckman Coulter) with compounds at a 10 μ M starting concentration and serially diluted (1:4) for a total of 10 concentrations. Cells were incubated for approximately 72 hours with the compounds (solubilized in DMSO) at 37 °C. After 72 hours of treatment, cell plates were equilibrated to room temperature before adding 15 μ l of CTG to each well, plates were then covered in aluminum foil to protect from light, incubated at room temperature for 30 minutes on a microtiter plate shaker, and luminescence readings were collected using a CLARIOstar microplate reader (BMG Labtech, Germany). Percent of vehicle control values were plotted as log(inhibitor) vs. response – Variable slope (four parameters) for curve fitting and IC₅₀ values were determined using XLfit.

Table D

Viability in T47D (PI3K α H1047R mutant) cells by
representative compounds of formula (I)

Example #	T47D (H1047R mutant) Viability IC ₅₀ (nM)	Example #	T47D (H1047R mutant) Viability IC ₅₀ (nM)
1-1	586.2	1-43	228
1-2	2221	1-44	2760
1-3	686.7	1-45	708
1-4	3034	1-46	>10000
1-5	467.1	1-47	316.7
1-6	169.2	1-48	122.1
1-7	117.7	1-49	1493
1-8	1232	1-50	273
1-9	2067	1-51	156
1-10	164	1-52	44.8
1-11	174	1-53	153.4
1-13	72.8	1-54	108
1-14	195	1-55	57.1
1-15	3332	1-56	103
1-20	3500	1-57	220
1-21	2339	1-58	114
1-22	233	1-59	343
1-23	69.7	1-60	468
1-24	6292	1-61	282
1-31	>10000	1-62	304
1-32	>10000	1-63	53.1
1-33	668	1-64	289
1-34	697	1-65	165
1-35	117	1-66	267
1-36	60.4	1-67	159
1-37	>10000	1-68	893
1-38	1097	1-69	906
1-39	7675	1-70	282
1-40	>10000	1-71	178
1-41	8205	1-72	1265
1-42	1449	1-73	179
1-74	148	1-95	2781
1-75	86.1	1-96	247
1-76	41.7	1-97	69.1
1-77	48.9	1-98	>10000

Example #	T47D (H1047R mutant) Viability IC ₅₀ (nM)	Example #	T47D (H1047R mutant) Viability IC ₅₀ (nM)
1-78	288	1-99	>10000
1-79	185	1-100	262
1-80	130	1-101	42.3
1-81	179	1-102	118
1-82	154	1-103	131
1-83	127	1-104	109
1-84	>10000	1-105	60.1
1-87	617	1-106	1239
1-88	778	1-107	445
1-89	127	1-108	44.1
1-90	180	1-109	50.4
1-91	>10000	1-110	65.8
1-92	>10000	1-111	128
1-93	4442	1-112	68.5
1-94	2446	1-113	65.6

Table E

Viability in MKN1 (PI3Kα E545K mutant) cells by representative compounds of formula (I)

Example #	MKN1 (E545K) Viability IC ₅₀ (nM)
1-1	
1-2	>10000
1-3	2196.1
1-4	>10000

Table F

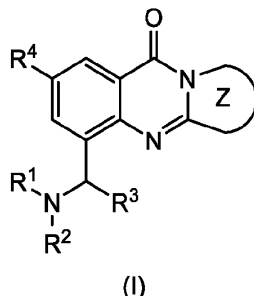
Viability in SKBR3 (PI3K α wild type) cells by representative compounds of formula (I)

Example #	SKBR3 (WT) Viability IC ₅₀ (nM)	Example #	SKBR3 (WT) Viability IC ₅₀ (nM)
1-1	>10000	1-43	>10000
1-2	>10000	1-44	>10000
1-3	>10000	1-45	>10000
1-4	>10000	1-46	>10000
1-5	>10000	1-47	8707
1-6	>10000	1-48	>10000
1-7	>10000	1-49	>10000
1-8	>10000	1-50	>10000
1-9	>10000	1-51	>10000
1-10	>10000	1-52	>10000
1-11	>10000	1-53	>10000
1-13	>10000	1-54	>10000
1-14	>10000	1-55	>10000
1-15	3776	1-56	>10000
1-20	>10000	1-57	>10000
1-21	3445	1-58	>10000
1-22	>10000	1-59	>10000
1-23	>10000	1-60	>10000
1-24	>10000	1-61	>10000
1-31	>10000	1-62	>10000
1-32	>10000	1-63	>10000
1-33	>10000	1-64	>10000
1-34	>10000	1-65	>10000
1-35	>10000	1-66	>10000
1-36	>10000	1-67	>10000
1-37	>10000	1-68	>10000
1-38	>10000	1-69	>10000
1-39	>10000	1-70	>10000
1-40	>10000	1-71	>10000
1-41	>10000	1-72	>10000
1-42	>10000	1-73	>10000
1-74	>10000	1-95	>10000
1-75	>10000	1-96	>10000
1-76	>10000	1-97	8314
1-77	5910	1-98	>10000

Example #	SKBR3 (WT) Viability IC ₅₀ (nM)	Example #	SKBR3 (WT) Viability IC ₅₀ (nM)
1-78	>10000	1-99	>10000
1-79	>10000	1-100	>10000
1-80	>10000	1-101	7763
1-81	>10000	1-102	>10000
1-82	>10000	1-103	>10000
1-83	>10000	1-104	>10000
1-84	>10000	1-105	9986
1-87	2444	1-106	1419
1-88	2656	1-107	2561
1-89	>10000	1-108	>10000
1-90	>10000	1-109	>10000
1-91	>10000	1-110	>10000
1-92	>10000	1-111	>10000
1-93	8984	1-112	>10000
1-94	4229	1-113	>10000

What is claimed is:

1. A compound of formula (I):



or a pharmaceutically acceptable salt or deuterated form thereof, wherein:

R¹ is H, C₁-C₃ alkyl, or C₃-C₆ cycloalkyl;

R² is phenyl or a 5-6 membered heteroaryl group, wherein each phenyl and heteroaryl is optionally substituted with 1-5 R⁷;

each R⁷ is independently C₁-C₄ alkyl; -OR^A, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, -C(O)N(R^B)₂, cyano, halogen or tetrazolyl;

each R^A is independently H, C₁-C₆ alkyl, or C₃-C₆ cycloalkyl;

each R^B is independently H, -OH, C₁-C₆ alkyl, C₁-C₆ alkoxy or C₃-C₆ cycloalkyl;

