

Substituted Tricyclic Compounds

Cross-reference to related applications

[0001] This application claims priority from U.S. Provisional Application No. 63/483,070, filed February 3, 2023, the disclosure of each of which is hereby incorporated by reference in its entirety.

Field

[0002] This disclosure is directed to substituted tricyclic compounds, including imidazoquinazolines, imidazopyridopyrimidines, triazoloquinazolines, pyridotriazolopyrimidines, triazoloquinoxalines, pyridotriazolopyrazines, thienonaphthyridines and thienoquinolines, 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.

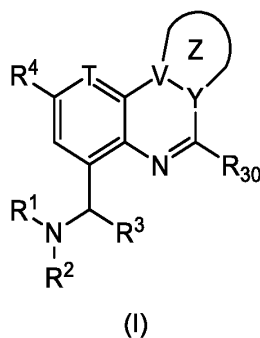
[0012] In the setting of cancer with mutated PI3K α , one way to overcome the problem of compensatory production of insulin and/or glucose upon systemic PI3K α inhibition would be to develop inhibitors with enhanced selectivity for mutant PI3K α over wild-type PI3K α . This would create an increased 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:



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 R¹²;

each R¹² is independently C₁-C₄ alkyl, -OR^A, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, -C(O)N(R^B)₂, cyano, tetrazolyl, or halogen;

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;

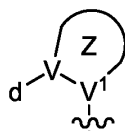
and

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;

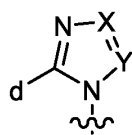
R⁴ is H, C₁-C₃ alkyl, C₁-C₃ alkoxy, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkyloxy, C₂-C₃ alkenyl, C₂-C₃ alkynyl, or C₅-C₆ cycloalkenyl, cyano, or halo, wherein each C₁-C₃ alkyl and C₃-C₆ cycloalkyl is optionally substituted with 1-5 halo groups;

T is N or CR⁶ wherein

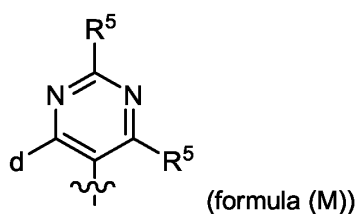
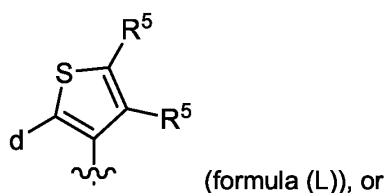
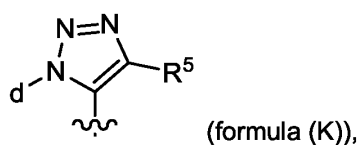
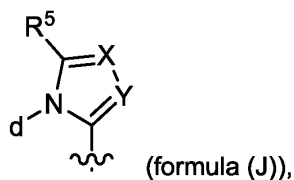
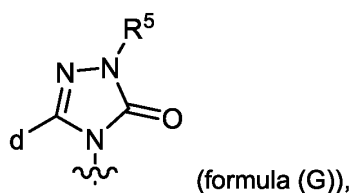
R⁶ is H or C₁-C₆ alkyl;



(formula (Z)) represents formula (E), (G), (J), (K), (L) or (M)



(formula (E)),



wherein

each d represents the point of attachment to the bridgehead carbon bonded to T;
in formulae (E) both of X and Y are CR⁵, or one of X and Y is CR⁵ and the other is N;

in formula (J), X and Y are both N;

each ring A is a 4-8 membered carbocyclic ring or 3-7 membered heterocyclic ring,

each R⁵ is independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, halogen, haloC₁-C₆ alkyl, cyano, hydroxy, hydroxy C₁-C₆ alkyl, amino, mono- or di(C₁-C₆ alkyl) amino, C₃-C₆ cycloalkyl, haloC₃-C₆ cycloalkyl, phenyl or 5-6 membered heteroaryl, wherein each alkyl and cycloalkyl is optionally substituted with 1-3 of hydroxy, C₁-C₃ alkyl, C₁-C₃ alkoxy, cyano, amino, or mono- or di(C₁-C₃) alkyl amino, and each 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;

R³⁰ represents

-NR⁷NR⁸ or R³¹,

R³¹ represents

(i) 5-7 membered heteroaryl, or

(ii) a 3-8 membered monocyclic heterocyclyl group connected to the tricyclic ring system via a carbon atom, wherein the heterocyclyl group is saturated or unsaturated and optionally fused to an aromatic or non-aromatic ring containing 3-6 ring members of which 1 or 2 are optionally nitrogen, oxygen or sulfur atoms and the remainder carbons, or with a carbon atom from the monocyclic heterocyclyl group and additional carbon or nitrogen atoms, forms a spirocyclic ring system having up to 10 total ring members, wherein the ring members are carbons or nitrogens, and wherein each heteroaryl and heterocyclyl group within R³¹ is optionally substituted, on an aromatic or non-aromatic portion, with 1-4 R³⁹ groups, wherein each R³⁹ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, hydroxy, oxo, halogen, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, amino, mono- or di-(C₁-C₆ alkyl) amino, or phenyl, phenyl(C₁-C₃ alkanoyl), 5-7 membered heterocyclyl, or 5-6 membered heteroaryl where each phenyl, 5-7 membered heterocyclyl and 5-6 membered heteroaryl is optionally substituted with C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, hydroxy, cyano, amino, or mono- or di(C₁-C₃ alkyl)amino;

R⁷ represents H or C₁-C₃ alkyl;

R⁸ represent (i) H, (ii) C₁-C₆ alkyl optionally substituted with a 5-8 membered heterocyclyl, (iii) C₃-C₆ cycloalkyl or (iv) C₃-C₆ cycloalkyl(C₁-C₃ alkyl); or

R⁷ and R⁸ together with the nitrogen to which they are attached form ring Q, wherein ring Q is a 3-8 membered monocyclic heterocyclyl group containing one or two ring nitrogens, wherein the heterocyclyl group

is optionally fused to an aromatic or non-aromatic ring containing 3-6 ring members of which 1 or 2 are optionally nitrogen, oxygen or sulfur atoms and the remainder carbons, or

with a carbon atom from the monocyclic heterocyclyl group and additional carbon or nitrogen atoms, forms a spirocyclic ring system having up to 10 total ring members, wherein the ring members are carbons or nitrogens (the spirocenter of the spirocyclic system is a carbon atom of the 3-7 membered monocyclic heterocyclyl group), and

wherein each ring Q is optionally substituted, on an aromatic or non-aromatic portion, with 1-4 R⁹ groups, wherein each R⁹ is independently C₁-C₆ alkyl, C₁-

C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, hydroxy, oxo, halogen, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, amino, mono- or di-(C₁-C₆ alkyl) amino, or phenyl, phenyl(C₁-C₃ alkanoyl), 5-7 membered heterocyclyl, or 5-6 membered heteroaryl where each phenyl, 5-7 membered heterocyclyl and 5-6 membered heteroaryl is optionally substituted with C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, hydroxy, cyano, amino, or mono- or di(C₁-C₃ 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., -CH₂-CH₂-), 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 -NH₂.

[0027] The term "acetyl" refers to -C(O)CH₃.

[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 C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, C₁₀, C₁₁ and C₁₂ 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 C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, C₁₀, C₁₁ and C₁₂ 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 C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, C₁₀, C₁₁ and C₁₂ 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 -O(C₁-C₆ 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 C₃, C₄, C₅, C₆, 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-C₆)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 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 $-\text{C}(\text{O})-$, N, NR^4 , 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 indoliny, 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 acridiny, azociny, 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, benzimidazoliny, carbazolyl, 4aH-carbazolyl, carboliny, chromanyl, chromenyl, cinnoliny, furanyl, furazanyl, imidazoliny, imidazolyl, 1H-indazolyl,

indolenyl, indolinyl, indoliziny, 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-quinoliziny, quinoxalyl, 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 xanthylenyl.

[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.

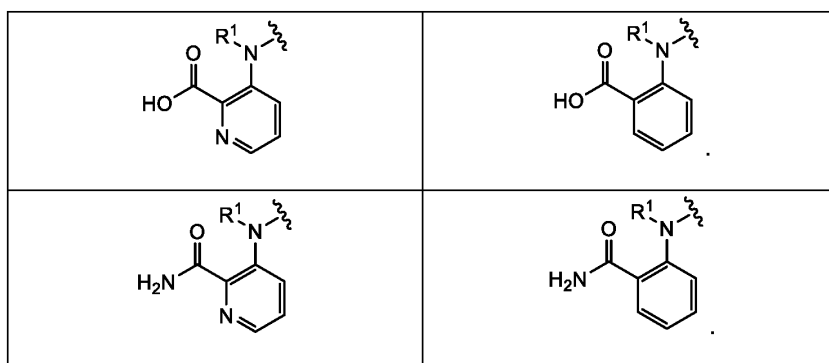
[0043] The term "halogen" or "halo" as employed herein refers to chlorine, bromine, fluorine, or iodine.

[0044] The term "haloalkyl", e.g., haloC₁-C₆ alkyl, refers to an alkyl chain in which one or more hydrogens have been replaced by a halogen. Representative haloalkyls are trifluoromethyl, difluoromethyl, fluorochloromethyl, chloromethyl, fluoromethyl, trifluoroethyl, pentafluoroethyl (perfluoroethyl), heptafluoropropyl (perfluoropropyl), tetrafluorocyclopropyl, and pentafluorocyclopropyl (perfluorocyclopropyl).

[0045] The term "halocycloalkyl", e.g., haloC₃-C₆ cycloalkyl, , refers to a cycloalkyl group in which one or more hydrogens have been replaced by a halogen. Representative halocycloalkyls are 2,2-difluorocyclopropyl, 2,2,3,3-tetrafluorocyclopropyl, 2,3,4-trifluorocyclobutyl, and 2,4-difluorocyclopentyl.

[0046] The term "hydroxyalkyl" refers to -alkylene-OH.

[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 .

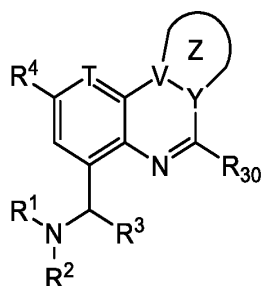
[0050] As used herein, a “therapeutically effective amount” of a compound is an amount that is sufficient to ameliorate or in some manner reduce a symptom or stop or reverse progression of a condition, or negatively modulate or inhibit the activity of PI3K α . Such amount may be administered as a single 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 R¹²;

each R¹² is independently C₁-C₄ alkyl, -OR^A, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, -C(O)N(R^B)₂, cyano, or halogen;

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;

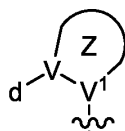
and

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

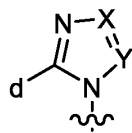
R⁴ is H, C₁-C₃ alkyl, C₃-C₆ cycloalkyl, C₁-C₃ alkenyl, C₂-C₃ alkynyl, or C₅-C₆ cycloalkenyl, cyano, or halo, wherein each C₁-C₃ alkyl and C₃-C₆ cycloalkyl is optionally substituted with 1-5 halo groups;

T is N or CR⁶ wherein

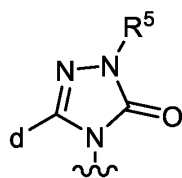
R⁶ is H or C₁-C₆ alkyl;



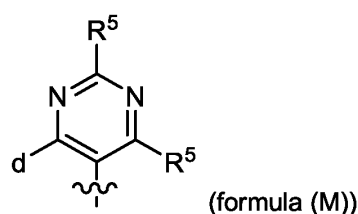
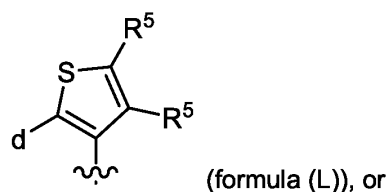
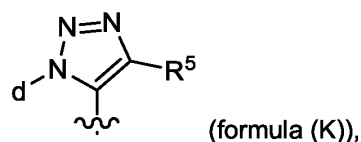
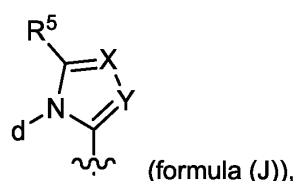
(formula (Z)) represents formula (E), (G), (J), (K), (L) or (M)



(formula (E)),



(formula (G)),



wherein

each d represents the point of attachment to the bridgehead carbon bonded to T;
in formulae (E) both of X and Y are CR⁵, or one of X and Y is CR⁵ and the other is N;

in formula (J), X and Y are both N;

each ring A is a 4-8 membered carbocyclic ring or 3-7 membered heterocyclic ring,

each R⁵ is independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, halogen, haloC₁-C₆ alkyl, cyano, hydroxy, hydroxy C₁-C₆ alkyl, amino, mono- or di(C₁-C₆ alkyl) amino, C₃-C₆ cycloalkyl, haloC₃-C₆ cycloalkyl, phenyl or 5-6 membered heteroaryl, wherein each alkyl and cycloalkyl is optionally substituted with 1-3 of hydroxy, C₁-C₃ alkyl, C₁-C₃ alkoxy, cyano, amino, or mono- or di(C₁-C₃) alkyl amino, and each 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;

R³⁰ represents

-NR⁷NR⁸ or R³¹,

R³¹ represents

(i) 5-7 membered heteroaryl, or

- (ii) a 3-8 membered monocyclic heterocyclyl group connected to the tricyclic ring system via a carbon atom, wherein the heterocyclyl group is saturated or unsaturated and optionally fused to an aromatic or non-aromatic ring containing 3-6 ring members of which 1 or 2 are optionally nitrogen, oxygen or sulfur atoms and the remainder carbons, or with a carbon atom from the monocyclic heterocyclyl group and additional carbon or nitrogen atoms, forms a spirocyclic ring system having up to 10 total ring members, wherein the ring members are carbons or nitrogens, and wherein each heteroaryl and heterocyclyl group within R³¹ is optionally substituted, on an aromatic or non-aromatic portion, with 1-4 R³⁹ groups, wherein each R³⁹ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, hydroxy, oxo, halogen, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, amino, mono- or di-(C₁-C₆ alkyl) amino, or phenyl, phenyl(C₁-C₃ alkanoyl), 5-7 membered heterocyclyl, or 5-6 membered heteroaryl where each phenyl, 5-7 membered heterocyclyl and 5-6 membered heteroaryl is optionally substituted with C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, hydroxy, cyano, amino, or mono- or di-(C₁-C₃ alkyl)amino;

R⁷ represents H or C₁-C₃ alkyl;

R⁸ represent H, C₁-C₆ alkyl optionally substituted with a 5-8 membered heterocyclyl, C₃-C₆ cycloalkyl or C₃-C₆ cycloalkyl(C₁-C₃ alkyl); or

R⁷ and R⁸ together with the nitrogen to which they are attached form ring Q, wherein ring Q is a 3-8 membered monocyclic heterocyclyl group containing one or two ring nitrogens and only nitrogen heteroatoms, wherein the heterocyclyl group is optionally fused to an aromatic or non-aromatic ring containing 3-6 ring members of which 1 or 2 are optionally nitrogen, oxygen or sulfur atoms and the remainder carbons, or with a carbon atom from the monocyclic heterocyclyl group and additional carbon or nitrogen atoms, forms a spirocyclic ring system having up to 10 total ring members, wherein the ring members are carbons or nitrogens (the spirocenter of the spirocyclic system is a carbon atom of the 3-7 membered monocyclic heterocyclyl group), and wherein each ring Q is optionally substituted, on an aromatic or non-aromatic portion, with 1-4 R⁹ groups, wherein each R⁹ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, hydroxy, oxo, halogen, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, amino, mono- or di-(C₁-C₆ alkyl) amino, or phenyl, phenyl(C₁-C₃ alkanoyl), 5-7 membered heterocyclyl, or 5-6 membered heteroaryl where each phenyl, 5-7 membered heterocyclyl and 5-6 membered

heteroaryl is optionally substituted with C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, hydroxy, cyano, amino, or mono- or di(C₁-C₃ alkyl)amino.

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

[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, formula (Z) represents formula (K).

[0058] In certain embodiments of formula (I) as otherwise described herein, formula (Z) represents formula (L).

[0059] In certain embodiments of formula (I) as otherwise described herein, formula (Z) represents formula (M).

[0060] In certain embodiments of formula (I) as otherwise described herein, T represents CR⁶.

[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, wherein R² is phenyl, pyridinyl, thienyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, pyrazinyl, pyridazinyl or pyrimidinyl, each of which is optionally substituted with 1-5 R¹².

[0063] In certain embodiments of formula (I) as otherwise described herein, R² is phenyl or pyridinyl, each of which is optionally substituted with 1-5 R¹².

[0064] 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 R¹² groups.

[0065] 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 R¹² groups.

[0066] 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 R¹² groups, and at least one R¹² group is -C(O)OR^A.

[0067] 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 R¹² groups, and at least one R¹² group is -C(O)OR^A.

[0068] 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, i.e., ortho, to the point of attachment of R² to the nitrogen atom to which R² is attached.

[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 R¹² groups, and at least one R¹² 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.

[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 R¹² groups, and at least one R¹² 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.

[0071] 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.

[0072] In certain embodiments of formula (I) as otherwise described herein, R² is phenyl optionally substituted with 1, 2, 3 or 4 R¹² groups.

[0073] In certain embodiments of formula (I) as otherwise described herein, R² is pyridinyl optionally substituted with 1, 2, 3 or 4 R¹² groups.

[0074] In certain embodiments of formula (I) as otherwise described herein, R² is thienyl optionally substituted with 1, 2, 3 or 4 R¹² groups.

[0075] In certain embodiments of formula (I) as otherwise described herein, R² is thiazolyl optionally substituted with 1, 2, 3 or 4 R¹² groups.

[0076] In certain embodiments of formula (I) as otherwise described herein, R² is oxazolyl optionally substituted with 1, 2, 3 or 4 R¹² groups.

[0077] In certain embodiments of formula (I) as otherwise described herein, R² is isoxazolyl optionally substituted with 1, 2, 3 or 4 R¹² groups.

[0078] In certain embodiments of formula (I) as otherwise described herein, R² is imidazolyl optionally substituted with 1, 2, 3 or 4 R¹² groups.

[0079] In certain embodiments of formula (I) as otherwise described herein, R² is pyrazolyl optionally substituted with 1, 2, 3 or 4 R¹² groups.

[0080] In certain embodiments of formula (I) as otherwise described herein, R² is pyrazinyl optionally substituted with 1, 2, 3 or 4 R¹² groups.

[0081] In certain embodiments of formula (I) as otherwise described herein, R² is pyridazinyl optionally substituted with 1, 2, 3 or 4 R¹² groups.

[0082] In certain embodiments of formula (I) as otherwise described herein, R² is pyrimidinyl optionally substituted with 1, 2, 3 or 4 R¹² groups.

[0083] In certain embodiments of formula (I) as otherwise described herein, R² is optionally substituted with one -C(O)OR^A.

[0084] In certain embodiments of formula (I) as otherwise described herein, R⁴ is hydrogen, fluoro, chloro, bromo, methyl, methoxy, ethyl, ethoxy, cyclopropyl, trifluoromethyl or cyano.

[0085] In certain embodiments of formula (I) as otherwise described herein, R⁴ is hydrogen, methyl, ethyl, or cyano.

[0086] In certain embodiments of formula (I) as otherwise described herein, R⁴ is methoxy.

[0087] In certain embodiments of formula (I) as otherwise described herein, R⁴ is fluoro, chloro, or bromo.

[0088] In certain embodiments of formula (I) as otherwise described herein, R⁴ is hydrogen.

[0089] In certain embodiments of formula (I) as otherwise described herein, R⁴ is fluoro.

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

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

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

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

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

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

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

[0097] In certain embodiments of formula (I) as otherwise described herein, if more than one R⁵ is present, one R⁵ is hydrogen and the other R⁵ is hydrogen, 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.

[0098] In certain embodiments of formula (I) as otherwise described herein, if more than one R⁵ is present, one R⁵ is hydrogen and the other R⁵ is hydrogen, 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.

[0099] In certain embodiments of formula (I) as otherwise described herein, when one R⁵ is present, R⁵ is hydrogen, 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.

[00100] In certain embodiments of formula (I) as otherwise described herein, when one R⁵ is present, R⁵ is hydrogen and the other 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.

[00101] In certain embodiments of formula (I) as otherwise described herein, when one R⁵ is present, R⁵ is hydrogen, halogen, hydroxy, cyano or amino.

[00102] In certain embodiments of formula (I) as otherwise described herein, if more than one R⁵ is present, one R⁵ is hydrogen and the other R⁵ is hydrogen, halogen, hydroxy, cyano or amino.

[00103] In certain embodiments of formula (I) as otherwise described herein, R² is optionally substituted phenyl.

[00104] In certain embodiments of formula (I) as otherwise described herein, R² is optionally substituted pyridinyl.

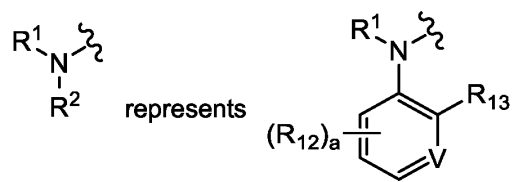
[00105] In certain embodiments of formula (I) as otherwise described herein, R⁷ is hydrogen and R⁸ represents hydrogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl or C₃-C₆ cycloalkyl(C₁-C₃ alkyl).

[00106] In certain embodiments of formula (I) as otherwise described herein, R⁷ and R⁸ together with the nitrogen to which they are attached form ring Q, wherein ring Q is

a 3-7 membered monocyclic heterocyclyl group containing one or two ring nitrogens and, in certain embodiments, only nitrogen heteroatoms, and the heterocyclyl group is optionally substituted with 1-4 R⁹ groups, wherein each R⁹ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, hydroxy, oxo, halogen, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, amino, mono- or di-(C₁-C₆ alkyl) amino, or phenyl or phenyl(C₁-C₃ alkanoyl) where each phenyl is optionally

substituted with C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, hydroxy, cyano, amino, or mono- or di(C₁-C₃ alkyl)amino.

[00107] In certain embodiments of formula (I) as otherwise described herein, the group



wherein

a is 0, 1, 2 or 3;

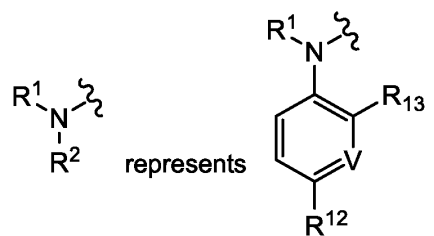
V is CR¹⁴ or N;

each R¹² is independently C₁-C₄ alkyl, -OR^A, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, -C(O)N(R^B)₂, cyano, or halogen;

R¹³ is (i) cyano, (ii) tetrazolyl, (iii) -C(O)OR^A where R^A is H, C₁-C₆ alkyl, or C₃-C₆ cycloalkyl, or (iv) -C(O)N(R^B)₂ where R^B is H, -OH, C₁-C₆ alkyl, C₁-C₆ alkoxy or C₃-C₆ cycloalkyl; and

R₁₄ is hydrogen, cyano, halogen, hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkyl, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, or -C(O)N(R^B)₂.

[00108] In other certain embodiments of formula (I) as otherwise described herein, the group



wherein

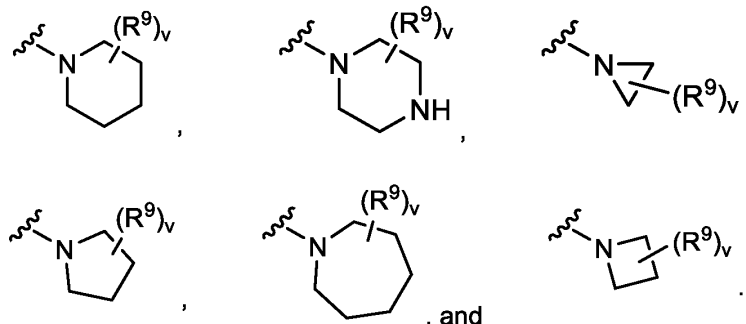
V is CR¹⁴ or N;

each R¹² is independently C₁-C₄ alkyl, -OR^A, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, -C(O)N(R^B)₂, cyano, or halogen;

R¹³ is (i) cyano, (ii) tetrazolyl, (iii) -C(O)OR^A where R^A is H, C₁-C₆ alkyl, or C₃-C₆ cycloalkyl, or (iv) -C(O)N(R^B)₂ where R^B is H, -OH, C₁-C₆ alkyl, C₁-C₆ alkoxy or C₃-C₆ cycloalkyl; and

R₁₄ is hydrogen, cyano, halogen, hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkyl, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, or -C(O)N(R^B)₂.

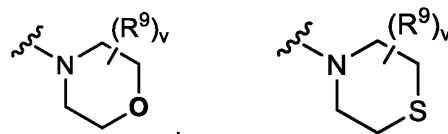
[00109] In certain embodiments of formula (I) as otherwise described herein, R^7 and R^8 together with the nitrogen to which they are attached form ring Q, wherein ring Q represents a nitrogen-containing ring selected from



wherein each v represents 0, 1, 2, 3 or 4.

[00110] In certain embodiments of formula (I) as otherwise described herein, nitrogen-containing ring Q contains only nitrogen atoms.

[00111] In certain embodiments of formula (I) as otherwise described herein, nitrogen-containing ring Q contains one nitrogen atom and one other heteroatom selected from oxygen and sulfur. Examples of such groups include



wherein each R^{39} is defined as for formula (I) and each v represents 0, 1, 2, 3 or 4.

[00112] In certain embodiments, the nitrogen-containing ring is substituted independently with 1, 2 or 3 halogens. In certain embodiments, the halogens are independently fluorine atoms or chlorine atoms.

[00113] In certain embodiments, the nitrogen-containing ring is substituted with phenyl or phenyl(C_1 - C_3 alkanoyl) where each phenyl is optionally substituted with C_1 - C_3 alkyl, C_1 - C_3 alkoxy, halogen, hydroxy, cyano, amino, or mono- or di(C_1 - C_3 alkyl)amino.

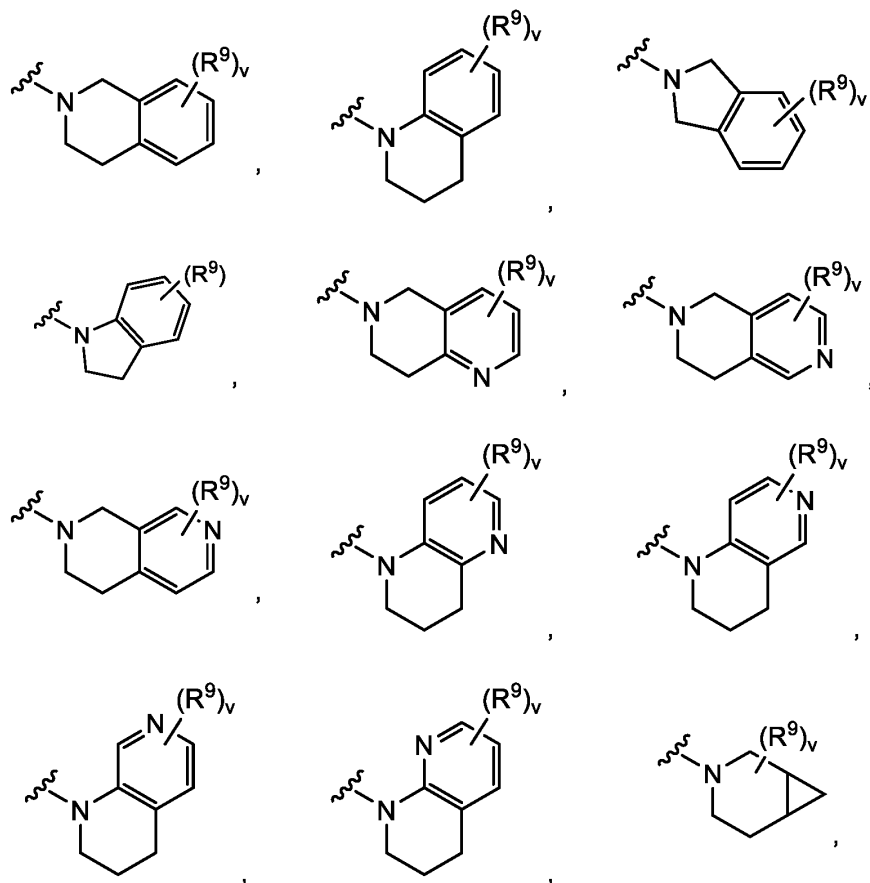
[00114] In certain embodiments of formula (I) as otherwise described herein, R^7 and R^8 together with the nitrogen to which they are attached form ring Q, wherein ring Q is

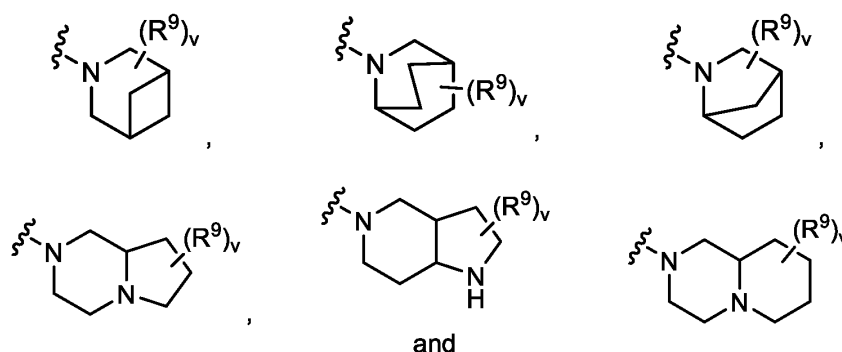
a 3-7 membered monocyclic heterocyclyl group containing one or two ring nitrogens and, optionally, one or two additional heteroatoms selected from oxygen and sulfur, and

the heterocyclyl group is fused to an aromatic or non-aromatic ring containing 3-6 ring members of which 1 or 2 are optionally nitrogen atoms and the remainder carbons, wherein

the fused heterocyclyl group is optionally substituted, on an aromatic or non-aromatic portion, with 1-4 R^9 groups, wherein each R^9 is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, cyano, hydroxy, oxo, halogen, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, amino, mono- or di-(C_1 - C_6 alkyl) amino, or phenyl or phenyl(C_1 - C_3 alkanoyl) where each phenyl is optionally substituted with C_1 - C_3 alkyl, C_1 - C_3 alkoxy, halogen, hydroxy, cyano, amino, or mono- or di(C_1 - C_3 alkyl)amino.

[00115] In certain embodiments of formula (I) as otherwise described herein, R^7 and R^8 together with the nitrogen to which they are attached form ring Q, wherein ring Q represents a fused bicyclic group selected from





wherein each v represents 0, 1, 2, 3 or 4 and the R^9 groups can be on either ring.

[00116] In certain embodiments, the fused bicyclic group is substituted independently with 1, 2, 3 or 4 of C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_3 haloalkyl or halogen.

[00117] In certain embodiments, the fused bicyclic group is substituted independently with 1, 2, 3 or 4 halogens. In certain embodiments, the halogens are independently fluorine atoms or chlorine atoms. In other embodiments, the halogens are fluorine atoms.

[00118] In other embodiments, the fused bicyclic group is substituted with phenyl or phenyl(C_1 - C_3 alkanoyl) where each phenyl is optionally substituted with C_1 - C_3 alkyl, C_1 - C_3 alkoxy, halogen, hydroxy, cyano, amino, or mono- or di(C_1 - C_3 alkyl)amino.

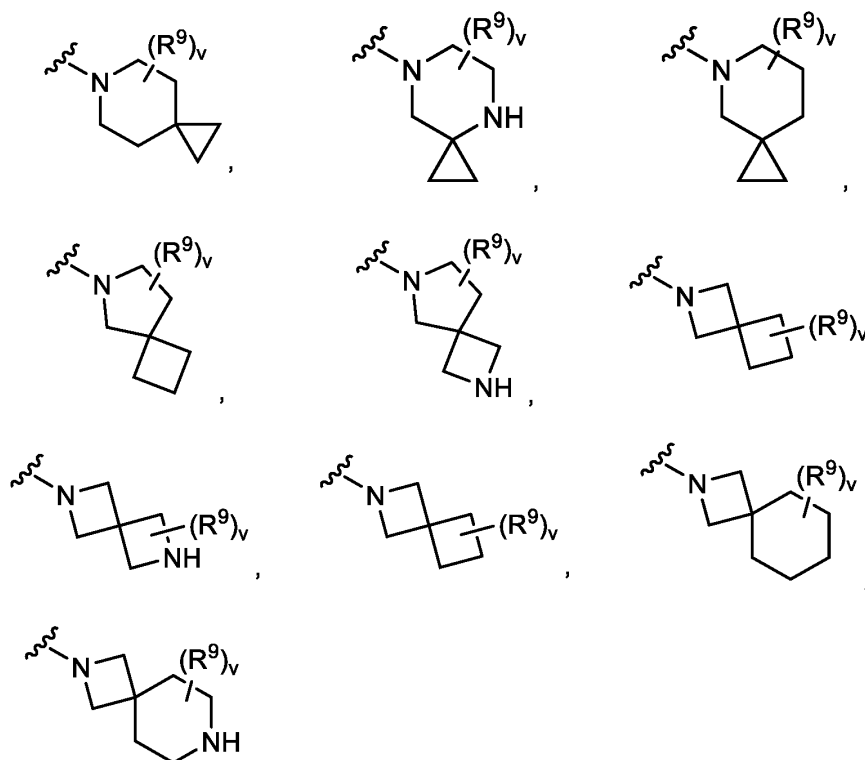
[00119] In certain embodiments of formula (I) as otherwise described herein, R^7 and R^8 together with the nitrogen to which they are attached form a 3-7 membered monocyclic heterocyclyl group containing one or two ring nitrogens and, in certain embodiments, only nitrogen heteroatoms, and

the heterocyclyl group forms a spirocyclic ring system having up to 10 total ring members with a carbon atom from the monocyclic heterocyclyl group and additional carbon or nitrogen atoms, wherein

wherein the spirocyclic ring system is optionally substituted with 1-4 R^9 groups, wherein each R^9 is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, cyano, hydroxy, oxo, halogen, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, amino, mono- or di-(C_1 - C_6 alkyl) amino, or phenyl or phenyl(C_1 - C_3 alkanoyl) where each phenyl is optionally substituted with C_1 - C_3 alkyl, C_1 - C_3 alkoxy, halogen, hydroxy, cyano, amino, or mono- or di(C_1 - C_3 alkyl)amino.

[00120] In certain embodiments of formula (I) as otherwise described herein, R^7 and R^8 together with the nitrogen to which they are attached represent a spirocyclic ring system having one or two nitrogen atoms and up to 10 total ring members. The spirocyclic ring system is

optionally substituted with up to 4 R^9 groups. Examples of such optionally substituted spirocyclic ring systems are



wherein each v represents 0, 1, 2, 3 or 4 and the R^9 groups can be on either ring.

[00121] In certain embodiments, the spirocyclic ring system is substituted independently with 1, 2, 3 or 4 of C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_3 haloalkyl or halogen.

[00122] In certain embodiments, the spirocyclic ring system is substituted independently with 1, 2, 3 or 4 halogens. In certain embodiments, the halogens are independently fluorine atoms or chlorine atoms. In other embodiments, the halogens are fluorine atoms.

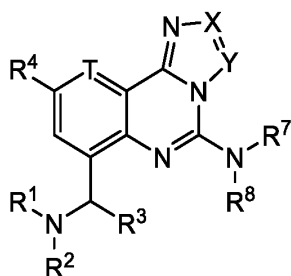
[00123] In certain embodiments, the spirocyclic ring system is substituted with phenyl or phenyl(C_1 - C_3 alkanoyl) where each phenyl is optionally substituted with C_1 - C_3 alkyl, C_1 - C_3 alkoxy, halogen, hydroxy, cyano, amino, or mono- or di(C_1 - C_3 alkyl)amino.

[00124] In certain embodiments of formula (I) as otherwise described herein, T is N.

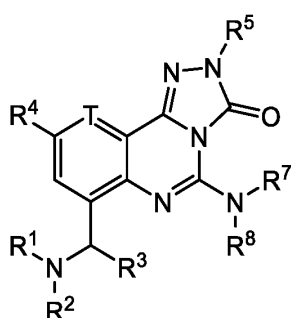
[00125] In certain embodiments of formula (I) as otherwise described herein, T is CR^6 and R^6 is H or C_1 - C_2 alkyl, particularly methyl.

[00126] In certain embodiments of formula (I) as otherwise described herein, T is CR^6 and R^6 is H.

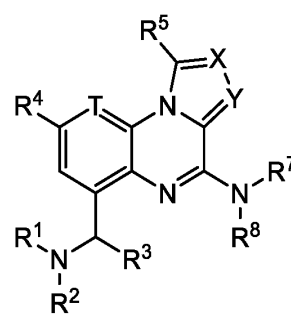
[00127] In certain embodiments of formula (I) as otherwise described herein, the compound is of formula (II-e), (II-g), (II-j), (II-k), (II-l), or (II-m):



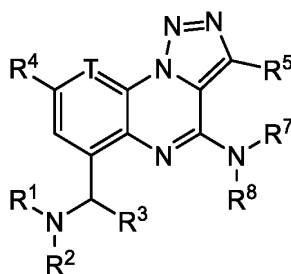
(II-e)



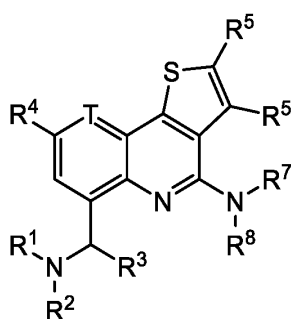
(II-g)



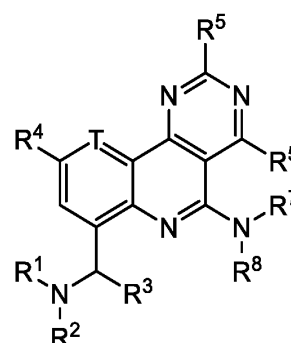
(II-j)



(II-k)



(II-l)



(II-m)

or a pharmaceutically acceptable salt thereof.

[00128] In certain embodiments of formula (II-e), (II-g), (II-j), (II-k), (II-l), and (II-m) as otherwise described herein,

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 R¹²;

each R¹² is independently C₁-C₄ alkyl; -OR^A, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, -C(O)N(R^B)₂, cyano, or halogen;

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

[00129] In certain embodiments of formula (II-e), (II-g), (II-j), (II-k), (II-l), and (II-m) as otherwise described herein, T is N.

[00130] In certain embodiments of formula (II-e), (II-g), (II-j), (II-k), (II-l), and (II-m) as otherwise described herein, T is CR⁶ and R⁶ is H or C₁-C₂ alkyl, particularly methyl.

[00131] In certain embodiments of formula (II-e), (II-g), (II-j), (II-k), (II-l), and (II-m) as otherwise described herein, T is CR⁶ and R⁶ is H.

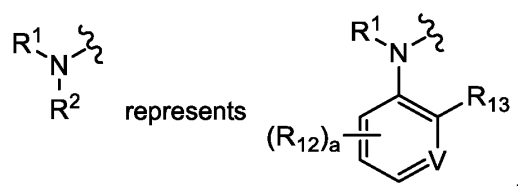
[00132] In certain embodiments of formula (II-e), (II-g), (II-j), (II-k), (II-l), and (II-m) as otherwise described herein, R³ is C₁-C₃ alkyl.

[00133] In certain embodiments of formula (II-e), (II-g), (II-j), (II-k), (II-l), and (II-m) as otherwise described herein, R³ is methyl.

[00134] In certain embodiments of formula (II-e), (II-g), (II-j), (II-k), (II-l), and (II-m) as otherwise described herein, R⁴ is H, C₁-C₃ alkyl, C₃-C₄ cycloalkyl or cyano.

[00135] In certain embodiments of formula (II-e), (II-g), (II-j), (II-k), (II-l), and (II-m) as otherwise described herein, R² is optionally substituted with one -C(O)OR^A.

[00136] In certain embodiments of formula (II-e), (II-g), (II-j), (II-k), (II-l), and (II-m) as otherwise described herein, the group



wherein

a is 0, 1, 2 or 3;

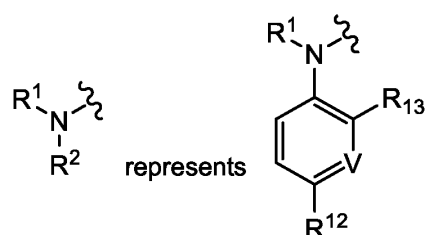
V is CR¹⁴ or N;

each R¹² is independently C₁-C₄ alkyl, -OR^A, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, -C(O)N(R^B)₂, cyano, or halogen;

R¹³ is (i) cyano, (ii) tetrazolyl, (iii) -C(O)OR^A where R^A is H, C₁-C₆ alkyl, or C₃-C₆ cycloalkyl, or (iv) -C(O)N(R^B)₂ where R^B is H, -OH, C₁-C₆ alkyl, C₁-C₆ alkoxy or C₃-C₆ cycloalkyl; and

R¹⁴ is hydrogen, cyano, halogen, hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkyl, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, or -C(O)N(R^B)₂.

[00137] In certain embodiments of formula (II-e), (II-g), (II-j), (II-k), (II-l), and (II-m) as otherwise described herein, the group



wherein

V is CR¹⁴ or N;

each R¹² is independently C₁-C₄ alkyl, -OR^A, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, -C(O)N(R^B)₂, cyano, or halogen;

R¹³ is (i) cyano, (ii) tetrazolyl, (iii) -C(O)OR^A where R^A is H, C₁-C₆ alkyl, or C₃-C₆ cycloalkyl, or (iv) -C(O)N(R^B)₂ where R^B is H, -OH, C₁-C₆ alkyl, C₁-C₆ alkoxy or C₃-C₆ cycloalkyl; and

R₁₄ is hydrogen, cyano, halogen, hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkyl, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, or -C(O)N(R^B)₂.

[00138] In certain embodiments of formula (II-e), (II-g), (II-j), (II-k), (II-l), and (II-m) as otherwise described herein, R⁷ is hydrogen and R⁸ represents hydrogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl or C₃-C₆ cycloalkyl(C₁- In certain embodiments of formula (II-e), (II-g), (II-j), (II-k), (II-l), and (II-m) as otherwise described herein, R⁷ and R⁸ together with the nitrogen to which they are attached form ring Q, and ring Q is a C₁-C₆ heterocyclyl

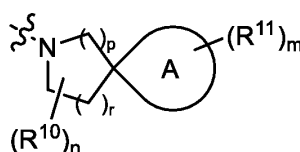
[00139] In certain embodiments of formula (II-e), (II-g), (II-j), (II-k), (II-l), and (II-m) as otherwise described herein, R⁷ and R⁸ together with the nitrogen to which they are attached form ring Q, and ring Q is aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, or azepanyl, each of which is optionally substituted with 1-2 R⁹ groups, wherein each R⁹ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, hydroxy, oxo, halogen, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, amino, mono- or di-(C₁-C₆ alkyl) amino, phenyl, 5-7 membered heterocyclyl, or 5-6 membered heteroaryl where each phenyl, 5-7 membered heterocyclyl and 5-6 membered heteroaryl is optionally substituted with C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, hydroxy, cyano, amino, or mono- or di(C₁-C₃ alkyl)amino.

[00140] In certain embodiments of formula (II-e), (II-g), (II-j), (II-k), (II-l), and (II-m) as otherwise described herein, R⁷ and R⁸ together with the nitrogen to which they are attached form ring Q, and ring Q is aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, or azepanyl, each of which is optionally substituted with 1, 2, 3 or 4 halogens.

[00141] In certain embodiments of formula (II-e), (II-g), (II-j), (II-k), (II-l), and (II-m) as otherwise described herein, R⁷ and R⁸ together with the nitrogen to which they are attached form ring Q, and ring Q is a 5-6 membered monocyclic heterocyclyl group containing one or

two ring nitrogens and, in certain embodiments, only nitrogen heteroatoms, and the heterocyclyl group is fused to an aromatic or non-aromatic ring containing 3-6 ring members of which 1 or 2 are optionally nitrogen atoms and the remainder carbons, and the fused ring system is optionally substituted, on either ring, with 1-4 R^9 groups, wherein each R^9 is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, cyano, hydroxy, oxo, halogen, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, amino, or mono- or di- $(C_1$ - C_6 alkyl) amino.

[00142] In certain embodiments of formula (II-e), (II-g), (II-j), (II-k), (II-l), and (II-m) as otherwise described herein, wherein R^7 and R^8 together with the nitrogen to which they are attached form ring Q, where ring Q is a group of the formula:



wherein

each ring A is a 3-6 membered carbocyclic ring or 3-6 membered heterocyclic ring,

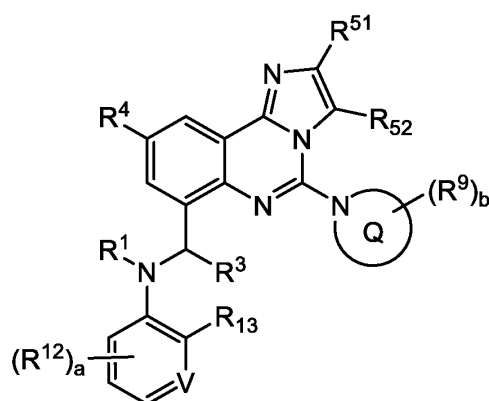
m is 0, 1, 2, 3, or 4;

n is 0, 1 or 2;

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

each R^{10} and R^{11} 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.

[00143] In certain embodiments of formula (I) as otherwise described herein, the compound is of formula (III):



(III)

or a pharmaceutically acceptable salt or deuterated form thereof, wherein:

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

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-C₃ 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;

a is 0, 1, 2 or 3;

V is CR¹⁴ or N;

each R¹² is independently C₁-C₄ alkyl, -OR^A, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, -C(O)N(R^B)₂, cyano, or halogen;

R¹³ is (i) cyano, (ii) tetrazolyl, (iii) -C(O)OR^A where R^A is H, C₁-C₆ alkyl, or C₃-C₆ cycloalkyl, or (iv) -C(O)N(R^B)₂ where R^B is H, -OH, C₁-C₆ alkyl, C₁-C₆ alkoxy or C₃-C₆ cycloalkyl;

R¹⁴ is hydrogen, cyano, halogen, hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkyl, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, or -C(O)N(R^B)₂;

Q represents a 4-8 membered saturated or unsaturated monocyclic, bicyclic or polycyclic heterocyclyl group having 0, 1 or 2 additional ring heteroatoms selected from oxygen and nitrogen;

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

each R⁹ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, hydroxy, oxo, halogen, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, amino, mono- or di-(C₁-C₆ alkyl) amino, or phenyl, phenyl(C₁-C₃ alkanoyl), 5-7 membered heterocyclyl, or 5-6 membered heteroaryl where each phenyl, 5-7 membered heterocyclyl and 5-6

membered heteroaryl is optionally substituted with C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, hydroxy, cyano, amino, or mono- or di(C₁-C₃ alkyl)amino; and

R⁵¹ and R⁵² independently represent hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, halogen, haloC₁-C₆ alkyl, cyano, hydroxy, hydroxy C₁-C₆ alkyl, amino, mono- or di(C₁-C₆ alkyl) amino, C₃-C₆ cycloalkyl, haloC₃-C₆ cycloalkyl, phenyl or 5-6 membered heteroaryl, wherein each alkyl and cycloalkyl is optionally substituted with 1-3 of hydroxy, C₁-C₃ alkyl, C₁-C₃ alkoxy, cyano, amino, or mono- or di(C₁-C₃) alkyl amino, and each 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.

[00144] In certain embodiments of formula (III) R¹ is H or CH₃ (Embodiment 3-1).

[00145] In certain embodiments of formula (III) or Embodiment 3-1, R³ is C₁-C₃ alkyl, wherein the alkyl group is unsubstituted, substituted with 1-5 halo groups, or perfluorinated (Embodiment 3-2).

[00146] In certain embodiments of formula (III) or Embodiment 3-1, R³ is methyl (Embodiment 3-3).

[00147] In certain embodiments of formula (III) or Embodiments 3-1 to 3-3, R⁴ is hydrogen (Embodiment 3-4).

[00148] In certain embodiments of formula (III) or Embodiments 3-1 to 3-3, R⁴ is methyl (Embodiment 3-5).

[00149] In certain embodiments of formula (III) or Embodiments 3-1 to 3-3, R⁴ is ethyl (Embodiment 3-5A).

[00150] In certain embodiments of formula (III) or Embodiments 3-1 to 3-3, R⁴ is cyclopropyl (Embodiment 3-5B).

[00151] In certain embodiments of formula (III) or Embodiments 3-1 to 3-3, R⁴ is methoxy (Embodiment 3-5C).

[00152] In certain embodiments of formula (III) or Embodiments 3-1 to 3-3, R⁴ is fluoro (Embodiment 3-6).

[00153] In certain embodiments of formula (III) or Embodiments 3-1 to 3-3, R⁴ is chloro (Embodiment 3-7).

[00154] In certain embodiments of formula (III) or Embodiments 3-1 to 3-3, R⁴ is bromo (Embodiment 3-8).

[00155] In certain embodiments of formula (III) or Embodiments 3-1 to 3-8, V is CR¹² (Embodiment 3-9).

[00156] In certain embodiments of formula (III) or Embodiments 3-1 to 3-8, V is N (Embodiment 3-10).

[00157] In certain embodiments of formula (III) or Embodiments 3-1 to 3-9, V is CH, a is 1, and R¹² is hydrogen, C₁-C₃ alkyl or halogen (Embodiment 3-11).

[00158] In certain embodiments of formula (III) or Embodiments 3-1 to 3-9, V is CH, a is 1, and R¹² is hydrogen, methyl, chloro, bromo or fluoro (Embodiment 3-12).

[00159] In certain embodiments of formula (III) or Embodiments 3-1 to 3-9, V is CH, a is 1, and R¹² is hydrogen (Embodiment 3-13).

[00160] In certain embodiments of formula (III) or Embodiments 3-1 to 3-9, V is CH, a is 1, and R¹² is chloro (Embodiment 3-14).

[00161] In certain embodiments of formula (III) or Embodiments 3-1 to 3-9, V is CH, a is 1, and R¹² is bromo (Embodiment 3-15).

[00162] In certain embodiments of formula (III) or Embodiments 3-1 to 3-9, V is CH, a is 1, and R¹² is methyl (Embodiment 3-15.1).

[00163] In certain embodiments of formula (III) or Embodiments 3-1 to 3-9, V is CH, a is 1, and R¹² is fluoro (Embodiment 3-16).

[00164] In certain embodiments of formula (III) or Embodiments 3-1 to 3-8 or 3-10, V is N, a is 1, and R¹² is hydrogen, C₁-C₃ alkyl or halogen (Embodiment 3-17).

[00165] In certain embodiments of formula (III) or Embodiments 3-1 to 3-8 or 3-10, V is N, a is 1, and R¹² is hydrogen, methyl, chloro, bromo or fluoro (Embodiment 3-18).

[00166] In certain embodiments of formula (III) or Embodiments 3-1 to 3-8 or 3-10, V is N, a is 1, and R¹² is hydrogen (Embodiment 3-19).

[00167] In certain embodiments of formula (III) or Embodiments 3-1 to 3-8 or 3-10, V is N, a is 1, and R¹² is chloro (Embodiment 3-20).

[00168] In certain embodiments of formula (III) or Embodiments 3-1 to 3-8 or 3-10, V is N, a is 1, and R¹² is bromo (Embodiment 3-21).

[00169] In certain embodiments of formula (III) or Embodiments 3-1 to 3-8 or 3-10, V is N, a is 1, and R¹² is methyl (Embodiment 3-21.1).

[00170] In certain embodiments of formula (III) or Embodiments 3-1 to 3-8 or 3-10, V is N, a is 1, and R¹² is fluoro (Embodiment 3-22).

[00171] In certain embodiments of formula (III) or Embodiments 3-1 to 3-22, R^{51} and R^{52} independently represent hydrogen, C_1 - C_3 alkyl, cyano, halogen, cyclopropyl or halo(C_1 - C_6)alkyl (Embodiment 3-23).

[00172] In certain embodiments of formula (III) or Embodiments 3-1 to 3-22, one of R^{51} and R^{52} is hydrogen and the other is methyl, ethyl, cyano, halogen, cyclopropyl or halo(C_1 - C_6)alkyl (Embodiment 3-24).

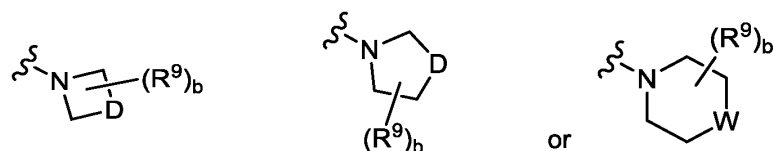
[00173] In certain embodiments of formula (III) or Embodiments 3-1 to 3-22, R^{51} is hydrogen and R^{52} is methyl, ethyl, cyano, halogen, cyclopropyl or halo(C_1 - C_6)alkyl (Embodiment 3-25).

[00174] In certain embodiments of formula (III) or Embodiments 3-1 to 3-22, R^{51} is hydrogen and R^{52} is methyl, ethyl, cyano, halogen, cyclopropyl, difluoromethyl or trifluoromethyl (Embodiment 3-26).

[00175] In certain embodiments of formula (III) or Embodiments 3-1 to 3-22, R^{52} is hydrogen and R^{51} is methyl, ethyl, cyano, halogen, cyclopropyl or halo(C_1 - C_6)alkyl (Embodiment 3-27).

[00176] In certain embodiments of formula (III) or Embodiments 3-1 to 3-22, R^{52} is hydrogen and R^{51} is methyl, ethyl, cyano, halogen, cyclopropyl, difluoromethyl or trifluoromethyl (Embodiment 3-28).

[00177] In certain embodiments of formula (III) or Embodiments 3-1 to 3-28, Q represents a group of the formula



wherein

each b is 0, 1 or 2;

D represents $C(R^{29})_2$,

W represents O, NR^{19} or $C(R^{29})_2$, and

R^{19} is hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, or amino- or mono- or di-(C_1 - C_6 alkyl) amino(C_1 - C_6 alkyl); and

each R^{29} is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, cyano, hydroxy, oxo, halogen, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, amino, mono- or di-(C_1 - C_6 alkyl) amino (Embodiment 3-29).

[00178] In certain embodiments of Embodiment 3-29, W is oxygen, b is 0 or 1, and R^9 is methyl or cyano (Embodiment 3-30).

[00179] In certain embodiments of Embodiment 3-29, W is oxygen and b is 0 (Embodiment 3-31).

[00180] In certain embodiments of Embodiment 3-29, D and W are $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, C_1 - C_2 alkyl, C_1 - C_2 alkoxy, cyclopropyl, cyano, hydroxy, halogen, halo C_1 - C_2 alkyl, hydroxy C_1 - C_2 alkyl, amino, mono- or di- $(C_1$ - C_2 alkyl) amino (Embodiment 3-32).

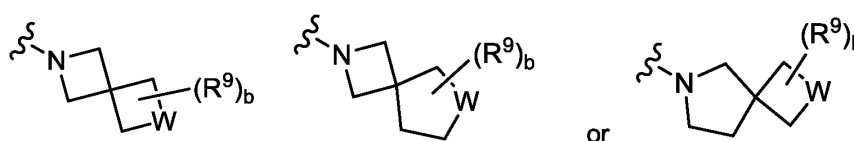
[00181] In certain embodiments of Embodiment 3-29, D and W are $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, methyl, methoxy, cyano, hydroxy, chloro, fluoro, amino, methylamino or dimethylamino (Embodiment 3-33).

[00182] In certain embodiments of Embodiment 3-29, D and W are $C(R^{29})_2$, b is 0, and each R^{29} is independently chloro or fluoro (Embodiment 3-34).

[00183] In certain embodiments of Embodiment 3-29, D and W are $C(R^{29})_2$, b is 0, and each R^{29} is fluoro (Embodiment 3-35).

[00184] In certain embodiments of Embodiment 3-29, D and W are $C(R^{29})_2$, b is 0, and each R^{29} is hydrogen (Embodiment 3-36).

[00185] In certain embodiments of formula (III) or Embodiments 3-1 to 3-28, Q represents a group of the formula



wherein

each b is 0, 1 or 2; and

W represents O, NR^{19} or $C(R^{29})_2$, wherein

R^{19} is hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, or amino- or mono- or di- $(C_1$ - C_6 alkyl) amino(C_1 - C_6 alkyl); and

each R^{29} is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, cyano, hydroxy, oxo, halogen, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, amino, mono- or di- $(C_1$ - C_6 alkyl) amino (Embodiment 3-37).

[00186] In certain embodiments of Embodiment 3-37, W is oxygen, b is 0 or 1, and R^9 is methyl or cyano (Embodiment 3-38).

[00187] In certain embodiments of Embodiment 3-37, W is oxygen and b is 0 (Embodiment 3-39).

[00188] In certain embodiments of Embodiment 3-37, W is $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, C_1 - C_2 alkyl, C_1 - C_2 alkoxy, cyclopropyl, cyano, hydroxy, halogen, halo C_1 - C_2 alkyl, hydroxy C_1 - C_2 alkyl, amino, mono- or di-(C_1 - C_2 alkyl) amino (Embodiment 3-40).

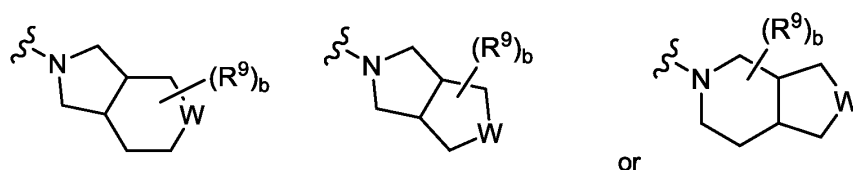
[00189] In certain embodiments of Embodiment 3-37, W is $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, methyl, methoxy, cyano, hydroxy, chloro, fluoro, amino, methylamino or dimethylamino (Embodiment 3-41).

[00190] In certain embodiments of Embodiment 3-37, W is $C(R^{29})_2$, b is 0, and each R^{29} is independently chloro or fluoro (Embodiment 3-42).

[00191] In certain embodiments of Embodiment 3-37, W is $C(R^{29})_2$, b is 0, and each R^{29} is fluoro (Embodiment 3-43).

[00192] In certain embodiments of Embodiment 3-37, W is $C(R^{29})_2$, b is 0, and each R^{29} is hydrogen (Embodiment 3-44).

[00193] In certain embodiments of formula (III) or Embodiments 3-1 to 3-28, Q represents a group of the formula



wherein

each b is 0, 1 or 2; and

W represents O, NR^{19} or $C(R^{29})_2$, wherein

R^{19} is hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, or amino- or mono- or di-(C_1 - C_6 alkyl) amino(C_1 - C_6 alkyl); and

each R^{29} is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, cyano, hydroxy, oxo, halogen, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, amino, mono- or di-(C_1 - C_6 alkyl) amino (Embodiment 3-45).

[00194] In certain embodiments of Embodiment 3-45, W is oxygen, b is 0 or 1, and R^9 is methyl, chloro, fluoro or cyano (Embodiment 3-46).

[00195] In certain embodiments of Embodiment 3-45, W is oxygen and b is 0 (Embodiment 3-47).

[00196] In certain embodiments of Embodiment 3-45, wherein W is $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, C_1 - C_2 alkyl, C_1 - C_2 alkoxy, cyclopropyl, cyano, hydroxy,

halogen, halo C₁-C₂ alkyl, hydroxy C₁-C₂ alkyl, amino, mono- or di-(C₁-C₂ alkyl) amino (Embodiment 3-48).

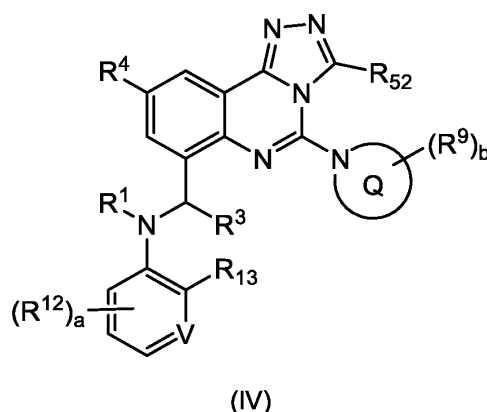
[00197] In certain embodiments of Embodiment 3-45, W is C(R²⁹)₂, b is 0, and each R²⁹ is independently hydrogen, methyl, methoxy, cyano, hydroxy, chloro, fluoro, amino, methylamino or dimethylamino (Embodiment 3-49).

[00198] In certain embodiments of Embodiment 3-45, W is C(R²⁹)₂, b is 0, and each R²⁹ is independently chloro or fluoro (Embodiment 3-50).

[00199] In certain embodiments of Embodiment 3-45, W is C(R²⁹)₂, b is 0, and each R²⁹ is fluoro (Embodiment 3-51).

[00200] In certain embodiments of Embodiment 3-45, W is C(R²⁹)₂, b is 0, and each R²⁹ is hydrogen (Embodiment 3-52).

[00201] In certain embodiments of formula (I) as otherwise described herein, the compound is of formula (IV):



or a pharmaceutically acceptable salt or deuterated form thereof, wherein:

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

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-C₃ 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;

a is 0, 1, 2 or 3;

V is CR¹⁴ or N;

each R¹² is independently C₁-C₄ alkyl, -OR^A, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, -C(O)N(R^A)₂, cyano, or halogen;

R¹³ is (i) cyano, (ii) tetrazolyl, (iii) -C(O)OR^A where R^A is H, C₁-C₆ alkyl, or C₃-C₆ cycloalkyl, or (iv) -C(O)N(R^B)₂ where R^B is H, -OH, C₁-C₆ alkyl, C₁-C₆ alkoxy or C₃-C₆ cycloalkyl;

R₁₄ is hydrogen, cyano, halogen, hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkyl, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, or -C(O)N(R^B)₂;

Q represents a 4-8 membered saturated or unsaturated monocyclic, bicyclic or polycyclic heterocyclyl group having 0, 1 or 2 additional ring heteroatoms selected from oxygen and nitrogen;

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

each R⁹ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, hydroxy, oxo, halogen, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, amino, mono- or di-(C₁-C₆ alkyl) amino, or phenyl, phenyl(C₁-C₃ alkanoyl), 5-7 membered heterocyclyl, or 5-6 membered heteroaryl where each phenyl, 5-7 membered heterocyclyl and 5-6 membered heteroaryl is optionally substituted with C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, hydroxy, cyano, amino, or mono- or di-(C₁-C₃ alkyl)amino; and

R⁵² represents hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, 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, wherein each alkyl, 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.

[00202] In certain embodiments of formula (IV) R¹ is H or CH₃ (Embodiment 4-1).

[00203] In certain embodiments of formula (IV) or Embodiment 4-1, R³ is C₁-C₃ alkyl, wherein the alkyl group is unsubstituted, substituted with 1-5 halo groups, or perfluorinated (Embodiment 4-2).

[00204] In certain embodiments of formula (IV) or Embodiment 4-1, R³ is methyl (Embodiment 4-3).

[00205] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-3, R⁴ is hydrogen (Embodiment 4-4).

[00206] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-3, R⁴ is methyl (Embodiment 4-5).

[00207] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-3, R⁴ is ethyl (Embodiment 4-6).

[00208] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-3, R⁴ is cyclopropyl (Embodiment 4-7).

[00209] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-3, R⁴ is methoxy (Embodiment 4-8).

[00210] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-3, R⁴ is fluoro (Embodiment 4-9).

[00211] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-3, R⁴ is chloro (Embodiment 4-10).

[00212] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-3, R⁴ is bromo (Embodiment 4-11).

[00213] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-8, V is CR¹² (Embodiment 4-12).

[00214] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-8, V is N (Embodiment 4-13).

[00215] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-12, V is CH, a is 1, and R¹² is hydrogen, C₁-C₃ alkyl or halogen (Embodiment 4-14).

[00216] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-12, V is CH, a is 1, and R¹² is hydrogen, methyl, chloro, bromo or fluoro (Embodiment 4-15).

[00217] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-12, V is CH, a is 1, and R¹² is hydrogen (Embodiment 4-16).

[00218] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-12, V is CH, a is 1, and R¹² is chloro (Embodiment 4-17).

[00219] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-12, V is CH, a is 1, and R¹² is bromo (Embodiment 4-18).

[00220] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-12, V is CH, a is 1, and R¹² is methyl (Embodiment 4-18.1).

[00221] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-12, V is CH, a is 1, and R¹² is fluoro (Embodiment 4-19).

[00222] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-11 or 4-13, V is N, a is 1, and R¹² is hydrogen, C₁-C₃ alkyl or halogen (Embodiment 4-20).

[00223] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-11 or 4-13, V is N, a is 1, and R¹² is hydrogen, methyl, chloro, bromo or fluoro (Embodiment 4-21).

[00224] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-11 or 4-13, V is N, a is 1, and R¹² is hydrogen (Embodiment 4-22).

[00225] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-11 or 4-13, V is N, a is 1, and R¹² is chloro (Embodiment 4-23).

[00226] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-11 or 4-13, V is N, a is 1, and R¹² is bromo (Embodiment 4-24).

[00227] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-11 or 4-13, V is N, a is 1, and R¹² is methyl (Embodiment 4-24.1).

[00228] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-11 or 4-13, V is N, a is 1, and R¹² is fluoro (Embodiment 4-25).

[00229] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-25, R⁵² represents hydrogen, C₁-C₃ alkyl, cyano, halogen, cyclopropyl or halo(C₁-C₆)alkyl (Embodiment 4-26).

[00230] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-25, R⁵² is hydrogen, methyl, ethyl, cyano, halogen, cyclopropyl or halo(C₁-C₆)alkyl (Embodiment 4-27).

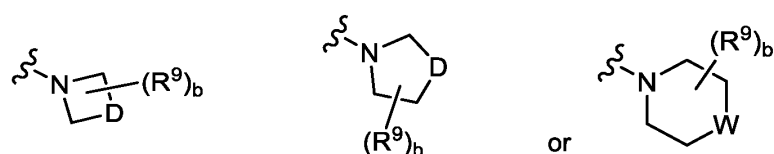
[00231] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-25, R⁵² is methyl, ethyl, cyano, halogen, cyclopropyl or halo(C₁-C₆)alkyl (Embodiment 4-28).

[00232] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-25, R⁵² is methyl, ethyl, cyano, halogen, cyclopropyl, difluoromethyl or trifluoromethyl (Embodiment 4-29).

[00233] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-25, R⁵² is hydrogen (Embodiment 4-30).

[00234] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-25, R⁵² is difluoromethyl or trifluoromethyl (Embodiment 4-31).

[00235] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-31, Q represents a group of the formula



wherein

each b is 0, 1 or 2; and

D represents C(R²⁹)₂,

W represents O, NR¹⁹ or C(R²⁹)₂, and

R¹⁹ is hydrogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, or amino- mono- or di-(C₁-C₆ alkyl) amino(C₁-C₆ alkyl); and

each R^{29} is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, cyano, hydroxy, oxo, halogen, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, amino, mono- or di- $(C_1$ - C_6 alkyl) amino (Embodiment 4-32).

[00236] In certain embodiments of Embodiment 4-32, W is oxygen, b is 0 or 1, and R^9 is methyl or cyano (Embodiment 4-33).

[00237] In certain embodiments of Embodiment 4-32, W is oxygen and b is 0 (Embodiment 4-34).

[00238] In certain embodiments of Embodiment 4-32, D and W are $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, C_1 - C_2 alkyl, C_1 - C_2 alkoxy, cyclopropyl, cyano, hydroxy, halogen, halo C_1 - C_2 alkyl, hydroxy C_1 - C_2 alkyl, amino, mono- or di- $(C_1$ - C_2 alkyl) amino (Embodiment 4-35).

