PHOSPHATIDYLINOSITOL 3-KINASE INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

FIELD

[0001] The present application relates to novel compounds that selectively inhibit the activities of PI3K isoforms and their uses in therapeutic treatments.

BACKGROUND

[0002] Cell signaling via 3'-phosphorylated phosphoinositides has been implicated in a variety of cellular processes, *e.g.*, malignant transformation, growth factor signaling, inflammation, and immunity (Rameh *et al.*, *J. Biol. Chem.*, *274*:8347-8350, 1999). Phosphatidylinositol 3-kinase (PI 3-kinase or PI3K) is responsible for generating these phosphorylated signaling products. PI3K was initially identified as a protein associated with viral oncoproteins and growth factor receptor tyrosine kinases that phosphorylate phosphatidylinositol (PI) and its phosphorylated derivatives at the 3'-hydroxyl of the inositol ring (Panayotou *et al.*, *Trends Cell Biol.*, *2*:358-60, 1992).

[0003] Three classes of the PI 3-kinase (PI3K) are proposed based on the substrate specificities. Class I PI3Ks phosphorylate phosphatidylinositol (PI), phosphatidylinositol-4-phosphate, and phosphatidylinositol-4,5-biphosphate (PIP_2) to produce phosphatidylinositol-3-phosphate (PIP), phosphatidylinositol-3,4-biphosphate, and phosphatidylinositol-3,4,5-triphosphate, respectively. Also, Class II PI3Ks phosphorylate PI and phosphatidylinositol-4-phosphate, and Class III PI3Ks phosphorylate PI.

[0004] The initial purification and molecular cloning of PI 3-kinase revealed that it was a heterodimer consisting of p85 and p110 subunits (Otsu *et al.*, *Cell*, *65*:91-104, 1991; Hiles *et al.*, *Cell*, *70*:419-29, 1992). Later, four distinct Class I PI3Ks were identified and designated as PI3Kα, β, δ, and γ isoforms. Each isoform consists of a distinct 110 kDa catalytic subunit and a regulatory subunit. The catalytic subunits of PI3Kα, β, and δ (*i.e.*, p110α, p110β, and p110δ, respectively) interacts, individually, with the same regulatory subunit p85, whereas the catalytic subunit of PI3Kγ (p110γ) interacts with a distinct regulatory subunit p101.

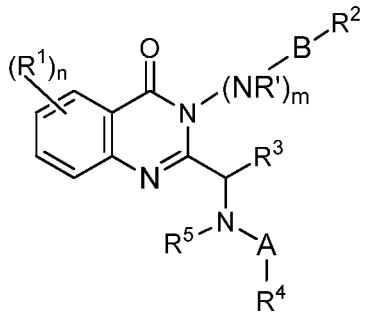
[0005] Studies have also showed that each PI3K isoform has distinct expression pattern. For example, *PIK3CA* which encodes PI3Kα is frequently mutated in human cancers (Engelman, *Nat. Rev. Cancer*, *9*: 550-562, 2009). Also, PI3Kδ is generally expressed in hematopoietic cells. Moreover, PI3K isoforms are shown to be associated with proliferation or survival signaling in cancers, inflammatory, or autoimmune diseases. As each PI3K isoform has different biological function, PI3K isoforms are potential targets to treat cancer or disorder (US Patent Nos. 6,800,620; 8,435,988; 8,673,906; US Patent Application Publication No. US2013/0274253).

[0006] Therefore, there is a need for developing therapeutic agents that inhibit PI3K isoforms to treat diseases, disorders, or conditions that are mediated by PI3K.

SUMMARY

[0007] The present application provides novel compounds that are inhibitors of PI3K isoforms. The application also provides compositions, including pharmaceutical compositions, kits that include the compounds, and methods of using and making the compounds. The compounds provided herein are useful in treating diseases, disorders, or conditions that are mediated by PI3K isoforms. The application also provides compounds for use in therapy. The application further provides compounds for use in a method of treating a disease, disorder, or condition that is mediated by PI3K isoforms. Moreover, the application provides uses of the compounds in the manufacture of a medicament for the treatment of a disease, disorder or condition that is mediated by PI3K isoforms.

[0008] The applications provides the compounds having the structure of formula (I):



(I)

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

m is 0 or 1;

A is a single bond or C(O);

B is alkyl or cycloalkyl, wherein each of the alkyl and cycloalkyl moieties is optionally substituted with hydroxyl or alkoxy;

R′ is hydrogen or optionally substituted alkyl;

R^1 is independently selected from halo, cyano, optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted alkoxy, optionally substituted sulfonyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl;

R^2 is cyano, $-NR^{2x}R^{2x}$, $-NR^{2y}C(O)R^{2x}$, $-C(O)NR^{2x}R^{2y}$, $-OR^{2y}$, or $-SO_2R^{2z}$; wherein R^{2x} is hydrogen, optionally substituted alkyl, heteroalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl; wherein R^{2y} is hydrogen and alkyl, wherein R^{2z} is alkyl;

R^3 is hydrogen, optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted cycloalkyl, or optionally substituted aryl;

R^4 is heteroaryl optionally substituted with one, two, or three members independently selected from halo, cyano, optionally substituted haloalkyl, optionally substituted alkyl, and $-NH_2$; and

R^5 is hydrogen or optionally substituted alkyl, wherein R^5 and R^3 together with the atoms to which they are attached optionally form a heterocyclic ring;

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0009] The application also provides the compound having the structure of formula (I), wherein

n is 0, 1, 2 or 3;

m is 0 or 1;

A is a single bond or C(O);

B is C_{1-6} alkyl or C_{3-8} cycloalkyl, wherein each of the alkyl and cycloalkyl moieties is optionally substituted with hydroxyl or C_{1-6} alkoxy;

R′ is hydrogen or optionally substituted C_{1-6} alkyl;

each R^1 is independently selected from halo, cyano, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} haloalkyl, optionally substituted C_{1-6} alkoxy, optionally substituted sulfonyl, optionally substituted C_{3-8} aryl, optionally substituted C_{3-8}

heteroaryl, optionally substituted C_{3-8} cycloalkyl, and optionally substituted C_{2-8} heterocycloalkyl;

R^2 is cyano, $-NR^{2x}R^{2x}$, $-NR^{2y}C(O)R^{2x}$, $-C(O)NR^{2x}R^{2y}$, $-OR^{2y}$, or $-SO_2R^{2z}$,

where R^{2x} is hydrogen, optionally substituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{2-8} heterocycloalkyl, C_{4-8} heteroaryl;

wherein R^{2y} is independently selected from hydrogen and C_{1-6} alkyl; and

wherein R^{2z} is C_{1-6} alkyl;

R^3 is hydrogen, optionally substituted C_{1-6} alkyl, C_{3-8} cycloalkyl, or C_{6-10} aryl;

R^4 is a six- to twelve-membered heteroaryl having at least one aromatic group and at least two heteroatoms selected from N, O, or S, wherein the heteroaryl is optionally substituted with one, two, or three members independently selected from halo, cyano, optionally substituted haloalkyl, optionally substituted C_{1-6} alkyl, and $-NH_2$; and

R^5 is hydrogen or optionally substituted C_{1-6} alkyl, wherein R^5 and R^3 together with the atoms to which they are attached optionally form a four- or eight-membered heterocyclic ring;

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0010] In some embodiments, the compounds have the structure of formula (I), wherein B is methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, each of which is optionally substituted with methoxy, ethoxy, or hydroxyl. In certain embodiments, wherein R′ is methyl, ethyl, propyl, phenylmethyl, phenylethyl, or phenylpropyl. In other embodiments, wherein each R^1 is independently selected from chloro, fluoro, bromo, iodo, methyl, ethyl, propyl, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoroethyl, difluoroethyl, and fluoroethyl. In some other embodiments, wherein R^2 is selected from cyano, morpholinyl, $-NH_2$, $-NHR^{2x}$, $-NR^{2x}R^{2x}$, $-NHC(O)R^{2y}$, $-NR^{2y}C(O)R^{2x}$, $-C(O)NHR^{2y}$, $-C(O)NR^{2x}R^{2y}$, $-OH$, $-OR^{2y}$, or $-SO_2R^{2z}$; wherein each R^{2x} is independently methyl, butyl, propyl, butyl, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoroethyl, difluoroethyl, fluoroethyl, phenyl, phenylmethyl, phenylethyl, pyridinyl, pyrimidinyl, cyclopropyl, cyclobutyl, cyclohexyl, oxetanyl, or morpholinyl, each of R^{2x} is optionally substituted with one, two, or three members selected from fluoro, chloro, bromo, or iodo; wherein each R^{2y} is independently hydrogen, methyl, ethyl, propyl, butyl; and wherein each R^{2z} is independently methyl, ethyl, propyl, or butyl. In certain other embodiments, wherein R^3 is selected from

hydrogen, methyl, ethyl, propyl, butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, or phenyl. In additional embodiments, wherein R^5 is hydrogen, methyl, ethyl, or propyl. In other additional embodiments, R^5 and R^3 together with the atoms to which they are attached optionally form pyrrolidinyl. In further embodiments, wherein R^4 is a monocyclic heteroaryl having at least two nitrogen atoms, wherein R^4 is optionally substituted with two or three members independently selected from bromo, chloro, fluoro, cyano, methyl, ethyl, propyl, and $-NH_2$. In yet further embodiments, wherein R^4 is bicyclic heteroaryl having at least one aromatic ring, at least two nitrogen atoms, and at least one additional heteroatom selected from N, O, or S; wherein R^4 is optionally substituted with two or three members independently selected from bromo, chloro, fluoro, cyano, methyl, ethyl, propyl, and $-NH_2$.

[0011] In certain embodiments, the PI3K inhibitors are the compounds selected from Table 1, a pharmaceutically acceptable salt, isomer, or a mixture thereof. In certain embodiments, the PI3K inhibitors are the compounds selected from Table 1a, a pharmaceutically acceptable salt, isomer, or a mixture thereof. In additional embodiments, the compound is an (S)-enantiomer. In other embodiments, the compound is an (R)-enantiomer. In other additional embodiments, the compound is an atropisomer.

[0012] The application also provides a pharmaceutical composition that comprises a compound of formula (I), a pharmaceutically acceptable salt, isomer, or a mixture thereof, together with at least one pharmaceutically acceptable vehicle. Examples of a pharmaceutically acceptable vehicle may be selected from carriers, adjuvants, and excipients.

[0013] Further provided herein is a method of treating a disease, disorder, or condition in a human in need thereof by administering to the human a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, isomer, or a mixture thereof. Further provided is a compound of formula (I) for use in a method of treating a disease, disorder or condition that is mediated by PI3K isoforms. The application also provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment of a disease, disorder or condition that is mediated by PI3K isoforms. In certain embodiments, the disease, disorder, or condition is associated or mediated by PI3K. In some embodiments, the disease, disorder, or condition is an

inflammatory disorder. In other embodiments, the disease, disorder, or condition is a cancer.

[0014] Also provided herein is a method of inhibiting the activity of a phosphatidylinositol 3-kinase polypeptide by contacting the polypeptide with a compound of formula (I) or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0015] Further provided is a method of inhibiting excessive or destructive immune reactions, comprising administering an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0016] Also provided is a method of inhibiting growth or proliferation of cancer cells comprising contacting the cancer cells with an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0017] Also provided is a kit that includes a compound of formula (I) or a pharmaceutically acceptable salt, isomer, or a mixture thereof. The kit may further comprise a label and/or instructions for use of the compound in treating a disease, disorder, or condition in a human in need thereof. In some embodiments, the disease, disorder, or condition may be associated or mediated by PI3K activity.

[0018] Also provided are articles of manufacture that include a compound of formula (I) or a pharmaceutically acceptable salt, isomer, or a mixture thereof, and a container. In one embodiment, the container may be a vial, jar, ampoule, preloaded syringe, or an intravenous bag.

DETAILED DESCRIPTION

[0019] The following description sets forth exemplary methods, parameters and the like. Such description is not intended as a limitation on the scope of the present application but is instead provided as exemplary embodiments.

[0020] As used herein, the following words, phrases and symbols are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[0021] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -$CONH_2$ is attached through the carbon atom. A dash at the front or end of a chemical group is a matter of convenience; chemical groups may be depicted with or without one or more dashes without losing their ordinary meaning. A wavy line drawn through a line in a structure indicates a point of attachment of a group. Unless chemically or structurally required, no directionality is indicated or implied by the order in which a chemical group is written or named.

[0022] The prefix "C_{u-v}" indicates that the following group has from u to v carbon atoms. For example, "C_{1-6} alkyl" indicates that the alkyl group has from 1 to 6 carbon atoms.

[0023] Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. In certain embodiments, the term "about" includes the indicated amount ± 10%. In other embodiments, the term "about" includes the indicated amount ± 5%. In certain other embodiments, the term "about" includes the indicated amount ± 1%. Also, to the term "about X" includes description of "X". Also, the singular forms "a" and "the" include plural references unless the context clearly dictates otherwise. Thus, e.g., reference to "the compound" includes a plurality of such compounds and reference to "the assay" includes reference to one or more assays and equivalents thereof known to those skilled in the art.

[0024] "Alkyl" refers to an unbranched or branched saturated hydrocarbon chain. As used herein, alkyl has 1 to 20 carbon atoms (*i.e.*, C_{1-20} alkyl), 1 to 8 carbon atoms (*i.e.*, C_{1-8} alkyl), 1 to 6 carbon atoms (*i.e.*, C_{1-6} alkyl), or 1 to 4 carbon atoms (*i.e.*, C_{1-4} alkyl). Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. When an alkyl residue having a specific number of carbons is named by chemical name or identified by molecular formula, all geometric isomers having that number of carbons may be encompassed; thus, for example, "butyl" includes n-butyl (i.e. -$(CH_2)_3CH_3$), sec-butyl (i.e. -$CH(CH_3)CH_2CH_3$), isobutyl (i.e. -$CH_2CH(CH_3)_2$) and tert-butyl (i.e. -$C(CH_3)_3$); and "propyl" includes n-propyl (i.e. -$(CH_2)_2CH_3$) and isopropyl (i.e. -$CH(CH_3)_3$).

[0025] "Alkenyl" refers to an aliphatic group containing at least one carbon-carbon double bond and having from 2 to 20 carbon atoms (*i.e.*, C_{2-20} alkenyl), 2 to 8 carbon atoms (*i.e.*, C_{2-8} alkenyl), 2 to 6 carbon atoms (*i.e.*, C_{2-6} alkenyl), or 2 to 4 carbon atoms (*i.e.*, C_{2-4} alkenyl). Examples of alkenyl groups include ethenyl, propenyl, butadienyl (including 1,2-butadienyl and 1,3-butadienyl).

[0026] "Alkynyl" refers to an aliphatic group containing at least one carbon-carbon triple bond and having from 2 to 20 carbon atoms (*i.e.*, C_{2-20} alkynyl), 2 to 8 carbon atoms (*i.e.*, C_{2-8} alkynyl), 2 to 6 carbon atoms (*i.e.*, C_{2-6} alkynyl), or 2 to 4 carbon atoms (*i.e.*, C_{2-4} alkynyl). The term "alkynyl" also includes those groups having one triple bond and one double bond.

[0027] "Alkoxy" refers to the group "alkyl-O-". Examples of alkoxy groups include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy.

[0028] "Acyl" refers to a group -C(=O)R, wherein R is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of acyl include formyl, acetyl, cylcohexylcarbonyl, cyclohexylmethyl-carbonyl, and benzoyl.

[0029] "Amido" refers to both a "C-amido" group which refers to the group -$C(=O)NR^yR^z$ and an "N-amido" group which refers to the group -$NR^yC(=O)R^z$, wherein R^y and R^z are independently selected from the group consisting of hydrogen, alkyl, aryl, haloalkyl, or heteroaryl; each of which may be optionally substituted.

[0030] "Amino" refers to the group -NR^yR^z wherein R^y and R^z are independently selected from the group consisting of hydrogen, alkyl, haloalkyl, aryl, or heteroaryl; each of which may be optionally substituted.

[0031] "Aryl" refers to an aromatic carbocyclic group having a single ring (e.g. monocyclic) or multiple rings (e.g. bicyclic or tricyclic) including fused systems. As used herein, aryl has 6 to 20 ring carbon atoms (*i.e.*, C_{6-20} aryl), 6 to 12 carbon ring atoms (*i.e.*, C_{6-12} aryl), or 6 to 10 carbon ring atoms (*i.e.*, C_{6-10} aryl). Examples of aryl groups include phenyl, naphthyl, fluorenyl, and anthryl. Aryl, however, does not encompass or

overlap in any way with heteroaryl defined below. If one or more aryl groups are fused with a heteroaryl ring, the resulting ring system is heteroaryl.

[0032] "Cyano" or "carbonitrile" refers to the group -CN.

[0033] "Cycloalkyl" refers to a saturated or partially saturated cyclic alkyl group having a single ring or multiple rings including fused, bridged, and spiro ring systems. The term "cycloalkyl" includes cycloalkenyl groups (i.e. the cyclic group having at least one alkenyl). As used herein, cycloalkyl has from 3 to 20 ring carbon atoms (*i.e.*, C_{3-20} cycloalkyl), 3 to 12 ring carbon atoms (*i.e.*, C_{3-12} cycloalkyl), 3 to 10 ring carbon atoms (*i.e.*, C_{3-10} cycloalkyl), 3 to 8 ring carbon atoms (*i.e.*, C_{3-8} cycloalkyl), or 3 to 6 ring carbon atoms (*i.e.*, C_{3-6} cycloalkyl). Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0034] "Halogen" or "halo" includes fluoro, chloro, bromo, and iodo. "Haloalkyl" refers to an unbranched or branched alkyl group as defined above, wherein one or more hydrogen atoms are replaced by a halogen. For example, where a residue is substituted with more than one halogen, it may be referred to by using a prefix corresponding to the number of halogen moieties attached. Dihaloalkyl and trihaloalkyl refer to alkyl substituted with two ("di") or three ("tri") halo groups, which may be, but are not necessarily, the same halogen. Examples of haloalkyl include difluoromethyl ($-CHF_2$) and trifluoromethyl ($-CF_3$).

[0035] "Heteroalkyl" refers to an alkyl group in which one or more of the carbon atoms (and any associated hydrogen atoms) are each independently replaced with the same or different heteroatomic group. The term "heteroalkyl" includes unbranched or branched saturated chain having carbon and heteroatoms. By way of example, 1, 2 or 3 carbon atoms may be independently replaced with the same or different heteroatomic group. Heteroatomic groups include, but are not limited to, -NR-, -O-, -S-, -S(O)-, $-S(O)_2-$, and the like, where R is H, alkyl, aryl, cycloalkyl, heteroalkyl, heteroaryl or heterocycloalkyl, each of which may be optionally substituted. Examples of heteroalkyl groups include $-OCH_3$, $-CH_2OCH_3$, $-SCH_3$, $-CH_2SCH_3$, $-NRCH_3$, and $-CH_2NRCH_3$, where R is hydrogen, alkyl, aryl, arylalkyl, heteroalkyl, or heteroaryl, each of which may be optionally substituted. As used herein, heteroalkyl include 1 to 10 carbon atoms, 1 to

8 carbon atoms, or 1 to 4 carbon atoms; and 1 to 3 heteroatoms, 1 to 2 heteroatoms, or 1 heteroatom.

[0036] "Heteroaryl" refers to an aromatic group having a single ring, multiple rings, or multiple fused rings, with one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. As used herein, heteroaryl include 1 to 20 ring carbon atoms (*i.e.*, C_{1-20} heteroaryl), 3 to 12 ring carbon atoms (*i.e.*, C_{3-12} heteroaryl), or 3 to 8 carbon ring atoms (*i.e.*, C_{3-8} heteroaryl); and 1 to 5 heteroatoms, 1 to 4 heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen, and sulfur. Examples of heteroaryl groups include pyrimidinyl, purinyl, pyridyl, pyridazinyl, benzothiazolyl, and pyrazolyl. Heteroaryl does not encompass or overlap with aryl as defined above.