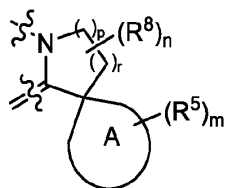
and

R³ is C₁-C₃ alkyl optionally substituted, polysubstituted or persubstituted with fluoro, C₃-C₆ cycloalkyl, C₂-C₃ alkenyl, C₂-C₃ alkynyl, or C₅-C₆ cycloalkenyl;

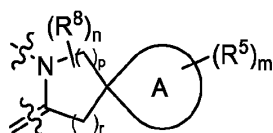
R⁴ is H, C₁-C₃ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkyloxy, C₂-C₃ alkenyl, C₂-C₃ alkynyl, or C₅-C₆ cycloalkenyl, cyano, or halo, wherein each C₁-C₃ alkyl and C₃-C₆ cycloalkyl is optionally substituted with 1-5 halo groups;



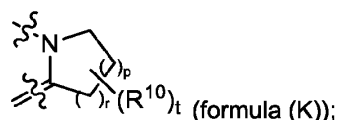
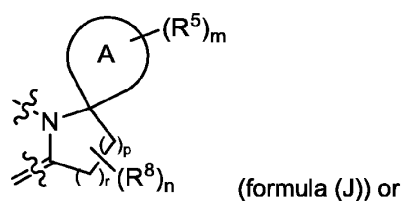
(formula (Z)) represents formula (D), (G), (J) or (K)



(formula (D)),



(formula (G)),



wherein

each ring A is a 3-8 membered carbocyclic ring or 3-7 membered heterocyclic ring,

m is 0, 1, 2, 3, 4 or 5;

p and r are independently 1 or 2, provided that the sum of p and r is 2 or 3;

each R^5 is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halogen, cyano, hydroxy, hydroxy C_1 - C_6 alkyl, amino, mono- or di(C_1 - C_6 alkyl) amino, C_3 - C_8 cycloalkyl, phenyl or 5-6 membered heteroaryl, where each cycloalkyl, phenyl and heteroaryl is optionally substituted with 1-3 of halogen, hydroxy, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, cyano, amino, or mono- or di(C_1 - C_3) alkyl amino;

n is 0, 1 or 2;

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

each R^8 is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, cyano, hydroxy, oxo, halogen, halo(C_1 - C_6)alkyl, hydroxy C_1 - C_6 alkyl, amino, or mono- or di(C_1 - C_6 alkyl) amino; and

each R^{10} is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, cyano, hydroxy, oxo, halogen, halo(C_1 - C_6)alkyl, hydroxy C_1 - C_6 alkyl, amino, or mono- or di(C_1 - C_6 alkyl) amino, R^{11} , R^{12} , R^{13} , R^{14} , R^{15} or R^{16} wherein

R^{11} is aryl or aryl(C_1 - C_6)alkyl where each aryl is optionally substituted independently with up to 4 of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, cyano, hydroxy, oxo, halogen, halo(C_1 - C_6)alkyl, hydroxy C_1 - C_6 alkyl, amino, or mono- or di(C_1 - C_6 alkyl) amino;

R^{12} is 5-8 membered heteroaryl or 5-8 membered heteroaryl(C_1 - C_6)alkyl where each heteroaryl is optionally substituted independently with up to 4 of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, cyano, hydroxy, oxo, halogen, halo(C_1 - C_6)alkyl, hydroxy C_1 - C_6 alkyl, amino, or mono- or di(C_1 - C_6 alkyl) amino;

R¹³ is aryl(C₁-C₆)alkoxy, aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, aryl(C₁-C₆)alkylamino or aryl(C₁-C₆)alkylamino(C₁-C₆)alkyl where each aryl is optionally substituted independently with up to 4 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino;

R¹⁴ is 5-8 membered heteroaryl(C₁-C₆)alkoxy, 5-8 membered heteroaryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, 5-8 membered heteroaryl(C₁-C₆)alkylamino or 5-8 membered heteroaryl(C₁-C₆)alkylamino(C₁-C₆)alkyl where each up to 4 of heteroaryl is optionally substituted independently with C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino;

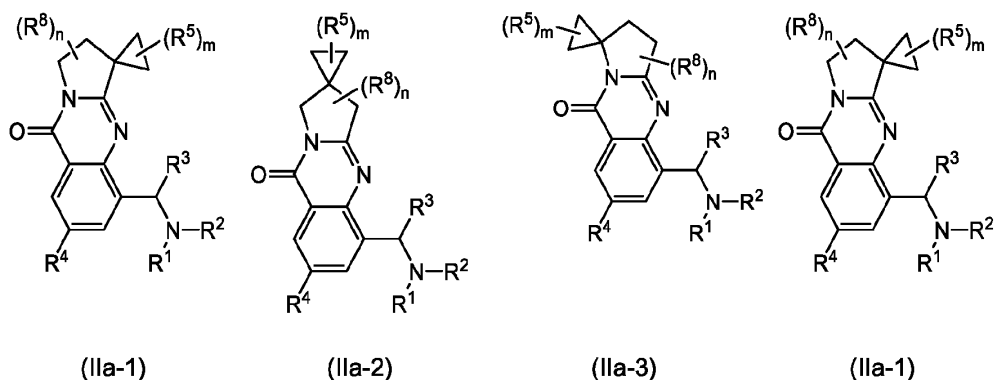
R¹⁵ is (C₁-C₆)cycloalkyl or (C₁-C₆)cycloalkyl(C₁-C₆)alkyl where each cycloalkyl is optionally substituted independently with up to 4 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino; and