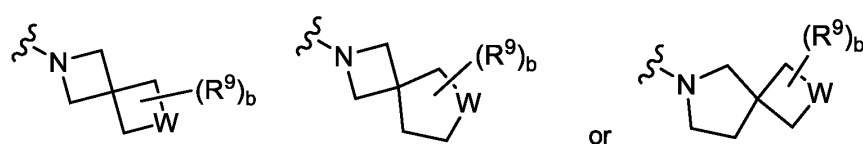
[00239] In certain embodiments of Embodiment 4-32, D and W are $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, methyl, methoxy, cyano, hydroxy, chloro, fluoro, amino, methylamino or dimethylamino (Embodiment 4-36).

[00240] In certain embodiments of Embodiment 4-32, D and W are $C(R^{29})_2$, b is 0, and each R^{29} is independently chloro or fluoro (Embodiment 4-).

[00241] In certain embodiments of Embodiment 4-32, D and W are $C(R^{29})_2$, b is 0, and each R^{29} is fluoro (Embodiment 4-37).

[00242] In certain embodiments of Embodiment 4-32, D and W are $C(R^{29})_2$, b is 0, and each R^{29} is hydrogen (Embodiment 4-38).

[00243] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-31, Q represents a group of the formula



wherein

each b is 0, 1 or 2; and

W represents O, NR^{19} or $C(R^{29})_2$, wherein

R^{19} is hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, or amino- or mono- or di- $(C_1$ - C_6 alkyl) amino(C_1 - C_6 alkyl); and

each R^{29} is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, cyano, hydroxy, oxo, halogen, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, amino, mono- or di- $(C_1$ - C_6 alkyl) amino (Embodiment 4-39).

[00244] In certain embodiments of Embodiment 4-39, W is oxygen, b is 0 or 1, and R⁹ is methyl or cyano (Embodiment 4-40).

[00245] In certain embodiments of Embodiment 4-39, W is oxygen and b is 0 (Embodiment 4-41).

[00246] In certain embodiments of Embodiment 4-39, W is C(R²⁹)₂, b is 0, and each R²⁹ is independently hydrogen, C₁-C₂ alkyl, C₁-C₂ alkoxy, cyclopropyl, cyano, hydroxy, halogen, halo C₁-C₂ alkyl, hydroxy C₁-C₂ alkyl, amino, mono- or di-(C₁-C₂ alkyl) amino (Embodiment 4-42).

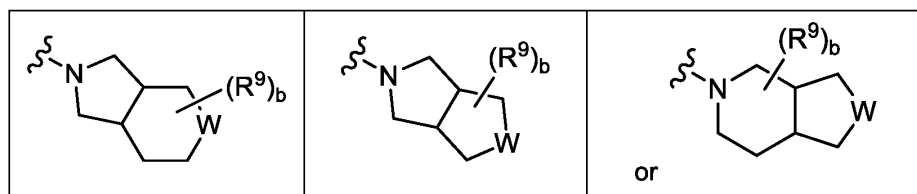
[00247] In certain embodiments of Embodiment 4-39, W is C(R²⁹)₂, b is 0, and each R²⁹ is independently hydrogen, methyl, methoxy, cyano, hydroxy, chloro, fluoro, amino, methylamino or dimethylamino (Embodiment 4-43).

[00248] In certain embodiments of Embodiment 4-39, W is C(R²⁹)₂, b is 0, and each R²⁹ is independently chloro or fluoro (Embodiment 4-44).

[00249] In certain embodiments of Embodiment 4-39, W is C(R²⁹)₂, b is 0, and each R²⁹ is fluoro (Embodiment 4-45).

[00250] In certain embodiments of Embodiment 4-39, W is C(R²⁹)₂, b is 0, and each R²⁹ is hydrogen (Embodiment 4-46).

[00251] In certain embodiments of formula (IV) or Embodiments 4-1 to 4-31, Q represents a group of the formula



wherein

each b is 0, 1 or 2; and

W represents O, NR¹⁹ or C(R²⁹)₂, wherein

R¹⁹ is hydrogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, or amino- or mono- or di-(C₁-C₆ alkyl) amino(C₁-C₆ alkyl); and

each R²⁹ is independently hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, hydroxy, oxo, halogen, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, amino, mono- or di-(C₁-C₆ alkyl) amino (Embodiment 4-47).

[00252] In certain embodiments of Embodiment 4-47, W is oxygen, b is 0 or 1, and R⁹ is methyl, chloro, fluoro or cyano (Embodiment 4-48).

[00253] In certain embodiments of Embodiment 4-47, W is oxygen and b is 0 (Embodiment 4-49).

[00254] In certain embodiments of Embodiment 4-47, W is $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, C_1 - C_2 alkyl, C_1 - C_2 alkoxy, cyclopropyl, cyano, hydroxy, halogen, halo C_1 - C_2 alkyl, hydroxy C_1 - C_2 alkyl, amino, mono- or di- $(C_1$ - C_2 alkyl) amino (Embodiment 4-50).

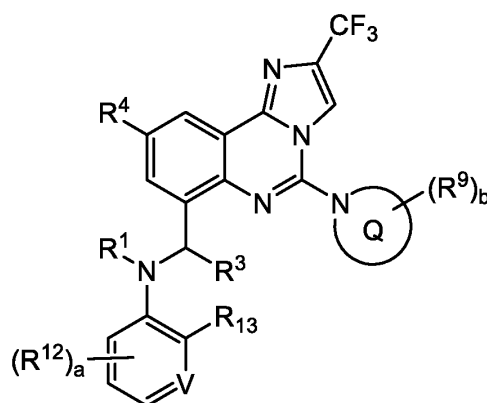
[00255] In certain embodiments of Embodiment 4-47, W is $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, methyl, methoxy, cyano, hydroxy, chloro, fluoro, amino, methylamino or dimethylamino (Embodiment 4-51).

[00256] In certain embodiments of Embodiment 4-47, W is $C(R^{29})_2$, b is 0, and each R^{29} is independently chloro or fluoro (Embodiment 4-52).

[00257] In certain embodiments of Embodiment 4-47, W is $C(R^{29})_2$, b is 0, and each R^{29} is fluoro (Embodiment 4-53).

[00258] In certain embodiments of Embodiment 4-47, W is $C(R^{29})_2$, b is 0, and each R^{29} is hydrogen (Embodiment 4-54).

[00259] In certain embodiments of formula (I) as otherwise described herein, the compound is of formula (III-A):



(III-A)

or a pharmaceutically acceptable salt or deuterated form thereof, wherein:

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

R^3 is C_1 - C_3 alkyl optionally substituted, polysubstituted or persubstituted with fluoro, C_3 - C_6 cycloalkyl, C_2 - C_3 alkenyl, C_2 - C_3 alkynyl, or C_5 - C_6 cycloalkenyl;

R^4 is H, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkyloxy, C_2 - C_3 alkenyl, C_2 - C_3 alkynyl, or C_5 - C_6 cycloalkenyl, cyano, or halo, wherein each C_1 - C_3 alkyl and C_3 - C_6 cycloalkyl is optionally substituted with 1-5 halo groups;

a is 0, 1, 2 or 3;

V is CR¹⁴ or N;

each R¹² is independently C₁-C₄ alkyl, -OR^A, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, -C(O)N(R^A)₂, cyano, or halogen;

R¹³ is (i) cyano, (ii) tetrazolyl, (iii) -C(O)OR^A where R^A is H, C₁-C₆ alkyl, or C₃-C₆ cycloalkyl, or (iv) -C(O)N(R^B)₂ where R^B is H, -OH, C₁-C₆ alkyl, C₁-C₆ alkoxy or C₃-C₆ cycloalkyl;

R₁₄ is hydrogen, cyano, halogen, hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkyl, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, or -C(O)N(R^B)₂;

Q represents a 4-8 membered saturated or unsaturated monocyclic, bicyclic or polycyclic heterocyclyl group having 0, 1 or 2 additional ring heteroatoms selected from oxygen and nitrogen;

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

each R⁹ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, hydroxy, oxo, halogen, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, amino, mono- or di-(C₁-C₆ alkyl) amino, or phenyl, phenyl(C₁-C₃ alkanoyl), 5-7 membered heterocyclyl, or 5-6 membered heteroaryl where each phenyl, 5-7 membered heterocyclyl and 5-6 membered heteroaryl is optionally substituted with C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, hydroxy, cyano, amino, or mono- or di(C₁-C₃ alkyl)amino.

[00260] In certain embodiments of formula (III-A) R¹ is H or CH₃ (Embodiment 3A-1).

[00261] In certain embodiments of formula (III-A) or Embodiment 3A-1, R³ is C₁-C₃ alkyl, wherein the alkyl group is unsubstituted, substituted with 1-5 halo groups, or perfluorinated (Embodiment 3A-2).

[00262] In certain embodiments of formula (III-A) or Embodiment 3A-1, R³ is methyl (Embodiment 3A-3).

[00263] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-3, R⁴ is hydrogen (Embodiment 3A-4).

[00264] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-3, R⁴ is methyl (Embodiment 3A-5).

[00265] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-3, R⁴ is fluoromethyl (Embodiment 3A-5.1).

[00266] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-3, R⁴ is difluoromethyl (Embodiment 3A-5.2).

[00267] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-3, R⁴ is trifluoromethyl (Embodiment 3A-5.3).

[00268] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-3, R⁴ is ethyl (Embodiment 3A-6).

[00269] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-3, R⁴ is cyclopropyl (Embodiment 3A-7).

[00270] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-3, R⁴ is methoxy (Embodiment 3A-8).

[00271] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-3, R⁴ is fluoro (Embodiment 3A-9).

[00272] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-3, R⁴ is chloro (Embodiment 3A-10).

[00273] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-3, R⁴ is bromo (Embodiment 3A-11).

[00274] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-8, V is CR¹² (Embodiment 3A-12).

[00275] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-8, V is N (Embodiment 3A-13).

[00276] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-12, V is CH, a is 1, and R¹² is hydrogen, C₁-C₃ alkyl or halogen (Embodiment 3A-14).

[00277] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-12, V is CH, a is 1, and R¹² is hydrogen, methyl, chloro, bromo or fluoro (Embodiment 3A-15).

[00278] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-12, V is CH, a is 1, and R¹² is hydrogen (Embodiment 3A-16).

[00279] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-12, V is CH, a is 1, and R¹² is chloro (Embodiment 3A-17).

[00280] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-12, V is CH, a is 1, and R¹² is bromo (Embodiment 3A-18).

[00281] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-12, V is CH, a is 1, and R¹² is methyl (Embodiment 3A-18.1).

[00282] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-12, V is CH, a is 1, and R¹² is fluoro (Embodiment 3A-19).

[00283] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-11 or 3A-13, V is N, a is 1, and R¹² is hydrogen, C₁-C₃ alkyl or halogen (Embodiment 3A-20).

[00284] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-11 or 3A-13, V is N, a is 1, and R¹² is hydrogen, methyl, chloro, bromo or fluoro (Embodiment 3A-21).

[00285] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-11 or 3A-13, V is N, a is 1, and R¹² is hydrogen (Embodiment 3A-22).

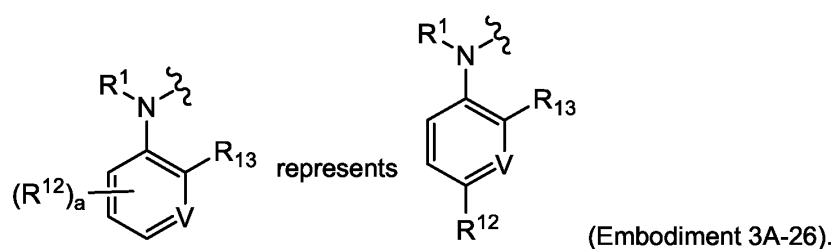
[00286] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-11 or 3A-13, V is N, a is 1, and R¹² is chloro (Embodiment 3A-23).

[00287] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-11 or 3A-13, V is N, a is 1, and R¹² is bromo (Embodiment 3A-24).

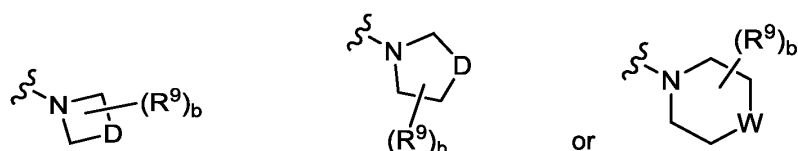
[00288] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-11 or 3A-13, V is N, a is 1, and R¹² is methyl (Embodiment 3A-24.1).

[00289] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-11 or 3A-13, V is N, a is 1, and R¹² is fluoro (Embodiment 3A-25).

[00290] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-25, the group



[00291] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-26, Q represents a group of the formula



wherein

each b is 0, 1 or 2;

D represents C(R²⁹)₂,

W represents O, NR¹⁹ or C(R²⁹)₂, and

R¹⁹ is hydrogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, or amino- or mono- or di-(C₁-C₆ alkyl) amino(C₁-C₆ alkyl); and

each R²⁹ is independently hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, hydroxy, oxo, halogen, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, amino, mono- or di-(C₁-C₆ alkyl) amino (Embodiment 3A-27).

[00292] In certain embodiments of Embodiment 3A-27, W is oxygen, b is 0 or 1, and R⁹ is methyl or cyano (Embodiment 3A-28).

[00293] In certain embodiments of Embodiment 3A-27, W is oxygen and b is 0 (Embodiment 3A-29).

[00294] In certain embodiments of Embodiment 3A-27, D and W are C(R²⁹)₂, b is 0, and each R²⁹ is independently hydrogen, C₁-C₂ alkyl, C₁-C₂ alkoxy, cyclopropyl, cyano, hydroxy, halogen, halo C₁-C₂ alkyl, hydroxy C₁-C₂ alkyl, amino, mono- or di-(C₁-C₂ alkyl) amino (Embodiment 3A-30).

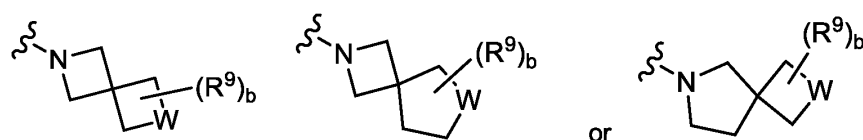
[00295] In certain embodiments of Embodiment 3A-27, D and W are C(R²⁹)₂, b is 0, and each R²⁹ is independently hydrogen, methyl, methoxy, cyano, hydroxy, chloro, fluoro, amino, methylamino or dimethylamino (Embodiment 3A-31).

[00296] In certain embodiments of Embodiment 3A-27, D and W are C(R²⁹)₂, b is 0, and each R²⁹ is independently chloro or fluoro (Embodiment 3A-31).

[00297] In certain embodiments of Embodiment 3A-27, D and W are C(R²⁹)₂, b is 0, and each R²⁹ is fluoro (Embodiment 3A-33).

[00298] In certain embodiments of Embodiment 3A-27, D and W are C(R²⁹)₂, b is 0, and each R²⁹ is hydrogen (Embodiment 3A-34).

[00299] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-26, Q represents a group of the formula



wherein

each b is 0, 1 or 2; and

W represents O, NR¹⁹ or C(R²⁹)₂, wherein

R¹⁹ is hydrogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, or amino- or mono- or di-(C₁-C₆ alkyl) amino(C₁-C₆ alkyl); and

each R²⁹ is independently hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, hydroxy, oxo, halogen, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, amino, mono- or di-(C₁-C₆ alkyl) amino (Embodiment 3A-35).

[00300] In certain embodiments of Embodiment 3A-35, W is oxygen, b is 0 or 1, and R⁹ is methyl or cyano (Embodiment 3A-36).

[00301] In certain embodiments of Embodiment 3A-35, W is oxygen and b is 0 (Embodiment 3A-37).

[00302] In certain embodiments of Embodiment 3A-35, W is $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, C_1 - C_2 alkyl, C_1 - C_2 alkoxy, cyclopropyl, cyano, hydroxy, halogen, halo C_1 - C_2 alkyl, hydroxy C_1 - C_2 alkyl, amino, mono- or di- $(C_1$ - C_2 alkyl) amino (Embodiment 3A-38).

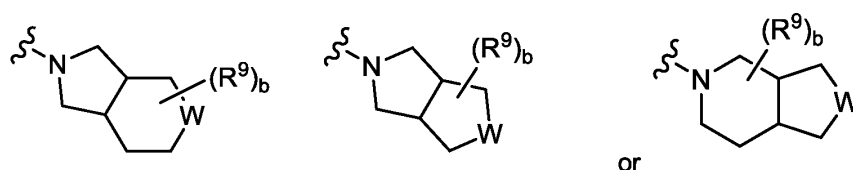
[00303] In certain embodiments of Embodiment 3A-35, W is $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, methyl, methoxy, cyano, hydroxy, chloro, fluoro, amino, methylamino or dimethylamino (Embodiment 3A-39).

[00304] In certain embodiments of Embodiment 3A-35, W is $C(R^{29})_2$, b is 0, and each R^{29} is independently chloro or fluoro (Embodiment 3A-40).

[00305] In certain embodiments of Embodiment 3A-35, W is $C(R^{29})_2$, b is 0, and each R^{29} is fluoro (Embodiment 3A-41).

[00306] In certain embodiments of Embodiment 3A-35, W is $C(R^{29})_2$, b is 0, and each R^{29} is hydrogen (Embodiment 3A-42).

[00307] In certain embodiments of formula (III-A) or Embodiments 3A-1 to 3A-26, Q represents a group of the formula



wherein

each b is 0, 1 or 2; and

W represents O, NR^{19} or $C(R^{29})_2$, wherein

R^{19} is hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, or amino- or mono- or di- $(C_1$ - C_6 alkyl) amino(C_1 - C_6 alkyl); and

each R^{29} is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, cyano, hydroxy, oxo, halogen, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, amino, mono- or di- $(C_1$ - C_6 alkyl) amino (Embodiment 3A-43).

[00308] In certain embodiments of Embodiment 3A-43, W is oxygen, b is 0 or 1, and R^9 is methyl, chloro, fluoro or cyano (Embodiment 3A-44).

[00309] In certain embodiments of Embodiment 3A-43, W is oxygen and b is 0 (Embodiment 3A-45).

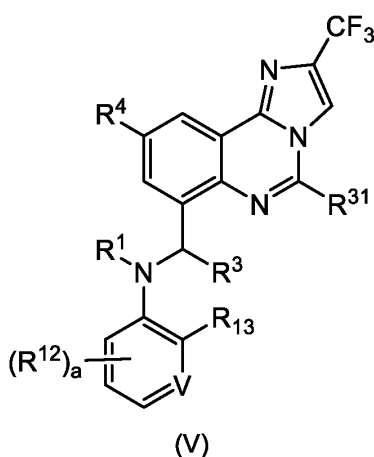
[00310] In certain embodiments of Embodiment 3A-43, W is $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, C_1 - C_2 alkyl, C_1 - C_2 alkoxy, cyclopropyl, cyano, hydroxy, halogen, halo C_1 - C_2 alkyl, hydroxy C_1 - C_2 alkyl, amino, mono- or di- $(C_1$ - C_2 alkyl) amino (Embodiment 3A-46).

[00311] In certain embodiments of Embodiment 3A-43, W is $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, methyl, methoxy, cyano, hydroxy, chloro, fluoro, amino, methylamino or dimethylamino (Embodiment 3A-47).

[00312] In certain embodiments of Embodiment 3A-43, W is $C(R^{29})_2$, b is 0, and each R^{29} is independently chloro or fluoro (Embodiment 3A-48).

[00313] In certain embodiments of Embodiment 3A-43, W is $C(R^{29})_2$, b is 0, and each R^{29} is fluoro (Embodiment 3A-49).

[00314] In certain embodiments of Embodiment 3A-43, W is $C(R^{29})_2$, b is 0, and each R^{29} is hydrogen (Embodiment 3A-50). In certain embodiments of formula (I) as otherwise described herein, the compound is of formula (V):



or a pharmaceutically acceptable salt or deuterated form thereof, wherein:

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

R^3 is C_1 - C_3 alkyl optionally substituted, polysubstituted or persubstituted with fluoro, C_3 - C_6 cycloalkyl, C_2 - C_3 alkenyl, C_2 - C_3 alkynyl, or C_5 - C_6 cycloalkenyl;

R^4 is H, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkyloxy, C_2 - C_3 alkenyl, C_2 - C_3 alkynyl, or C_5 - C_6 cycloalkenyl, cyano, or halo, wherein each C_1 - C_3 alkyl and C_3 - C_6 cycloalkyl is optionally substituted with 1-5 halo groups;

a is 0, 1, 2 or 3;

V is CR^{14} or N;

each R^{12} is independently C_1 - C_4 alkyl, $-OR^A$, $-C(O)OR^A$, $(C_1$ - C_3 alkyl)- OR^A , $-C(O)N(R^A)_2$, cyano, or halogen;

R¹³ is (i) cyano, (ii) tetrazolyl, (iii) -C(O)OR^A where R^A is H, C₁-C₆ alkyl, or C₃-C₆ cycloalkyl, or (iv) -C(O)N(R^B)₂ where R^B is H, -OH, C₁-C₆ alkyl, C₁-C₆ alkoxy or C₃-C₆ cycloalkyl;

R₁₄ is hydrogen, cyano, halogen, hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkyl, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, or -C(O)N(R^B)₂; and

R³¹ represents

- (i) 5-7 membered heteroaryl, or
- (ii) a 3-8 membered monocyclic heterocyclyl group connected to the tricyclic ring system via a carbon atom, wherein the heterocyclyl group is saturated or unsaturated and optionally fused to an aromatic or non-aromatic ring containing 3-6 ring members of which 1 or 2 are optionally nitrogen, oxygen or sulfur atoms and the remainder carbons, or with a carbon atom from the monocyclic heterocyclyl group and additional carbon or nitrogen atoms, forms a spirocyclic ring system having up to 10 total ring members, wherein the ring members are carbons or nitrogens, and wherein each heteroaryl and heterocyclyl group within R³¹ is optionally substituted, on an aromatic or non-aromatic portion, with 1-4 R³⁹ groups, wherein each R³⁹ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, hydroxy, oxo, halogen, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, amino, mono- or di-(C₁-C₆ alkyl) amino, or phenyl, phenyl(C₁-C₃ alkanoyl), 5-7 membered heterocyclyl, or 5-6 membered heteroaryl where each phenyl, 5-7 membered heterocyclyl and 5-6 membered heteroaryl is optionally substituted with C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, hydroxy, cyano, amino, or mono- or di(C₁-C₃ alkyl)amino;

[00315] In certain embodiments of formula (V) R¹ is H or CH₃ (Embodiment 5-1).

[00316] In certain embodiments of formula (V) or Embodiment 5-1, R³ is C₁-C₃ alkyl, wherein the alkyl group is unsubstituted, substituted with 1-5 halo groups, or perfluorinated (Embodiment 5-2).

[00317] In certain embodiments of formula (V) or Embodiment 5-1, R³ is methyl (Embodiment 5-3).

[00318] In certain embodiments of formula (V) or Embodiments 5-1 to 5-3, R⁴ is hydrogen (Embodiment 5-4).

[00319] In certain embodiments of formula (V) or Embodiments 5-1 to 5-3, R⁴ is methyl (Embodiment 5-5).

[00320] In certain embodiments of formula (V) or Embodiments 5-1 to 5-3, R⁴ is fluoro (Embodiment 5-6).

[00321] In certain embodiments of formula (V) or Embodiments 5-1 to 5-3, R⁴ is chloro (Embodiment 5-7).

[00322] In certain embodiments of formula (V) or Embodiments 5-1 to 5-3, R⁴ is fluoromethyl (Embodiment 5-8).

[00323] In certain embodiments of formula (V) or Embodiments 5-1 to 5-3, R⁴ is difluoromethyl (Embodiment 5-9).

[00324] In certain embodiments of formula (V) or Embodiments 5-1 to 5-3, R⁴ is trifluoromethyl (Embodiment 5-10).

[00325] In certain embodiments of formula (V) or Embodiments 5-1 to 5-3, R⁴ is bromo (Embodiment 5-11).

[00326] In certain embodiments of formula (V) or Embodiments 5-1 to 5-11, V is CR¹² (Embodiment 5-12).

[00327] In certain embodiments of formula (V) or Embodiments 5-1 to 5-11, V is N (Embodiment 5-13).

[00328] In certain embodiments of formula (V) or Embodiments 5-1 to 5-12, V is CH, a is 1, and R¹² is hydrogen, C₁-C₃ alkyl or halogen (Embodiment 5-14).

[00329] In certain embodiments of formula (V) or Embodiments 5-1 to 5-12, V is CH, a is 1, and R¹² is hydrogen, methyl, chloro, bromo or fluoro (Embodiment 5-15).

[00330] In certain embodiments of formula (V) or Embodiments 5-1 to 5-12, V is CH, a is 1, and R¹² is hydrogen (Embodiment 5-16).

[00331] In certain embodiments of formula (V) or Embodiments 5-1 to 5-12, V is CH, a is 1, and R¹² is methyl (Embodiment 5-17).

[00332] In certain embodiments of formula (V) or Embodiments 5-1 to 5-12, V is CH, a is 1, and R¹² is chloro (Embodiment 5-18).

[00333] In certain embodiments of formula (V) or Embodiments 5-1 to 5-12, V is CH, a is 1, and R¹² is bromo (Embodiment 5-19).

[00334] In certain embodiments of formula (V) or Embodiments 5-1 to 5-12, V is CH, a is 1, and R¹² is fluoro (Embodiment 5-20).

[00335] In certain embodiments of formula (V) or Embodiments 5-1 to 5-11 or 5-13, V is N, a is 1, and R¹² is hydrogen, C₁-C₃ alkyl or halogen (Embodiment 5-21).

[00336] In certain embodiments of formula (V) or Embodiments 5-1 to 5-11 or 5-13, V is N, a is 1, and R¹² is hydrogen, methyl, chloro, bromo or fluoro (Embodiment 5-22).

[00337] In certain embodiments of formula (V) or Embodiments 5-1 to 5-11 or 5-13, N, a is 1, and R¹² is hydrogen (Embodiment 5-23).

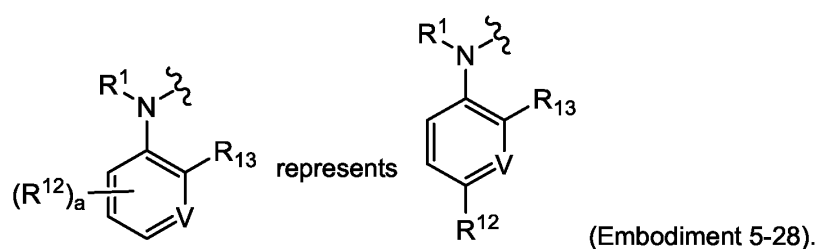
[00338] In certain embodiments of formula (V) or Embodiments 5-1 to 5-11 or 5-13, N, a is 1, and R¹² is chloro (Embodiment 5-24).

[00339] In certain embodiments of formula (V) or Embodiments 5-1 to 5-11 or 5-13, N, a is 1, and R¹² is bromo (Embodiment 5-25).

[00340] In certain embodiments of formula (V) or Embodiments 5-1 to 5-11 or 5-13, N, a is 1, and R¹² is methyl (Embodiment 5-26).

[00341] In certain embodiments of formula (V) or Embodiments 5-1 to 5-11 or 5-13, N, a is 1, and R¹² is fluoro (Embodiment 5-27).

[00342] In certain embodiments of formula (V) or Embodiments 5-1 to 5-27, the group



[00343] In certain embodiments of formula (V) or Embodiments 5-1 to 5-28, R³¹ is a 4, 5 or 6 membered heterocyclyl group which is optionally substituted with one or two R³⁹ groups where each R³⁹ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, hydroxy, oxo, halogen, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, amino, mono- or di-(C₁-C₆ alkyl) amino. (Embodiment 5-29).

[00344] In certain embodiments of formula (V) or Embodiments 5-1 to 5-28, R³¹ is tetrahydrofuranyl optionally substituted independently with one or two of R³⁹ (Embodiment 5-30).

[00345] In certain embodiments of formula (V) or Embodiments 5-1 to 5-28, R³¹ is tetrahydrofuranyl optionally substituted independently with one or two of methyl, cyano or trifluoromethyl (Embodiment 5-31).

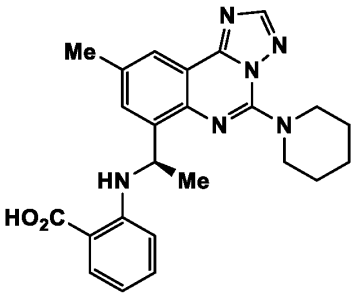
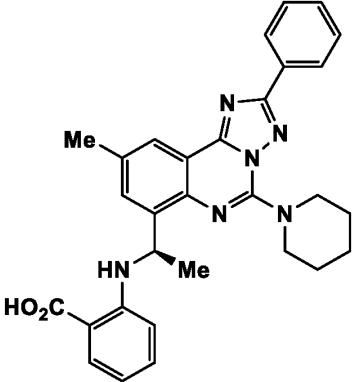
[00346] In certain embodiments of formula (V) or Embodiments 5-1 to 5-28, R³¹ is tetrahydropyranyl optionally substituted independently with one or two of R³⁹ (Embodiment 5-32).

[00347] In certain embodiments of formula (V) or Embodiments 5-1 to 5-28, R³¹ is tetrahydropyranyl optionally substituted independently with one or two of methyl, cyano or trifluoromethyl (Embodiment 5-33).

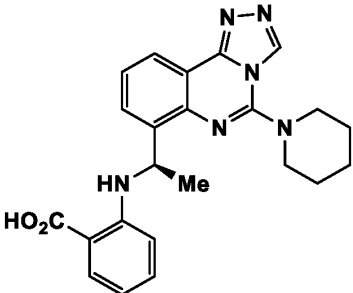
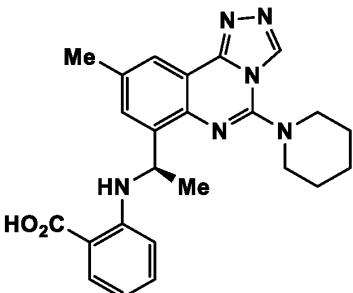
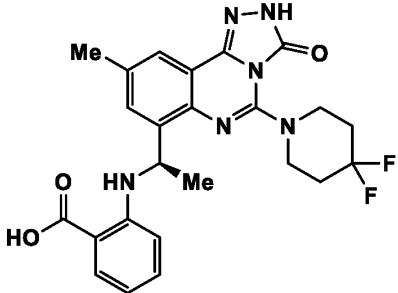
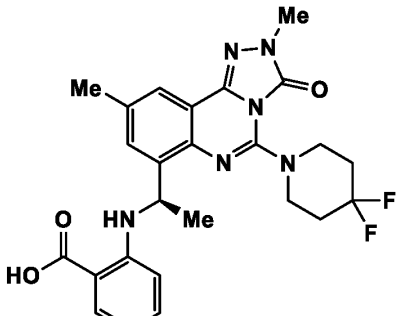
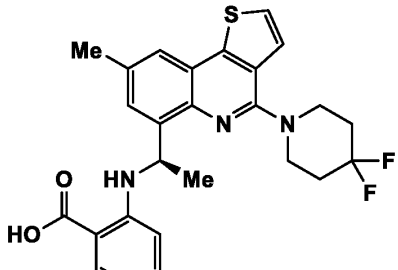
[00348] In certain embodiments of formula (V) or Embodiments 5-1 to 5-28, R³¹ is pyridyl optionally substituted with one or two R³⁹ groups where each R³⁹ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, hydroxy, oxo, halogen, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl (Embodiment 5-34).

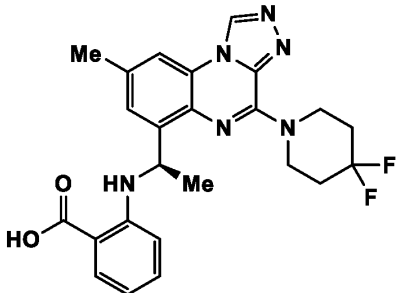
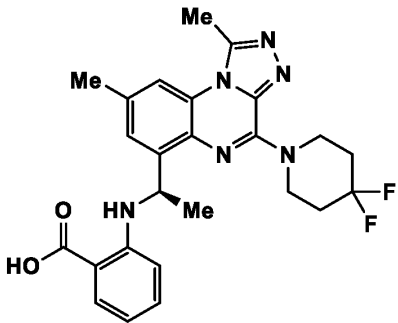
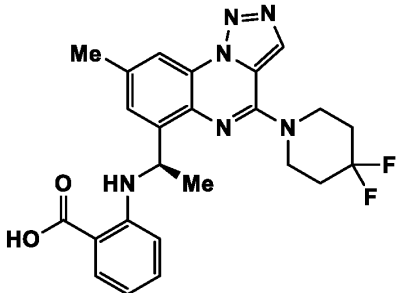
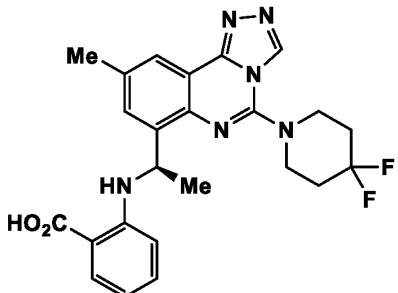
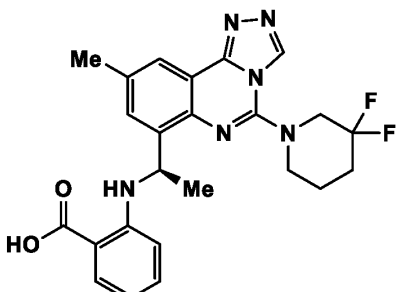
[00349] In one embodiment, the compound of Formula (I) is selected from the compounds disclosed below in Table 1 .

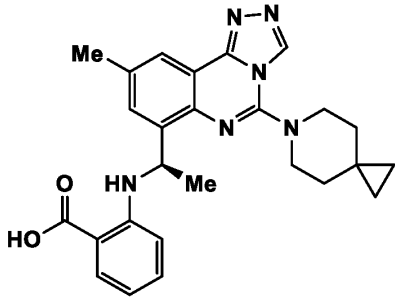
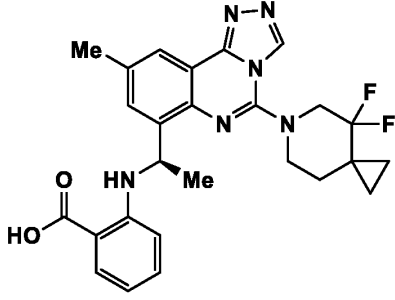
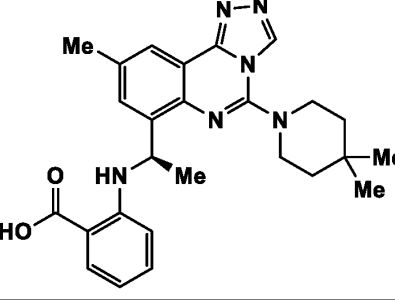
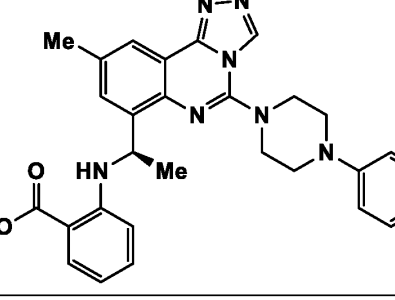
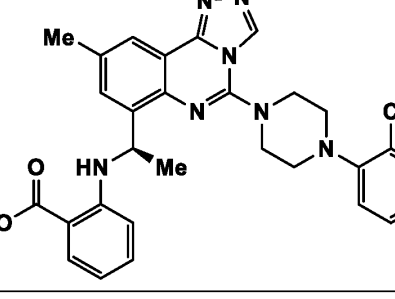
Table 1

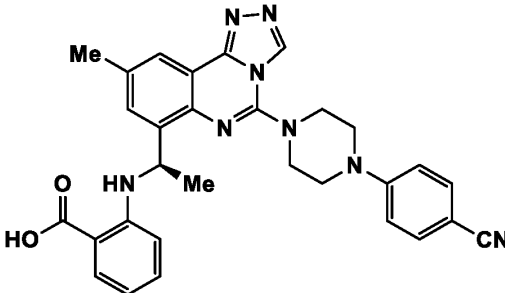
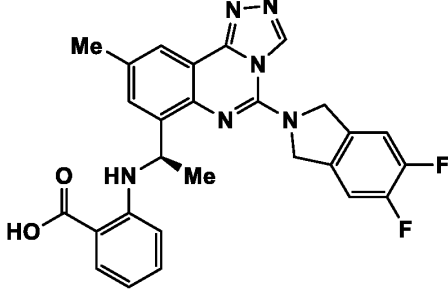
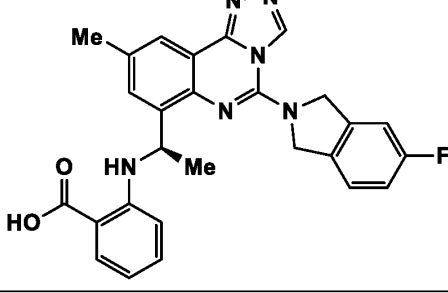
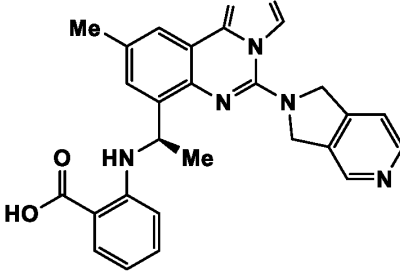
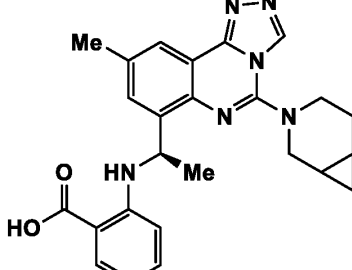
Structure	Name
	(<i>R</i>)-2-((1-(9-methyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(9-methyl-2-phenyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethyl)amino)benzoic acid

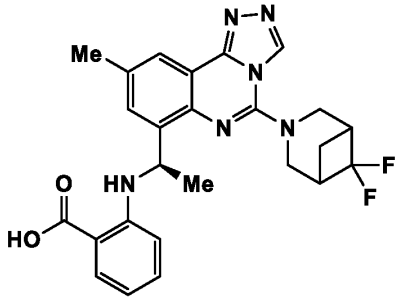
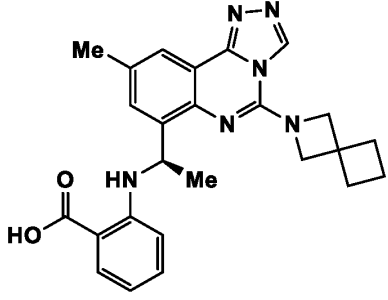
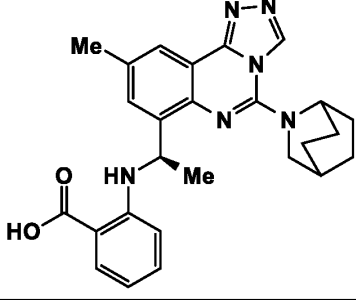
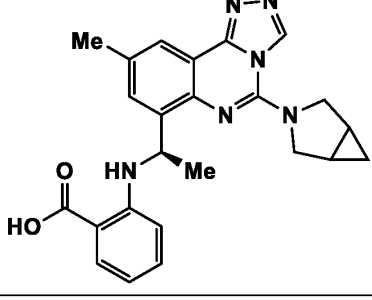
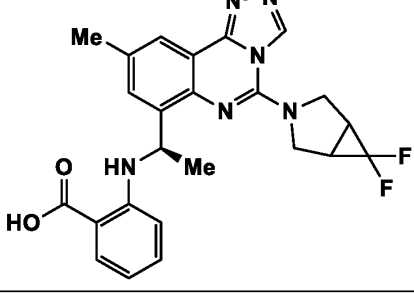
	(<i>R</i>)-2-((1-(9-methyl-5-(piperidin-1-yl)-2-(pyrazin-2-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(9-methyl-5-(piperidin-1-yl)-2-(thiazol-4-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	2-((1-(9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(2-cyano-9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid

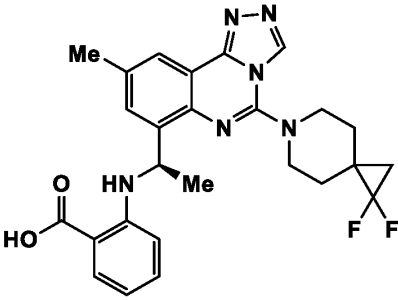
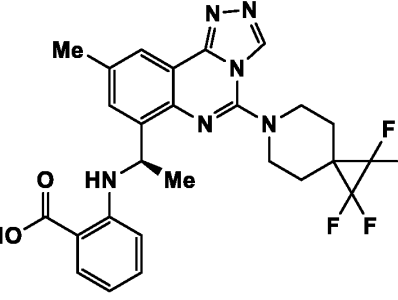
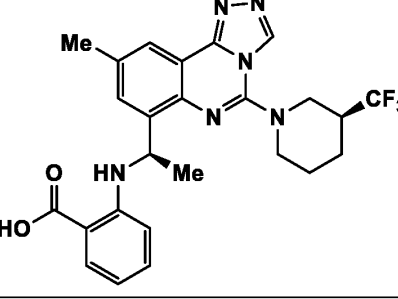
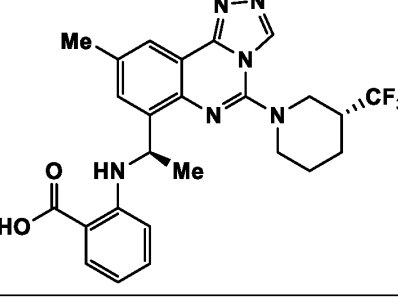
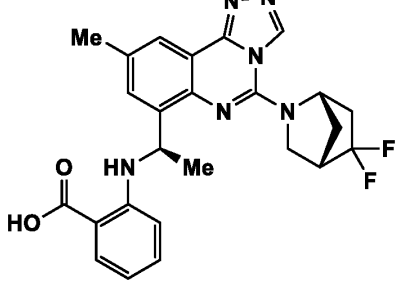
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	(<i>R</i>)-2-((1-(9-methyl-5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-2,9-dimethyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(4-(4,4-difluoropiperidin-1-yl)-8-methylthieno[3,2-c]quinolin-6-yl)ethyl)amino)benzoic acid

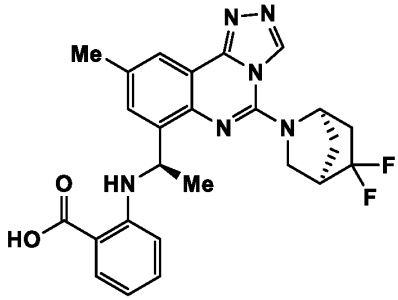
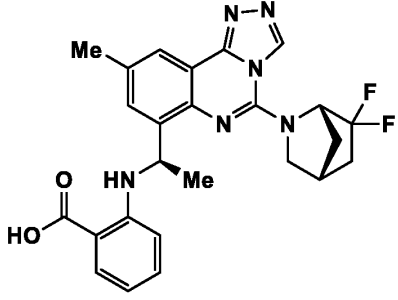
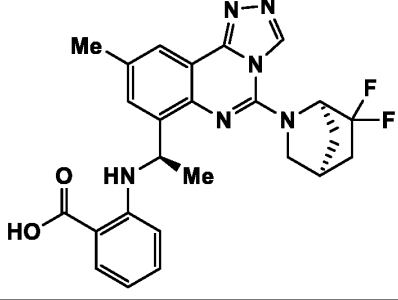
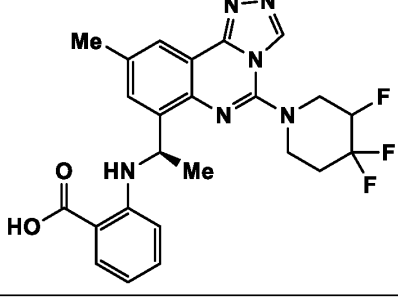
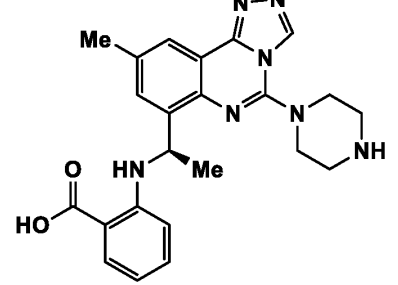
	(<i>R</i>)-2-((1-(4-(4,4-difluoropiperidin-1-yl)-8-methyl-[1,2,4]triazolo[4,3-a]quinoxalin-6-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(4-(4,4-difluoropiperidin-1-yl)-1,8-dimethyl-[1,2,4]triazolo[4,3-a]quinoxalin-6-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(4-(4,4-difluoropiperidin-1-yl)-8-methyl-[1,2,3]triazolo[1,5-a]quinoxalin-6-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(5-(4-(4,4-difluoropiperidin-1-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(5-(3,3-difluoropiperidin-1-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid

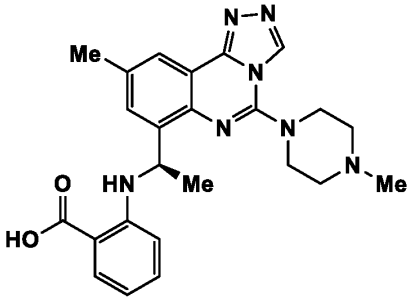
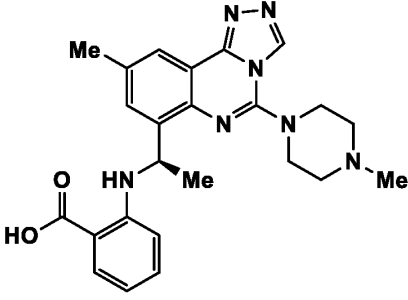
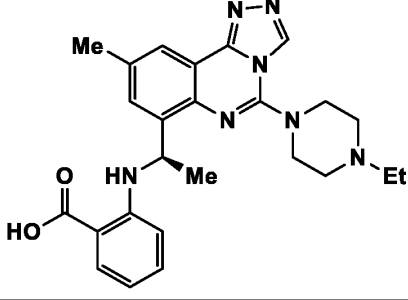
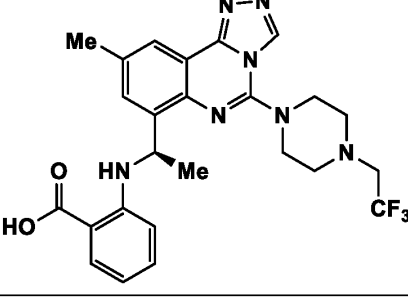
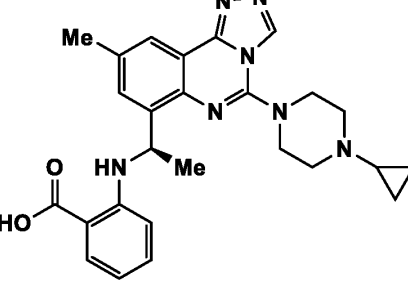
	(<i>R</i>)-2-((1-(9-methyl-5-(6-azaspiro[2.5]octan-6-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(5-(4,4-difluoro-6-azaspiro[2.5]octan-6-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(5-(4,4-dimethylpiperidin-1-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(9-methyl-5-(4-phenylpiperazin-1-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(5-(4-(2-cyanophenyl)piperazin-1-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid

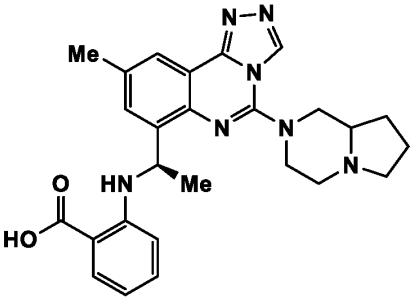
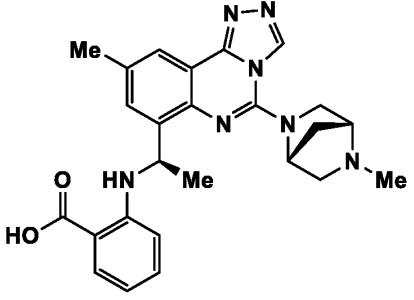
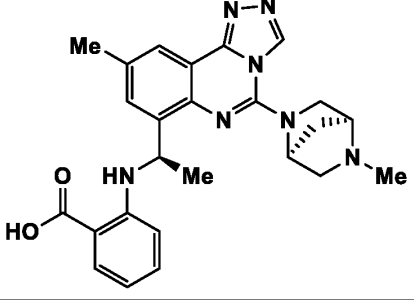
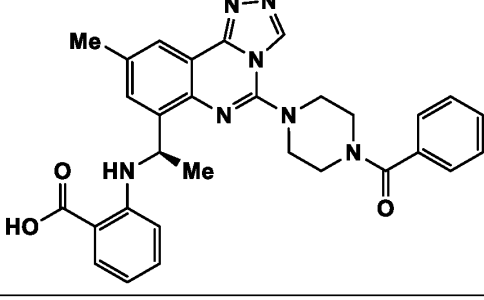
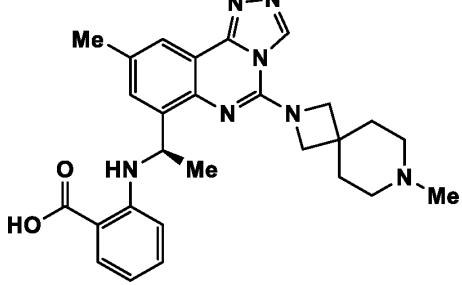
	(<i>R</i>)-2-((1-(5-(4-(4-cyanophenyl)piperazin-1-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(5-(5,6-difluoroisoindolin-2-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(5-(5-fluoroisoindolin-2-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(5-(1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	2-(((1<i>R</i>)-1-(5-(3-azabicyclo[4.1.0]heptan-3-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid

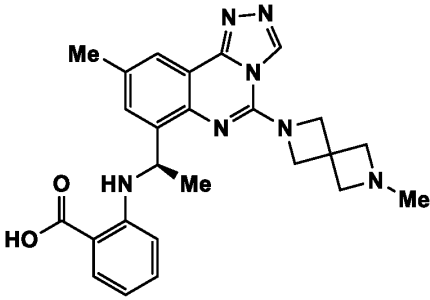
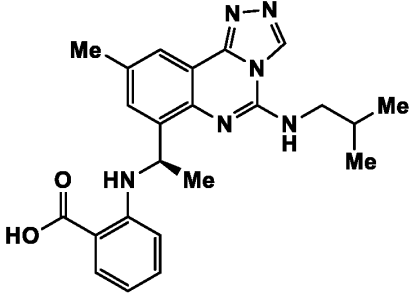
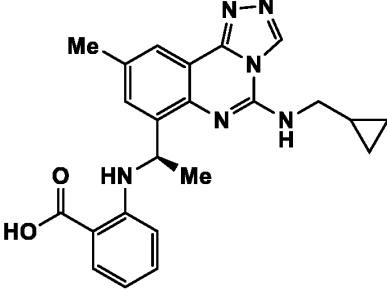
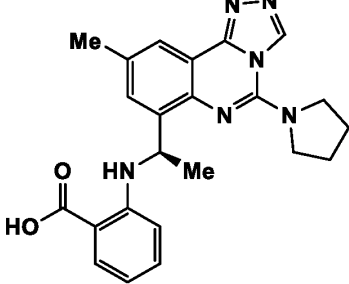
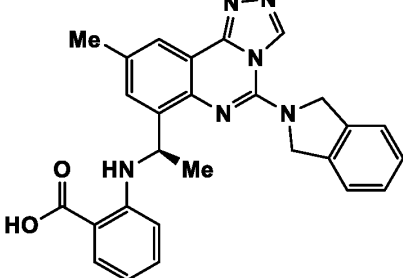
	2-(((1<i>R</i>)-1-(5-(6,6-difluoro-3-azabicyclo[3.1.1]heptan-3-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(9-methyl-5-(2-azaspiro[3.3]heptan-2-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(5-(2-azabicyclo[2.2.2]octan-2-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	2-(((1<i>R</i>)-1-(5-(3-azabicyclo[3.1.0]hexan-3-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	2-(((1<i>R</i>)-1-(5-(6,6-difluoro-3-azabicyclo[3.1.0]hexan-3-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid

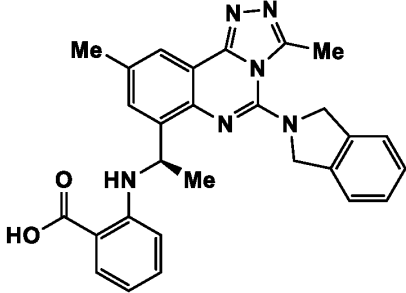
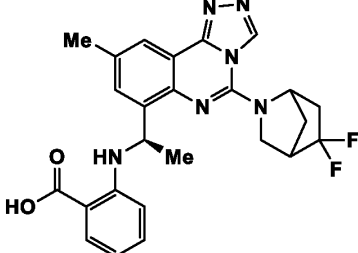
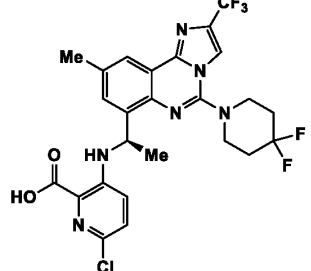
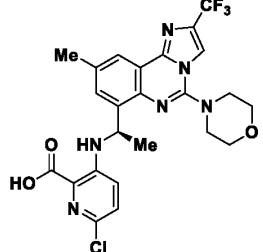
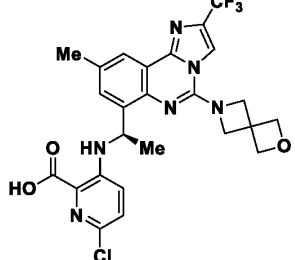
	(<i>R</i>)-2-((1-(5-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(9-methyl-5-(1,1,2,2-tetrafluoro-6-azaspiro[2.5]octan-6-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	2-(((<i>R</i>)-1-(9-methyl-5-((<i>S</i>)-3-(trifluoromethyl)piperidin-1-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	2-(((<i>R</i>)-1-(9-methyl-5-((<i>R</i>)-3-(trifluoromethyl)piperidin-1-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	2-(((<i>R</i>)-1-(5-((1<i>S</i>,4<i>S</i>)-5,5-difluoro-2-azabicyclo[2.2.1]heptan-2-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid

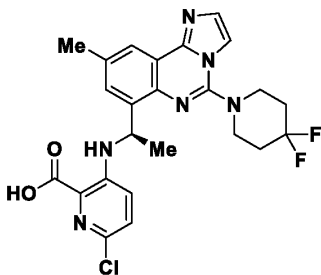
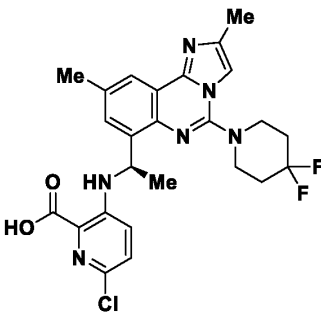
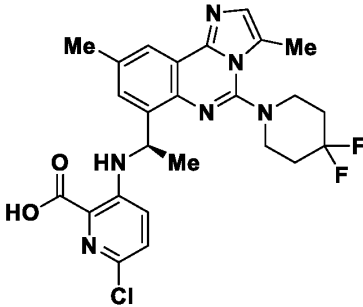
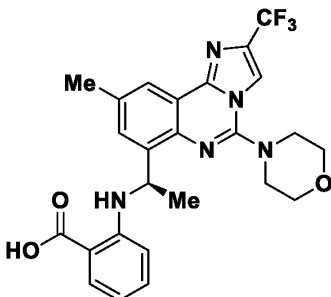
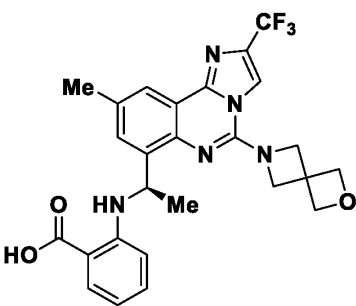
	2-(((<i>R</i>)-1-(5-((1<i>R</i>,4<i>R</i>)-5,5-difluoro-2-azabicyclo[2.2.1]heptan-2-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	2-(((<i>R</i>)-1-(5-((1<i>S</i>,4<i>R</i>)-6,6-difluoro-2-azabicyclo[2.2.1]heptan-2-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	2-(((<i>R</i>)-1-(5-((1<i>R</i>,4<i>S</i>)-6,6-difluoro-2-azabicyclo[2.2.1]heptan-2-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	2-(((1<i>R</i>)-1-(9-methyl-5-(3,4,4-trifluoropiperidin-1-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(9-methyl-5-(piperazin-1-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid

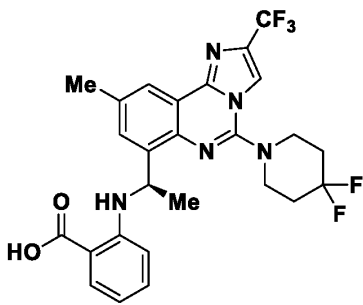
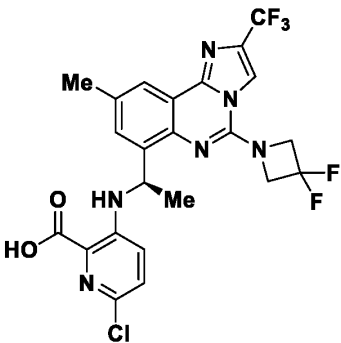
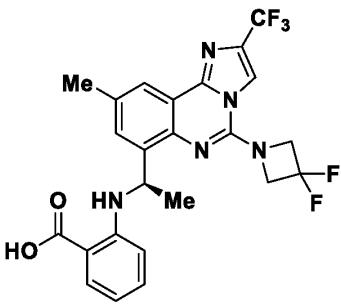
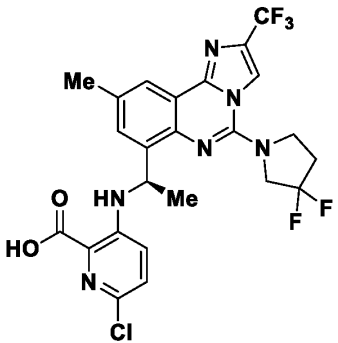
	(<i>R</i>)-2-((1-(9-methyl-5-(4-methylpiperazin-1-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(9-methyl-5-(4-methylpiperazin-1-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(5-(4-ethylpiperazin-1-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(9-methyl-5-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(5-(4-cyclopropylpiperazin-1-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid

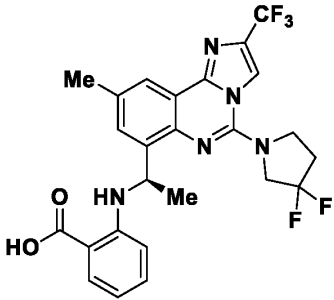
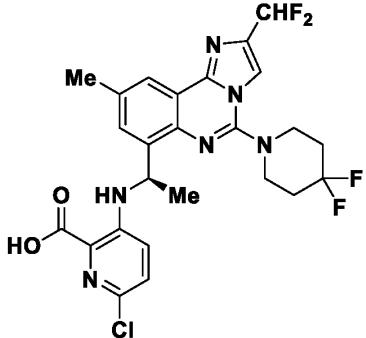
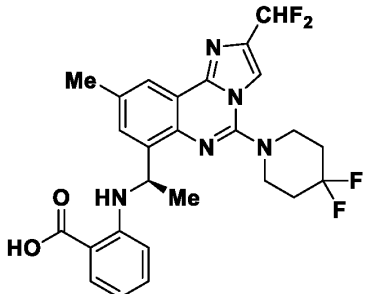
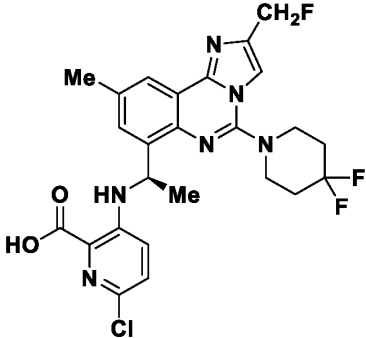
	2-(((1<i>R</i>)-1-(5-(hexahydropyrrolo[1,2-<i>a</i>]pyrazin-2(1<i>H</i>)-yl)-9-methyl-[1,2,4]triazolo[4,3-<i>c</i>]quinazolin-7-yl)ethyl)amino)benzoic acid
	2-(((<i>R</i>)-1-(9-methyl-5-((1<i>R</i>,4<i>R</i>)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-[1,2,4]triazolo[4,3-<i>c</i>]quinazolin-7-yl)ethyl)amino)benzoic acid
	2-(((<i>R</i>)-1-(9-methyl-5-((1<i>S</i>,4<i>S</i>)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-[1,2,4]triazolo[4,3-<i>c</i>]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-(((1-(5-(4-benzoylpiperazin-1-yl)-9-methyl-[1,2,4]triazolo[4,3-<i>c</i>]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-(((1-(9-methyl-5-(7-methyl-2,7-diazaspiro[3.5]nonan-2-yl)-[1,2,4]triazolo[4,3-<i>c</i>]quinazolin-7-yl)ethyl)amino)benzoic acid

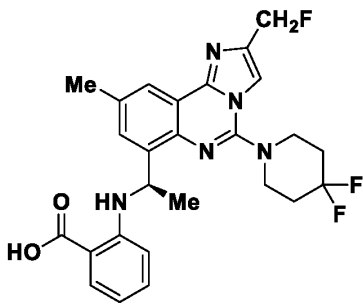
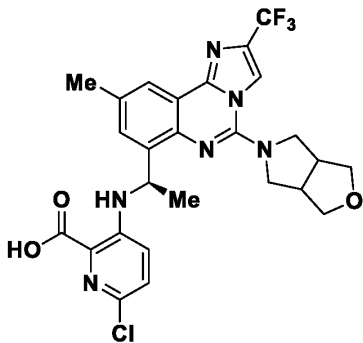
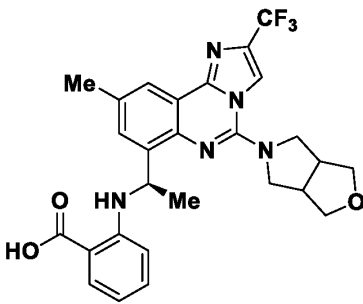
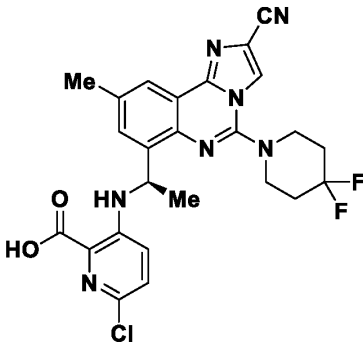
	(<i>R</i>)-2-((1-(9-methyl-5-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(5-(isobutylamino)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(5-(cyclopropylmethyl)amino)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(9-methyl-5-(pyrrolidin-1-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-2-((1-(5-(isoindolin-2-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid

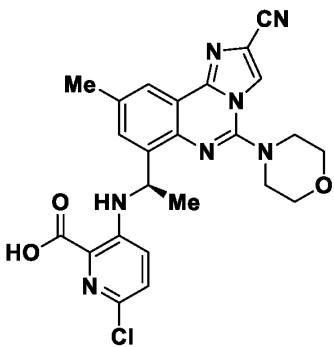
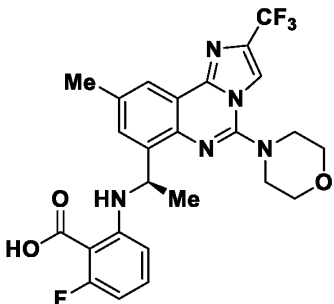
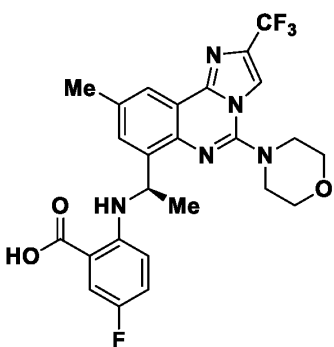
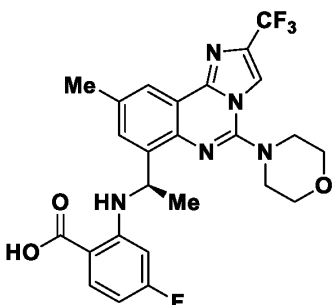
	(<i>R</i>)-2-((1-(5-(isoindolin-2-yl)-3,9-dimethyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	2-(((1<i>R</i>)-1-(5-(5,5-difluoro-2-azabicyclo[2.2.1]heptan-2-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid;
	(<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-6-chloro-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-6-chloro-3-((1-(9-methyl-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;

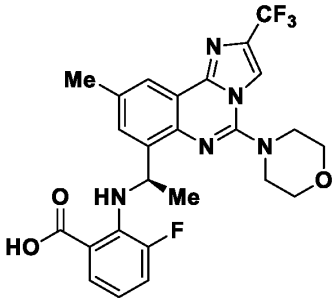
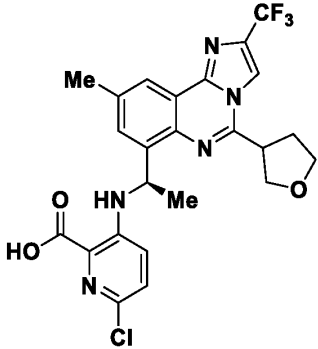
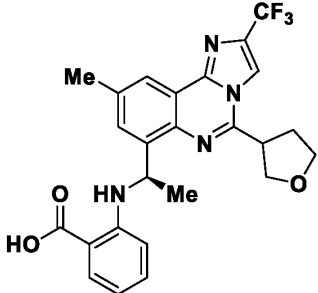
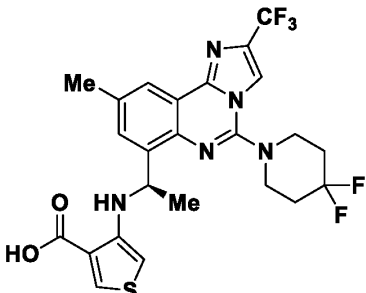
	(<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2,9-dimethylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-3,9-dimethylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid;
	(<i>R</i>)-2-((1-(9-methyl-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid;

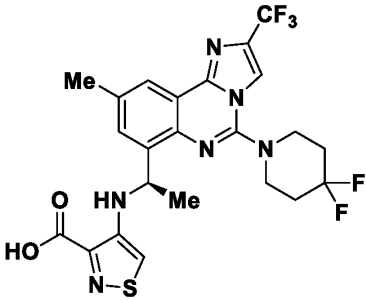
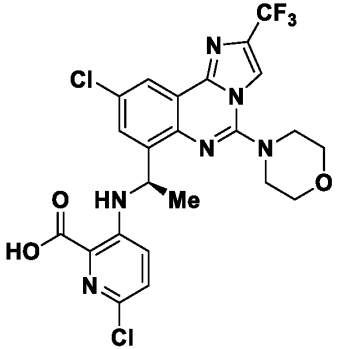
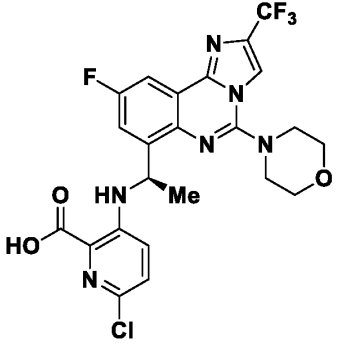
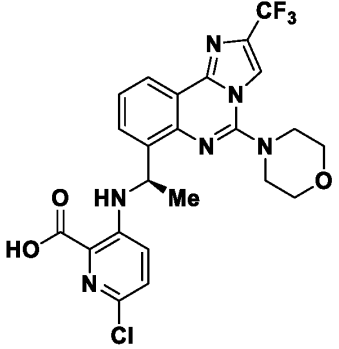
	(<i>R</i>)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid;
	(<i>R</i>)-6-chloro-3-((1-(5-(3,3-difluoroazetidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-2-((1-(5-(3,3-difluoroazetidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid;
	(<i>R</i>)-6-chloro-3-((1-(5-(3,3-difluoropyrrolidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;