[0037] "Heterocycloalkyl" refers to a saturated or unsaturated cyclic alkyl group, with one or more ring heteroatoms independently selected from nitrogen, oxygen and sulfur. The term "heterocycloalkyl" includes heterocycloalkenyl groups (i.e. the heterocycloalkyl group having at least one alkenyl). A heterocycloalkyl may be a single ring or multiple rings wherein the multiple rings may be fused, bridged, or spiro. As used herein, heterocycloalkyl has 2 to 20 ring carbon atoms (*i.e.*, C_{2-20} heterocycloalkyl), 2 to 12 ring carbon atoms (*i.e.*, C_{2-12} heterocycloalkyl), 2 to 10 ring carbon atoms (*i.e.*, C_{2-10} heterocycloalkyl), 2 to 8 ring carbon atoms (*i.e.*, C_{2-8} heterocycloalkyl), 3 to 12 ring carbon atoms (*i.e.*, C_{3-12} heterocycloalkyl), 3 to 8 ring carbon atoms (*i.e.*, C_{3-8} heterocycloalkyl), or 3 to 6 ring carbon atoms (*i.e.*, C_{3-6} heterocycloalkyl); having 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, sulfur or oxygen. Examples of heterocycloalkyl groups include pyrrolidinyl, piperidinyl, piperazinyl, oxetanyl, dioxolanyl, azetidinyl, and morpholinyl.

[0038] "Hydroxy" or "hydroxyl" refers to the group -OH.

[0039] "Oxo" refers to the group (=O) or (O).

[0040] "Sulfonyl" refers to the group $-S(O)_2R$, where R is alkyl, haloalkyl, heterocycloalkyl, cycloalkyl, heteroaryl, or aryl. Examples of sulfonyl are methylsulfonyl, ethylsulfonyl, phenylsulfonyl, and toluenesulfonyl.

[0041] Certain commonly used alternative chemical names may be used. For example, a divalent group such as a divalent "alkyl" group, a divalent "aryl" group, etc., may also be referred to as an "alkylene" group or an "alkylenyl" group, an "arylene" group or an "arylenyl" group, respectively. Also, unless indicated explicitly otherwise, where combinations of groups are referred to herein as one moiety, *e.g.* arylalkyl, the last mentioned group contains the atom by which the moiety is attached to the rest of the molecule.

[0042] The terms "optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. Also, the term "optionally substituted" refers to any one or more hydrogen atoms on the designated atom or group may or may not be replaced by a moiety other than hydrogen.

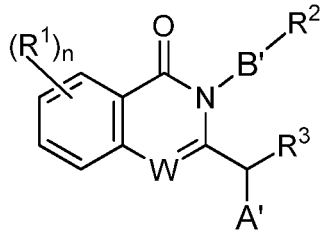
[0043] The term "substituted" means that any one or more hydrogen atoms on the designated atom or group is replaced with one or more substituents other than hydrogen, provided that the designated atom's normal valence is not exceeded. The one or more substituents include, but are not limited to, alkyl, alkenyl, alkynyl, alkoxy, acyl, amino, amido, amidino, aryl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, guanidino, halo, haloalkyl, heteroalkyl, heteroaryl, heterocycloalkyl, hydroxy, hydrazino, imino, oxo, nitro, alkylsulfinyl, sulfonic acid, alkylsulfonyl, thiocyanate, thiol, thione, or combinations thereof. By way of example, there may be one, two, three, four, five, or six substitutents. Polymers or similar indefinite structures arrived at by defining substituents with further substituents appended ad infinitum (e.g., a substituted aryl having a substituted alkyl which is itself substituted with a substituted aryl group, which is further substituted by a substituted heteroalkyl group, etc.) are not intended for inclusion herein. Unless otherwise noted, the maximum number of serial substitutions in compounds described herein is three. For example, serial substitutions of substituted aryl groups with two other substituted aryl groups are limited to substituted aryl (substituted aryl) substituted aryl. Similarly, the above definitions are not intended to include impermissible substitution patterns (e.g., methyl substituted with 5 fluorines or heteroaryl groups having two adjacent oxygen ring atoms). Such impermissible substitution patterns are well known to the skilled artisan. When used to modify a chemical group, the term "substituted" may describe other chemical groups defined

herein. For example, the term "substituted aryl" includes, but is not limited to, "alkylaryl." Unless specified otherwise, where is a group is described as optionally substituted, any substituents of the group are themselves unsubstituted.

[0044] In some embodiments, the term "substituted alkyl" refers to an alkyl group having one or more substituents including hydroxyl, halo, alkoxy, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl. In additional embodiments, "substituted cycloalkyl" refers to a cycloalkyl group having one or more substituents including alkyl, haloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, halo, hydroxyl; "substituted aryl" refers to an aryl group having one or more substituents including halo, alkyl, haloalkyl, heterocycloalkyl, heteroaryl, alkoxy, and cyano; and "substituted sulfonyl" refers to a group $-S(O)_2R$, in which R is substituted with one or more substituents including alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl. In other embodiments, the one or more substituents may be further substituted with halo, alkyl, haloalkyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each of which is substituted. In other embodiments, the substituents may be further substituted with halo, alkyl, haloalkyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each of which is unsubstituted.

PI3K Inhibitor Compounds

[0045] The present application provides the compounds that function as inhibitors of PI3K isoforms. In one aspect, the PI3K inhibitors are the compounds having the structure of formula (J):



(J)

wherein:

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

W is CH or N;

A′ is NR^5R^4, OR^4, or $NR^5C(O)R^4$;

B′ is alkyl, cycloalkyl, or heteroalkyl, wherein each of the alkyl and cycloalkyl moieties is optionally substituted with hydroxyl or alkoxy, wherein the heteroalkyl is optionally substituted with optionally substituted alkyl;

R^1 is independently selected from halo, cyano, optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted alkoxy, optionally substituted sulfonyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl;

R^2 is cyano, C_{3-8} heterocycloalkyl, $-NR^{2x}R^{2x}$, $-NR^{2x}C(O)R^{2y}$, $-C(O)NR^{2x}R^{2y}$, $-OR^{2y}$, or $-SO_2R^{2z}$; wherein R^{2x} is hydrogen, optionally substituted alkyl, heteroalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl; wherein R^{2y} is hydrogen and alkyl, wherein R^{2z} is alkyl;

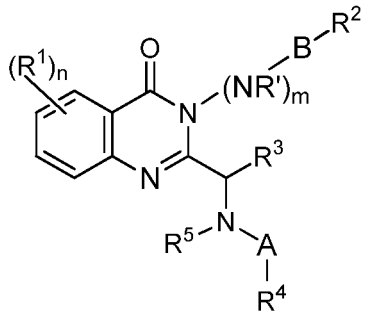
R^3 is hydrogen, optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted cycloalkyl, or optionally substituted aryl;

R^4 is heteroaryl optionally substituted with one, two, or three members independently selected from halo, cyano, optionally substituted haloalkyl, optionally substituted alkyl, and $-NH_2$; and

R^5 is hydrogen or optionally substituted alkyl, wherein R^5 and R^3 together with the atoms to which they are attached optionally form a heterocyclic ring;

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0046] In another aspect, the PI3K inhibitors are the compounds having the structure of formula (I)



(I)

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

m is 0 or 1;

A is a single bond or C(O);

B is C_{1-6} alkyl or C_{3-8} cycloalkyl, wherein each of the alkyl and cycloalkyl moieties is optionally substituted with hydroxyl or C_{1-6} alkoxy;

R′ is hydrogen or optionally substituted C_{1-6} alkyl;

each R^1 is independently selected from halo, cyano, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} haloalkyl, optionally substituted C_{1-6} alkoxy, optionally substituted sulfonyl, optionally substituted C_{3-8} aryl, optionally substituted C_{3-8} heteroaryl, optionally substituted C_{3-8} cycloalkyl, and optionally substituted C_{2-8} heterocycloalkyl;

R^2 is cyano, morpholinyl, $-NR^{2x}R^{2x}$, $-NR^{2y}C(O)R^{2x}$, $-C(O)NR^{2x}R^{2y}$, $-OR^{2y}$, or $-SO_2R^{2z}$,

where R^{2x} is hydrogen, optionally substituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{2-8} heterocycloalkyl, C_{4-8} heteroaryl;

wherein R^{2y} is independently selected from hydrogen and C_{1-6} alkyl; and

wherein R^{2z} is C_{1-6} alkyl;

R^3 is hydrogen, optionally substituted C_{1-6} alkyl, C_{3-8} cycloalkyl, or C_{6-10} aryl;

R^4 is a six- to twelve-membered heteroaryl having at least one aromatic group and at least two heteroatoms selected from N, O, or S, wherein the heteroaryl is optionally substituted with one, two, or three members independently selected from halo, cyano, optionally substituted haloalkyl, optionally substituted C_{1-6} alkyl, and $-NH_2$; and

R^5 is hydrogen or optionally substituted C_{1-6} alkyl, wherein R^5 and R^3 together with the atoms to which they are attached optionally form a four- or eight-membered heterocyclic ring;

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0047] In additional aspect, the compounds have the structure of formula (I) wherein:

n is 0, 1, 2 or 3;

m is 0 or 1;

A is a single bond or C(O);

B is alkyl, cycloalkyl, or heteroalkyl, wherein each of the alkyl and cycloalkyl moieties is optionally substituted with hydroxyl or alkoxy;

R′ is hydrogen or C_{1-6} alkyl optionally substituted with C_{6-10} aryl;

each R^1 is independently selected from halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} alkylsulfonyl;

R^2 is cyano, morpholinyl, $-NR^{2x}R^{2x}$, $-NR^{2y}C(O)R^{2x}$, $-C(O)NR^{2x}R^{2y}$, $-OR^{2y}$, or $-SO_2R^{2z}$; wherein R^{2x} is hydrogen, optionally substituted alkyl, heteroalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl; wherein R^{2y} is hydrogen and alkyl, wherein R^{2z} is alkyl;

where R^{2x} is hydrogen, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-8} cycloalkyl, C_{2-8} heterocycloalkyl, C_{4-8} heteroaryl, C_{1-6} alkyl, each of R^{2x} is optionally substituted with one, two, or three members independently selected from halo, C_{1-6} alkyl, C_{6-10} aryl, and C_{3-8} cycloalkyl;

wherein R^{2y} is independently selected from hydrogen and C_{1-6} alkyl; and

wherein R^{2z} is C_{1-6} alkyl;

R^3 is hydrogen, C_{3-8} cycloalkyl, C_{6-10} aryl, or C_{1-6} alkyl optionally substituted with C_{1-6} alkyl or C_{6-10} aryl, each of which is optionally substituted with C_{1-6} alkoxy, C_{1-6} alkyl, or C_{6-10} aryl;

R^4 is a six- to twelve-membered heteroaryl having at least one aromatic group and at least two heteroatoms selected from N, O, or S, wherein the heteroaryl is optionally substituted with one, two, or three members independently selected from halo, cyano, C_{1-6} haloalkyl, C_{1-6} alkyl, and $-NH_2$; and

R^5 is hydrogen or C_{1-6} alkyl, wherein R^5 and R^3 together with the atoms to which they are attached optionally form a four- or eight-membered heterocyclic ring;

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0048] In some other aspect, the compounds have the structure of formula (I), wherein

n is 1 or 2;

m is 0 or 1;

A is a single bond or C(O);

B is methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl, each of which is optionally substituted with methoxy, ethoxy, or hydroxyl;

R′ is methyl, ethyl, propyl, phenylmethyl, phenylethyl, or phenylpropyl;

each R^1 is independently selected from chloro, fluoro, bromo, iodo, methyl, ethyl, propyl, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoroethyl, difluoroethyl, and fluoroethyl;

R^2 is cyano, morpholinyl, $-NH_2$, $-NHR^{2x}$, $-NR^{2x}R^{2x}$, $-NHC(O)R^{2y}$, $-NR^{2y}C(O)R^{2x}$, $-C(O)NHR^{2y}$, $-C(O)NR^{2x}R^{2y}$, -OH, $-OR^{2y}$, or $-SO_2R^{2z}$;

wherein each R^{2x} is independently methyl, butyl, propyl, butyl, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoroethyl, difluoroethyl, fluoroethyl, phenyl, phenylmethyl, phenylethyl, pyridinyl, pyrimidinyl, cyclopropyl, cyclobutyl, cyclohexyl, or oxetanyl, each of R^{2x} is optionally substituted with one, two, or three members selected from fluoro, chloro, bromo, or iodo;

wherein each R^{2y} is independently hydrogen, methyl, ethyl, propyl, butyl; and

wherein each R^{2z} is independently methyl, ethyl, propyl, or butyl;

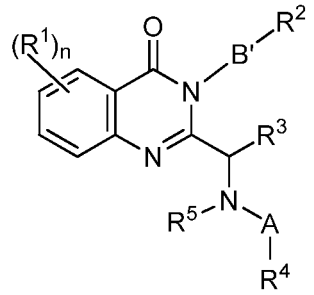
R^3 is hydrogen, methyl, ethyl, propyl, butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, or phenyl;

R^4 is a six- to ten-membered heteroaryl having at least one aromatic ring and at least two nitrogen atoms, wherein the heteroaryl is optionally substituted with one, two, or three members independently selected from fluoro, chloro, bromo, iodo, cyano, $-NH_2$, methyl, ethyl, and propyl; and

R^5 is hydrogen;

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0049] The compounds of formulae (J) or (I) may have the structure of formula (II):

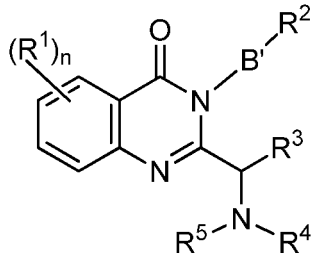


(II),

wherein n, A, B′, R^1, R^2, R^3, R^4, and R^5 are described herein,

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0050] The compounds of formulae (J) or (I) may have the structure of formula (IIa):

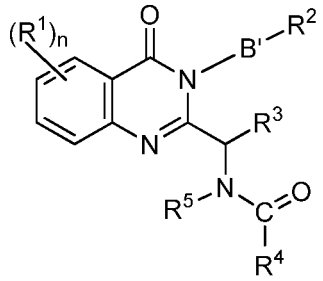


(IIa),

wherein n, B′, R^1, R^2, R^3, R^4, and R^5 are described herein,

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0051] The compounds of formulae (J) or (I) may have the structure of formula (IIb):

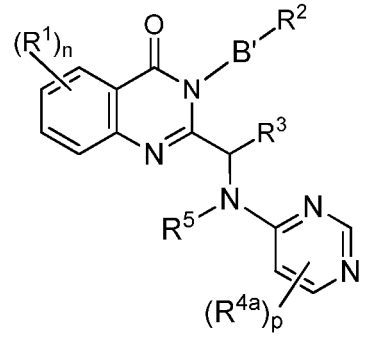


(IIb),

wherein n, B′, R^1, R^2, R^3, R^4, and R^5 are described herein,

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0052] The compounds of formulae (J) or (I) may have the structure of formula (IIc):



(IIc),

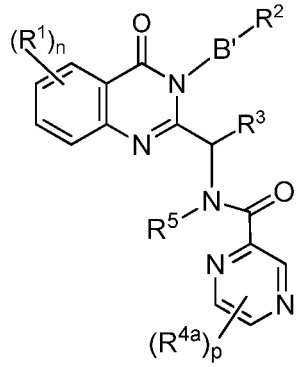
wherein n, B′, R^1, R^2, R^3, and R^5 are described herein,

p is 0, 1, 2, or 3;

each R^{4a} is independently selected from halo, cyano, C_{1-4} haloalkyl, and C_{1-4} alkyl;

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0053] The compounds of formulae (J) or (I) may have the structure of formula (IId):

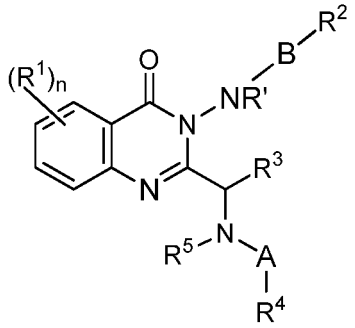


(IId)

wherein n, p, B′, R^1, R^2, R^3, R^{4a}, and R^5 are described herein,

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0054] The compounds of formulae (J) or (I) may have the structure of formula (III):



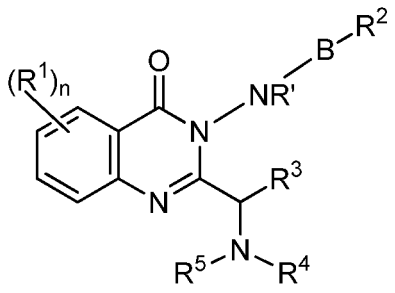
(III),

wherein n, A, R′, R^1, R^2, R^3, R^4, and R^5 are described herein,

B is alkyl or cycloalkyl, wherein each of the alkyl and cycloalkyl moieties is optionally substituted with hydroxyl, alkoxy, or heterocycloalkyl;

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0055] The compounds of formulae (J) or (I) may have the structure of formula (IIIa):

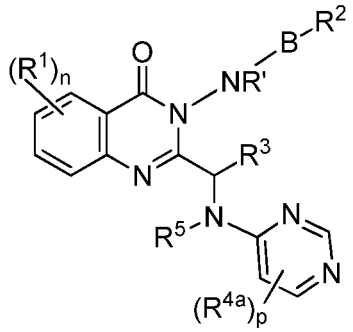


(IIIa),

wherein n, B, R′, R^1, R^2, R^3, R^4, and R^5 are described herein,

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0056] The compounds of formulae (J) or (I) may have the structure of formula (IIIb):

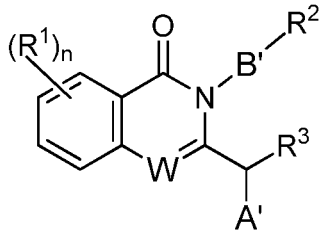


(IIIb),

wherein n, p, B, R′, R^1, R^2, R^3, R^{4a}, and R^5 are described herein,

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0057] In one aspect, the PI3K inhibitors are the compounds having the structure of formula (IV):



(IV)

wherein:

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

W is CH or N;

A′ is NR^5R^4, OR^4, or $NR^5C(O)R^4$;

B' is alkyl, cycloalkyl, heteroalkyl, or heterocycloalkyl wherein each of the alkyl and cycloalkyl moieties is optionally substituted with hydroxyl or alkoxy, wherein the heteroalkyl is optionally substituted with optionally substituted alkyl;

R^1 is independently selected from halo, cyano, optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted alkoxy, optionally substituted sulfonyl, optionally substituted alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl;

R^2 is hydrogen, cyano, $-NR^{2x}R^{2x}$, $-NR^{2y}C(O)R^{2x}$, $-C(O)NR^{2x}R^{2y}$, $-OR^{2y}$, $-SO_2R^{2z}$, optionally substituted C_{3-8} heterocycloalkyl, or optionally substituted C_{3-8} heteroaryl; wherein R^{2x} is hydrogen, optionally substituted alkyl, heteroalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl; wherein R^{2y} is hydrogen and alkyl, wherein R^{2z} is alkyl;

R^3 is hydrogen, optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted cycloalkyl, or optionally substituted aryl;

R^4 is heteroaryl optionally substituted with one, two, or three members independently selected from halo, cyano, optionally substituted haloalkyl, optionally substituted alkyl, and $-NH_2$; and

R^5 is hydrogen or optionally substituted alkyl, wherein R^5 and R^3 together with the atoms to which they are attached optionally form a heterocyclic ring;
or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0058] In certain other embodiments, the compounds have the structure of formula (IV)

wherein:

R^2 is hydrogen, cyano, morpholinyl, piperidinyl, pyrrolidinyl, piperazinyl optionally substituted with methyl, pyrazolyl, triazolyl, $NR^{2x}R^{2x}$, $NR^{2y}C(O)R^{2x}$, $C(O)NR^{2x}R^{2y}$, OR^{2y}, or SO_2R^{2z} wherein

R^{2x} is hydrogen, pyrimidinyl, pyridinyl, methyl, ethyl, propyl, tert-butyl, methyl optionally substituted with phenyl or three fluoro, cyclobutyl, cyclohexyl optionally substituted with two fluoro, or oxetanyl;

R^{2y} is hydrogen, methyl, tert-butyl;

R^{2z} is methyl.