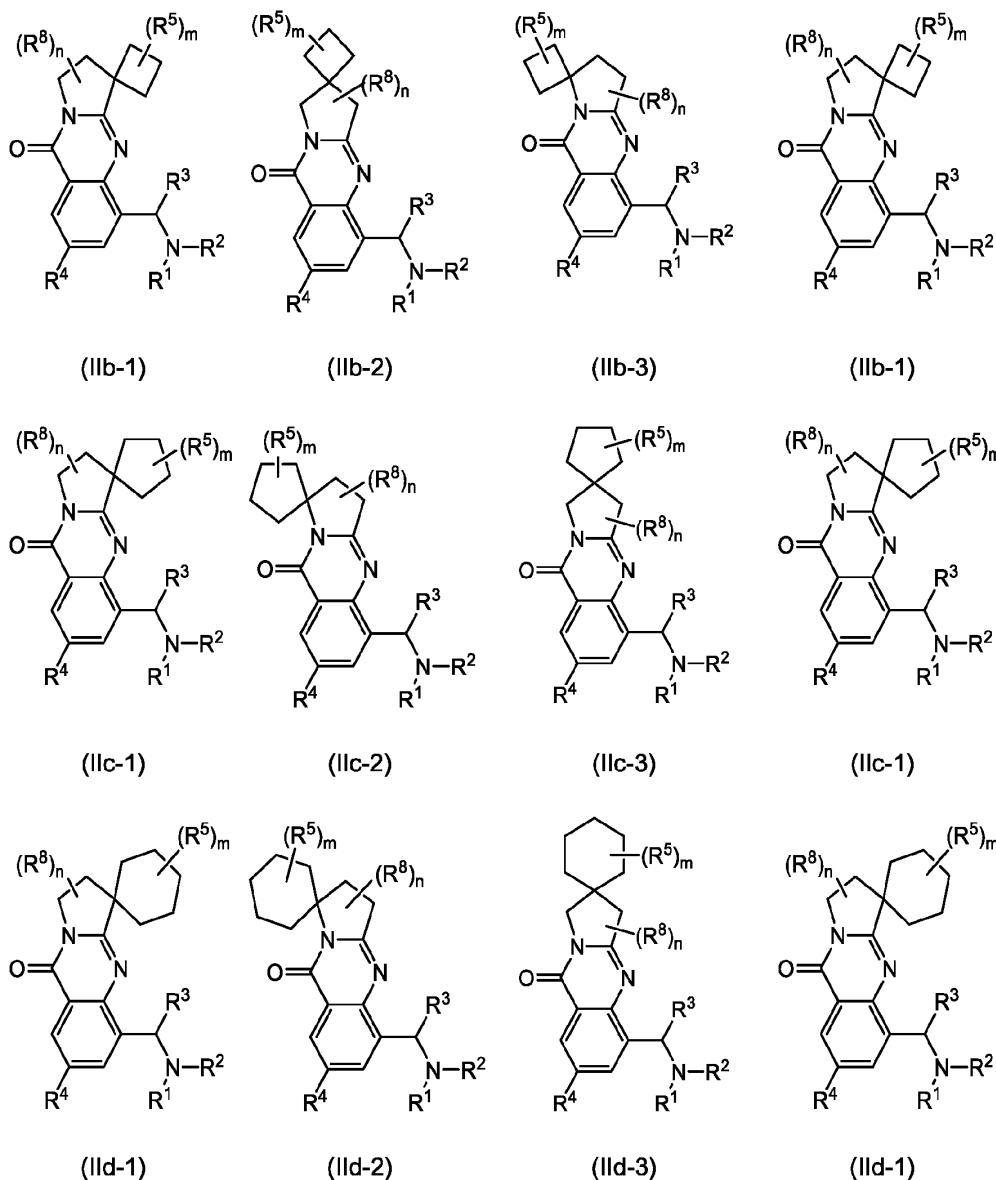
R¹⁶ is (C₁-C₆)cycloalkyl(C₁-C₆)alkoxy, (C₁-C₆)cycloalkyl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)cycloalkyl(C₁-C₆)alkylamino or (C₁-C₆)cycloalkyl(C₁-C₆)alkylamino(C₁-C₆)alkyl where each cycloalkyl is optionally substituted independently with up to 4 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino.

2. A compound according to claim 1, wherein formula (Z) represents formula (D).
3. A compound according to claim 1, wherein formula (Z) represents formula (G).
4. A compound according to claim 1, wherein formula (Z) represents formula (J).
5. A compound according to claim 1, wherein formula (Z) represents formula (K).
6. A compound according to any one of claims 1-5, wherein ring A is a 5-7 membered carbocyclic ring.

7. A compound according to any one of claims 1-5, wherein ring A is a 5-7 membered heterocyclic ring.
8. A compound according to any one of claims 1-5, wherein ring A is cyclohexyl, cyclopentyl, pyranyl or azetidiny.
9. A compound according to any of claims 1-6, wherein R¹ is H or CH₃.
10. A compound according to any of claims 1-9, wherein R² is phenyl, pyridinyl, thienyl, thiazolyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, pyrazinyl, pyridazinyl or pyrimidinyl, each of which is optionally substituted with 1-5 R⁷.
11. A compound according to any of claims 1-9, wherein R² is phenyl or pyridinyl, each of which is optionally substituted with 1-5 R⁷.
12. A compound according to any of claims 1-9, wherein R² is phenyl or a 5- 7 membered heteroaryl, each of which is substituted with 1, 2 or 3 R⁷ groups.
13. A compound according to any of claims 1-9, wherein R² is phenyl or a 5- 7 membered heteroaryl, each of which is substituted with 1, 2 or 3 R⁷ groups, and at least one R⁷ group is -C(O)OR^A.
14. A compound according to any of claims 1-13, wherein R³ is C₁-C₃ alkyl, wherein the alkyl group is unsubstituted, substituted with 1-5 halo groups, or perfluorinated.
15. A compound according to any of claims 1-13, wherein m is 1 or 2 and each R⁵ is halogen, C₃-C₆ cycloalkyl, phenyl or 5-6 membered heteroaryl, where each cycloalkyl, phenyl and heteroaryl is optionally substituted with 1-3 of halogen, hydroxy, C₁-C₃ alkyl, C₁-C₃ alkoxy, cyano, amino, or mono- or di(C₁-C₃) alkyl amino.
16. A compound according to any of claims 1-13, wherein m is 1 or 2 and each R⁵ is halogen, C₃-C₆ cycloalkyl, phenyl or 5-6 membered heteroaryl, where each cycloalkyl, phenyl and heteroaryl is optionally substituted with 1 or 2 of halogen, hydroxy, C₁-C₂ alkyl, C₁-C₂ alkoxy, cyano, amino, or mono- or di(C₁-C₂) alkylamino.