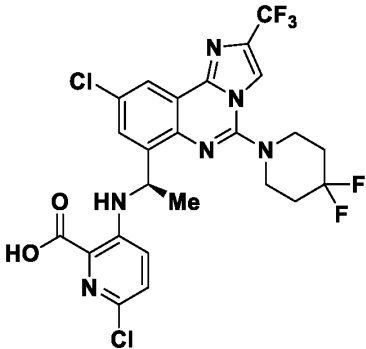
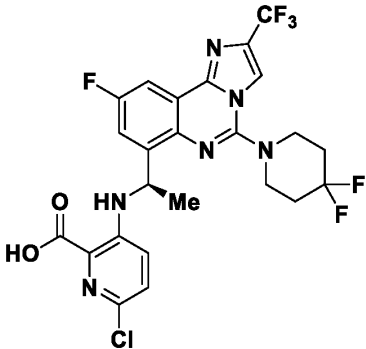
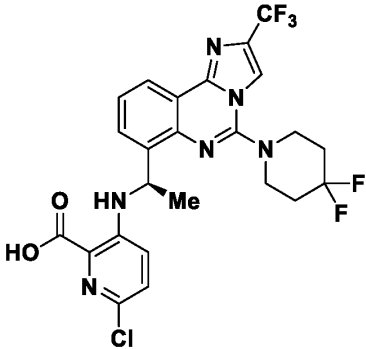
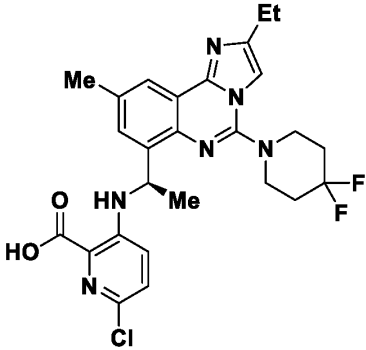
	(<i>R</i>)-2-((1-(5-(3,3-difluoropyrrolidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid;
	(<i>R</i>)-6-chloro-3-((1-(2-(difluoromethyl)-5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-2-((1-(2-(difluoromethyl)-5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid;
	(<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2-(fluoromethyl)-9-methylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;

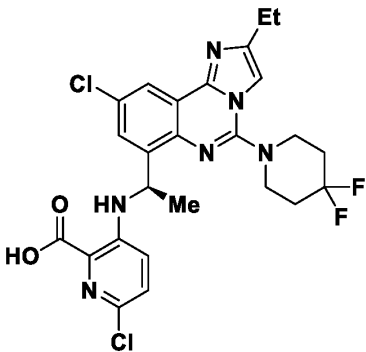
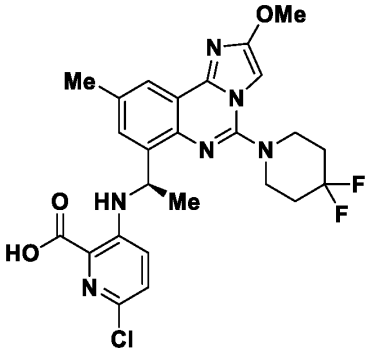
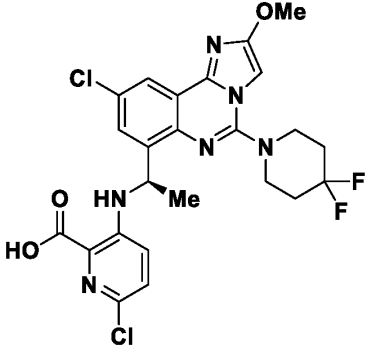
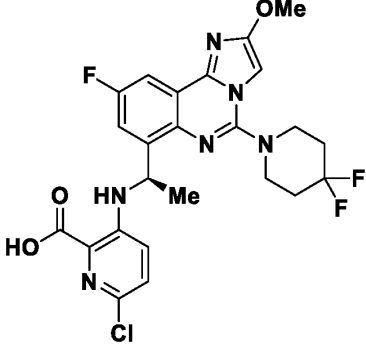
	(<i>R</i>)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-2-(fluoromethyl)-9-methylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid;
	6-chloro-3-(((1<i>R</i>)-1-(9-methyl-5-(tetrahydro-1<i>H</i>-furo[3,4-<i>c</i>]pyrrol-5(3<i>H</i>)-yl)-2-(trifluoromethyl)imidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)picolinic acid;
	2-(((1<i>R</i>)-1-(9-methyl-5-(tetrahydro-1<i>H</i>-furo[3,4-<i>c</i>]pyrrol-5(3<i>H</i>)-yl)-2-(trifluoromethyl)imidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)benzoic acid;
	(<i>R</i>)-6-chloro-3-((1-(2-cyano-5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;

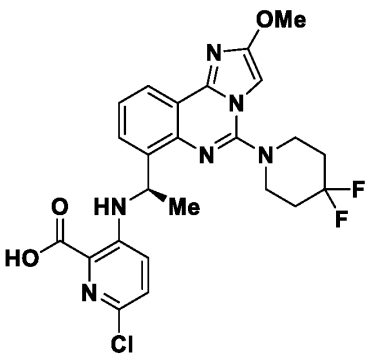
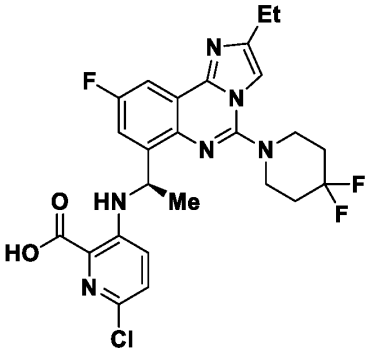
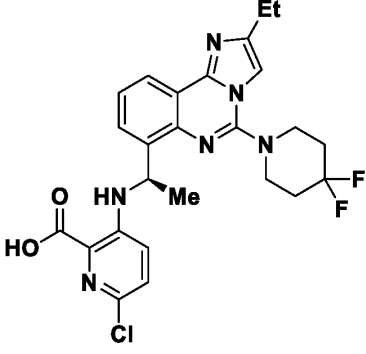
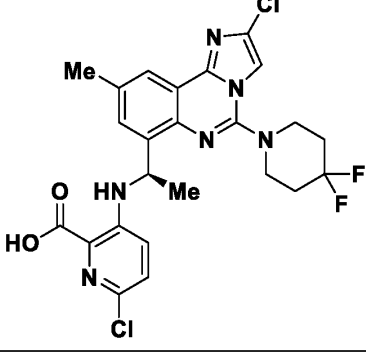
	(R)-6-chloro-3-((1-(2-cyano-9-methyl-5-morpholinoimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(R)-2-fluoro-6-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid;
	(R)-5-fluoro-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid;
	(R)-4-fluoro-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid;

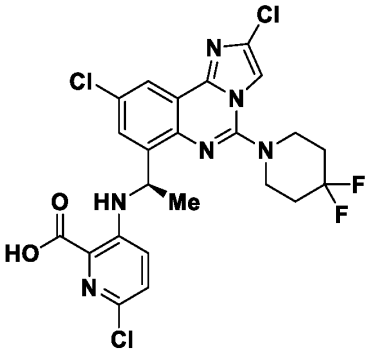
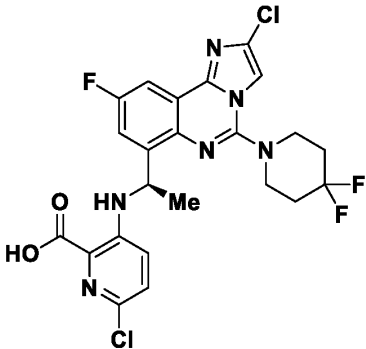
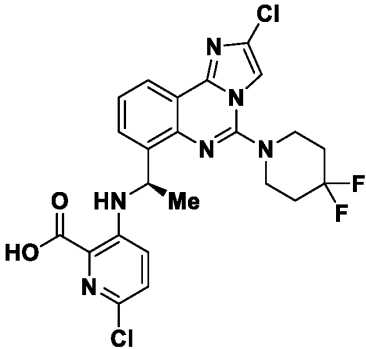
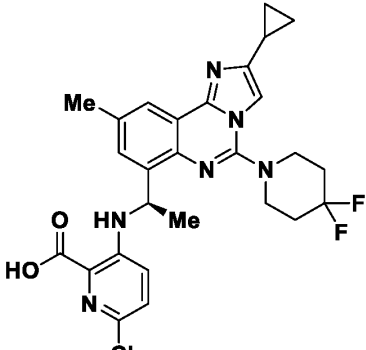
	(<i>R</i>)-3-fluoro-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid;
	6-chloro-3-(((1<i>R</i>)-1-(9-methyl-5-(tetrahydrofuran-3-yl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	2-(((1<i>R</i>)-1-(9-methyl-5-(tetrahydrofuran-3-yl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid;
	(<i>R</i>)-4-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)thiophene-3-carboxylic acid;

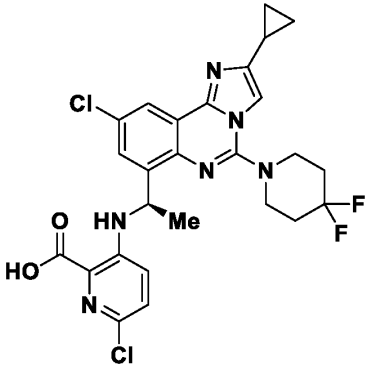
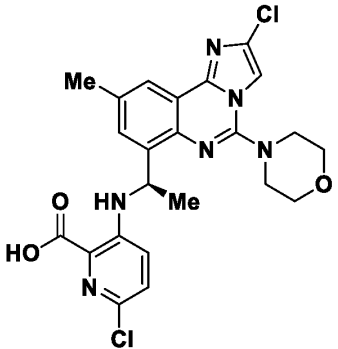
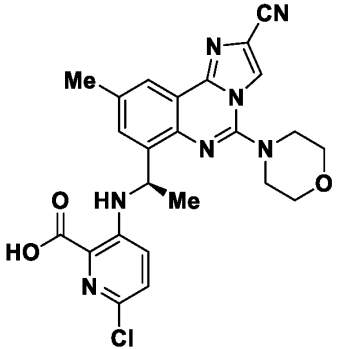
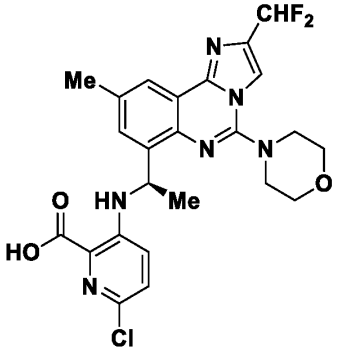
	(<i>R</i>)-4-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)isothiazole-3-carboxylic acid;
	(<i>R</i>)-6-chloro-3-((1-(9-chloro-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-6-chloro-3-((1-(9-fluoro-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-6-chloro-3-((1-(5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;

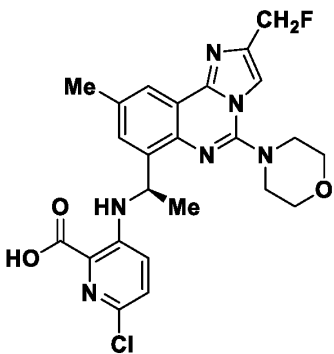
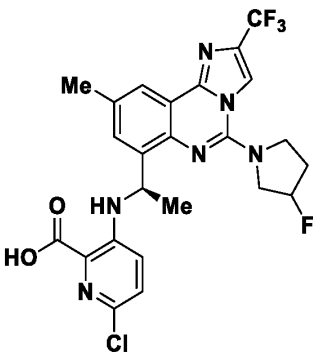
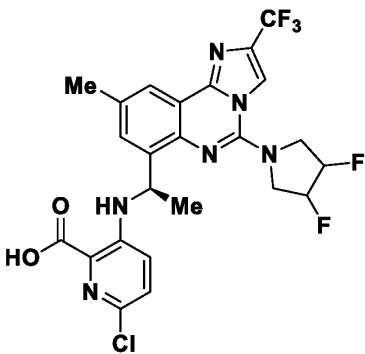
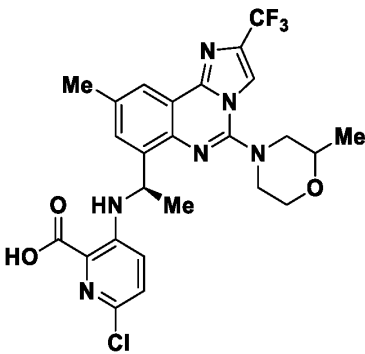
	(<i>R</i>)-6-chloro-3-((1-(9-chloro-5-(4,4-difluoropiperidin-1-yl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-fluoro-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2-ethyl-9-methylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;

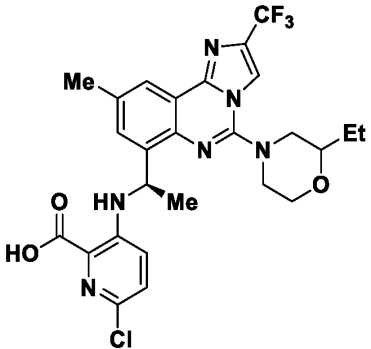
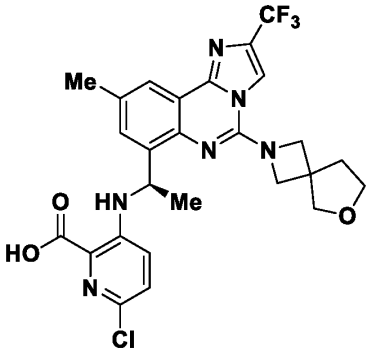
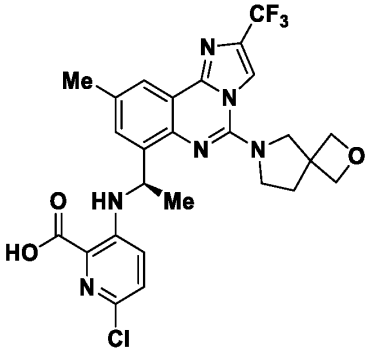
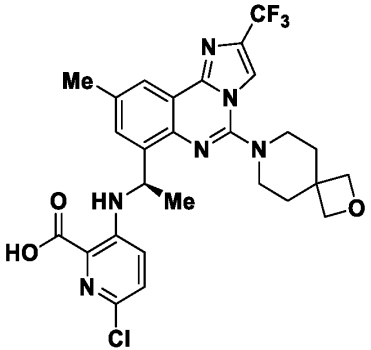
	(<i>R</i>)-6-chloro-3-((1-(9-chloro-5-(4,4-difluoropiperidin-1-yl)-2-ethylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2-methoxy-9-methylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-6-chloro-3-((1-(9-chloro-5-(4,4-difluoropiperidin-1-yl)-2-methoxyimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-fluoro-2-methoxyimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;

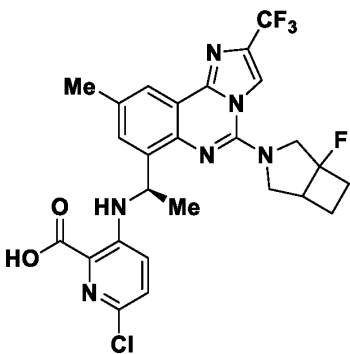
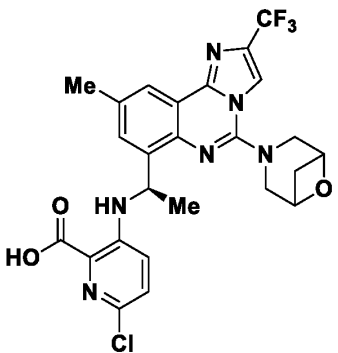
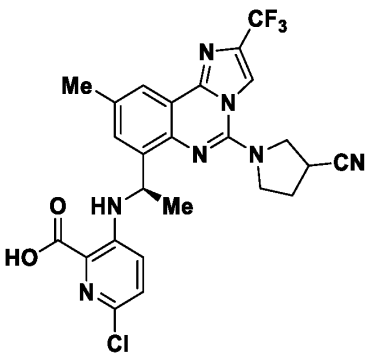
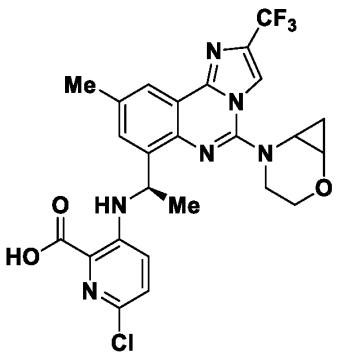
	(R)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2-methoxyimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(R)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2-ethyl-9-fluoroimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(R)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2-ethylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(R)-6-chloro-3-((1-(2-chloro-5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;

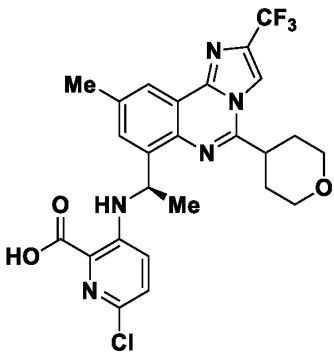
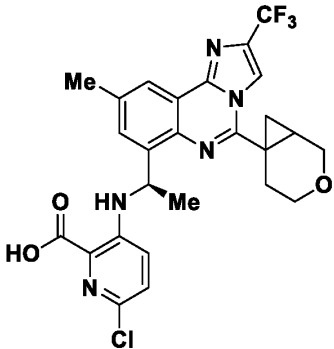
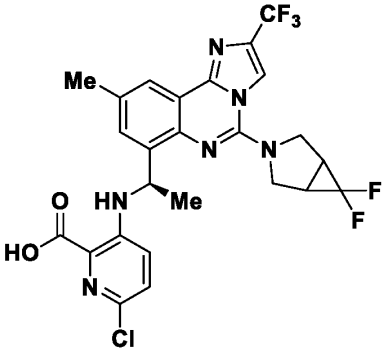
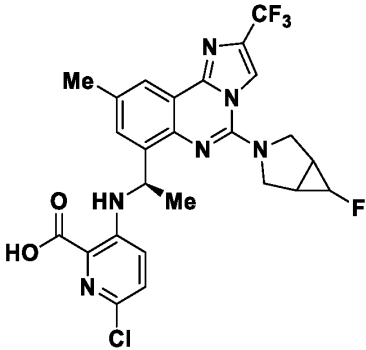
	(R)-6-chloro-3-((1-(2,9-dichloro-5-(4,4-difluoropiperidin-1-yl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(R)-6-chloro-3-((1-(2-chloro-5-(4,4-difluoropiperidin-1-yl)-9-fluoroimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(R)-6-chloro-3-((1-(2-chloro-5-(4,4-difluoropiperidin-1-yl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(R)-6-chloro-3-((1-(2-cyclopropyl-5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;

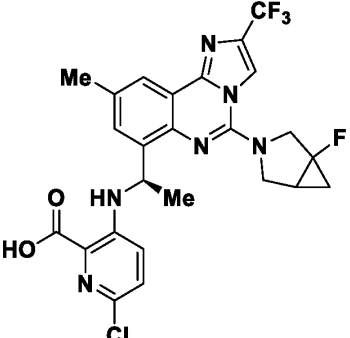
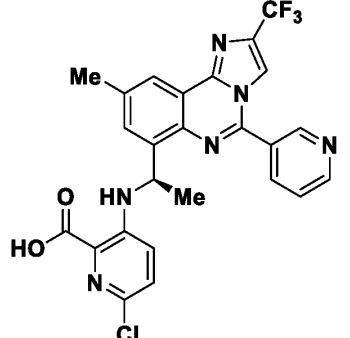
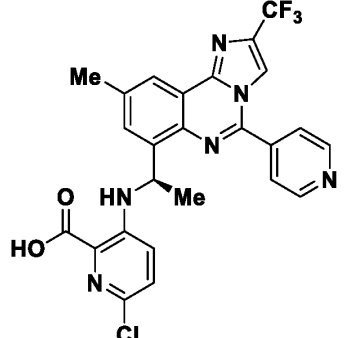
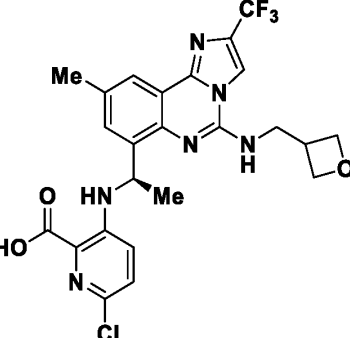
	(<i>R</i>)-6-chloro-3-((1-(9-chloro-2-cyclopropyl-5-(4,4-difluoropiperidin-1-yl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-6-chloro-3-((1-(2-chloro-9-methyl-5-morpholinoimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-6-chloro-3-((1-(2-cyano-9-methyl-5-morpholinoimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-6-chloro-3-((1-(2-(difluoromethyl)-9-methyl-5-morpholinoimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;

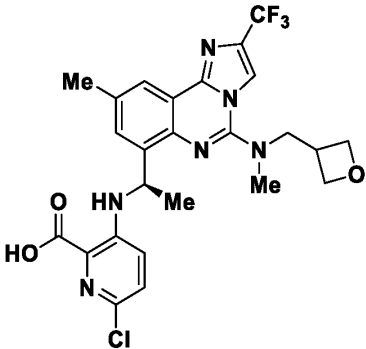
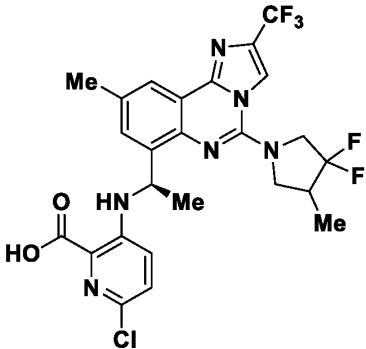
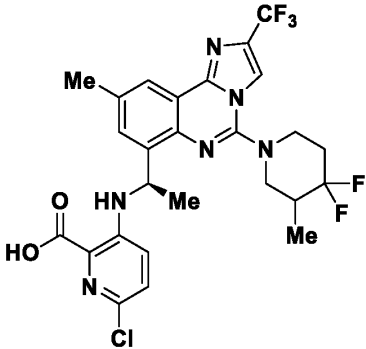
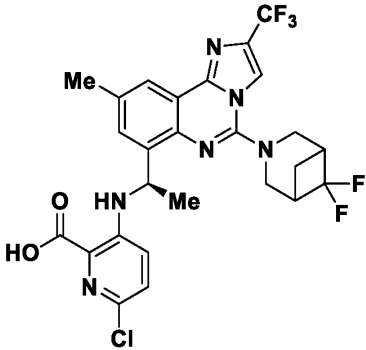
	(<i>R</i>)-6-chloro-3-((1-(2-(fluoromethyl)-9-methyl-5-morpholinoimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	6-chloro-3-(((1 <i>R</i>)-1-(5-(3-fluoropyrrolidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	6-chloro-3-(((1 <i>R</i>)-1-(5-(3,4-difluoropyrrolidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	6-chloro-3-(((1 <i>R</i>)-1-(9-methyl-5-(2-methylmorpholino)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;

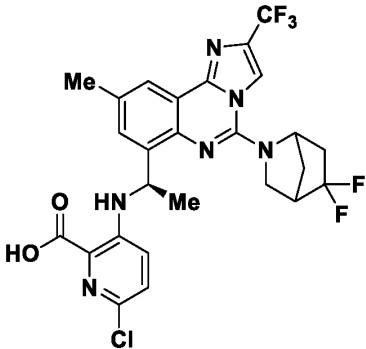
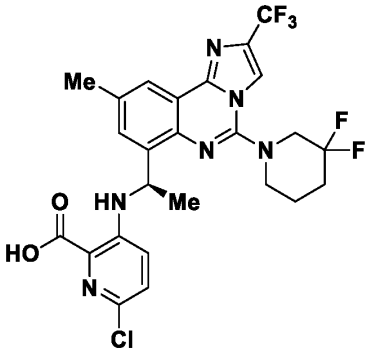
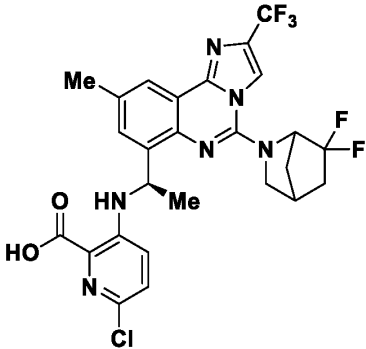
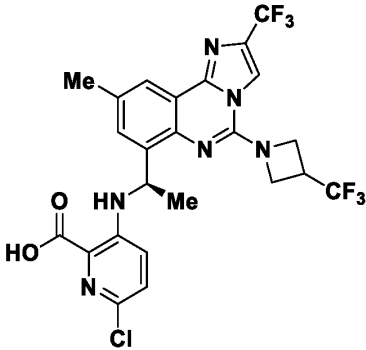
	6-chloro-3-(((1<i>R</i>)-1-(5-(2-ethylmorpholino)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-6-chloro-3-((1-(9-methyl-5-(6-oxa-2-azaspiro[3.4]octan-2-yl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-6-chloro-3-((1-(9-methyl-5-(2-oxa-6-azaspiro[3.4]octan-6-yl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-6-chloro-3-((1-(9-methyl-5-(2-oxa-7-azaspiro[3.5]nonan-7-yl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;

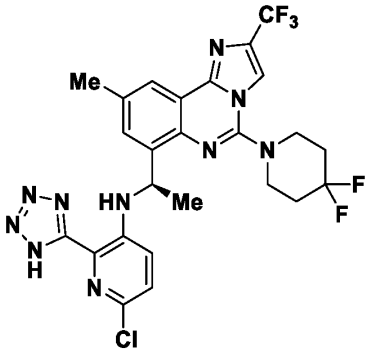
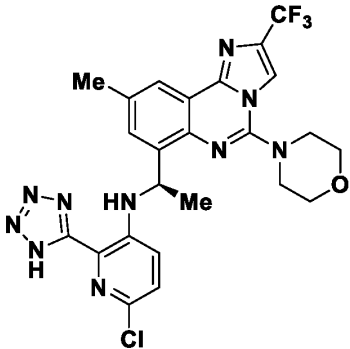
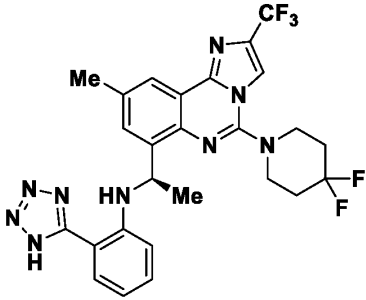
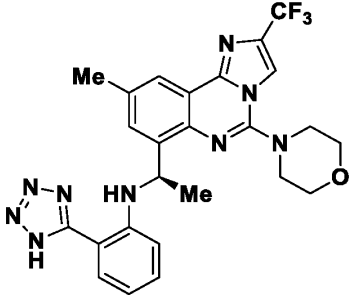
	6-chloro-3-(((1 <i>R</i>)-1-(5-(1-fluoro-3-azabicyclo[3.2.0]heptan-3-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	3-(((1 <i>R</i>)-1-(5-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)-6-chloropicolinic acid;
	6-chloro-3-(((1 <i>R</i>)-1-(5-(3-cyanopyrrolidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	3-(((1 <i>R</i>)-1-(5-(2-oxa-5-azabicyclo[4.1.0]heptan-5-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)-6-chloropicolinic acid;

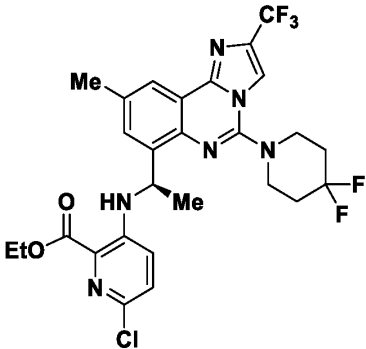
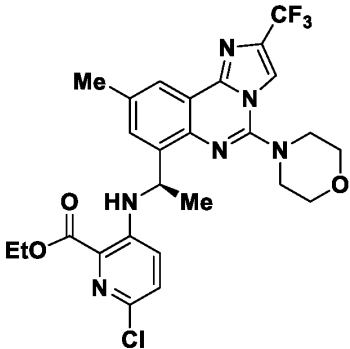
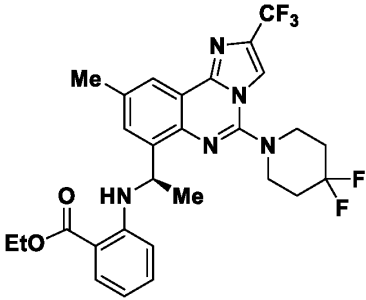
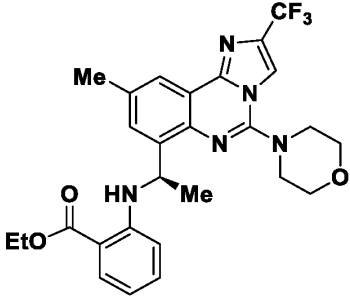
	(<i>R</i>)-6-chloro-3-(((1-(9-methyl-5-(tetrahydro-2<i>H</i>-pyran-4-yl)-2-(trifluoromethyl)imidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)picolinic acid;
	3-(((1<i>R</i>)-1-(5-(3-oxabicyclo[4.1.0]heptan-6-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)-6-chloropicolinic acid;
	6-chloro-3-(((1<i>R</i>)-1-(5-(6,6-difluoro-3-azabicyclo[3.1.0]hexan-3-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)picolinic acid;
	6-chloro-3-(((1<i>R</i>)-1-(5-(6-fluoro-3-azabicyclo[3.1.0]hexan-3-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)picolinic acid;

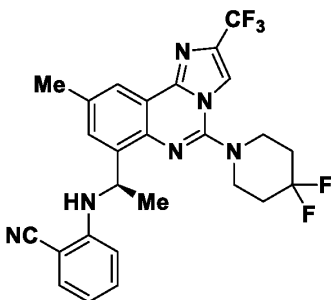
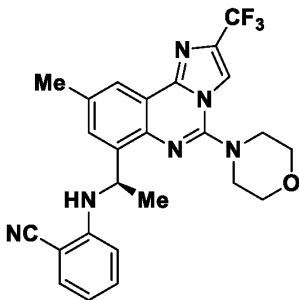
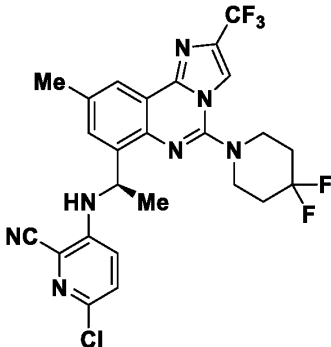
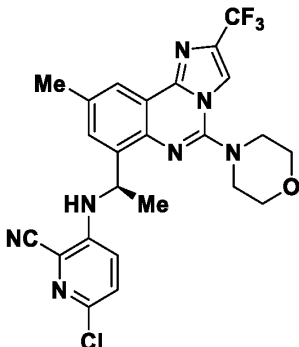
	6-chloro-3-(((1 <i>R</i>)-1-(5-(1-fluoro-3-azabicyclo[3.1.0]hexan-3-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-6-chloro-3-((1-(9-methyl-5-(pyridin-3-yl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-6-chloro-3-((1-(9-methyl-5-(pyridin-4-yl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-6-chloro-3-((1-(9-methyl-5-((oxetan-3-yl)methyl)amino)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;

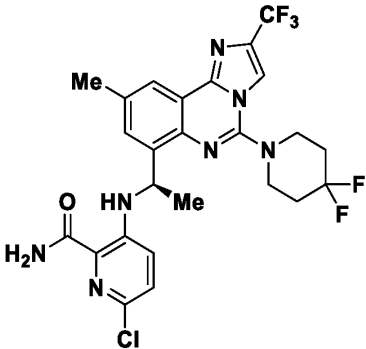
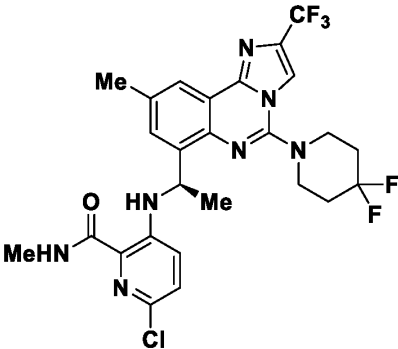
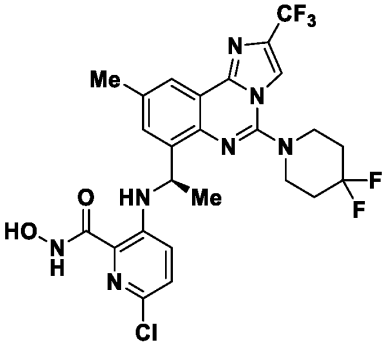
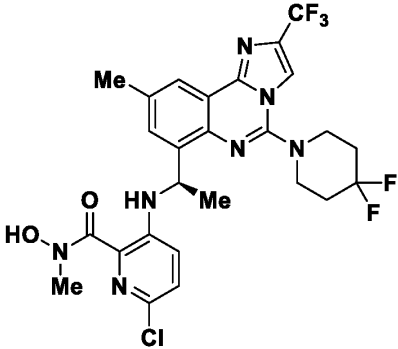
	(<i>R</i>)-6-chloro-3-(((1-(9-methyl-5-(methyl(oxetan-3-ylmethyl)amino)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	6-chloro-3-(((1<i>R</i>)-1-(5-(3,3-difluoro-4-methylpyrrolidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	6-chloro-3-(((1<i>R</i>)-1-(5-(4,4-difluoro-3-methylpiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	6-chloro-3-(((1<i>R</i>)-1-(5-(6,6-difluoro-3-azabicyclo[3.1.1]heptan-3-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;

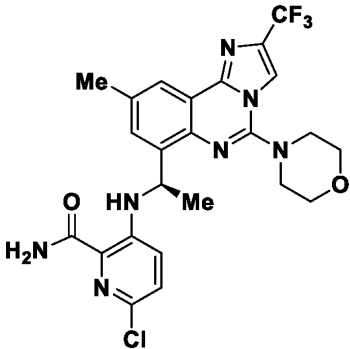
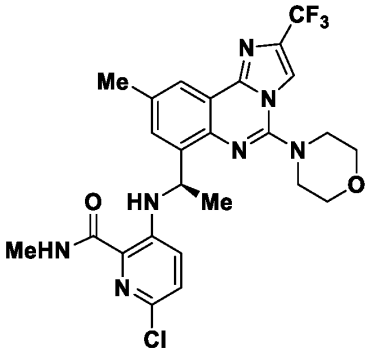
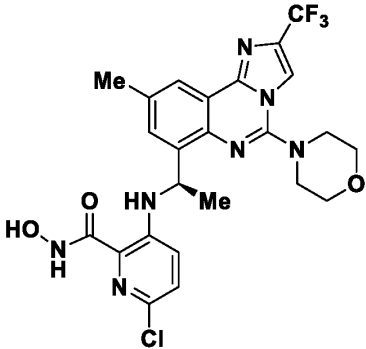
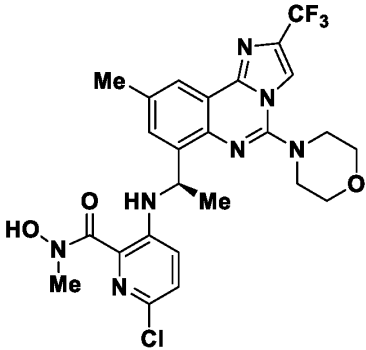
	6-chloro-3-(((1<i>R</i>)-1-(5-(5,5-difluoro-2-azabicyclo[2.2.1]heptan-2-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-6-chloro-3-((1-(5-(3,3-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	6-chloro-3-(((1<i>R</i>)-1-(5-(6,6-difluoro-2-azabicyclo[2.2.1]heptan-2-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;
	(<i>R</i>)-6-chloro-3-((1-(9-methyl-2-(trifluoromethyl)-5-(3-(trifluoromethyl)azetidin-1-yl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid;

	(R)-6-chloro-N-(1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)-2-(1H-tetrazol-5-yl)pyridin-3-amine;
	(R)-6-chloro-N-(1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)-2-(1H-tetrazol-5-yl)pyridin-3-amine;
	(R)-N-(1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)-2-(1H-tetrazol-5-yl)aniline;
	(R)-N-(1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)-2-(1H-tetrazol-5-yl)aniline

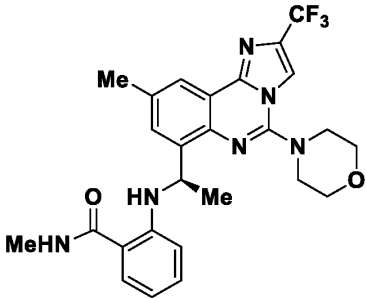
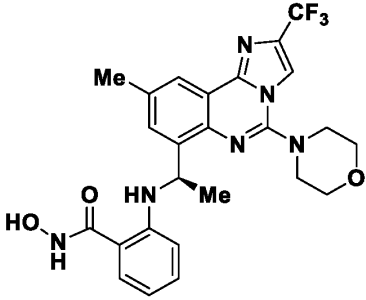
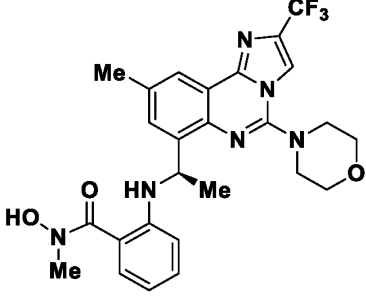
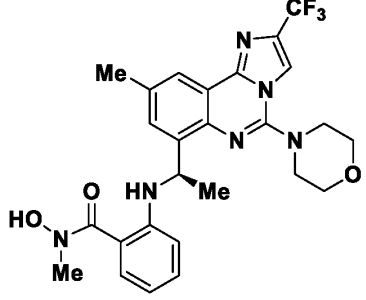
	ethyl (<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinate;
	ethyl (<i>R</i>)-6-chloro-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinate;
	ethyl (<i>R</i>)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoate;
	ethyl (<i>R</i>)-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoate;

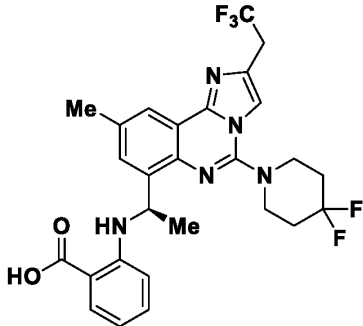
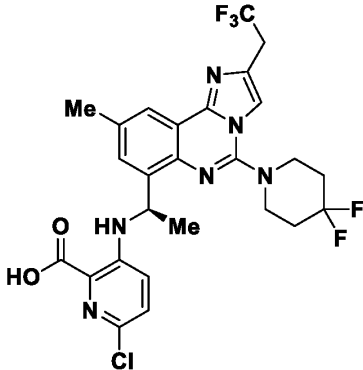
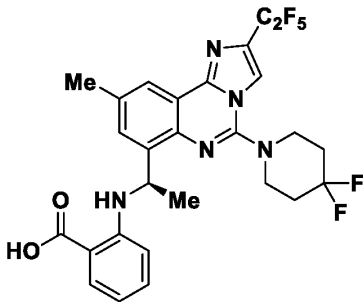
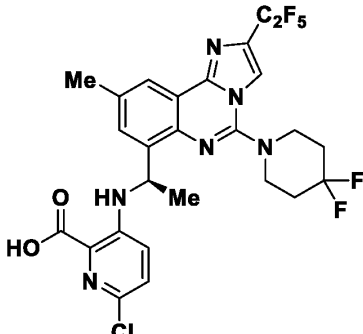
	(R)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzonitrile;
	(R)-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzonitrile;
	(R)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinonitrile
	(R)-6-chloro-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinonitrile;

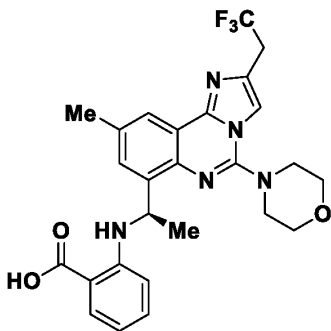
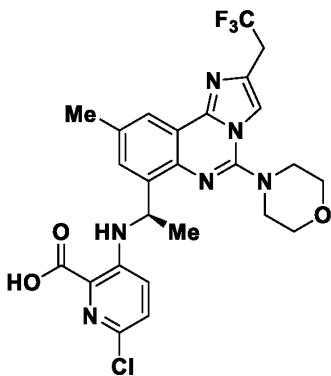
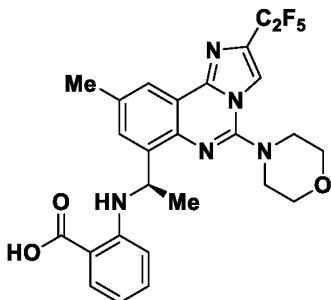
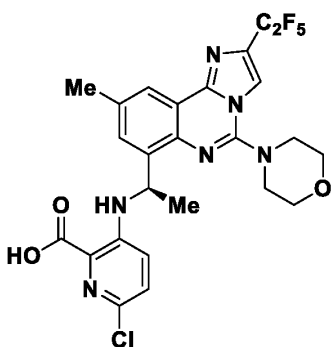
	(<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinamide;
	(<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)-N-methylpicolinamide;
	(<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)-N-hydroxypicolinamide;
	(<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)-N-methyl-N-hydroxy-N-methylpicolinamide;

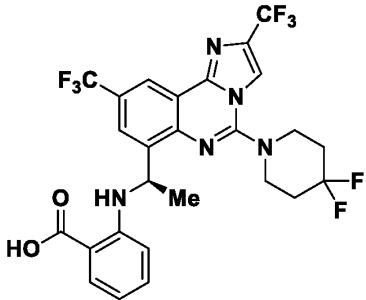
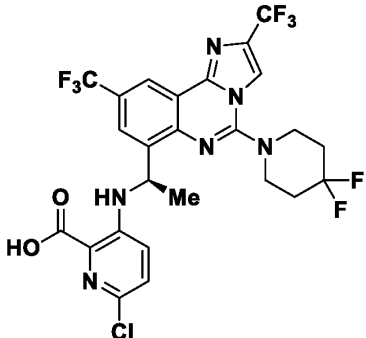
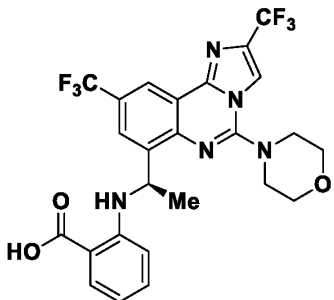
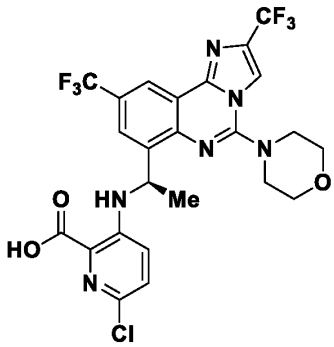
	(<i>R</i>)-6-chloro-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinamide;
	(<i>R</i>)-6-chloro- <i>N</i> -methyl-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinamide;
	(<i>R</i>)-6-chloro- <i>N</i> -hydroxy-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinamide;
	(<i>R</i>)-6-chloro- <i>N</i> -hydroxy- <i>N</i> -methyl-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinamide;

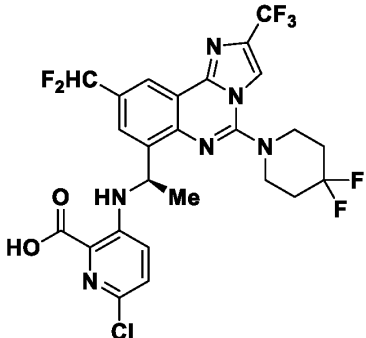
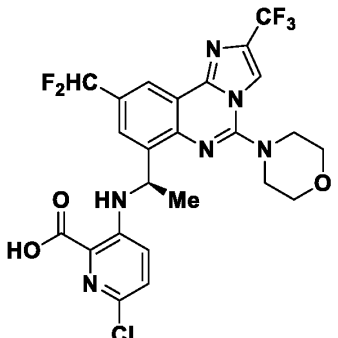
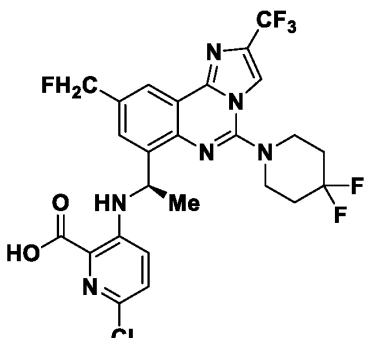
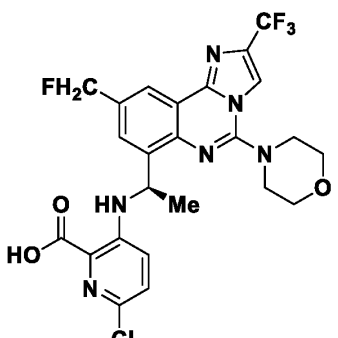
Chemical structure of (R)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzamide; The structure features a quinazoline core with a trifluoromethyl group at position 2, a methyl group at position 9, and a 4,4-difluoropiperidin-1-yl group at position 5. The quinazoline is substituted at position 7 with a 1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl group, which is further substituted with an amino group at position 1. The amino group is attached to a benzamide moiety at position 2.	(R)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzamide;
Chemical structure of (R)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)-N-methylbenzamide; The structure is identical to the first entry, except the benzamide moiety is replaced by an N-methylbenzamide moiety.	(R)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)-N-methylbenzamide;
Chemical structure of (R)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)-N-hydroxybenzamide; The structure is identical to the first entry, except the benzamide moiety is replaced by an N-hydroxybenzamide moiety.	(R)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)-N-hydroxybenzamide;
Chemical structure of (R)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)-N-methyl-N-hydroxybenzamide; The structure is identical to the first entry, except the benzamide moiety is replaced by an N-methyl-N-hydroxybenzamide moiety.	(R)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)-N-methyl-N-hydroxybenzamide;
Chemical structure of (R)-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzamide; The structure features a quinazoline core with a trifluoromethyl group at position 2, a methyl group at position 9, and a morpholino group at position 5. The quinazoline is substituted at position 7 with a 1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl group, which is further substituted with an amino group at position 1. The amino group is attached to a benzamide moiety at position 2.	(R)-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzamide;

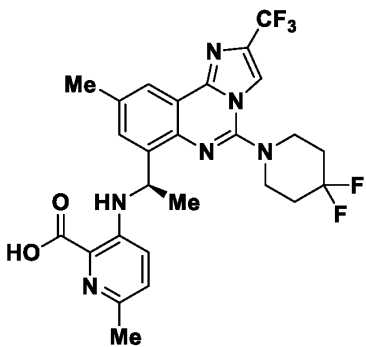
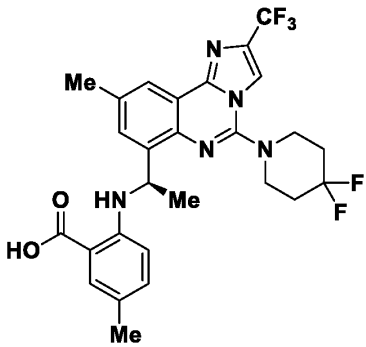
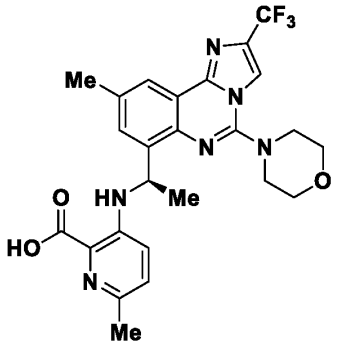
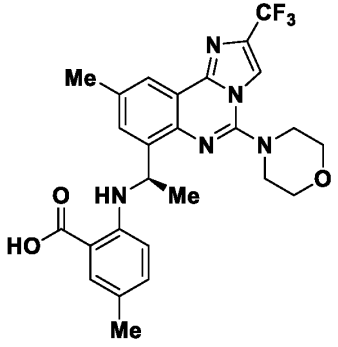
	(<i>R</i>)-<i>N</i>-methyl-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzamide;
	(<i>R</i>)-<i>N</i>-hydroxy-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzamide;
	(<i>R</i>)-<i>N</i>-hydroxy-<i>N</i>-methyl-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzamide;
	(<i>R</i>)-<i>N</i>-hydroxy-<i>N</i>-methyl-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzamide

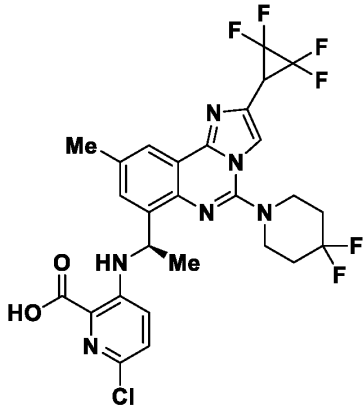
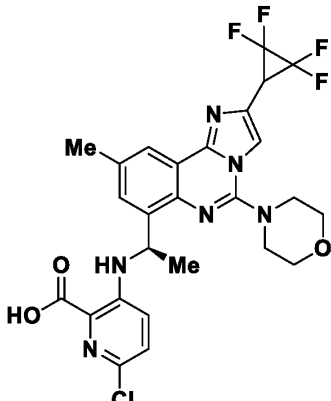
	(<i>R</i>)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(2,2,2-trifluoroethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(2,2,2-trifluoroethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
	(<i>R</i>)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(perfluoroethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(perfluoroethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid

	(R)-2-((1-(9-methyl-5-morpholino-2-(2,2,2-trifluoroethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(R)-6-chloro-3-((1-(9-methyl-5-morpholino-2-(2,2,2-trifluoroethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
	(R)-2-((1-(9-methyl-5-morpholino-2-(perfluoroethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(R)-6-chloro-3-((1-(9-methyl-5-morpholino-2-(perfluoroethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid

	(R)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-2,9-bis(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(R)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2,9-bis(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
	(R)-2-((1-(5-morpholino-2,9-bis(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid
	(R)-6-chloro-3-((1-(5-morpholino-2,9-bis(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid

	(R)-6-chloro-3-((1-(9-(difluoromethyl)-5-(4,4-difluoropiperidin-1-yl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
	(R)-6-chloro-3-((1-(9-(difluoromethyl)-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
	(R)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-(fluoromethyl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
	(R)-6-chloro-3-((1-(9-(fluoromethyl)-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid

	(<i>R</i>)-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)-6-methylpicolinic acid
	(<i>R</i>)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)-5-methylbenzoic acid
	(<i>R</i>)-6-methyl-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
	(<i>R</i>)-5-methyl-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid

	(<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(2,2,3,3-tetrafluorocyclopropyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
	(<i>R</i>)-6-chloro-3-((1-(9-methyl-5-morpholino-2-(2,2,3,3-tetrafluorocyclopropyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid

and pharmaceutically acceptable salts of the foregoing compounds.

PHARMACEUTICAL COMPOSITIONS

[00350] The compounds of Formula I may be formulated into pharmaceutical compositions.

[00351] 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.

[00352] 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.

[00353] 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).

[00354] 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.

[00355] The pharmaceutical compositions comprising compounds of the present invention may be used in the methods described herein.

[00356] METHODS OF USE

[00357] 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).

[00358] In some embodiments, the PI3K inhibitor (e.g., PI3K α inhibitor or PI3K α H1047R mutant inhibitor) is a compound of Formula (I), (IIa), (IIb), (IIc) 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.

[00359] 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).

[00360] In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (I), (IIa), (IIb), (IIc), or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, and a pharmaceutically acceptable diluent or carrier.

[00361] 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).

[00362] 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), (IIa), (IIb), (IIc), or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof.

[00363] 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 .

[00364] 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.

[00365] The compositions and methods provided herein may be used for the treatment of a wide variety of cancer 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).

[00366] 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,

[00367] 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.

[00368] In another embodiment, the cancer is gastric, breast, colorectal, or endometrial cancer.

[00369] In another embodiment, the cancer is gastric cancer.

[00370] In another embodiment, the cancer is breast cancer.

[00371] In another embodiment, the cancer is colorectal cancer.

[00372] In another embodiment, the cancer is endometrial cancer.

[00373] 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.

[00374] 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.

[00375] 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.

[00376] 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.

[00377] 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.

[00378] 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.

[00379] 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.

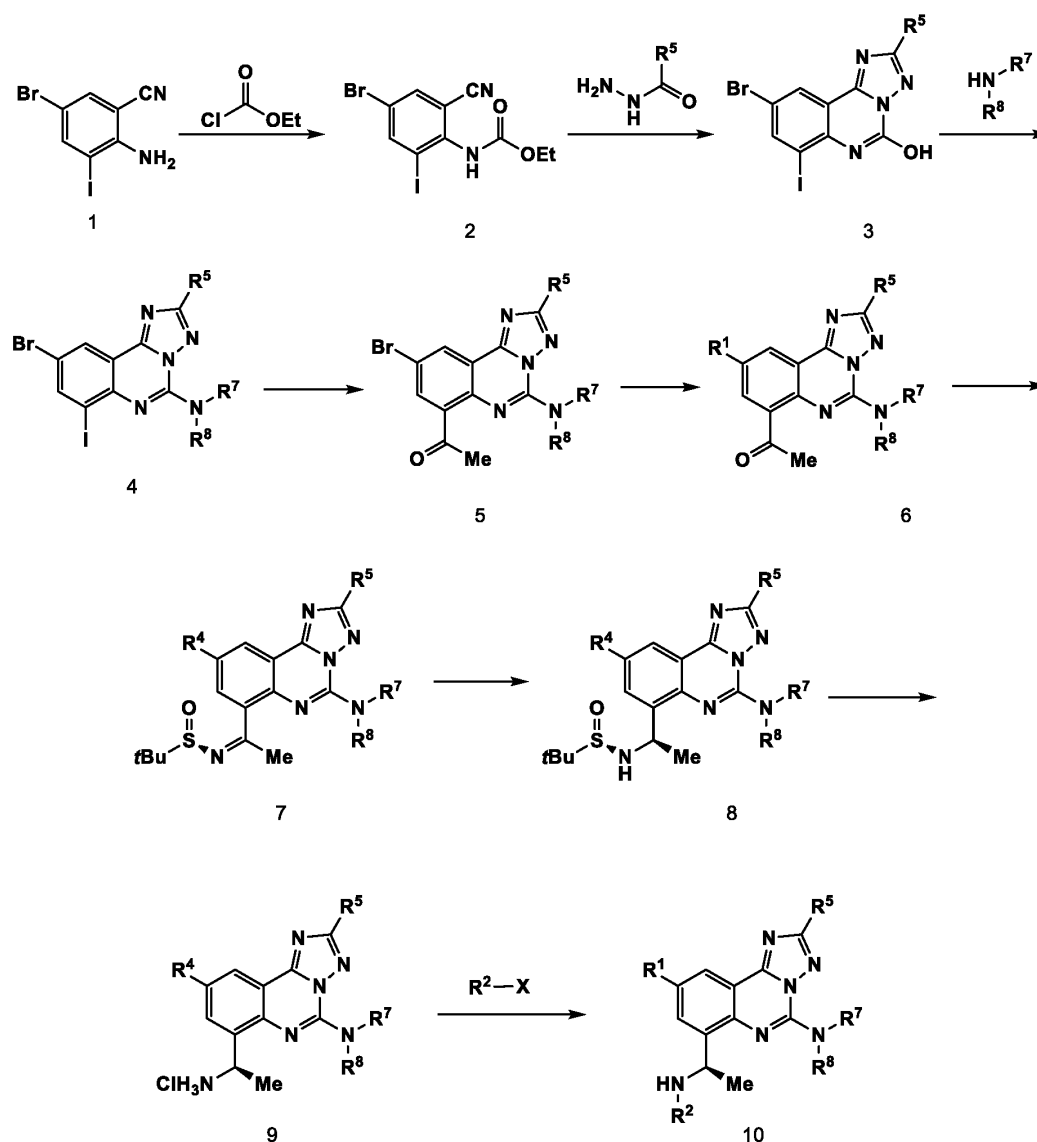
GENERAL REACTION SCHEMES, INTERMEDIATES AND EXAMPLES

[00380] 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.

[00381] 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.

[00382] For instance, intermediates for preparing compounds and compounds of Formula (I) of the present invention may be prepared according to General Reaction Schemes I, II, III, and IV:

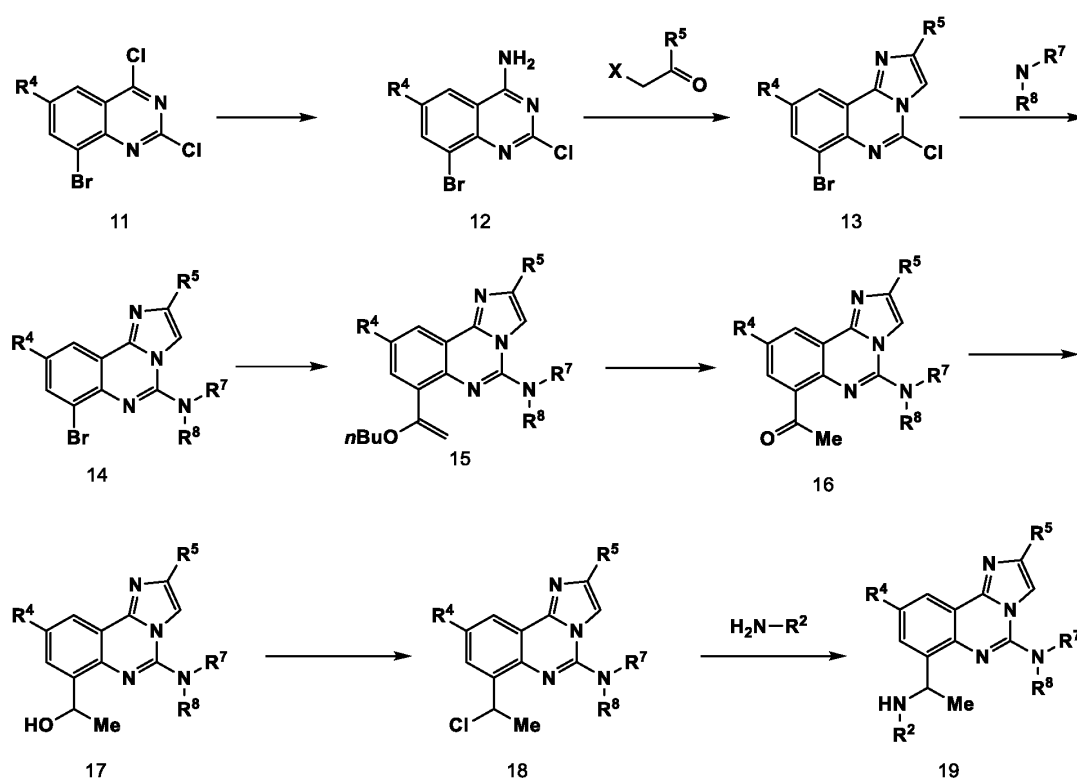
General Reaction Scheme I



[00383] For General Reaction Scheme I, Compound 10 is an example of Formula (I). In this General Reaction Scheme I, Compound 1 is reacted with ethyl chloroformate at elevated temperature, to yield Compound 2. Reaction of compound 2 with an appropriate hydrazide at elevated temperature can produce compound 3. Compound 3 can then undergo an activation such as with phosphorous oxychloride to yield an aryl chloride that is capable of reacting with an amine, or can be activated in situ through the use of a coupling reagent such as benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate followed by addition of a desired amine to yield compound 4. Compound 4 can undergo a Heck or Stille coupling using an enol ether coupling partner to form ketone product 5 upon acidic work-up. Compound

5 could then undergo a cross-coupling such as a Suzuki reaction with an alkyl boronic acid to produce compound 6. After condensation with a chiral sulfinamide, for example Ellman's auxiliary, using a Lewis acid such as titanium (IV) ethoxide, imine 7 can be produced. The reduction of compound 7 to form sulfinamide 8 could be effected using a reductant such as diisobutylaluminum hydride, sodium borohydride, or zirconocene chloride hydride. After acidic deprotection of 8 using, for example, hydrochloric acid in dioxane, amine salt 9 could be substituted to prepare compound 10 through nucleophilic substitution or metal catalyzed reaction in the presence of an appropriate base.

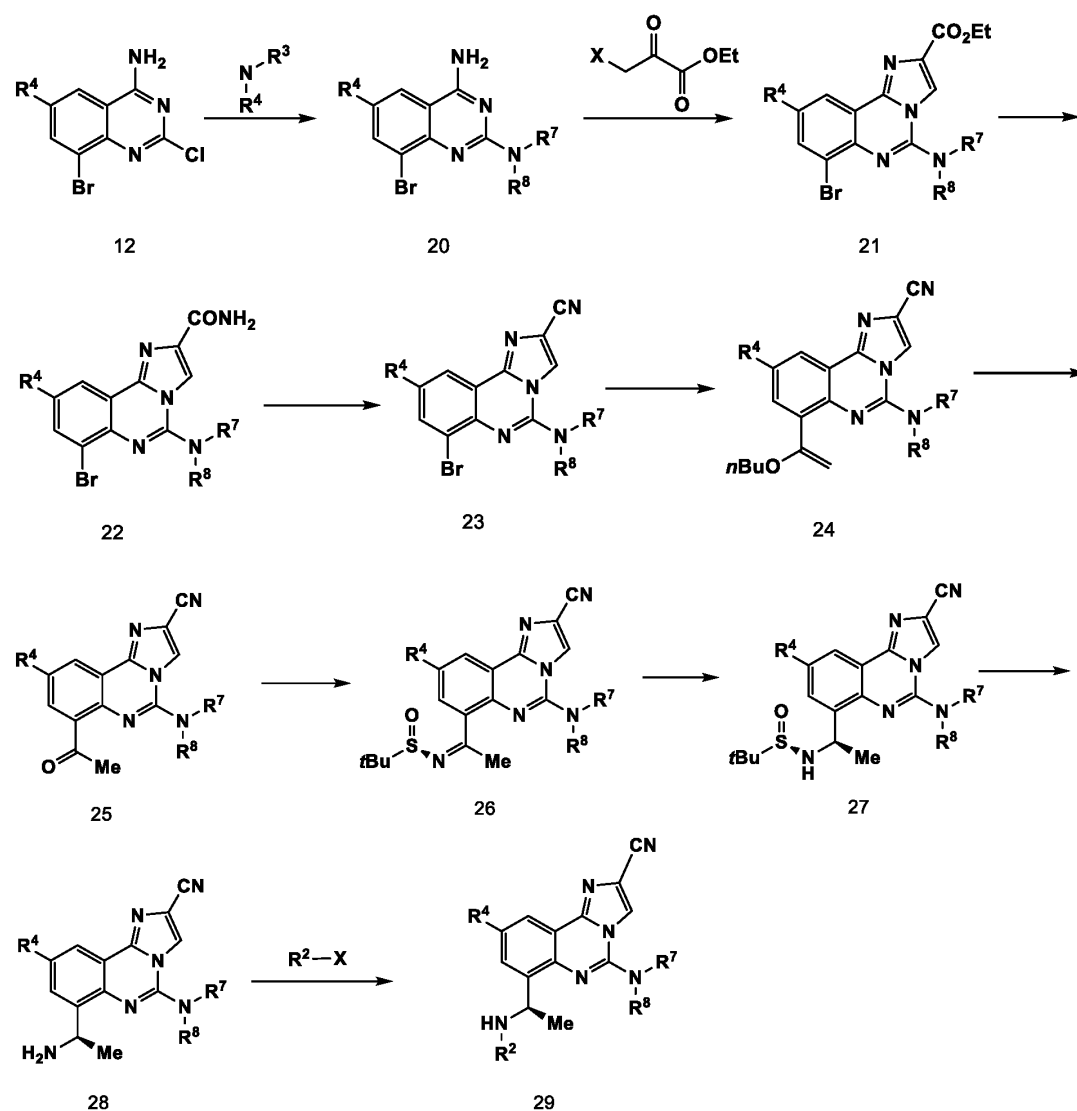
General Reaction Scheme II



[00384] For General Reaction Scheme II, Compound 19 is an example of Formula (I). In this General Reaction Scheme II, 11 is reacted with ammonia in methanol to prepare Compound 12. Compound 12 can undergo condensation with a suitable α -halo aldehyde or ketone at elevated temperature to prepare 13. Compound 13 is subsequently reacted with a substituted amine in the presence of a suitable base such as diisopropylethylamine at elevated temperatures to provide 14. Aryl bromide 14 can undergo a Heck or Stille coupling using an

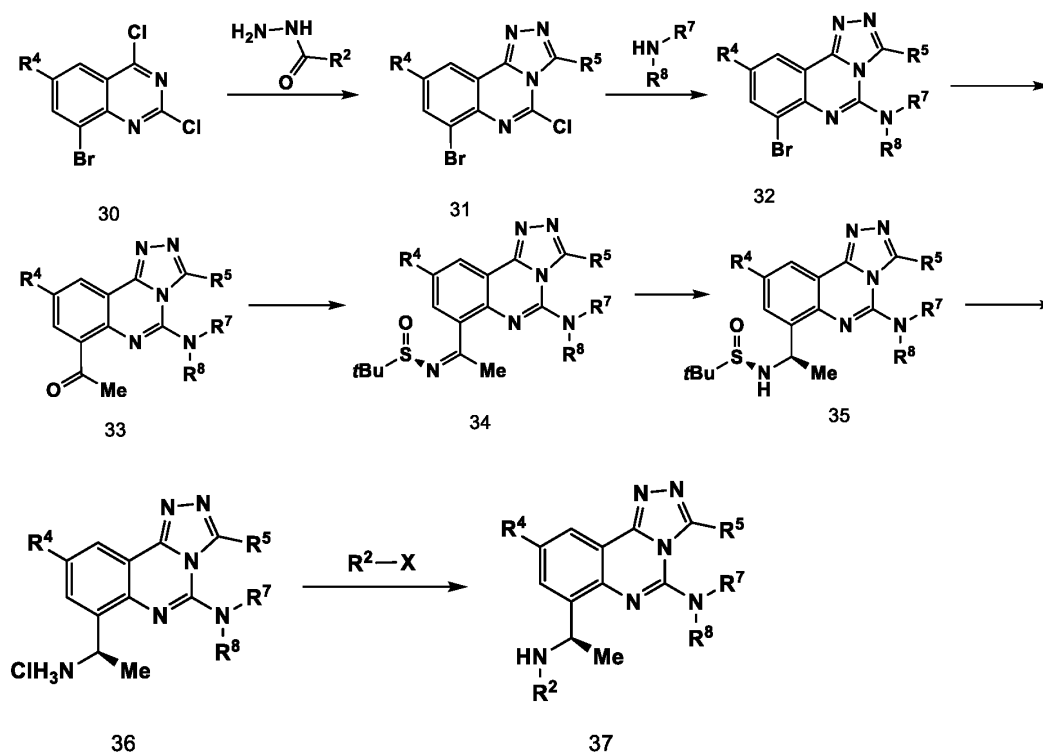
enol ether coupling partner to form vinyl ether 15, which, upon exposure to a suitable acid such as hydrogen chloride or trifluoroacetic acid, will provide 16. Reduction of ketone 16 can be effected using common reductants such as sodium borohydride to provide compound 17. Conversion of alcohol 17 to chloride 18 can be effected with chlorinating reagents such as thionyl chloride. Compound 19 can be accessed through nucleophilic displacement of the alkyl chloride using a desired aniline in the presence of a salt such as potassium iodide and suitable base such as diisopropylethylamine.