[0059] In some other aspect, the compounds have the structure of formula (IV), wherein

n is 1 or 2;

m is 0 or 1;

A is a single bond or C(O);

B is methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl, each of which is optionally substituted with methoxy, ethoxy, or hydroxyl;

R′ is methyl, ethyl, propyl, phenylmethyl, phenylethyl, or phenylpropyl;

each R^1 is independently selected from chloro, fluoro, bromo, iodo, methyl, ethyl, propyl, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoroethyl, difluoroethyl, and fluoroethyl;

R^2 is cyano, morpholinyl, $-NH_2$, $-NHR^{2x}$, $-NR^{2x}R^{2x}$, $-NHC(O)R^{2y}$, $-NR^{2y}C(O)R^{2x}$, $-C(O)NHR^{2y}$, $-C(O)NR^{2x}R^{2y}$, -OH, $-OR^{2y}$, or $-SO_2R^{2z}$;

wherein each R^{2x} is independentlyhydrogen, methyl optionally substituted with phenyl or three fluoro, ethyl, propyl, butyl, tert-butyl, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoroethyl, difluoroethyl, fluoroethyl, phenyl, phenylmethyl, phenylethyl, pyridinyl, pyrimidinyl, cyclopropyl, cyclobutyl, cyclohexyl optionally substituted with two fluoro or oxetanyl, or oxetanyl, wherein each of R^{2x} is optionally substituted with one, two, or three members selected from fluoro, chloro, bromo, or iodo;

wherein each R^{2y} is independently hydrogen, methyl, ethyl, propyl, butyl, or tert-butyl; and

wherein each R^{2z} is independently methyl, ethyl, propyl, or butyl;

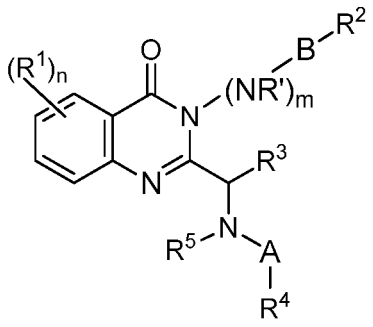
R^3 is hydrogen, methyl, ethyl, propyl, butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, or phenyl;

R^4 is a six- to ten-membered heteroaryl having at least one aromatic ring and at least two nitrogen atoms, wherein the heteroaryl is optionally substituted with one, two, or three members independently selected from fluoro, chloro, bromo, iodo, cyano, $-NH_2$, methyl, ethyl, and propyl; and

R^5 is hydrogen;

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0060] In another aspect, the PI3K inhibitors are the compounds having the structure of formula (IVa)



(IVa)

wherein:

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

m is 0 or 1;

A is a single bond or C(O);

B is C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} heterocycloalkyl or C_{3-8} heterocycloalkyl wherein each of the alkyl, cycloalkyl, heterocycloalkyl, and heterocycloalkyl moieties is optionally substituted with hydroxyl or C_{1-6} alkoxy;

R′ is hydrogen or optionally substituted C_{1-6} alkyl;

each R^1 is independently selected from halo, cyano, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} haloalkyl, optionally substituted C_{1-6} alkoxy, optionally substituted sulfonyl, optionally substituted alkylsulfonyl, optionally substituted C_{3-8} aryl, optionally substituted C_{3-8} heteroaryl, optionally substituted C_{3-8} cycloalkyl, and optionally substituted C_{2-8} heterocycloalkyl;

R^2 is hydrogen, cyano, optionally substituted C_{3-8} heterocycloalkyl, optionally substituted C_{3-8} heteroaryl, $-NR^{2x}R^{2x}$, $-NR^{2y}C(O)R^{2x}$, $-C(O)NR^{2x}R^{2y}$, $-OR^{2y}$, or $-SO_2R^{2z}$,

where R^{2x} is hydrogen, optionally substituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{2-8} heterocycloalkyl, C_{4-8} heteroaryl;

wherein R^{2y} is independently selected from hydrogen and C_{1-6} alkyl; and

wherein R^{2z} is C_{1-6} alkyl;

R^3 is hydrogen, optionally substituted C_{1-6} alkyl, C_{3-8} cycloalkyl, or C_{6-10} aryl;

R^4 is a six- to twelve-membered heteroaryl having at least one aromatic group and at least two heteroatoms selected from N, O, or S, wherein the heteroaryl is optionally substituted with one, two, or three members independently selected from halo, cyano, optionally substituted haloalkyl, optionally substituted C_{1-6} alkyl, and $-NH_2$; and

R^5 is hydrogen or optionally substituted C_{1-6} alkyl, wherein R^5 and R^3 together with the atoms to which they are attached optionally form a four- or eight-membered heterocyclic ring;

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0061] In certain other embodiments, the compounds have the structure of formula (IVa)

wherein:

n is 0, 1, 2 or 3;

m is 0 or 1;

A is a single bond or C(O);

B is C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} heteroalkyl or C_{3-8} heterocycloalkyl wherein each of the alkyl, cycloalkyl, heteroalkyl, and heterocycloalkyl moieties is optionally substituted with hydroxyl or C_{1-6} alkoxy;

R′ is hydrogen or C_{1-6} alkyl optionally substituted with C_{6-10} aryl;

each R^1 is independently selected from halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} alkylsulfonyl;

R^2 is hydrogen, cyano, morpholinyl, $-NR^{2x}R^{2x}$, $-NR^{2y}C(O)R^{2x}$, $-C(O)NR^{2x}R^{2y}$, $-OR^{2y}$, or $-SO_2R^{2z}$, pyrrolidinyl , piperidinyl, optionally substituted piperazinyl, phenyl, pyrazolyl, or triazolyl.

where R^{2x} is hydrogen, optionally substituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{2-8} heterocycloalkyl, C_{4-8} heteroaryl;

wherein R^{2y} is independently selected from hydrogen and C_{1-6} alkyl; and

wherein R^{2z} is C_{1-6} alkyl;

R^3 is hydrogen, optionally substituted C_{1-6} alkyl, C_{3-8} cycloalkyl, or C_{6-10} aryl;

R^4 is a six- to twelve-membered heteroaryl having at least one aromatic group and at least two heteroatoms selected from N, O, or S, wherein the heteroaryl is optionally substituted with one, two, or three members independently selected from halo, cyano, optionally substituted haloalkyl, optionally substituted C_{1-6} alkyl, and $-NH_2$; and

R^5 is hydrogen or optionally substituted C_{1-6} alkyl, wherein R^5 and R^3 together with the atoms to which they are attached optionally form a four- or eight-membered heterocyclic ring;

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0062] In certain other embodiments, the compounds have the structure of formula (IVa)

wherein:

n is 1 or 2;

m is 0 or 1;

A is a single bond or C(O);

B is methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, each of which is optionally substituted with methoxy, ethoxy, or hydroxyl;

R′ is methyl, ethyl, propyl, phenylmethyl, phenylethyl, or phenylpropyl;

each R^1 is independently selected from chloro, fluoro, bromo, iodo, methyl, ethyl, propyl, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoroethyl, difluoroethyl, and fluoroethyl;

R^2 is hydrogen, cyano, morpholinyl, $-NH_2$, $-NHR^{2x}$, $-NR^{2x}R^{2x}$, $-NHC(O)R^{2y}$, $-NR^{2y}C(O)R^{2x}$, $-C(O)NHR^{2y}$, $-C(O)NR^{2x}R^{2y}$, $-OH$, $-OR^{2y}$, $-SO_2R^{2z}$, pyrrolidinyl , piperidinyl, optionally substituted piperazinyl, phenyl, pyrazolyl, or triazolyl.

wherein each R^{2x} is independently hydrogen, methyl, ethyl, propyl, butyl, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoroethyl, difluoroethyl, fluoroethyl, phenyl, phenylmethyl, phenylethyl, pyridinyl, pyrimidinyl, cyclopropyl, cyclobutyl, cyclohexyl, or oxetanyl, each of R^{2x} is optionally substituted with one, two, or three members selected from fluoro, chloro, bromo, or iodo;

wherein each R^{2y} is independently hydrogen, methyl, ethyl, propyl, butyl; and

wherein each R^{2z} is independently methyl, ethyl, propyl, or butyl;

R^3 is hydrogen, methyl, ethyl, propyl, butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, or phenyl;

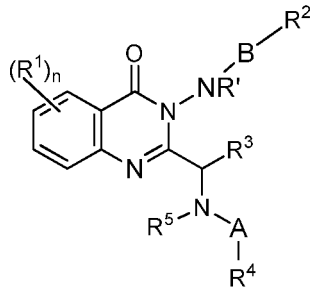
R^4 is a six- to ten-membered heteroaryl having at least one aromatic ring and at least two nitrogen atoms, wherein the heteroaryl is optionally substituted with one, two,

or three members independently selected from fluoro, chloro, bromo, iodo, cyano, $-NH_2$, methyl, ethyl, and propyl; and

R^5 is hydrogen;

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0063] In one embodiment, the compounds of formula (IV) may have the structure of formula (IVb):



(IVb),

wherein n, A, R′, R^1, R^2, R^3, R^4, and R^5 are described herein,

B is alkyl or cycloalkyl, wherein each of the alkyl and cycloalkyl moieties is optionally substituted with hydroxyl, alkoxy, or heterocycloalkyl;

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0064] In some other embodiments, the compounds have the structure of formula (IVb)

wherein:

n is 1 or 2;

A is a single bond or C(O);

B is methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, each of which is optionally substituted with methoxy, ethoxy, or hydroxyl;

R′ is methyl, ethyl, propyl, phenylmethyl, phenylethyl, or phenylpropyl;

each R^1 is independently selected from chloro, fluoro, bromo, iodo, methyl, ethyl, propyl, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoroethyl, difluoroethyl, and fluoroethyl;

R^2 is hydrogen, cyano, morpholinyl, $-NH_2$, $-NHR^{2x}$, $-NR^{2x}R^{2x}$, $-NHC(O)R^{2y}$, $-NR^{2y}C(O)R^{2x}$, $-C(O)NHR^{2y}$, $-C(O)NR^{2x}R^{2y}$, $-OH$, $-OR^{2y}$, $-SO_2R^{2z}$, pyrrolidinyl , piperidinyl, optionally substituted piperazinyl, phenyl, pyrazolyl, or triazolyl.

wherein each R^{2x} is independently hydrogen, methyl, ethyl, propyl, butyl, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoroethyl, difluoroethyl, fluoroethyl, phenyl, phenylmethyl, phenylethyl, pyridinyl, pyrimidinyl, cyclopropyl, cyclobutyl, cyclohexyl, or oxetanyl, each of R^{2x} is optionally substituted with one, two, or three members selected from fluoro, chloro, bromo, or iodo;

wherein each R^{2y} is independently hydrogen, methyl, ethyl, propyl, butyl; and

wherein each R^{2z} is independently methyl, ethyl, propyl, or butyl;

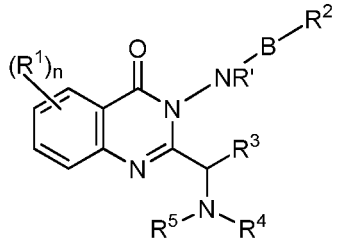
R^3 is hydrogen, methyl, ethyl, propyl, butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, or phenyl;

R^4 is a six- to ten-membered heteroaryl having at least one aromatic ring and at least two nitrogen atoms, wherein the heteroaryl is optionally substituted with one, two, or three members independently selected from fluoro, chloro, bromo, iodo, cyano, $-NH_2$, methyl, ethyl, and propyl; and

R^5 is hydrogen;

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0065] The compounds of formula (IV) may have the structure of formula (IVc):



(IVc),

wherein n, B, R′, R^1, R^2, R^3, R^4, and R^5 are described herein,

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0066] In some other embodiments, the compounds have the structure of formula (IVc)

wherein:

n is 1 or 2;

B is methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, each of which is optionally substituted with methoxy, ethoxy, or hydroxyl;

R′ is methyl, ethyl, propyl, phenylmethyl, phenylethyl, or phenylpropyl;

each R^1 is independently selected from chloro, fluoro, bromo, iodo, methyl, ethyl, propyl, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoroethyl, difluoroethyl, and fluoroethyl;

R^2 is hydrogen, cyano, morpholinyl, $-NH_2$, $-NHR^{2x}$, $-NR^{2x}R^{2x}$, $-NHC(O)R^{2y}$, $-NR^{2y}C(O)R^{2x}$, $-C(O)NHR^{2y}$, $-C(O)NR^{2x}R^{2y}$, -OH, $-OR^{2y}$, $-SO_2R^{2z}$, pyrrolidinyl , piperidinyl, optionally substituted piperazinyl, phenyl, pyrazolyl, or triazolyl.

wherein each R^{2x} is independently hydrogen, methyl, ethyl, propyl, butyl, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoroethyl, difluoroethyl, fluoroethyl, phenyl, phenylmethyl, phenylethyl, pyridinyl, pyrimidinyl, cyclopropyl, cyclobutyl, cyclohexyl, or oxetanyl, each of R^{2x} is optionally substituted with one, two, or three members selected from fluoro, chloro, bromo, or iodo;

wherein each R^{2y} is independently hydrogen, methyl, ethyl, propyl, butyl; and

wherein each R^{2z} is independently methyl, ethyl, propyl, or butyl;

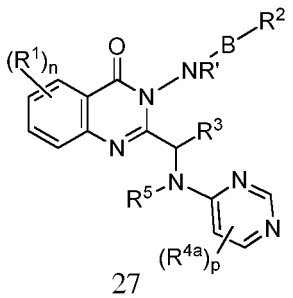
R^3 is hydrogen, methyl, ethyl, propyl, butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, or phenyl;

R^4 is a six- to ten-membered heteroaryl having at least one aromatic ring and at least two nitrogen atoms, wherein the heteroaryl is optionally substituted with one, two, or three members independently selected from fluoro, chloro, bromo, iodo, cyano, $-NH_2$, methyl, ethyl, and propyl; and

R^5 is hydrogen;

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0067] The compounds of formula (IV) may have the structure of formula (IVd):



(IVd),

wherein n, p, B, R′, R^1, R^2, R^3, R^{4a}, and R^5 are described herein,

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0068] In some other embodiments, the compounds have the structure of formula (IVd)

wherein:

n is 1 or 2;

R′ is methyl, ethyl, propyl, phenylmethyl, phenylethyl, or phenylpropyl;

each R^1 is independently selected from chloro, fluoro, bromo, iodo, methyl, ethyl, propyl, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoroethyl, difluoroethyl, and fluoroethyl;

R^2 is hydrogen, cyano, morpholinyl, $-NH_2$, $-NHR^{2x}$, $-NR^{2x}R^{2x}$, $-NHC(O)R^{2y}$, $-NR^{2y}C(O)R^{2x}$, $-C(O)NHR^{2y}$, $-C(O)NR^{2x}R^{2y}$, -OH, $-OR^{2y}$, $-SO_2R^{2z}$, pyrrolidinyl , piperidinyl, optionally substituted piperazinyl, phenyl, pyrazolyl, or triazolyl.

wherein each R^{2x} is independently hydrogen, methyl, ethyl, propyl, butyl, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoroethyl, difluoroethyl, fluoroethyl, phenyl, phenylmethyl, phenylethyl, pyridinyl, pyrimidinyl, cyclopropyl, cyclobutyl, cyclohexyl, or oxetanyl, each of R^{2x} is optionally substituted with one, two, or three members selected from fluoro, chloro, bromo, or iodo;

wherein each R^{2y} is independently hydrogen, methyl, ethyl, propyl, butyl; and

wherein each R^{2z} is independently methyl, ethyl, propyl, or butyl;

R^3 is hydrogen, methyl, ethyl, propyl, butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, or phenyl;

R^{4a} is cyano, $-NH_2$, fluoro, chloro, bromo, iodo, fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl, or trifluoroethyl;

R^5 is hydrogen;

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

[0069] In one embodiment, the PI3K inhibitors are compounds having the structures of any of the foregoing formulae (IIc), (IId), and (IIIb), wherein n, R^1, R^2, R^3, and R^5 are described herein; p is 2 or 3; and each R^{4a} is independently selected from cyano, $-NH_2$, fluoro, chloro, bromo, iodo, fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl, or trifluoroethyl. In some embodiment, the PI3K inhibitors are compounds having the structures of formula (IVd), wherein n, R^1, R^2, R^3, and R^5 are described herein; p is 2 or 3; and each R^{4a} is independently selected from cyano, $-NH_2$, fluoro, chloro, bromo, iodo, fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl, or trifluoroethyl. In other embodiment, the PI3K inhibitors are compounds having the structures of any of the foregoing formulae (J), (II), (IIa), (IIb), (IIc), and (IId), wherein B′ is C_{1-6} alkyl or C_{3-8} cycloalkyl, each of which is substituted with one or two members independently selected from cyano, $-OR^{2y}$, or $-SO_2R^{2z}$, wherein R^{2y} is hydrogen, methyl, ethyl, propyl, butyl, or pentyl, and wherein R^{2z} is methyl, ethyl, propyl, butyl, or pentyl. In other embodiment, the PI3K inhibitors are compounds having the structures of formula (IV), wherein B is C_{1-6} alkyl or C_{3-8} cycloalkyl, each of which is substituted with one or two members independently selected from cyano, $-OR^{2y}$, or $-SO_2R^{2z}$, wherein R^{2y} is hydrogen, methyl, ethyl, propyl, butyl, or pentyl, and wherein R^{2z} is methyl, ethyl, propyl, butyl, or pentyl. In some embodiments, the PI3K inhibitors are compounds having the structures of any of the foregoing formulae (J), (II) (IIa), (IIb), (IIc), and (IId), wherein B′ is C_{1-6} alkyl or C_{3-8} cycloalkyl, each of which is substituted with one member of $-SO_2R^{2z}$, wherein R^{2z} is methyl, ethyl, propyl, butyl, or pentyl. In certain embodiments, the PI3K inhibitors are compounds having the structures of any of the foregoing formulae (J), (II) (IIa), (IIb), (IIc), and (IId), wherein B′ is C_{1-6} alkyl or C_{3-8} cycloalkyl, each of which is substituted with one or two members of $-OR^{2y}$, wherein R^{2z} is hydrogen, methyl, ethyl, propyl, butyl, or pentyl. In other embodiments, compounds having the structures of any of the foregoing formulae (J), (II) (IIa), (IIb), (IIc), and (IId) wherein B′ is C_{1-6} alkyl or C_{3-8} cycloalkyl, each of which is substituted with one member of cyano. In other embodiment, the PI3K inhibitors are compounds having the structures of formula (IV), wherein B is C_{1-6} alkyl or C_{3-8} cycloalkyl, each of which is substituted with one or two members independently selected from cyano, $-OR^{2y}$, or $-SO_2R^{2z}$, wherein R^{2y} is hydrogen, methyl, ethyl, propyl, butyl, or pentyl, and wherein R^{2z} is methyl, ethyl, propyl, butyl, or pentyl. In certain embodiments, the PI3K inhibitors are compounds having the structures of formula (IV), wherein B is C_{1-6} alkyl or C_{3-8}

cycloalkyl, each of which is substituted with one or two members of $-OR^{2y}$, wherein R^{2z} is hydrogen, methyl, ethyl, propyl, butyl, or pentyl. In other embodiments, compounds having the structures of formulae (IV) wherein B is C_{1-6} alkyl or C_{3-8} cycloalkyl, each of which is substituted with one member of cyano. In other embodiment, the PI3K inhibitors are compounds having the structures of formulae (I), wherein B is C_{1-6} alkyl or C_{3-8} cycloalkyl, each of which is substituted with one or two members independently selected from cyano, $-OR^{2y}$, or $-SO_2R^{2z}$, wherein R^{2y} is hydrogen, methyl, ethyl, propyl, butyl, or pentyl, and wherein R^{2z} is methyl, ethyl, propyl, butyl, or pentyl. In some embodiments, the PI3K inhibitors are compounds having the structures of formulae (I) wherein B is C_{1-6} alkyl or C_{3-8} cycloalkyl, each of which is substituted with one member of $-SO_2R^{2z}$, wherein R^{2z} is methyl, ethyl, propyl, butyl, or pentyl. In certain embodiments, the PI3K inhibitors are compounds having the structures of formulae (I), wherein B is C_{1-6} alkyl or C_{3-8} cycloalkyl, each of which is substituted with one or two members of $-OR^{2y}$, wherein R^{2z} is hydrogen, methyl, ethyl, propyl, butyl, or pentyl. In other embodiments, compounds having the structures of any of the foregoing formulae (I), wherein B is C_{1-6} alkyl or C_{3-8} cycloalkyl, each of which is substituted with one member of cyano. In other embodiment, the PI3K inhibitors are compounds having the structures of any of the foregoing formulae (IVa), (IVb), (IVc), and (IVd), wherein B is C_{1-6} alkyl or C_{3-8} cycloalkyl, each of which is substituted with one or two members independently selected from cyano, $-OR^{2y}$, or $-SO_2R^{2z}$, wherein R^{2y} is hydrogen, methyl, ethyl, propyl, butyl, or pentyl, and wherein R^{2z} is methyl, ethyl, propyl, butyl, or pentyl. In certain embodiments, the PI3K inhibitors are compounds having the structures of the foregoing formulae (IVa), (IVb), (IVc), and (IVd),, wherein B is C_{1-6} alkyl or C_{3-8} cycloalkyl, each of which is substituted with one or two members of $-OR^{2y}$, wherein R^{2z} is hydrogen, methyl, ethyl, propyl, butyl, or pentyl. In other embodiments, compounds having the structures of any of the foregoing formulae (IVa), (IVb), (IVc), and (IVd), wherein B is C_{1-6} alkyl or C_{3-8} cycloalkyl, each of which is substituted with one member of cyano.