17. A compound according to any of claims 1-14, wherein m is 0, 1, or 2 and each R^5 is halogen, hydroxy, cyano or amino.
18. A compound according to any of claims 1-16, wherein R^2 is optionally substituted phenyl.
19. A compound according to any of claims 1-16, wherein R^2 is optionally substituted pyridinyl.
20. A compound according to any of claims 1-19, wherein R^4 is hydrogen, methyl, methoxy, ethyl, ethoxy, fluoro, bromo, chloro, cyclopropyl, trifluoromethyl or cyano.
21. A compound according to any of claims 1-20, wherein R^8 is hydrogen or C_1 - C_6 alkyl.
22. A compound according claim 1, wherein the compound is of formula (IIa-1), (IIa-2), (IIa-3), (IIb-1), (IIb-2), (IIb-3), (IIc-1), (IIc-2), (IIc-3), (IId-1), (IId-2), or (IId-3):





or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, C_1 - C_3 alkyl, or C_3 - C_6 cycloalkyl;

R^2 is phenyl or pyridinyl, wherein each phenyl and pyridinyl is optionally substituted with 1-5 R^7 ;

each R^7 is independently C_1 - C_4 alkyl; $-OR^A$, $-C(O)OR^A$, $(C_1$ - C_3 alkyl)- OR^A , $-C(O)N(R^B)_2$, cyano, halogen or tetrazolyl;

each R^A is independently H, C_1 - C_6 alkyl, or C_3 - C_6 cycloalkyl;

each R³ is independently H, -OH, C₁-C₆ alkyl, C₁-C₆ alkoxy or C₃-C₆ cycloalkyl;
and

R³ is C₁-C₃ alkyl or C₃-C₆ cycloalkyl;

R⁴ is H, C₁-C₃ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, or halo, wherein each C₁-C₃ alkyl is optionally substituted with 1-5 halo groups;

m is 0, 1, 2, 3, 4 or 5;

each R⁵ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, cyano, hydroxy, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino, C₃-C₆ cycloalkyl, phenyl or 5-6 membered heteroaryl, where each cycloalkyl, phenyl and heteroaryl is optionally substituted with 1-3 of halogen, hydroxy, C₁-C₃ alkyl, C₁-C₃ alkoxy, cyano, amino, or mono- or di(C₁-C₃) alkyl amino;

wherein each non-spiro carbon in the ring carrying R⁵ is optionally replaced with a heteroatom which is nitrogen, oxygen, or sulfur;

n is 0, 1 or 2; and

each R⁸ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, halogen, oxo, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino.

23. A compound according to claim 22, wherein m is 0, 1, or 2 and each R⁵ is independently halogen, hydroxy, cyano or amino.

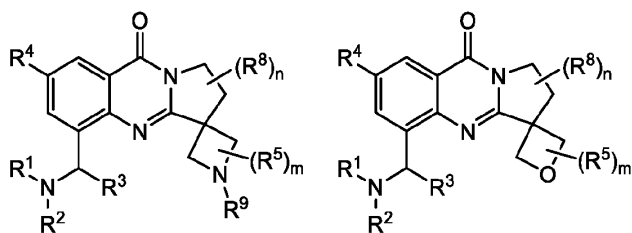
24. A compound according to claim 22 or claim 23, wherein n is 0 or 1 and each R⁸ is halogen, hydroxy, cyano or amino.

25. A compound according to any of claims 22-24 wherein R³ is C₁-C₃ alkyl.

26. A compound according to any of claims 22-24 wherein R³ is methyl.

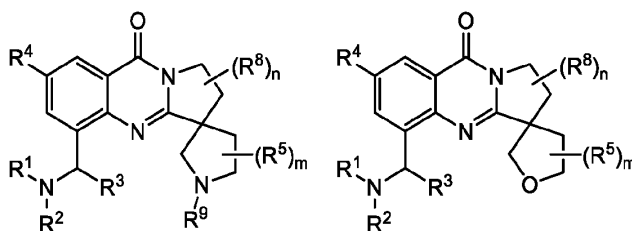
27. A compound according to any of claims 22-26 wherein R⁴ is H, C₁-C₃ alkyl, C₁-C₆ alkoxy, C₃-C₄ cycloalkyl, halo, trifluoromethyl or cyano.

28. A compound according to claim 1, wherein the compound is of formula (IIb-1A), (IIb-1B), (IIc-1A), (IIc-1B), (IId-1A) or (IId-1B):



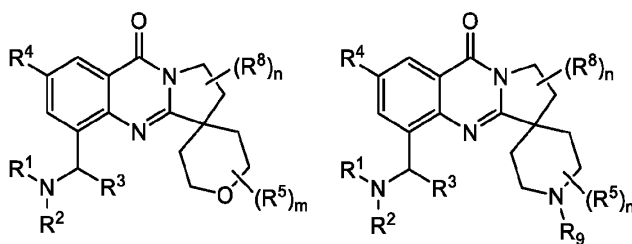
(IIb-1A)

(IIb-1B)



(IIc-1A)

(IIc-1B)



(IId-1A)

(IId-1B)

or a pharmaceutically acceptable salt thereof, wherein:

R¹ is H, C₁-C₃ alkyl, or C₃-C₆ cycloalkyl;

R² is phenyl or pyridinyl, wherein each phenyl and pyridinyl is optionally substituted with 1-5 R⁷;

each R⁷ is independently C₁-C₄ alkyl; -OR^A, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, -C(O)N(R^B)₂, cyano, halogen or tetrazolyl;

each R^A is independently H, C₁-C₆ alkyl, or C₃-C₆ cycloalkyl;

each R^B is independently H, -OH, C₁-C₆ alkyl, C₁-C₆ alkoxy or C₃-C₆ cycloalkyl;

and

R³ is C₁-C₃ alkyl or C₃-C₆ cycloalkyl;

R⁴ is H, C₁-C₃ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, or halo, wherein each C₁-C₃ alkyl is optionally substituted with 1-5 halo groups;

m is 0 or 1;

each R⁵ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, cyano, hydroxy, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino, C₃-C₆ cycloalkyl, phenyl or 5-6 membered heteroaryl, where each cycloalkyl, phenyl and heteroaryl is optionally substituted with 1-3 of halogen, hydroxy, C₁-C₃ alkyl, C₁-C₃ alkoxy, cyano, amino, or mono- or di(C₁-C₃) alkyl amino;

R⁹ is hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, cyano, hydroxy, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino, C₃-C₆ cycloalkyl, phenyl or 5-6 membered heteroaryl, where each cycloalkyl, phenyl and heteroaryl is optionally substituted with 1-3 of halogen, hydroxy, C₁-C₃ alkyl, C₁-C₃ alkoxy, cyano, amino, or mono- or di(C₁-C₃) alkyl amino;

n is 0, 1 or 2; and

each R⁸ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, halogen, oxo, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino.