General Reaction Scheme III



[00385] For General Reaction Scheme III, Compound 29 is an example of Formula (I). In this General Reaction Scheme III, the preparation of compound 12 is identical to General Reaction Scheme II. Compound 12 is subsequently reacted with a substituted amine in the presence of a suitable base such as diisopropylethylamine at elevated temperatures to provide 20. Compound 20 can undergo condensation and with a 3-halo-2-oxopropanoate to provide ester 21. Ester aminolysis can be effected using a reagent such as ammonia in methanol to prepare amide 22. Reaction of 22 with a suitable dehydrating reagent such as trifluoroacetic anhydride can provide 23. Aryl bromide 23 can undergo a Heck or Stille coupling using an enol ether coupling partner to form vinyl ether 24, which, upon exposure to a suitable acid such as hydrogen chloride or trifluoroacetic acid, will provide 25. After condensation with a chiral sulfinamide, for example Ellman's auxiliary, using a Lewis acid such as titanium (IV) ethoxide, imine 26 can be produced. The reduction of compound 26 to form sulfinamide 27 could be effected using a reductant such as diisobutylaluminum hydride, sodium borohydride, or zirconocene chloride hydride. After oxidative deprotection of 27 using, for example, molecular iodine, the resulting amine 28 could be substituted to prepare compound 29 through nucleophilic substitution or metal catalyzed reaction in the presence of an appropriate base.

General Reaction Scheme IV

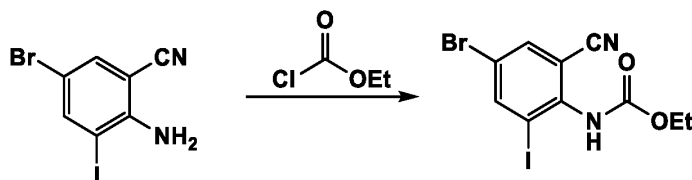


[00386] For General Reaction Scheme IV, Compound 37 is an example of Formula (I). In this General Reaction Scheme IV, compound 30 can undergo nucleophilic aromatic substitution and condensation with an appropriate hydrazide in the presence of a suitable base such as diisopropylethylamine and dehydrating reagent such as phosphorous oxychloride to provide 31. A substituted amine can be used in a nucleophilic aromatic substitution of compound 31 in the presence of a suitable base such as diisopropylethylamine to provide compound 32. Aryl bromide 32 can undergo a Heck or Stille coupling using an enol ether coupling partner to form ketone product 33 upon acidic work-up. After condensation with a chiral sulfinamide, for example Ellman's auxiliary, using a Lewis acid such as titanium (IV) ethoxide, imine 34 can be produced. The reduction of compound 34 to form sulfinamide 35 could be effected using a reductant such as diisobutylaluminum hydride, sodium borohydride, or zirconocene chloride hydride. After acidic deprotection of 35 using, for example, hydrochloric acid in dioxane, amine salt 36 could be substituted to prepare compound 37 through nucleophilic substitution or metal catalyzed reaction in the presence of an appropriate base.

[00387] Substituents shown in Schemes I, II, III, and IV carry the same definitions as set forth above for formula (I).

INTERMEDIATE A

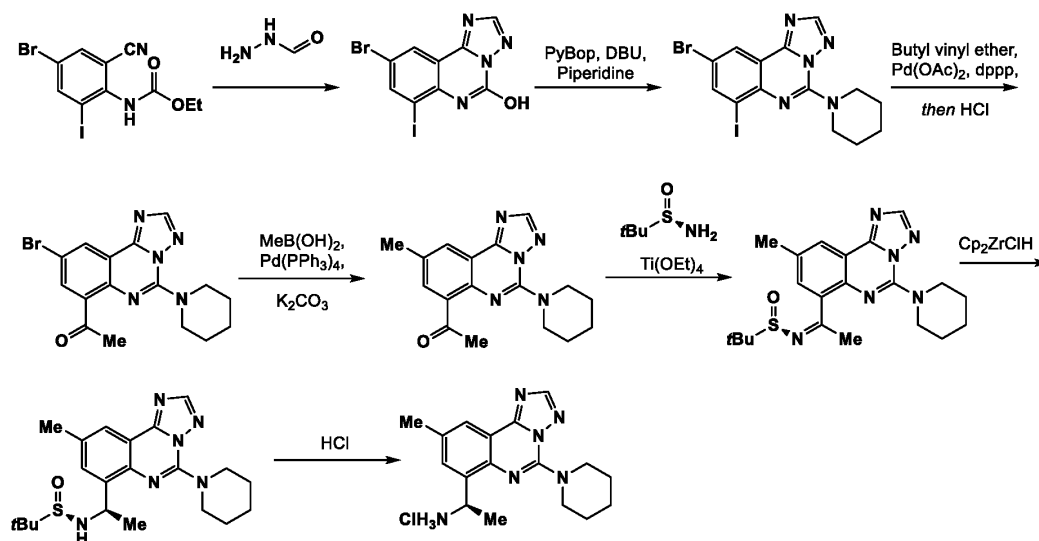
Ethyl (4-bromo-2-cyano-6-iodophenyl)carbamate



[00388] Step A: To a flask fitted with a reflux condenser was added 2-amino-5-bromo-3-iodobenzonitrile (5.4 g, 1.0 eq., 17 mmol), ethyl chloroformate (36 g, 32 mL, 20 eq., 0.33 mol) and a stir bar. This flask was heated to 100 °C for 3 days before being allowed to cool to room temperature. Once cooled, the reaction was concentrated via rotary evaporation. Next, the residue was suspended in diethyl ether and heptane was slowly added to induce crystallization. The suspension was filtered and rinsed with heptane to afford ethyl (4-bromo-2-cyano-6-iodophenyl)carbamate (5.64 g, 14.3 mmol, 85 % yield) as a tan solid. LCMS [M+1]⁺ = 394.8.

[00389] ¹H NMR (500 MHz, CDCl₃) δ ppm = 8.19 (d, *J* = 2.19 Hz, 1 H), 7.79 (d, *J* = 2.19 Hz, 1 H), 6.45 (br s, 1 H), 4.30 (q, *J* = 7.12 Hz, 2 H), 1.34 (t, *J* = 7.12 Hz, 3 H).

INTERMEDIATE B



[00390] Step A: A mixture of ethyl (4-bromo-2-cyano-6-iodophenyl)carbamate (204 mg, 1.0 eq., 516 μ mol) and formylhydrazine (31 mg, 1.0 eq., 520 μ mol) in *N*-methyl-2-pyrrolidinone (2.6 mL) was heated at 160 °C for 3 hour. The reaction mixture was allowed to cool to room temperature and water (2mL) was added followed by pouring the mixture on to ice. The resulting precipitate was collected, washed with diethyl ether, and dried to afford 9-bromo-7-iodo-[1,2,4]triazolo[1,5-c]quinazolin-5(6H)-one (181 mg, 462 μ mol, 89 % yield) as a yellow solid which was used without further purification. LCMS $[M+1]^+ = 390.8$.

[00391] ^1H NMR (400 MHz, CDCl_3) δ ppm = 8.56 (br s, 1 H), 8.48 (d, $J = 2.00$ Hz, 1 H), 8.42 (s, 1 H), 8.21 (d, $J = 1.88$ Hz, 1 H).

[00392] Step B: To a solution of 9-bromo-7-iodo-[1,2,4]triazolo[1,5-c]quinazolin-5(6H)-one (90 mg, 1.0 eq., 0.23 mmol) and Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (0.16 g, 1.3 eq., 0.30 mmol) in dimethyl sulfoxide (0.80 mL) was added 1,8-Diazabicyclo[5.4.0]undec-7-ene (53 mg, 52 μ L, 1.5 eq., 0.35 mmol) at room temperature. The resultant mixture was stirred for 1 hour, at which time piperidine (22 mg, 25 μ L, 1.1 eq., 0.25 mmol) was added dropwise and the reaction was stirred for 12 hours. The reaction was quenched with 10% sodium carbonate and extracted with ethyl acetate. The combined organics were washed successively with water and brine then dried over magnesium sulfate, filtered, and concentrated to a residue. This residue was purified via silica gel chromatography (0% to 70% ethyl acetate in heptane) to provide 9-bromo-7-iodo-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazolin-5(6H)-one (40 mg, 87 μ mol, 38 % yield). LCMS $[M+3]^+ = 460.0$.

[00393] Step C: To a vial and a stir bar was added palladium (II) acetate (7.11 mg, 0.05 eq., 31.7 μ mol), 1,3-bis(diphenylphosphino)propane (26.1 mg, 0.10 eq., 63.3 μ mol), and 9-bromo-7-iodo-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazoline (290 mg, 1.0 eq., 633 μ mol). The flask evacuated and backfilled with nitrogen three times. Next, ethylene glycol (2.53 mL), *N,N*-Dicyclohexylmethylamine (371 mg, 405 μ L, 3.0 eq., 1.90 mmol), and *n*-butyl vinyl ether (317 mg, 410 μ L, 5.0 eq., 3.17 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 (8 mL) was added to the reaction. The reaction was stirred until the ketone deprotection went to completion (ca. 1 hour). 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 1-(9-bromo-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethan-1-one (118 mg, 315 μ mol, 50% yield) as a yellow solid. LCMS [M+1] $\pm$ 374.3.

[00394] ^1H NMR (500 MHz, CDCl_3) δ ppm = 8.64 (d, J = 2.46 Hz, 1 H), 8.34 (s, 1 H), 8.07 (d, J = 2.19 Hz, 1 H), 4.05 - 4.11 (m, 4 H), 2.91 (s, 3 H), 1.81 (br m, 6 H).

[00395] Step D: To a vial was added methylboronic acid (44.4 mg, 2.5 eq., 742 μ mol), 1-(9-bromo-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethan-1-one (111 mg, 1.0 eq., 297 μ mol), potassium carbonate (102 mg, 2.5 eq., 742 μ mol) and Tetrakis(triphenylphosphine)palladium(0) (34.3 mg, 0.1 eq., 29.7 μ mol). The vial was evacuated and backfilled three times with nitrogen. Next, a solution of deoxygenated 1,4-dioxane (1.19 mL) and Water (297 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 1-(9-methyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethan-1-one (56 mg, 0.18 mmol, 61% yield) was obtained as a yellow solid. LCMS [M+1] $\pm$ 310.2.

[00396] ^1H NMR (400 MHz, CDCl_3) δ ppm = 8.36 (d, J = 1.25 Hz, 1 H), 8.34 (s, 1 H), 7.86 (d, J = 2.00 Hz, 1 H), 3.99 - 4.07 (m, 4 H), 2.93 (s, 3 H), 2.53 (s, 3 H), 1.75 - 1.88 (m, 6 H).

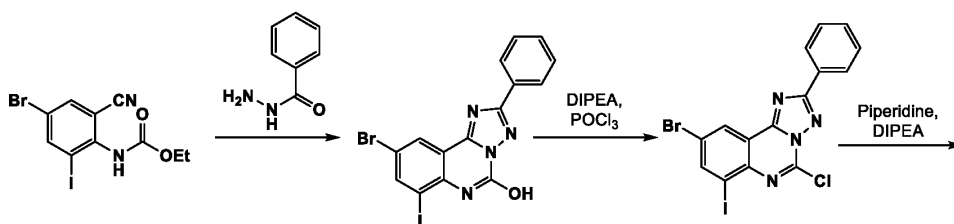
[00397] Step E: To a solution of 1-(9-methyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethan-1-one (56 mg, 1.0 eq., 0.18 mmol) and (*R*)-2-methylpropane-2-sulfinamide (26 mg, 1.2 eq., 0.22 mmol) in tetrahydrofuran (0.72 mL) was added Titanium ethoxide (0.21 g, 0.19 mL, 5.0 eq., 0.91 mmol). 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

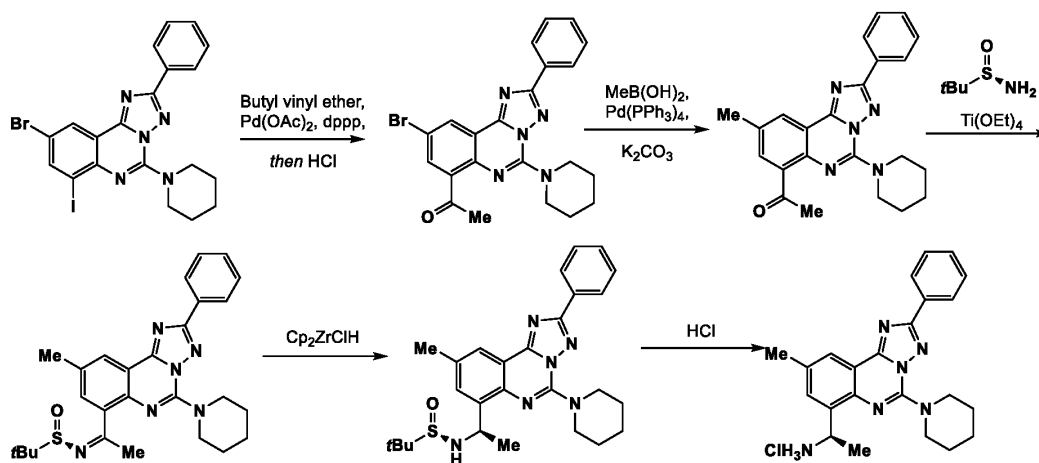
added to form a suspension. The resulting suspension was diluted with ethyl acetate, filtered through a plug of celite, and the filter cake was washed with ethyl acetate several times. The filtrate was concentrated via rotary evaporation to provide (*R*)-2-methyl-*N*-(1-(9-methyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-*c*]quinazolin-7-yl)ethylidene)propane-2-sulfonamide (92 mg crude mass) as a crude yellow solid which was carried forward without further purification.

[00398] Step F: To a solution of (*R*)-2-methyl-*N*-(1-(9-methyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-*c*]quinazolin-7-yl)ethylidene)propane-2-sulfonamide (92 mg, 1.0 eq., 0.22 mmol) in anhydrous dichloromethane (1.5 mL) at room temperature was added Schwartz's reagent (63 mg, 1.1 eq., 0.25 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-(9-methyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-*c*]quinazolin-7-yl)ethyl)propane-2-sulfonamide (47 mg, 0.11 mmol, 51% yield) as a white solid. LCMS $[M+1]^+ = 415.2$.

[00399] Step G: To a solution of (*R*)-2-methyl-*N*-((*R*)-1-(9-methyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-*c*]quinazolin-7-yl)ethyl)propane-2-sulfonamide (47 mg, 1.0 eq., 0.11 mmol) in methanol (0.45 mL) at room temperature was added 71 μ L of HCl (4M in 1,4-dioxane). The reaction was monitored for conversion by LCMS and once complete, triturated with diethyl ether to provide (*R*)-1-(9-methyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-*c*]quinazolin-7-yl)ethan-1-amine, hydrochloride as a salt which was used without further purification. LCMS $[M+1]^+ = 311.1$.

INTERMEDIATE C





[00400] Step A: A mixture of ethyl (4-bromo-2-cyano-6-iodophenyl)carbamate (500 mg, 1.0 eq., 1.27 mmol) and benzohydrazide (181 mg, 1.05 eq., 1.33 mmol) in *N*-methyl-2-pyrrolidinone (6.33 mL) was heated at 160 °C for 3 hour. The reaction mixture was allowed to cool to room temperature and water (10 mL) added followed by pouring the mixture on to ice. The resulting precipitate was collected and washed with diethyl ether to afford 9-bromo-7-iodo-2-phenyl-[1,2,4]triazolo[1,5-c]quinazolin-5(6H)-one (548 mg, 1.17 mmol, 93% yield) as a yellow solid which was used without further purification. LCMS $[M+1]^+ = 466.9$.

[00401] ^1H NMR (500 MHz, DMSO- d_6) δ ppm = 10.93 (br s, 1 H), 8.39 (d, $J = 2.19$ Hz, 1 H), 8.34 (d, $J = 2.19$ Hz, 1 H), 8.19 - 8.26 (m, 2 H), 7.55 - 7.61 (m, 3 H).

[00402] Step B: To a vial charged with 9-bromo-7-iodo-2-phenyl-[1,2,4]triazolo[1,5-c]quinazolin-5(6H)-one (291 mg, 1.0 eq., 623 μmol) and stir bar was added successively phosphorous oxychloride (955 mg, 581 μL , 10 eq., 6.23 mmol) and *N,N*-diisopropylethylamine (322 mg, 434 μL , 4.0 eq., 2.49 mmol). This vial was sealed and heated to 100 °C for 12 hours. The reaction was next allowed to cool to room temperature and its contents were concentrated under vacuum to provide a dark residue. To this residue was added ice and the contents were mixed. After melting, the aqueous suspension was filtered and the solids were rinsed with water three times and dried to provide a brown solid which was purified by silica gel chromatography (0% to 70% ethyl acetate in heptane) to provide 9-bromo-5-chloro-7-iodo-2-phenyl-[1,2,4]triazolo[1,5-c]quinazoline (273 mg, 562 μmol , 90% yield) as a white solid.

[00403] ^1H NMR (500 MHz, DMSO- d_6) δ ppm = 8.69 (d, $J = 2.19$ Hz, 1 H), 8.65 (d, $J = 2.19$ Hz, 1 H), 8.28 - 8.33 (m, 2 H), 7.58 - 7.66 (m, 3 H).

[00404] Step C: To a vial and stir bar was added 9-bromo-5-chloro-7-iodo-2-phenyl-[1,2,4]triazolo[1,5-c]quinazoline (273 mg, 1.0 eq., 562 μmol) as a solid which was dissolved in

anhydrous 1,2-dichloroethane (2.25 mL). Next, diisopropylethylamine (145 mg, 196 μ L, 2.0 *eq.*, 1.12 mmol) and piperidine (52.7 mg, 61.1 μ L, 1.1 *eq.*, 619 μ mol) were added successively and the reaction was sealed and stirred at room temperature overnight. To the reaction was added saturated sodium bicarbonate and this solution was diluted with dichloromethane. The aqueous layer was separated and extracted three times. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated to give a solid which was purified via silica gel chromatography (0% to 70% ethyl acetate in heptane) to provide 9-bromo-7-iodo-2-phenyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazoline (278 mg, 520 μ mol, 93% yield) as a white solid.

[00405] ^1H NMR (500 MHz, DMSO- d_6) δ ppm = 8.40 (s, 2 H), 8.24 - 8.28 (m, 2 H), 7.55 - 7.64 (m, 3 H), 4.20 (br m, 4 H), 1.72 - 1.81 (m, 6 H).

[00406] Step D: To a vial and a stir bar was added palladium (II) acetate (5.84 mg, 0.05 *eq.*, 26.0 μ mol), 1,3-bis(diphenylphosphino)propane (21.5 mg, 0.10 *eq.*, 52.0 μ mol), and 9-bromo-7-iodo-2-phenyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazoline (278 mg, 1.0 *eq.*, 520 μ mol). The flask evacuated and backfilled with nitrogen three times. Next, ethylene glycol (1.30 mL), *N,N*-Dicyclohexylmethylamine (305 mg, 333 μ L, 3.0 *eq.*, 1.56 mmol), and *n*-butyl vinyl ether (261 mg, 337 μ L, 5.0 *eq.*, 2.60 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 $^{\circ}\text{C}$. After full conversion, the reaction was allowed to cool to room temperature and 1N HCl (5 mL) was added to the reaction. The reaction was stirred until the ketone deprotection went to completion (ca. 1 hour). 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 1-(9-bromo-2-phenyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethan-1-one (202 mg, 449 μ mol, 86% yield) as a yellow solid. LCMS $[\text{M}+1]^+ = 452.1$.

[00407] ^1H NMR (400 MHz, CDCl_3) δ ppm 8.75 (d, $J = 2.38$ Hz, 1 H), 8.30 - 8.38 (m, 2 H), 8.08 (d, $J = 2.50$ Hz, 1 H), 7.52 (br d, $J = 1.88$ Hz, 3 H), 4.12 - 4.21 (m, 4 H), 2.92 (s, 3 H), 1.78 - 1.92 (m, 6 H).

[00408] Step E: To a vial was added methylboronic acid (67.1 mg, 2.5 *eq.*, 1.12 mmol), 1-(9-bromo-2-phenyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethan-1-one (202 mg, 1.0 *eq.*, 449 μ mol), potassium carbonate (155 mg, 2.5 *eq.*, 1.12 mmol) and Tetrakis(triphenylphosphine)palladium(0) (51.8 mg, 0.1 *eq.*, 44.9 μ mol). The vial was evacuated and backfilled three times with nitrogen. Next, a solution of deoxygenated 1,4-dioxane (1.79 mL) and water (449 μ L) was added, and the reaction was heated to 100 $^{\circ}\text{C}$ 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 1-(9-methyl-2-phenyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethan-1-one was obtained as a yellow solid. LCMS [M+1]⁺ = 386.2.

[00409] ¹H NMR (400 MHz, CDCl₃) δ ppm = 8.48 (s, 1 H), 8.37 (dd, *J* = 7.63, 1.88 Hz, 2 H), 7.87 (d, *J* = 2.13 Hz, 1 H), 7.49 - 7.56 (m, 3 H), 4.06 - 4.14 (m, 4 H), 2.95 (s, 3 H), 2.55 (s, 3 H), 1.85 (br m, 4 H), 1.75 - 1.82 (m, 2 H).

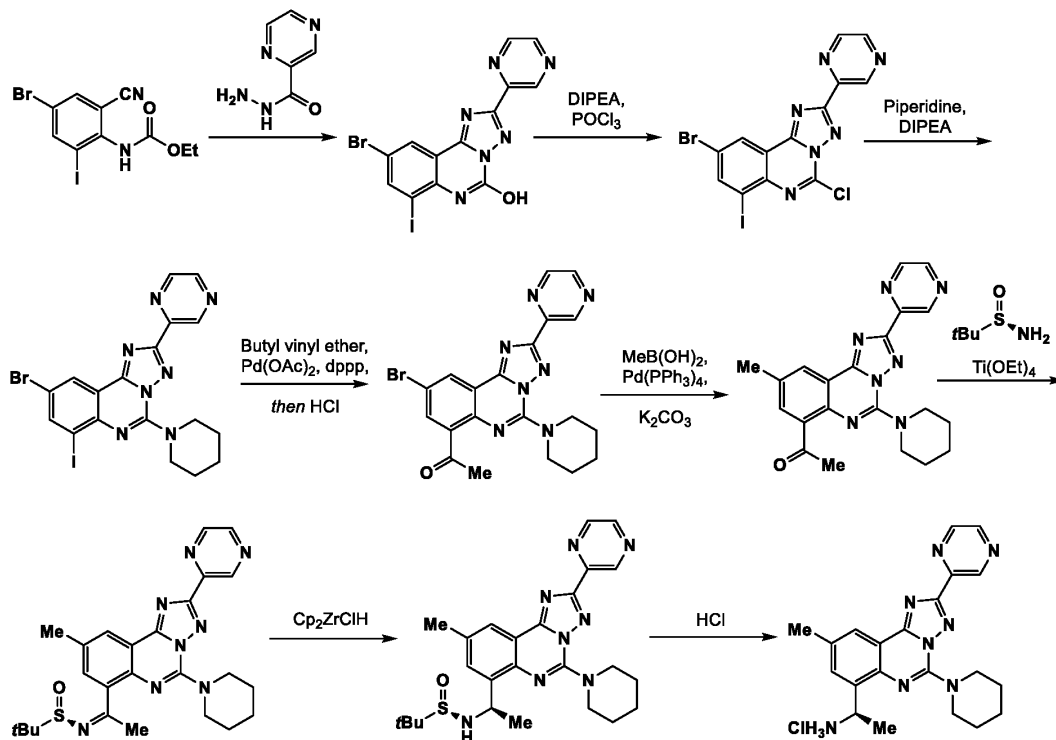
[00410] Step F: To a solution of 1-(9-methyl-2-phenyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethan-1-one (36 mg, 1.0 eq., 93 μmol) and (*R*)-2-methylpropane-2-sulfonamide (14 mg, 1.2 eq., 0.11 mmol) in tetrahydrofuran (0.37 mL) was added titanium (IV) ethoxide (0.11 g, 97 μL, 5.0 eq., 0.47 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 via rotary evaporation to provide (*R*)-2-methyl-*N*-(1-(9-methyl-2-phenyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethylidene)propane-2-sulfonamide (52 mg, crude mass) as a crude yellow solid. The product was carried forward without further purification.

[00411] Step G: To a solution of (*R*)-2-methyl-*N*-(1-(9-methyl-2-phenyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethylidene)propane-2-sulfonamide (52 mg, 1.0 eq., 0.11 mmol) in anhydrous dichloromethane (0.71 mL) at room temperature was added Schwartz's Reagent (30 mg, 1.1 eq., 0.12 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-(9-methyl-2-phenyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethyl)propane-2-sulfonamide (17 mg, 35 μmol, 33% yield) as a white solid. LCMS [M+1]⁺ = 491.3.

[00412] Step H: To a solution of (*R*)-2-methyl-*N*-((*R*)-1-(9-methyl-2-phenyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethyl)propane-2-sulfonamide (17 mg, 1.0 eq., 35 μmol) in methanol (0.35 mL) at room temperature was added 22 μL of HCl (4 molar in dioxane). The reaction was monitored and once complete, triturated with diethyl ether and dried under vacuum to provide (*R*)-1-(9-methyl-2-phenyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazolin-

7-yl)ethan-1-amine, hydrochloride as a salt which was used without further purification. LCMS $[M+1]^+ = 387.1$.

INTERMEDIATE D



[00413] Step A: A mixture of ethyl (4-bromo-2-cyano-6-iodophenyl)carbamate (500 mg, 1.00 eq., 1.27 mmol) and pyrazine-2-carbohydrazide (184 mg, 1.05 eq., 1.33 mmol) in *N*-methyl-2-pyrrolidinone (6.33 mL) was heated at 160 °C for 3 hours. The reaction mixture was allowed to cool to room temperature and water (10 mL) was added followed by pouring the mixture on to ice. The resulting precipitate was collected and washed with diethyl ether to afford 9-bromo-7-iodo-2-(pyrazin-2-yl)-[1,2,4]triazolo[1,5-c]quinazolin-5(6H)-one (581 mg, 1.24 mmol, 98% yield), which was used without further purification. LCMS: $[M+1]^+ = 468.9$.

[00414] ^1H NMR (500 MHz, DMSO- d_6) δ ppm = 11.05 (br s, 1 H), 9.46 (d, $J = 1.37$ Hz, 1 H), 8.87 (dd, $J = 2.33, 1.51$ Hz, 1 H), 8.84 (d, $J = 2.46$ Hz, 1 H), 8.42 (d, $J = 2.19$ Hz, 1 H), 8.37 (d, $J = 2.19$ Hz, 1 H).

[00415] Step B: To a vial charged with 9-bromo-7-iodo-2-(pyrazin-2-yl)-[1,2,4]triazolo[1,5-c]quinazolin-5(6H)-one (330 mg, 1 eq., 704 μmol) and stir bar was added successively phosphorous oxychloride (1.08 g, 656 μL , 10 eq., 7.04 mmol) and diisopropylethylamine (364 mg, 490 μL , 4 eq., 2.81 mmol). This vial was sealed and heated to 100 °C for 12 hours. The reaction was next allowed to cool to room temperature and its contents were concentrated

under vacuum to provide a dark residue. To this residue was added ice and the contents were mixed. After melting, the aqueous suspension was filtered and the solids were rinsed with water three times and dried to provide a brown solid which was purified by silica gel chromatography (0% to 70% ethyl acetate in heptane) to provide 9-bromo-5-chloro-7-iodo-2-(pyrazin-2-yl)-[1,2,4]triazolo[1,5-c]quinazoline (312 mg, 640 μ mol, 91% yield) as a white solid. LCMS: $[M+1]^+ = 486.7$.

[00416] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm = 9.53 (d, $J = 1.10$ Hz, 1 H), 8.90 - 8.94 (m, 1 H), 8.88 (d, $J = 2.19$ Hz, 1 H), 8.71 (d, $J = 1.92$ Hz, 1 H), 8.67 (d, $J = 1.92$ Hz, 1 H).

[00417] Step C: To a vial and stir bar was added 9-bromo-5-chloro-7-iodo-2-(pyrazin-2-yl)-[1,2,4]triazolo[1,5-c]quinazoline (312 mg, 1.0 eq., 640 μ mol) as a solid which was dissolved in anhydrous 1,2-dichloroethane (2.56 mL). Next, diisopropylethylamine (165 mg, 223 μ L, 2.0 eq., 1.28 mmol) and piperidine (59.9 mg, 69.5 μ L, 1.1 eq., 704 μ mol) were added successively and the reaction was sealed and stirred at room temperature overnight. To the reaction was added saturated sodium bicarbonate and this solution was diluted with dichloromethane. The aqueous layer was separated and extracted three times. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated and purified via silica gel chromatography (0% to 70% ethyl acetate in heptane) to provide 9-bromo-7-iodo-5-(piperidin-1-yl)-2-(pyrazin-2-yl)-[1,2,4]triazolo[1,5-c]quinazoline (295 mg, 550 μ mol, 86% yield) as a white solid. LCMS: $[M+1]^+ = 536.3$.

[00418] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm = 9.52 (d, $J = 1.64$ Hz, 1 H), 8.87 - 8.90 (m, 1 H), 8.85 (d, $J = 2.46$ Hz, 1 H), 8.42 - 8.45 (m, 2 H), 4.21 (br m, 4 H), 1.77 (br m, 6 H).

[00419] Step D: To a vial and a stir bar was added palladium (II) acetate (6 mg, 0.05 eq., 27.5 μ mol), 1,3-bis(diphenylphosphino)propane (23 mg, 0.10 eq., 55.0 μ mol), and 9-bromo-7-iodo-5-(piperidin-1-yl)-2-(pyrazin-2-yl)-[1,2,4]triazolo[1,5-c]quinazoline (295 mg, 1.0 eq., 550 μ mol). The flask evacuated and backfilled with nitrogen three times. Next, ethylene glycol (1.4 mL), *N,N*-Dicyclohexylmethylamine (322 mg, 352 μ L, 3.0 eq., 1.65 mmol), and *n*-butyl vinyl ether (276 mg, 356 μ L, 5.0 eq., 2.75 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 $^{\circ}\text{C}$. After full conversion, the reaction was allowed to cool to room temperature and 1N HCl (5 mL) was added to the reaction. The reaction was stirred until the ketone deprotection went to completion (ca. 1 hour). 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 1-(9-bromo-5-(piperidin-1-yl)-2-(pyrazin-2-yl)-[1,2,4]triazolo[1,5-

c]quinazolin-7-yl)ethan-1-one (118 mg, 261 μ mol, 47% yield) as a yellow solid. LCMS: [M+1]⁺ = 452.0.

[00420] Step E: To a vial was added methylboronic acid (39.0 mg, 2.5 eq., 652 μ mol), 1-(9-bromo-5-(piperidin-1-yl)-2-(pyrazin-2-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethan-1-one (118 mg, 1.0 eq., 261 μ mol), potassium carbonate (90.1 mg, 2.5 eq., 652 μ mol) and tetrakis(triphenylphosphine)palladium(0) (30.1 mg, 0.1 eq., 26.1 μ mol). The vial was evacuated and backfilled three times with nitrogen. Next, a solution of deoxygenated 1,4-dioxane (1.0 mL) and water (260 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 1-(9-methyl-5-(piperidin-1-yl)-2-(pyrazin-2-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethan-1-one (44 mg, 0.11 mmol, 44% yield) was obtained as a yellow solid. LCMS: [M+1]⁺ = 388.1.

[00421] ¹H NMR (400 MHz, CDCl₃) δ ppm = 9.62 (d, *J* = 1.38 Hz, 1 H), 8.82 (dd, *J* = 2.38, 1.50 Hz, 1 H), 8.72 (d, *J* = 2.50 Hz, 1 H), 8.55 (d, *J* = 1.25 Hz, 1 H), 7.89 (d, *J* = 2.00 Hz, 1 H), 4.07 - 4.14 (m, 4 H), 2.95 (s, 3 H), 2.54 (s, 3 H), 1.77 - 1.92 (m, 6 H).

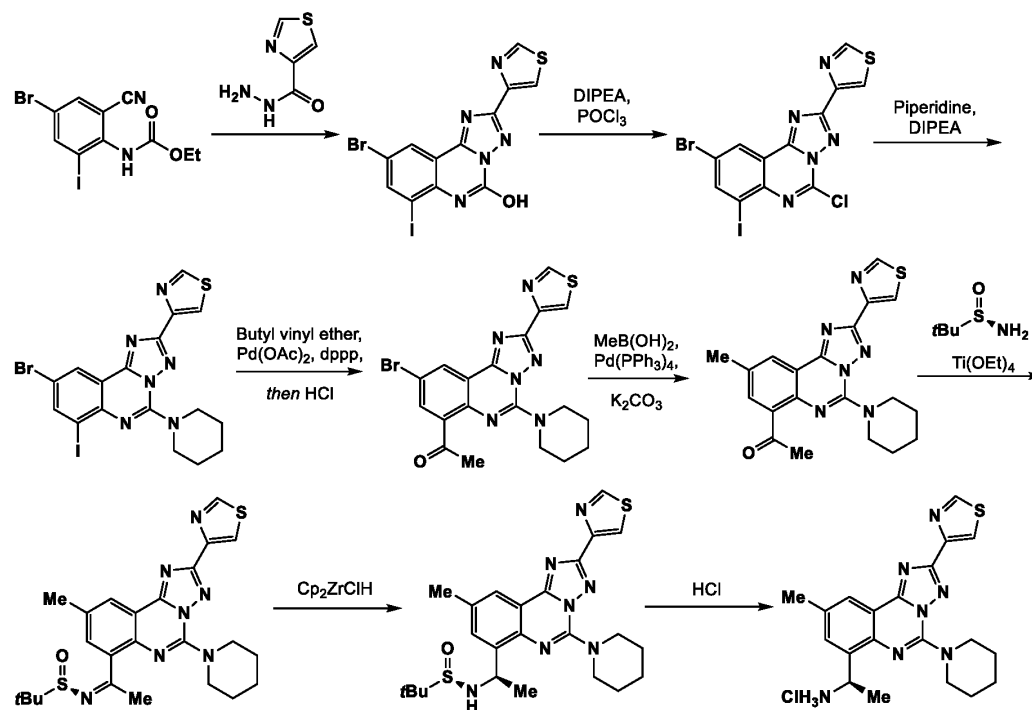
[00422] Step F: To a solution of 1-(9-methyl-5-(piperidin-1-yl)-2-(pyrazin-2-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethan-1-one (44 mg, 1.0 eq., 0.11 mmol) and (*R*)-2-methylpropane-2-sulfinamide (17 mg, 1.2 eq., 0.14 mmol) in tetrahydrofuran (0.45 mL) was added titanium (IV) ethoxide (0.13 g, 0.12 mL, 5.0 eq., 0.57 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 via rotary evaporation to provide (*R*)-2-methyl-*N*-(1-(9-methyl-5-(piperidin-1-yl)-2-(pyrazin-2-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethylidene)propane-2-sulfinamide (55 mg crude mass) as a crude yellow solid. The product was carried forward without further purification.

[00423] Step G: To a solution of (*R*)-2-methyl-*N*-(1-(9-methyl-5-(piperidin-1-yl)-2-(pyrazin-2-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethylidene)propane-2-sulfinamide (55 mg, 1.0 eq., 0.11 mmol) in anhydrous dichloromethane (0.75 mL) at room temperature was added Schwartz's reagent (32 mg, 1.1 eq., 0.12 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-(9-methyl-5-(piperidin-1-yl)-2-(pyrazin-2-yl)-[1,2,4]triazolo[1,5-*c*]quinazolin-7-yl)ethyl)propane-2-sulfonamide (23 mg, 47 μ mol, 42% yield) as a white solid. LCMS $[M+1]^+ = 493.3$.

[00424] Step H: To a solution of (*R*)-2-methyl-*N*-((*R*)-1-(9-methyl-5-(piperidin-1-yl)-2-(pyrazin-2-yl)-[1,2,4]triazolo[1,5-*c*]quinazolin-7-yl)ethyl)propane-2-sulfonamide (23 mg, 1.0 eq., 47 μ mol) in methanol (0.23 mL) at room temperature was added 29 μ L of HCl (4 molar in dioxane). The reaction was monitored and once complete, triturated with diethyl ether and dried under vacuum to provide (*R*)-1-(9-methyl-5-(piperidin-1-yl)-2-(pyrazin-2-yl)-[1,2,4]triazolo[1,5-*c*]quinazolin-7-yl)ethan-1-amine, hydrochloride as a salt which was used without further purification. LCMS $[M+1]^+ = 389.2$.

INTERMEDIATE E



[00425] Step A: A mixture of ethyl (4-bromo-2-cyano-6-iodophenyl)carbamate (500 mg, 1.00 eq., 1.27 mmol) and thiazole-4-carbohydrazide (190 mg, 1.05 eq., 1.33 mmol) in *N*-methyl-2-pyrrolidinone (6.33 mL) was heated at 160 °C for 3 hours. The reaction mixture was allowed to cool to room temperature and water (10 mL) was added followed by pouring the mixture on to ice. The resulting precipitate was collected and washed with diethyl ether to

afford 9-bromo-7-iodo-2-(thiazol-4-yl)-[1,2,4]triazolo[1,5-c]quinazolin-5(6H)-one (568 mg, 1.20 mmol, 95% yield) which was used without further purification. LCMS: $[M+1]^+ = 473.9$.

[00426] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm = 9.31 (d, $J = 1.92$ Hz, 1 H), 8.53 (d, $J = 1.92$ Hz, 1 H), 8.40 (d, $J = 2.19$ Hz, 1 H), 8.32 (d, $J = 2.19$ Hz, 1 H).

[00427] Step B: To a vial charged with 9-bromo-7-iodo-2-(thiazol-4-yl)-[1,2,4]triazolo[1,5-c]quinazolin-5(6H)-one (319 mg, 1.0 eq., 673 μmol) and stir bar was added successively phosphorous oxychloride (1.03 g, 627 μL , 10.0 eq., 6.73 mmol) and diisopropylethylamine (348 mg, 469 μL , 4.0 eq., 2.69 mmol). This vial was sealed and heated to 100 °C for 12 hours. The reaction was next allowed to cool to room temperature and its contents were concentrated under vacuum to provide a dark residue. To this residue was added ice and the contents were mixed. After melting, the aqueous suspension was filtered and the solids were rinsed with water three times and dried to provide a brown solid which was purified by silica gel chromatography (0% to 70% ethyl acetate in heptane) to provide 4-(9-bromo-5-chloro-7-iodo-[1,2,4]triazolo[1,5-c]quinazolin-2-yl)thiazole (302 mg, 613 μmol , 91% yield) as a white solid. LCMS: $[M+1]^+ = 491.6$.

[00428] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm = 9.34 (d, $J = 1.92$ Hz, 1 H), 8.69 (d, $J = 2.19$ Hz, 1 H), 8.65 (d, $J = 1.92$ Hz, 1 H), 8.62 (d, $J = 2.19$ Hz, 1 H).

[00429] Step C: To a vial and stir bar was added 4-(9-bromo-5-chloro-7-iodo-[1,2,4]triazolo[1,5-c]quinazolin-2-yl)thiazole (302 mg, 1.0 eq., 613 μmol) as a solid which was dissolved in anhydrous 1,2-dichloroethane (2.45 mL). Next, diisopropylethylamine (159 mg, 214 μL , 2.0 eq., 1.23 mmol) and piperidine (57.4 mg, 66.6 μL , 1.1 eq., 674 μmol) were added successively and the reaction was sealed and stirred at room temperature overnight. To the reaction was added saturated sodium bicarbonate and this solution was diluted with dichloromethane. The aqueous layer was separated and extracted three times. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated and purified via silica gel chromatography (0% to 70% ethyl acetate in heptane) to provide 4-(9-bromo-7-iodo-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazolin-2-yl)thiazole (304 mg, 562 μmol , 92% yield) as a white solid. LCMS: $[M+1]^+ = 541.2$.

[00430] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm = 9.31 (d, $J = 1.92$ Hz, 1 H), 8.56 (d, $J = 1.92$ Hz, 1 H), 8.41 (d, $J = 2.19$ Hz, 1 H), 8.38 (d, $J = 2.19$ Hz, 1 H), 4.20 (br m, 4 H), 1.75 (br m, 6 H).

[00431] Step D: To a vial and a stir bar was added palladium (II) acetate (6.31 mg, 0.05 eq., 28.1 μmol), 1,3-bis(diphenylphosphino)propane (23.2 mg, 0.10 eq., 56.2 μmol), and 4-(9-bromo-7-iodo-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazolin-2-yl)thiazole (304 mg, 1.0 eq., 562 μmol). The flask evacuated and backfilled with nitrogen three times. Next, ethylene glycol

(1.40 mL), *N,N*-dicyclohexylmethylamine (329 mg, 359 μ L, 3.0 *eq.*, 1.69 mmol), and *n*-butyl vinyl ether (281 mg, 363 μ L, 5.0 *eq.*, 2.81 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 (5 mL) was added to the reaction. The reaction was stirred until the ketone deprotection went to completion (ca. 1 hour). 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 1-(9-bromo-5-(piperidin-1-yl)-2-(thiazol-4-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethan-1-one (149 mg, 326 μ mol, 58% yield) as a yellow solid. LCMS: [M+1]⁺ = 457.0.

[00432] ¹H NMR (400 MHz, CDCl₃) δ ppm = 9.05 (d, *J* = 2.00 Hz, 1 H), 8.81 (d, *J* = 2.38 Hz, 1 H), 8.36 (d, *J* = 2.13 Hz, 1 H), 8.12 (d, *J* = 2.38 Hz, 1 H), 4.19 (br m, 4 H), 2.95 (s, 3 H), 1.85 (br m, 6 H).

[00433] Step E: To a vial was added methylboronic acid (48.8 mg, 2.5 *eq.*, 814 μ mol), 1-(9-bromo-5-(piperidin-1-yl)-2-(thiazol-4-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethan-1-one (149 mg, 1.0 *eq.*, 326 μ mol), potassium carbonate (113 mg, 2.5 *eq.*, 814 μ mol) and tetrakis(triphenylphosphine)palladium(0) (37.6 mg, 0.1 *eq.*, 32.6 μ mol). The vial was evacuated and backfilled three times with nitrogen. Next, a solution of deoxygenated 1,4-dioxane (1.3 mL) and water (326 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 1-(9-methyl-5-(piperidin-1-yl)-2-(thiazol-4-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethan-1-one (60 mg, 0.15 mmol, 47% yield) was obtained as a yellow solid. LCMS [M+1]⁺ = 393.1.

[00434] ¹H NMR (400 MHz, CDCl₃) δ ppm = 9.01 (d, *J* = 2.00 Hz, 1 H), 8.51 (d, *J* = 1.00 Hz, 1 H), 8.37 (d, *J* = 2.00 Hz, 1 H), 7.88 (d, *J* = 2.13 Hz, 1 H), 4.08 - 4.12 (m, 4 H), 2.95 (s, 3 H), 2.54 (s, 3 H), 1.84 (br m, 6 H).

[00435] Step F: To a solution of 1-(9-methyl-5-(piperidin-1-yl)-2-(thiazol-4-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethan-1-one (60 mg, 1.0 *eq.*, 0.15 mmol) and (*R*)-2-methylpropane-2-sulfinamide (22 mg, 1.2 *eq.*, 0.18 mmol) in tetrahydrofuran (0.6 mL) was added titanium (IV) ethoxide (0.17 g, 0.16 mL, 5.0 *eq.*, 0.76 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

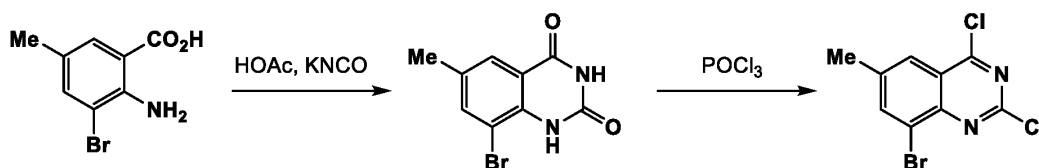
ethyl acetate. Filtered through a plug of celite, and the filter cake was washed with ethyl acetate several times. The filtrate was concentrated via rotary evaporation to provide (*R*)-2-methyl-*N*-(1-(9-methyl-5-(piperidin-1-yl)-2-(thiazol-4-yl)-[1,2,4]triazolo[1,5-*c*]quinazolin-7-yl)ethylidene)propane-2-sulfonamide (93 mg crude mass) as a crude yellow solid. The product was carried forward without further purification.

[00436] Step G: To a solution of (*R*)-2-methyl-*N*-(1-(9-methyl-5-(piperidin-1-yl)-2-(thiazol-4-yl)-[1,2,4]triazolo[1,5-*c*]quinazolin-7-yl)ethylidene)propane-2-sulfonamide (93 mg, 1.0 *eq.*, 0.19 mmol) in anhydrous dichloromethane (1.3 mL) at room temperature was added Schwartz's reagent (53 mg, 1.1 *eq.*, 0.21 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-(9-methyl-5-(piperidin-1-yl)-2-(thiazol-4-yl)-[1,2,4]triazolo[1,5-*c*]quinazolin-7-yl)ethyl)propane-2-sulfonamide (38 mg, 76 μ mol, 41% yield) as a white solid. LCMS $[M+1]^+ = 498.2$.

[00437] Step H: To a solution of (*R*)-2-methyl-*N*-((*R*)-1-(9-methyl-5-(piperidin-1-yl)-2-(thiazol-4-yl)-[1,2,4]triazolo[1,5-*c*]quinazolin-7-yl)ethyl)propane-2-sulfonamide (38 mg, 1.0 *eq.*, 76 μ mol) in methanol (0.31 mL) at room temperature was added 48 μ L of HCl (4.0 molar in dioxane). The reaction was monitored and once complete, triturated with diethyl ether and dried under vacuum to provide (*R*)-1-(9-methyl-5-(piperidin-1-yl)-2-(thiazol-4-yl)-[1,2,4]triazolo[1,5-*c*]quinazolin-7-yl)ethan-1-amine, hydrochloride as a salt which was used without further purification. LCMS $[M+1]^+ = 394.2$.

INTERMEDIATE F

8-bromo-2,4-dichloro-6-methylquinazoline



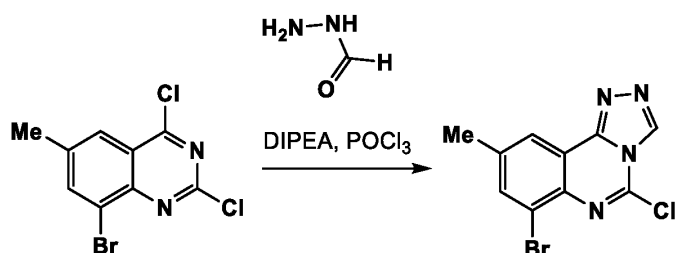
[00438] Step A: To a solution of 2-amino-3-bromo-5-methylbenzoic acid (30.0 g, 130 mmol, 1.00 *eq.*) in water (1000 mL) was added acetic acid (23.5 g, 391 mmol, 22.4 mL, 3.00 *eq.*). The mixture was stirred at 35 °C for 0.2 hour. Then sodium cyanate (25.4 g, 391 mmol, 3.00 *eq.*) in water (400 mL) was added to the mixture. The mixture was stirred at 35 °C for 12 hours. Then sodium hydroxide (235 g, 5.87 mol, 45.0 *eq.*) was added to this mixture. The mixture was stirred at 35 °C for 0.2 hours. After completion of the reaction, the reaction mixture was

adjusted pH to 4 with hydrochloric acid at 0 °C, the mixture was filtered and rinsed with water (1L), then the crude product was purified by re-crystallization from ethyl acetate (30 mL) at 25 °C for 10 minutes to give 8-bromo-6-methyl-1*H*-quinazoline-2,4-dione (30 g) as a white solid. LCMS [M+2]⁺ = 257.0.

[00439] Step B: To a solution of 8-bromo-6-methyl-1*H*-quinazoline-2,4-dione (9.50 g, 37.2 mmol, 1.00 eq.) in phosphorous oxychloride (70 mL) was stirred at 120 °C for 12 hours. The reaction mixture was concentrated under reduced pressure to remove the excess phosphorous oxychloride. The reaction mixture was quenched by addition water (100 mL) at 0 °C, and then extracted with ethyl acetate (100 mL ×3). The combined organic layers were washed with brine (50.0 mL), dried over sodium sulfate, 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 2/1) to give 8-bromo-2,4-dichloro-6-methyl-quinazoline (4.3 g) as a yellow solid. LCMS [M+2]⁺ = 293.0.

INTERMEDIATE G

7-bromo-5-chloro-9-methyl-[1,2,4]triazolo[4,3-*c*]quinazoline

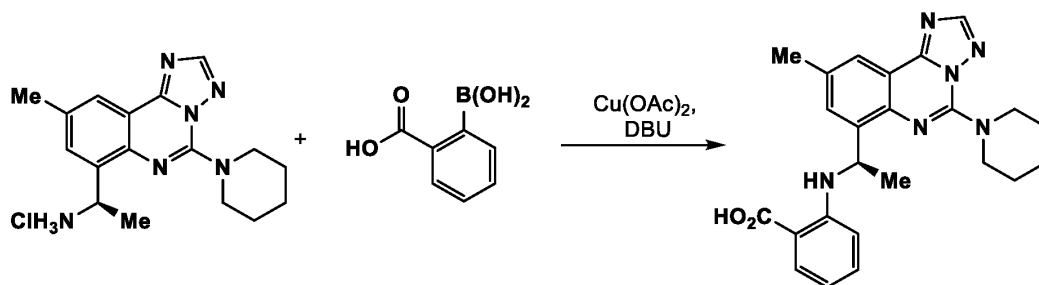


[00440] Step A: To a solution of 8-bromo-2,4-dichloro-6-methyl-quinazoline (4.3 g, 14.7 mmol, 1.00 eq.) in tetrahydrofuran (40.0 mL) was added diisopropylethylamine (1.90 g, 14.7 mmol, 2.57 mL, 1.00 eq.) at 0 °C for 0.2 hour, and then formylhydrazine (884 mg, 14.7 mmol, 1.00 eq.) was added and the mixture was stirred at 0 °C and upon full conversion to the intermediate aryl hydrazide, phosphorous oxychloride (3.39 g, 22.1 mmol, 2.06 mL, 1.50 eq.) was added to the mixture at 25 °C and the reaction was heated to 60 °C for 6 hours. After completion of the reaction, the reaction was carefully poured onto ice and the resulting aqueous suspension was neutralized to pH= 7 with sodium hydroxide. The product was filtered and rinsed with water, and the mixture was suspended in water (100 mL) and extracted with ethyl acetate (100 mL×2), then the aqueous phase was adjusted to pH= 10 with sodium hydroxide aqueous solution and extracted with ethyl acetate (100 mL×2). 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 silica

gel chromatography (0% to 100% ethyl acetate in petroleum ether) to give 7-bromo-5-chloro-9-methyl-[1,2,4]triazolo[4,3-c]quinazoline (6 g, crude) as a yellow solid. LCMS $[M+2]^+ = 299.0$.

EXAMPLE 1-1

(*R*)-2-((1-(9-methyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethyl)amino)benzoic acid

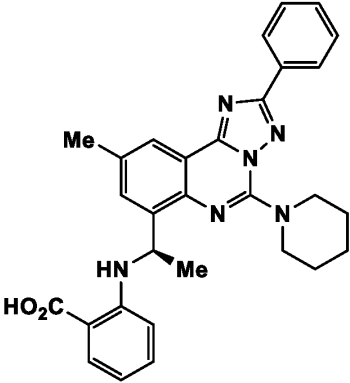
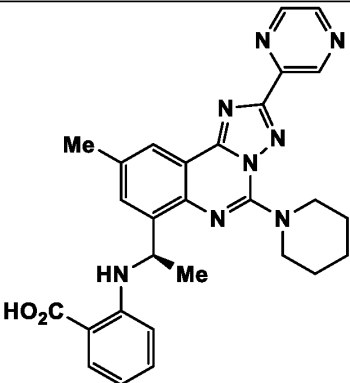


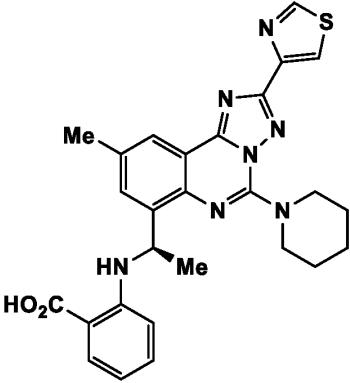
[00441] To a vial and stir bar was added (*R*)-1-(9-methyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethan-1-amine, hydrochloride (39 mg, 1.0 *eq.*, 0.11 mmol), 2-carboxyphenylboronic acid (56 mg, 3.0 *eq.*, 0.34 mmol) and copper (II) acetate (31 mg, 1.5 *eq.*, 0.17 mmol) as solids. Next, the vial was sealed with a septum cap and dimethylformamide (1.1 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (86 mg, 85 μ L, 5.0 *eq.*, 0.56 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 100% ethyl acetate in heptane) to provide (*R*)-2-((1-(9-methyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethyl)amino)benzoic acid (16 mg, 37 μ mol, 33% yield) as a white solid. LCMS $[M+1]^+ = 431.2$.

[00442] ^1H NMR (400 MHz, CDCl_3) δ ppm = 8.35 (s, 1 H), 8.15 (br s, 1 H), 7.97 (d, $J = 7.88$ Hz, 1 H), 7.56 - 7.71 (m, 1 H), 7.13 - 7.21 (m, 1 H), 6.59 - 6.73 (m, 1 H), 6.44 - 6.57 (m, 1 H), 5.69 (br m, $J = 1.63$ Hz, 1 H), 3.99 (br m, 4 H), 2.47 (s, 3 H), 1.73 - 1.89 (m, 9 H).

[00443] The compounds in Table 2 are prepared essentially according to the procedures set forth in the above schemes and examples.

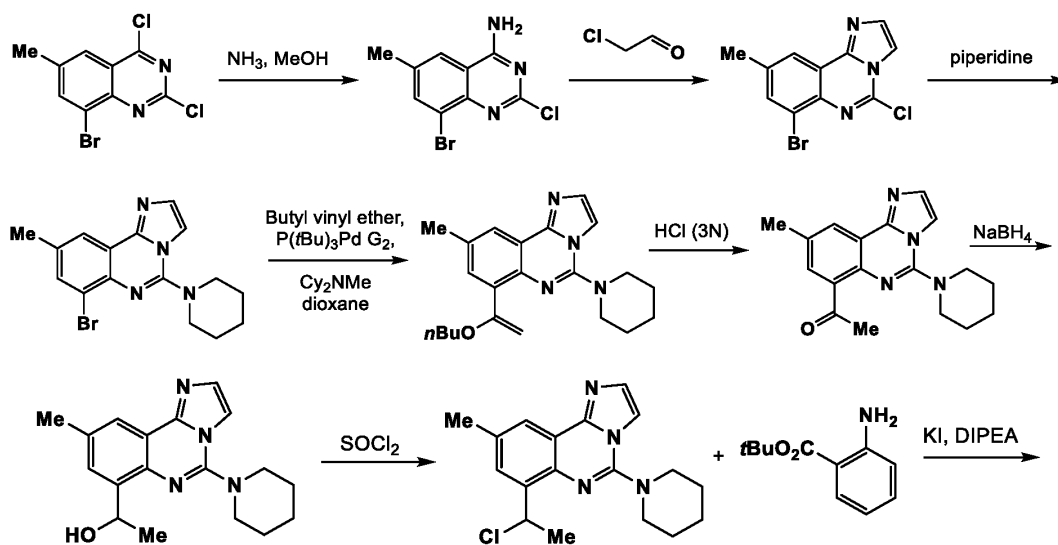
Table 2

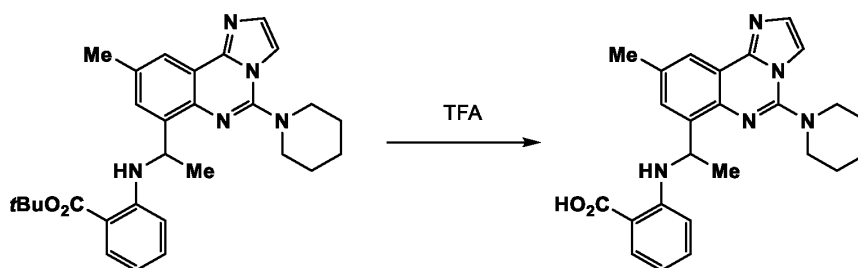
Example No.	Structure	Spectral Data
1-2	 (R)-2-((1-(9-methyl-2-phenyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ ppm = 8.39 (dd, <i>J</i> = 7.63, 1.63 Hz, 2 H), 8.24 (s, 1 H), 7.97 (dd, <i>J</i> = 7.94, 1.31 Hz, 1 H), 7.47 - 7.59 (m, 4 H), 7.13 - 7.21 (m, 1 H), 6.54 - 6.62 (m, 1 H), 6.49 (br d, <i>J</i> = 8.50 Hz, 1 H), 5.67 (q, <i>J</i> = 6.55 Hz, 1 H), 4.07 (br s, 4 H), 2.47 (s, 3 H), 1.87 (br m, 4 H), 1.80 (br d, <i>J</i> = 4.75 Hz, 2 H), 1.72 (br d, <i>J</i> = 6.38 Hz, 3 H). LCMS [M+1] ⁺ = 507.2.
1-3	 (R)-2-((1-(9-methyl-5-(piperidin-1-yl)-2-(pyrazin-2-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ ppm = 9.62 (s, 1 H), 8.81 (m 1 H), 8.70 (d, <i>J</i> = 2.38 Hz, 1 H), 8.31 (s, 1 H), 7.97 (d, <i>J</i> = 7.63 Hz, 1 H), 7.55 - 7.76 (m, 1 H), 7.14 - 7.22 (m, 1 H), 6.59 - 6.74 (m, 1 H), 6.46 - 6.56 (m, 1 H), 5.71 (br m, 6.69 Hz, 1 H), 4.06 (br m, 4 H), 2.47 (s, 3 H), 1.86 (br m, 5 H), 1.69 - 1.82 (m, 5 H). LCMS [M+1] ⁺ = 509.2.

1-4	 (R)-2-((1-(9-methyl-5-(piperidin-1-yl)-2-(thiazol-4-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CDCl ₃) δ ppm = 9.02 (d, <i>J</i> = 2.00 Hz, 1 H), 8.36 (d, <i>J</i> = 2.00 Hz, 1 H), 8.24 (s, 1 H), 7.98 (dd, <i>J</i> = 8.00, 1.50 Hz, 1 H), 7.56 (br s, 1 H), 7.13 - 7.22 (m, 1 H), 6.58 (br t, <i>J</i> = 6.94 Hz, 1 H), 6.49 (d, <i>J</i> = 8.88 Hz, 1 H), 5.67 (q, <i>J</i> = 6.67 Hz, 1 H), 4.09 (br m, 4 H), 2.45 (s, 3 H), 1.85 (br m, 4 H), 1.76 - 1.81 (m, 2 H), 1.72 (br d, <i>J</i> = 6.25 Hz, 3 H). LCMS [<i>M</i> +1] ⁺ = 514.2.
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EXAMPLE 2-1

2-((1-(9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid





[00444] Step A: To a solution of 8-bromo-2,4-dichloro-6-methyl-quinazoline (3.17 g, 10.7 mmol, 1.00 *eq.*) in dichloromethane (5 mL) was added 16 mL ammonia (7 molar in methanol). The mixture was stirred at 25 °C for 16 hours. After completion the reaction mixture was concentrated in vacuum to give the crude product. The crude product was triturated with petroleum ether (50.0 mL) for 1 hour at 25 °C and then dried under reduced pressure to give 8-bromo-2-chloro-6-methyl-quinazolin-4-amine (3.06 g, 10.7 mmol, 98% yield) as a white solid. LCMS [M+3]⁺ = 273.8.

[00445] Step B: To a solution of 8-bromo-2-chloro-6-methyl-quinazolin-4-amine (3.00 g, 11.0 mmol, 1.0 *eq.*) in dioxane (50 mL) was added 2-chloroacetaldehyde (19.4 g, 99.1 mmol, 15.9 mL, 40% purity, 9.00 *eq.*), the mixture was stirred at 100 °C for 16 hours. Upon completion the mixture was cooled to 25 °C and concentrated under reduced pressure to give a residue. The residue was diluted with water (30 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with brine (50 mL × 3), dried over sodium sulfate and concentrated in vacuum to give compound 7-bromo-5-chloro-9-methyl-imidazo[1,2-*c*]quinazoline (2.95 g, 7.96 mmol, 72% yield,) as a white solid. LCMS [M+3]⁺ = 297.8.

[00446] ¹H NMR (400 MHz, CDCl₃) 8.35 (s, 1 H), 7.86 (d, *J* = 1.2 Hz, 1 H), 7.81 (d, *J* = 1.2 Hz, 1 H), 7.70 (d, *J* = 1.2 Hz, 1 H), 2.57 (s, 3 H),

[00447] Step C: To a solution of 7-bromo-5-chloro-9-methyl-imidazo[1,2-*c*]quinazoline (2.95 g, 9.95 mmol, 1.00 *eq.*) in acetonitrile (5 mL) was added piperidine (847 mg, 9.95 mmol, 982 uL, 1.00 *eq.*), the mixture was stirred at 60 °C for 16 hours. Upon completion the mixture was cooled to 25 °C and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel (0% to 40% ethyl acetate in petroleum ether) to afford 7-bromo-9-methyl-5-(1-piperidyl)imidazo[1,2-*c*]quinazoline (2.16 g, 4.38 mmol, 44% yield) as a yellow solid. LCMS [M+3]⁺ = 346.8.

[00448] ¹H NMR (400 MHz, CDCl₃) δ ppm = 8.96 (s, 1 H), 8.18 (br s, 1 H), 8.06 - 7.92 (m, 1 H), 7.74 - 7.62 (m, 1 H), 3.56 (br d, *J* = 5.2 Hz, 3 H), 2.64 - 2.50 (m, 3 H), 1.72 - 1.68 (m, 6 H).

[00449] Step D: A mixture of 7-bromo-9-methyl-5-(1-piperidyl)imidazo[1,2-c]quinazoline (400 mg, 1.16 mmol, 1.00 eq.), butyl vinyl ether (116 mg, 1.16 mmol, 149 μ L, 1.00 eq.), *N,N*-dicyclohexylmethylamine (231 mg, 1.27 mmol, 254 μ L, 1.10 eq.) and chloro[(tri-*tert*-butylphosphine)-2-(2-aminobiphenyl)] palladium(II) (89.1 mg, 174 μ mol, 0.15 eq.) in dioxane (5.0 mL) was degassed and purged with nitrogen for 3 times, and then stirred at 100 °C for 12 hours under nitrogen atmosphere. Upon completion the mixture was cooled to 25 °C, filtered and concentrated under reduced pressure to give the crude product which was used for next step directly without purification. LCMS [M+1]⁺ = 365.1.

[00450] Step E: To a solution of 7-(1-butoxyvinyl)-9-methyl-5-(1-piperidyl)imidazo[1,2-c]quinazoline (325 mg, 892 μ mol, 1.00 eq.) in tetrahydrofuran (2.00 mL) was added 2.00 mL aqueous hydrochloric acid (3 M in water), the mixture was stirred at 25 °C for 3 hours. Upon completion the mixture was adjusted to pH = 8 with saturated sodium bicarbonate solution and then extracted with ethyl acetate (20 mL $\times$ 3). The combined organic layers were washed with brine (30 mL $\times$ 3), dried over sodium sulfate and concentrated in vacuum to give a residue. The residue was purified by flash silica gel chromatography (0% to 50% ethyl acetate in petroleum ether) to afford 1-(9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazolin-7-yl)ethan-1-one (65.0 mg, 179 μ mol, 20% yield) as a yellow solid. LCMS [M+1]⁺ = 309.0.

[00451] Step F: To a solution of 1-(9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazolin-7-yl)ethan-1-one (60.0 mg, 195 μ mol, 1.0 eq.) in methanol (1.0 mL) was added sodium borohydride (8 mg, 200 μ mol, 1.1 eq.) at 0 °C, after addition, the reaction mixture was stirred at 0 °C for 1 hour. The mixture was quenched by addition water (5 mL), and then extracted with ethyl acetate (5 mL $\times$ 3). The combined organic layers were washed with brine (5 mL $\times$ 3), dried over sodium sulfate, filtered and concentrated under reduced pressure to give 1-(9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazolin-7-yl)ethan-1-ol (40.0 mg, 129 μ mol, 66% yield) as a yellow solid. LCMS [M+1]⁺ = 310.9.

[00452] Step G: A mixture of 1-(9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazolin-7-yl)ethan-1-ol (50 mg, 160 μ mol, 1.0 eq.) in thionyl chloride (1.64 g, 14 mmol, 1.0 mL, 86 eq.) was stirred at 50 °C for 30 minutes. Upon completion the mixture was cooled to 25 °C and concentrated under reduced pressure to give 7-(1-chloroethyl)-9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazoline (55 mg, crude) as a light brown gum.

[00453] Step H: A mixture of 7-(1-chloroethyl)-9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazoline (40 mg, 120 μ mol, 1.0 eq.), *tert*-butyl 2-aminobenzoate (47 mg, 240 μ mol, 44 μ L, 2.0 eq.), potassium iodide (20 mg, 120 μ mol, 1.0 eq.) and diisopropylethylamine (63 mg, 490 μ mol, 85 μ L, 4.0 eq.) in dimethylformamide (2.0 mL) was stirred at 80 °C for 4 hours under nitrogen atmosphere. Upon completion, the mixture was cooled to 25 °C and diluted with ethyl

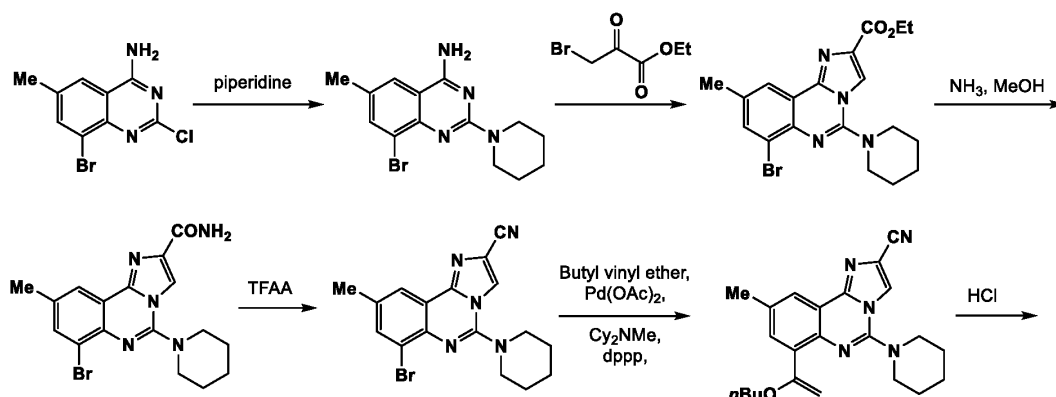
acetate (20 mL), the resulting mixture was washed with brine (10 mL $\times$ 3), the separated organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0% to 20% ethyl acetate in petroleum ether) to afford *tert*-butyl 2-((1-(9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoate (15 mg, 24 μ mol, 20% yield) as a light yellow solid. LCMS $[M+1]^+ = 486.2$.