[0070] In one embodiment, n is 0. In some embodiments, n is 1, 2, 3, or 4. In some embodiments, n is 1, 2, or 3. In other embodiments, n is 1 or 2. In certain embodiments, n is 1 and the R^1 moiety may be located on any position of the phenyl of the quinazolinone ring. In another embodiment, n is 2. Both R^1 substituents or moieties may be the same or different. Two R^1 moieties may be located on any two positions of

the phenyl of the quinazolinone ring. By way of example, the first R^1 may be ortho, meta, or para to the second R^1. In yet another embodiment, n is 3. All the R^1 substituents or moieties may be the same or different, or two R^1 may be the same and different from the third R^1. Three R^1 moieties may be located on any three positions of the phenyl of the quinazolinone ring. For example, the first R^1 may be ortho to the second R^1, and the first R^1 may be para to the third R^1. In yet another embodiment, n is 4. All the R^1 substituents may be the same or different, three R^1 may be the same and different from the fourth R^1, two R^1 may be the same and different from the third and the fourth R^1.

[0071] In some other embodiments, each R^1 is independently halo, cyano, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} haloalkyl, optionally substituted C_{1-6} alkoxy, hydroxy, optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{4-8} heteroaryl, or optionally substituted C_{1-6} alkylsulfonyl. In certain embodiments, each R^1 is independently halo, cyano, optionally substituted C_{1-4} alkyl, optionally substituted C_{1-4} haloalkyl, optionally substituted C_{1-4} alkoxy, optionally substituted C_{3-6} cycloalkyl, or optionally substituted C_{1-4} alkylsulfonyl. In other embodiments, each R^1 is independently halo, cyano, C_{1-4} haloalkyl, C_{1-4} alkyl, or C_{1-4} alkylsulfonyl. In certain embodiments, each R^1 is independently selected from fluoro, chloro, iodo, bromo, cyano, methyl, ethyl, propyl, butyl, fluoromethyl, fluoroethyl, difluoromethyl, difluoroethyl, trifluoromethyl, trifluoroethyl, methylsulfonyl, ethylsulfonyl, or propylsulfonyl. In some embodiments, each R^1 is independently fluoro, chloro, bromo, iodo, cyano, methyl, ethyl, difluoromethyl (-CHF_2), trifluoromethyl (-CF_3), methoxy, methylsulfonyl (-SO_2CH_3), cyclopropylmethyl, or cyclopropyl. In certain embodiments, each R^1 is independently selected from chloro, fluoro, bromo, iodo, methyl, ethyl, or propyl. In one embodiment, each R^1 is independently fluoro, chloro, cyano, methylsulfonyl, methyl, or trifluoromethyl.

[0072] In one embodiment, m is 0. In some embodiments, m is 1. In the embodiment where m is 1, the compounds of the present application may have the structures of any of formulae (III), (IIIa), and (IIIb). In the embodiments where m is 1, the N atom of the NR′ moiety is attached to (or connects to) the quinazolinone ring. R′ is hydrogen or C_{1-6} alkyl optionally substituted with C_{6-10} aryl. In some embodiments, R′

is hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, phenylmethyl, phenylethyl, or phenylpropyl. R′ is hydrogen methyl, ethyl, propyl, phenylmethyl, or phenylethyl.

[0073] The present application provides that R^2 is cyano, morpholinyl, $-NR^{2x}R^{2x}$, $-NR^{2y}C(O)R^{2x}$, $-C(O)NR^{2x}R^{2y}$, $-OR^{2y}$, or $-SO_2R^{2z}$; where R^{2x} is hydrogen, optionally substituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{2-8} heterocycloalkyl, C_{4-8} heteroaryl; where R^{2y} is independently selected from hydrogen and C_{1-6} alkyl; wherein R^{2z} is C_{1-6} alkyl; and each of R^{2x}, R^{2y}, and R^{2z} is optionally substituted with one, two, or three members of halogens. Additionally, R^2 is hydrogen, cyano, $-NR^{2x}R^{2x}$, $-NR^{2y}C(O)R^{2x}$, $-C(O)NR^{2x}R^{2y}$, $-OR^{2y}$, $-SO_2R^{2z}$, optionally substituted C_{3-8} heterocycloalkyl, or optionally substituted C_{3-8} heteroaryl; where R^{2x} is hydrogen, optionally substituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{2-8} heterocycloalkyl, C_{4-8} heteroaryl; where R^{2y} is independently selected from hydrogen and C_{1-6} alkyl; wherein R^{2z} is C_{1-6} alkyl; and each of R^{2x}, R^{2y}, and R^{2z} is optionally substituted with one, two, or three members of halogens. In some embodiment, R^2 is hydrogen, cyano, $-NR^{2x}R^{2x}$, $-NR^{2y}C(O)R^{2x}$, $-C(O)NR^{2x}R^{2y}$, $-OR^{2y}$, or $-SO_2R^{2z}$, morpholinyl, pyrrolidinyl , piperidinyl, optionally substituted piperazinyl, phenyl, pyrazolyl, or triazolyl; where R^{2x} is hydrogen, optionally substituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{2-8} heterocycloalkyl, C_{4-8} heteroaryl; where R^{2y} is independently selected from hydrogen and C_{1-6} alkyl; wherein R^{2z} is C_{1-6} alkyl; and each of R^{2x}, R^{2y}, and R^{2z} is optionally substituted with one, two, or three members of halogens. In certain embodiments, R^2 is hydrogen, pyrrolidinyl, piperidinyl, optionally substituted piperazinyl, phenyl, pyrazolyl, or triazolyl. In certain other embodiments, R^2 is hydrogen, pyrrolidinyl, piperidinyl, phenyl, pyrazolyl, or triazolyl piperazinyl optionally substituted with C_{1-6} alkyl . In additional embodiments, R2 is hydrogen, pyrrolidinyl, piperidinyl, phenyl, pyrazolyl, or triazolyl piperazinyl optionally substituted with methyl, ethyl, propyl, or butyl. In certain embodiments, R^2 is cyano, morpholinyl, $-NR^{2x}R^{2x}$, $-NR^{2y}C(O)R^{2x}$, $-C(O)NR^{2x}R^{2x}$, $-OR^{2y}$, $-SO_2R^{2z}$, wherein R^{2x} is hydrogen, C_{1-6} alkyl optionally substituted with C_{6-10} aryl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-8} cycloalkyl optionally substituted with one to three members of halogen atoms, C_{2-8} heterocycloalkyl, or C_{4-8} heteroaryl; R^{2y} is independently selected from hydrogen and C_{1-6} alkyl; and R^{2z} is C_{1-6} alkyl. In further embodiments, R^2 is cyano, $-NH_2$, $-NHR^{2x}$ (wherein R^{2x} is methyl, butyl, propyl, phenylmethyl, phenylethyl, phenyl, pyridinyl,

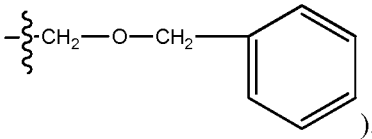
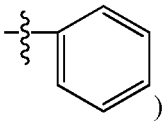
pyrimidinyl, cyclobutyl, oxetanyl, cyclohexyl which is optionally substituted with one or two fluoro atoms), -NHC(O)H, -NHC(O)R^{2y} (wherein R^{2y} is methyl, ethyl, propyl, or butyl), $NR^{2x}R^{2y}$ (where R^{2x} is methyl, ethyl, propyl, butyl, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoroethyl, difluoroethyl, fluoroethyl, phenylmethyl, or phenylethyl; and R^{2y} is methyl, ethyl, or propyl), -OH, -OR^{2y} (wherein R^{2y} is methyl, ethyl, propyl, or butyl), and -SO_2 NHR^{2x} (wherein R^{2z} is methyl, ethyl, propyl, or butyl). In further other embodiments, R^2 is cyano, morpholinyl, -NH_2, -$NHCH_3$, -$NHCH_2CH_3$, -NHC_2H_5, -$NH(CH_2)_2CH_3$, -$NHCH(CH_3)_2$, -$NH(CH_2)_3CH_3$, -$NH(CH_2)_4CH_3$, -$NH(CH_2)_5CH_3$, -$NHC(CH_3)_3$, -$NHCH_2C_6H_5$, NH-pyridinyl, NH-pyrimidinyl, -NHcyclopropyl (i.e. -NHC_3H_5), -NHcycylobutyl (i.e. -NHC_4H_7), -NHcyclopentyl (i.e. -NHC_6H_{11}), -NHcyclohexyl (i.e. -NHC_6H_{11}) substituted with two fluoride atoms (which may also be referred to as -NH(difulorocyclohexyl)), -NHoxetanyl (i.e. NHC_3H_5O), -$NHC(O)CH_3$, -$NHC(O)C_2H_5$, -NHC(O)H, -$N(CH_3)(CH_3)$, -$N(CH_3)(CH_2CF_3)$, -$N(CH_3)(CH_2C_6H_5)$, -OH, -OCH_3, -OC_2H_5, -$CONH_2$, $CON(CH_3)(CH_3)$, -SO_2CH_3, -$SO2C_2H_5$, and -$SO_2C_3H_7$.

[0074] In the present application, B′ is C_{1-6} alkyl optionally substituted with hydroxyl, C_{1-6} alkoxy, or C_{3-8} cycloalkyl; C_{3-8} cycloalkyl optionally substituted with hydroxyl or C_{1-6} alkoxy; or C_{1-6} heteroalkyl optionally substituted with C_{1-6} alkyl or C_{6-10} arylC_{1-6} alkyl. In some embodiments, B′ is C_{1-6} alkyl optionally substituted with one, two, or three members independently selected from hydroxyl and C_{1-6} alkoxy. In certain embodiments, B′ is C_{3-8} cycloalkyl optionally substituted with one, two, or three members independently selected from hydroxyl and C_{1-6} alkoxy. In other embodiments, B′ is C_{1-6} alkyl or C_{3-8} cycloalkyl, each of the alkyl or cycloalkyl moieties is optionally substituted with one, two, or three members independently selected from hydroxyl and C_{1-6} alkoxy. In other embodiments, B′ is C_{1-6} heteroalkyl optionally substituted with one, two, or three members selected from C_{1-6} alkyl and C_{6-10} arylC_{1-6} alkyl. In some other embodiments, B′ is C_{1-6} alkyl, which is optionally substituted with one, two, or three members independently selected from methoxy, ethoxy, and hydroxyl. In yet some other embodiments, B′ is C_{3-8} cycloalkyl optionally substituted with one, two, or three members independently selected from methoxy, ethoxy, and hydroxyl. In additional other embodiments, B′ is C_{1-6} haloalkyl optionally substituted with one, two, or three members independently selected from methyl, ethyl, propyl, phenylmethyl, phenylethyl,

and phenylpropyl. In further embodiments, B′ is methyl, ethyl, propyl, butyl, pentyl, or hexyl, each of which is optionally substituted with one, two, or three members independently selected from methoxy, ethoxy, and hydroxyl. In other further embodiments, B′ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, each of which is optionally substituted with one, two, or three members independently selected from methoxy, ethoxy, and hydroxyl. In additional other embodiments, B′ is C_{1-6} haloalkyl having nitrogen atom, wherein carbon atoms of the haloalkyl moiety is optionally substituted with one, two, or three members independently selected from methyl, ethyl, propyl, phenylmethyl, phenylethyl, and phenylpropyl.

[0075] Also in the present application, B is C_{1-6} alkyl or C_{3-8} cycloalkyl, each of which is optionally substituted with hydroxyl or C_{1-6} alkoxy. In some embodiments, B is C_{1-6} alkyl optionally substituted with one, two, or three members independently selected from hydroxyl and C_{1-6} alkoxy. In certain embodiments, B is C_{3-8} cycloalkyl optionally substituted with one, two, or three members independently selected from hydroxyl and C_{1-6} alkoxy. In some other embodiments, B is C_{1-6} alkyl, which is optionally substituted with one, two, or three members independently selected from methoxy, ethoxy, or hydroxyl. In yet some other embodiments, B is C_{3-8} cycloalkyl optionally substituted with one, two, or three members independently selected from methoxy, ethoxy, and hydroxyl. In further embodiments, B is methyl, ethyl, propyl, butyl, pentyl, or hexyl, each of which is optionally substituted with one, two, or three members independently selected from methoxy, ethoxy, and hydroxyl. In other further embodiments, B is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, each of which is optionally substituted with one, two, or three members independently selected from methoxy, ethoxy, and hydroxyl. Each and every variation of B or B′ may be combined with each and every variation of n, m, R′, R^1, R^2, R^3, R^4, and R^5 as described herein. It is understood that the divalent groups B and B′ may be represented by the alkyl terms as defined above. For example, B is methylene, ethylene, propylene, butylene, pentylene, hexylene, cyclopropylene, cyclobutylene, cyclopentylene, or cyclohexylene may be represented by methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, respectively.

[0076] In certain embodiments, R^3 is hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} cycloalkyl, or optionally substituted C_{6-10} aryl. In one

embodiment, R^3 is hydrogen, C_{3-6} cycloalkyl, C_{6-10} aryl, or C_{1-6} alkyl optionally substituted with hydroxy, C_{6-10} arylC_{1-6} alkoxy, or C_{3-6} cycloalkyl. In some embodiments, R^3 is hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclobutylethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -CH_2OH, -C_2H_4OH, -C_3H_6OH, benzyloxymethyl (i.e. ), or phenyl (i.e. ). In some other embodiments, R^3 is methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, or phenyl.

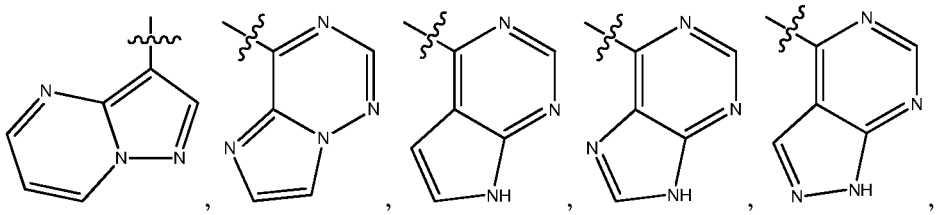
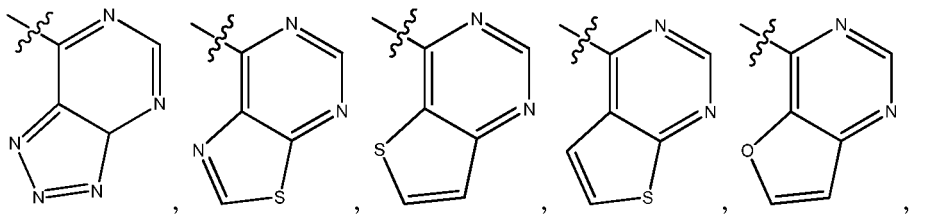
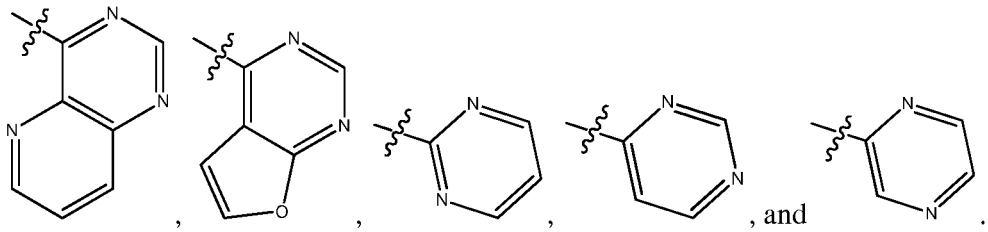
[0077] In additional embodiments, R^5 is hydrogen or optionally substituted C_{1-6} alkyl. In some embodiments, R^5 is hydrogen or C_{1-4} alkyl. In certain embodiments, R^5 is hydrogen, methyl, ethyl, propyl or butyl. In certain other embodiments, R^5 is hydrogen.

[0078] In further embodiments, R^3 and R^5 with the atoms to which they are attached (e.g. carbon and nitrogen, respectively) optionally form a heterocyclic ring. In some embodiments, the R^3-R^5 heterocyclic ring is optionally substituted with fluoro, chloro, bromo, or iodo. In other embodiments, the R^3-R^5 heterocyclic ring is a three- to eight-membered heterocycloalkyl (i.e. heterocycloalkyl having three to eight ring members and at least one ring member is a heteroatom). In other embodiments, the R^3-R^5 heterocyclic ring is a four- to seven-membered heterocycloalkyl (i.e. heterocycloalkyl having four to seven ring members and at least one ring member is a heteroatom). In one embodiment, the R^3-R^5 heterocyclic ring is a five-membered heterocycloalkyl. In certain other embodiments, the R^3-R^5 heterocyclic ring is C_{3-8} heterocycloalkyl. In certain embodiments, the R^3-R^5 heterocyclic ring is azepanyl, azetidinyl, piperidinyl, or pyrrolidinyl. In some other embodiments, the R^3-R^5 heterocyclic ring is pyrrolidinyl. In one other embodiment, the R^3-R^5 heterocyclic ring is a five-membered heterocycloalkyl substituted with halo. In other additional embodiments, the R^3-R^5 heterocyclic ring is pyrrolidinyl substituted with fluoro, chloro, bromo, or iodo.

[0079] In one embodiment, R^4 is heteroaryl having at least two nitrogen atoms and at least one aromatic ring, and R^4 heteroaryl is optionally substituted one, two, or three members independently selected from halo, cyano, -NH_2, C_{1-6} alkyl, and C_{1-6} haloalkyl. In certain embodiments, R^4 heteroaryl is a six- to twelve-membered heteroaryl (i.e.

heteroaryl having six to twelve ring members). In certain other embodiments, R^4 heteroaryl is a six- to ten-membered heteroaryl (i.e. heteroaryl having six to ten ring members). R^4 heteroaryl may be a monocyclic or bicyclic heteroaryl. In some embodiments, R^4 heteroaryl is a monocyclic heteroaryl having at least two nitrogen atoms. In certain embodiments, R^4 heteroaryl is a bicyclic heteroaryl having at least one aromatic ring, at least two nitrogen atoms, and at least one additional heteroatom selected from N, O, or S. In certain other embodiments, R^4 is selected from purinyl, pyrimidinyl, thiazolopyrimidinyl, pyridopyrimidinyl, thienopyrimidinyl, pyrrolopyrimidinyl, furopyrimidinyl, or imidazotriazinyl.

[0080] In any of the foregoing formulae, R^4 is heteroaryl optionally substituted with one, two, or three members independently selected from halo, cyano, $-NH_2$, C_{1-6} alkyl, and C_{1-6} haloalkyl, wherein the R^4 heteroaryl is selected from the group consisting of

[0081] In some other embodiments, R^4 is optionally substituted with one to three members independently selected from fluoro, chloro, bromo, iodo, cyano, methyl, ethyl, propyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl, and $-NH_2$. In yet other embodiments, R^4 is optionally substituted with one to three members independently selected from fluoro, chloro, and bromo.