29. The compound of claim 28, wherein m is 0, 1, or 2 and each R⁵ is independently C₁-C₆ alkyl or hydroxy C₁-C₆ alkyl.

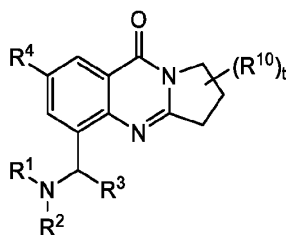
30. The compound of claim 28 or claim 29, wherein n is 0 or 1 and each R⁸ is halogen, hydroxy, cyano or amino.

31. A compound according to any of claims 28-30 wherein R³ is C₁-C₃ alkyl.

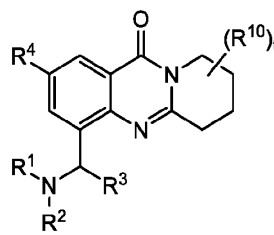
32. A compound according to any of claims 28-31 wherein R³ is methyl.

33. A compound according to any of claims 28-32 wherein R⁴ is H, C₁-C₃ alkyl, C₁-C₆ alkoxy, C₃-C₄ cycloalkyl, halo, trifluoromethyl or cyano.

34. A compound according to claim 1, wherein the compound is of formula (IIIa) or (IIIb):



(IIIa)



(IIIb)

or a pharmaceutically acceptable salt thereof, wherein:

R¹ is H, C₁-C₃ alkyl, or C₃-C₆ cycloalkyl;

R² is phenyl or pyridinyl, wherein each phenyl and pyridinyl is optionally substituted with 1-5 R⁷;

each R⁷ is independently C₁-C₄ alkyl; -OR^A, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, -C(O)N(R^B)₂, cyano, halogen or tetrazolyl;

each R^A is independently H, C₁-C₆ alkyl, or C₃-C₆ cycloalkyl;

each R^B is independently H, -OH, C₁-C₆ alkyl, C₁-C₆ alkoxy or C₃-C₆ cycloalkyl;

and

R³ is C₁-C₃ alkyl or C₃-C₆ cycloalkyl; and

R⁴ is H, C₁-C₃ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, or halo, wherein each C₁-C₃ alkyl is optionally substituted with 1-5 halo groups.

35. A compound according to claim 1 or claim 34, wherein each R¹⁰ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino.

36. A compound according to claim 34 wherein t is 1.

37. A compound according to claim 34 wherein t is 2 and both R¹⁰ groups are attached to the same carbon atom.

38. A compound according to claim 34 wherein t is 2 and the R¹⁰ groups are attached to different carbon atoms.

39. A compound according to any one of claims 34-38, wherein each R¹⁰ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₃)alkyl, hydroxy C₁-C₃ alkyl, amino, or mono- or di(C₁-C₃ alkyl) amino.
40. A compound according to any one of claims 34-38, wherein each R¹⁰ is independently C₁-C₂ alkyl, C₁-C₂ alkoxy, cyano, hydroxy, halogen, or halo(C₁-C₂)alkyl.
41. A compound according to any one of claims 34-38, wherein each R¹⁰ is independently C₁-C₂ alkyl, chloro, fluoro, fluoromethyl, difluoromethyl, or trifluoromethyl.
42. A compound according to claim 36 where R¹⁰ is C₁-C₂ alkyl, chloro, fluoro, fluoromethyl, difluoromethyl, or trifluoromethyl.
43. A compound according to claim 37 where both R¹⁰ groups are the same and are C₁-C₂ alkyl, chloro, fluoro, or fluoromethyl.
44. A compound according to claim 1 or claim 34, wherein t is 1 and R¹⁰ is R¹¹, R¹², R¹³, R¹⁴, R¹⁵ or R¹⁶.
45. A compound according to claim 1 or claim 34, wherein t is 2 and one R¹⁰ is C₁-C₆ alkyl, halogen or halo(C₁-C₂)alkyl and the other is R¹¹, R¹², R¹³, R¹⁴, R¹⁵ or R¹⁶.
46. A compound according to claim 1 or claim 34, wherein t is 1 and R¹⁰ is R¹¹.
47. A compound according to claim 1 or claim 34, wherein t is 1 and R¹⁰ is R¹².
48. A compound according to claim 1 or claim 34, wherein t is 1 and R¹⁰ is R¹³.
49. A compound according to claim 1 or claim 34, wherein t is 1 and R¹⁰ is R¹⁴.
50. A compound according to claim 1 or claim 34, wherein t is 1 and R¹⁰ is R¹⁵.
51. A compound according to claim 1 or claim 34, wherein t is 1 and R¹⁰ is R¹⁶.