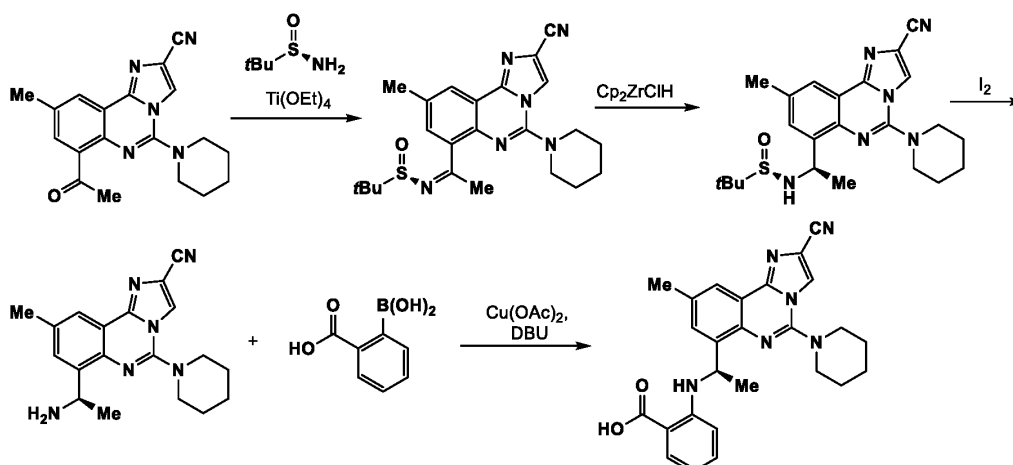
[00454] Step I: A mixture of *tert*-butyl 2-((1-(9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoate (15 mg, 31 μ mol, 1.0 *eq.*) and trifluoroacetic acid (1.5 mL) in dichloroethane (2.0 mL) was stirred at 50 °C for 2 hours. After completion the reaction mixture was concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (Column Phenomenex C18 $\times$ 80 $\times$ 40mm 3 μ m, Mobile Phase A: water (NH₃H₂O + NH₄HCO₃), Mobile Phase B: acetonitrile, Flow rate: 25 mL/min, gradient condition from 30% B to 60%) to afford 2-((1-(9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid (5 mg, 11 μ mol, 36 % yield) as a white solid. LCMS $[M+1]^+ = 430.1$.

[00455] ¹H NMR (400 MHz, CD₃OD) δ ppm = 8.06 (s, 1 H), 7.93 - 7.86 (m, 1 H), 7.83 - 7.78 (m, 1 H), 7.63 - 7.55 (m, 1 H), 7.51 - 7.44 (m, 1 H), 7.14 - 7.05 (m, 1 H), 6.53 - 6.43 (m, 2 H), 5.68 (q, *J* = 6.8 Hz, 1 H), 3.60 - 3.50 (m, 4 H), 2.45 (s, 3 H), 1.96 - 1.75 (m, 6 H), 1.68 (d, *J* = 6.8 Hz, 3 H).

EXAMPLE 2-2

(*R*)-2-((1-(2-cyano-9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid





[00456] Step A: 8-bromo-2-chloro-6-methyl-quinazolin-4-amine (3.70 g, 13.6 mmol, 1.00 eq.) was added as a solid to piperidine (5.78 g, 67.9 mmol, 6.70 mL, 5.00 eq.). The mixture was heated and stirred at 130 °C for 1 hour. Upon completion of the reaction, the mixture was cooled to 25 °C, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0% to 50% ethyl acetate in petroleum ether) to give 8-bromo-6-methyl-2-(piperidin-1-yl)quinazolin-4-amine (4.00 g, 12.3 mmol, 90% yield) as a yellow solid. LCMS [M+1]⁺ = 321.2.

[00457] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm = 7.79 (s, 1 H), 7.70 (d, *J* = 1.6 Hz, 1 H), 7.38 (br s, 2 H), 3.82 - 3.75 (m, 4 H), 2.31 (s, 3 H), 1.60 (br d, *J* = 4.4 Hz, 2 H), 1.51 (br d, *J* = 4.0 Hz, 4 H)

[00458] Step B: To a solution of 8-bromo-6-methyl-2-(piperidin-1-yl)quinazolin-4-amine (3.00 g, 9.34 mmol, 1.00 eq.) in toluene (360 mL) was added ethyl 3-bromo-2-oxopropanoate (9.11 g, 46.7 mmol, 5.84 mL, 5.00 eq.) and 4Å molecular sieves (40.0 g). The mixture was sealed and stirred at 140 °C for 15 hours. Upon completion of the reaction, the mixture was cooled to 25 °C, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0% to 100% ethyl acetate in petroleum ether) to give ethyl 7-bromo-9-methyl-5-(piperidin-1-yl)imidazo[1,2-*c*]quinazoline-2-carboxylate (3.50 g, 8.39 mmol) as a yellow solid. LCMS [M+3]⁺ = 419.1.

[00459] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm = 8.24 (s, 1 H), 8.13 (s, 1 H), 7.84 (d, *J* = 1.6 Hz, 1 H), 4.36 (q, *J* = 7.2 Hz, 2 H), 3.52 - 3.45 (m, 4 H), 2.47 (s, 3 H), 1.77 (br d, *J* = 3.6 Hz, 4 H), 1.69 (br d, *J* = 4.4 Hz, 2 H), 1.35 (t, *J* = 7.2 Hz, 3 H).

[00460] Step C: To a solution of ethyl 7-bromo-9-methyl-5-(piperidin-1-yl)imidazo[1,2-*c*]quinazoline-2-carboxylate (900 mg, 2.16 mmol, 1.00 eq.) in methanol (2.00 mL) was added 9.00 mL ammonia (7.00 M in methanol). The mixture was stirred at 35 °C for 48 hours. The

reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0% to 100% ethyl acetate in petroleum ether) to give 7-bromo-9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazoline-2-carboxamide (500 mg, 1.29 mmol, 60% yield) as a yellow solid. LCMS [M+3]⁺ = 390.1.

[00461] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm = 8.11 (s, 2 H), 7.83 (s, 2 H), 7.57 (br s, 1 H), 3.47 (br d, *J* = 4.8 Hz, 4 H), 2.47 (s, 3 H), 1.77 (br d, *J* = 2.8 Hz, 4 H), 1.69 (br d, *J* = 4.0 Hz, 2 H).

[00462] Step D: To a solution of 7-bromo-9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazoline-2-carboxamide (480 mg, 1.24 mmol, 1.00 eq.) and triethylamine (188 mg, 1.85 mmol, 258 μL, 1.50 eq.) in dichloromethane (50.0 mL) was added trifluoroacetic anhydride (389 mg, 1.85 mmol, 258 μL, 1.50 eq.) dropwise at 0 °C and. The mixture was stirred at 0 °C for 30 minutes. The reaction mixture was quenched by addition water (20 mL) at 25 °C, and then extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine 30 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 (0% to 30% ethyl acetate in petroleum ether) to give 7-bromo-9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazoline-2-carbonitrile (301 mg, 813 μmol) as a yellow solid. LCMS [M+1]⁺ = 370.2.

[00463] Step E: A mixture of 7-bromo-9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazoline-2-carbonitrile (270 mg, 729 μmol, 1.00 eq.), *n*-butyl vinyl ether (365 mg, 3.65 mmol, 469 μL, 5.00 eq.), *N,N*-dicyclohexylmethylamine (397 mg, 2.19 mmol, 436 μL, 3.00 eq.), chloro[(tri-*tert*-butylphosphine)-2-(2-aminobiphenyl)] palladium(II) (37.4 mg, 72.9 μmol, 0.10 eq.) was evacuated and backfilled with nitrogen 3 times and deoxygenated dioxane (6.00 mL) was added, then the mixture was stirred at 100 °C for 10 hours under a nitrogen atmosphere. Upon completion of the reaction, the mixture was cooled to 25 °C, the reaction mixture was filtered and concentrated under reduced pressure to give the crude product 7-(1-butoxyvinyl)-9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazoline-2-carbonitrile (280 mg, 719 μmol, 99% yield) as a yellow solid. LCMS [M+1]⁺ = 390.3.

[00464] Step F: To a solution of 7-(1-butoxyvinyl)-9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazoline-2-carbonitrile (249 mg, 639 μmol, 1.00 eq.) in dichloromethane (2.50 mL) was added trifluoroacetic acid (729 mg, 6.39 mmol, 475 μL, 10.0 eq.). The mixture was stirred at 25 °C for 1 hour. The reaction mixture filtered and concentrated filtrate under reduced pressure to give the residue. The residue was purified by silica gel chromatography (10% to 20% ethyl acetate in petroleum ether) to give 7-acetyl-9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazoline-2-carbonitrile (201 mg, 603 μmol, 94% yield) as a yellow solid.

[00465] ¹H NMR (400 MHz, CDCl₃) δ ppm = 8.38 (s, 1 H), 8.00 (s, 1 H), 7.80 (d, *J* = 1.6 Hz, 1 H), 3.49 - 3.40 (m, 4 H), 2.90 (s, 3 H), 2.55 - 2.51 (m, 3 H), 2.02 - 1.85 (m, 6 H).

[00466] Step G: To a solution of 7-acetyl-9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazoline-2-carbonitrile (190 mg, 570 μmol, 1.00 eq.) in 2-methyltetrahydrofuran (10.0 mL) was added (*R*)-2-methylpropane-2-sulfinamide (345.37 mg, 2.85 mmol, 5.00 eq.), titanium (IV) ethoxide (650 mg, 2.85 mmol, 591 μL, 5.00 eq.) and 1,2-dimethoxyethane (51.4 mg, 570 μmol, 59.2 μL, 1.00 eq.). The mixture was stirred at 95 °C for 12 hours. Upon completion of the reaction, the mixture was cooled to 25 °C, the reaction mixture was added water (15 mL) to stirred 30 minutes. The reaction mixture was filtered. The filtrate was extracted with ethyl acetate 60.0 mL (20 mL × 3). The combined organic layers were washed with brine 60 mL (20 mL × 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 (0% to 100% ethyl acetate in petroleum ether) to give (*R*)-*N*-(1-(2-cyano-9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazolin-7-yl)ethylidene)-2-methylpropane-2-sulfinamide (160 mg, 360 μmol, 63% yield, 98% purity) as a yellow solid. LCMS [*M*+1]⁺ = 437.4.

[00467] Step H: To a solution of (*R*)-*N*-(1-(2-cyano-9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazolin-7-yl)ethylidene)-2-methylpropane-2-sulfinamide (130 mg, 298 μmol, 1.00 eq.) in dichloromethane (1.50 mL) was added Schwartz's reagent (95.4 mg, 357 μmol, 1.20 eq.) portionwise. The mixture was stirred at 25 °C for 1 hour. The reaction mixture was partitioned between ethyl acetate 30.0 mL and water 30.0 mL. The organic phase was separated, washed with brine 90 mL (30 mL × 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 (0% to 100% ethyl acetate in petroleum ether) to give (*R*)-*N*-((*R*)-1-(2-cyano-9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazolin-7-yl)ethyl)-2-methylpropane-2-sulfinamide (80 mg, 170 μmol, 57% yield) as a yellow solid. LCMS [*M*+1]⁺ = 439.2.

[00468] ¹H NMR (400 MHz, CDCl₃) δ ppm = 8.18 (s, 1 H), 7.98 (s, 1 H), 7.46 (d, *J* = 1.2 Hz, 1 H), 5.09 (t, *J* = 6.8 Hz, 1 H), 3.44 - 3.39 (m, 4 H), 2.52 (s, 3 H), 1.86 (br s, 4 H), 1.77 (br d, *J* = 4.4 Hz, 2 H), 1.66 (d, *J* = 6.8 Hz, 3 H), 1.24 (s, 8H).

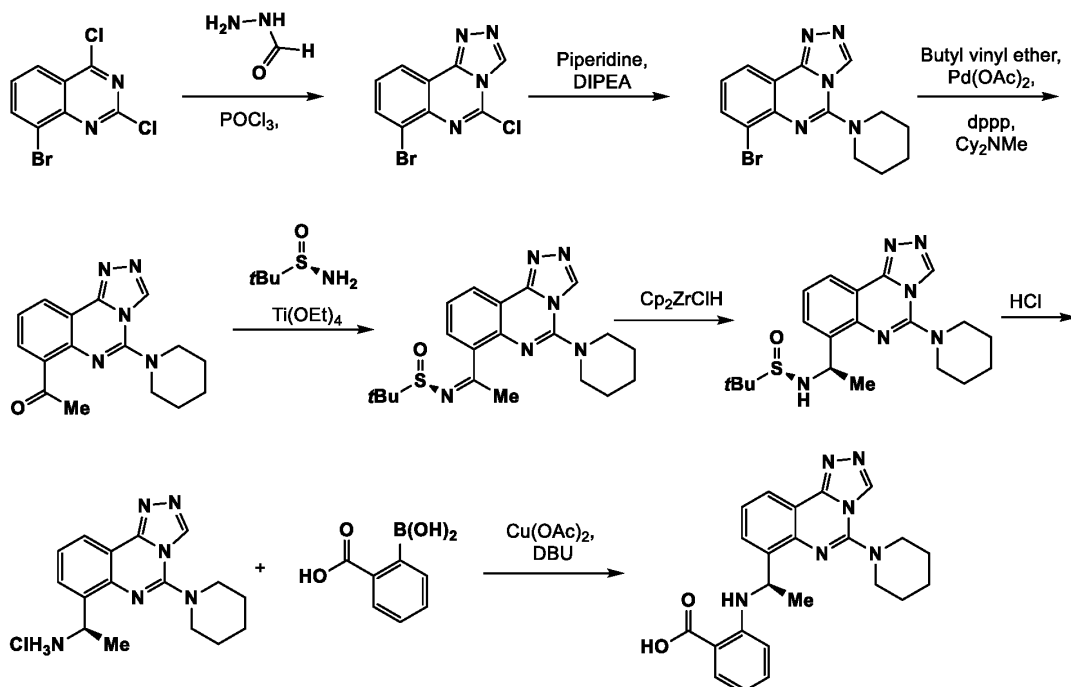
[00469] Step I: To a solution of (*R*)-*N*-((*R*)-1-(2-cyano-9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazolin-7-yl)ethyl)-2-methylpropane-2-sulfinamide (70 mg, 160 μmol, 1.0 eq.) in dioxane (1.00 mL) was added 300 μL HCl (4 molar in dioxane). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give crude product (*R*)-7-(1-aminoethyl)-9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazoline-2-carbonitrile, hydrochloride (50 mg, 150 μmol, 84% yield) as a yellow solid. LCMS [*M*+1]⁺ = 335.3.

[00470] Step J: To a solution of (*R*)-7-(1-aminoethyl)-9-methyl-5-(piperidin-1-yl)imidazo[1,2-*c*]quinazoline-2-carbonitrile, hydrochloride (50 mg, 150 μ mol, 1.0 *eq.*) in dimethylformamide (0.50 mL) was added 2-carboxyphenylboronic acid (74 mg, 450 μ mol, 3.0 *eq.*), diazabicyclo[5.4.0]undec-7-ene (114 mg, 748 μ mol, 113 μ L, 5.0 *eq.*), copper (II) acetate (41 mg, 220 μ mol, 1.5 *eq.*) and 4Å molecular sieves (40.0 mg). The mixture was stirred at 25 °C for 12 hours. To the reaction mixture was added ammonium chloride saturated aqueous solution 20 mL at 25 °C, and extracted with ethyl acetate (20 mL $\times$ 3). The combined organic layers were washed with brine (20 mL $\times$ 3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by preparative TLC (33% ethyl acetate in petroleum ether) 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(FA)-ACN]; gradient: 62%-92% B over 9 min) to give (*R*)-2-((1-(2-cyano-9-methyl-5-(piperidin-1-yl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid (24 mg, 53 μ mol, 35% yield) as a white solid. LCMS [*M*+1]⁺ = 455.2.

[00471] ¹H NMR (400 MHz, CDCl₃) δ ppm = 11.81 - 10.40 (m, 1 H), 8.46 - 8.09 (m, 2 H), 8.05 - 7.98 (m, 2 H), 7.53 (s, 1 H), 7.18 (br t, *J* = 7.6 Hz, 1 H), 6.58 (t, *J* = 7.6 Hz, 1 H), 6.45 (d, *J* = 8.8 Hz, 1 H), 5.63 (q, *J* = 6.4 Hz, 1 H), 3.48 (br s, 4 H), 2.47 (s, 3 H), 1.88 (br s, 4 H), 1.80 (br d, *J* = 4.4 Hz, 2 H), 1.70 (br d, *J* = 6.8 Hz, 3 H).

EXAMPLE 3-1

(*R*)-2-((1-(5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid



[00472] Step A: To a reaction vial and stir bar charged with tetrahydrofuran (36.0 mL) was added 8-bromo-2,4-dichloroquinazoline (3.00 g, 1.0 eq. 10.8 mmol) as a solid and diisopropylethylamine (1.40 g, 1.88 mL, 1.0 eq. 10.8 mmol). After dissolution, the vial was cooled to 0 °C and formylhydrazine (648 mg, 1.0 eq. 10.8 mmol) was added portion-wise. Once the addition was complete, the cooling bath was removed, and the reaction was stirred at room temperature for 12 hours. Upon full conversion to the intermediate aryl hydrazide (observed by LCMS), phosphorous oxychloride (2.48 g, 1.51 mL, 1.5 eq. 16.2 mmol) was added and the reaction was heated to 60 °C until full conversion to the tricyclic product was observed. The reaction was carefully poured onto ice and the resulting aqueous suspension was neutralized to pH 7 with sodium hydroxide. The product was filtered and rinsed with water, dried and purified by silica gel chromatography (0% to 100% ethyl acetate in heptane) to provide 7-bromo-5-chloro-[1,2,4]triazolo[4,3-c]quinazoline (1.0 g, 3.5 mmol, 33% yield) as an orange solid. LCMS [M+1]⁺ = 284.9.

[00473] ¹H NMR (500 MHz, CDCl₃) δ ppm = 8.98 (s, 1 H), 8.60 (dd, *J* = 7.94, 1.37 Hz, 1 H), 8.10 (dd, *J* = 7.80, 1.23 Hz, 1 H), 7.61 (t, *J* = 7.94 Hz, 1 H).

[00474] Step B: To a vial and stir bar was added 7-bromo-5-chloro-[1,2,4]triazolo[4,3-c]quinazoline (500 mg, 1 eq. 1.76 mmol) as a solid which was dissolved in anhydrous 1,2-dichloroethane (7.05 mL). Next, diisopropylethylamine (456 mg, 614 μL, 2.0 eq. 3.53 mmol) and piperidine (165 mg, 192 μL, 1.1 eq. 1.94 mmol) were added successively and the reaction was sealed and heated to 80 °C overnight. To the reaction was added saturated sodium bicarbonate and this solution was diluted with dichloromethane. The aqueous layer was separated and extracted three times. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated and purified via silica gel chromatography (0% to 70% ethyl acetate in heptane) to provide 7-bromo-5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-c]quinazoline (270 mg, 813 μmol, 46% yield) as a white solid. LCMS [M+1]⁺ = 332.0.

[00475] ¹H NMR (500 MHz, CDCl₃) δ ppm = 8.77 (s, 1 H), 8.50 (dd, *J* = 7.80, 1.23 Hz, 1 H), 7.96 (dd, *J* = 7.67, 1.37 Hz, 1 H), 7.34 (t, *J* = 7.94 Hz, 1 H), 3.59 - 3.66 (m, 4 H), 1.83 - 1.91 (m, 4 H), 1.76 - 1.83 (m, 2 H).

[00476] Step C: To a vial and a stir bar was added palladium (II) acetate (9.12 mg, 0.05 eq. 40.6 μmol), 1,3-bis(diphenylphosphino)propane (33.5 mg, 0.10 eq. 81.3 μmol), and 7-bromo-5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-c]quinazoline (270 mg, 1.0 eq. 813 μmol). The flask evacuated and backfilled with nitrogen three times. Next, ethylene glycol (4.1 mL), *N,N*-dicyclohexylmethylamine (476 mg, 519 μL, 3.0 eq. 2.44 mmol), and *n*-butyl vinyl ether (407 mg, 526 μL, 5.0 eq. 4.06 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 (15 mL) was added to the reaction. The reaction was stirred until the ketone deprotection went to completion (ca. 1 hour). 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 1-(5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethan-1-one (107 mg, 362 μ mol, 45% yield) as a yellow solid. LCMS [M+H]⁺ = 296.1.

[00477] ¹H NMR (400 MHz, CDCl₃) δ ppm = 8.86 (br m, 1 H), 8.83 (s, 1 H), 8.05 (d, *J* = 7.50 Hz, 1 H), 7.61 (t, *J* = 7.75 Hz, 1 H), 3.58 - 3.65 (m, 4 H), 2.92 (s, 3 H), 1.89 (br m, 4 H), 1.78 - 1.85 (m, 2 H).

[00478] Step D: To a solution of 1-(5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethan-1-one (156 mg, 1.0 eq. 528 μ mol) and (*R*)-2-methylpropane-2-sulfinamide (76.8 mg, 1.2 eq. 634 μ mol) in tetrahydrofuran (2.1 mL) was added titanium (IV) ethoxide (602 mg, 550 μ L, 5.0 eq. 2.64 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 evaporation 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-(5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethylidene)propane-2-sulfinamide (145 mg, 364 μ mol, 69% yield) as a yellow solid.

[00479] Step E: To a solution of (*R*)-2-methyl-*N*-(1-(5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethylidene)propane-2-sulfinamide (145 mg, 1.0 eq. 364 μ mol) in anhydrous dichloromethane (2.4 mL) at room temperature was added Schwartz's Reagent (103 mg, 1.1 eq. 400 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 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-(5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)propane-2-sulfinamide (8.8 mg, 22 μ mol, 6% yield) as a white solid. LCMS [M+1]⁺ = 401.1.

[00480] Step F: To a solution of (*R*)-2-methyl-*N*-((*R*)-1-(5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)propane-2-sulfinamide (8.8 mg, 1.0 eq. 22 μ mol) in methanol (0.22 mL) at room temperature was added 14 μ L of HCl (4.0 molar in dioxane). The reaction was monitored and once complete, triturated with diethyl ether and dried under vacuum to provide

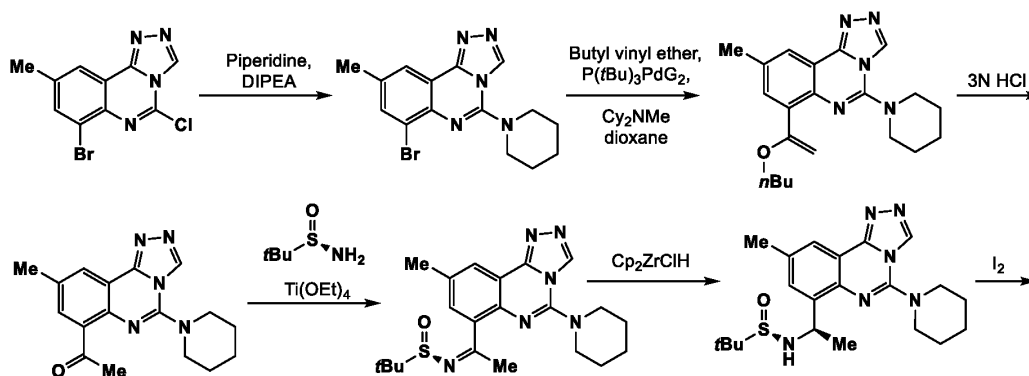
(*R*)-1-(5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethan-1-amine, hydrochloride as a salt which was used without further purification. LCMS $[M+1]^+ = 297.2$.

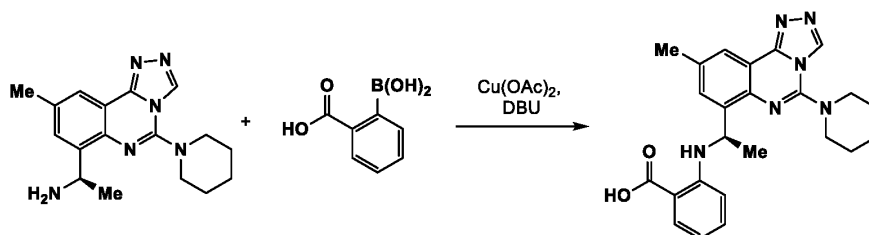
[00481] Step G: To a vial and stir bar was added (*R*)-1-(5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethan-1-amine, HCl (7.3 mg, 1.0 eq. 22 μ mol), 2-carboxyphenylboronic acid (11 mg, 3.0 eq. 66 μ mol) and copper (II) acetate (6.0 mg, 1.5 eq. 33 μ mol) as solids. Next, the vial was sealed with a septum cap and dimethylformamide (0.22 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (17 mg, 17 μ L, 5.0 eq. 0.11 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 preparative thin layer chromatography to provide (*R*)-2-((1-(5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid (2.0 mg, 4.8 μ mol, 22% yield) as a white solid. LCMS $[M+1]^+ = 417.2$.

[00482] ^1H NMR (400 MHz, CDCl_3) δ ppm = 8.81 (s, 1 H), 8.41 - 8.51 (m, 1 H), 8.00 (dd, $J = 8.00$, 1.38 Hz, 1 H), 7.72 (d, $J = 7.50$ Hz, 1 H), 7.44 (t, $J = 7.75$ Hz, 1 H), 7.10 - 7.20 (m, 1 H), 6.57 (t, $J = 7.50$ Hz, 1 H), 6.42 (d, $J = 8.63$ Hz, 1 H), 5.63 (q, $J = 6.67$ Hz, 1 H), 3.53 - 3.63 (m, 4 H), 1.88 (br m, 4 H), 1.80 (br m, 2 H), 1.70 (d, $J = 6.63$ Hz, 3 H).

EXAMPLE 4-1

(*R*)-2-((1-(9-methyl-5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid





[00483] Step A: To a solution of 7-bromo-5-chloro-9-methyl-[1,2,4]triazolo[4,3-c]quinazoline (6.00 g, 20.2 mmol, 1.00 eq.) in acetonitrile (50 mL) was added piperidine (1.89 g, 22.2 mmol, 1.10 eq.). The reaction was stirred at 60 °C for 16 hours. Upon completion, the mixture was cooled to 25 °C, the mixture was filtered and the filter residue was washed with acetonitrile (30 mL) to give a residue, which was triturated with water (150 mL) at 20 °C for 30 min, filtered and dried under reduced pressure to give 7-bromo-9-methyl-5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-c]quinazoline (4.20 g, 12.1 mmol, 60% yield) as a yellow solid. LCMS [M+1]⁺ = 346.1.

[00484] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm = 9.38 (s, 1 H), 8.15 (d, *J* = 0.8 Hz, 1 H), 7.88 (d, *J* = 1.6 Hz, 1 H), 3.60 - 3.51 (m, 4 H), 2.47 (s, 3 H), 1.81 - 1.62 (m, 6 H).

[00485] Step B: A mixture of 7-bromo-9-methyl-5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-c]quinazoline (2.00 g, 5.78 mmol, 1.00 eq.), butyl vinyl ether (868 mg, 8.66 mmol, 1.11 mL, 1.5 eq.), chloro[(tri-*tert*-butylphosphine)-2-(2-aminobiphenyl)] palladium(II) (148 mg, 289 μmol, 0.05 eq.), *N,N*-dicyclohexylmethylamine (2.09 g, 11.5 mmol, 2.30 mL, 2.00 eq) was evacuated and backfilled with nitrogen for 3 times and deoxygenated dioxane (50 mL) was added. The reaction was stirred at 100 °C for 2 hours under nitrogen atmosphere. Upon completion, the mixture was cooled to 25 °C. The mixture was diluted with water (20.0 mL) and used into the next step without further purification. LCMS [M+1]⁺ = 366.2.

[00486] Step C: To a solution of 7-(1-butoxyvinyl)-9-methyl-5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-c]quinazoline (2.10 g, 5.75 mmol, 1.00 eq.) in tetrahydrofuran (30 mL) was added 5.75 mL HCl (3 molar in water). The reaction was stirred at 20 °C for 4 hours. Next, the mixture was diluted with water (150 mL) and filtered to give the filter residue, which was triturated with ethyl acetate (50 mL) at 20 °C for 30 min, filtered and dried under reduced pressure to give 1-(9-methyl-5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethan-1-one (1.50 g, 4.85 mmol, 84% yield) as a yellow solid. LCMS [M+1]⁺ = 310.3.

[00487] Step D: To a solution of 1-(9-methyl-5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethan-1-one (1.00 g, 3.23 mmol, 1.00 eq.), (*R*)-2-methylpropane-2-sulfinamide (509 mg, 4.20 mmol, 1.30 eq.) in tetrahydrofuran (30 mL) was added titanium (IV) ethoxide (1.47 g, 6.46 mmol, 1.34 mL, 2.00 eq.). The reaction was stirred at 70 °C for 12 hours. The mixture was concentrated under reduced pressure to give a residue, which was used into the next step without further purification. LCMS [M+1]⁺ = 413.3.

[00488] Step E: To a solution of (*R*)-2-methyl-*N*-(1-(9-methyl-5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethylidene)propane-2-sulfonamide (1.20 g, 2.91 mmol, 1.00 eq.) in dichloromethane (30 mL) was added Schwartz's reagent (1.55 g, 5.82 mmol, 2.00 eq.) portion wise. The reaction was stirred at 25 °C for 3 hours. The mixture was concentrated under reduced pressure to give a residue, which was used into the next step without further purification. LCMS [M+1]⁺ = 415.3.

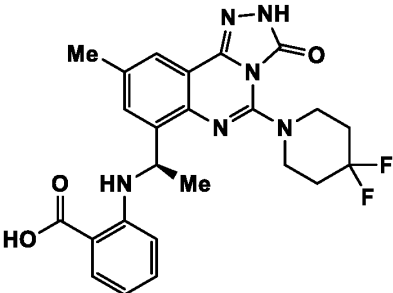
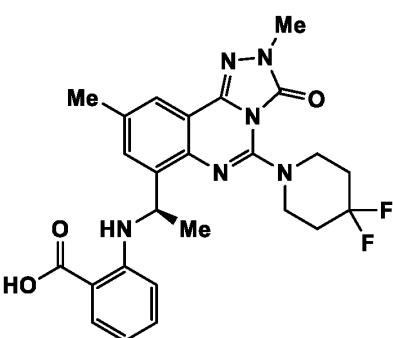
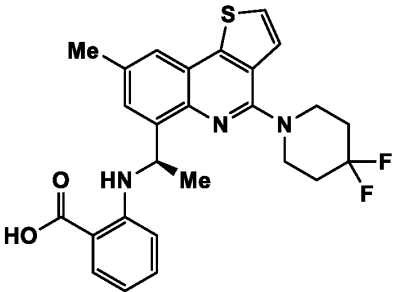
[00489] Step F: To a solution of (*R*)-2-methyl-*N*-((*R*)-1-(9-methyl-5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)propane-2-sulfonamide (1.10 g, 2.65 mmol, 1.00 eq.) in tetrahydrofuran (30 mL) was added iodine (878 mg, 3.45 mmol, 1.30 eq.) and water (6 mL). The reaction was stirred at 50 °C for 2 hours. Upon completion, the mixture was cooled to 25 °C. Next, the mixture was concentrated under reduced pressure, purified by reversed phase flash (0% to 40% Acetonitrile in Water(0.3%FA)) and lyophilized to give (*R*)-1-(9-methyl-5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethan-1-amine (500 mg, 1.61 mmol, 61% yield) as a yellow solid. LCMS [M+1]⁺ = 311.2.

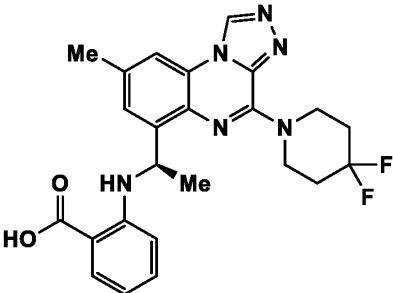
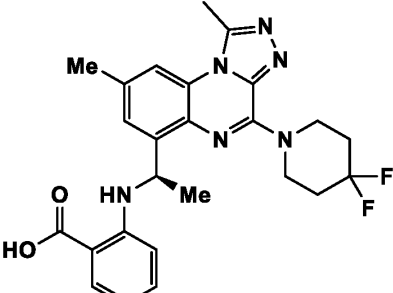
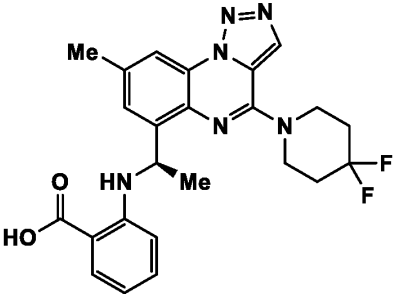
[00490] Step G: A mixture of (*R*)-1-(9-methyl-5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethan-1-amine (200 mg, 644 μmol, 1.00 eq.), 2-carboxyphenylboronic acid (214 mg, 1.29 mmol, 2.00 eq.), copper (II) acetate (234 mg, 1.29 mmol, 2.00 eq.), diazabicyclo[5.4.0]undec-7-ene (294 mg, 1.93 mmol, 291 μL, 3.00 eq.) in dimethylformamide (3 mL) was purged with oxygen 3 times. The reaction was stirred at 25 °C for 12 hours under an oxygen atmosphere. The mixture was filtered and then purified by prep-HPLC (column: Phenomenex luna C18 150 × 25mm × 10μm; mobile phase: [water(FA)-ACN]; gradient: 52%-82% B over 9 min) and lyophilized to give (*R*)-2-((1-(9-methyl-5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid (8 mg, 18 μmol, 3% yield) as a yellow solid. LCMS [M+1]⁺ = 431.3.

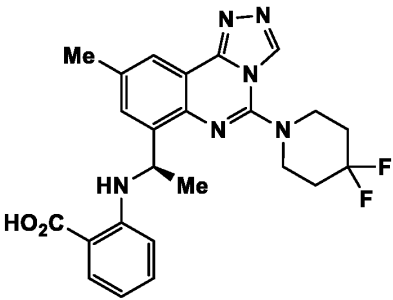
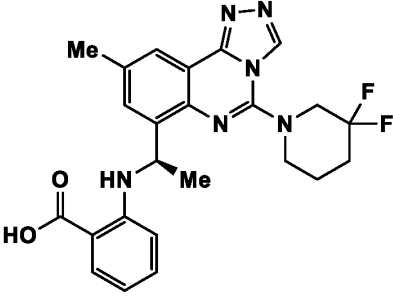
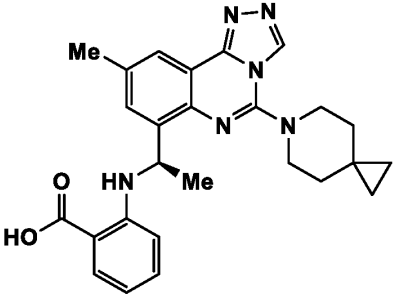
[00491] ¹H NMR (400 MHz, CD₃OD) δ ppm = 9.22 (br s, 1 H), 8.10 (s, 1 H), 7.86 (br d, *J* = 7.6 Hz, 1 H), 7.55 (s, 1 H), 7.07 (t, *J* = 7.6 Hz, 1 H), 6.55 - 6.37 (m, 2 H), 5.60 (q, *J* = 6.4 Hz, 1 H), 3.58 (s, 4 H), 2.43 (s, 3 H), 1.88 (s, 4 H), 1.79 (d, *J* = 5.2 Hz, 2 H), 1.65 (d, *J* = 6.4 Hz, 3 H).

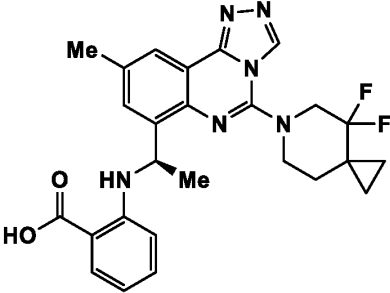
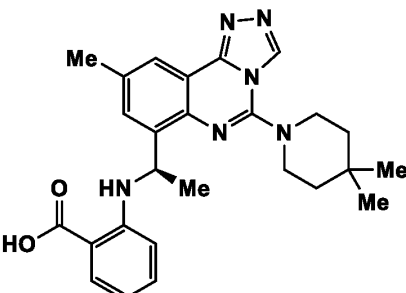
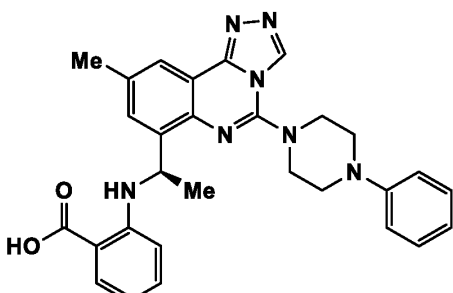
EXAMPLES 5-1 to 5-50

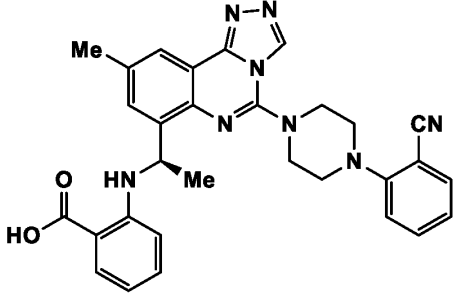
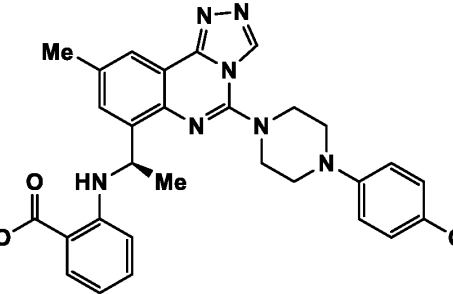
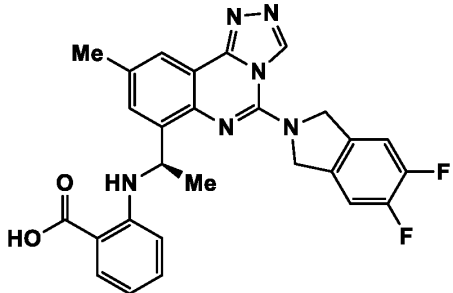
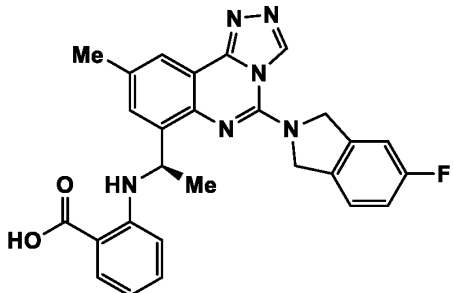
The following compounds are prepared essentially according to the procedures set forth above in Schemes I-IV and Examples 1-1, 2-1, 2-2, 3-1 and 4-1.

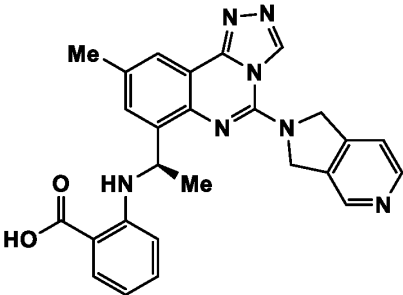
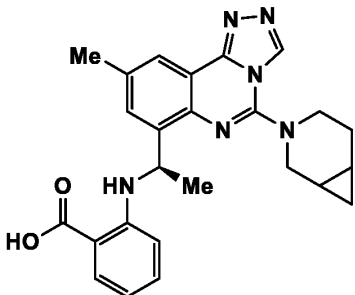
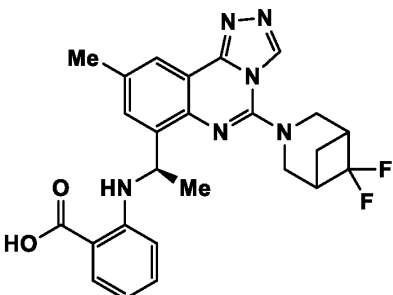
Example No.	Compound	Spectral Data
5-1	 (R)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	
5-2	 (R)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-2,9-dimethyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CD ₃ OD) δ ppm = 7.87 (dd, <i>J</i> = 1.6, 8.0 Hz, 1H), 7.71 (d, <i>J</i> = 1.6 Hz, 1H), 7.40 (d, <i>J</i> = 1.6 Hz, 1H), 7.14 - 7.06 (m, 1H), 6.51 - 6.46 (m, 1H), 6.43 (d, <i>J</i> = 8.4 Hz, 1H), 5.44 (q, <i>J</i> = 6.4 Hz, 1H), 3.63 (br t, <i>J</i> = 5.6 Hz, 4H), 3.59 (s, 3H), 2.34 (s, 3H), 2.30 - 2.17 (m, 4H), 1.60 (d, <i>J</i> = 6.8 Hz, 3H). LCMS [M+1] ⁺ = 497.2.
5-3	 (R)-2-((1-(4-(4,4-difluoropiperidin-1-yl)-8-methylthieno[3,2-c]quinolin-6-yl)ethyl)amino)benzoic acid	

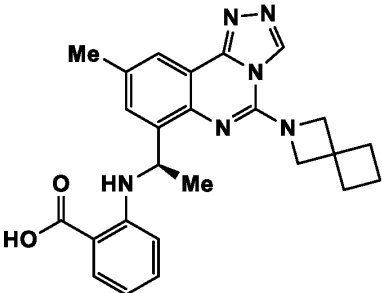
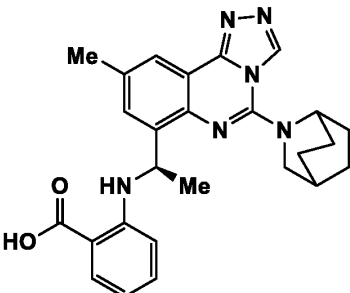
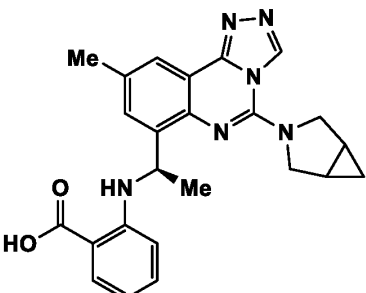
5-4	 (R)-2-((1-(4-(4,4-difluoropiperidin-1-yl)-8-methyl-[1,2,4]triazolo[4,3-a]quinoxalin-6-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm = 9.99 (s, 1H), 8.76 - 8.55 (br s, 1H), 7.97 (s, 1H), 7.78 (br d, <i>J</i> = 6.8 Hz, 1H), 7.30 (s, 1H), 7.18 - 7.03 (m, 1H), 6.54 - 6.37 (m, 2H), 5.51 (q, <i>J</i> = 6.0 Hz, 1H), 4.47 (br s, 4H), 2.39 (s, 3H), 2.26 - 2.10 (m, 4H), 1.58 (d, <i>J</i> = 6.4 Hz, 3H). LCMS [M+1] ⁺ = 467.2.
5-5	 (R)-2-((1-(4-(4,4-difluoropiperidin-1-yl)-1,8-dimethyl-[1,2,4]triazolo[4,3-a]quinoxalin-6-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm = 12.68 (br s, 1H), 8.52 (br s, 1H), 7.87 (s, 1H), 7.78 (dd, <i>J</i> = 1.6, 7.8 Hz, 1H), 7.30 (s, 1H), 7.18 - 7.09 (m, 1H), 6.48 (t, <i>J</i> = 7.2 Hz, 1H), 6.41 (d, <i>J</i> = 8.4 Hz, 1H), 5.54 (br s, 1H), 4.44 (br s, 4H), 3.06 (s, 3H), 2.40 (s, 3H), 2.23 - 2.11 (m, 4H), 1.58 (d, <i>J</i> = 6.4 Hz, 3H). LCMS [M+1] ⁺ = 481.2.
5-6	 (R)-2-((1-(4-(4,4-difluoropiperidin-1-yl)-8-methyl-[1,2,3]triazolo[1,5-a]quinoxalin-6-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm = 12.67 (br s, 1H), 8.85 (s, 1H), 8.49 (br s, 1H), 8.18 (s, 1H), 7.78 (dd, <i>J</i> = 1.6, 8.0 Hz, 1H), 7.41 (d, <i>J</i> = 1.6 Hz, 1H), 7.15 (s, 1H), 6.53 - 6.44 (m, 2H), 5.59 - 5.51 (m, 1H), 4.05 (br t, <i>J</i> = 5.6 Hz, 4H), 2.44 (s, 3H), 2.13 - 2.07 (m, 4H), 1.61 (d, <i>J</i> = 6.8 Hz, 3H). LCMS [M+1] ⁺ = 467.2.

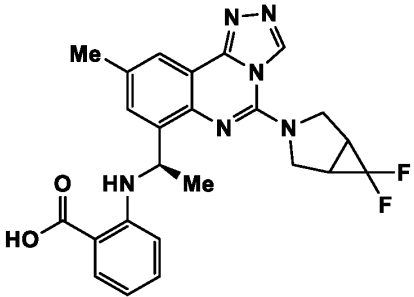
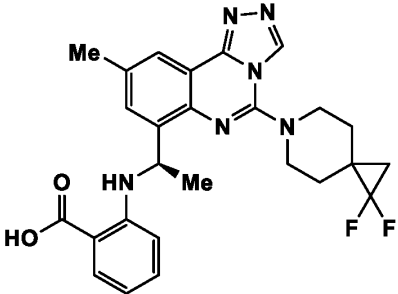
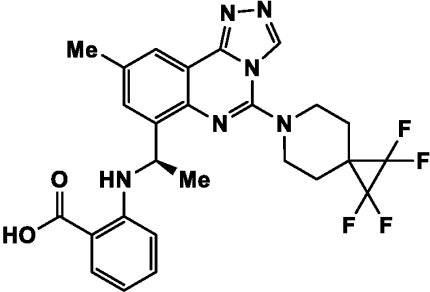
5-7	 (<i>R</i>)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CD ₃ OD) δ ppm = 9.34 (s, 1H), 8.13 (s, 1H), 7.88 (dd, <i>J</i> = 1.6, 8.0 Hz, 1H), 7.59 (d, <i>J</i> = 1.6 Hz, 1H), 7.15 - 7.05 (m, 1H), 6.57 - 6.40 (m, 2H), 5.59 (q, <i>J</i> = 6.8 Hz, 1H), 3.78 (br t, <i>J</i> = 5.6 Hz, 4H), 2.45 (s, 3H), 2.38 - 2.25 (m, 4H), 1.67 (d, <i>J</i> = 6.8 Hz, 3H). LCMS [<i>M</i> +1] ⁺ = 467.2.
5-8	 (<i>R</i>)-2-((1-(5-(3,3-difluoropiperidin-1-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	LCMS [<i>M</i> +1] ⁺ = 467.2.
5-9	 (<i>R</i>)-2-((1-(9-methyl-5-(6-azaspiro[2.5]octan-6-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	

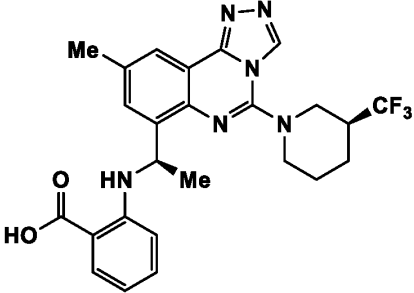
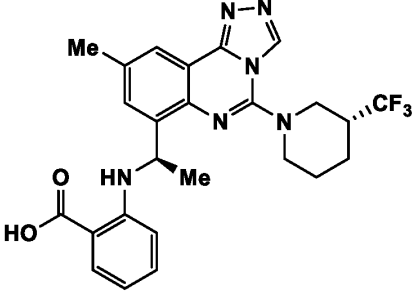
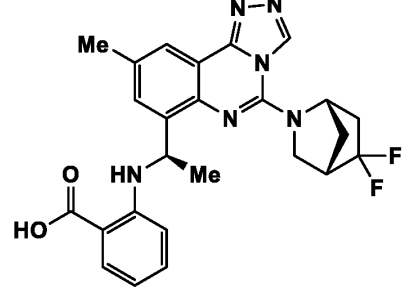
5-10	 (R)-2-((1-(5-(4,4-difluoro-6-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	LCMS [M+1] ⁺ = 493.5.
5-11	 (R)-2-((1-(5-(4,4-dimethylpiperidin-1-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	
5-12	 (R)-2-((1-(9-methyl-5-(4-phenylpiperazin-1-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	

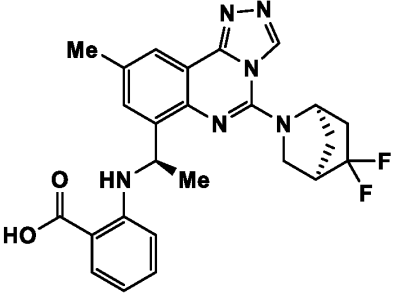
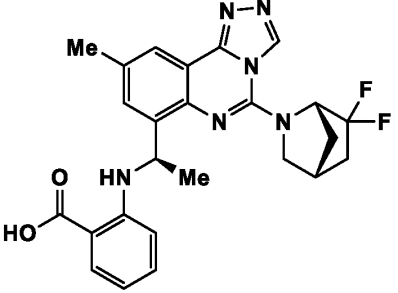
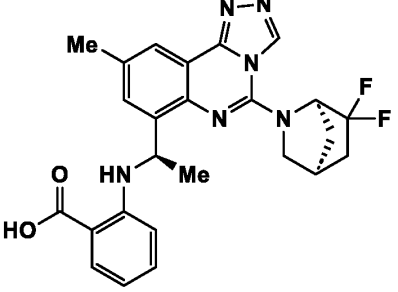
5-13	 (R)-2-((1-(5-(4-(2-cyanophenyl)piperazin-1-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	
5-14	 (R)-2-((1-(5-(4-(4-cyanophenyl)piperazin-1-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	
5-15	 (R)-2-((1-(5-(5,6-difluoroisoindolin-2-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	
5-16	 (R)-2-((1-(5-(5-fluoroisoindolin-2-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	

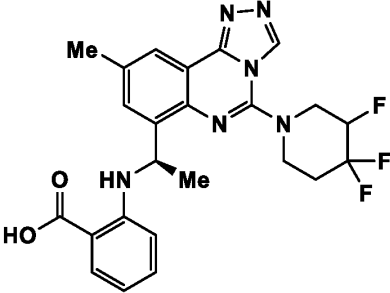
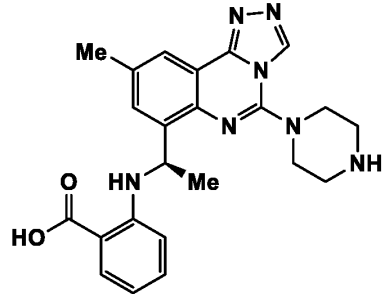
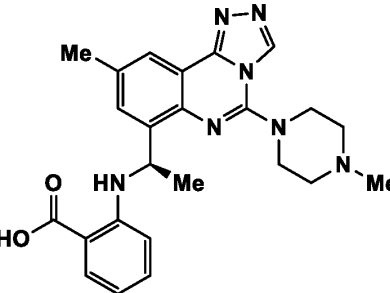
5-17	 (<i>R</i>)-2-(((1-(5-(1,3-dihydro-2<i>H</i>-pyrrolo[3,4-<i>c</i>]pyridin-2-yl)-9-methyl-[1,2,4]triazolo[4,3-<i>c</i>]quinazolin-7-yl)ethyl)amino)benzoic acid	
5-18	 2-(((1<i>R</i>)-1-(5-(3-azabicyclo[4.1.0]heptan-3-yl)-9-methyl-[1,2,4]triazolo[4,3-<i>c</i>]quinazolin-7-yl)ethyl)amino)benzoic acid	
5-19	 2-(((1<i>R</i>)-1-(5-(6,6-difluoro-3-azabicyclo[3.1.1]heptan-3-yl)-9-methyl-[1,2,4]triazolo[4,3-<i>c</i>]quinazolin-7-yl)ethyl)amino)benzoic acid	

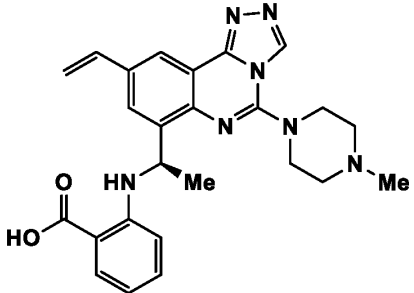
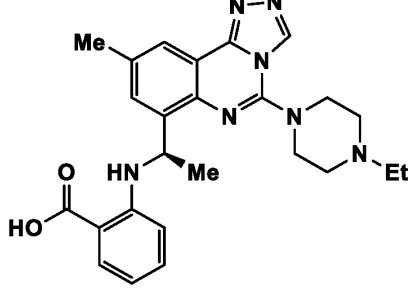
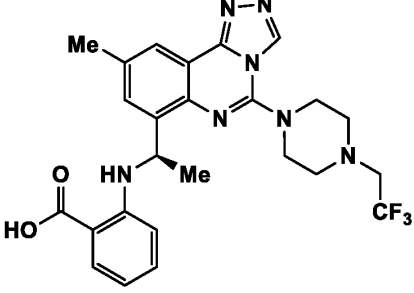
5-20	 (R)-2-((1-(9-methyl-5-(2-azaspiro[3.3]heptan-2-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	
5-21	 (R)-2-((1-(5-(2-azabicyclo[2.2.2]octan-2-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	
5-22	 2-(((1R)-1-(5-(3-azabicyclo[3.1.0]hexan-3-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	

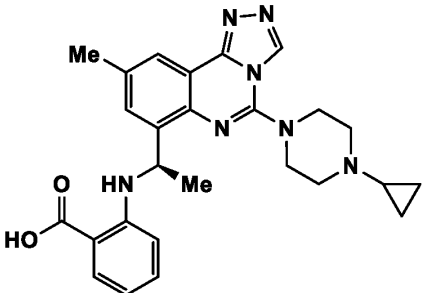
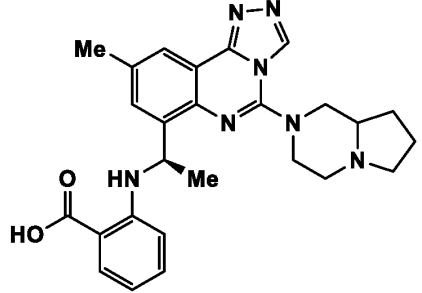
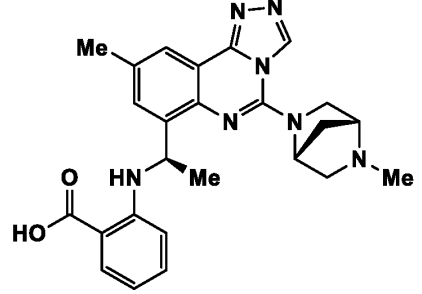
5-23	 2-(((1<i>R</i>)-1-(5-(6,6-difluoro-3-azabicyclo[3.1.0]hexan-3-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	
5-24	 (<i>R</i>)-2-((1-(5-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	
5-25	 (<i>R</i>)-2-((1-(9-methyl-5-(1,1,2,2-tetrafluoro-6-azaspiro[2.5]octan-6-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	

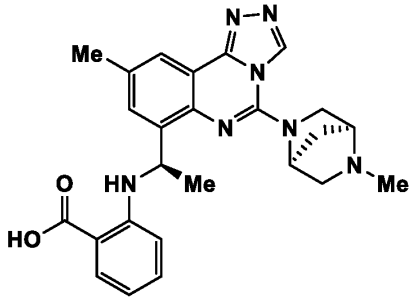
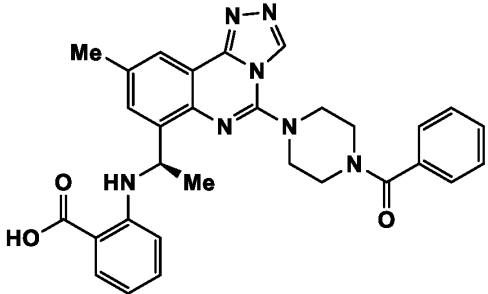
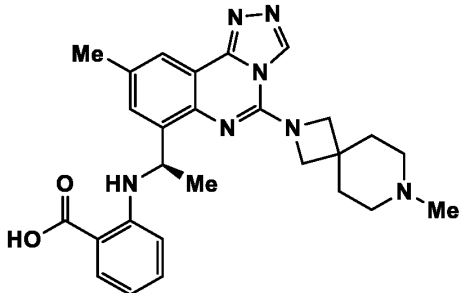
5-26	 2-(((<i>R</i>)-1-(9-methyl-5-((<i>S</i>)-3-(trifluoromethyl)piperidin-1-yl)-[1,2,4]triazolo[4,3-<i>c</i>]quinazolin-7-yl)ethyl)amino)benzoic acid	
5-27	 2-(((<i>R</i>)-1-(9-methyl-5-((<i>R</i>)-3-(trifluoromethyl)piperidin-1-yl)-[1,2,4]triazolo[4,3-<i>c</i>]quinazolin-7-yl)ethyl)amino)benzoic acid	
5-28	 2-(((<i>R</i>)-1-(5-((1<i>S</i>,4<i>S</i>)-5,5-difluoro-2-azabicyclo[2.2.1]heptan-2-yl)-9-methyl-[1,2,4]triazolo[4,3-<i>c</i>]quinazolin-7-yl)ethyl)amino)benzoic acid	

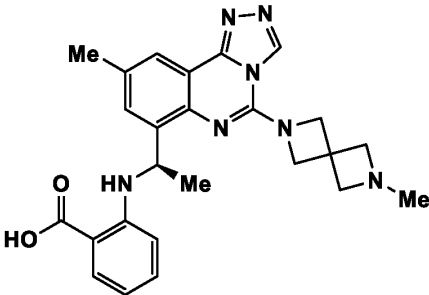
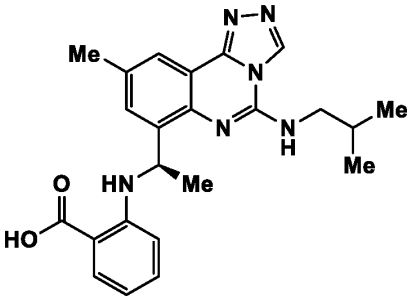
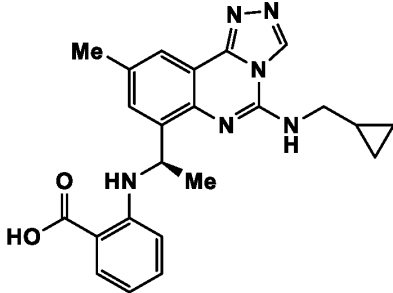
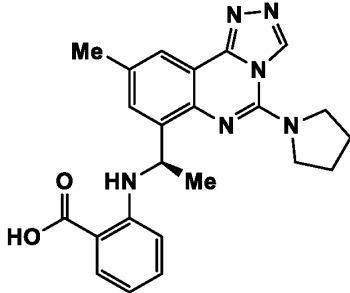
5-29	 2-(((<i>R</i>)-1-(5-((1<i>R</i>,4<i>R</i>)-5,5-difluoro-2-azabicyclo[2.2.1]heptan-2-yl)-9-methyl-[1,2,4]triazolo[4,3-<i>c</i>]quinazolin-7-yl)ethyl)amino)benzoic acid	
5-30	 2-(((<i>R</i>)-1-(5-((1<i>S</i>,4<i>R</i>)-6,6-difluoro-2-azabicyclo[2.2.1]heptan-2-yl)-9-methyl-[1,2,4]triazolo[4,3-<i>c</i>]quinazolin-7-yl)ethyl)amino)benzoic acid	
5-31	 2-(((<i>R</i>)-1-(5-((1<i>R</i>,4<i>S</i>)-6,6-difluoro-2-azabicyclo[2.2.1]heptan-2-yl)-9-methyl-[1,2,4]triazolo[4,3-<i>c</i>]quinazolin-7-yl)ethyl)amino)benzoic acid	

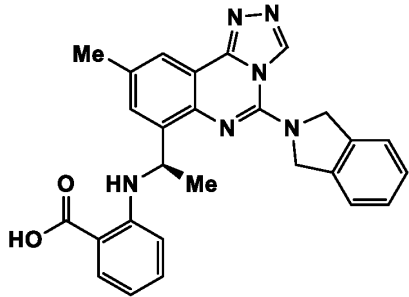
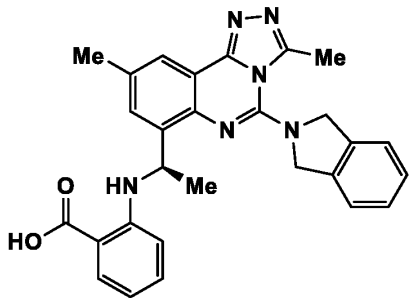
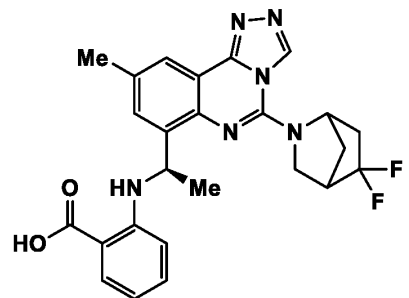
5-32	 2-(((1<i>R</i>)-1-(9-methyl-5-(3,4,4-trifluoropiperidin-1-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	
5-33	 (<i>R</i>)-2-((1-(9-methyl-5-(piperazin-1-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	
5-34	 (<i>R</i>)-2-((1-(9-methyl-5-(4-methylpiperazin-1-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	

5-35	 (R)-2-((1-(5-(4-methylpiperazin-1-yl)-9-vinyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	
5-36	 (R)-2-((1-(5-(4-ethylpiperazin-1-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	
5-37	 (R)-2-((1-(9-methyl-5-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	[M+H] ⁺ = 514.2.

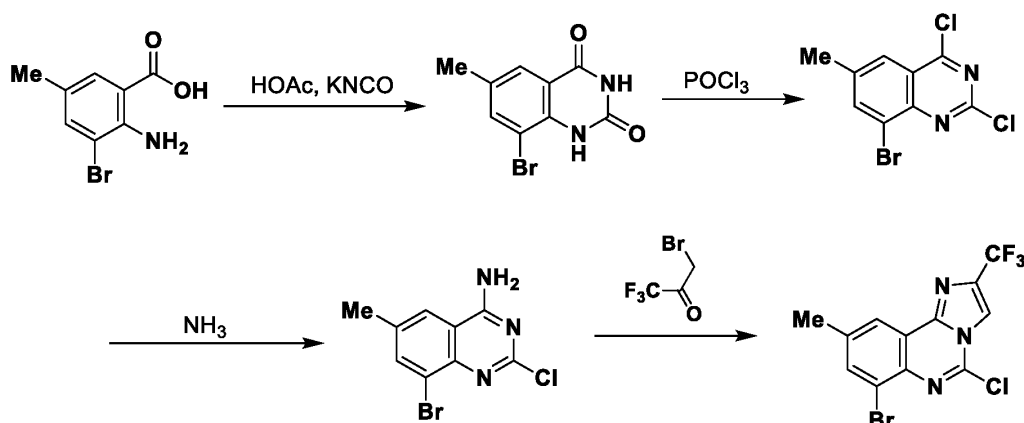
5-38	 (R)-2-((1-(5-(4-cyclopropylpiperazin-1-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	¹ H NMR (400 MHz, CD ₃ OD) δ ppm = 9.41 (s, 1H), 8.17 (s, 1H), 7.89 (d, <i>J</i> = 8.0 Hz, 1H), 7.63 (s, 1H), 7.13 (t, <i>J</i> = 7.8 Hz, 1H), 6.54 - 6.46 (m, 2H), 5.58 (q, <i>J</i> = 6.6 Hz, 1H), 3.74 (m, 4H), 4.12 - 3.64 (m, 4H), 2.97 (m, 1H), 2.47 (s, 3H), 1.70 (d, <i>J</i> = 6.8 Hz, 3H), 1.12 - 1.01 (m, 4H). LCMS [<i>M</i> + <i>H</i>] ⁺ = 472.6.
5-39	 2-(((1R)-1-(5-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	
5-40	 2-(((R)-1-(9-methyl-5-((1R,4R)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	

5-41	 2-(((<i>R</i>)-1-(9-methyl-5-((1<i>S</i>,4<i>S</i>)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-[1,2,4]triazolo[4,3-<i>c</i>]quinazolin-7-yl)ethyl)amino)benzoic acid	
5-42	 (<i>R</i>)-2-((1-(5-(4-benzoylpiperazin-1-yl)-9-methyl-[1,2,4]triazolo[4,3-<i>c</i>]quinazolin-7-yl)ethyl)amino)benzoic acid	
5-43	 (<i>R</i>)-2-((1-(9-methyl-5-(7-methyl-2,7-diazaspiro[3.5]nonan-2-yl)-[1,2,4]triazolo[4,3-<i>c</i>]quinazolin-7-yl)ethyl)amino)benzoic acid	

5-44	 (<i>R</i>)-2-((1-(9-methyl-5-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	
5-45	 (<i>R</i>)-2-((1-(5-(isobutylamino)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	LCMS [M+H] ⁺ = 419.2.
5-46	 (<i>R</i>)-2-((1-(5-((cyclopropylmethyl)amino)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	LCMS [M+H] ⁺ = 417.4.
5-47	 (<i>R</i>)-2-((1-(9-methyl-5-(pyrrolidin-1-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	

5-48	 (R)-2-((1-(5-(isoindolin-2-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	
5-49	 (R)-2-((1-(5-(isoindolin-2-yl)-3,9-dimethyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	
5-50	 2-(((1R)-1-(5-(5,5-difluoro-2-azabicyclo[2.2.1]heptan-2-yl)-9-methyl-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid	LCMS [M+H] ⁺ = 479.4.

INTERMEDIATE H



[00492] Step A: To a suspension of 2-amino-3-bromo-5-methylbenzoic acid (5.21 g, 22.7 mmol, 1.00 eq.) in water (35.0 mL) was added acetic acid (2.72 g, 45.3 mmol, 2.59 mL, 2.00 eq.), the mixture was heated to 45 °C and then a solution of potassium cyanate (5.79 g, 67.9 mmol, 3.00 eq.) in water (10.0 mL) was added drop-wise over 5 min, after addition stirring continue for 1 hour at 45 °C . After completion, the reaction solution was cooled to 25 °C and adjusted to ~ pH = 6 with 10% sodium hydroxide aqueous solution. The precipitate was collected by filtration and then dried under vacuum to give 8-bromo-6-methylquinazoline-2,4(1*H*,3*H*)-dione (3.00 g, 9.41 mmol, 42% yield) as a white solid.

[00493] Step B: A solution of 8-bromo-6-methylquinazoline-2,4(1*H*,3*H*)-dione (3.00 g, 11.8 mmol, 1.00 eq.) in phosphorus oxychloride (30.0 mL) was stirred at 100 °C for 16 hours. After completion, the reaction solution was cooled to 25 °C and then poured into iced water (300 mL) slowly. Next, the solution was diluted and extracted with ethyl acetate (100 mL× 3), washed with brine (50 mL× 2), dried over sodium sulfate, filtered, and concentrated under vacuum to give 8-bromo-2,4-dichloro-6-methylquinazoline (3.17 g, 10.6 mmol, 91% yield) as a white solid. LCMS [M+2]⁺ = 292.6.