[0082] In certain other embodiments, R^4 is selected from purinyl, pyrimidinyl, thiazolopyrimidinyl, pyridopyrimidinyl, thienopyrimidinyl, pyrrolopyrimidinyl, furopyrimidinyl, and imidazotriazinyl, each of which is optionally substituted with one, two, or three members independently selected from chloro, fluoro, bromo, iodo, methyl, ethyl, propyl, cyano, and $-NH_2$. In certain other embodiments, R^4 is selected from thiazolopyrimidinyl, pyridopyrimidinyl, thienopyrimidinyl, pyrrolopyrimidinyl, furopyrimidinyl, and imidazotriazinyl, each of which is optionally substituted with one or two members independently selected from chloro, fluoro, bromo, iodo, methyl, ethyl, propyl, cyano, and $-NH_2$. In other embodiments, R^4 is selected from thiazolopyrimidinyl, pyridopyrimidinyl, thienopyrimidinyl, pyrrolopyrimidinyl, furopyrimidinyl, and imidazotriazinyl, each of which is optionally substituted with independently chloro, fluoro, bromo, iodo, methyl, ethyl, propyl, cyano, and $-NH_2$. In other embodiments, R^4 is selected from thiazolopyrimidinyl, pyridopyrimidinyl, thienopyrimidinyl, pyrrolopyrimidinyl, furopyrimidinyl, and imidazotriazinyl, each of which is optionally substituted with independently with one member selected from chloro, fluoro, bromo, and iodo. In other embodiments, R^4 is selected from thiazolopyrimidinyl, pyridopyrimidinyl, thienopyrimidinyl, pyrrolopyrimidinyl, furopyrimidinyl, and imidazotriazinyl, each of which is optionally substituted with one or two members independently selected from chloro, fluoro, bromo, iodo, methyl, ethyl, propyl, cyano, and $-NH_2$. In certain other embodiments, R^4 is pyrimidinyl or pyrazinyl, each substituted with two or three members independently selected from chloro, fluoro, bromo, iodo, methyl, ethyl, propyl, cyano, and $-NH_2$. Each and every variation of n, m, R′, R^2, R^1, R^2, R^3, R^4, and R^5 may be combined with each and every variation thereof as described above.

[0083] In some embodiments, A is C(O). In certain embodiments, A is a single bond. Each and every variation of A may be combined with each and every variation of n, m, R′, R^1, R^2, R^3, R^4, and R^5 as described above. In some other embodiments, A is C(O) and R^4 heteroaryl is a bicyclic group defined above. In other embodiments, A is a single bond and R^4 heteroaryl is a bicyclic group defined above. In additional embodiments, A is C(O) and R^4 heteroaryl is a monocyclic group selected from pyrimidinyl and pyrazinyl. In other embodiments, A is a single bond and R^4 heteroaryl is a monocyclic group selected from pyrimidinyl and pyrazinyl.

[0084] In further embodiments, A′ is OR^4. In some further embodiments, A′ is $N(R^5)C(O)R^4$. In yet further embodiments, A′ is NR^5R^4. Each and every variation of A′ may be combined with each and every variation of n, m, $R^{2'}$, R^1, R^3, R^4, and R^5 as described above.

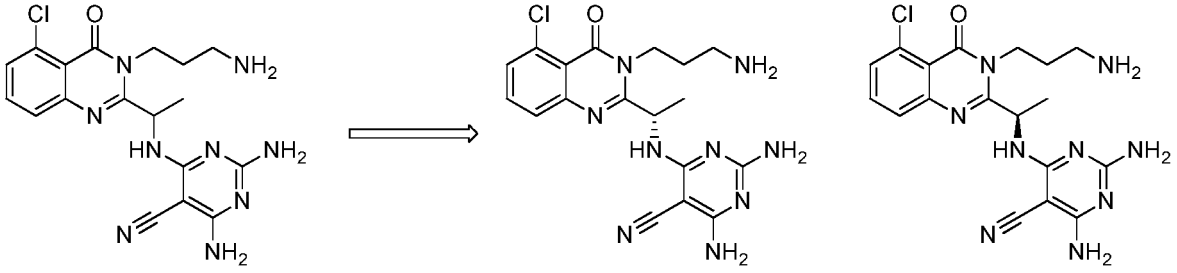
[0085] In certain embodiments, W is CH or N. In certain other embodiments, W is CH. In yet other embodiments, W is N. Each and every variation of W may be combined with each and every variation of n, m, A′, $R^{2'}$, R^1, R^2, R^3, R^4, and R^5 as described above.

[0086] In the formulae (IIc), (IId), (IIIa), and (IIIb), n, R^1, R^2, R^3, and R^5 as described herein; p is 0, 1, 2, or 3; and R^{4a} is independently selected from halo, cyano, $-NH_2$, and optionally substituted C_{1-6} alkyl. In the formula (IVd), n, R^1, R^2, R^3, and R^5 as described herein; p is 0, 1, 2, or 3; and R^{4a} is independently selected from halo, cyano, $-NH_2$, and optionally substituted C_{1-6} alkyl. In one embodiment, p is 0. In certain embodiments, p is 1, 2, or 3. In some embodiments, p is 1 or 2. In some embodiments, p is 1 and R^{4a} moiety may be located on any position of the pyrimdinyl or pyrazinyl ring. In another embodiment, p is 2 and both R^{4a} substituents or moieties may be the same or different; each of the two R^{4a} moiety may be located on any position of the pyrimdinyl or pyrazinyl ring. In yet another embodiment, p is 3 and all R^{4a} substituents may be the same or different, or two R^{4a} may be the same and different from the third R^{4a}.

[0087] In the present application, each R^{4a} is independently selected from halo, $-NH_2$, cyano, C_{1-6} haloalkyl, and C_{1-6} alkyl. In some embodiments, each R^{4a} is independently selected from fluoro, chloro, bromo, iodo, cyano, $-NH_2$, methyl, ethyl, propyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, and difluoroethyl. In additional embodiments, p is 2 or 3, and each R^{4a} is independently selected from fluoro, chloro, bromo, iodo, cyano, $-NH_2$, methyl, and ethyl. Each and every variation of p and R^{4a} may be combined with each and every variation of n, R′, R^1, R^2, R^3, and R^5 as described above.

[0088] The compounds of the present application may bear one or more chiral centers. The compounds bearing the chiral center have the same molecular formula and the same chemical name with different stereoisomer designations. For example, the below 2,4-diamino-6-((1-(3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-

yl)ethyl)amino)pyrimidine-5-carbonitrile bearing one chiral center can be resolved into the (S) and (R) enantiomers, (S)-2,4-diamino-6-((1-(3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile and (R)-2,4-diamino-6-((1-(3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile.



[0089] Representative compounds of the present application are listed in Table 1 below. Additional compounds are listed in Table 1a. The compounds may be named using the nomenclature systems and symbols that are commonly recognized in the art of chemistry including, for example, ChemBioDraw Ultra 12.0, Chemical Abstract Service (CAS), and International Union of Pure and Applied Chemistry (IUPAC). For example, compound 42 in table 1 may be named as tert-butyl N-[3-[5-chloro-2-[(1S)-1-[(2,6-diamino-5-cyano-pyrimidin-4-yl)amino]ethyl]-4-oxo-quinazolin-3-yl]propyl]carbamateor (S)-2,4-diamino-6-((1-(3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile by using IUPAC or ChemBioDraw Ultra 12.0, respectively.

Table 1. Representative Compounds

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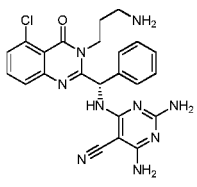
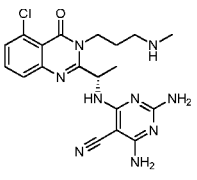
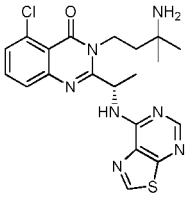
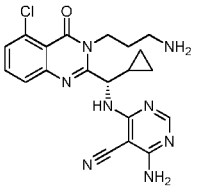
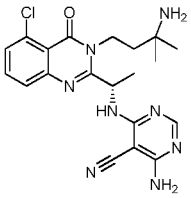
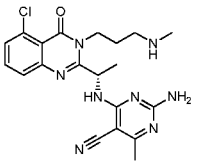
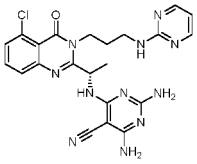
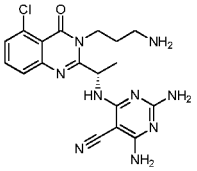
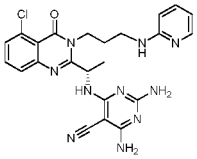
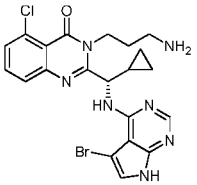
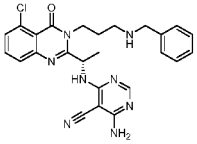
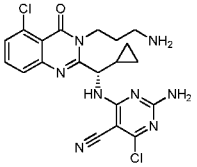
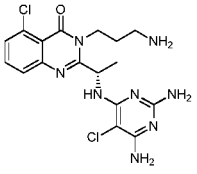
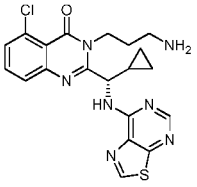
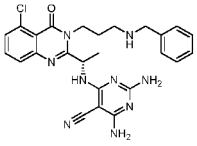
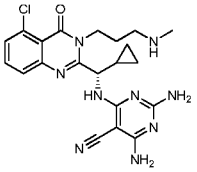
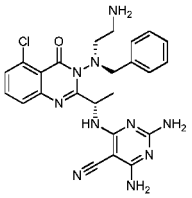
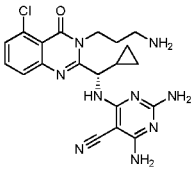
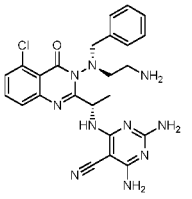
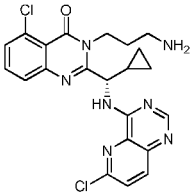
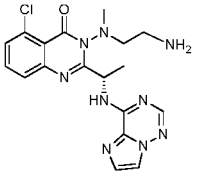
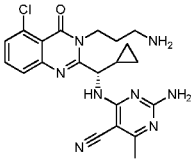
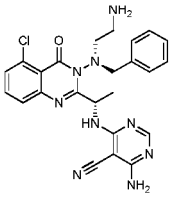
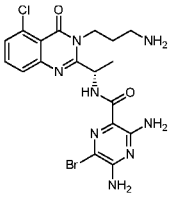
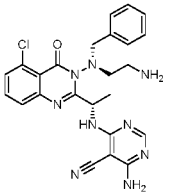
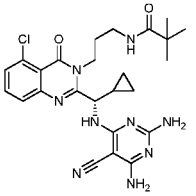
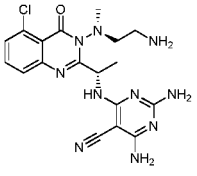
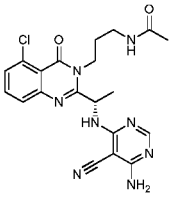
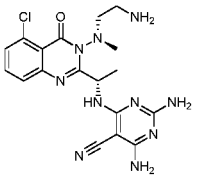
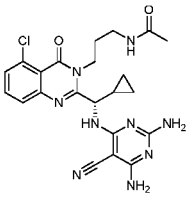
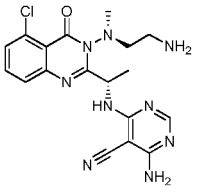
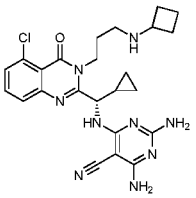
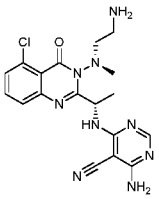
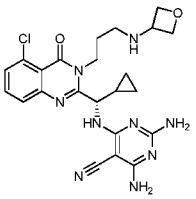
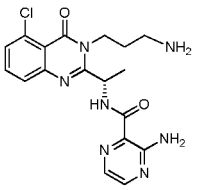
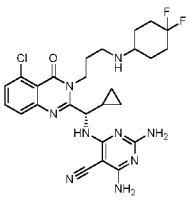
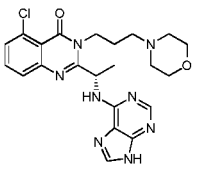
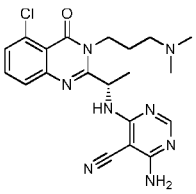
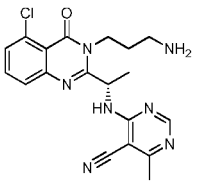
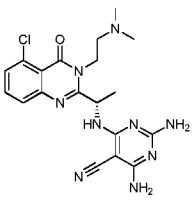
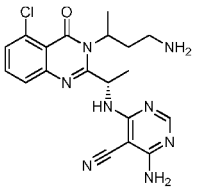
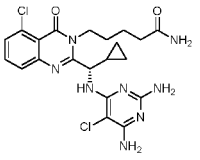
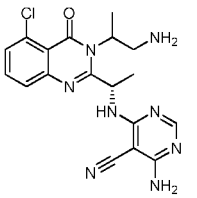
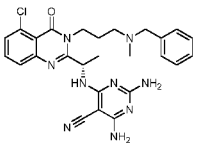
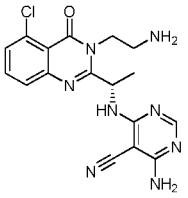
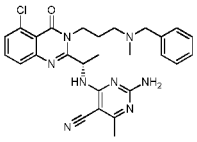
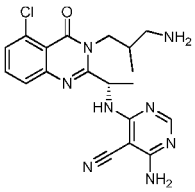
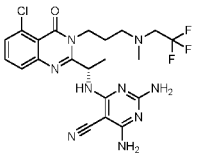
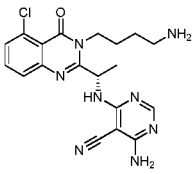
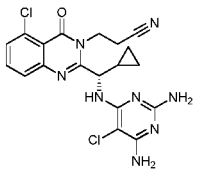
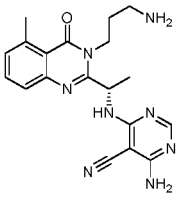
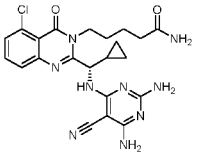
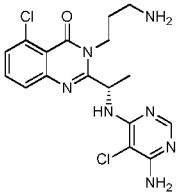
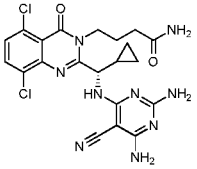
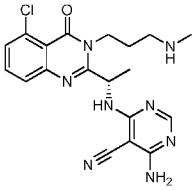
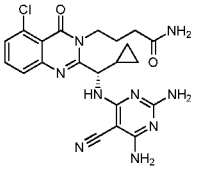
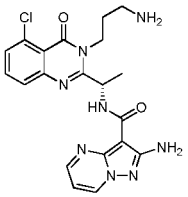
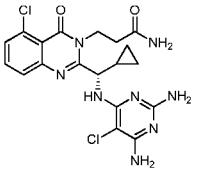
1		39	

2		40	
3		41	
4		42	
5		43	
6		44	
7		45	
8		46	

9		47	
10		48	
11		49	
12		50	
13		52	
14		51	
15		53	

16		54	
17		55	
18		56	
19		57	
23		58	
24		59	
25		60	

26		61	
27		62	
28		63	
29		64	
30		65	
31		66	
32		68	

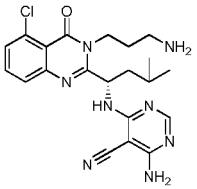
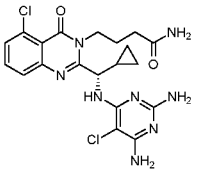
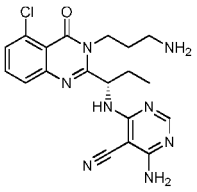
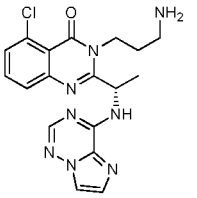
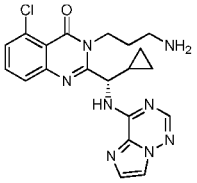
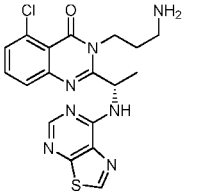
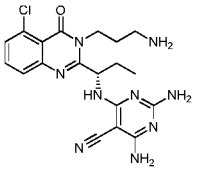
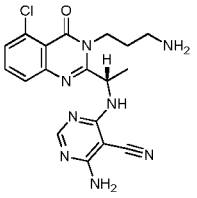
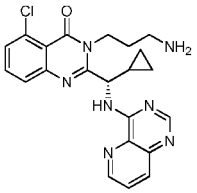
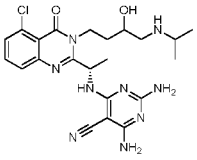
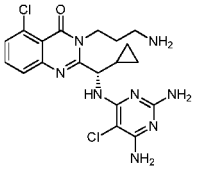
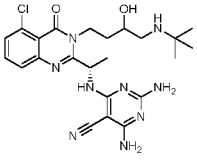
33		69	
34		71	
35		72	
36		73	
37		74	
38		75	