52. A compound according to any one of claims 46-51 wherein R¹⁰ is R¹¹ or R¹².
53. A compound according to claim 52 wherein R¹¹ and R¹² are unsubstituted.
54. A compound according to claim 52 wherein R¹¹ and R¹² are substituted with C₁-C₂ alkyl, bromo, chloro, fluoro, fluoromethyl, difluoromethyl, or trifluoromethyl.
55. A compound according to claim 1 or claim 34, wherein t is 2 and one R¹⁰ is C₁-C₆ alkyl, halogen or halo(C₁-C₂)alkyl and the other is R¹¹ wherein R¹¹ is phenyl(C₁-C₆)alkyl and the phenyl is optionally substituted with 1, 2 or 3 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino.
56. A compound according to claim 1 or claim 34, wherein t is 2 and one R¹⁰ is C₁-C₆ alkyl, halogen or halo(C₁-C₂)alkyl and the other is R¹¹ wherein R¹¹ is 5- or 6-membered heteroaryl(C₁-C₆)alkyl and the heteroaryl is optionally substituted with 1, 2 or 3 of C₁-C₆ alkyl, C₁-C₆ alkoxy, cyano, hydroxy, oxo, halogen, halo(C₁-C₆)alkyl, hydroxy C₁-C₆ alkyl, amino, or mono- or di(C₁-C₆ alkyl) amino.
57. A compound according to claim 56, wherein the heteroaryl is an optionally substituted pyridyl, thiazolyl, imidazolyl, oxazolyl, or isoxazolyl,
58. The compound of claim 1, which is:
(*R*)-2-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;
2-((1-(9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;
2-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;
2-((1-(7'-bromo-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;
(*R*)-2-((1-(7'-cyclopropyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;
(*R*)-2-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(7'-cyano-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(7'-methyl-9'-oxo-1',2,2',3,5,6-hexahydro-9'*H*-spiro[pyran-4,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid; or

(*R*)-5-fluoro-2-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)-5-fluorobenzoic acid;

(*R*)-4-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)pyridazine-3-carboxylic acid;

(*R*)-6-chloro-3-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

(*R*)-3-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)pyrazine-2-carboxylic acid;

(*R*)-4-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)thiazole-5-carboxylic acid;

(*R*)-4-((1-(4,4-difluoro-7'-methyl-5'-oxo-2',3'-dihydro-5'*H*-spiro[cyclohexane-1,1'-pyrrolo[1,2-*b*]isoquinolin]-9'-yl)ethyl)amino)thiazole-5-carboxylic acid;

(*R*)-4-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)pyridazine-3-carboxylic acid;

(*R*)-5-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)thiazole-4-carboxylic acid;

(*R*)-5-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)thiazole-4-carboxylic acid;

(*R*)-3-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)pyrazine-2-carboxylic acid;

(*R*)-6-chloro-3-((1-(7'-methyl-9'-oxo-1',2,2',3,5,6-hexahydro-9'*H*-spiro[pyran-4,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

(*R*)-2-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(7'-methyl-9'-oxo-3',9'-dihydro-1'*H*-spiro[cyclobutane-1,2'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(7'-methyl-9'-oxo-1-phenyl-1',2'-dihydro-9'*H*-spiro[azetidine-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(1-(4-cyanophenyl)-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[azetidine-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(1-(4-cyano-2-methylphenyl)-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[azetidine-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(2'-methyl-10'-oxo-7',8'-dihydro-10'*H*-spiro[cyclopentane-1,6'-pyrido[3,2-*d*]pyrrolo[1,2-*a*]pyrimidin]-4'-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(2'-methyl-11'-oxo-8',9'-dihydro-7'*H*,11'*H*-spiro[cyclopentane-1,6'-pyrido[2,1-*b*]quinazolin]-4'-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(4,4-difluoro-2'-methyl-10'-oxo-7',8'-dihydro-10'*H*-spiro[cyclohexane-1,6'-pyrido[3,2-*d*]pyrrolo[1,2-*a*]pyrimidin]-4'-yl)ethyl)amino)benzoic acid;

2-((1-(7-methyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-5-yl)ethyl)amino)benzoic acid;

2-((1-(3,3-difluoro-7-methyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-5-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(3,3-diethyl-7-methyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-5-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(3,3,7-trimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-5-yl)ethyl)amino)benzoic acid;

(*R*)-6-chloro-3-((1-(3,3,7-trimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-5-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-4-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)pyridazine-3-carboxylic acid;

(*R*)-2-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopropane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

(*R*)-3-((1-(3,3,7-trimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-5-yl)ethyl)amino)pyrazine-2-carboxylic acid;

(*R*)-5-((1-(7'-methyl-9'-oxo-1',2,2',3,5,6-hexahydro-9'*H*-spiro[pyran-4,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)thiazole-4-carboxylic acid;

(*R*)-3-((1-(7'-methyl-9'-oxo-1',2,2',3,5,6-hexahydro-9'*H*-spiro[pyran-4,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)pyrazine-2-carboxylic acid;

(*R*)-2-((1-(7'-cyclopropyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

(*R*)-6-chloro-3-((1-(7'-cyclopropyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

2-(((*R*)-1-((*S*)-3-benzyl-3,7-dimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-5-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-((*R*)-3-benzyl-3,7-dimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-5-yl)ethyl)amino)benzoic acid;

(*R*)-6-chloro-3-((1-(10'-oxo-7',8'-dihydro-10'*H*-spiro[cyclobutane-1,6'-pyrido[4,3-*d*]pyrrolo[1,2-*a*]pyrimidin]-4'-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(7'-cyclopropyl-4,4-difluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(7'-fluoro-9'-oxo-1',2,2',3,5,6-hexahydro-9'*H*-spiro[pyran-4,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

(*R*)-3-((1-(7'-fluoro-9'-oxo-1',2,2',3,5,6-hexahydro-9'*H*-spiro[pyran-4,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)-6-methylpicolinic acid;

(*R*)-2-((1-(7'-fluoro-9'-oxo-1',2,2',3,5,6-hexahydro-9'*H*-spiro[pyran-4,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(7'-chloro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

(*R*)-6-chloro-3-((1-(7'-chloro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(7'-cyclopropyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

(*R*)-2-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

(*R*)-6-chloro-3-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

(*R*)-2-((1-(7'-chloro-3,3-difluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(3,3-difluoro-9'-oxo-7'-(trifluoromethyl)-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

(*R*)-6-chloro-3-((1-(3,3-difluoro-9'-oxo-7'-(trifluoromethyl)-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