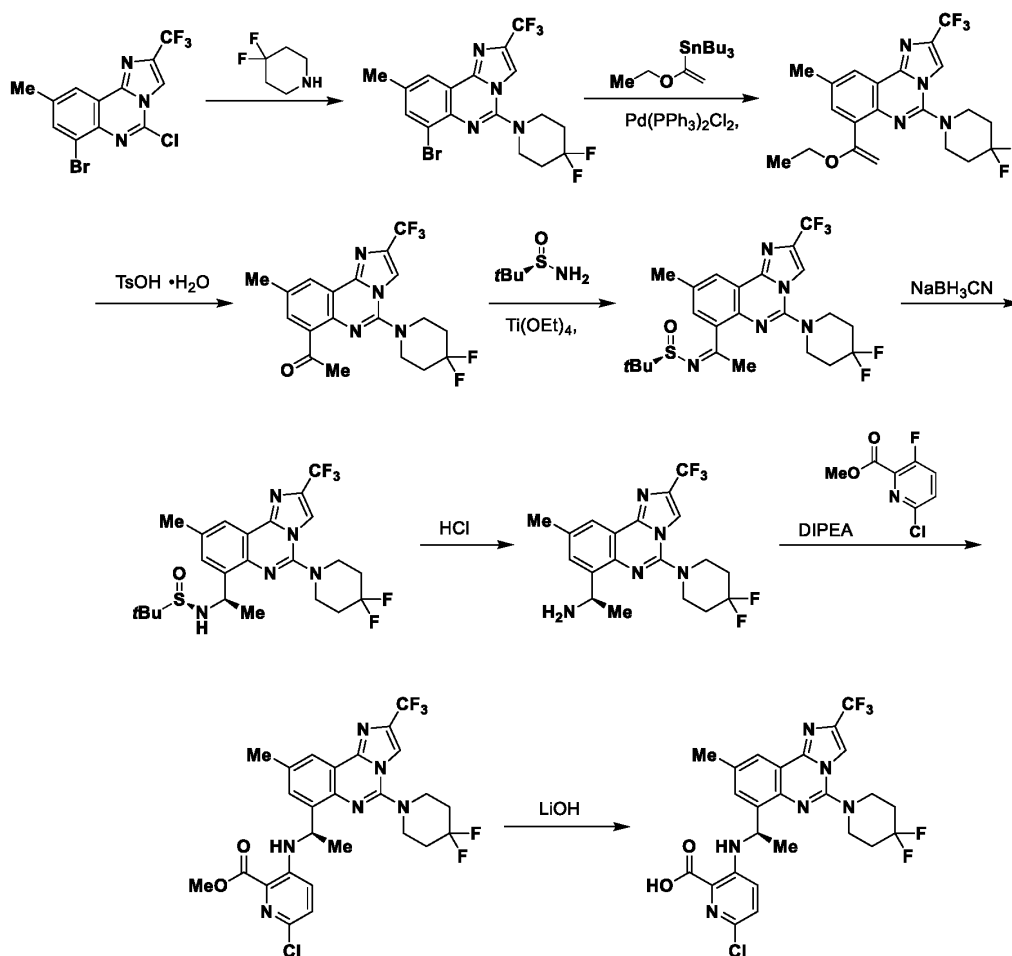
[00494] Step C: To a solution of 8-bromo-2,4-dichloro-6-methylquinazoline (3.17 g, 10.7 mmol, 1.00 eq.) in dichloromethane (5.00 mL) was added an ammonia in methanol solution (7 M, 15.5 mL, 10.0 eq.). The mixture was stirred at 25 °C for 16 hours. After completion, the reaction mixture was concentrated under vacuum to give the crude product. The crude product was triturated with petroleum ether (50.0 mL) for 1 hour at 25 °C and then dried under reduced pressure to give 8-bromo-2-chloro-6-methylquinazolin-4-amine (3.06 g, 10.7 mmol, 98% yield) as a white solid. LCMS [M+3]⁺ = 273.8.

[00495] Step D: A solution of 8-bromo-2-chloro-6-methylquinazolin-4-amine (1.30 g, 4.77 mmol, 1.00 eq.) and 3-bromo-1,1,1-trifluoropropan-2-one (1.82 g, 9.54 mmol, 991 µL, 2.00 eq.)

in dioxane (8.00 mL) was stirred at 100 °C for 12 hours. After completion of the reaction, the reaction mixture was cooled to 25 °C and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate= 10:1 to 8:1) to give 7-bromo-5-chloro-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazoline (1.00 g, 2.58 mmol, 54% yield) as a yellow solid. LCMS [M+3]⁺ = 365.8.

EXAMPLE 6-1

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid



[00496] Step A: To a solution of 7-bromo-5-chloro-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazoline (1.00 g, 2.74 mmol, 1.00 eq.) and 4,4-difluoropiperidine (498 mg, 4.11 mmol, 1.50 eq.) in acetonitrile (10.0 mL). The mixture was stirred at 80 °C for 1 hour. After completion of the reaction, the reaction mixture was cooled 25 °C, diluted with water (100 mL) and extracted with ethyl acetate (100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced

pressure to give 7-bromo-5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazoline (1.25 g, 2.41 mmol, 88% yield) as a white solid. LCMS $[M+1]^+ = 449.0$.

[00497] Step B: A mixture of 7-bromo-5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazoline (1.25 g, 2.78 mmol, 1.00 eq.), tributyl(1-ethoxyvinyl)stannane (1.51 g, 4.17 mmol, 1.41 mL, 1.50 eq.) and bis(triphenylphosphine)palladium(II) dichloride (195 mg, 278 μ mol, 0.10 eq.) in dioxane (10.0 mL) was evacuated and backfilled with nitrogen three times, and then the mixture was stirred at 100 °C for 2 hours under nitrogen atmosphere. After completion of the reaction, the mixture was poured into a saturated aqueous solution of potassium fluoride (100 mL) at 25 °C and stirred for 1 hour. The aqueous phase was extracted with dichloromethane (50.0 mL $\times$ 3), the combined organic phase was washed with brine (50.0 mL $\times$ 3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 5-(4,4-difluoropiperidin-1-yl)-7-(1-ethoxyvinyl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazoline (1.22 g, crude) as a yellow solid. LCMS $[M+1]^+ = 441.3$.

[00498] Step C: To a solution of 5-(4,4-difluoropiperidin-1-yl)-7-(1-ethoxyvinyl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazoline (1.22 g, 2.77 mmol, 1.00 eq.) in tetrahydrofuran (10.0 mL) was added *p*-toluenesulfonic acid (527 mg, 2.77 mmol, 1.00 eq.). The mixture was stirred at 25 °C for 1 hour. After completion of the reaction, the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (100 mL). 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 column chromatography (SiO₂, petroleum ether: ethyl acetate = 8:1 to 6:1) to give 1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethan-1-one (1.08 g, 2.54 mmol, 92% yield) as a yellow solid. LCMS $[M+1]^+ = 413.1$.

[00499] ¹H NMR (400 MHz, CDCl₃) δ ppm = 8.49 (s, 1H), 7.96 (s, 1H), 7.90 (s, 1H), 3.83 (br s, 4H), 2.86 (s, 3H), 2.59 - 2.52 (m, 3H), 2.43 - 2.33 (m, 4H).

[00500] Step D: To a solution of 1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethan-1-one (1.08 g, 2.62 mmol, 1.00 eq.) and (*R*)-2-methylpropane-2-sulfinamide (476 mg, 3.93 mmol, 1.50 eq.) in 2-methyltetrahydrofuran (15.0 mL) was added titanium (IV) ethoxide (1.79 g, 7.86 mmol, 1.63 mL, 3.00 eq.). The mixture was stirred at 90 °C for 12 hours. After completion of the reaction, the reaction mixture was diluted with water (4.00 mL) and ethyl acetate (20.0 mL) at 25 °C, and the obtained suspension was filtered to give a filtrate. The filtrate was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column

chromatography (SiO₂, petroleum ether: ethyl acetate = 6:1 to 4:1) to give (*R*)-*N*-(1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethylidene)-2-methylpropane-2-sulfonamide (810 mg, 1.49 mmol, 57% yield) as a yellow solid. LCMS [*M*+1]⁺ = 516.2.

[00501] Step E: To a solution of (*R*)-*N*-(1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethylidene)-2-methylpropane-2-sulfonamide (810 mg, 1.57 mmol, 1.00 eq.) in methanol (8.00 mL) and dichloromethane (8.00 mL) was added sodium cyanoborohydride (296 mg, 4.71 mmol, 3.00 eq.) and acetic acid (9.44 mg, 157 μmol, 8.99 μL, 0.10 eq.). The mixture was stirred at 25 °C for 1.5 hours. After completion of the reaction, the pH of the mixture was adjusted to ~ pH = 8 with saturated sodium bicarbonate aqueous solution. Then the obtained solution was extracted with dichloromethane (30.0 mL x 3), and the combined organic layer was washed with brine (50.0 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, dichloromethane: methanol = 15:1 to 10:1) to give (*R*)-*N*-((*R*)-1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)-2-methylpropane-2-sulfonamide (600 mg, 1.05 mmol, 67% yield) as a white solid. Then the (*R*)-*N*-((*R*)-1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)-2-methylpropane-2-sulfonamide was purified by SFC (column: (S, S) WHELK-O1 (250 mm x 30 mm, 10 μm); mobile phase: [CO₂ - EtOH]; B%: 25%, isocratic elution mode) to give (*R*)-*N*-((*R*)-1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)-2-methylpropane-2-sulfonamide as a white solid. LCMS [*M*+1]⁺ = 518.1.

[00502] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm = 8.59 (s, 1H), 8.08 (s, 1H), 7.69 (d, *J* = 1.2 Hz, 1H), 5.74 (d, *J* = 8.0 Hz, 1H), 5.44 - 5.19 (m, 1H), 3.60 (t, *J* = 5.2 Hz, 4H), 2.50 (s, 3H), 2.42 - 2.23 (m, 4H), 1.50 (d, *J* = 6.8 Hz, 3H), 1.11 (s, 9H).

[00503] Step F: To a solution of (*R*)-*N*-((*R*)-1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)-2-methylpropane-2-sulfonamide (540 mg, 1.04 mmol, 1.00 eq.) in ethyl acetate was added hydrochloric acid in ethyl acetate (10.0 mL, 2M) was stirred at 25 °C for 1.5 hours. After completion of the reaction, the pH of the mixture was adjusted to ~ pH = 8 with a saturated sodium bicarbonate aqueous solution. Then, the solution was extracted with dichloromethane (30.0 mL x 3), and the combined organic layers were washed with brine (50.0 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give (*R*)-1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethan-1-amine (420 mg, 782 μmol, 75% yield) as a white solid. LCMS [*M*+1]⁺ = 414.1.

[00504] Step G: To a solution of (*R*)-1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethan-1-amine (420 mg, 1.02 mmol, 1.00 eq.), methyl 6-chloro-3-fluoropicolinate (289 mg, 1.52 mmol, 1.50 eq.) in dimethylformamide (10.0 mL) was added diisopropylethylamine (394 mg, 3.05 mmol, 531 μ L, 3.00 eq.). The mixture was stirred at 90 °C for 12 hours. After completion of the reaction, the reaction mixture was diluted with water (100 mL) at 25 °C and extracted with ethyl acetate (100 mL). 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 column chromatography (SiO₂, petroleum ether: ethyl acetate = 7:1 to 5:1) to give methyl (*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinate (450 mg, 687 μ mol, 68% yield) as a white solid. LCMS [M+1]⁺ = 583.1.

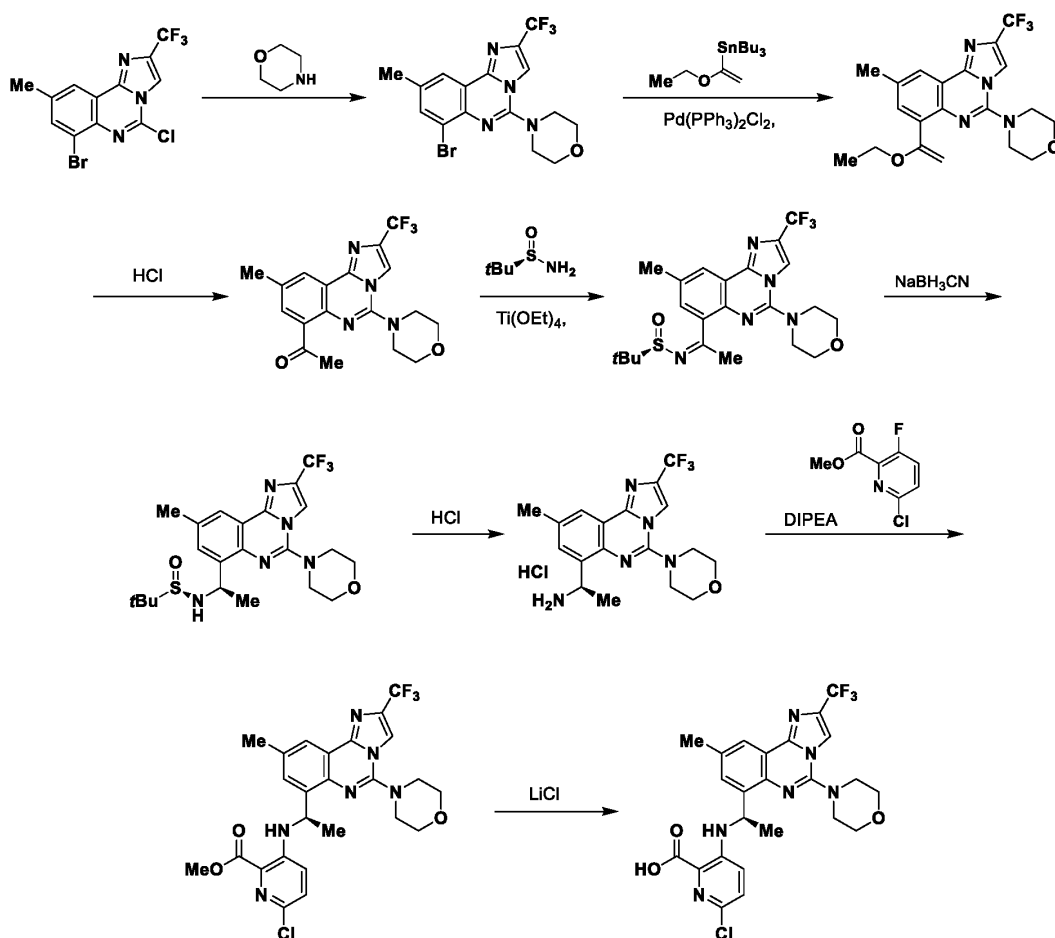
[00505] Step H: To a solution of methyl (*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinate (50.0 mg, 85.8 μ mol, 1.00 eq.) in tetrahydrofuran (1.00 mL) and methanol (1.00 mL) was added lithium hydroxide (2 M, 428 μ L, 10.0 eq.). The mixture was stirred at 40 °C for 1 hour. After completion of the reaction, the pH of the mixture was adjusted to ~ pH = 5 with an aqueous solution of citric acid. Then the solution was extracted with dichloromethane (30.0 mL x 3), and the combined organic layers were 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 *prep*-HPLC (column: Phenomenex luna C18 150 x 25 mm x 10 μ m; mobile phase: [water (formic acid) - acetonitrile]; gradient: 60% - 90% acetonitrile over 9 min) to give (*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid (11.0 mg, 19.2 μ mol, 22% yield) as an off-white solid. LCMS [M+1]⁺ = 569.1.

[00506] ¹H NMR (400 MHz, CD₃OD) δ = 8.34 (s, 1H), 8.16 (s, 1H), 7.54 (d, *J* = 1.6 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 7.03 (d, *J* = 9.2 Hz, 1H), 5.57 (d, *J* = 6.4 Hz, 1H), 3.72 (t, *J* = 5.2 Hz, 4H), 2.46 (s, 3H), 2.39 - 2.21 (m, 4H), 1.72 (d, *J* = 6.8 Hz, 3H).

[00507] ¹⁹F NMR (377 MHz, CD₃OD) δ ppm = -64.0, -64.2.

Example 6-2

(*R*)-6-chloro-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid



[00508] Step A: To the mixture of 7-bromo-5-chloro-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazoline (50.0 g, 137 mmol, 1.00 eq) in acetonitrile (300 mL) was added morpholine (23.9 g, 274 mmol, 24.1 mL, 2.00 eq), the mixture was heated to 60 °C for 0.5 hr. After completion, the mixture was poured into water (1000 mL), extracted with ethyl acetate (1500 mL), the organic layer was concentrated under vacuum to give a crude. The crude was purified by silica gel chromatography (SiO₂, Petroleum ether : Ethyl acetate = 10/1 to 2/1) to give 4-(7-bromo-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-5-yl)morpholine (43.0 g, 104 mmol, 76% yield) as a yellow solid.

[00509] ¹H NMR (400 MHz, CDCl₃) δ ppm = 8.25 (s, 1H), 7.83 (s, 1H), 7.78 (s, 1H), 4.00 - 3.97 (m, 4H), 3.61 - 3.59 (m, 4H), 2.50 (s, 3H).

[00510] Step B: To a solution of 4-(7-bromo-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-5-yl)morpholine (40.0 g, 96.3 mmol, 1.00 eq) and tributyl(1-ethoxyvinyl)stannane (52.2 g, 145 mmol, 48.8 mL, 1.50 eq) in dioxane (400 mL) was added bis(triphenylphosphine)palladium(II) dichloride (6.76 g, 9.63 mmol, 0.10 eq), the mixture

was evacuated and backfilled with nitrogen, then heated to 100 °C under nitrogen atmosphere for 16 hr. After completion, the mixture was quenched with an aqueous saturated potassium fluoride solution (1000 mL) and extracted with ethyl acetate (500 mL). The organic layer was concentrated under vacuum to give 4-(7-(1-ethoxyvinyl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-5-yl)morpholine (39.2 g, crude) as a yellow solid and used in the next reaction without further purification.

[00511] Step C: To the mixture of 4-(7-(1-ethoxyvinyl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-5-yl)morpholine (39.2 g, 96.3 mmol, 1.00 eq) in tetrahydrofuran (400 mL) was added aqueous hydrochloric acid (4 M, 24.1 mL, 1.00 eq), the mixture was stirred at 25 °C for 1 hr. After completion, the mixture was diluted with water (1000 mL) to give a suspension, the solid was collected by filtration and dried under vacuum to give 1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethan-1-one (32.0 g, 84.6 mmol, 88% yield) as a yellow solid.

[00512] Step D: To the mixture of 1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethan-1-one (32.0 g, 84.6 mmol, 1.00 eq) in 2-methyltetrahydrofuran (500 mL) was added (*R*)-2-methylpropane-2-sulfinamide (61.5 g, 507 mmol, 6.00 eq), followed by titanium (IV) ethoxide (116 g, 507 mmol, 105 mL, 6.00 eq), the mixture was heated to 90 °C for 16 hr. After completion of the reaction, The mixture was diluted with water (1500 mL) and extracted with ethyl acetate (1000 mL), the solid was filtered, the organic layer was concentrated under vacuum to give (*R*)-2-methyl-*N*-(1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethylidene)propane-2-sulfinamide (40.7 g, crude) as a yellow oil and used in the next without further purification.

[00513] Step E: To the mixture (*R*)-2-methyl-*N*-(1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethylidene)propane-2-sulfinamide (40.7 g, 84.6 mmol, 1.00 eq) in dichloromethane (200 mL) and methanol (200 mL) was added acetic acid (25.4 g, 423 mmol, 24.2 mL, 5.00 eq), and then sodium cyanoborohydride (21.3 g, 338 mmol, 4.00 eq) was added to the mixture in portions at 25 °C. The mixture was stirred at 25 °C for 2 hr. After completion, the mixture was diluted with water (1000 mL) and extracted with dichloromethane (500 mL), the organic layer was concentrated under vacuum to give a crude solid. The crude solid was purified by silica chromatography (SiO₂, Petroleum ether/Ethyl acetate = 10/1 to 1/1) to give (*R*)-2-methyl-*N*-((*R*)-1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)propane-2-sulfinamide (27.0 g, 51.4 mmol, 61% yield) as a yellow solid. LCMS [M+1]⁺ = 484.3.

[00514] ^1H NMR (400 MHz, CDCl_3) δ ppm = 8.27 - 8.26 (m, 1H), 7.83 (s, 1H), 7.48 (s, 1H), 5.21 - 5.19 (m, 1H), 4.00 - 3.98 (m, 4H), 3.52 - 3.49 (m, 4H), 2.52 (s, 3H), 1.66 (d, J = 7.2 Hz, 3H), 1.25 (s, 9H).

[00515] Step F: To the mixture of (*R*)-2-methyl-*N*-((*R*)-1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)propane-2-sulfonamide (8.00 g, 16.5 mmol, 1.00 eq) in acetonitrile (50 mL) was added a solution of hydrochloric acid in ethyl acetate (2 M, 24.8 mL, 3.00 eq), the mixture was stirred at 25 °C for 1 hr. After completion, the mixture was concentrated under vacuum to give a yellow solid. The solid was triturated with ethyl acetate (50 mL), filtered, and dried under vacuum to give (*R*)-1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethan-1-amine (5.70 g, 13.6 mmol, 82%) as a white hydrochloride salt. LCMS [$M+1$] $^+$ = 380.1.

[00516] Step G: To a solution of (*R*)-1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethan-1-amine, hydrochloride (5.40 g, 14.2 mmol, 1.00 eq) and methyl 6-chloro-3-fluoropicolinate (4.05 g, 21.4 mmol, 1.50 eq) in dimethylformamide (30 mL) was added diisopropylethylamine (9.20 g, 71.2 mmol, 12.4 mL, 5.00 eq), the mixture was heated to 90 °C for 16 hr. After completion, the mixture was poured into water (50 mL) and extracted with ethyl acetate (100 mL), the combined organic layers were washed with brine (50 mL) and concentrated under vacuum to give methyl (*R*)-6-chloro-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinate (7.10 g, crude) as a light yellow solid which was used without further purification in the next step. LCMS [$M+1$] $^+$ = 549.1.

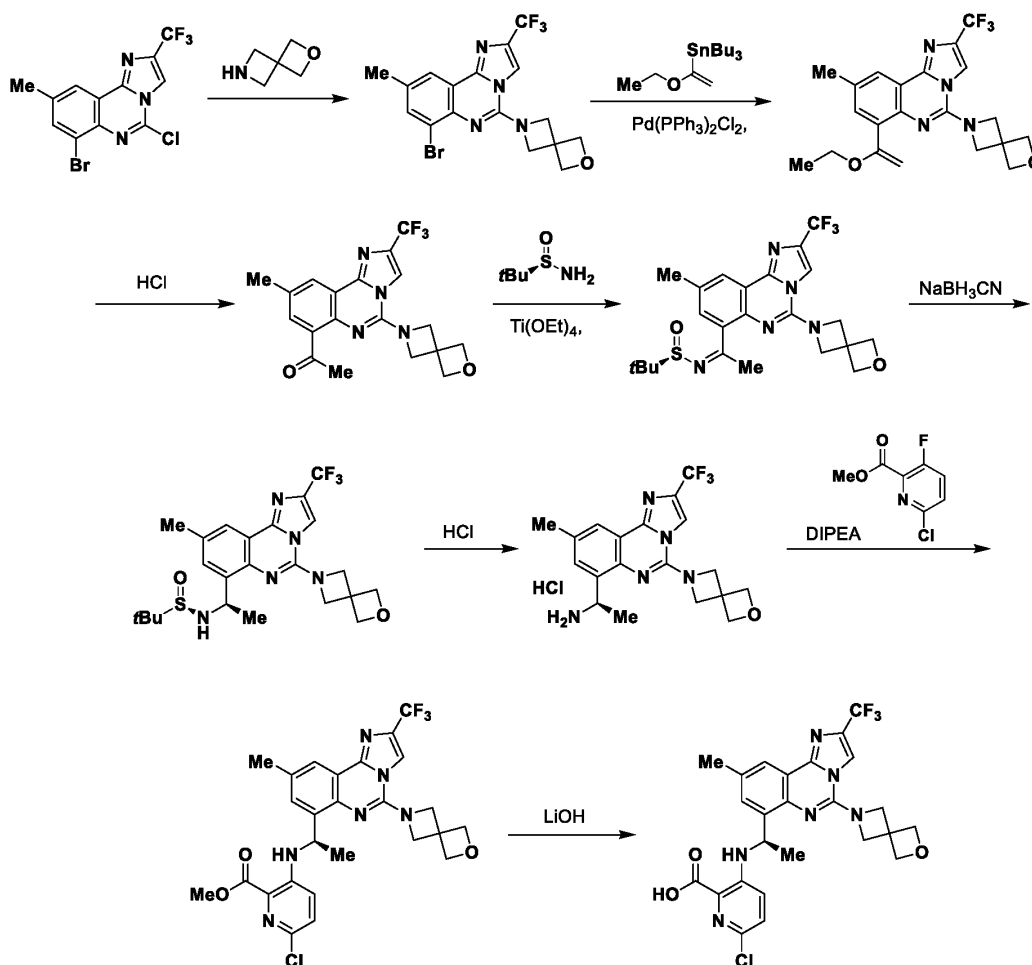
[00517] Step H: To the mixture of methyl (*R*)-6-chloro-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinate (7.10 g, 12.9 mmol, 1.00 eq) in dimethylsulfoxide (70 mL) was added lithium chloride (5.48 g, 129 mmol, 10.0 eq), the mixture was heated to 130 °C for 16 hr. After completion, the mixture was cooled to 25 °C and poured into water (200 mL) to give a suspension, the solid was collected by filtration and then dissolved in ethyl acetate (100 mL). The organic layer was washed with brine (50 mL $\times$ 2) and concentrated under vacuum to give a crude solid. The solid was purified by silical chromatography (SiO_2 , Petroleum ether/Ethyl acetate = 10/1 to 0/1 to dichloromethane/methanol = 10/1) and further purified by prep-HPLC (column: Phenomenex luna C18 250*50mm*10 μm ; mobile phase: [water (0.1% formic acid)-acetonitrile]; gradient: 50%-80% acetonitrile over 20 min) to give (*R*)-6-chloro-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid (3.90 g, 7.28 mmol, 56% yield) as a yellow solid. LCMS [$M+23$] $^+$ = 557.1.

[00518] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm = 13.00 (s, 1H), 8.63 (s, 1H), 8.57 (d, J = 6.8 Hz, 1H), 8.09 (s, 1H), 7.55 (s, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 9.2 Hz, 1H), 5.50 (t, J = 6.4 Hz, 1H), 3.97 - 3.80 (m, 4H), 3.65 - 3.45 (m, 4H), 2.44 (s, 3H), 1.68 (d, J = 6.4 Hz, 3H).

[00519] ^{19}F NMR (377 MHz, $\text{DMSO}-d_6$) δ ppm = -61.15.

Example 6-3

(*R*)-6-chloro-3-((1-(9-methyl-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid



[00520] Step A: To a mixture of 7-bromo-5-chloro-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazoline (20.0 g, 54.8 mmol, 1.00 eq) in acetonitrile (400 mL) was added triethylamine (16.6 g, 164 mmol, 22.9 mL, 3.00 eq) and 2-oxa-6-azaspiro[3.3]heptane (11.8 g, 82.3 mmol, 1.50 eq, 0.5 oxalic acid). The mixture was stirred at 60 °C for 2 hrs. After completion, the mixture was poured into water and extracted with ethyl acetate (400 mL × 4). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under

vacuum to give 6-(7-bromo-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-5-yl)-2-oxa-6-azaspiro[3.3]heptane (14.2 g, 69%) as yellow solid.

[00521] ¹H NMR (400 MHz, CDCl₃) δ ppm = 8.18 (d, *J* = 2.0 Hz, 1H), 7.74 (dd, *J* = 1.6, 5.2 Hz, 1H), 4.92 (s, 4H), 4.66 (s, 4H), 2.47 (s, 3H).

[00522] Step B: To a mixture of 6-(7-bromo-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-5-yl)-2-oxa-6-azaspiro[3.3]heptane (14.2 g, 33.2 mmol, 1.00 eq) in dioxane (500 mL) was added tributyl(1-ethoxyvinyl)stannane (18.0 g, 49.8 mmol, 16.8 mL, 1.50 eq) and bis(triphenylphosphine)palladium (II) dichloride (2.33 g, 3.32 mmol, 0.10 eq) under nitrogen. The mixture was stirred at 100 °C for 10 hours under nitrogen atmosphere. After completion, the mixture was cooled to 20 °C and quenched with a potassium fluoride aqueous solution (10%, 1.5 L). Next, ethyl acetate (2 L) was added to the mixture and stirred for 10 min. The mixture was filtered and the filtrate was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give 6-(7-(1-ethoxyvinyl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-5-yl)-2-oxa-6-azaspiro[3.3]heptane (10.7 g, crude) as yellow solid which was used for next step without further purification.

[00523] Step C: To a mixture of 6-(7-(1-ethoxyvinyl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-5-yl)-2-oxa-6-azaspiro[3.3]heptane (10.7 g, 25.5 mmol, 1.00 eq) in tetrahydrofuran (120 mL) was added aqueous hydrochloric acid (1 M, 25.5 mL, 1.00 eq). The mixture was stirred at 20 °C 1 hour. After completion, the mixture was poured into water (400 mL) and filtered. The filter cake was dried under vacuum to give 1-(9-methyl-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethan-1-one (9.00 g, 23.0 mmol, 90% yield) as yellow solid which was used without further purification. LCMS [M+1]⁺ = 391.2.

[00524] Step D: To a mixture of 1-(9-methyl-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethan-1-one (7.70 g, 19.7 mmol, 1.00 eq) and (*R*)-2-methylpropane-2-sulfinamide (14.3 g, 118 mmol, 6.00 eq) in 2-methyltetrahydrofuran (100 mL) was added titanium (IV) ethoxide (27.0 g, 118 mmol, 24 mL, 6.00 eq). The mixture was stirred at 90 °C for 10 hrs. After completion, the mixture was cooled to 20 °C and poured into water (300 mL) and ethyl acetate (300 mL) and the mixture was stirred for 10 min. The mixture was filtered and the filtrate was separated and dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give (*R*)-2-methyl-*N*-(1-(9-methyl-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethylidene)propane-2-sulfinamide (10 g, crude) as yellow oil which was used without further purification.

[00525] Step E: To a mixture of (*R*)-2-methyl-*N*-(1-(9-methyl-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethylidene)propane-

2-sulfonamide (10.0 g, 20.3 mmol, 1.00 eq) in dichloromethane (250 mL) and methanol (250 mL) was added acetic acid (6.08 g, 101 mmol, 5.80 mL, 5.00 eq) and sodium cyanoborohydride (5.09 g, 81.0 mmol, 4.00 eq). The mixture was stirred at 20 °C for 2 hrs. After completion, the mixture was poured into water (500 mL) and extracted with dichloromethane (200 mL × 2). The organic phase was dried over anhydrous sodium sulfate and concentrated under vacuum to give a residue. The residue was purified by silica gel chromatography (SiO₂, Petroleum ether/Ethyl acetate=15/1 to 5/1) to afford (*R*)-2-methyl-*N*-((*R*)-1-(9-methyl-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)propane-2-sulfonamide (8.00 g, 15.3 mmol, 76% yield) as yellow solid. LCMS [M+1]⁺= 496.1.

[00526] Step F: To a mixture of (*R*)-2-methyl-*N*-((*R*)-1-(9-methyl-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)propane-2-sulfonamide (14.0 g, 28.2 mmol, 1.00 eq) in acetonitrile (100 mL) was added a solution of hydrochloric acid in ethyl acetate (1 M, 28.2 mL, 1.00 eq). The mixture was stirred at 20 °C for 30 min. After completion, the mixture was filtered and the filter cake was washed with ethyl acetate (50 mL) and dried under vacuum to give (*R*)-1-(9-methyl-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethan-1-amine (8.00 g, crude) as yellow hydrochloride salt. LCMS [M+1]⁺= 392.0.

[00527] Step G: To a mixture of (*R*)-1-(9-methyl-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethan-1-amine hydrochloride (8.00 g, 18.7 mmol, 1.00 eq) and methyl 6-chloro-3-fluoropicolinate (3.54 g, 18.7 mmol, 1.00 eq) was added diisopropyl ethyl amine (12.1 g, 93.5 mmol, 16.3 mL, 5.00 eq). The mixture was stirred at 90 °C for 10 hrs. After completion, the mixture was cooled to 25 °C and poured into water (500 mL) and stirred for 10 min. The suspension was filtered, the filter cake was washed with water (100 mL × 2) and dried under vacuum to give methyl (*R*)-6-chloro-3-((1-(9-methyl-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinate (8.00 g, crude) as yellow solid.

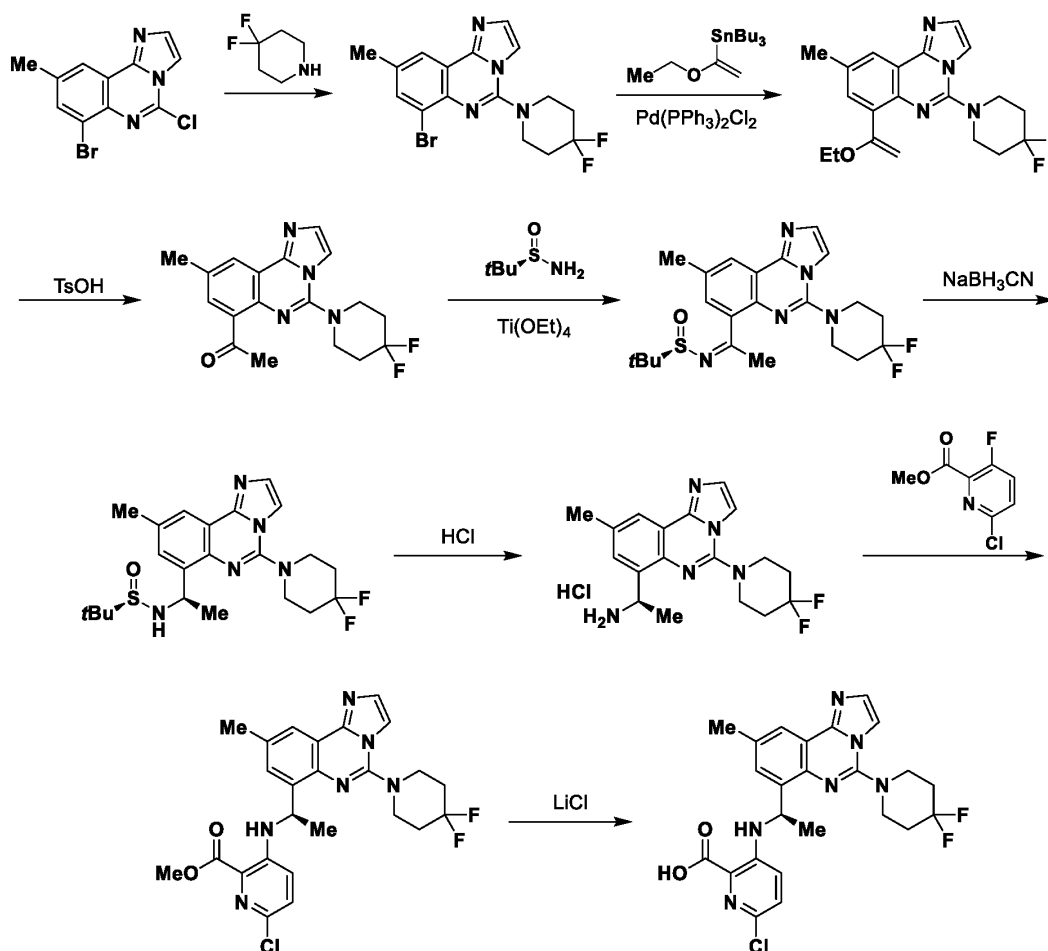
[00528] Step H: To a mixture of methyl (*R*)-6-chloro-3-((1-(9-methyl-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinate (8.00 g, 14.3 mmol, 1.00 eq) in tetrahydrofuran (80 mL) and water (20 mL) was added lithium hydroxide monohydrate (1.20 g, 28.5 mmol, 2.00 eq). The mixture was stirred at 40 °C for 1 hr. After completion, the mixture was poured into water (300 mL) and the mixture was adjusted to ~ pH = 6 by an aqueous solution of hydrochloric acid (0.5 M). The aqueous solution was extracted with ethyl acetate (200 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give a residue. The residue was further purification by prep-HPLC (column: Phenomenex luna C18 250*70mm*10 um; mobile phase: [water (0.1%trifluoroacetic acid)-acetonitrile]; gradient:52%-

82% acetonitrile over 20 min) to give (*R*)-6-chloro-3-((1-(9-methyl-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid (2.09 g, 26% yield, 97% purity) as yellow solid. LCMS $[M+1]^+ = 547.1$

[00529] ^1H NMR (400 MHz, CDCl_3) δ ppm = 8.48 (d, $J = 6.4$ Hz, 1H), 8.17 (s, 1H), 7.78 (s, 1H), 7.38 (d, $J = 1.2$ Hz, 1H), 7.11 (d, $J = 9.2$ Hz, 1H), 6.91 (d, $J = 8.8$ Hz, 1H), 5.39 - 5.34 (m, 1H), 4.98 - 4.93 (m, 4H), 4.75 (d, $J = 9.2$ Hz, 2H), 4.63 (d, $J = 8.8$ Hz, 2H), 2.43 (s, 3H), 1.74 (d, $J = 6.8$ Hz, 3H).

Example 6-4

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid



[00530] Step A: To a solution of 7-bromo-5-chloro-9-methylimidazo[1,2-*c*]quinazoline (3.00 g, 10.1 mmol, 1.00 eq.) in acetonitrile (35.0 mL) was added 4,4-difluoropiperidine (2.45 g, 20.2

mmol, 2.00 eq.) and diisopropylethylamine (3.92 g, 30.4 mmol, 5.29 mL, 3.00 eq.). The mixture was stirred at 60 °C for 1 hour. After completion of the reaction, the reaction mixture was cooled to room temperature and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to give 7-bromo-5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-c]quinazoline (1.60 g, 2.81 mmol, 28% yield) as a yellow solid. LCMS [M+3]⁺ = 383.0.

[00531] Step B: A mixture of 7-bromo-5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-c]quinazoline (1.60 g, 2.81 mmol, 1.00 eq.), tributyl(1-ethoxyvinyl)stannane (1.29 g, 3.56 mmol, 1.20 mL, 1.27 eq.) and bis(triphenylphosphine)palladium (II) chloride (197 mg, 281 µmol, 0.10 eq.) in dioxane (16.0 mL) was evacuated and backfilled with nitrogen 3 times, then the mixture was stirred at 100 °C for 6 hours under nitrogen atmosphere. After completion of the reaction, the mixture was cooled to 25 °C and poured into a saturated solution of potassium fluoride (80.0 mL) and stirred for 1 hour. The aqueous phase was extracted with dichloromethane (80.0 mL × 3), the combined organic phase was washed with brine (80.0 mL × 3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 5-(4,4-difluoropiperidin-1-yl)-7-(1-ethoxyvinyl)-9-methylimidazo[1,2-c]quinazoline (1.00 g, 2.69 mmol, crude) as a yellow oil. LCMS [M+1]⁺ = 373.1.

[00532] Step C: To a solution of 5-(4,4-difluoropiperidin-1-yl)-7-(1-ethoxyvinyl)-9-methylimidazo[1,2-c]quinazoline (1.00 g, 2.69 mmol, 1.00 eq.) in acetone (15.0 mL) was added *p*-toluenesulfonic acid hydrate (511 mg, 2.69 mmol, 1.00 eq.). The mixture was stirred at 25 °C for 1 hour. After completion of the reaction, the mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in dichloromethane (80.0 mL), washed with saturated sodium bicarbonate aqueous solution (80.0 mL × 3) and brine (80.0 mL × 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®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~60% Ethyl acetate/Petroleum ether gradient @ 36 mL/min) to give 1-(5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-c]quinazolin-7-yl)ethan-1-one (800 mg, 2.32 mmol, 87% yield) as a yellow solid. LCMS [M+1]⁺ = 345.3.

[00533] ¹H NMR (400 MHz, CDCl₃) δ ppm = 8.43 (d, *J* = 1.2 Hz, 1H), 7.75 (d, *J* = 2.0 Hz, 1H), 7.63 (d, *J* = 1.2 Hz, 1H), 7.53 (d, *J* = 1.6 Hz, 1H), 3.70 - 3.63 (m, 4H), 2.90 (s, 3H), 2.55 (s, 3H), 2.36 - 2.19 (m, 4H).

[00534] Step D: To a solution of 1-(5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-c]quinazolin-7-yl)ethan-1-one (800 mg, 2.32 mmol, 1.00 eq.) in 2-methyltetrahydrofuran (10.0 mL) was added (*R*)-2-methylpropane-2-sulfinamide (563 mg, 4.65 mmol, 2.00 eq.) and

titanium (IV) ethoxide (1.80 g, 7.88 mmol, 1.63 mL, 3.39 eq.). The mixture was stirred at 80 °C for 12 hours. After completion of the reaction, the mixture was cooled to 25 °C and water (0.60 mL) and dichloromethane (30.0 mL) were added. The mixture was allowed to stir for 30 minutes. The obtained mixture was filtered and the filter cake was washed with dichloromethane (50.0 mL × 3). The combined organics were 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 0~100% Ethyl acetate/Petroleum ether gradient @ 36 mL/min) to give (*R*)-*N*-(1-(5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-*c*]quinazolin-7-yl)ethylidene)-2-methylpropane-2-sulfinamide (900 mg, 2.01 mmol, 87% yield) as a yellow oil. LCMS [M+1]⁺ = 448.1.

[00535] Step E: To a solution of (*R*)-*N*-(1-(5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-*c*]quinazolin-7-yl)ethylidene)-2-methylpropane-2-sulfinamide (800 mg, 1.79 mmol, 1.00 eq.) in dichloromethane (4.00 mL) and methanol (4.00 mL) was added acetic acid (1.07 g, 17.9 mmol, 1.02 mL, 10.0 eq.) and sodium cyanoborohydride (337 mg, 5.36 mmol, 3.00 eq.) at 0 °C. The mixture was stirred at 0 °C for 2 hours. After completion of the reaction, the mixture was warmed to 25 °C and adjusted to ~ pH = 7 with saturated sodium bicarbonate aqueous solution (15.0 mL). The obtained mixture was concentrated under reduced pressure to remove methanol and dichloromethane and then diluted with dichloromethane (20.0 mL). The organic phase was separated, washed with brine (20.0 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 150 × 40mm × 15um; mobile phase: [water(formic acid)-acetonitrile]; gradient: 35%-65% acetonitrile over 15 min) to give (*R*)-*N*-((*R*)-1-(5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)-2-methylpropane-2-sulfinamide (500 mg, 1.10 mmol, 62% yield, 99% purity) as a yellow solid. LCMS [M+1]⁺ = 450.2.

[00536] ¹H NMR (400 MHz, CDCl₃) δ ppm = 8.22 (d, *J* = 0.8 Hz, 1H), 7.60 (d, *J* = 1.2 Hz, 1H), 7.50 (d, *J* = 1.2 Hz, 1H), 7.43 (d, *J* = 1.6 Hz, 1H), 5.21 (quin, *J* = 6.8 Hz, 1H), 3.71 - 3.58 (m, 4H), 2.53 (s, 3H), 2.36 - 2.21 (m, 4H), 1.66 (d, *J* = 6.8 Hz, 3H), 1.23 (s, 9H).

[00537] Step F: To a solution of (*R*)-*N*-((*R*)-1-(5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)-2-methylpropane-2-sulfinamide (121 mg, 267 μmol, 1.00 eq.) in acetonitrile (1.00 mL) was added a solution of hydrochloric acid in ethyl acetate (2.00 M, 1.33 mL, 10.0 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. The residue was triturated with ethyl acetate (10.0 mL) at 25 °C for 10 min, filtered, the filter cake was dried under vacuum to give (*R*)-1-(5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-*c*]quinazolin-7-

yl)ethan-1-amine (100 mg, 262 μ mol, 98% yield) as a yellow hydrochloride salt. LCMS [M+1]⁺ = 346.2.

[00538] Step G: To a solution of (*R*)-1-(5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-c]quinazolin-7-yl)ethan-1-amine, hydrochloride (100 mg, 262 μ mol, 1.00 eq.) in dimethylformamide (1.00 mL) was added methyl 6-chloro-3-fluoropicolinate (124 mg, 655 μ mol, 2.50 eq.) and diisopropylethylamine (101 mg, 786 μ mol, 137 μ L, 3.00 eq.). The mixture was stirred at 90 °C for 12 hours. After completion of the reaction, 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 0~100% Ethyl acetate/Petroleum ether gradient @ 36 mL/min) to give methyl (*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinate (100 mg, 194 μ mol, 74% yield) as a yellow solid. LCMS [M+1]⁺ = 515.1.

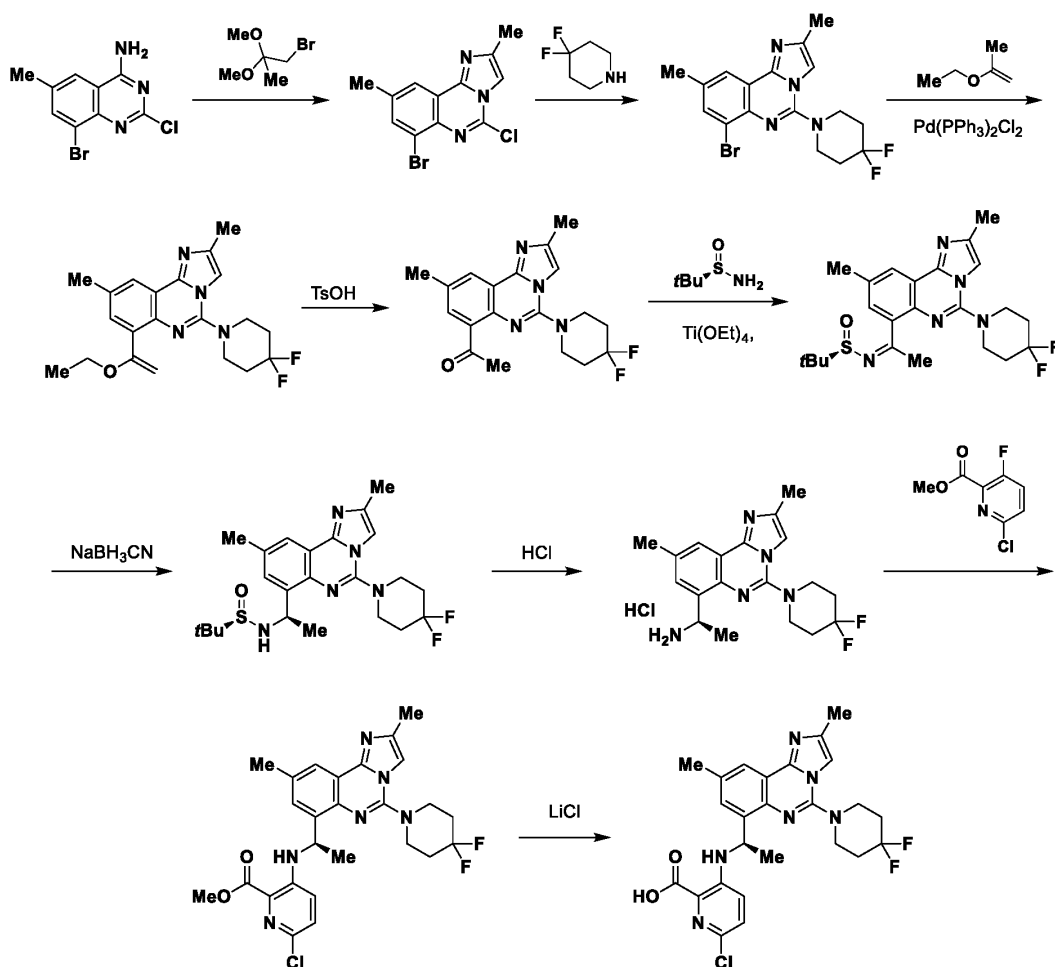
[00539] Step H: To a solution of methyl (*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinate (90.0 mg, 175 μ mol, 1.00 eq.) in dimethyl sulfoxide (1.00 mL) was added lithium chloride (74.1 mg, 1.75 mmol, 35.8 μ L, 10.0 eq.). The mixture was stirred at 120 °C for 4 hours. After completion of the reaction, the mixture was cooled to 25 °C and filtered. The filtrate was purified by *prep*-HPLC (column: Welch Xtimate C18 150 $\times$ 25mm $\times$ 5 μ m; mobile phase: [water(formic acid)-acetonitrile]; gradient: 45%-75% acetonitrile over 40 min) to give (*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid (34.8 mg, 69.0 μ mol, 40% yield) as an off-white solid. LCMS [M+1]⁺ = 501.2.

[00540] ¹H NMR (400 MHz, CDCl₃) δ ppm = 8.39 (br d, *J* = 6.4 Hz, 1H), 8.20 (d, *J* = 0.8 Hz, 1H), 7.63 (d, *J* = 1.6 Hz, 1H), 7.54 (d, *J* = 1.6 Hz, 1H), 7.40 (d, *J* = 2.0 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 5.53 (quin, *J* = 6.8 Hz, 1H), 3.79 - 3.59 (m, 4H), 2.46 (s, 3H), 2.37 - 2.23 (m, 4H), 1.72 (d, *J* = 6.4 Hz, 3H).

[00541] ¹⁹F NMR (377 MHz, CDCl₃) δ ppm = -97.4.

Example 6-5

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2,9-dimethylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid



[00542] Step A: To a solution of 8-bromo-2-chloro-6-methylquinazolin-4-amine (2.20 g, 8.07 mmol, 1.00 eq.) in dioxane (25.0 mL) was added 1-bromo-2,2-dimethoxypropane (7.39 g, 40.4 mmol, 5.45 mL, 5.00 eq.). The mixture was stirred at 100 °C for 16 hours. After completion of the reaction, the reaction mixture was cooled to 25 °C to give a suspension, the suspension was filtered, the filter cake was triturated with petroleum ether/ethyl acetate=1/1 (25.0 mL) at 25 °C for 5 minutes and filtered, the filter cake was collected and dried under vacuum to give 7-bromo-5-chloro-2,9-dimethylimidazo[1,2-c]quinazoline (2.50 g, 8.05 mmol, 99% yield) as a gray solid. LCMS $[M+3]^+ = 311.9$.

[00543] Step B: To a solution of 7-bromo-5-chloro-2,9-dimethylimidazo[1,2-c]quinazoline (2.50 g, 8.05 mmol, 1.00 eq.) and 4,4-difluoropiperidine (1.27 g, 10.5 mmol, 1.30 eq.) in acetonitrile (15.0 mL) was added diisopropylethylamine (5.20 g, 40.3 mmol, 7.01 mL, 5.00 eq.). The mixture was stirred at 60 °C for 2 hours. After completion of the reaction, the mixture was cooled to 25 °C and concentrated under reduced pressure to give a solid. The solid was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 0/1) to give

7-bromo-5-(4,4-difluoropiperidin-1-yl)-2,9-dimethylimidazo[1,2-c]quinazoline (2.40 g, 6.07 mmol, 75% yield) as a yellow solid. LCMS [M+1]⁺ = 395.1.

[00544] ¹H NMR (400 MHz, CDCl₃) δ ppm = 8.20 (d, *J* = 0.8 Hz, 1H), 7.72 (d, *J* = 1.6 Hz, 1H), 7.24 (d, *J* = 0.8 Hz, 1H), 3.77 - 3.68 (m, 4H), 2.50 (d, *J* = 0.4 Hz, 3H), 2.49 (s, 3H), 2.36 - 2.21 (m, 4H).

[00545] Step C: To a solution of 7-bromo-5-(4,4-difluoropiperidin-1-yl)-2,9-dimethylimidazo[1,2-c]quinazoline (3.10 g, 7.84 mmol, 1.00 eq.) in dioxane (40.0 mL) was added bis(triphenylphosphine)palladium (II) chloride (551 mg, 784 μmol, 0.10 eq.) and tributyl(1-ethoxyvinyl)stannane (4.14 g, 11.5 mmol, 3.87 mL, 1.46 eq.). The mixture was stirred at 100 °C for 3.5 hours under nitrogen atmosphere. After completion of the reaction, the mixture was cooled to 25 °C and quenched by the addition of an aqueous saturated solution of potassium fluoride (100 mL) and diluted with dichloromethane (100 mL) at 25 °C. The reaction was stirred for 1 hour, filtered and the filter cake was washed with dichloromethane (60.0 mL × 3) three times. The combined organic layers were washed with brine (20.0 mL × 3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 5-(4,4-difluoropiperidin-1-yl)-7-(1-ethoxyvinyl)-2,9-dimethylimidazo[1,2-c]quinazoline (2.70 g, crude) as a yellow solid which was used without further purification. LCMS [M+1]⁺ = 387.1.

[00546] Step D: To a solution of 5-(4,4-difluoropiperidin-1-yl)-7-(1-ethoxyvinyl)-2,9-dimethylimidazo[1,2-c]quinazoline (2.70 g, 6.99 mmol, 1.00 eq.) in acetone (25.0 mL) was added p-toluenesulfonic acid, hydrate (1.33 g, 6.99 mmol, 1.00 eq.). The mixture was stirred at 25 °C for 1 hour. After completion of the reaction, the mixture was adjusted to ~ pH = 7 with a saturated sodium bicarbonate aqueous solution, then diluted with water (20.0 mL) and extracted with dichloromethane (60.0 mL × 3). The combined organic layers were washed with brine (20.0 mL × 3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a solid. The solid was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=3/1 to dichloromethane/methanol=10/1) to give 1-(5-(4,4-difluoropiperidin-1-yl)-2,9-dimethylimidazo[1,2-c]quinazolin-7-yl)ethan-1-one (2.13 g, 5.94 mmol, 85% yield) as a yellow solid. LCMS [M+1]⁺ = 359.1.

[00547] ¹H NMR (400 MHz, CDCl₃) δ ppm = 8.39 (d, *J* = 0.8 Hz, 1H), 7.72 (d, *J* = 1.6 Hz, 1H), 7.24 (d, *J* = 0.8 Hz, 1H), 3.73 - 3.52 (m, 4H), 2.89 (s, 3H), 2.52 (s, 3H), 2.51 (d, *J* = 0.8 Hz, 3H), 2.36 - 2.16 (m, 4H).

[00548] Step E: To a solution of 1-(5-(4,4-difluoropiperidin-1-yl)-2,9-dimethylimidazo[1,2-c]quinazolin-7-yl)ethan-1-one (1.00 g, 2.79 mmol, 1.00 eq.) and (*R*)-2-methylpropane-2-sulfinamide (846 mg, 6.98 mmol, 2.50 eq.) in toluene (10.0 mL) was added titanium (IV) ethoxide (1.91 g, 8.37 mmol, 1.74 mL, 3.00 eq.). The mixture was stirred at 100 °C for 16

hours. After completion of the reaction, the mixture was cooled to 25 °C and quenched by the addition of water (4.00 mL) at 25 °C, during this period, a yellow precipitate was formed. The suspension was filtered, the filtrate was saved, filter cake was collected and triturated with dichloromethane/methanol=10/1 (70.0 mL×3) and filtered, 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 (SiO₂, Petroleum ether/Ethyl acetate=3/1 to dichloromethane/methanol = 10/1) to give (*R*)-*N*-(1-(5-(4,4-difluoropiperidin-1-yl)-2,9-dimethylimidazo[1,2-*c*]quinazolin-7-yl)ethylidene)-2-methylpropane-2-sulfonamide (1.10 g, 2.38 mmol, 85% yield) as a yellow solid. LCMS [M+1]⁺ = 462.2.

[00549] Step F: To a solution of (*R*)-*N*-(1-(5-(4,4-difluoropiperidin-1-yl)-2,9-dimethylimidazo[1,2-*c*]quinazolin-7-yl)ethylidene)-2-methylpropane-2-sulfonamide (1.10 g, 2.38 mmol, 1.00 eq.) in dichloromethane (10.0 mL) and methanol (10.0 mL) was added glacial acetic acid (1.43 g, 23.8 mmol, 1.36 mL, 10.0 eq.) and sodium cyanoborohydride (450 mg, 7.15 mmol, 3.00 eq.). The mixture was stirred at 25 °C for 2 hours. After completion of the reaction, the mixture was quenched by the addition of an aqueous solution of sodium bicarbonate to bring the pH to ~ pH = 7 at 25 °C. The obtained solution was extracted with dichloromethane/methanol=10/1 (90.0 mL × 3). The combined organic layers were washed with brine (30.0 mL × 3), 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 150×40mm× 15um; mobile phase: [water(formic acid)-acetonitrile]; gradient: 30%-60% acetonitrile over 15 min) to give (*R*)-*N*-((*R*)-1-(5-(4,4-difluoropiperidin-1-yl)-2,9-dimethylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)-2-methylpropane-2-sulfonamide (750 mg, 1.62 mmol, 68% yield) as a yellow solid. LCMS [M+1]⁺ = 464.3.

[00550] ¹H NMR (400 MHz, CDCl₃) δ ppm = 8.18 (s, 1H), 7.40 (d, *J* = 1.6 Hz, 1H), 7.22 (s, 1H), 5.19 (quin, *J* = 6.4 Hz, 1H), 4.60 (br d, *J* = 6.4 Hz, 1H), 3.67 - 3.57 (m, 4H), 2.50 (s, 3H), 2.50 (s, 3H), 2.35 - 2.18 (m, 4H), 1.65 (d, *J* = 6.8 Hz, 3H), 1.23 (s, 9H).

[00551] Step G: To a solution of (*R*)-*N*-((*R*)-1-(5-(4,4-difluoropiperidin-1-yl)-2,9-dimethylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)-2-methylpropane-2-sulfonamide (200 mg, 431 μmol, 1.00 eq.) in ethyl acetate (2.00 mL) was added a solution of hydrochloric acid in ethyl acetate (2 M, 1.29 mL, 6.00 eq.). The mixture was stirred at 0 °C for 1 hour. After completion of the reaction, the mixture was concentrated under vacuum to give a residue. The residue was triturated with ethyl acetate (3.00 mL) at 25 °C for 5 minutes and filtered. The filter cake was dried under vacuum to give (*R*)-1-(5-(4,4-difluoropiperidin-1-yl)-2,9-dimethylimidazo[1,2-*c*]quinazolin-7-yl)ethan-1-amine (150 mg, 379 μmol, 88% yield) as a yellow hydrochloride salt. LCMS [M-16]⁺ = 343.2.

[00552] Step H: To a solution of (*R*)-1-(5-(4,4-difluoropiperidin-1-yl)-2,9-dimethylimidazo[1,2-*c*]quinazolin-7-yl)ethan-1-amine, hydrochloride (150 mg, 379 μ mol, 1.00 *eq.*) in dimethylformamide (3.00 mL) was added diisopropylethylamine (245 mg, 1.89 mmol, 330 μ L, 5.00 *eq.*) and methyl 6-chloro-3-fluoropicolinate (180 mg, 947 μ mol, 2.50 *eq.*). The mixture was stirred at 90 °C for 16 hours. After completion of the reaction, the mixture was cooled to 25 °C, diluted with water (10.0 mL) and extracted with dichloromethane (30 mL $\times$ 3). The combined organic layers were washed with brine (10 mL $\times$ 3), dried over anhydrous sodium sulfate, 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 methyl (*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2,9-dimethylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinate (150 mg, 284 μ mol, 75% yield) as a yellow solid. LCMS [M+1]⁺ = 529.3.

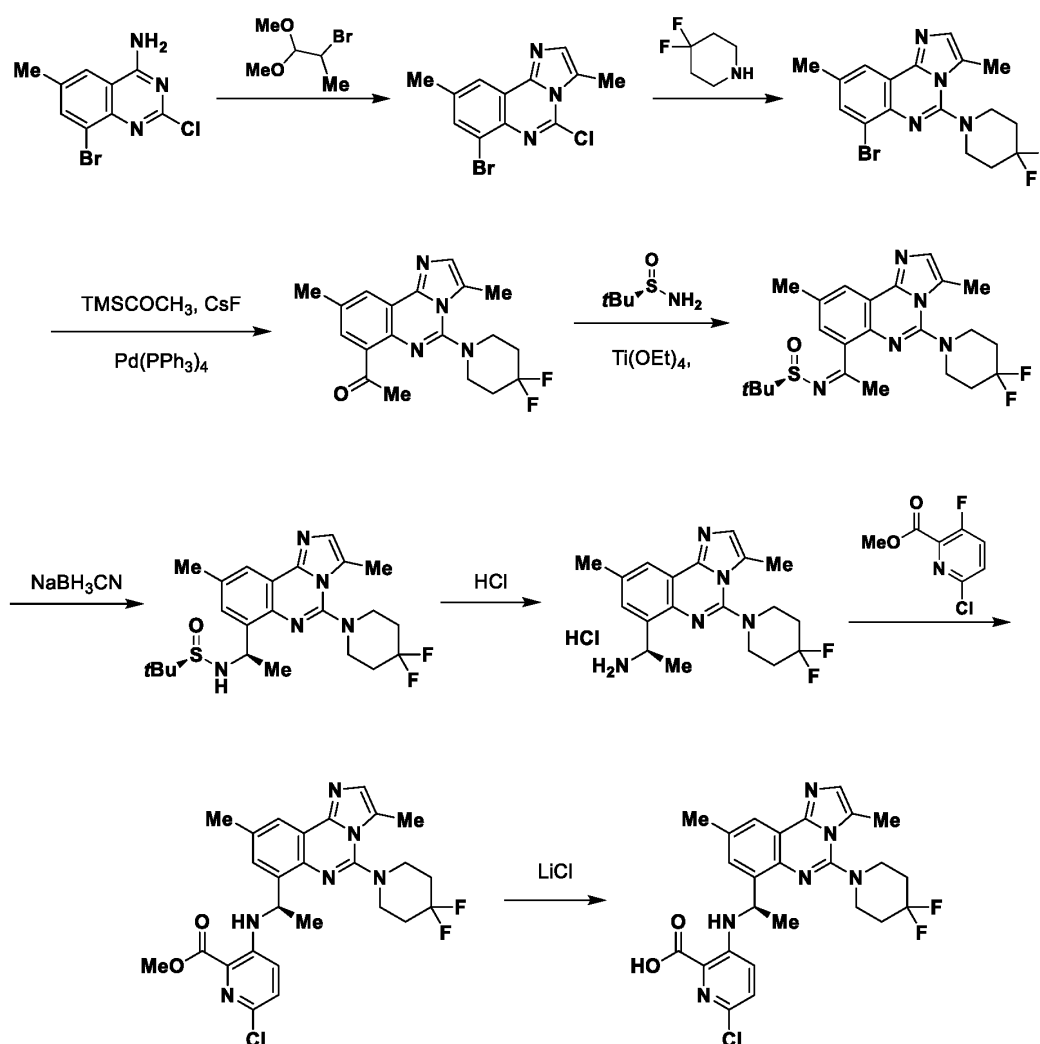
[00553] Step I: To a solution of methyl (*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2,9-dimethylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinate (130 mg, 246 μ mol, 1.00 *eq.*) in dimethylsulfoxide (1.50 mL) was added anhydrous lithium chloride (125 mg, 2.95 mmol, 60.5 μ L, 12.0 *eq.*). The mixture was stirred at 120 °C for 7 hours. After completion of the reaction, the reaction mixture was directly filtered to give a filtrate. The filtrate was purified by *prep*-HPLC (column: Welch Xtimate C18 150 $\times$ 25mm $\times$ 5 μ m; mobile phase: [water(formic acid)-acetonitrile]; gradient: 35%-65% acetonitrile over 15 min) to give (*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2,9-dimethylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid (22.8 mg, 43.6 μ mol, 18% yield) as an off-white solid. LCMS [M+1]⁺ = 515.2.

[00554] ¹H NMR (400 MHz, CD₃OD) δ ppm = 8.06 (d, *J* = 0.8 Hz, 1H), 7.61 (s, 1H), 7.46 (d, *J* = 1.6 Hz, 1H), 7.15 (d, *J* = 8.8 Hz, 1H), 7.02 (d, *J* = 9.2 Hz, 1H), 5.58 (q, *J* = 6.8 Hz, 1H), 3.68 (br t, *J* = 5.2 Hz, 4H), 2.47 (s, 3H), 2.44 (s, 3H), 2.38 - 2.22 (m, 4H), 1.71 (d, *J* = 6.8 Hz, 3H).

[00555] ¹⁹F NMR (377 MHz, CD₃OD) δ ppm = -98.7.

Example 6-6

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-3,9-dimethylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid



[00556] Step A: To a solution of 8-bromo-2-chloro-6-methylquinazolin-4-amine (3.50 g, 12.8 mmol, 1.00 eq.) in dioxane (40.0 mL) was added 2-bromo-1,1-dimethoxypropane (4.70 g, 25.6 mmol, 2.00 eq.). The mixture was stirred at 100 °C for 12 hours. After completion of the reaction, the reaction mixture was cooled to 25 °C to give a suspension, the suspension was filtered. The filter cake was triturated with petroleum ether/ethyl acetate = 1/1 (50.0 mL) at 25 °C for 5 minutes and filtered, this filter cake was collected and dried under vacuum to give 7-bromo-5-chloro-3,9-dimethylimidazo[1,2-c]quinazoline (3.50 g, 11.2 mmol, 88% yield) as a yellow solid. LCMS $[M+1]^+ = 311.9$.

[00557] Step B: To a solution of 7-bromo-5-chloro-3,9-dimethylimidazo[1,2-c]quinazoline (3.40 g, 10.9 mmol, 1.00 eq.) and 4,4-difluoropiperidine (2.65 g, 21.9 mmol, 2.00 eq.) in acetonitrile (30.0 mL) was added diisopropylethylamine (4.24 g, 32.8 mmol, 5.72 mL, 3.00 eq.). The mixture was stirred at 60 °C for 12 hours. After completion of the reaction, the mixture was

cooled to 25 °C and added water (100 mL) to give a suspension, and then filtered, the filter cake was dried under vacuum to give 7-bromo-5-(4,4-difluoropiperidin-1-yl)-3,9-dimethylimidazo[1,2-c]quinazoline (3.00 g, 7.59 mmol, 69% yield) as a yellow solid. LCMS [M+3]⁺ = 396.9.

[00558] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm = 8.06 (d, *J* = 0.8 Hz, 1H), 7.77 (d, *J* = 1.6 Hz, 1H), 7.37 (d, *J* = 0.8 Hz, 1H), 3.46 (s, 4H), 2.70 (s, 3H), 2.46 (s, 3H), 2.33 - 2.24 (m, 4H).

[00559] Step C: To a solution of 7-bromo-5-(4,4-difluoropiperidin-1-yl)-3,9-dimethylimidazo[1,2-c]quinazoline (2.50 g, 6.33 mmol, 1.00 eq.) and 1-trimethylsilyl ethanone (1.47 g, 12.6 mmol, 2.00 eq.) in 1,2-dichloroethane (10.0 mL) was added tetrakis(triphenylphosphine)palladium (0) (730 mg, 632 μmol, 0.10 eq.) and cesium fluoride (2.88 g, 18.9 mmol, 3.00 eq.). The mixture was stirred at 80 °C for 2 hrs under nitrogen atmosphere. After completion of the reaction, the mixture was cooled to 25 °C filtered, and concentrated under reduced pressure to give a solid. The solid was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give 1-(5-(4,4-difluoropiperidin-1-yl)-3,9-dimethylimidazo[1,2-c]quinazolin-7-yl)ethan-1-one (2.20 g, 6.14 mmol, 97% yield) as a yellow solid. LCMS [M+1]⁺ = 359.2.

[00560] Step D: To a solution of 1-(5-(4,4-difluoropiperidin-1-yl)-3,9-dimethylimidazo[1,2-c]quinazolin-7-yl)ethan-1-one (2.20 g, 6.14 mmol, 1.00 eq.) and (*R*)-2-methylpropane-2-sulfinamide (1.49 g, 12.2 mmol, 2.00 eq.) in tetrahydrofuran (20.0 mL) was added titanium (IV) ethoxide (4.20 g, 18.4 mmol, 3.82 mL, 3.00 eq.) and 1,2-dimethoxyethane (774.5 mg, 8.59 mmol, 893 μL, 1.40 eq.). The mixture was stirred at 70 °C for 2 hr under nitrogen atmosphere. After completion of the reaction, the mixture was cooled to 25 °C and water (2.00 mL) was added to give a suspension. The suspension was filtered, and the filtrate was 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 0~50% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give (*R*)-*N*-(1-(5-(4,4-difluoropiperidin-1-yl)-3,9-dimethylimidazo[1,2-c]quinazolin-7-yl)ethylidene)-2-methylpropane-2-sulfinamide (2.00 g, 4.33 mmol, 71% yield) as a yellow solid. LCMS [M+1]⁺ = 462.1.