Table 1a. Representative Compounds

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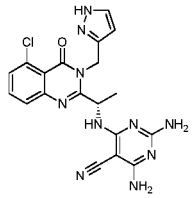
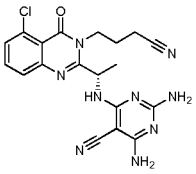
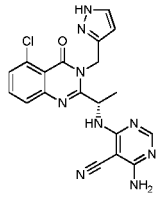
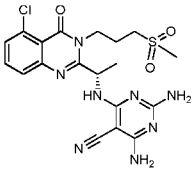
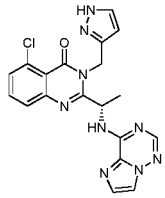
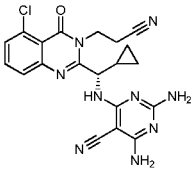
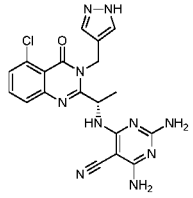
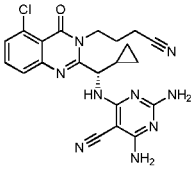
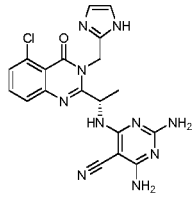
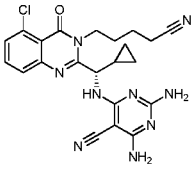
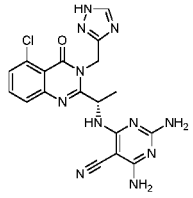
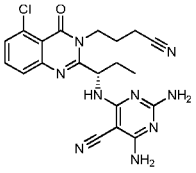
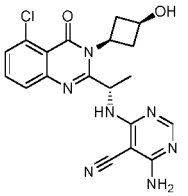
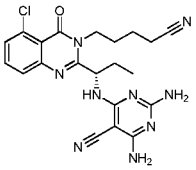
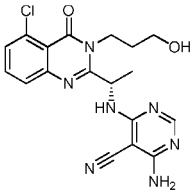
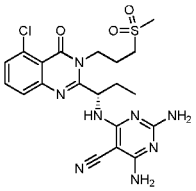
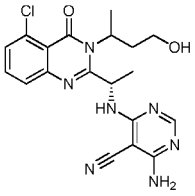
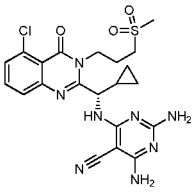
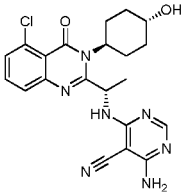
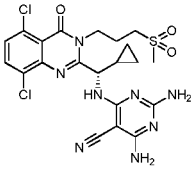
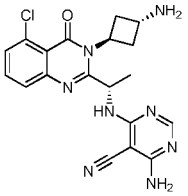
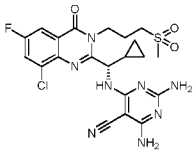
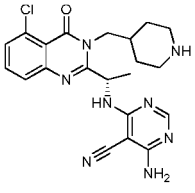
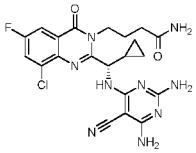
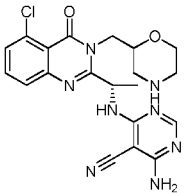
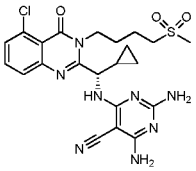
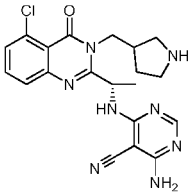
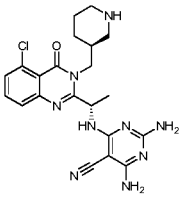
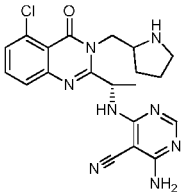
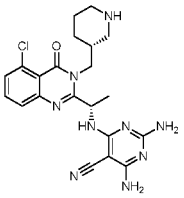
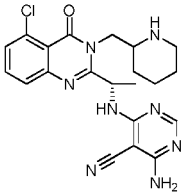
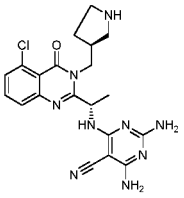
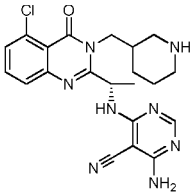
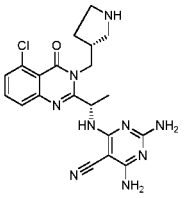
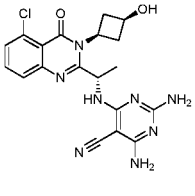
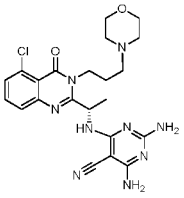
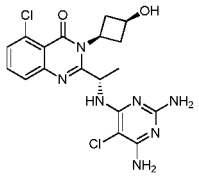
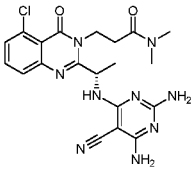
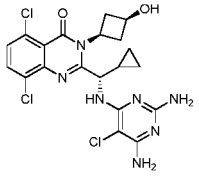
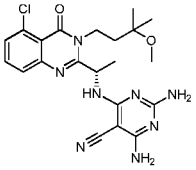
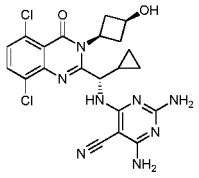
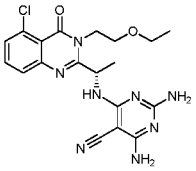
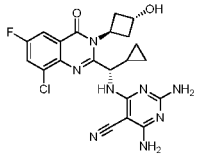
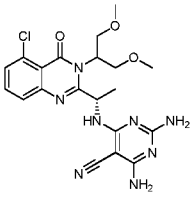
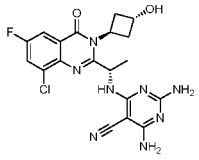
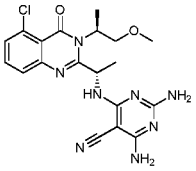
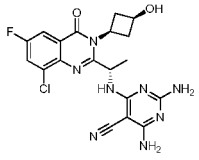
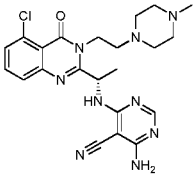
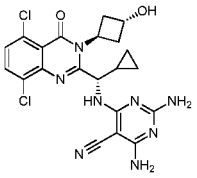
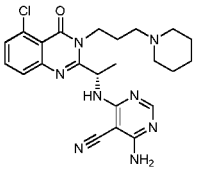
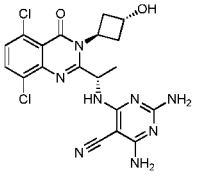
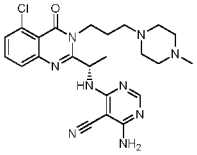
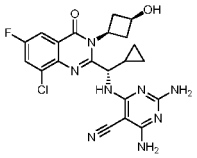
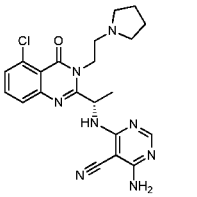
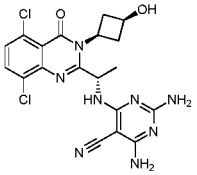
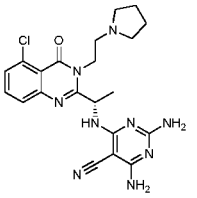
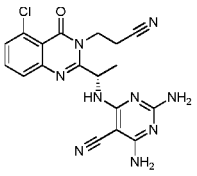
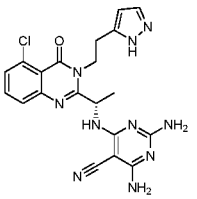
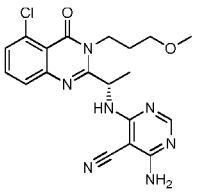
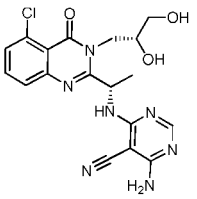
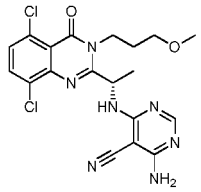
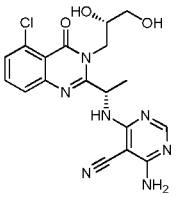
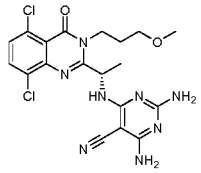
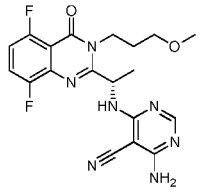
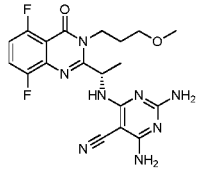
76		110	
77		111	
78		112	
79		113	
80		114	
81		115	

82		116	
83		117	
84		118	
85		119	
86		120	
87		121	

88		122	
89		123	
90		124	
91		125	
92		126	
93		127	

94		128	
95		129	
96		130	
97		131	
98		132	
99		133	

100		134	
101		135	
102		136	
103		137	
104		140	
105		142	

106		143	
107			
108			
109			

[0090] The present application provides pharmaceutically acceptable salts, hydrates, solvates, isomers, tautomers, stereoisomers, enantiomers, racemates, atropisomers, polymorphs, prodrugs, or a mixture thereof, of the compounds described herein. In addition, the present application provides the compounds in which from 1 to n hydrogen atoms attached to a carbon atom may be replaced by a deuterium atom or D, in which n is the number of hydrogen atoms in the molecule. It is known that the deuterium atom is a non-radioactive isotope of the hydrogen atom. Such compounds may increase resistance to metabolism, and thus may be useful for increasing the half-life of the compounds of any of the formulae described herein or pharmaceutically acceptable salts, isomers, prodrugs, or solvates thereof, when administered to a mammal. *See, e.g.*,

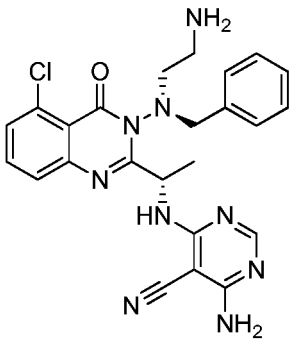
Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism", Trends Pharmacol. Sci., 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogen atoms have been replaced by deuterium.

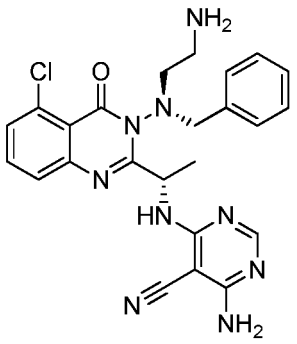
[0092] The terms "a compound of the present application," "a compound described herein," "a compound of any of the formulae described herein," or variant thereof refer to a compound having the structure of any of the formulae (J), (I), (II), (IIa), (IIb), (IIc), (IId), (III), (IIIa), and (IIIb). The terms "a compound of the present application," "a compound described herein," "a compound of any of the formulae described herein," or variant thereof also refer to a compound having the structure of any of the formulae (IV), (IVa), (IVb), (IVc), and (IVd). In one embodiment, compounds of the present application are Compounds 1-143 as described herein.

[0093] "Pharmaceutically acceptable" or "physiologically acceptable" refer to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use. "Pharmaceutically acceptable salts" or "physiologically acceptable salts" refer to salts of pharmaceutical compounds that retain the biological effectiveness and properties of the underlying compound, and which are not biologically or otherwise undesirable. There are acid addition salts and base addition salts. Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Acids and bases useful for reaction with an underlying compound to form pharmaceutically acceptable salts (acid addition or base addition salts respectively) are known to one of skill in the art. Similarly, methods of preparing pharmaceutically acceptable salts from an underlying compound (upon disclosure) are known to one of skill in the art and are disclosed in for example, Berge, at al. Journal of Pharmaceutical Science, Jan. 1977 vol. 66, No.1, and other sources. If the compounds described herein are obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds.

[0094] "Isomers" refers to compounds that have the same molecular formula. As used herein, the term isomers include double bond isomers, racemates, stereoisomers, enantiomers, diastereomers, and atropisomers. Single isomers, such as enantiomers or diastereomers, can be obtained by asymmetric synthesis or by resolution of a mixture of isomers. Resolution of a mixture of isomers (e.g. racemates) maybe accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral high pressure liquid chromatography (HPLC) column. "Double bond isomers" refer to Z- and E- forms (or *cis*- and *trans*- forms) of the compounds with carbon-carbon double bonds.

[0095] "Atropisomers" refers to conformational stereoisomers which occur when rotation about a single bond in the molecule is prevented, or greatly hindered, as a result of steric interactions with other parts of the molecule and the substituents at both ends of the single bond are asymmetrical, *i.e.*, they do not require a stereocenter. Where the rotational barrier about the single bond is high enough, and interconversion between conformations is slow enough, separation and isolation of the isomeric species may be permitted. Atropisomers may be separated by the methods well known in the art. Unless otherwise indicated, the description is intended to include individual atropisomers as well as mixtures. Also, as understood by those skilled in the art, the atropisomers may be represented by the same chemical name with different atropisomer designations. By way of example, the below structures are atropisomers of compound 11, (S)-3-((2-aminoethyl)(methyl)amino)-5-chloro-2-(1-(imidazo[2,1-f][1,2,4]triazin-4-ylamino)ethyl)quinazolin-4(3H)-one.





[0096] "Racemates" refers to a mixture of enantiomers.

[0097] "Stereoisomers" or "stereoisomeric forms" refer to compounds that differ in the chirality of one or more stereocenters. Stereoisomers include enantiomers and diastereomers. The compounds may exist in stereoisomeric form if they possess one or more asymmetric centers or a double bond with asymmetric substitution and, therefore, can be produced as individual stereoisomers or as mixtures. Unless otherwise indicated, the description is intended to include individual stereoisomers as well as mixtures. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (*see, e.g.,* Chapter 4 of Advanced Organic Chemistry, 4th ed., J. March, John Wiley and Sons, New York, 1992).

[0098] "Tautomers" or "tautomeric formers" refer to alternate forms of a compound that differ in the position of a proton, such as enol-keto and imine-enamine tautomers, or heteroaryls such as pyrazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles.

[0099] A "solvate" is formed by the interaction of a solvent and a compound. Solvates of salts of the compounds of any of the formulae described herein are also provided. Hydrates of the compounds of any of the formulae are also provided.

[00100] A "prodrug" is defined in the pharmaceutical field as a biologically inactive derivative of a drug that upon administration to the human body is converted to the biologically active parent drug according to some chemical or enzymatic pathway.

[00101] In any one of the foregoing embodiments, the compound described herein or a pharmaceutically acceptable salt thereof is an (S)-enantiomer. In any one of the foregoing embodiments, the compound described herein or a pharmaceutically acceptable salt thereof is an (R)-enantiomer. In any one of the foregoing embodiments, the compound described herein or a pharmaceutically acceptable salt thereof is an atropisomer.

[00102] The application also provides a composition containing a mixture of enantiomers of the compound or a pharmaceutically acceptable salt thereof. In one embodiment, the mixture is a racemic mixture. In other embodiments, the composition comprises the (S)-enantiomer of a compound in excess of over the corresponding the (R)-enantiomer of the compound. In some embodiments, the composition contains the (S)-enantiomer of the compound and is substantially free of its corresponding (R)-enantiomer. In certain embodiments, a composition substantially free of the (R)-

enantiomer has less than or about 40%, 35%, 30%, 25%, 20%, 15%, 10%, 5%, 1%, 0.05%, or 0.01% of the (R)-enantiomer. In other embodiments, the composition containing the (S)-enantiomer of a compound or a pharmaceutically acceptable salt thereof, predominates over its corresponding (R)-enantiomer by a molar ratio of at least or about 9:1, at least or about 19:1, at least or about 40:1, at least or about 80:1, at least or about 160:1, or at least or about 320:1.

[00103] The composition containing a compound according to any of the formulae described herein or a pharmaceutically acceptable salt thereof, may also contain the compound in enantiomeric excess (e.e.). By way of example, a compound with 95% (S)-isomer and 5% (R)-isomer will have an e.e. of 90%. In some embodiments, the compound has an e.e. of at least or about 60%, 75%, 80%, 85%, 90%, 95%, 98% or 99%.

[00104] In any one of the foregoing embodiments, the compound or a pharmaceutically acceptable salt thereof, is an atropisomer. Another embodiment provides the composition containing a mixture of atropisomers of the compound or a pharmaceutically acceptable salt thereof. By way of example, a compound with 95% of one atropisomer and 5% of the other atropisomers. In some embodiments, a compound with about 90, 80, 70, 60, 50, 40, 30, 20, or 10% of one atropisomer and 10, 20, 30, 40, 50, 60, 70, 80, or 90%, respectively, of the other atropisomers.

[00105] The application also provides the free base forms of the compounds described herein. In certain embodiments, provided herein are the enantiomers, (R) or (S), of the compounds of the formulae described herein. In other embodiments, provided herein are the atropisomers of the compounds of the formulae described herein.

[00106] The application further provides compositions comprising the compounds described herein or a pharmaceutically acceptable salt, isomer, prodrug, or solvate thereof. The composition may include racemic mixtures, mixtures containing an enantiomeric excess of one enantiomer or single diastereomers or diastereomeric mixtures. All such isomeric forms of these compounds are expressly included herein, the same as if each and every isomeric form were specifically and individually listed.

[00107] In certain embodiments, provided herein are also polymorphs, such as crystalline and amorphous forms, of the compounds described herein. In some

embodiments, provided are also chelates, non-covalent complexes, and mixtures thereof, of the compounds of the formula described herein or pharmaceutically acceptable salts, prodrugs, or solvates thereof. A "chelate" is formed by the coordination of a compound to a metal ion at two (or more) points. A "non-covalent complex" is formed by the interaction of a compound and another molecule wherein a covalent bond is not formed between the compound and the molecule. For example, complexation can occur through van der Waals interactions, hydrogen bonding, and electrostatic interactions (also called ionic bonding).

[00108] Therapeutic Uses of the Compounds

[00109] The compounds of the formulae described herein or a pharmaceutically acceptable salt, isomer, prodrug, or solvate thereof may be used for the treatment of diseases and/or conditions mediated by PI3K isoforms. In addition, the application provides the compounds for use in therapy. Also, provided herein are methods for inhibiting one or more PI3K isoforms. In one embodiment, provided are methods for inhibiting PI3Kδ activity using the compound described herein or a pharmaceutically acceptable salt, isomer, prodrug, or solvate thereof. In other embodiment, provided are methods for inhibiting PI3Kδ and/or PI3Kβ activities using the compound or a pharmaceutically acceptable salt, isomer, prodrug, or solvate thereof. The application further provides methods for use in such methods. The PI3K isoforms may be selectively or specifically inhibited. Additionally, the compounds may be used to inhibit PI3K activity therapeutically or prophylactically, such as PI3Kδ and/or PI3Kβ.

[00110] The compounds according to the present application may be used in combination with one or more additional therapeutic agents. The therapeutic agents may be in the forms of compounds, antibodies, polypeptides, or polynucleotides. The therapeutic agent includes, but is not limited to, a chemotherapeutic agent, an immunotherapeutic agent, a radiotherapeutic agent, an anti-neoplastic agent, an anti-cancer agent, an anti-proliferation agent, an anti-fibrotic agent, an anti-angiogenic agent, a therapeutic antibody, or any combination thereof. In one embodiment, the application provides a product comprising a compound described herein and an additional therapeutic agent as a combined preparation for simultaneous, separate or sequential use in therapy, *e.g.* a method of treating a disease, disorder, or condition that is mediated by PI3K isoforms.

[00111] Also, the therapeutic agents may be those that inhibit or modulate the activities of Bruton's tyrosine kinase, spleen tyrosine kinase, apoptosis signal-regulating kinase, Janus kinase, lysyl oxidase, lysyl oxidase-like proteins, matrix metallopeptidase, bromodomain-containing protein, adenosine A2B receptor, isocitrate dehydrogenase, serine/threonine kinase TPL2, discoidin domain receptor, serine/threonine-protein kinases, IKK, MEK, EGFR, histone deacetylase, protein kinase C, or any combination thereof. In certain embodiments, the therapeutic agent may be selected from a PI3K (including PI3Kγ, PI3Kδ, PI3Kβ, PI3Kα, and/or pan-PI3K) inhibitor, a JAK (Janus kinase, including JAK1,JAK2, and/or JAK3) inhibitor, a SYK (spleen tyrosine kinase) inhibitor, a BTK (Bruton's tyrosine kinase) inhibitor, an A2B (adenosine A2B receptor) inhibitor, an ACK (activated CDC kinase, including ACK1) inhibitor, an ASK (apoptosis signal-regulating kinase, including ASK1) inhibitor, Auroa kinase, a BRD (bromodomain-containing protein, including BRD4) inhibitor, a Bcl (B-cell CLL/lymphoma, including Bcl-1 and/or Bcl-2) inhibitor, a CAK (CDK-activating kinase) inhibitor, a CaMK (calmodulin-dependent protein kinases) inhibitor, a CDK (cyclin-dependent kinases, including CDK1, 2, 3, 4, and/or 6) inhibitor, a CK (casein kinase, including CK1 and/or CK2) inhibitor, a DDR (discoidin domain receptor, including DDR1 and/or DDR2) inhibitor, a EGFR inhibitor, a FXR (farnesoid x receptor) inhibitor, a FAK (focal adhesion kinase) inhibitor, a GSK (glycogen synthase kinase) inhibitor, a HDAC (histone deacetylase) inhibitor, an IDO (indoleamine 2,3-dioxygenase) inhibitor, an IDH (isocitrate dehydrogenase, including IDH1) inhibitor, an IKK (l-Kappa-B kinase) inhibitor, a KDM5 (lysine demethylase) inhibitor, a LCK (lymphocyte-specific protein tyrosine kinase) inhibitor, a LOX (lysyl oxidase) inhibitor, a LOXL (lysyl oxidase like protein, including LOXL1, LOXL2, LOXL3, LOXL4, and/or LOXL5) inhibitor, a MTH (mut T homolog) inhibitor, a MEK (mitogen-activated protein kinase kinase) inhibitor, a matrix metalloprotease (MMP, including MMP2 and/or MMP9) inhibitor, a mitogen-activated protein kinases (MAPK) inhibitor, a PD-1 (programmed cell death protein 1) inhibitor, a PD-L1 (programmed death-ligand 1) inhibitor, a PDGF (platelet-derived growth factor) inhibitor, a phosphorylase kinase (PK) inhibitor, a PLK (polo-like kinase, including PLK1, 2, 3) inhibitor, a protein kinase (PK, including protein kinase A, B, C) inhibitor, a STK (serine/threonine kinase) inhibitor, a STAT (signal transduction and transcription) inhibitor, a serine/threonine-protein kinase inhibitor, a TBK (tank-binding kinase) inhibitor, a TLR (toll-like receptor modulators,

including TLR-1, TLR-2, TLR-3, TLR-4, TLR-5, TLR-6, TLR-7, TLR-8, TLR-9, TLR-10, TLR-11, TLR-12, and/or TLR-13) inhibitor, a TK (tyrosine kinase) inhibitor, a TPL2 (serine/threonine kinase) inhibitor, a NEK9 inhibitor, an Abl inhibitor, a p38 kinase inhibitor, a PYK inhibitor, a PYK inhibitor, a c-Kit inhibitor, a NPM-ALK inhibitor, a Flt-3 inhibitor, a c-Met inhibitor, a KDR inhibitor, a TIE-2 inhibitor, a VEGFR inhibitor, a SRC inhibitor, a HCK inhibitor, a LYN inhibitor, a FYN inhibitor, a YES inhibitor, a chemotherapeutic agent, an immunotherapeutic agent, a radiotherapeutic agent, an anti-neoplastic agent, an anti-cancer agent, an anti-proliferation agent, an anti-fibrotic agent, an anti-angiogenic agent, a therapeutic antibody, or any combination thereof. In some embodiments, the JAK inhibitor is N-(cyanomethyl)-4-[2-(4-morpholinoanilino)pyrimidin-4-yl]benzamide as named by ChemDraw (may also be referred to as CYT0387 or momelotinib) and may be synthesized by the methods described in U.S. Patent No. 8,486,941. In certain embodiment, the SyK inhibitor is 6-(1H-indazol-6-yl)-N-(4-morpholinophenyl)imidazo[1,2-a]pyrazin-8-amine as named by ChemDraw (may also be referred to as 6-(1H-indazol-6-yl)-N-[4-(morpholin-4-yl)phenyl]imidazo[1,2-a]pyrazin-8-amine) and may be synthesized by the methods described in U.S. Patent No. 8,450,321. In other embodiments, the BTK inhibitor is (S)-6-amino-9-(1-(but-2-ynoyl)pyrrolidin-3-yl)-7-(4-phenoxyphenyl)-7H-purin-8(9H)-one as named by ChemDraw (may also be 6-amino-9-[(3R)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4-phenoxyphenyl)-7 ,9-dihydro-8H -purin-8-one) and may be synthesized by the methods in U.S. Pat. No. 8,557,803.