2-(((*R*)-1-((*S*)-2,2-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-((*R*)-2,2-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-
spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;
(*R*)-2-((1-(7'-ethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-
b]quinazolin]-5'-yl)ethyl)amino)benzoic acid;
(*R*)-2-((1-(7'-ethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-
b]quinazolin]-5'-yl)ethyl)amino)benzoic acid;
(*R*)-6-chloro-3-((1-(7'-ethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-
pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;
2-(((*R*)-1-((*S*)-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-
spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;
2-(((*R*)-1-((*R*)-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-
spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;
6-chloro-3-(((*R*)-1-((*S*)-2,2-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-
spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;
6-chloro-3-(((*R*)-1-((*R*)-2,2-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-
spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;
2-(((1*R*)-1-(3,7-dimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-5-
yl)ethyl)amino)benzoic acid;
(*R*)-2-((1-(7'-methoxy-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-
pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;
2-(((1*R*)-1-(3,7-dimethyl-9-oxo-3-(4-(trifluoromethyl)benzyl)-1,2,3,9-
tetrahydropyrrolo[2,1-*b*]quinazolin-5-yl)ethyl)amino)benzoic acid;
(*R*)-6-chloro-3-((1-(7'-methoxy-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-
pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;
(*R*)-2-((1-(3,3-difluoro-7'-methoxy-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-
1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;
(*R*)-2-((1-(3,3,7'-trifluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-
pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;
(*R*)-2-((1-(7'-ethyl-3,3-difluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-
pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;
(*R*)-6-chloro-3-((1-(3,3-difluoro-7'-methoxy-9'-oxo-1',2'-dihydro-9'*H*-
spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;
(*R*)-6-chloro-3-((1-(3,3,7'-trifluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-
1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;
(*R*)-6-chloro-3-((1-(7'-ethyl-3,3-difluoro-9'-oxo-1',2'-dihydro-9'*H*-
spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

2-(((*R*)-1-((*R*)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-((*S*)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-((*R*)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-((*S*)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

6-chloro-3-(((*R*)-1-((*R*)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((*S*)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

(*R*)-2-((1-(7-methyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-5-yl)ethyl)amino)benzoic acid;

(*R*)-6-chloro-3-((1-(7'-methoxy-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((1(*R*)-1-(7-methyl-9-oxo-3-(4-(trifluoromethyl)benzyl)-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-5-yl)ethyl)amino)picolinic acid;

3-(((*R*)-1-((*R*)-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

3-(((*R*)-1-((*S*)-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((*R*)-7'-ethyl-3,3-difluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((*S*)-7'-ethyl-3,3-difluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

2-((1-(3,3-difluoro-7-methyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-5-yl)ethyl)amino)benzoic acid;

(*R*)-3-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)thiophene-2-carboxylic acid;

(*R*)-2-((1-(4,4-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)thiophene-3-carboxylic acid;

(*R*)-3-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)pyrazine-2-carboxylic acid;

(*R*)-5-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)thiazole-4-carboxylic acid;

3-(((*R*)-1-((*R*)-3-benzyl-3,7-dimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-5-yl)ethyl)amino)-6-chloropicolinic acid;

3-(((*R*)-1-((*S*)-3-benzyl-3,7-dimethyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-5-yl)ethyl)amino)-6-chloropicolinic acid;

(*R*)-2-((1-(10'-oxo-7',8'-dihydro-10'*H*-spiro[cyclobutane-1,6'-pyrido[4,3-*d*]pyrrolo[1,2-*a*]pyrimidin]-4'-yl)ethyl)amino)benzoic acid;

(*R*)-7'-fluoro-5'-((1-((3-(hydroxymethyl)phenyl)amino)ethyl)-1',2,2',3,5,6-hexahydro-9'*H*-spiro[pyran-4,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one

(*R*)-6-methyl-3-((1-(7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(7'-chloro-3,3-difluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((*R*)-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((*S*)-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((*R*)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((*S*)-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-(2,2-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((*R*)-2,2-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((*S*)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((*R*)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((*S*)-3,3,7'-trifluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((*R*)-3,3,7'-trifluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((*S*)-7'-chloro-3,3-difluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((*R*)-7'-chloro-3,3-difluoro-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclopentane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

2-(((*R*)-1-((*R*)-3,3-difluoro-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-((*S*)-3,3-difluoro-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

6-chloro-3-(((*R*)-1-((*R*)-3,3-difluoro-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((*S*)-3,3-difluoro-1',7'-dimethyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

2-(((*R*)-1-((*R*)-1'-ethyl-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-((*S*)-1'-ethyl-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

6-chloro-3-(((*R*)-1-((*R*)-1'-ethyl-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((*S*)-1'-ethyl-3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

2-(((*R*)-1-((*S*)-3,3-difluoro-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-((*R*)-3,3-difluoro-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

6-chloro-3-(((*R*)-1-((*S*)-3,3-difluoro-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((*R*)-3,3-difluoro-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

2-(((*R*)-1-((*R*)-7'-chloro-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-((*S*)-7'-chloro-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

6-chloro-3-(((*R*)-1-((*R*)-7'-chloro-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((*S*)-7'-chloro-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

2-(((*R*)-1-((*R*)-7'-fluoro-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-((*S*)-7'-fluoro-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

6-chloro-3-(((*R*)-1-((*R*)-7'-fluoro-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((*S*)-7'-fluoro-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

2-(((*R*)-1-((1'*R*,3*R*)-1',7'-dimethyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-((1'*S*,3*R*)-1',7'-dimethyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-((1'*R*,3*S*)-1',7'-dimethyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-((1'*S*,3*S*)-1',7'-dimethyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

6-chloro-3-(((*R*)-1-((1'*R*,3*R*)-1',7'-dimethyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((1'*S*,3*R*)-1',7'-dimethyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((1'*R*,3*S*)-1',7'-dimethyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((1'*S*,3*S*)-1',7'-dimethyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

2-(((*R*)-1-((1'*R*,3*R*)-1'-ethyl-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-((1'*S*,3*R*)-1'-ethyl-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-((1'*R*,3*S*)-1'-ethyl-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-((1'*S*,3*S*)-1'-ethyl-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

6-chloro-3-(((*R*)-1-((1'*R*,3*R*)-1'-ethyl-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((1'*S*,3*R*)-1'-ethyl-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((1'*R*,3*S*)-1'-ethyl-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((1'*S*,3*S*)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

2-(((*R*)-1-((1'*S*,3*R*)-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-((1'*R*,3*R*)-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-((1'*S*,3*S*)-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-((1'*R*,3*S*)-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoic acid;