[00561] Step E: To a solution of (*R*)-*N*-(1-(5-(4,4-difluoropiperidin-1-yl)-3,9-dimethylimidazo[1,2-c]quinazolin-7-yl)ethylidene)-2-methylpropane-2-sulfinamide (2.00 g, 4.33 mmol, 1.00 eq.) in dichloromethane (20.0 mL) was added sodium cyanoborohydride (1.09 g, 17.3 mmol, 4.00 eq.) and acetic acid (260 mg, 4.33 mmol, 248 μL, 1.00 eq.). The mixture was stirred at 0 °C for 1 hour. After completion of the reaction, the reaction mixture was quenched by the addition of water (2 mL) at 25 °C, filtered and 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 0~80% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give (*R*)-*N*-((*R*)-1-(5-(4,4-difluoropiperidin-1-yl)-3,9-dimethylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)-2-methylpropane-2-sulfinamide (2.00 g, 4.31 mmol, 99% yield) as a white solid. LCMS [M+1]⁺ = 464.2.

[00562] ¹H NMR (400 MHz, CDCl₃) δ ppm = 8.07 (s, 1H), 7.29 (d, *J* = 1.6 Hz, 1H), 5.06 (t, *J* = 6.8 Hz, 1H), 4.51 (d, *J* = 6.8 Hz, 1H), 3.68 - 3.18 (m, 4H), 2.66 (s, 3H), 2.42 (s, 3H), 2.33 - 2.05 (m, 4H), 1.57 (d, *J* = 6.8 Hz, 3H), 1.17 - 1.15 (m, 9H).

[00563] Step F: A solution of (*R*)-*N*-((*R*)-1-(5-(4,4-difluoropiperidin-1-yl)-3,9-dimethylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)-2-methylpropane-2-sulfinamide (800 mg, 1.73 mmol, 1.00 eq.), 4.0 molar hydrochloric acid in dioxane (5.00 mL) was stirred at 25 °C for 2 hours. After completion of the reaction, the reaction mixture was concentrated under vacuum to give (*R*)-1-(5-(4,4-difluoropiperidin-1-yl)-3,9-dimethylimidazo[1,2-*c*]quinazolin-7-yl)ethan-1-amine (600 mg, 1.67 mmol, 97% yield) as a white hydrochloride salt. LCMS [M+1]⁺ = 360.1.

[00564] Step G: To a solution of (*R*)-1-(5-(4,4-difluoropiperidin-1-yl)-3,9-dimethylimidazo[1,2-*c*]quinazolin-7-yl)ethan-1-amine, hydrochloride (500 mg, 1.39 mmol, 1.00 eq.) and methyl 6-chloro-3-fluoropicolinate (527 mg, 2.78 mmol, 2.00 eq.) in dimethylformamide (10.0 mL) was added diisopropylethylamine (539 mg, 4.17 mmol, 726 μL, 3.00 eq.). The mixture was stirred at 100 °C for 2 hours. After completion of the reaction, the mixture was cooled to 25 °C and diluted with water (10.0 mL) and extracted with dichloromethane (30.0 mL × 3). The combined organic layers were washed with brine (10.0 mL × 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 @ 40 mL/min) to give methyl (*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-3,9-dimethylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinate (400 mg, 756 μmol, 54% yield) as a white solid. LCMS [M+1]⁺ = 529.1.

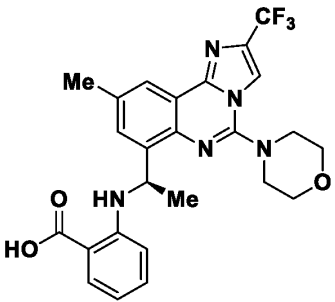
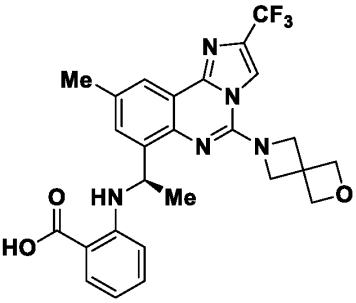
[00565] Step H: To a solution of methyl (*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-3,9-dimethylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinate (300 mg, 567 μmol, 1.00 eq.) in dimethyl sulfoxide (1.00 mL) was added lithium chloride (240 mg, 5.67 mmol, 116 μL, 10.0 eq.). The mixture was stirred at 130 °C for 2 hours. After completion of the reaction, the mixture was cooled to 25 °C and diluted with water (10.0 mL) and extracted with dichloromethane (30.0 mL × 3). The combined organic layers were washed with brine (10.0 mL × 3), 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 150 × 40mm × 15μm;

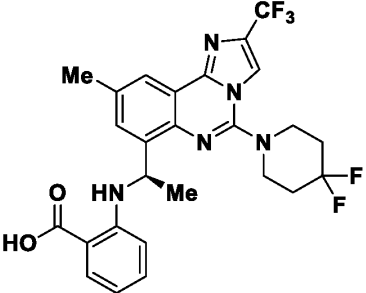
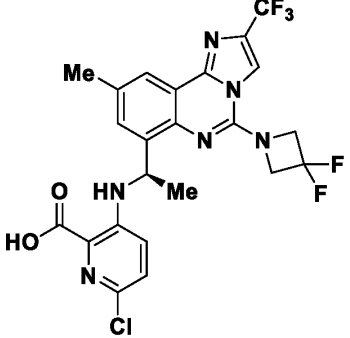
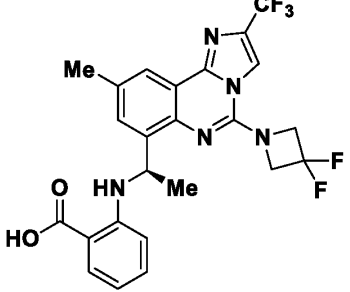
mobile phase: [water(0.1%formic acid)-acetonitrile];gradient:38%-68% acetonitrile over 15 min) to give (*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-3,9-dimethylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid (58.7 mg, 112 μ mol, 19% yield) as a yellow solid. LCMS [M+1]⁺ = 515.2.

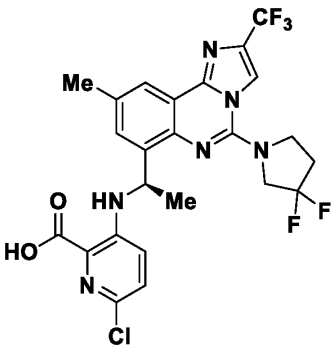
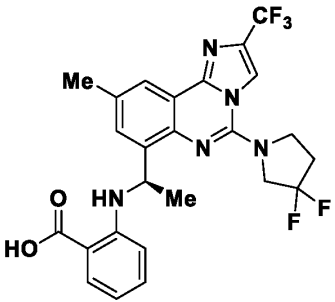
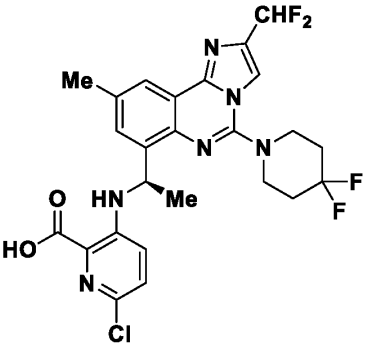
[00566] ¹H NMR (400 MHz, CD₃OD) δ ppm = 8.04 (s, 1H), 7.44 (d, *J* = 1.6 Hz, 1H), 7.30 (d, *J* = 0.8 Hz, 1H), 7.17 (d, *J* = 9.2 Hz, 1H), 7.04 (d, *J* = 9.2 Hz, 1H), 5.56 (q, *J* = 6.8 Hz, 1H), 3.81 - 3.36 (m, 4H), 2.80 (s, 3H), 2.44 (s, 3H), 2.29 (br d, *J* = 7.6 Hz, 4H), 1.71 (d, *J* = 6.8 Hz, 3H).

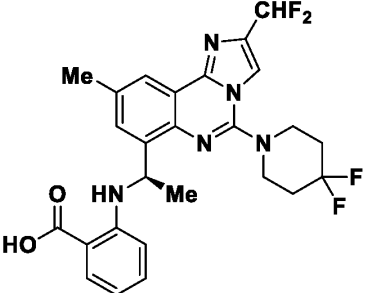
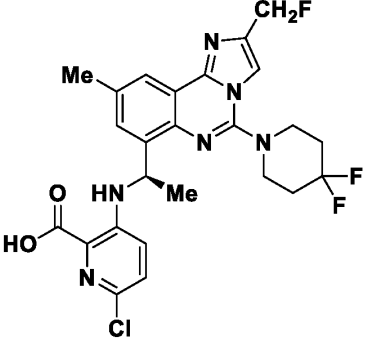
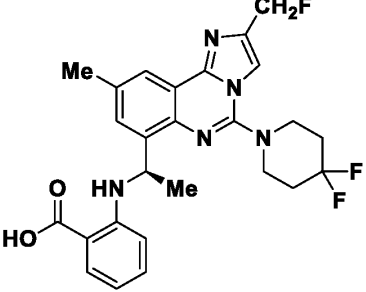
EXAMPLES 6-7 to 6-130

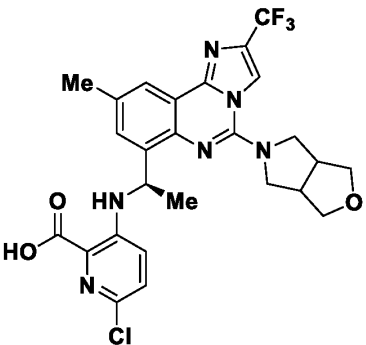
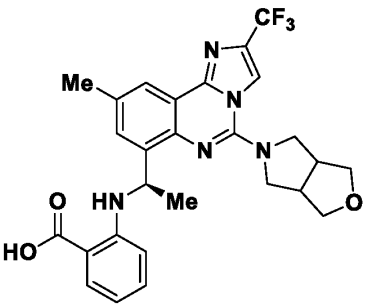
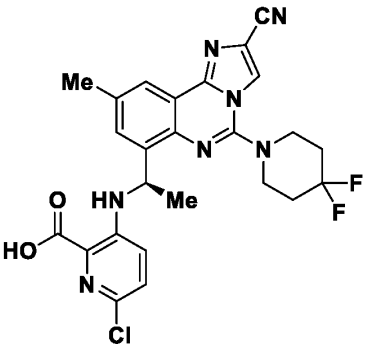
[00567] The following compounds are prepared essentially according to the procedures set forth above in Schemes I-IV and Examples 2-2, 3-1, 6-1, 6-2, 6-3, 6-4, 6-5 and 6-6.

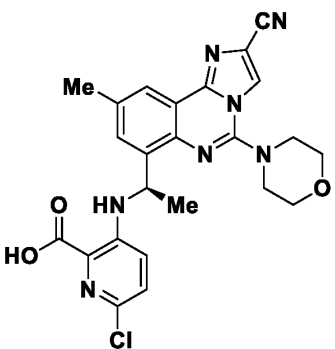
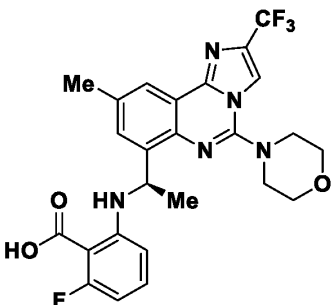
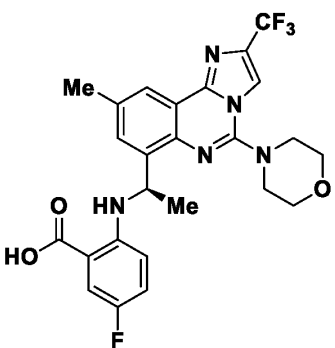
Example No.	Compound
6-7	 (<i>R</i>)-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)benzoic acid
6-8	 (<i>R</i>)-2-((1-(9-methyl-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-2-(trifluoromethyl)imidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)benzoic acid

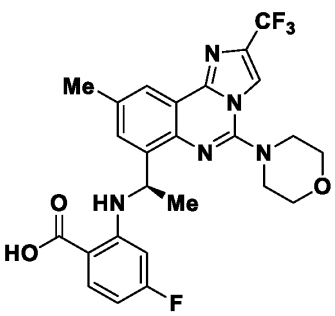
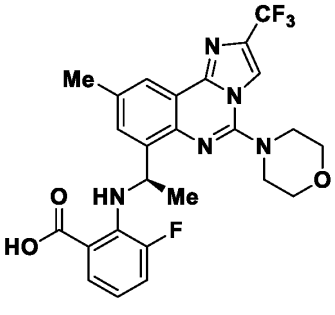
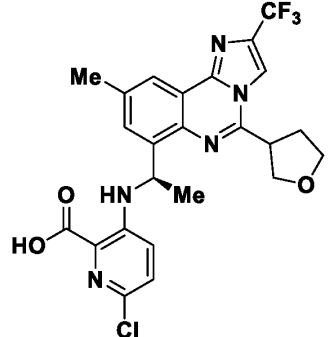
6-9	 (R)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid
6-10	 (R)-6-chloro-3-((1-(5-(3,3-difluoroazetidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-11	 (R)-2-((1-(5-(3,3-difluoroazetidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid

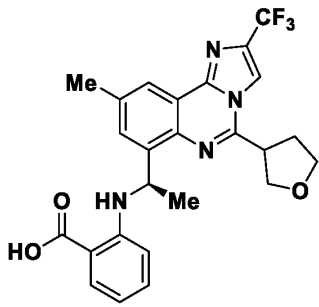
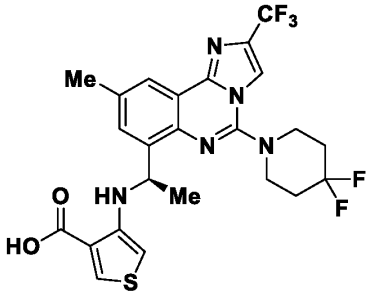
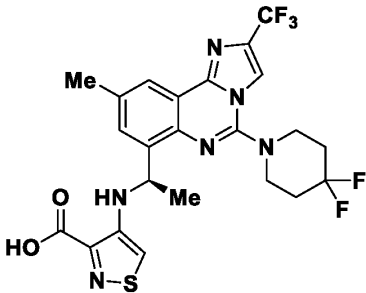
6-12	 (<i>R</i>)-6-chloro-3-((1-(5-(3,3-difluoropyrrolidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-13	 (<i>R</i>)-2-((1-(5-(3,3-difluoropyrrolidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid
6-14	 (<i>R</i>)-6-chloro-3-((1-(2-(difluoromethyl)-5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid

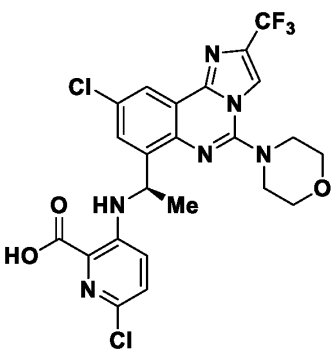
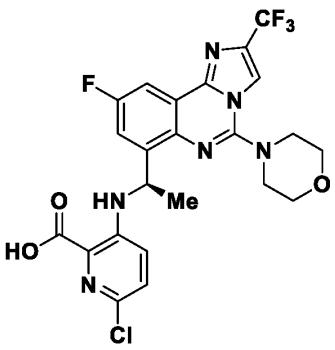
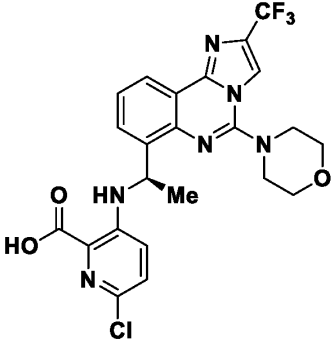
6-15	 (R)-2-((1-(2-(difluoromethyl)-5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid
6-16	 (R)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2-(fluoromethyl)-9-methylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-17	 (R)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-2-(fluoromethyl)-9-methylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid

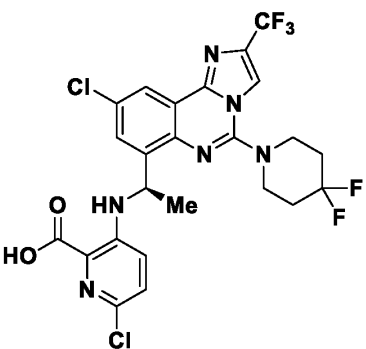
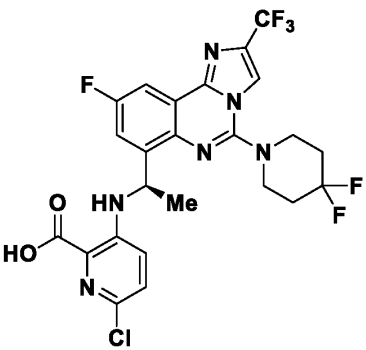
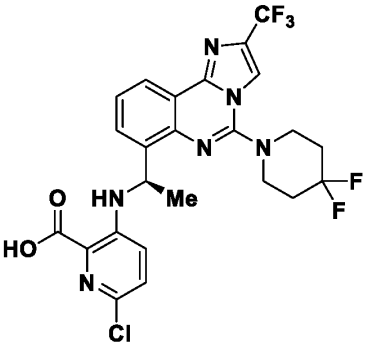
6-18	 6-chloro-3-(((1<i>R</i>)-1-(9-methyl-5-(tetrahydro-1<i>H</i>-furo[3,4-<i>c</i>]pyrrol-5(3<i>H</i>)-yl)-2-(trifluoromethyl)imidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)picolinic acid
6-19	 2-(((1<i>R</i>)-1-(9-methyl-5-(tetrahydro-1<i>H</i>-furo[3,4-<i>c</i>]pyrrol-5(3<i>H</i>)-yl)-2-(trifluoromethyl)imidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)benzoic acid
6-20	 (<i>R</i>)-6-chloro-3-((1-(2-cyano-5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)picolinic acid

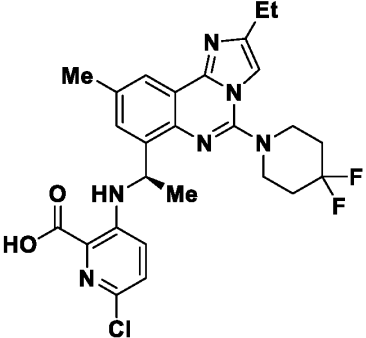
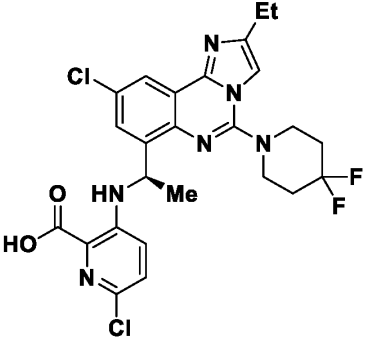
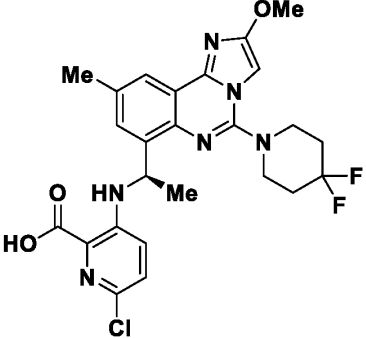
6-21	 (<i>R</i>)-6-chloro-3-((1-(2-cyano-9-methyl-5-morpholinoimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-22	 (<i>R</i>)-2-fluoro-6-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid
6-23	 (<i>R</i>)-5-fluoro-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid

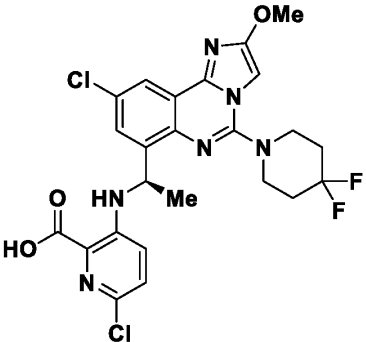
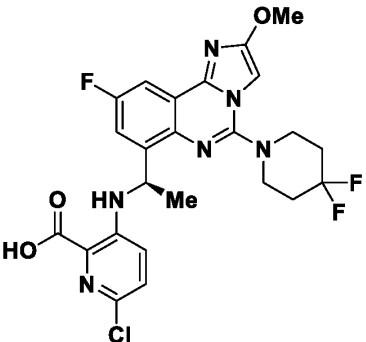
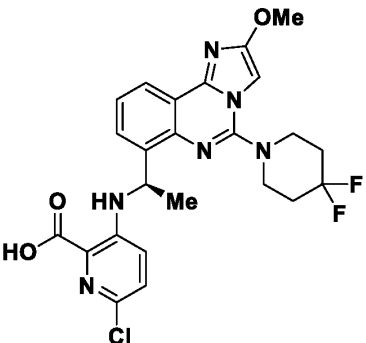
6-24	 (<i>R</i>)-4-fluoro-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid
6-25	 (<i>R</i>)-3-fluoro-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid
6-26	 6-chloro-3-(((1<i>R</i>)-1-(9-methyl-5-(tetrahydrofuran-3-yl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid

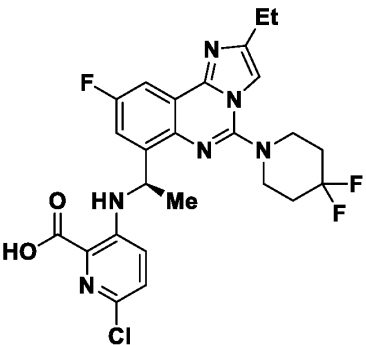
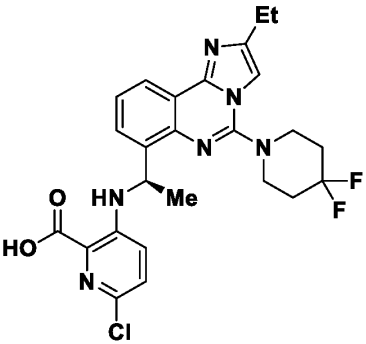
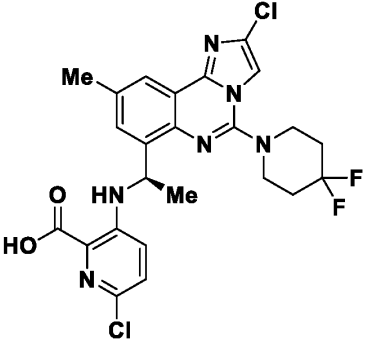
6-27	 2-(((1<i>R</i>)-1-(9-methyl-5-(tetrahydrofuran-3-yl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid
6-28	 (<i>R</i>)-4-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)thiophene-3-carboxylic acid
6-29	 (<i>R</i>)-4-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)isothiazole-3-carboxylic acid

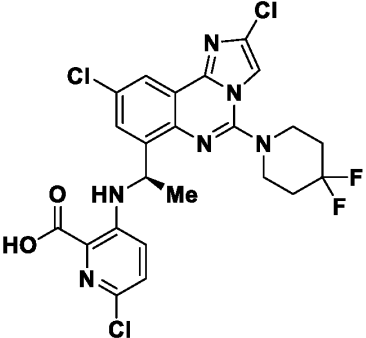
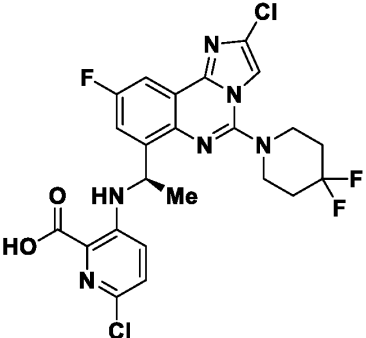
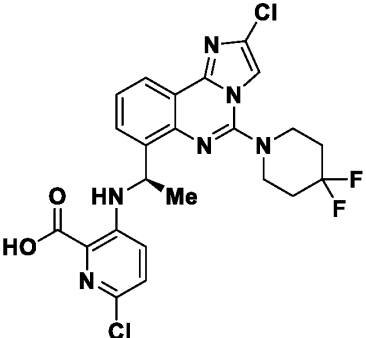
6-30	 (R)-6-chloro-3-((1-(9-chloro-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-31	 (R)-6-chloro-3-((1-(9-fluoro-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-32	 (R)-6-chloro-3-((1-(5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid

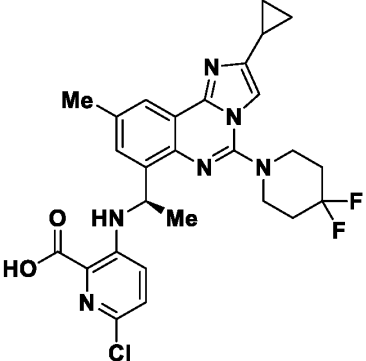
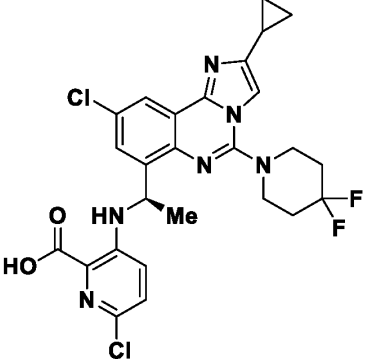
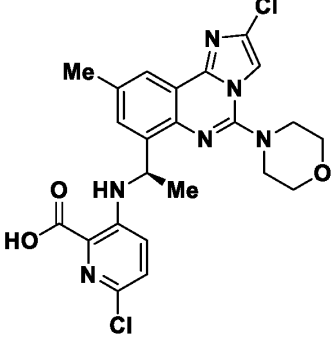
6-33	 (<i>R</i>)-6-chloro-3-((1-(9-chloro-5-(4,4-difluoropiperidin-1-yl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-34	 (<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-fluoro-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-35	 (<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid

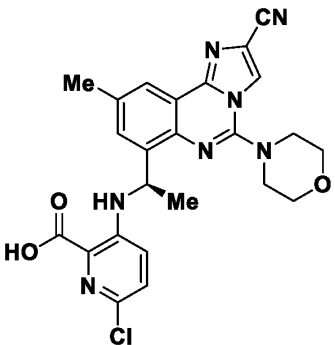
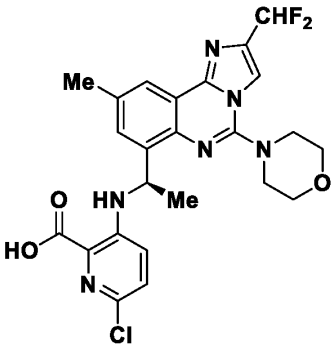
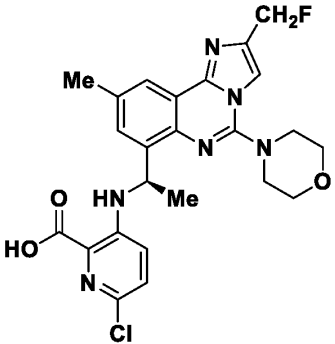
6-36	 (<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2-ethyl-9-methylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-37	 (<i>R</i>)-6-chloro-3-((1-(9-chloro-5-(4,4-difluoropiperidin-1-yl)-2-ethylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-38	 (<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2-methoxy-9-methylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid

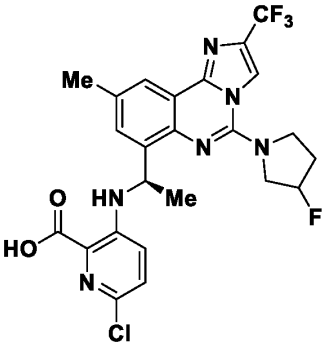
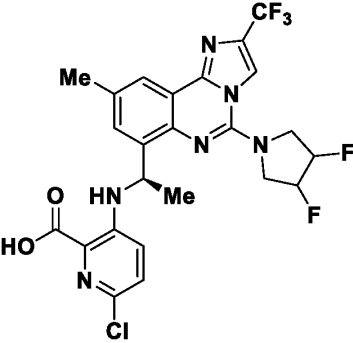
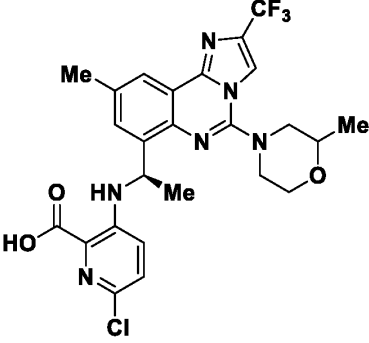
6-39	 <i>(R)</i>-6-chloro-3-((1-(9-chloro-5-(4,4-difluoropiperidin-1-yl)-2-methoxyimidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)picolinic acid
6-40	 <i>(R)</i>-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-fluoro-2-methoxyimidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)picolinic acid
6-41	 <i>(R)</i>-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2-methoxyimidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)picolinic acid

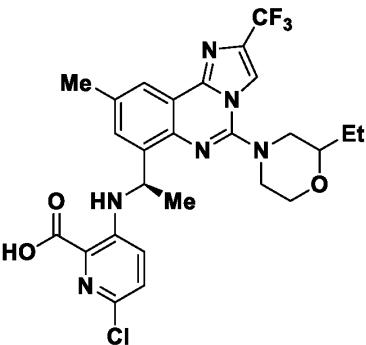
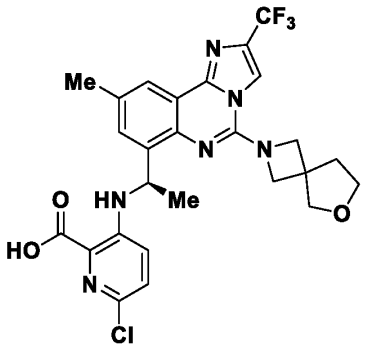
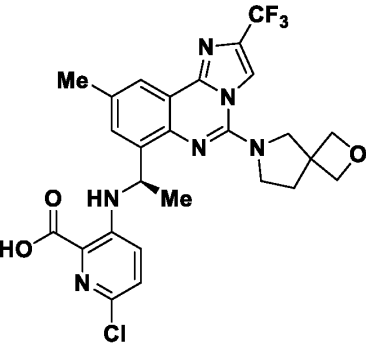
6-42	 (<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2-ethyl-9-fluoroimidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)picolinic acid
6-43	 (<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2-ethylimidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)picolinic acid
6-44	 (<i>R</i>)-6-chloro-3-((1-(2-chloro-5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)picolinic acid

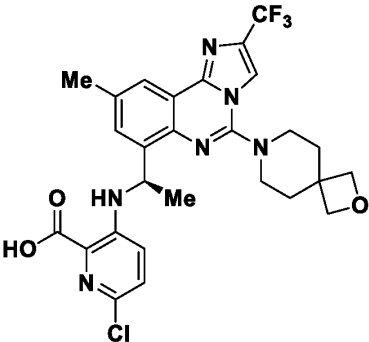
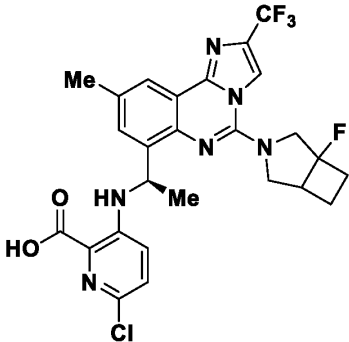
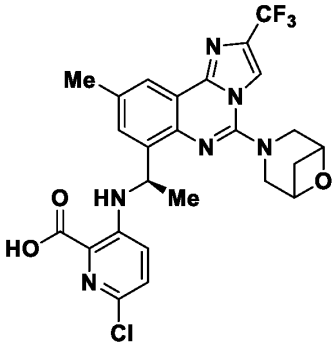
6-45	 (<i>R</i>)-6-chloro-3-((1-(2,9-dichloro-5-(4,4-difluoropiperidin-1-yl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-46	 (<i>R</i>)-6-chloro-3-((1-(2-chloro-5-(4,4-difluoropiperidin-1-yl)-9-fluoroimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-47	 (<i>R</i>)-6-chloro-3-((1-(2-chloro-5-(4,4-difluoropiperidin-1-yl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid

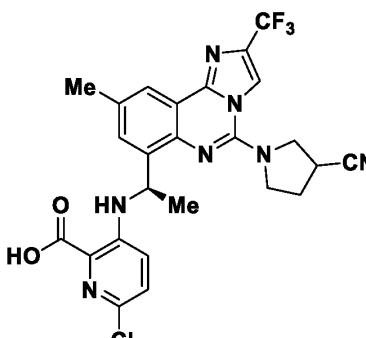
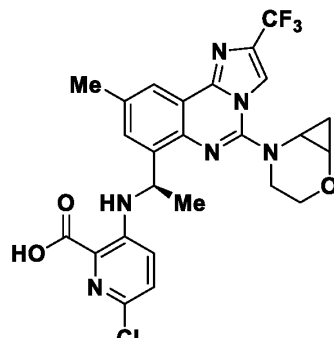
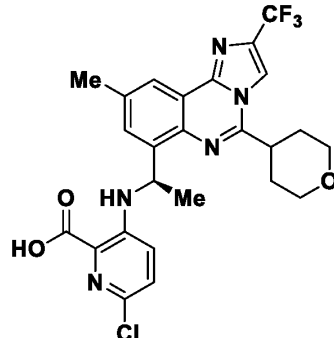
6-48	 (R)-6-chloro-3-((1-(2-cyclopropyl-5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-49	 (R)-6-chloro-3-((1-(9-chloro-2-cyclopropyl-5-(4,4-difluoropiperidin-1-yl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-50	 (R)-6-chloro-3-((1-(2-chloro-9-methyl-5-morpholinoimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid

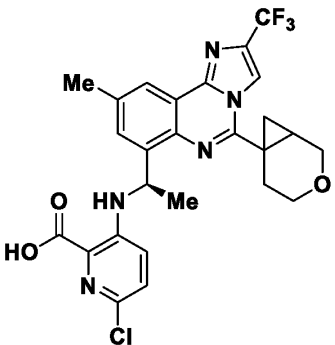
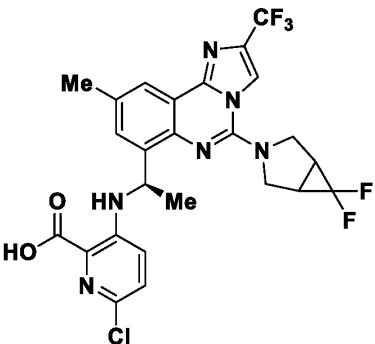
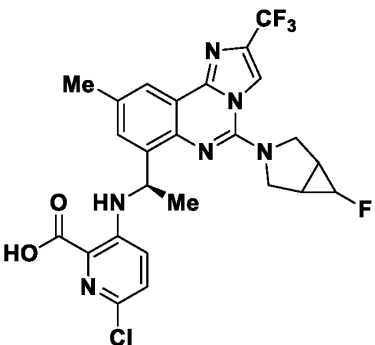
6-51	 (<i>R</i>)-6-chloro-3-((1-(2-cyano-9-methyl-5-morpholinoimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-52	 (<i>R</i>)-6-chloro-3-((1-(2-(difluoromethyl)-9-methyl-5-morpholinoimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-53	 (<i>R</i>)-6-chloro-3-((1-(2-(fluoromethyl)-9-methyl-5-morpholinoimidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid

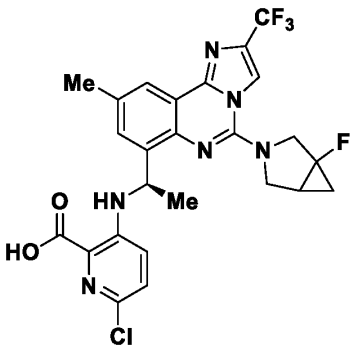
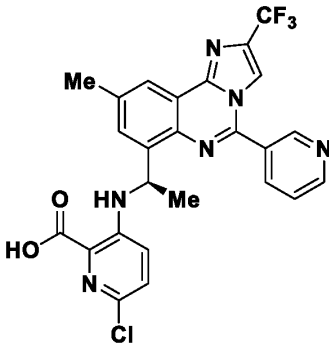
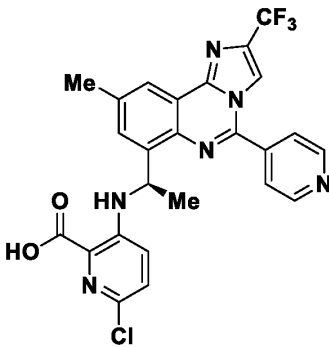
6-54	 6-chloro-3-(((1<i>R</i>)-1-(5-(3-fluoropyrrolidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)picolinic acid
6-55	 6-chloro-3-(((1<i>R</i>)-1-(5-(3,4-difluoropyrrolidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)picolinic acid
6-56	 6-chloro-3-(((1<i>R</i>)-1-(9-methyl-5-(2-methylmorpholino)-2-(trifluoromethyl)imidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)picolinic acid

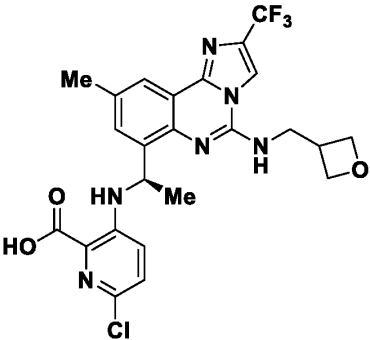
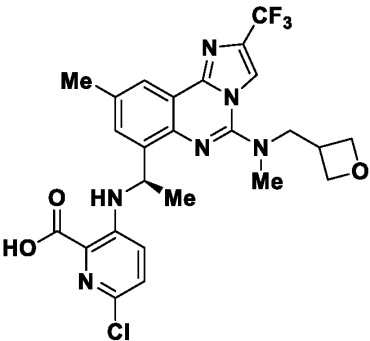
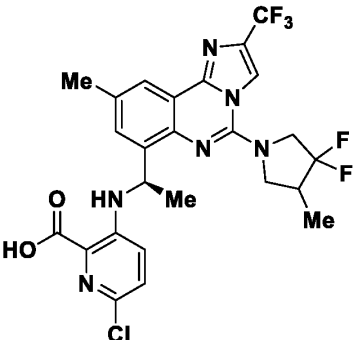
6-57	 6-chloro-3-(((1<i>R</i>)-1-(5-(2-ethylmorpholino)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-58	 (<i>R</i>)-6-chloro-3-((1-(9-methyl-5-(6-oxa-2-azaspiro[3.4]octan-2-yl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-59	 (<i>R</i>)-6-chloro-3-((1-(9-methyl-5-(2-oxa-6-azaspiro[3.4]octan-6-yl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid

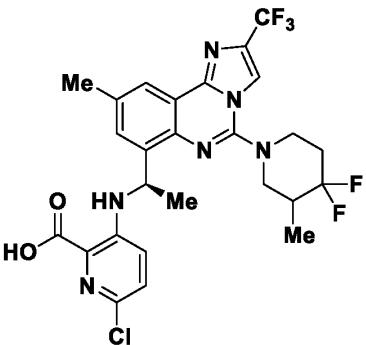
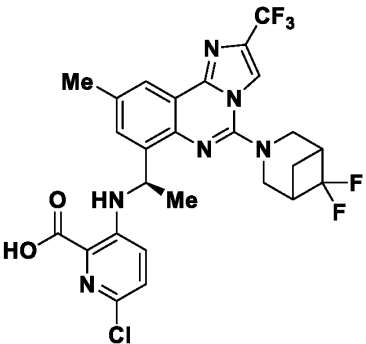
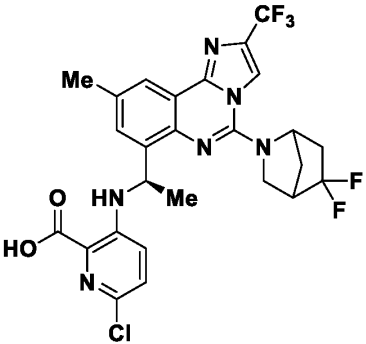
6-60	 (<i>R</i>)-6-chloro-3-(((1-(9-methyl-5-(2-oxa-7-azaspiro[3.5]nonan-7-yl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-61	 6-chloro-3-(((1<i>R</i>)-1-(5-(1-fluoro-3-azabicyclo[3.2.0]heptan-3-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-62	 3-(((1<i>R</i>)-1-(5-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)-6-chloropicolinic acid

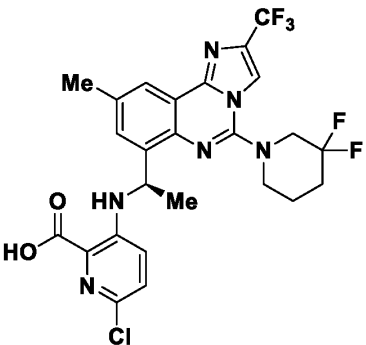
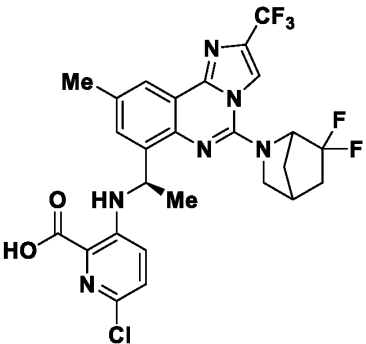
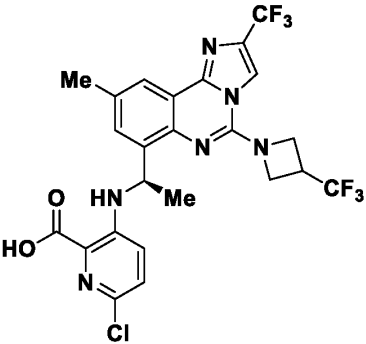
6-63	 6-chloro-3-(((1<i>R</i>)-1-(5-(3-cyanopyrrolidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)picolinic acid
6-64	 3-(((1<i>R</i>)-1-(5-(2-oxa-5-azabicyclo[4.1.0]heptan-5-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)-6-chloropicolinic acid
6-65	 (<i>R</i>)-6-chloro-3-((1-(9-methyl-5-(tetrahydro-2<i>H</i>-pyran-4-yl)-2-(trifluoromethyl)imidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)picolinic acid

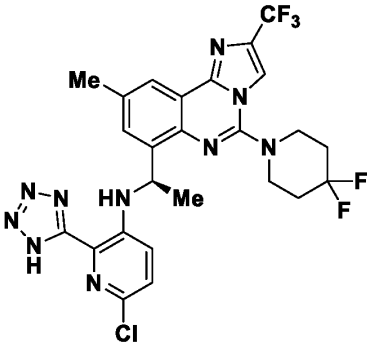
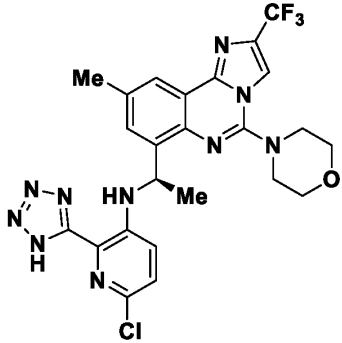
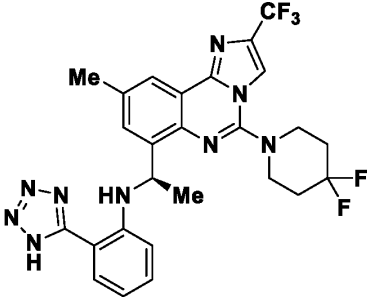
6-66	 3-(((1<i>R</i>)-1-(5-(3-oxabicyclo[4.1.0]heptan-6-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)-6-chloropicolinic acid
6-67	 6-chloro-3-(((1<i>R</i>)-1-(5-(6,6-difluoro-3-azabicyclo[3.1.0]hexan-3-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)picolinic acid
6-68	 6-chloro-3-(((1<i>R</i>)-1-(5-(6-fluoro-3-azabicyclo[3.1.0]hexan-3-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)picolinic acid

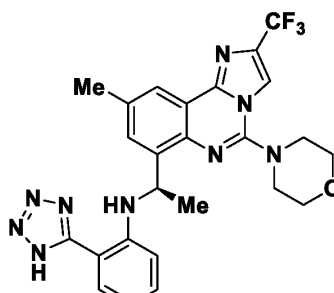
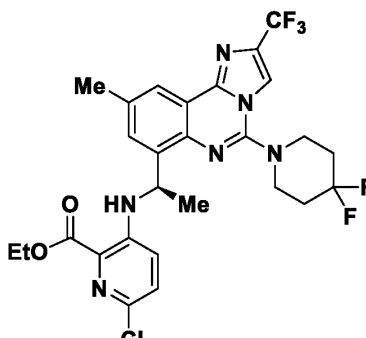
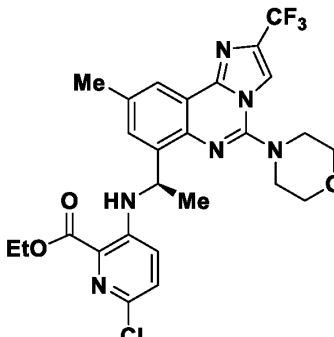
6-69	 6-chloro-3-(((1<i>R</i>)-1-(5-(1-fluoro-3-azabicyclo[3.1.0]hexan-3-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)picolinic acid
6-70	 (<i>R</i>)-6-chloro-3-((1-(9-methyl-5-(pyridin-3-yl)-2-(trifluoromethyl)imidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)picolinic acid
6-71	 (<i>R</i>)-6-chloro-3-((1-(9-methyl-5-(pyridin-4-yl)-2-(trifluoromethyl)imidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)picolinic acid

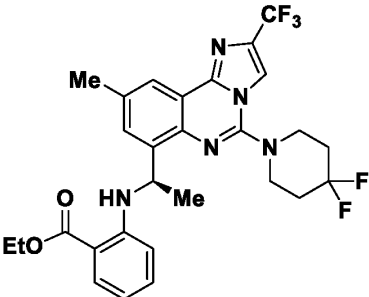
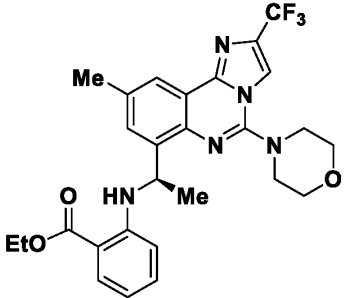
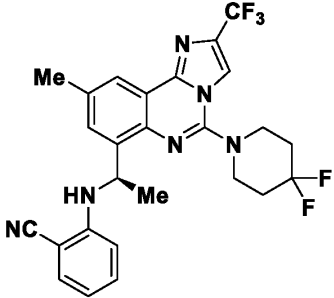
6-72	 (R)-6-chloro-3-((1-(9-methyl-5-((oxetan-3-ylmethyl)amino)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-73	 (R)-6-chloro-3-((1-(9-methyl-5-(methyl(oxetan-3-ylmethyl)amino)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-74	 6-chloro-3-(((1R)-1-(5-(3,3-difluoro-4-methylpyrrolidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid

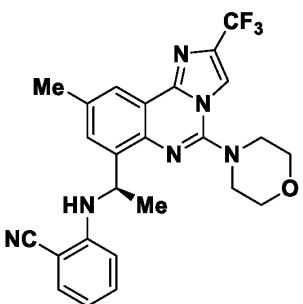
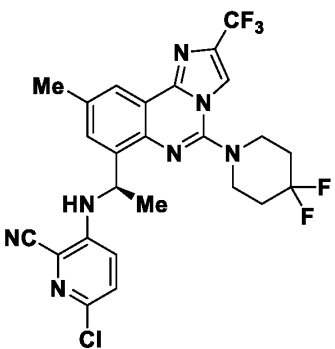
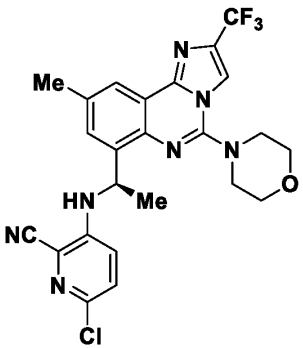
6-75	 6-chloro-3-(((1<i>R</i>)-1-(5-(4,4-difluoro-3-methylpiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)picolinic acid
6-76	 6-chloro-3-(((1<i>R</i>)-1-(5-(6,6-difluoro-3-azabicyclo[3.1.1]heptan-3-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)picolinic acid
6-77	 6-chloro-3-(((1<i>R</i>)-1-(5-(5,5-difluoro-2-azabicyclo[2.2.1]heptan-2-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-<i>c</i>]quinazolin-7-yl)ethyl)amino)picolinic acid

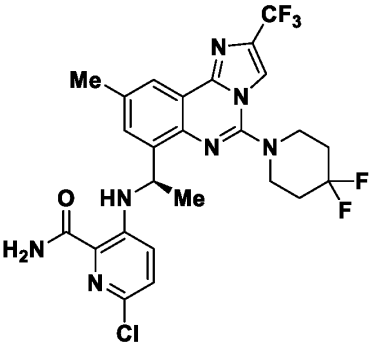
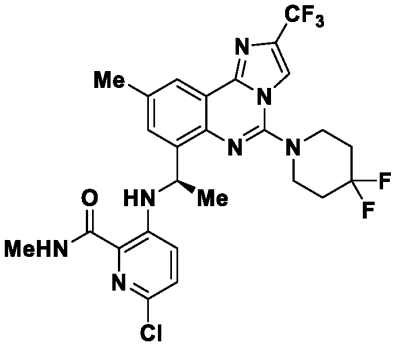
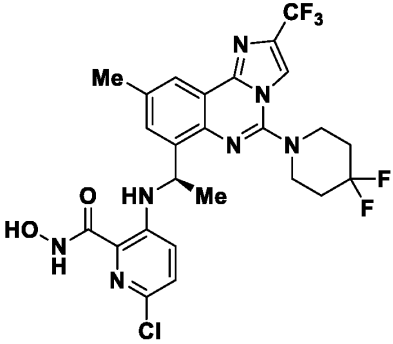
6-78	 (<i>R</i>)-6-chloro-3-((1-(5-(3,3-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-79	 6-chloro-3-(((1<i>R</i>)-1-(5-(6,6-difluoro-2-azabicyclo[2.2.1]heptan-2-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-80	 (<i>R</i>)-6-chloro-3-((1-(9-methyl-2-(trifluoromethyl)-5-(3-(trifluoromethyl)azetidin-1-yl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid

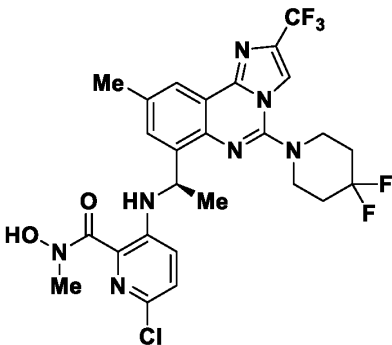
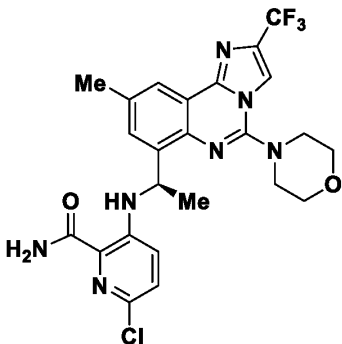
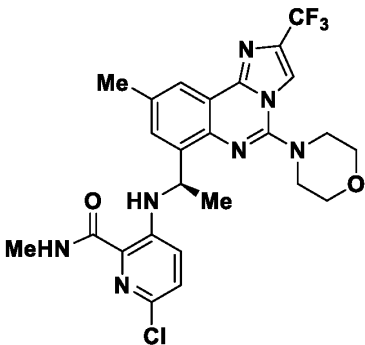
6-81	 (R)-6-chloro-N-(1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)-2-(1H-tetrazol-5-yl)pyridin-3-amine
6-82	 (R)-6-chloro-N-(1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)-2-(1H-tetrazol-5-yl)pyridin-3-amine
6-83	 (R)-N-(1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)-2-(1H-tetrazol-5-yl)aniline

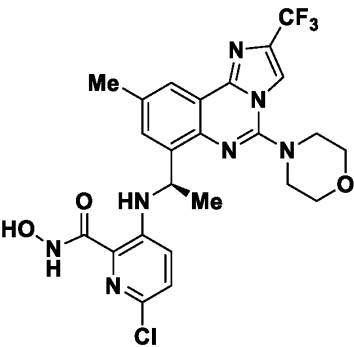
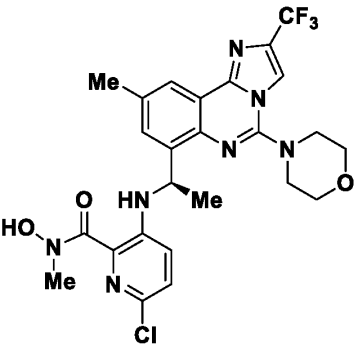
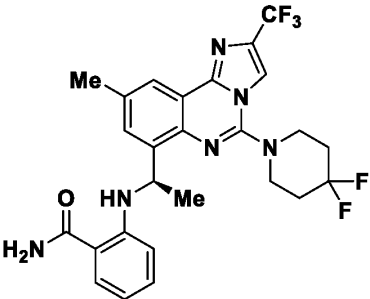
6-84	 (R)-N-(1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)-2-(1H-tetrazol-5-yl)aniline
6-85	 ethyl (R)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinate
6-86	 ethyl (R)-6-chloro-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinate

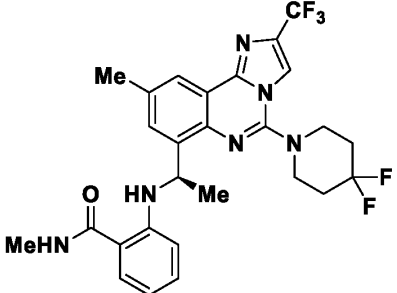
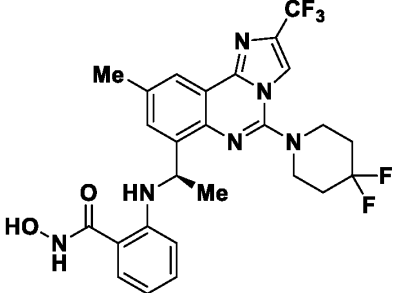
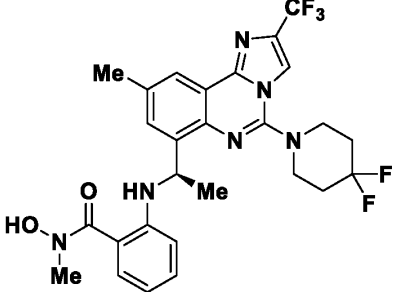
6-87	 ethyl (<i>R</i>)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoate
6-88	 ethyl (<i>R</i>)-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoate
6-89	 (<i>R</i>)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzonitrile

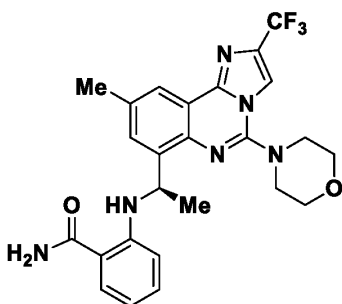
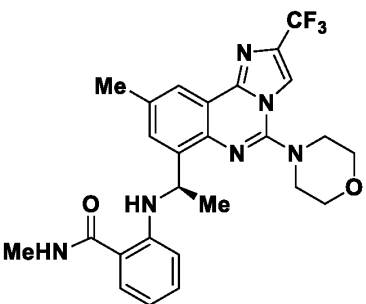
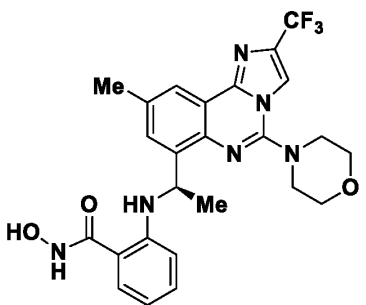
6-90	 (R)-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzonitrile
6-91	 (R)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinonitrile
6-92	 (R)-6-chloro-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinonitrile

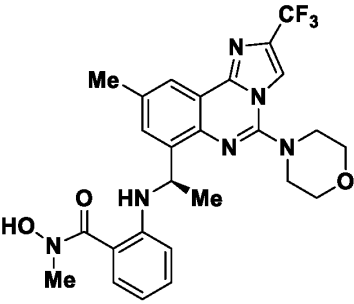
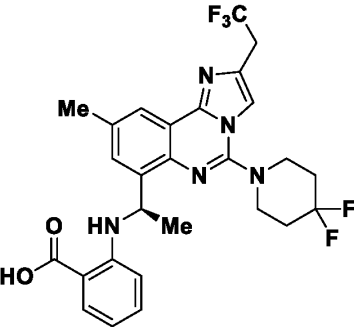
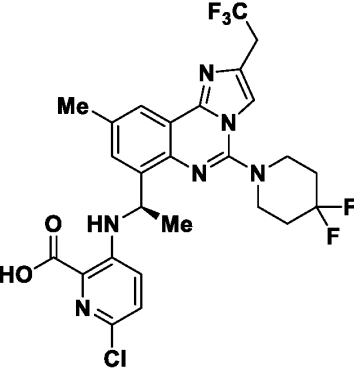
6-93	 (<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinamide
6-94	 (<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)-<i>N</i>-methylpicolinamide
6-95	 (<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)-<i>N</i>-hydroxypicolinamide

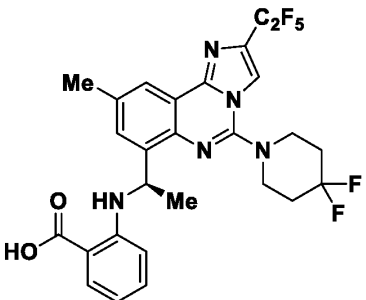
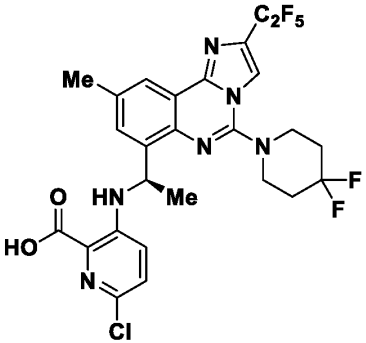
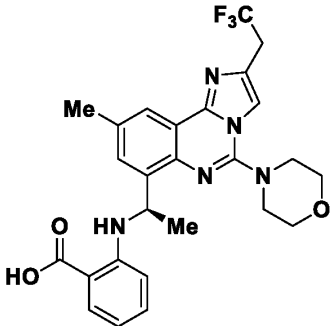
6-96	 (<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)-N-hydroxy-N-methylpicolinamide
6-97	 (<i>R</i>)-6-chloro-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinamide
6-98	 (<i>R</i>)-6-chloro-<i>N</i>-methyl-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinamide

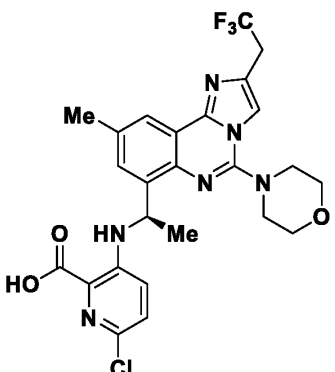
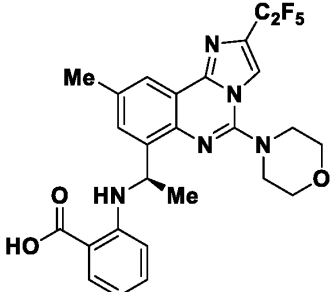
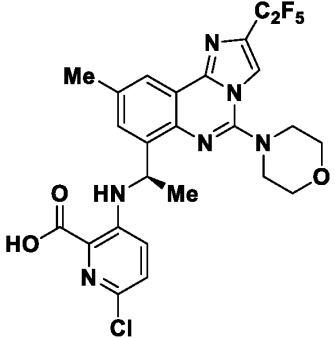
6-99	 (R)-6-chloro-N-hydroxy-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinamide
6-100	 (R)-6-chloro-N-hydroxy-N-methyl-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinamide
6-101	 (R)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzamide

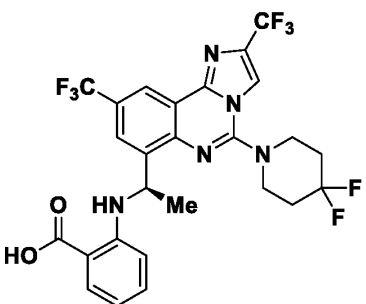
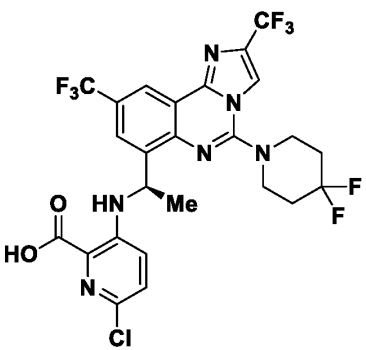
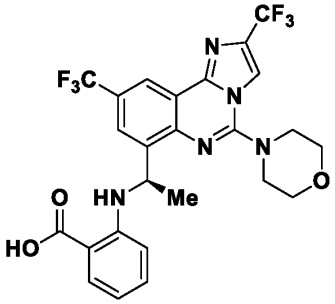
6-102	 (R)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)-N-methylbenzamide
6-103	 (R)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)-N-hydroxybenzamide
6-104	 (R)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)-N-methyl-N-hydroxybenzamide

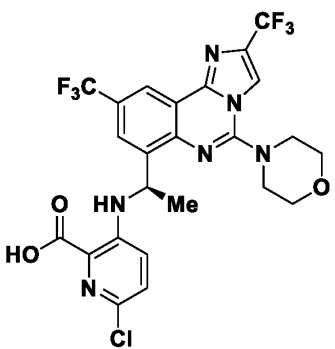
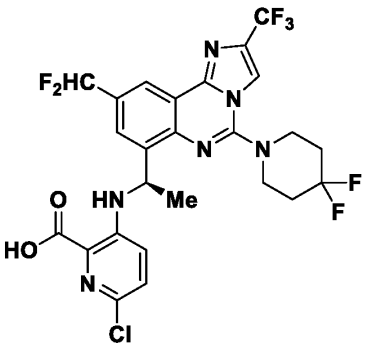
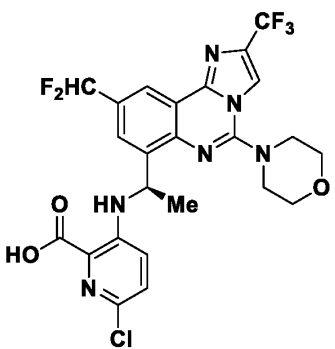
6-105	 (R)-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzamide
6-106	 (R)-N-methyl-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzamide
6-107	 (R)-N-hydroxy-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzamide

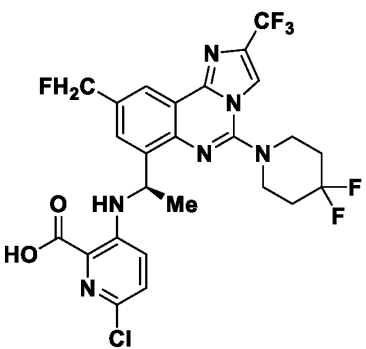
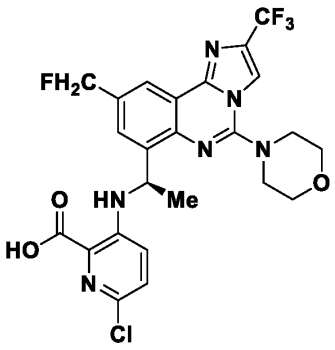
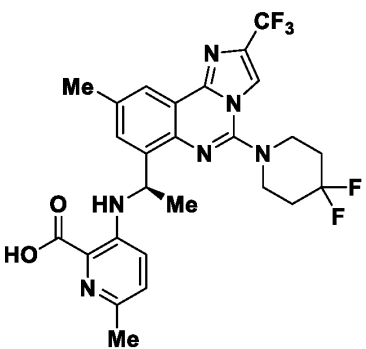
6-108	 (<i>R</i>)-<i>N</i>-hydroxy-<i>N</i>-methyl-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzamide
6-109	 (<i>R</i>)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(2,2,2-trifluoroethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid
6-110	 (<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(2,2,2-trifluoroethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid

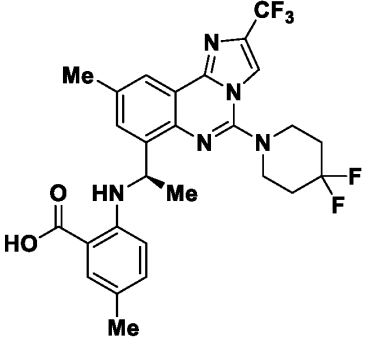
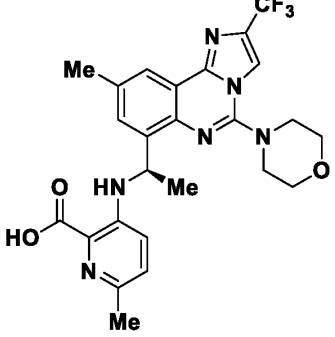
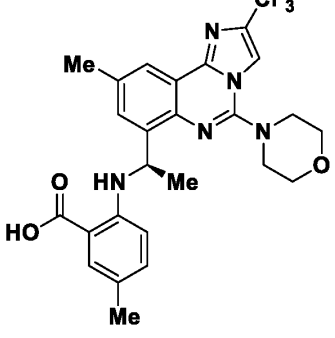
6-111	 (R)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(perfluoroethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid
6-112	 (R)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(perfluoroethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-113	 (R)-2-((1-(9-methyl-5-morpholino-2-(2,2,2-trifluoroethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid

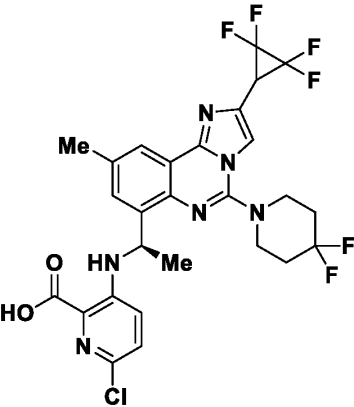
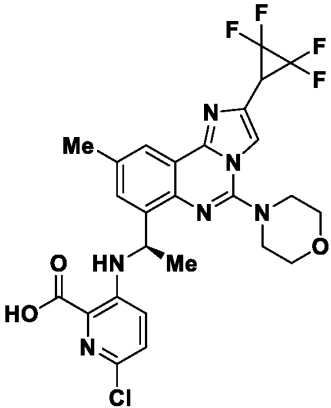
6-114	 (R)-6-chloro-3-((1-(9-methyl-5-morpholino-2-(2,2,2-trifluoroethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-115	 (R)-2-((1-(9-methyl-5-morpholino-2-(perfluoroethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid
6-116	 (R)-6-chloro-3-((1-(9-methyl-5-morpholino-2-(perfluoroethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid

6-117	 (<i>R</i>)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-2,9-bis(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid
6-118	 (<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2,9-bis(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-119	 (<i>R</i>)-2-((1-(5-morpholino-2,9-bis(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid

6-120	 (<i>R</i>)-6-chloro-3-((1-(5-morpholino-2,9-bis(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-121	 (<i>R</i>)-6-chloro-3-((1-(9-(difluoromethyl)-5-(4,4-difluoropiperidin-1-yl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-122	 (<i>R</i>)-6-chloro-3-((1-(9-(difluoromethyl)-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid

6-123	 (<i>R</i>)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-(fluoromethyl)-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-124	 (<i>R</i>)-6-chloro-3-((1-(9-(fluoromethyl)-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-125	 (<i>R</i>)-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)-6-methylpicolinic acid

6-126	 (R)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)-5-methylbenzoic acid
6-127	 (R)-6-methyl-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-128	 (R)-5-methyl-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid

6-129	 (R)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(2,2,3,3-tetrafluorocyclopropyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid
6-130	 (R)-6-chloro-3-((1-(9-methyl-5-morpholino-2-(2,2,3,3-tetrafluorocyclopropyl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)picolinic acid

EXAMPLE A

[00568] This Example illustrates that representative compounds of the present invention inhibit the formation of phospho-AKT (pAKT) in a cell.

[00569] 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).

[00570] 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).

[00571] 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 or 24 hours 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).

[00572] 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.

[00573] The results are shown in Tables below.