[00112] Chemotherapeutic agents may be categorized by their mechanism of action into, for example, the following groups: anti-metabolites/anti-cancer agents, such as pyrimidine analogs (floxuridine, capecitabine, and cytarabine); purine analogs, folate antagonists and related inhibitors, antiproliferative/antimitotic agents including natural products such as vinca alkaloid (vinblastine, vincristine) and microtubule such as taxane (paclitaxel, docetaxel), vinblastin, nocodazole, epothilones and navelbine, epidipodophyllotoxins (etoposide, teniposide); DNA damaging agents (actinomycin, amsacrine, busulfan, carboplatin, chlorambucil, cisplatin, cyclophosphamide, Cytoxan, dactinomycin, daunorubicin, doxorubicin, epirubicin, iphosphamide, melphalan, merchlorehtamine, mitomycin, mitoxantrone, nitrosourea, procarbazine, taxol, taxotere, teniposide, etoposide, triethylenethiophosphoramide); antibiotics such as dactinomycin (actinomycin D), daunorubicin, doxorubicin (adriamycin), idarubicin, anthracyclines,

mitoxantrone, bleomycins, plicamycin (mithramycin) and mitomycin; enzymes (L-asparaginase which systemically metabolizes L-asparagine and deprives cells which do not have the capacity to synthesize their own asparagine); antiplatelet agents; antiproliferative/ antimitotic alkylating agents such as nitrogen mustards cyclophosphamide and analogs, melphalan, chlorambucil), and (hexamethylmelamine and thiotepa), alkyl nitrosoureas (BCNU) and analogs, streptozocin), trazenes-dacarbazinine (DTIC); antiproliferative/antimitotic antimetabolites such as folic acid analogs (methotrexate); platinum coordination complexes (cisplatin, oxiloplatinim, carboplatin), procarbazine, hydroxyurea, mitotane, aminoglutethimide; hormones, hormone analogs (estrogen, tamoxifen, goserelin, bicalutamide, nilutamide) and aromatase inhibitors (letrozole, anastrozole); anticoagulants (heparin, synthetic heparin salts and other inhibitors of thrombin); fibrinolytic agents (such as tissue plasminogen activator, streptokinase and urokinase), aspirin, dipyridamole, ticlopidine, clopidogrel; antimigratory agents; antisecretory agents (breveldin); immunosuppressives tacrolimus sirolimus azathioprine, mycophenolate; compounds (TNP-470, genistein) and growth factor inhibitors (vascular endothelial growth factor inhibitors, fibroblast growth factor inhibitors); angiotensin receptor blocker, nitric oxide donors; anti-sense oligonucleotides; antibodies (trastuzumab, rituximab); cell cycle inhibitors and differentiation inducers (tretinoin); inhibitors, topoisomerase inhibitors (doxorubicin (adriamycin), daunorubicin, dactinomycin, eniposide, epirubicin, etoposide, idarubicin, irinotecan and mitoxantrone, topotecan, irinotecan, camptothesin), corticosteroids (cortisone, dexamethasone, hydrocortisone, methylpednisolone, prednisone, and prenisolone); growth factor signal transduction kinase inhibitors; dysfunction inducers, toxins such as Cholera toxin, ricin, Pseudomonas exotoxin, Bordetella pertussis adenylate cyclase toxin, or diphtheria toxin, and caspase activators; and chromatin.

[00113] As used herein the term "chemotherapeutic agent" or "chemotherapeutic" (or "chemotherapy," in the case of treatment with a chemotherapeutic agent) is meant to encompass any non-proteinaceous (i.e, non-peptidic) chemical compound useful in the treatment of cancer. Examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclophosphamide (CYTOXAN); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; emylerumines and memylamelamines including alfretamine, triemylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and

trimemylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including synthetic analogue topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (articularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CBI-TMI); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine, chlorozotocin, foremustine, lomustine, nimustine, ranimustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin gammaII and calicheamicin phiI1, see, e.g., Agnew, Chem. Intl. Ed. Engl, 33:183-186 (1994); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromomophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, carrninomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as demopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogues such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replinisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; hestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformthine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; leucovorin; lonidamine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; losoxantrone; fluoropyrimidine; folinic acid; podophyllinic acid; 2-ethylhydrazide; procarbazine;

PSK(r); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-tricUorotriemylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethane; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiopeta; taxoids, e.g., paclitaxel (TAXOL(r) and docetaxel (TAXOTERE(r)); chlorambucil; gemcitabine (Gemzar(r)); 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitroxantrone; vancristine; vinorelbine (Navelbine(r)); novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeoloda; ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; capecitabine; FOLFIRI (fluorouracil, leucovorin, and irinotecan) and pharmaceutically acceptable salts, acids or derivatives of any of the above. One or more chemotherapeutic agent are used or included in the present application.

[00114] Also included in the definition of "chemotherapeutic agent" are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including Nolvadex^{TM}), raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and toremifene (Fareston(r)); inhibitors of the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, megestrol acetate (Megace(r)), exemestane, formestane, fadrozole, vorozole (Rivisor(r)), letrozole (Femara(r)), and anastrozole (Arimidex(r).); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprohde, and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

[00115] The anti-angiogenic agents include, but are not limited to, retinoid acid and derivatives thereof, 2-methoxyestradiol, ANGIOSTATIN(r), ENDOSTATIN(r), suramin, squalamine, tissue inhibitor of metalloproteinase-1, tissue inhibitor of metalloproternase-2, plasminogen activator inhibitor-1, plasminogen activator inbibitor-2, cartilage-derived inhibitor, paclitaxel (nab-paclitaxel), platelet factor 4, protamine sulphate (clupeine), sulphated chitin derivatives (prepared from queen crab shells), sulphated polysaccharide peptidoglycan complex (sp-pg), staurosporine, modulators of matrix metabolism, including for example, proline analogs ((1-azetidine-2-carboxylic

acid (LACA), cishydroxyproline, d,I-3,4-dehydroproline, thiaproline, .alpha.-dipyridyl, beta-aminopropionitrile fumarate, 4-propyl-5-(4-pyridinyl)-2(3h)-oxazolone; methotrexate, mitoxantrone, heparin, interferons, 2 macroglobulin-serum, chimp-3, chymostatin, beta-cyclodextrin tetradecasulfate, eponemycin; fumagillin, gold sodium thiomalate, d-penicillamine (CDPT), beta-1-anticollagenase-serum, alpba-2-antiplasmin, bisantrene, lobenzarit disodium, n-2-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA", thalidomide; angiostatic steroid, cargboxynaminolmidazole; metalloproteinase inhibitors such as BB94. Other anti-angiogenesis agents include antibodies, preferably monoclonal antibodies against these angiogenic growth factors: beta-FGF, alpha-FGF, FGF-5, VEGF isoforms, VEGF-C, HGF/SF and Ang-1/Ang-2. See Ferrara N. and Alitalo, K. "Clinical application of angiogenic growth factors and their inhibitors" (1999) Nature Medicine 5:1359-1364.

[00116] The anti-fibrotic agents include, but are not limited to, the compounds such as beta-aminoproprionitrile (BAPN), as well as the compounds disclosed in U.S. Pat. No. 4,965,288 to Palfreyman, et al., issued Oct. 23, 1990, entitled "Inhibitors of lysyl oxidase," relating to inhibitors of lysyl oxidase and their use in the treatment of diseases and conditions associated with the abnormal deposition of collagen; U.S. Pat. No. 4,997,854 to Kagan, et al., issued Mar. 5, 1991, entitled "Anti-fibrotic agents and methods for inhibiting the activity of lysyl oxidase in situ using adjacently positioned diamine analogue substrate," relating to compounds which inhibit LOX for the treatment of various pathological fibrotic states, which are herein incorporated by reference. Further exemplary inhibitors are described in U.S. Pat. No. 4,943,593 to Palfreyman, et al., issued Jul. 24, 1990, entitled "Inhibitors of lysyl oxidase," relating to compounds such as 2-isobutyl-3-fluoro-, chloro-, or bromo-allylamine; as well as, e.g., U.S. Pat. No. 5,021,456; U.S. Pat. No. 5,5059,714; U.S. Pat. No. 5,120,764; U.S. Pat. No. 5,182,297; U.S. Pat. No. 5,252,608 (relating to 2-(1-naphthyloxymemyl)-3-fluoroallylamine); and U.S. Patent Application No. 2004/0248871, which are herein incorporated by reference. Exemplary anti-fibrotic agents also include the primary amines reacting with the carbonyl group of the active site of the lysyl oxidases, and more particularly those which produce, after binding with the carbonyl, a product stabilized by resonance, such as the following primary amines: emylenemamine, hydrazine, phenylhydrazine, and their derivatives, semicarbazide, and urea derivatives, aminonitriles, such as beta-aminopropionitrile (BAPN), or 2-nitroethylamine, unsaturated or saturated haloamines,

such as 2-bromo-ethylamine, 2-chloroethylamine, 2-trifluoroethylamine, 3-bromopropylamine, p-halobenzylamines, selenohomocysteine lactone. Also, the anti-fibrotic agents are copper chelating agents, penetrating or not penetrating the cells. Exemplary compounds include indirect inhibitors such compounds blocking the aldehyde derivatives originating from the oxidative deamination of the lysyl and hydroxylysyl residues by the lysyl oxidases, such as the thiolamines, in particular D-penicillamine, or its analogues such as 2-amino-5-mercapto-5-methylhexanoic acid, D-2-amino-3-methyl-3-((2-acetamidoethyl)dithio)butanoic acid, p-2-amino-3-methyl-3-((2-aminoethyl)dithio)butanoic acid, sodium-4-((p-1-dimethyl-2-amino-2-carboxyethyl)dithio)butane sulphurate, 2-acetamidoethyl-2-acetamidoethanethiol sulphanate, sodium-4-mercaptobutanesulphinate trihydrate.

[00117] The immunotherapeutic agents include and are not limited to therapeutic antibodies suitable for treating patients; such as abagovomab, adecatumumab, afutuzumab, alemtuzumab, altumomab, amatuximab, anatumomab, arcitumomab, bavituximab, bectumomab, bevacizumab, bivatuzumab, blinatumomab, brentuximab, cantuzumab, catumaxomab, cetuximab, citatuzumab, cixutumumab, clivatuzumab, conatumumab, daratumumab, drozitumab, duligotumab, dusigitumab, detumomab, dacetuzumab, dalotuzumab, ecromeximab, elotuzumab, ensituximab, ertumaxomab, etaracizumab, farietuzumab, ficlatuzumab, figitumumab, flanvotumab, futuximab, ganitumab, gemtuzumab, girentuximab, glembatumumab, ibritumomab, igovomab, imgatuzumab, indatuximab, inotuzumab, intetumumab, ipilimumab, iratumumab, labetuzumab, lexatumumab, lintuzumab, lorvotuzumab, lucatumumab, mapatumumab, matuzumab, milatuzumab, minretumomab, mitumomab, moxetumomab, narnatumab, naptumomab, necitumumab, nimotuzumab, nofetumomabn, ocaratuzumab, ofatumumab, olaratumab, onartuzumab, oportuzumab, oregovomab, panitumumab, parsatuzumab, patritumab, pemtumomab, pertuzumab, pintumomab, pritumumab, racotumomab, radretumab, rilotumumab, rituximab, robatumumab, satumomab, sibrotuzumab, siltuximab, simtuzumab, solitomab, tacatuzumab, taplitumomab, tenatumomab, teprotumumab, tigatuzumab, tositumomab, trastuzumab, tucotuzumab, ublituximab, veltuzumab, vorsetuzumab, votumumab, zalutumumab, obinutuzumab, CC49 and 3F8. The exemplified therapeutic antibodies may be further labeled or combined with a radioisotope particle, such as indium In 111, yttrium Y 90, iodine I-131.

[00118] The application also provides method for treating a subject who is undergoing one or more standard therapies, such as chemotherapy, radiotherapy, immunotherapy, surgery, or combination thereof. Accordingly, one or more therapeutic agent or inhibitors may be administered before, during, or after administration of chemotherapy, radiotherapy, immunotherapy, surgery or combination thereof.

[00119] Other examples of chemotherapy treatments (including standard or experimental chemotherapies) are described below. In addition, treatment of certain lymphomas is reviewed in Cheson, B.D., Leonard, J.P., "Monoclonal Antibody Therapy for B-Cell Non-Hodgkin's Lymphoma" *The New England Journal of Medicine* 2008, 359(6), p. 613-626; and Wierda, W.G., "Current and Investigational Therapies for Patients with CLL" *Hematology* 2006, p. 285-294. Lymphoma incidence patterns in the United States is profiled in Morton, L.M., *et al.* "Lymphoma Incidence Patterns by WHO Subtype in the United States, 1992-2001" *Blood* 2006, 107(1), p. 265-276.

[00120] Examples of immunotherapeutic agents include, but are not limited to, rituximab (such as Rituxan), alemtuzumab (such as Campath, MabCampath), anti-CD19 antibodies, anti-CD20 antibodies, anti-MN-14 antibodies, anti-TRAIL, Anti-TRAIL DR4 and DR5 antibodies, anti-CD74 antibodies, apolizumab, bevacizumab, CHIR-12.12, epratuzumab (hLL2- anti-CD22 humanized antibody), galiximab, ha20, ibritumomab tiuxetan, lumiliximab, milatuzumab, ofatumumab, PRO131921, SGN-40, WT-1 analog peptide vaccine, WT1 126-134 peptide vaccine, tositumomab, autologous human tumor-derived HSPPC-96, and veltuzumab. Additional immunotherapy agents includes using cancer vaccines based upon the genetic makeup of an individual patient's tumor, such as lymphoma vaccine example is GTOP-99 (MyVax®).

[00121] Examples of chemotherapy agents include aldesleukin, alvocidib, antineoplaston AS2-1, antineoplaston A10, anti-thymocyte globulin, amifostine trihydrate, aminocamptothecin, arsenic trioxide, beta alethine, Bcl-2 family protein inhibitor ABT-263, ABT-199, BMS-345541, bortezomib (Velcade®), bryostatin 1, busulfan, carboplatin, campath-1H, CC-5103, carmustine, caspofungin acetate, clofarabine, cisplatin, Cladribine (Leustarin), Chlorambucil (Leukeran), Curcumin, cyclosporine, Cyclophosphamide (Cyloxan, Endoxan, Endoxana, Cyclostin), cytarabine, denileukin diftitox, dexamethasone, DT PACE, docetaxel, dolastatin 10, Doxorubicin (Adriamycin®, Adriblastine), doxorubicin hydrochloride, enzastaurin, epoetin alfa,

etoposide, Everolimus (RAD001), fenretinide, filgrastim, melphalan, mesna, Flavopiridol, Fludarabine (Fludara), Geldanamycin (17-AAG), ifosfamide, irinotecan hydrochloride, ixabepilone, Lenalidomide (Revlimid®, CC-5013), lymphokine-activated killer cells, melphalan, methotrexate, mitoxantrone hydrochloride, motexafin gadolinium, mycophenolate mofetil, nelarabine, oblimersen (Genasense) Obatoclax (GX15-070), oblimersen, octreotide acetate, omega-3 fatty acids, oxaliplatin, paclitaxel, PD0332991, PEGylated liposomal doxorubicin hydrochloride, pegfilgrastim, Pentstatin (Nipent), perifosine, Prednisolone, Prednisone, R-roscovitine (Selicilib, CYC202), recombinant interferon alfa, recombinant interleukin-12, recombinant interleukin-11, recombinant flt3 ligand, recombinant human thrombopoietin, rituximab, sargramostim, sildenafil citrate, simvastatin, sirolimus, Styryl sulphones, tacrolimus, tanespimycin, Temsirolimus (CCl-779), Thalidomide, therapeutic allogeneic lymphocytes, thiotepa, tipifarnib, Velcade® (bortezomib or PS-341), Vincristine (Oncovin), vincristine sulfate, vinorelbine ditartrate, Vorinostat (SAHA), vorinostat, and FR (fludarabine, rituximab), CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), CVP (cyclophosphamide, vincristine and prednisone), FCM (fludarabine, cyclophosphamide, mitoxantrone), FCR (fludarabine, cyclophosphamide, rituximab), hyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine), ICE (iphosphamide, carboplatin and etoposide), MCP (mitoxantrone, chlorambucil, and prednisolone), R-CHOP (rituximab plus CHOP), R-CVP (rituximab plus CVP), R-FCM (rituximab plus FCM), R-ICE (rituximab-ICE), and R-MCP (R-MCP).

[00122] The therapeutic treatments can be supplemented or combined with any of the abovementioned therapies with stem cell transplantation or treatment. One example of modified approach is radioimmunotherapy, wherein a monoclonal antibody is combined with a radioisotope particle, such as indium In 111, yttrium Y 90, iodine I-131. Examples of combination therapies include, but are not limited to, Iodine-131 tositumomab (Bexxar®), Yttrium-90 ibritumomab tiuxetan (Zevalin®), Bexxar® with CHOP.

[00123] Other therapeutic procedures include peripheral blood stem cell transplantation, autologous hematopoietic stem cell transplantation, autologous bone marrow transplantation, antibody therapy, biological therapy, enzyme inhibitor therapy,

total body irradiation, infusion of stem cells, bone marrow ablation with stem cell support, *in vitro*-treated peripheral blood stem cell transplantation, umbilical cord blood transplantation, immunoenzyme technique, pharmacological study, low-LET cobalt-60 gamma ray therapy, bleomycin, conventional surgery, radiation therapy, and nonmyeloablative allogeneic hematopoietic stem cell transplantation.

[00124] In some embodiments, the methods include administering a compound of the formula described herein or a pharmaceutically acceptable salt, isomer, prodrug, or solvate thereof, in a therapeutically effective amount to a human in need thereof. The method can be employed to treat a patient who has or is believed to have a disease or condition whose symptoms or pathology is mediated by expression or activity of PI3Kβ and/or PI3Kδ. The patient may be a mammal or a human. In certain embodiment, the patient may be a human.