6-chloro-3-(((*R*)-1-((1'*S*,3*R*)-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((1'*R*,3*R*)-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((1'*S*,3*S*)-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((*R*)-1-((1'*R*,3*S*)-7'-methyl-9'-oxo-1'-(trifluoromethyl)-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinic acid;

(*R*)-4-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)thiophene-3-carboxylic acid;

(*R*)-4-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)isothiazole-3-carboxylic acid;

4-(((*R*)-1-((*R*)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)thiophene-3-carboxylic acid;

4-(((*R*)-1-((*S*)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)thiophene-3-carboxylic acid;

4-(((*R*)-1-((*R*)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)isothiazole-3-carboxylic acid;

4-(((*R*)-1-((*S*)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)isothiazole-3-carboxylic acid;

(*R*)-2-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)-*N*-methylbenzamide

(R)-6-chloro-3-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)-*N*-methylpicolinamide
N-methyl-2-(((*R*)-1-((*R*)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzamide
N-methyl-2-(((*R*)-1-((*S*)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzamide
 6-chloro-*N*-methyl-3-(((*R*)-1-((*R*)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinamide
 6-chloro-*N*-methyl-3-(((*R*)-1-((*S*)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinamide
(R)-2-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzonitrile
(R)-6-chloro-3-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinonitrile
(R)-5'-(1-((2-(1*H*-tetrazol-5-yl)phenyl)amino)ethyl)-3,3-difluoro-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one
(R)-5'-(1-((6-chloro-2-(1*H*-tetrazol-5-yl)pyridin-3-yl)amino)ethyl)-3,3-difluoro-7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one
 ethyl *(R)*-2-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoate
 ethyl *(R)*-6-chloro-3-((1-(3,3-difluoro-7'-methyl-9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclobutane-1,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinate
 ethyl 2-(((*R*)-1-((*R*)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoate
 ethyl 2-(((*R*)-1-((*S*)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)benzoate
 ethyl 6-chloro-3-(((*R*)-1-((*R*)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinate
 ethyl 6-chloro-3-(((*R*)-1-((*S*)-7'-methyl-9'-oxo-1',2',4,5-tetrahydro-2*H*,9'*H*-spiro[furan-3,3'-pyrrolo[2,1-*b*]quinazolin]-5'-yl)ethyl)amino)picolinate
 a pharmaceutically acceptable salt thereof.

59. A pharmaceutical composition comprising a compound or salt according to any of claims 1-58 together with a pharmaceutically acceptable carrier, excipient or diluent.

60. A method of treating a disease or disorder associated with modulation of phosphoinositide 3-kinase (PI3K), comprising administering to a patient in need thereof a therapeutically effective amount of a compound of any one of claims 1 to 58 or a pharmaceutical composition of claim 59.
61. The method of claim 60, wherein the PI3K is PI3K α .
62. The method of claim 60 or claim 61, wherein the PI3K associated with the disease or disorder has a H1047R mutation.
63. The method of any one of claims 60 to 62, wherein the disease or disorder is a cancer.
64. The method of claim 63, wherein the cancer is endometrial cancer, gastric cancer, leukemia, lymphoma, sarcoma, colorectal cancer, lung cancer, ovarian cancer, skin cancer, head and neck cancer, breast cancer, brain cancer, or prostate cancer.
65. The method of any one of claims 60 to 62, wherein the disease or disorder is CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome), or PIK3C α -related overgrowth syndrome (PROS).
66. A method of inhibiting phosphoinositide 3-kinase (PI3K), comprising administering to a patient in need thereof a therapeutically effective amount of a compound of any one of claims 1 to 58 or a pharmaceutical composition of claim 59.
67. A method of treating cancer or a disorder, the method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of any one of claims 1 to 58 or a pharmaceutical composition of claim 59.
68. The method of claim 67, wherein the cancer is endometrial cancer, gastric cancer, leukemia, lymphoma, sarcoma, colorectal cancer, lung cancer, ovarian cancer, skin cancer, head and neck cancer, breast cancer, brain cancer, or prostate cancer.

69. The method of claim 65, wherein the disorder is CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome) or PIK3C α -related overgrowth syndrome (PROS).

70. A method of treating cancer comprising administering a compound according to any of claims 1-58 or a pharmaceutical composition of claim 59 and a KRAS inhibitor to a patient in need thereof, wherein the cancer is breast cancer, uterine carcinosarcoma, uterine endometrial carcinoma, colorectal adenocarcinoma, stomach adenocarcinoma, head and neck squamous cell carcinoma, cholangiocarcinoma, esophageal adenocarcinoma, bladder carcinoma, lung squamous cell carcinoma, brain glioma, adrenocortical carcinoma, liver hepatocellular carcinoma, sarcoma, prostate adenocarcinoma, kidney renal cell carcinoma, lung adenocarcinoma, ovarian cystadenocarcinoma, glioblastoma multiforme, melanoma.

71. A method treating cancer comprising administering a compound according to any of claims 1-58 or a pharmaceutical composition of claim 59 and a mutant selective KRAS inhibitor to a patient in need thereof, wherein the cancer is breast cancer, uterine carcinosarcoma, uterine endometrial carcinoma, colorectal adenocarcinoma, stomach adenocarcinoma, head and neck squamous cell carcinoma, cholangiocarcinoma, esophageal adenocarcinoma, bladder carcinoma, lung squamous cell carcinoma, brain glioma, adrenocortical carcinoma, liver hepatocellular carcinoma, sarcoma, prostate adenocarcinoma, kidney renal cell carcinoma, lung adenocarcinoma, ovarian cystadenocarcinoma, glioblastoma multiforme, melanoma.

72. A compound according to any of claims 1-58 or a pharmaceutical composition of claim 59 for use in the treatment of cancer in combination with a KRAS inhibitor, wherein the cancer is breast cancer, uterine carcinosarcoma, uterine endometrial carcinoma, colorectal adenocarcinoma, stomach adenocarcinoma, head and neck squamous cell carcinoma, cholangiocarcinoma, esophageal adenocarcinoma, bladder carcinoma, lung squamous cell carcinoma, brain glioma, adrenocortical carcinoma, liver hepatocellular carcinoma, sarcoma, prostate adenocarcinoma, kidney renal cell carcinoma, lung adenocarcinoma, ovarian cystadenocarcinoma, glioblastoma multiforme, melanoma.