Table A

Inhibition of pAKT in T47D (PI3K α H1047R mutant) cells by
representative compounds of Formula (I)

Example No.	T47D pAKT (H1047R mutant) IC ₅₀ (nM)	Example No.	T47D pAKT (H1047R mutant) IC ₅₀ (nM)
1-1	199	5-10	22.3
1-2	495	5-23	15.4
1-3	426	5-24	58.8
1-4	211	5-37	44.8
2-1	21.8	5-38	13.9
2-2	1.25	5-45	29.1
3-1	41.2	5-46	73.4

Example No.	T47D pAKT (H1047R mutant) IC ₅₀ (nM)	Example No.	T47D pAKT (H1047R mutant) IC ₅₀ (nM)
4-1	2.5	5-50	65.5
5-2	69.6	6-1	2.4
5-3	2403.2	6-2	0.3
5-6	12.0	6-3	0.9
5-7	107.9	6-4	1.4
5-8	30.0	6-5	2.2
5-4	67.9	6-6	0.9
5-5	44.9		

Table B

Inhibition of pAKT in MKN1 (PI3K α E545K mutant) cells by representative compounds of Formula (I)

Example No.	MKN1 (E545K) pAKT IC ₅₀ (nM)
2-1	>10000

Table C

Inhibition of pAKT in SKBR3 (PI3K α wild type) cells by representative compounds of Formula (I)

Example No.	SKBR3 (WT) pAKT IC ₅₀ (nM)
1-1	>10000
1-2	>10000
1-3	>10000
1-4	>10000
2-2	>10000
3-1	>10000

EXAMPLE B

[00574] This Example illustrates that exemplary compounds of the present invention decrease the viability of cells.

[00575] 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).

[00576] 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.

[00577] 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 No.	T47D (H1047R mutant) Viability IC ₅₀ (nM)	Example #	T47D (H1047R mutant) Viability IC ₅₀ (nM)
1-1	1267	5-10	1430
1-2	1420	5-23	2656
1-3	2165	5-24	823.9
1-4	3929	5-37	1417
2-1	2366	5-38	952.4
2-2	481	5-45	1353
3-1	194	5-46	2757
4-1	221	5-50	1628
5-2	1648.0	6-1	54.8
5-3	2895.1	6-2	54.7
5-4	1640.8	6-3	246.0
5-5	1760.63	6-4	86.2
5-6	275.5	6-5	214.5
5-7	2813	6-6	294.2
5-8	1148		

Table F

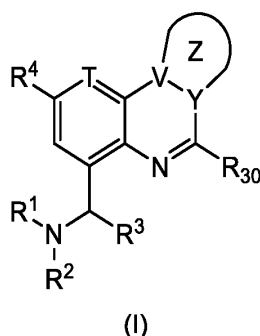
Viability in SKBR3 (PI3K α wild type) cells by representative compounds of Formula (I)

Example No.	SKBR3 (WT) Viability IC ₅₀ (nM)	Example #	SKBR3 (WT) Viability IC ₅₀ (nM)
1-1	>10000	5-10	>10000
1-2	>10000	5-23	>10000
1-3	>10000	5-24	>10000
1-4	>10000	5-37	>10000
2-1	>10000	5-38	>10000
2-2	>10000	5-45	>10000
3-1	>10000	5-46	>10000
4-1	>10000	5-50	>10000
5-2	>10000	6-1	9644
5-3	>10000	6-2	3966.5
5-4	>10000	6-3	>10000
5-5	>10000	6-4	>10000
5-6	>10000	6-5	>10000
5-7	>10000	6-6	>10000
5-8	>10000		

[00578] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be incorporated within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated herein by reference for all purposes.

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 R¹²;

each R¹² is independently C₁-C₄ alkyl, -OR^A, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, -C(O)N(R^B)₂, cyano, tetrazolyl, or halogen;

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;

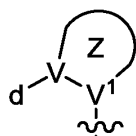
and

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;

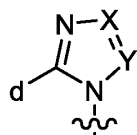
R⁴ is H, C₁-C₃ alkyl, C₁-C₃ alkoxy, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkyloxy, C₂-C₃ alkenyl, C₂-C₃ alkynyl, or C₅-C₆ cycloalkenyl, cyano, or halo, wherein each C₁-C₃ alkyl and C₃-C₆ cycloalkyl is optionally substituted with 1-5 halo groups;

T is N or CR⁶ wherein

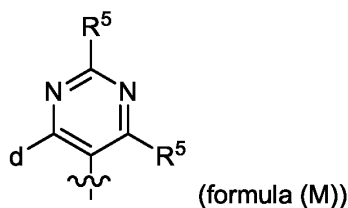
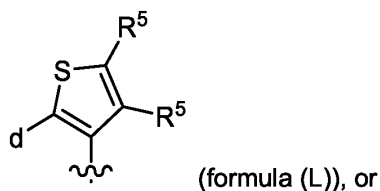
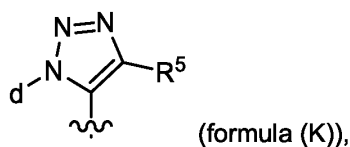
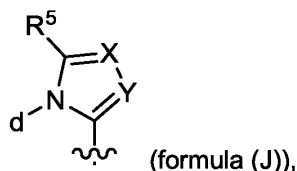
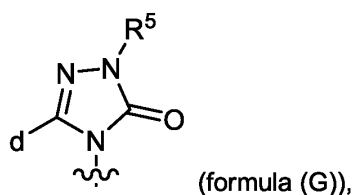
R⁶ is H or C₁-C₆ alkyl;



(formula (Z)) represents formula (E), (G), (J), (K), (L) or (M)



(formula (E)),



wherein

each d represents the point of attachment to the bridgehead carbon bonded to T;
in formulae (E) both of X and Y are CR⁵, or one of X and Y is CR⁵ and the other is N;

in formula (J), X and Y are both N;

each R⁵ is independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, halogen, haloC₁-C₆ alkyl, cyano, hydroxy, hydroxy C₁-C₆ alkyl, amino, mono- or di(C₁-C₆ alkyl) amino, C₃-C₆ cycloalkyl, haloC₃-C₆ cycloalkyl, phenyl or 5-6 membered heteroaryl, wherein each alkyl and cycloalkyl is optionally substituted with 1-3 of hydroxy, C₁-C₃ alkyl, C₁-C₃ alkoxy, cyano, amino, or mono- or di(C₁-C₃) alkyl amino, and each 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;

R³⁰ represents

-NR⁷NR⁸ or R³¹,

R³¹ represents

- (i) 5-7 membered heteroaryl, or
- (ii) a 3-8 membered monocyclic heterocyclyl group connected to the tricyclic ring system via a carbon atom, wherein the heterocyclyl group is saturated or unsaturated and optionally fused to an aromatic or non-aromatic ring containing 3-6 ring members of which 1 or 2 are optionally nitrogen, oxygen or sulfur atoms and the remainder carbons, or with a carbon atom from the monocyclic heterocyclyl group and additional carbon or nitrogen atoms, forms a spirocyclic ring system having up to 10 total ring members, wherein the ring members are carbons or nitrogens, and wherein each heteroaryl and heterocyclyl group within R³¹ is optionally substituted, on an aromatic or non-aromatic portion, with 1-4 R³⁹ groups, wherein each R³⁹ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, hydroxy, oxo, halogen, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, amino, mono- or di-(C₁-C₆ alkyl) amino, or phenyl, phenyl(C₁-C₃ alkanoyl), 5-7 membered heterocyclyl, or 5-6 membered heteroaryl where each phenyl, 5-7 membered heterocyclyl and 5-6 membered heteroaryl is optionally substituted with C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, hydroxy, cyano, amino, or mono- or di(C₁-C₃ alkyl)amino;

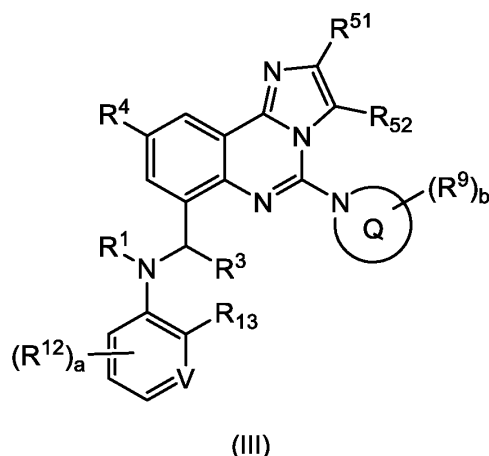
R⁷ represents H or C₁-C₃ alkyl;

R⁸ represent H, C₁-C₆ alkyl optionally substituted with a 5-8 membered heterocyclyl, C₃-C₆ cycloalkyl or C₃-C₆ cycloalkyl(C₁-C₃ alkyl); or

R⁷ and R⁸ together with the nitrogen to which they are attached form ring Q, wherein ring Q is a 3-8 membered monocyclic heterocyclyl group containing one or two ring nitrogens, wherein the heterocyclyl group is optionally fused to an aromatic or non-aromatic ring containing 3-6 ring members of which 1 or 2 are optionally nitrogen, oxygen or sulfur atoms and the remainder carbons, or with a carbon atom from the monocyclic heterocyclyl group and additional carbon or nitrogen atoms, forms a spirocyclic ring system having up to 10 total ring members, wherein the ring members are carbons or nitrogens, and wherein each ring Q is optionally substituted, on an aromatic or non-aromatic portion, with 1-4 R⁹ groups, wherein each R⁹ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, hydroxy, oxo, halogen, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, amino, mono- or di-(C₁-C₆ alkyl) amino, or phenyl, phenyl(C₁-C₃ alkanoyl), 5-7 membered heterocyclyl, or 5-6 membered heteroaryl where each phenyl, 5-7 membered heterocyclyl and 5-6 membered

heteroaryl is optionally substituted with C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, hydroxy, cyano, amino, or mono- or di(C₁-C₃ alkyl)amino.

2. A compound according to claim 1 which has formula (III):



or a pharmaceutically acceptable salt or deuterated form thereof, wherein:

a is 0, 1, 2 or 3;

V is CR¹⁴ or N;

each R¹² is independently C₁-C₄ alkyl, -OR^A, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, -C(O)N(R^A)₂, cyano, or halogen;

R¹³ is (i) cyano, (ii) tetrazolyl, (iii) -C(O)OR^A where R^A is H, C₁-C₆ alkyl, or C₃-C₆ cycloalkyl, or (iv) -C(O)N(R^B)₂ where R^B is H, -OH, C₁-C₆ alkyl, C₁-C₆ alkoxy or C₃-C₆ cycloalkyl;

R¹⁴ is hydrogen, cyano, halogen, hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkyl, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, or -C(O)N(R^B)₂;

Q represents a 4-8 membered saturated or unsaturated monocyclic, bicyclic or polycyclic heterocyclyl group having 0, 1 or 2 additional ring heteroatoms selected from oxygen and nitrogen;

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

each R⁹ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, hydroxy, oxo, halogen, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, amino, mono- or di-(C₁-C₆ alkyl) amino, or phenyl, phenyl(C₁-C₃ alkanoyl), 5-7 membered heterocyclyl, or 5-6 membered heteroaryl where each phenyl, 5-7 membered heterocyclyl and 5-6 membered heteroaryl is optionally substituted with C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, hydroxy, cyano, amino, or mono- or di(C₁-C₃ alkyl)amino; and

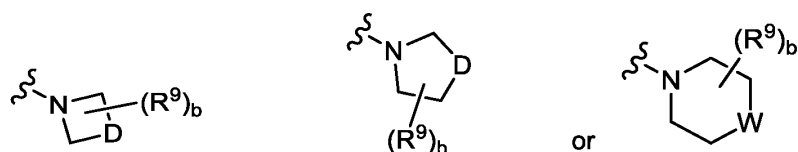
R⁵¹ and R⁵² independently represent hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, halogen, haloC₁-C₆ alkyl, cyano, hydroxy, hydroxy C₁-C₆ alkyl, amino, mono- or di(C₁-C₆ alkyl) amino, C₃-C₆ cycloalkyl, haloC₃-C₆ cycloalkyl, phenyl or 5-6 membered heteroaryl, wherein each alkyl and cycloalkyl is optionally substituted with 1-3 of hydroxy, C₁-C₃ alkyl, C₁-C₃ alkoxy, cyano, amino, or mono- or di(C₁-C₃) alkyl amino, and each 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.

3. A compound according to claim 2, wherein R¹ is H or CH₃.
4. A compound according to claim 2 or claim 3, wherein R³ is C₁-C₃ alkyl, wherein the alkyl group is unsubstituted, substituted with 1-5 halo groups, or perfluorinated.
5. A compound according to claim 2 or claim 3, wherein R³ is methyl.
6. A compound according to any one of claims 2-5, wherein R⁴ is hydrogen.
7. A compound according to any one of claims 2-5, wherein R⁴ is methyl.
8. A compound according to any one of claims 2-5, wherein R⁴ is fluoro.
9. A compound according to any one of claims 2-5, wherein R⁴ is chloro.
10. A compound according to any one of claims 2-5, wherein R⁴ is trifluoromethyl.
11. A compound according to any one of claims 2-5, wherein R⁴ is difluoromethyl.
12. A compound according to any one of claims 2-5, wherein R⁴ is fluoromethyl.
13. A compound according to any one of claims 2-5, wherein R⁴ is bromo.
14. A compound according to any one of claims 2-13 wherein V is CR¹².

15. A compound according to any one of claims 2-13 wherein V is N.
16. A compound according to any one of claims 2-13 wherein V is CH, a is 1, and R¹² is hydrogen or halogen.
17. A compound according to any one of claims 2-13 wherein V is CH, a is 1, and R¹² is hydrogen or chloro, bromo or fluoro.
18. A compound according to any one of claims 2-13 wherein V is CH, a is 1, and R¹² is hydrogen.
19. A compound according to any one of claims 2-13 wherein V is CH, a is 1, and R¹² is chloro.
20. A compound according to any one of claims 2-13 wherein V is CH, a is 1, and R¹² is bromo.
21. A compound according to any one of claims 2-13 wherein V is CH, a is 1, and R¹² is fluoro.
22. A compound according to any one of claims 2-13 wherein V is CH, a is 1, and R¹² is methyl.
23. A compound according to any one of claims 2-13 wherein V is N, a is 1, and R¹² is hydrogen or halogen.
24. A compound according to any one of claims 2-13 wherein V is N, a is 1, and R¹² is hydrogen or chloro, bromo or fluoro.
25. A compound according to any one of claims 2-13 wherein V is N, a is 1, and R¹² is hydrogen.
26. A compound according to any one of claims 2-13 wherein V is N, a is 1, and R¹² is chloro.

27. A compound according to any one of claims 2-13 wherein V is N, a is 1, and R¹² is bromo.
28. A compound according to any one of claims 2-13 wherein V is N, a is 1, and R¹² is methyl.
29. A compound according to any one of claims 2-13 wherein V is N, a is 1, and R¹² is fluoro.
30. A compound according to any of claims 2-29, wherein R⁵¹ and R⁵² independently represent hydrogen, C₁-C₃ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halogen, cyclopropyl, haloC₃-C₆ cycloalkyl or halo(C₁-C₆)alkyl.
31. A compound according to any of claims 2-29, wherein one of R⁵¹ and R⁵² is hydrogen and the other is methyl, ethyl, C₂ alkenyl, C₂ alkynyl, cyano, halogen, cyclopropyl, haloC₃-C₆ cycloalkyl or halo(C₁-C₆)alkyl.
32. A compound according to any of claims 2-29, wherein R⁵¹ is hydrogen and R⁵² is methyl, ethyl, C₂ alkenyl, C₂ alkynyl, cyano, halogen, cyclopropyl, haloC₃-C₆ cycloalkyl or halo(C₁-C₆)alkyl.
33. A compound according to any of claims 2-29, wherein R⁵¹ is hydrogen and R⁵² is methyl, ethyl, C₂ alkenyl, C₂ alkynyl, cyano, halogen, cyclopropyl, difluoromethyl, trifluoromethyl, trifluoroethyl, pentafluoroethyl, tetrafluorocyclopropyl or perfluorocyclopropyl.
34. A compound according to any of claims 2-29, wherein R⁵² is hydrogen and R⁵¹ is methyl, ethyl, C₂ alkenyl, C₂ alkynyl, cyano, halogen, cyclopropyl, haloC₃-C₆ cycloalkyl or halo(C₁-C₆)alkyl.
35. A compound according to any of claims 2-29, wherein R⁵² is hydrogen and R⁵¹ is methyl, ethyl, C₂ alkenyl, C₂ alkynyl, cyano, halogen, cyclopropyl, difluoromethyl, trifluoromethyl, trifluoroethyl, pentafluoroethyl, tetrafluorocyclopropyl or perfluorocyclopropyl.

36. A compound according to any one of claims 2-35 wherein Q represents a group of the formula



wherein

each b is 0, 1 or 2;

D represents $C(R^{29})_2$,

W represents O, NR^{19} or $C(R^{29})_2$, and

R^{19} is hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, or amino- or mono- or di- $(C_1$ - C_6 alkyl) amino(C_1 - C_6 alkyl); and

each R^{29} is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, cyano, hydroxy, oxo, halogen, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, amino, mono- or di- $(C_1$ - C_6 alkyl) amino.

37. A compound according to claim 36 wherein W is oxygen, b is 0 or 1, and R^9 is methyl or cyano.

38. A compound according to any one of claims 36-37 wherein W is oxygen and b is 0.

39. A compound according to claim 36 wherein D and W are $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, C_1 - C_2 alkyl, C_1 - C_2 alkoxy, cyclopropyl, cyano, hydroxy, halogen, halo C_1 - C_2 alkyl, hydroxy C_1 - C_2 alkyl, amino, mono- or di- $(C_1$ - C_2 alkyl) amino.

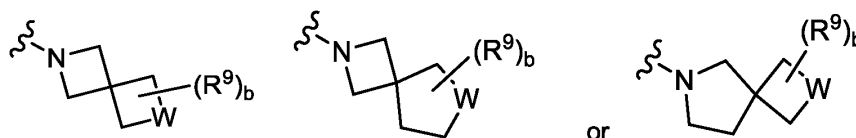
40. A compound according to claim 36 wherein D and W are $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, methyl, methoxy, cyano, hydroxy, chloro, fluoro, amino, methylamino or dimethylamino.

41. A compound according to claim 36 wherein D and W are $C(R^{29})_2$, b is 0, and each R^{29} is independently chloro or fluoro.

42. A compound according to claim 36 wherein D and W are $C(R^{29})_2$, b is 0, and each R^{29} is fluoro.

43. A compound according to claim 36 wherein D and W are $C(R^{29})_2$, b is 0, and each R^{29} is hydrogen.

44. A compound according to any one of claims 2-35 wherein Q represents a group of the formula



wherein

each b is 0, 1 or 2; and

W represents O, NR^{19} or $C(R^{29})_2$, wherein

R^{19} is hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, or amino- or mono- or di- $(C_1$ - C_6 alkyl) amino(C_1 - C_6 alkyl); and

each R^{29} is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, cyano, hydroxy, oxo, halogen, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, amino, mono- or di- $(C_1$ - C_6 alkyl) amino.

45. A compound according to claim 44 wherein W is oxygen, b is 0 or 1, and R^9 is methyl or cyano.

46. A compound according to claim 44 wherein W is oxygen and b is 0.

47. A compound according to claim 44 wherein W is $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, C_1 - C_2 alkyl, C_1 - C_2 alkoxy, cyclopropyl, cyano, hydroxy, halogen, halo C_1 - C_2 alkyl, hydroxy C_1 - C_2 alkyl, amino, mono- or di- $(C_1$ - C_2 alkyl) amino.

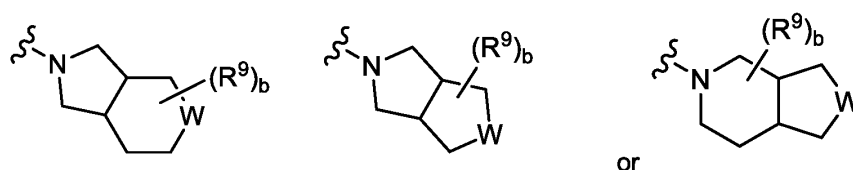
48. A compound according to claim 44 wherein W is $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, methyl, methoxy, cyano, hydroxy, chloro, fluoro, amino, methylamino or dimethylamino.

49. A compound according to claim 44 wherein W is $C(R^{29})_2$, b is 0, and each R^{29} is independently chloro or fluoro.

50. A compound according to claim 44 wherein W is $C(R^{29})_2$, b is 0, and each R^{29} is fluoro.

51. A compound according to claim 44 wherein W is $C(R^{29})_2$, b is 0, and each R^{29} is hydrogen.

52. A compound according to any one of claims 2-35 wherein Q represents a group of the formula



wherein

each b is 0, 1 or 2; and

W represents O, NR^{19} or $C(R^{29})_2$, wherein

R^{19} is hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, or amino- or mono- or di- $(C_1$ - C_6 alkyl) amino(C_1 - C_6 alkyl); and

each R^{29} is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, cyano, hydroxy, oxo, halogen, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, amino, mono- or di- $(C_1$ - C_6 alkyl) amino.

53. A compound according to claim 52 wherein W is oxygen, b is 0 or 1, and R^9 is methyl, chloro, fluoro or cyano.

54. A compound according to claim 52 wherein W is oxygen and b is 0.

55. A compound according to claim 52 wherein W is $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, C_1 - C_2 alkyl, C_1 - C_2 alkoxy, cyclopropyl, cyano, hydroxy, halogen, halo C_1 - C_2 alkyl, hydroxy C_1 - C_2 alkyl, amino, mono- or di- $(C_1$ - C_2 alkyl) amino.

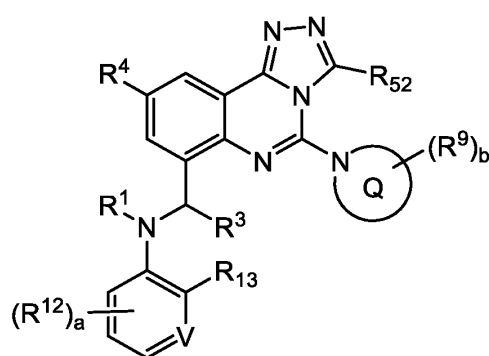
56. A compound according to claim 52 wherein W is $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, methyl, methoxy, cyano, hydroxy, chloro, fluoro, amino, methylamino or dimethylamino.

57. A compound according to claim 52 wherein W is $C(R^{29})_2$, b is 0, and each R^{29} is independently chloro or fluoro.

58. A compound according to claim 52 wherein W is $C(R^{29})_2$, b is 0, and each R^{29} is fluoro.

59. A compound according to claim 52 wherein W is $C(R^{29})_2$, b is 0, and each R^{29} is hydrogen.

60. A compound according to claim 1 which has formula (IV):



(IV)

or a pharmaceutically acceptable salt or deuterated form thereof, wherein:

a is 0, 1, 2 or 3;

V is CR^{14} or N;

each R^{12} 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, or halogen;

R^{13} is (i) cyano, (ii) tetrazolyl, (iii) $-C(O)OR^A$ where R^A is H, C_1 - C_6 alkyl, or C_3 - C_6 cycloalkyl, or (iv) $-C(O)N(R^B)_2$ where R^B is H, $-OH$, C_1 - C_6 alkyl, C_1 - C_6 alkoxy or C_3 - C_6 cycloalkyl;

R^{14} is hydrogen, cyano, halogen, hydroxy, C_1 - C_4 alkoxy, C_1 - C_4 alkyl, $-C(O)OR^A$, $(C_1$ - C_3 alkyl)- OR^A , or $-C(O)N(R^B)_2$;

Q represents a 4-8 membered saturated or unsaturated monocyclic, bicyclic or polycyclic heterocyclyl group having 0, 1 or 2 additional ring heteroatoms selected from oxygen and nitrogen;

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

each R^9 is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, cyano, hydroxy, oxo, halogen, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, amino, mono- or di- $(C_1$ - C_6 alkyl)

amino, or phenyl, phenyl(C₁-C₃ alkanoyl), 5-7 membered heterocyclyl, or 5-6 membered heteroaryl where each phenyl, 5-7 membered heterocyclyl and 5-6 membered heteroaryl is optionally substituted with C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, hydroxy, cyano, amino, or mono- or di(C₁-C₃ alkyl)amino; and

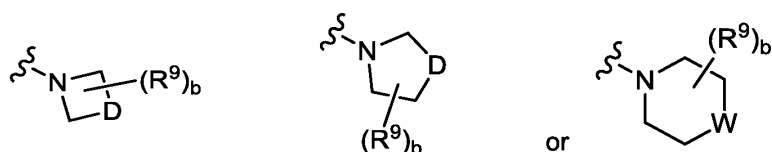
R⁵² represents hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, halogen, cyano, hydroxy, hydroxy C₁-C₆ alkyl, amino, mono- or di(C₁-C₆ alkyl) amino, C₃-C₆ cycloalkyl, phenyl or 5-6 membered heteroaryl, wherein each alkyl, cycloalkyl, phenyl and heteroaryl is optionally substituted with 1-3 of halogen, hydroxy, C₁-C₃ alkyl, C₁-C₃ alkoxy, cyano, amino, or mono- or di(C₁-C₃) alkyl amino.

61. A compound according to claim 60, wherein R¹ is H or CH₃.
62. A compound according to claim 60 or claim 61, wherein R³ is C₁-C₃ alkyl, wherein the alkyl group is unsubstituted, substituted with 1-5 halo groups, or perfluorinated.
63. A compound according to claim 60 or claim 61, wherein R³ is methyl.
64. A compound according to any one of claims 60-63, wherein R⁴ is hydrogen.
65. A compound according to any one of claims 60-63, wherein R⁴ is methyl.
66. A compound according to any one of claims 60-63, wherein R⁴ is ethyl.
67. A compound according to any one of claims 60-63, wherein R⁴ is cyclopropyl.
68. A compound according to any one of claims 60-63, wherein R⁴ is methoxy.
69. A compound according to any one of claims 60-63, wherein R⁴ is fluoro.
70. A compound according to any one of claims 60-63, wherein R⁴ is chloro.
71. A compound according to any one of claims 60-63, wherein R⁴ is trifluoromethyl.
72. A compound according to any one of claims 60-63, wherein R⁴ is difluoromethyl.

73. A compound according to any one of claims 60-63, wherein R⁴ is fluoromethyl.
74. A compound according to any one of claims 60-63, wherein R⁴ is bromo.
75. A compound according to any one of claims 60-74 wherein V is CR¹².
76. A compound according to any one of claims 60-74 wherein V is N.
77. A compound according to any one of claims 60-74 wherein V is CH, a is 1, and R¹² is hydrogen or halogen.
78. A compound according to any one of claims 60-74 wherein V is CH, a is 1, and R¹² is hydrogen or chloro, bromo or fluoro.
79. A compound according to any one of claims 60-74 wherein V is CH, a is 1, and R¹² is hydrogen.
80. A compound according to any one of claims 60-74 wherein V is CH, a is 1, and R¹² is methyl.
81. A compound according to any one of claims 60-74 wherein V is CH, a is 1, and R¹² is chloro.
82. A compound according to any one of claims 60-74 wherein V is CH, a is 1, and R¹² is bromo.
83. A compound according to any one of claims 60-74 wherein V is CH, a is 1, and R¹² is fluoro.
84. A compound according to any one of claims 60-74 wherein V is N, a is 1, and R¹² is hydrogen or halogen.
85. A compound according to any one of claims 60-74 wherein V is N, a is 1, and R¹² is hydrogen or chloro, bromo or fluoro.

86. A compound according to any one of claims 60-74 wherein V is N, a is 1, and R¹² is hydrogen.
87. A compound according to any one of claims 60-74 wherein V is N, a is 1, and R¹² is chloro.
88. A compound according to any one of claims 60-74 wherein V is N, a is 1, and R¹² is bromo.
89. A compound according to any one of claims 60-74 wherein V is N, a is 1, and R¹² is methyl.
90. A compound according to any one of claims 60-74 wherein V is N, a is 1, and R¹² is fluoro.
91. A compound according to any of claims 60-90, wherein R⁵² represents hydrogen, C₁-C₃ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halogen, cyclopropyl or halo(C₁-C₆)alkyl.
92. A compound according to any of claims 60-90, wherein R⁵² is hydrogen, methyl, ethyl, C₂ alkenyl, C₂ alkynyl, cyano, halogen, cyclopropyl or halo(C₁-C₆)alkyl.
93. A compound according to any of claims 60-90, wherein R⁵² is methyl, ethyl, C₂ alkenyl, C₂ alkynyl, cyano, halogen, cyclopropyl or halo(C₁-C₆)alkyl.
94. A compound according to any of claims 60-90, wherein R⁵² is methyl, ethyl, cyano, halogen, cyclopropyl, fluoromethyl, difluoromethyl or trifluoromethyl.
95. A compound according to any of claims 60-90, wherein R⁵² is C₂ alkenyl or C₂ alkynyl.
96. A compound according to any of claims 60-90, wherein R⁵² is hydrogen.
97. A compound according to any of claims 60-90, wherein R⁵² is fluoromethyl, difluoromethyl or trifluoromethyl.

98. A compound according to any one of claims 60-97 wherein Q represents a group of the formula



wherein

each b is 0, 1 or 2; and

D represents $C(R^{29})_2$,

W represents O, NR^{19} or $C(R^{29})_2$, and

R^{19} is hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, or amino- or mono- or di- $(C_1$ - C_6 alkyl) amino(C_1 - C_6 alkyl); and

each R^{29} is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, cyano, hydroxy, oxo, halogen, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, amino, mono- or di- $(C_1$ - C_6 alkyl) amino.

99. A compound according to claim 98 wherein W is oxygen, b is 0 or 1, and R^9 is methyl or cyano.

100. A compound according claim 98 wherein W is oxygen and b is 0.

101. A compound according to claim 98 wherein D and W are $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, C_1 - C_2 alkyl, C_1 - C_2 alkoxy, cyclopropyl, cyano, hydroxy, halogen, halo C_1 - C_2 alkyl, hydroxy C_1 - C_2 alkyl, amino, mono- or di- $(C_1$ - C_2 alkyl) amino.

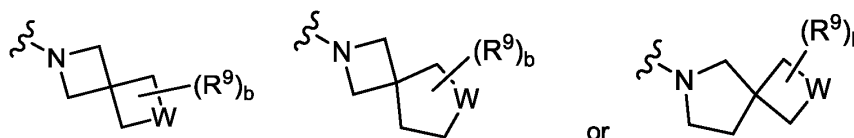
102. A compound according to claim 98 wherein D and W are $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, methyl, methoxy, cyano, hydroxy, chloro, fluoro, amino, methylamino or dimethylamino.

103. A compound according to claim 98 wherein D and W are $C(R^{29})_2$, b is 0, and each R^{29} is independently chloro or fluoro.

104. A compound according to claim 98 wherein D and W are $C(R^{29})_2$, b is 0, and each R^{29} is fluoro.

105. A compound according to claim 98 wherein D and W are $C(R^{29})_2$, b is 0, and each R^{29} is hydrogen.

106. A compound according to any one of claims 60-97 wherein Q represents a group of the formula



wherein

each b is 0, 1 or 2; and

W represents O, NR^{19} or $C(R^{29})_2$, wherein

R^{19} is hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, or amino- or mono- or di- $(C_1$ - C_6 alkyl) amino(C_1 - C_6 alkyl); and

each R^{29} is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, cyano, hydroxy, oxo, halogen, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, amino, mono- or di- $(C_1$ - C_6 alkyl) amino.

107. A compound according to claim 106 wherein W is oxygen, b is 0 or 1, and R^9 is methyl or cyano.

108. A compound according to claim 106 wherein W is oxygen and b is 0.

109. A compound according to claim 106 wherein W is $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, C_1 - C_2 alkyl, C_1 - C_2 alkoxy, cyclopropyl, cyano, hydroxy, halogen, halo C_1 - C_2 alkyl, hydroxy C_1 - C_2 alkyl, amino, mono- or di- $(C_1$ - C_2 alkyl) amino.

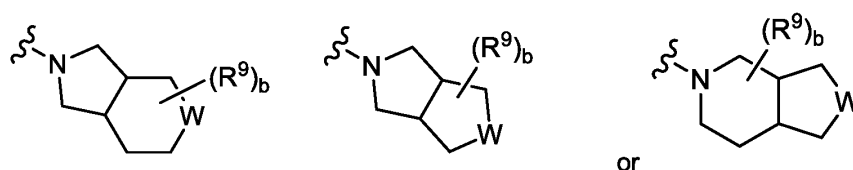
110. A compound according to claim 106 wherein W is $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, methyl, methoxy, cyano, hydroxy, chloro, fluoro, amino, methylamino or dimethylamino.

111. A compound according to claim 106 wherein W is $C(R^{29})_2$, b is 0, and each R^{29} is independently chloro or fluoro.

112. A compound according to claim 106 wherein W is $C(R^{29})_2$, b is 0, and each R^{29} is fluoro.

113. A compound according to claim 106 wherein W is $C(R^{29})_2$, b is 0, and each R^{29} is hydrogen.

114. A compound according to any one of claims 60-97 wherein Q represents a group of the formula



wherein

each b is 0, 1 or 2; and

W represents O, NR^{19} or $C(R^{29})_2$, wherein

R^{19} is hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, or amino- or mono- or di- $(C_1$ - C_6 alkyl) amino(C_1 - C_6 alkyl); and

each R^{29} is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, cyano, hydroxy, oxo, halogen, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, amino, mono- or di- $(C_1$ - C_6 alkyl) amino.

115. A compound according to claim 114 wherein W is oxygen, b is 0 or 1, and R^9 is methyl, chloro, fluoro or cyano.

116. A compound according to claim 114 wherein W is oxygen and b is 0.

117. A compound according to claim 114 wherein W is $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, C_1 - C_2 alkyl, C_1 - C_2 alkoxy, cyclopropyl, cyano, hydroxy, halogen, halo C_1 - C_2 alkyl, hydroxy C_1 - C_2 alkyl, amino, mono- or di- $(C_1$ - C_2 alkyl) amino.

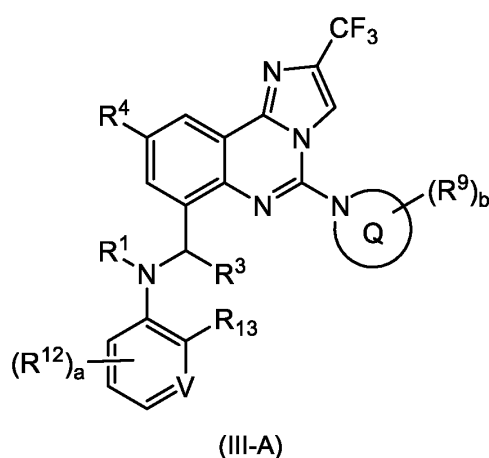
118. A compound according to claim 114 wherein W is $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, methyl, methoxy, cyano, hydroxy, chloro, fluoro, amino, methylamino or dimethylamino.

119. A compound according to claim 114 wherein W is $C(R^{29})_2$, b is 0, and each R^{29} is independently chloro or fluoro.

120. A compound according to claim 114 wherein W is $C(R^{29})_2$, b is 0, and each R^{29} is fluoro.

121. A compound according to claim 114 wherein W is $C(R^{29})_2$, b is 0, and each R^{29} is hydrogen.

122. A compound according to claim 1 which has formula (III-A):



or a pharmaceutically acceptable salt or deuterated form thereof, wherein:

a is 0, 1, 2 or 3;

V is CR^{14} or N;

each R^{12} is independently C_1 - C_4 alkyl, $-OR^A$, $-C(O)OR^A$, $(C_1$ - C_3 alkyl)- OR^A , $-C(O)N(R^A)_2$, cyano, or halogen;

R^{13} is (i) cyano, (ii) tetrazolyl, (iii) $-C(O)OR^A$ where R^A is H, C_1 - C_6 alkyl, or C_3 - C_6 cycloalkyl, or (iv) $-C(O)N(R^B)_2$ where R^B is H, $-OH$, C_1 - C_6 alkyl, C_1 - C_6 alkoxy or C_3 - C_6 cycloalkyl;

R^{14} is hydrogen, cyano, halogen, hydroxy, C_1 - C_4 alkoxy, C_1 - C_4 alkyl, $-C(O)OR^A$, $(C_1$ - C_3 alkyl)- OR^A , or $-C(O)N(R^B)_2$;

Q represents a 4-8 membered saturated or unsaturated monocyclic, bicyclic or polycyclic heterocyclyl group having 0, 1 or 2 additional ring heteroatoms selected from oxygen and nitrogen;

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

each R⁹ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, hydroxy, oxo, halogen, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, amino, mono- or di-(C₁-C₆ alkyl) amino, or phenyl, phenyl(C₁-C₃ alkanoyl), 5-7 membered heterocyclyl, or 5-6 membered heteroaryl where each phenyl, 5-7 membered heterocyclyl and 5-6 membered heteroaryl is optionally substituted with C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, hydroxy, cyano, amino, or mono- or di(C₁-C₃ alkyl)amino.

123. A compound according to claim 122, wherein R¹ is H or CH₃.
124. A compound according to claim 122 or claim 123, wherein R³ is C₁-C₃ alkyl, wherein the alkyl group is unsubstituted, substituted with 1-5 halo groups, or perfluorinated.
125. A compound according to claim 122 or claim 123, wherein R³ is methyl.
126. A compound according to any one of claims 122-125, wherein R⁴ is hydrogen.
127. A compound according to any one of claims 122-125, wherein R⁴ is methyl.
128. A compound according to any one of claims 122-125, wherein R⁴ is fluoro.
129. A compound according to any one of claims 122-125, wherein R⁴ is chloro.
130. A compound according to any one of claims 122-125, wherein R⁴ is fluoromethyl.
131. A compound according to any one of claims 122-125, wherein R⁴ is difluoromethyl.
132. A compound according to any one of claims 122-125, wherein R⁴ is trifluoromethyl.
133. A compound according to any one of claims 122-125, wherein R⁴ is bromo.
134. A compound according to any one of claims 122-133 wherein V is CR¹².
135. A compound according to any one of claims 122-133 wherein V is N.

136. A compound according to any one of claims 122-133 wherein V is CH, a is 1, and R¹² is hydrogen or halogen.

137. A compound according to any one of claims 122-133 wherein V is CH, a is 1, and R¹² is hydrogen or chloro, bromo or fluoro.

138. A compound according to any one of claims 122-133 wherein V is CH, a is 1, and R¹² is hydrogen.

139. A compound according to any one of claims 122-133 wherein V is CH, a is 1, and R¹² is methyl.

140. A compound according to any one of claims 122-133 wherein V is CH, a is 1, and R¹² is chloro.

141. A compound according to any one of claims 122-133 wherein V is CH, a is 1, and R¹² is bromo.

142. A compound according to any one of claims 122-133 wherein V is CH, a is 1, and R¹² is fluoro.

143. A compound according to any one of claims 122-133 wherein V is N, a is 1, and R¹² is hydrogen or halogen.

144. A compound according to any one of claims 122-133 wherein V is N, a is 1, and R¹² is hydrogen or chloro, bromo or fluoro.

145. A compound according to any one of claims 122-133 wherein V is N, a is 1, and R¹² is hydrogen.

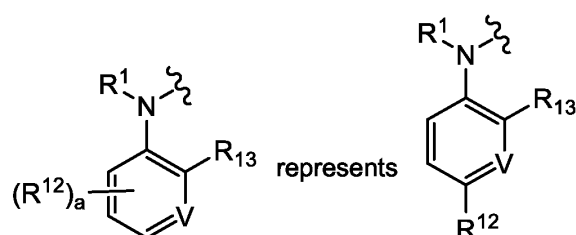
146. A compound according to any one of claims 122-133 wherein V is N, a is 1, and R¹² is chloro.

147. A compound according to any one of claims 122-133 wherein V is N, a is 1, and R¹² is bromo.

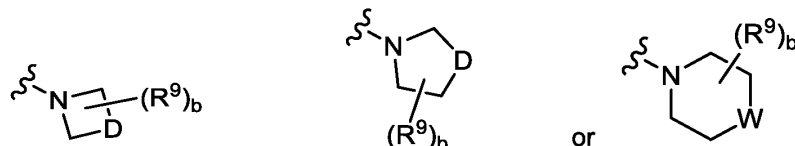
148. A compound according to any one of claims 122-133 wherein V is N, a is 1, and R¹² is methyl.

149. A compound according to any one of claims 122-133 wherein V is N, a is 1, and R¹² is fluoro.

150. A compound according to any one of claims 122-149, wherein the group



151. A compound according to any one of claims 122-150 wherein Q represents a group of the formula



wherein

each b is 0, 1 or 2;

D represents C(R²⁹)₂,

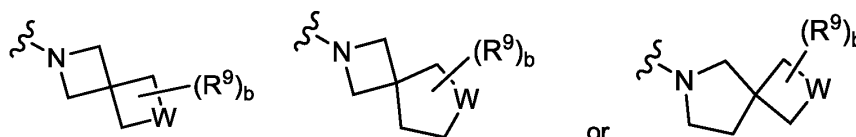
W represents O, NR¹⁹ or C(R²⁹)₂, and

R¹⁹ is hydrogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, or amino- or mono- or di-(C₁-C₆ alkyl) amino(C₁-C₆ alkyl); and

each R²⁹ is independently hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, hydroxy, oxo, halogen, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, amino, mono- or di-(C₁-C₆ alkyl) amino.

152. A compound according to claim 151 wherein W is oxygen, b is 0 or 1, and R⁹ is methyl or cyano.

153. A compound according to claim 151 wherein W is oxygen and b is 0.
154. A compound according to claim 151 wherein D and W are $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, C_1 - C_2 alkyl, C_1 - C_2 alkoxy, cyclopropyl, cyano, hydroxy, halogen, halo C_1 - C_2 alkyl, hydroxy C_1 - C_2 alkyl, amino, mono- or di- $(C_1$ - C_2 alkyl) amino.
155. A compound according to claim 151 wherein D and W are $C(R^{29})_2$, b is 0, and each R^{29} is independently hydrogen, methyl, methoxy, cyano, hydroxy, chloro, fluoro, amino, methylamino or dimethylamino.
156. A compound according to claim 151 wherein D and W are $C(R^{29})_2$, b is 0, and each R^{29} is independently chloro or fluoro.
157. A compound according to claim 151 wherein D and W are $C(R^{29})_2$, b is 0, and each R^{29} is fluoro.
158. A compound according to claim 151 wherein D and W are $C(R^{29})_2$, b is 0, and each R^{29} is hydrogen.
159. A compound according to any one of claims 122-150 wherein Q represents a group of the formula



wherein

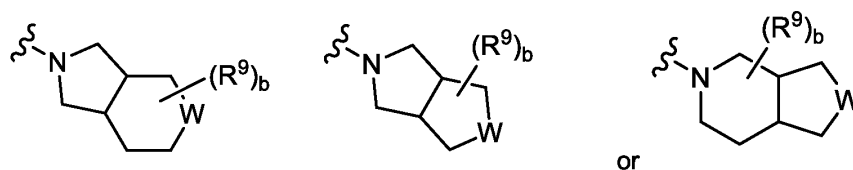
each b is 0, 1 or 2; and

W represents O, NR^{19} or $C(R^{29})_2$, wherein

R^{19} is hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, or amino- or mono- or di- $(C_1$ - C_6 alkyl) amino(C_1 - C_6 alkyl); and

each R^{29} is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, cyano, hydroxy, oxo, halogen, halo C_1 - C_3 alkyl, hydroxy C_1 - C_6 alkyl, amino, mono- or di- $(C_1$ - C_6 alkyl) amino.

160. A compound according to claim 159 wherein W is oxygen, b is 0 or 1, and R⁹ is methyl or cyano.
161. A compound according to claim 159 wherein W is oxygen and b is 0.
162. A compound according to claim 159 wherein W is C(R²⁹)₂, b is 0, and each R²⁹ is independently hydrogen, C₁-C₂ alkyl, C₁-C₂ alkoxy, cyclopropyl, cyano, hydroxy, halogen, halo C₁-C₂ alkyl, hydroxy C₁-C₂ alkyl, amino, mono- or di-(C₁-C₂ alkyl) amino.
163. A compound according to claim 159 wherein W is C(R²⁹)₂, b is 0, and each R²⁹ is independently hydrogen, methyl, methoxy, cyano, hydroxy, chloro, fluoro, amino, methylamino or dimethylamino.
164. A compound according to claim 159 wherein W is C(R²⁹)₂, b is 0, and each R²⁹ is independently chloro or fluoro.
165. A compound according to claim 159 wherein W is C(R²⁹)₂, b is 0, and each R²⁹ is fluoro.
166. A compound according to any claim 159 wherein W is C(R²⁹)₂, b is 0, and each R²⁹ is hydrogen.
167. A compound according to any one of claims 122-150 wherein Q represents a group of the formula



wherein

each b is 0, 1 or 2; and

W represents O, NR¹⁹ or C(R²⁹)₂, wherein

R¹⁹ is hydrogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, or amino- or mono- or di-(C₁-C₆ alkyl) amino(C₁-C₆ alkyl); and

each R²⁹ is independently hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, hydroxy, oxo, halogen, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, amino, mono- or di-(C₁-C₆ alkyl) amino.

168. A compound according to claim 167 wherein W is oxygen, b is 0 or 1, and R⁹ is methyl, chloro, fluoro or cyano.

169. A compound according to claim 167 wherein W is oxygen and b is 0.

170. A compound according to claim 167 wherein W is C(R²⁹)₂, b is 0, and each R²⁹ is independently hydrogen, C₁-C₂ alkyl, C₁-C₂ alkoxy, cyclopropyl, cyano, hydroxy, halogen, halo C₁-C₂ alkyl, hydroxy C₁-C₂ alkyl, amino, mono- or di-(C₁-C₂ alkyl) amino.

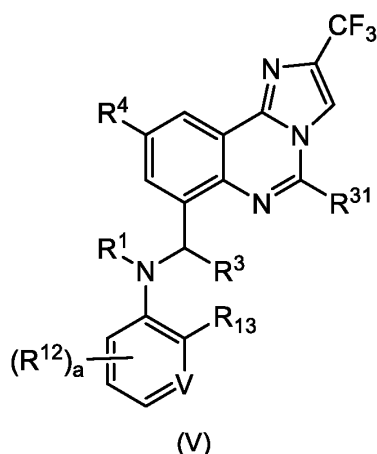
171. A compound according to claim 167 wherein W is C(R²⁹)₂, b is 0, and each R²⁹ is independently hydrogen, methyl, methoxy, cyano, hydroxy, chloro, fluoro, amino, methylamino or dimethylamino.

172. A compound according to claim 167 wherein W is C(R²⁹)₂, b is 0, and each R²⁹ is independently chloro or fluoro.

173. A compound according to claim 167 wherein W is C(R²⁹)₂, b is 0, and each R²⁹ is fluoro.

174. A compound according to claim 167 wherein W is C(R²⁹)₂, b is 0, and each R²⁹ is hydrogen.

175. A compound according to claim 1 which has formula (V):



or a pharmaceutically acceptable salt or deuterated form thereof, wherein:

a is 0, 1, 2 or 3;

V is CR¹⁴ or N;

each R¹² is independently C₁-C₄ alkyl, -OR^A, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, -C(O)N(R^A)₂, cyano, or halogen;

R¹³ is (i) cyano, (ii) tetrazolyl, (iii) -C(O)OR^A where R^A is H, C₁-C₆ alkyl, or C₃-C₆ cycloalkyl, or (iv) -C(O)N(R^B)₂ where R^B is H, -OH, C₁-C₆ alkyl, C₁-C₆ alkoxy or C₃-C₆ cycloalkyl;

R¹⁴ is hydrogen, cyano, halogen, hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkyl, -C(O)OR^A, (C₁-C₃ alkyl)-OR^A, or -C(O)N(R^B)₂.

176. A compound according to claim 175, wherein R¹ is H or CH₃.

177. A compound according to claim 175 or claim 176, wherein R³ is C₁-C₃ alkyl, wherein the alkyl group is unsubstituted, substituted with 1-5 halo groups, or perfluorinated.

178. A compound according to claim 175 or claim 176, wherein R³ is methyl.

179. A compound according to any one of claims 175-178, wherein R⁴ is hydrogen.

180. A compound according to any one of claims 175-178, wherein R⁴ is methyl.

181. A compound according to any one of claims 175-178, wherein R⁴ is fluoro.

182. A compound according to any one of claims 175-178, wherein R⁴ is chloro.
183. A compound according to any one of claims 175-178, wherein R⁴ is fluoromethyl.
184. A compound according to any one of claims 175-178, wherein R⁴ is difluoromethyl.
185. A compound according to any one of claims 175-178, wherein R⁴ is trifluoromethyl.
186. A compound according to any one of claims 175-178, wherein R⁴ is bromo.
187. A compound according to any one of claims 175 -186 wherein V is CR¹².
188. A compound according to any one of claims 175 -186 wherein V is N.
189. A compound according to any one of claims 175 -186 wherein V is CH, a is 1, and R¹² is hydrogen or halogen.
190. A compound according to any one of claims 175 -186 wherein V is CH, a is 1, and R¹² is hydrogen or chloro, bromo or fluoro.
191. A compound according to any one of claims 175 -186 wherein V is CH, a is 1, and R¹² is hydrogen.
192. A compound according to any one of claims 175 -186 wherein V is CH, a is 1, and R¹² is methyl.
193. A compound according to any one of claims 175 -186 wherein V is CH, a is 1, and R¹² is chloro.
194. A compound according to any one of claims 175 -186 wherein V is CH, a is 1, and R¹² is bromo.

195. A compound according to any one of claims 175 -186 wherein V is CH, a is 1, and R¹² is fluoro.

196. A compound according to any one of claims 175 -186 wherein V is N, a is 1, and R¹² is hydrogen or halogen.

197. A compound according to any one of claims 175 -186 wherein V is N, a is 1, and R¹² is hydrogen or chloro, bromo or fluoro.

198. A compound according to any one of claims 175 -186 wherein V is N, a is 1, and R¹² is hydrogen.

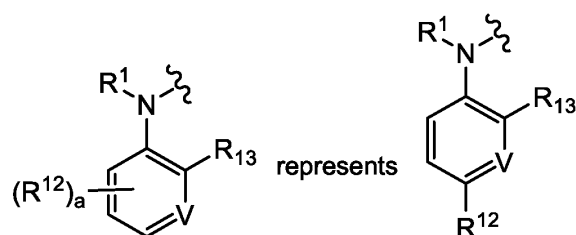
199. A compound according to any one of claims 175 -186 wherein V is N, a is 1, and R¹² is chloro.

200. A compound according to any one of claims 175 -186 wherein V is N, a is 1, and R¹² is bromo.

201. A compound according to any one of claims 175 -186 wherein V is N, a is 1, and R¹² is methyl.

202. A compound according to any one of claims 175 -186 wherein V is N, a is 1, and R¹² is fluoro.

203. A compound according to any one of claims 175-202, wherein the group



204. A compound according to any one of claims 175-203, wherein R³¹ is a 4, 5 or 6 membered heterocyclyl group which is optionally substituted with one or two R³⁹ groups

where each R³⁹ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, hydroxy, oxo, halogen, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl, amino, mono- or di-(C₁-C₆ alkyl) amino.

205. A compound according to claim 204 wherein R³¹ is tetrahydrofuranyl optionally substituted independently with one or two of R³⁹.

206. A compound according to claim 204 wherein R³¹ is tetrahydrofuranyl optionally substituted independently with one or two of methyl, cyano or trifluoromethyl.

207. A compound according to claim 204 wherein R³¹ is tetrahydropyranyl optionally substituted independently with one or two of R³⁹.

208. A compound according to claim 204 wherein R³¹ is tetrahydropyranyl optionally substituted independently with one or two of methyl, cyano or trifluoromethyl.

209. A compound according to any one of claims 175-203, wherein R³¹ is pyridyl optionally substituted with one or two R³⁹ groups where each R³⁹ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, cyano, hydroxy, oxo, halogen, halo C₁-C₃ alkyl, hydroxy C₁-C₆ alkyl,

210. The compound of claim 1, which is:

(R)-2-((1-(9-methyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethyl)amino)benzoic acid;

(R)-2-((1-(9-methyl-2-phenyl-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethyl)amino)benzoic acid;

(R)-2-((1-(9-methyl-5-(piperidin-1-yl)-2-(pyrazin-2-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethyl)amino)benzoic acid;

(R)-2-((1-(9-methyl-5-(piperidin-1-yl)-2-(thiazol-4-yl)-[1,2,4]triazolo[1,5-c]quinazolin-7-yl)ethyl)amino)benzoic acid;

2-((1-(9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid;

(R)-2-((1-(2-cyano-9-methyl-5-(piperidin-1-yl)imidazo[1,2-c]quinazolin-7-yl)ethyl)amino)benzoic acid;

(R)-2-((1-(5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-c]quinazolin-7-yl)ethyl)amino)benzoic acid;

- (*R*)-2-((1-(9-methyl-5-(piperidin-1-yl)-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;
- (*R*)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;
- (*R*)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-2,9-dimethyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;
- (*R*)-2-((1-(4-(4,4-difluoropiperidin-1-yl)-8-methylthieno[3,2-*c*]quinolin-6-yl)ethyl)amino)benzoic acid;
- (*R*)-2-((1-(4-(4,4-difluoropiperidin-1-yl)-8-methyl-[1,2,4]triazolo[4,3-*a*]quinoxalin-6-yl)ethyl)amino)benzoic acid;
- (*R*)-2-((1-(4-(4,4-difluoropiperidin-1-yl)-1,8-dimethyl-[1,2,4]triazolo[4,3-*a*]quinoxalin-6-yl)ethyl)amino)benzoic acid;
- (*R*)-2-((1-(4-(4,4-difluoropiperidin-1-yl)-8-methyl-[1,2,3]triazolo[1,5-*a*]quinoxalin-6-yl)ethyl)amino)benzoic acid;
- (*R*)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;
- (*R*)-2-((1-(5-(3,3-difluoropiperidin-1-yl)-9-methyl-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;
- (*R*)-2-((1-(9-methyl-5-(6-azaspiro[2.5]octan-6-yl)-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;
- (*R*)-2-((1-(5-(4,4-difluoro-6-azaspiro[2.5]octan-6-yl)-9-methyl-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;
- (*R*)-2-((1-(5-(4,4-dimethylpiperidin-1-yl)-9-methyl-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;
- (*R*)-2-((1-(9-methyl-5-(4-phenylpiperazin-1-yl)-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;
- (*R*)-2-((1-(5-(4-(2-cyanophenyl)piperazin-1-yl)-9-methyl-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;
- (*R*)-2-((1-(5-(4-(4-cyanophenyl)piperazin-1-yl)-9-methyl-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;
- (*R*)-2-((1-(5-(5,6-difluoroisoindolin-2-yl)-9-methyl-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;
- (*R*)-2-((1-(5-(5-fluoroisoindolin-2-yl)-9-methyl-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;
- (*R*)-2-((1-(5-(1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)-9-methyl-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

2-(((1*R*)-1-(5-(3-azabicyclo[4.1.0]heptan-3-yl)-9-methyl-[1,2,4]triazolo[4,3-
c]quinazolin-7-yl)ethyl)amino)benzoic acid;

2-(((1*R*)-1-(5-(6,6-difluoro-3-azabicyclo[3.1.1]heptan-3-yl)-9-methyl-
[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(9-methyl-5-(2-azaspiro[3.3]heptan-2-yl)-[1,2,4]triazolo[4,3-
c]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(5-(2-azabicyclo[2.2.2]octan-2-yl)-9-methyl-[1,2,4]triazolo[4,3-
c]quinazolin-7-yl)ethyl)amino)benzoic acid;

2-(((1*R*)-1-(5-(3-azabicyclo[3.1.0]hexan-3-yl)-9-methyl-[1,2,4]triazolo[4,3-
c]quinazolin-7-yl)ethyl)amino)benzoic acid;

2-(((1*R*)-1-(5-(6,6-difluoro-3-azabicyclo[3.1.0]hexan-3-yl)-9-methyl-
[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(5-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-9-methyl-[1,2,4]triazolo[4,3-
c]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(9-methyl-5-(1,1,2,2-tetrafluoro-6-azaspiro[2.5]octan-6-yl)-
[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-(9-methyl-5-((*S*)-3-(trifluoromethyl)piperidin-1-yl)-[1,2,4]triazolo[4,3-
c]quinazolin-7-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-(9-methyl-5-((*R*)-3-(trifluoromethyl)piperidin-1-yl)-[1,2,4]triazolo[4,3-
c]quinazolin-7-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-(5-((1*S*,4*S*)-5,5-difluoro-2-azabicyclo[2.2.1]heptan-2-yl)-9-methyl-
[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-(5-((1*R*,4*R*)-5,5-difluoro-2-azabicyclo[2.2.1]heptan-2-yl)-9-methyl-
[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-(5-((1*S*,4*R*)-6,6-difluoro-2-azabicyclo[2.2.1]heptan-2-yl)-9-methyl-
[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-(5-((1*R*,4*S*)-6,6-difluoro-2-azabicyclo[2.2.1]heptan-2-yl)-9-methyl-
[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

2-(((1*R*)-1-(9-methyl-5-(3,4,4-trifluoropiperidin-1-yl)-[1,2,4]triazolo[4,3-
c]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(9-methyl-5-(piperazin-1-yl)-[1,2,4]triazolo[4,3-*c*]quinazolin-7-
yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(9-methyl-5-(4-methylpiperazin-1-yl)-[1,2,4]triazolo[4,3-*c*]quinazolin-7-
yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(5-(4-methylpiperazin-1-yl)-9-vinyl-[1,2,4]triazolo[4,3-*c*]quinazolin-7-
yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(5-(4-ethylpiperazin-1-yl)-9-methyl-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(9-methyl-5-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(5-(4-cyclopropylpiperazin-1-yl)-9-methyl-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

2-(((1*R*)-1-(5-(hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)-9-methyl-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-(9-methyl-5-((1*R*,4*R*)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

2-(((*R*)-1-(9-methyl-5-((1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(5-(4-benzoylpiperazin-1-yl)-9-methyl-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(9-methyl-5-(7-methyl-2,7-diazaspiro[3.5]nonan-2-yl)-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(9-methyl-5-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(5-(isobutylamino)-9-methyl-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(5-((cyclopropylmethyl)amino)-9-methyl-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(9-methyl-5-(pyrrolidin-1-yl)-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(5-(isoindolin-2-yl)-9-methyl-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(5-(isoindolin-2-yl)-3,9-dimethyl-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

2-(((1*R*)-1-(5-(5,5-difluoro-2-azabicyclo[2.2.1]heptan-2-yl)-9-methyl-[1,2,4]triazolo[4,3-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(9-methyl-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2,9-dimethylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-3,9-dimethylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(9-methyl-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-6-chloro-3-((1-(5-(3,3-difluoroazetidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-2-((1-(5-(3,3-difluoroazetidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-6-chloro-3-((1-(5-(3,3-difluoropyrrolidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-2-((1-(5-(3,3-difluoropyrrolidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-6-chloro-3-((1-(2-(difluoromethyl)-5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-2-((1-(2-(difluoromethyl)-5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2-(fluoromethyl)-9-methylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-2-(fluoromethyl)-9-methylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

6-chloro-3-(((1*R*)-1-(9-methyl-5-(tetrahydro-1*H*-furo[3,4-*c*]pyrrol-5(3*H*)-yl)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

2-(((1*R*)-1-(9-methyl-5-(tetrahydro-1*H*-furo[3,4-*c*]pyrrol-5(3*H*)-yl)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-6-chloro-3-((1-(2-cyano-5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(2-cyano-9-methyl-5-morpholinoimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-2-fluoro-6-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-5-fluoro-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-4-fluoro-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-3-fluoro-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

6-chloro-3-(((1*R*)-1-(9-methyl-5-(tetrahydrofuran-3-yl)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

2-(((1*R*)-1-(9-methyl-5-(tetrahydrofuran-3-yl)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-4-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)thiophene-3-carboxylic acid;

(*R*)-4-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)isothiazole-3-carboxylic acid;

(*R*)-6-chloro-3-((1-(9-chloro-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(9-fluoro-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(9-chloro-5-(4,4-difluoropiperidin-1-yl)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-fluoro-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2-ethyl-9-methylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(9-chloro-5-(4,4-difluoropiperidin-1-yl)-2-ethylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2-methoxy-9-methylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(9-chloro-5-(4,4-difluoropiperidin-1-yl)-2-methoxyimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-fluoro-2-methoxyimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2-methoxyimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2-ethyl-9-fluoroimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2-ethylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(2-chloro-5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(2,9-dichloro-5-(4,4-difluoropiperidin-1-yl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(2-chloro-5-(4,4-difluoropiperidin-1-yl)-9-fluoroimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(2-chloro-5-(4,4-difluoropiperidin-1-yl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(2-cyclopropyl-5-(4,4-difluoropiperidin-1-yl)-9-methylimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(9-chloro-2-cyclopropyl-5-(4,4-difluoropiperidin-1-yl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(2-chloro-9-methyl-5-morpholinoimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(2-cyano-9-methyl-5-morpholinoimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(2-(difluoromethyl)-9-methyl-5-morpholinoimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(2-(fluoromethyl)-9-methyl-5-morpholinoimidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((1*R*)-1-(5-(3-fluoropyrrolidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((1*R*)-1-(5-(3,4-difluoropyrrolidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((1*R*)-1-(9-methyl-5-(2-methylmorpholino)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((1*R*)-1-(5-(2-ethylmorpholino)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(9-methyl-5-(6-oxa-2-azaspiro[3.4]octan-2-yl)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(9-methyl-5-(2-oxa-6-azaspiro[3.4]octan-6-yl)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(9-methyl-5-(2-oxa-7-azaspiro[3.5]nonan-7-yl)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((1*R*)-1-(5-(1-fluoro-3-azabicyclo[3.2.0]heptan-3-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

3-(((1*R*)-1-(5-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)-6-chloropicolinic acid;

6-chloro-3-(((1*R*)-1-(5-(3-cyanopyrrolidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

3-(((1*R*)-1-(5-(2-oxa-5-azabicyclo[4.1.0]heptan-5-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)-6-chloropicolinic acid;

(*R*)-6-chloro-3-((1-(9-methyl-5-(tetrahydro-2*H*-pyran-4-yl)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

3-(((1*R*)-1-(5-(3-oxabicyclo[4.1.0]heptan-6-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)-6-chloropicolinic acid;

6-chloro-3-(((1*R*)-1-(5-(6,6-difluoro-3-azabicyclo[3.1.0]hexan-3-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((1*R*)-1-(5-(6-fluoro-3-azabicyclo[3.1.0]hexan-3-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((1*R*)-1-(5-(1-fluoro-3-azabicyclo[3.1.0]hexan-3-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(9-methyl-5-(pyridin-3-yl)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(9-methyl-5-(pyridin-4-yl)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(9-methyl-5-((oxetan-3-yl)methyl)amino)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(9-methyl-5-(methyl(oxetan-3-yl)methyl)amino)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((1*R*)-1-(5-(3,3-difluoro-4-methylpyrrolidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((1*R*)-1-(5-(4,4-difluoro-3-methylpiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((1*R*)-1-(5-(6,6-difluoro-3-azabicyclo[3.1.1]heptan-3-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((1*R*)-1-(5-(5,5-difluoro-2-azabicyclo[2.2.1]heptan-2-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(5-(3,3-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

6-chloro-3-(((1*R*)-1-(5-(6,6-difluoro-2-azabicyclo[2.2.1]heptan-2-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(9-methyl-2-(trifluoromethyl)-5-(3-(trifluoromethyl)azetidin-1-yl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-*N*-(1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)-2-(1*H*-tetrazol-5-yl)pyridin-3-amine;

(*R*)-6-chloro-*N*-(1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)-2-(1*H*-tetrazol-5-yl)pyridin-3-amine;

(*R*)-*N*-(1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)-2-(1*H*-tetrazol-5-yl)aniline;

(*R*)-*N*-(1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)-2-(1*H*-tetrazol-5-yl)aniline;

ethyl (*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinate;

ethyl (*R*)-6-chloro-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinate;

ethyl (*R*)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzoate;

ethyl (*R*)-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzoate;

(*R*)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzonitrile;

(*R*)-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzonitrile;

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinonitrile

(*R*)-6-chloro-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinonitrile;

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinamide;

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)-*N*-methylpicolinamide;

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)-*N*-hydroxypicolinamide;

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)-*N*-hydroxy-*N*-methylpicolinamide;

(*R*)-6-chloro-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinamide;

(*R*)-6-chloro-*N*-methyl-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinamide;

(*R*)-6-chloro-*N*-hydroxy-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinamide;

(*R*)-6-chloro-*N*-hydroxy-*N*-methyl-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinamide;

(*R*)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzamide;

(*R*)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)-*N*-methylbenzamide;

(*R*)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)-*N*-hydroxybenzamide;

(*R*)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)-*N*-hydroxy-*N*-methylbenzamide;

(*R*)-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzamide;

(*R*)-*N*-methyl-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzamide;

(*R*)-*N*-hydroxy-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzamide;

(*R*)-*N*-hydroxy-*N*-methyl-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzamide;

(*R*)-*N*-hydroxy-*N*-methyl-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzamide;

(*R*)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(2,2,2-trifluoroethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(2,2,2-trifluoroethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(perfluoroethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(perfluoroethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-2-((1-(9-methyl-5-morpholino-2-(2,2,2-trifluoroethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-6-chloro-3-((1-(9-methyl-5-morpholino-2-(2,2,2-trifluoroethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-2-((1-(9-methyl-5-morpholino-2-(perfluoroethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-6-chloro-3-((1-(9-methyl-5-morpholino-2-(perfluoroethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-2,9-bis(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-2,9-bis(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-2-((1-(5-morpholino-2,9-bis(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-6-chloro-3-((1-(5-morpholino-2,9-bis(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(9-(difluoromethyl)-5-(4,4-difluoropiperidin-1-yl)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(9-(difluoromethyl)-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-(fluoromethyl)-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(9-(fluoromethyl)-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)-6-methylpicolinic acid;

(*R*)-2-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)-5-methylbenzoic acid;

(*R*)-6-methyl-3-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-5-methyl-2-((1-(9-methyl-5-morpholino-2-(trifluoromethyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)benzoic acid;

(*R*)-6-chloro-3-((1-(5-(4,4-difluoropiperidin-1-yl)-9-methyl-2-(2,2,3,3-tetrafluorocyclopropyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid;

(*R*)-6-chloro-3-((1-(9-methyl-5-morpholino-2-(2,2,3,3-tetrafluorocyclopropyl)imidazo[1,2-*c*]quinazolin-7-yl)ethyl)amino)picolinic acid; or
a pharmaceutically acceptable salt thereof.

211. A pharmaceutical composition comprising a compound or salt according to any of claims 1-210 together with a pharmaceutically acceptable carrier, excipient or diluent.

212. 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 210 or a pharmaceutical composition of claim 211.

213. The method of claim 212, wherein the PI3K is PI3K α .

214. The method of claim 212 or claim 213, wherein the PI3K associated with the disease or disorder has a H1047R mutation.

215. The method of any one of claims 212 to 214, wherein the disease or disorder is a cancer.

216. The method of claim 215, 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.

217. The method of any one of claims 212 to 214, 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).

218. 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 210 or a pharmaceutical composition of claim 211.

219. 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 210 or a pharmaceutical composition of claim 211.

220. The method of claim 219, 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.

221. The method of claim 219, wherein the disorder is CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome) or PIK3Cα-related overgrowth syndrome (PROS).

222. A method of treating cancer comprising administering a compound according to any of claims 1-210 or a pharmaceutical composition of claim 211 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.

223. A method treating cancer comprising administering a compound according to any of claims 1-210 or a pharmaceutical composition of claim 211 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.

224. A compound according to any of claims 1-210 or a pharmaceutical composition of claim 211 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.