[00125] "Treatment" or "treating" is an approach for obtaining beneficial or desired results including clinical results. Beneficial or desired clinical results may include one or more of the following: a) inhibiting the disease or condition (*e.g.*, decreasing one or more symptoms resulting from the disease or condition, and/or diminishing the extent of the disease or condition); b) slowing or arresting the development of one or more clinical symptoms associated with the disease or condition (*e.g.*, stabilizing the disease or condition, preventing or delaying the worsening or progression of the disease or condition, and/or preventing or delaying the spread (*e.g.*, metastasis) of the disease or condition); and/or c) relieving the disease, that is, causing the regression of clinical symptoms (*e.g.*, ameliorating the disease state, providing partial or total remission of the disease or condition, enhancing the effect of another medication, delaying the progression of the disease, increasing the quality of life, and/or prolonging survival.

[00126] "Prevention" or "preventing" mean any treatment of a disease or condition that causes the clinical symptoms of the disease or condition not to develop. Compounds may, in some embodiments, be administered to a subject (including a human) who is at risk or has a family history of the disease or condition.

[00127] "Subject" or "patient" refer to an animal, such as a mammal (including a human), that has been or will be the object of treatment, observation or experiment. The methods described herein may be useful in human therapy and/or veterinary applications.

In some embodiments, the subject is a mammal. In one embodiment, the subject is a human. "Human in need thereof" refers to a human who may have or is suspect to have diseases, or disorders, or conditions that would benefit from certain treatment; for example, being treated with the PI3K inhibitor of the compounds according to the present application. In certain embodiments, the subject may be a human who (i) has not received any treatment including chemotherapy treatment, (ii) is substantially refractory to at least one chemotherapy treatment, (iii) is in relapse after treatment with chemotherapy, or both (i) and (ii). In some of embodiments, the subject is refractory to at least one, at least two, at least three, or at least four chemotherapy treatments (including standard or experimental chemotherapies).

[00128] The terms "therapeutically effective amount" or "effective amount" of a compound of the present application or a pharmaceutically acceptable salt, isomers, prodrug, or solvate thereof, mean an amount sufficient to effect treatment when administered to a subject, to provide a therapeutic benefit such as amelioration of symptoms or slowing of disease progression. For example, a therapeutically effective amount may be an amount sufficient to decrease a symptom of a disease or condition responsive to inhibition of PI3Kδ and PI3Kβ activity. The therapeutically effective amount may vary depending on the subject, and disease or condition being treated, the weight and age of the subject, the severity of the disease or condition, and the manner of administering, which can readily be determined by one or ordinary skill in the art.

[00129] In addition to the therapeutic uses, the compounds described herein have the selectivity or selective inhibition to certain PI3K isoforms. In one embodiment, the compounds have selectivity to PI3Kβ. In some embodiments, the compounds have selectivity to PI3Kδ. In yet other embodiments, the compounds have selectivity to PI3Kβ and PI3Kδ. The selectivity to PI3K isoforms may be determined by measuring the compound's activity in inhibiting certain PI3K isoforms using the assay described in the example below or the methods commonly used. It is understood that the conditions (e.g. the reagent concentration or the incubation temperature) may be varied and the results of the assay may vary. In some instances, the value may vary within a range of one to three-folds.

[00130] The term "inhibition" indicates a decrease in the baseline activity of a biological activity or process. The term "inhibition of activity of PI3K isoforms" or

variants thereof refer to a decrease in activity in any PI3K isoform (*e.g.*, alpha, beta, gamma, or delta) as a direct or indirect response to the presence of a compound of any of the formula described herein relative to the activity of PI3K isoform in the absence of such compound. "Inhibition of PI3Kδ and/or PI3Kβ activities" or variants thereof refer to a decrease in PI3Kδ and/or PI3Kβ activities as a direct or indirect response to the presence of the compounds described herein, relative to the activities of PI3Kδ and/or PI3Kβ in the absence of such compound. In some embodiments, the inhibition of PI3K isoform activities may be compared in the same subject prior to treatment, or other subjects not receiving the treatment.

[00131] Without being bound to any theory, the decrease in the activity of PI3K may be due to the direct interaction of the compound with PI3K, or due to the interaction of the compounds described herein with one or more other factors that affect PI3K activity. For example, the presence of the compounds may decrease the activities of PI3Kδ and/or PI3Kβ by directly binding to PI3Kδ and/or PI3Kβ, by causing (directly or indirectly) another factor to decrease PI3Kδ and/or PI3Kβ activities, or by (directly or indirectly) decreasing the amount of PI3Kδ and/or PI3Kβ present in the cell or organism.

[00132] The term "PI3K inhibitor" or variant thereof refers to a compound that inhibits the activity of PI3K. The term "PI3K isoform selective inhibitor" or variant thereof refers to a compound that inhibits the activity of one or more PI3K isoforms more effectively than the other remaining PI3K isoforms. By way of example, the term "PI3Kβ selective inhibitor" generally refers to a compound that inhibits the activity of the PI3Kβ isoform more effectively than other isoforms of the PI3K family, and the term "PI3Kδ selective inhibitor" generally refers to a compound that inhibits the activity of the PI3Kδ isoform more effectively than other isoforms of the PI3K family. The term "dual PI3Kδ/β selective inhibitor" generally refers to a compound that inhibits the activity of both PI3Kδ and PI3Kβ isoforms more effectively than other isoforms of the PI3K family (*e.g.*, PI3Kα or γ).

[00133] The relative efficacies of compounds as inhibitors of an enzyme activity (or other biological activity) can be established by determining the concentrations at which each compound inhibits the activity to a predefined extent and then comparing the results. In one embodiment, the efficacy of a compound as an inhibitor of one or more

PI3K isoforms can be measured by the compound concentration that inhibits 50% of the activity in a biochemical assay, *i.e.*, the 50% inhibitory concentration or "IC_{50}". The determination of IC_{50} values can be accomplished using conventional techniques known in the art, including the techniques described in the Examples below. In general, an IC_{50} can be determined by measuring the activity of a given enzyme in the presence of a range of concentrations of the compound under the study. The experimentally obtained values of enzyme activity may then be plotted against the compound concentrations used. The concentration of the inhibitor that shows 50% enzyme activity (as compared to the activity in the absence of any inhibitor) is taken as the IC_{50} value. Analogously, other inhibitory concentrations can be defined through appropriate determinations of activity. For example, in some settings it may be desirable to establish a 90% inhibitory concentration, *i.e.*, IC_{90}.

[00134] According to the present application, a PI3Kβ selective inhibitor is a compound that exhibits a 50% inhibitory concentration (IC_{50}) with respect to PI3Kβ that is at least 10-fold, at least 20-fold, at least 30-fold, at least 50-fold, at least 100-fold, at least 200-fold, or at least 500-fold lower than the IC_{50} with respect to either PI3Kα or PI3Kγ or both PI3Kα and PI3Kγ. In addition, a PI3Kδ/β selective inhibitor is a compound that exhibits a 50% inhibitory concentration (IC_{50}) with respect to PI3Kβ and PI3Kδ that is at least 10-fold, at least 20-fold, at least 30-fold, at least 50-fold, at least 75-fold, at least 100-fold, at least 200-fold, and at least 500-fold lower than the IC_{50} with respect to either PI3Kα or PI3Kγ. The dual PI3Kδ/β selective inhibitor may have the same or similar IC_{50} to both PI3Kδ and PI3Kβ or may have different IC_{50} to either PI3Kδ or PI3Kβ. As used herein, the term "potency," "potent," or variants thereof refer to the compound exhibiting an IC_{50} value that is less than 100 nM. When comparing two compounds, the compound that exhibits a lower IC_{50} value is referred to as a more potent inhibitor.

[00135] The compounds of the present application exhibit unexpected selectivity to PI3Kβ. As shown in the example, certain compounds in Table 1 exhibit low IC_{50} values (e.g. 1 to 100 nM) to both PI3Kβ and PI3Kδ. Certain compounds in Table 1a also exhibited such activity to PI3K isoforms. Also, certain compounds of formula (I) exhibited at least between 10-fold to 400-fold lower IC_{50} values for PI3Kβ than PI3Kγ, suggesting the compounds exhibit selectivity to PI3Kβ compared to PI3Kγ (i.e., inhibits

the activity of the PI3Kβ isoform more effectively than the PI3Kγ isoform as shown by the PI3Kγ/PI3Kβ ratio). Some compounds of formula (IV) showed similar selectivity. Moreover, the compounds described herein exhibit selectivity to both PI3Kβ and PI3Kδ. The compound of (S)-2,4-diamino-6-((1-(5-chloro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile, described in US Provisional Application No. 61/745,437, exhibited less selectivity to PI3Kγ (e.g. the PI3Kγ/PI3Kβ ratio is less than 1-fold). The results of the present application suggest that the compounds described herein are dual selective inhibitors of PI3Kδ and PI3Kβ and exhibit selectivity to PI3Kβ compared to PI3Kγ. Each of the patents and the patent publications provided in the present application is hereby incorporated by reference in the entirety.

[00136] The methods described herein may be applied to cell populations *in vivo* or *ex vivo*. "*In vivo*" means within a living individual, as within an animal or human. In this context, the methods described herein may be used therapeutically in an individual. "*Ex vivo*" means outside of a living individual. Examples of *ex vivo* cell populations include in vitro cell cultures and biological samples including fluid or tissue samples obtained from individuals. Such samples may be obtained by methods well known in the art. Exemplary biological fluid samples include blood, cerebrospinal fluid, urine, and saliva. Exemplary tissue samples include tumors and biopsies thereof. In this context, the compounds may be used for a variety of purposes, including therapeutic and experimental purposes. For example, it may be used *ex vivo* to determine the optimal schedule and/or dosing of administration of a PI3K selective inhibitor for a given indication, cell type, individual, and other parameters. Information gleaned from such use may be used for experimental purposes or in the clinic to set protocols for *in vivo* treatment. Other *ex vivo* uses for which the invention may be suited are described below or will become apparent to those skilled in the art. The compounds of the formula described herein or a pharmaceutically acceptable salt, prodrug, or solvate thereof, may be further characterized to examine the safety or tolerance dosage in human or non-human subjects. Such properties may be examined using commonly known methods to those skilled in the art.

[00137] Compared to other PI3K isoforms, PI3Kδ is generally expressed in hematopoietic cells. Also, PI3Kβ is generally mis-regulated in certain cancer cells.

Aberrant proliferation of cells often interferes with normal tissue function, which may result in abnormal cellular response such as immunity, inflammation, and/or apoptosis. The selective inhibitors to PI3Kδ and/or PI3Kβ are useful in treating, inhibiting, or preventing aberrant proliferation of cancerous and/or hematopoietic cells and ameliorating the symptoms and secondary conditions.

[00138] The compounds described herein may be used to treat subjects having various disease states, disorders, and conditions (also collectively referred to as "indications") associated with PI3K isoforms or their activities. As used herein, the terms "diseases," "disorders," "conditions" are used interchangeably. Such indications may include, for example, cancer, including hematologic malignancies (e.g. leukemias and lymphomas, myeloproliferative disorders, myelodysplastic syndromes, plasma cell neoplasms) and solid tumors, inflammation, fibrosis, allergic conditions (including hypersensitivity), cardiovascular diseases, neurodegenerative diseases, renal disorders, viral infections, obesity, and autoimmune diseases.

[00139] In other embodiments, the compounds described herein may be used to treat cancers that are mediated by, dependent on, or associated with PI3K activity. In certain embodiments, the disease or condition is an autoimmune disease, an inflammatory disease, or a cancer. In some embodiments, the disease or condition is chosen from rheumatoid arthritis, osteoarthritis, atherosclerosis, psoriasis, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel disease, asthma, chronic obstructive airways disease, pneumonitis, dermatitis, alopecia, nephritis, vasculitis, atherosclerosis, Alzheimer's disease, hepatitis, primary biliary cirrhosis, sclerosing cholangitis, diabetes (including type I diabetes), acute rejection of transplanted organs, lymphomas, multiple myelomas, leukemias, neoplasms and solid tumors.

[00140] In other embodiments, the disease is a solid tumor. By way of examples, the solid tumor includes but is not limited to pancreatic cancer, bladder cancer, colorectal cancer, breast cancer, prostate cancer, renal cancer, hepatocellular cancer, lung cancer, ovarian cancer, cervical cancer, rectum cancer, liver cancer, kidney cancer, stomach cancer, skin cancer, gastric cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancers, CNS cancers (e.g., neuroblastoma), brain tumors (*e.g.*, glioma, anaplastic oligodendroglioma, adult glioblastoma multiforme, and adult anaplastic astrocytoma), bone cancer, or soft tissue sarcoma. In some embodiments, the solid

tumor is non-small cell lung cancer, small-cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, pancreatic cancer, prostate cancer, or breast cancer.

[00141] The present application also provides a method for treating a human in need thereof, who has or is suspected of having a disease or condition responsive or believed to be responsive to the inhibition of PI3Kδ and/or PI3Kβ activity by administering to the subject a compound of the formulae described herein or a pharmaceutically acceptable salt, enantiomer, atropisomer, tautomer, prodrug, or solvate thereof.

[00142] Additionally, the application provides a method of inhibiting kinase activity of a PI3Kδ and/or PI3Kβ polypeptides by contacting the polypeptides with a compound of the formulae described herein or a pharmaceutically acceptable salt, isomer, prodrug, solvate, or a mixture thereof.

[00143] Moreover, the application provides a method of decreasing cell viability, increasing cell death or apoptosis, increasing interference with PI3K signaling pathways (including AKT, S6RP, ERK phosphorylation), and/or reduction in chemokine production with an effective amount of a compound of any of the formulae described herein or a pharmaceutically acceptable salt, isomer, prodrug, solvate, or a mixture thereof.

[00144] The application further provides a method of disrupting leukocyte function comprising contacting the leukocytes with an effective amount of a compound of any of the formulae described herein or a pharmaceutically acceptable salt, isomer, prodrug, solvate, or a mixture thereof, in a human in need thereof.

[00145] Provided is also a method of inhibiting growth or proliferation of cancer cells comprising contacting the cancer cells with an effective amount of a compound of the formulae described herein or a pharmaceutically acceptable salt, isomer, prodrug, solvate, or a mixture thereof.

[00146] Kits

[00147] Provided herein are also kits that include a compound of the formulae of the present application or a pharmaceutically acceptable salt, isomer, prodrug, or solvate

thereof, and suitable packaging. In one embodiment, a kit further includes instructions for use. In one aspect, a kit includes a compound of the formulae described herein or a pharmaceutically acceptable salt, isomer, prodrug, or solvate thereof, and a label and/or instructions for use of the compounds in the treatment of the indications, including the diseases or conditions, described herein.

[00148] Provided herein are also articles of manufacture that include a compound of any of the formulae described herein or a pharmaceutically acceptable salt, isomer, prodrug, or solvate thereof, in a suitable container. The container may be a vial, jar, ampoule, preloaded syringe, and intravenous bag.

[00149] Pharmaceutical Compositions and Modes of Administration

[00150] Compounds provided herein are usually administered in the form of pharmaceutical compositions. Thus, provides herein are also pharmaceutical compositions that contain one or more of the compounds of any of the formulae disclosed herein or a pharmaceutically acceptable salt, isomers, prodrug, or solvate thereof, and one or more pharmaceutically acceptable vehicles selected from carriers, adjuvants and excipients. Suitable pharmaceutically acceptable vehicles may include, for example, inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants. Such compositions are prepared in a manner well known in the pharmaceutical art. *See, e.g.*, Remington's Pharmaceutical Sciences, Mace Publishing Co., Philadelphia, Pa. 17th Ed. (1985); and Modern Pharmaceutics, Marcel Dekker, Inc. 3rd Ed. (G.S. Banker & C.T. Rhodes, Eds.).

[00151] The pharmaceutical compositions may be administered in either single or multiple doses. The pharmaceutical composition may be administered by various methods including, for example, rectal, buccal, intranasal, and transdermal routes. In certain embodiments, the pharmaceutical composition may be administered by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, or as an inhalant. In some embodiments, the pharmaceutical composition is administered orally.

[00152] One mode for administration is parenteral, for example, by injection. The forms in which the pharmaceutical compositions described herein may be incorporated

for administration by injection include, for example, aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

[00153] Oral administration may be another route for administration of the compounds described herein. Administration may be via, for example, capsule or enteric coated tablets. In making the pharmaceutical compositions that include at least one compound of any of the formulae described herein or a pharmaceutically acceptable salt, prodrug, or solvate thereof, the active ingredient is usually diluted by an excipient and/or enclosed within such a carrier that can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be in the form of a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, sterile injectable solutions, and sterile packaged powders. In certain embodiments, the pharmaceutical composition is in the form of tablets.

[00154] Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl and propylhydroxy-benzoates; sweetening agents; and flavoring agents.

[00155] The compositions that include at least one compound of any of the formulae described herein or a pharmaceutically acceptable salt, isomer, prodrug, or solvate thereof, can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the subject by employing procedures known in the art. Controlled release drug delivery systems for oral administration include osmotic pump systems and dissolutional systems containing polymer-coated reservoirs or drug-polymer matrix formulations. Examples of controlled release systems are given in U.S. Patent Nos. 3,845,770; 4,326,525; 4,902,514; and 5,616,345. Another formulation for

use in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds described herein in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. *See, e.g.*, U.S. Patent Nos. 5,023,252, 4,992,445 and 5,001,139. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[00156] For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of any of the above formulae or a pharmaceutically acceptable salt, prodrug, or solvate thereof. When referring to these preformulation compositions as homogeneous, the active ingredient may be dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

[00157] The tablets or pills of the compounds described herein may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action, or to protect from the acid conditions of the stomach. For example, the tablet or pill can include an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

[00158] Compositions for inhalation or insufflation may include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. In other embodiments, compositions in pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the

nebulizing device or the nebulizing device may be attached to a facemask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

[00159] Dosing

[00160] The specific dose level of a compound of the formulae described herein for any particular subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease in the subject undergoing therapy. For example, a dosage may be expressed as a number of milligrams of a compound of the formula per kilogram of the subject's body weight (mg/kg). Dosages of between about 0.01 and 200 mg/kg may be appropriate. In some embodiments, about 0.01 and 150 mg/kg may be appropriate. In other embodiments a dosage of between 0.05 and 100 mg/kg may be appropriate. Normalizing according to the subject's body weight is particularly useful when adjusting dosages between subjects of widely disparate size, such as occurs when using the drug in both children and adult humans or when converting an effective dosage in a non-human subject such as dog to a dosage suitable for a human subject.

[00161] The daily dosage may also be described as a total amount of a compound of the formulae administered per dose or per day. Daily dosage of a compound may be between about 1 mg and 2,000 mg, between about 1,000 to 2,000 mg/day, between about 1 to 1,000 mg/day, between about 1 to 500 mg/day, between about 100 to 150 mg/day, between about 1 to 100 mg/day, between about between about 1 to 50 mg/day, between about 50 to 100 mg/day, between about 100 to 125 mg/day, between about 100 to 150 mg/day, between about 100 to 175 mg/day, between about 100 to 200 mg/day, between about 100 to 225 mg/day, between about 100 to 250 mg/day, between about 100 to 350 mg/day, between about 100 to 400 mg/day, between about 100 to 450 mg/day, or between about 100 to 500 mg/day.

[00162] When administered orally, the total daily dosage for a human subject may be between 1 mg and 1,000 mg/day, between about 1 to 100 mg/day, between about 1 to 50 mg/day, between about 50 to 100 mg/day, between 100 to 200 mg/day, between about

200 to 300 mg/day, between about 300 to 400 mg/day, between about 400 to 500 mg/day, between about 100 to 150 mg/day, between about 150 to 200 mg/day, between about 200 to 250 mg/day, between about 75 to 150 mg/day, or between about 150 to 300 mg/day.

[00163] The compounds of the present application or the compositions thereof may be administered once, twice, three, or four times daily, using any suitable mode described above. Also, administration or treatment with the compounds according to any of the formulae described herein may be continued for a number of days; for example, commonly treatment would continue for at least 7 days, 14 days, or 28 days, for one cycle of treatment. In some treatment, the compound or the composition thereof is administered continuously, i.e. every day. Treatment cycles are well known in cancer chemotherapy, and are frequently alternated with resting periods of about 1 to 28 days, commonly about 7 days or about 14 days, between cycles. The treatment cycles, in other embodiments, may also be continuous.

[00164] In a particular embodiment, the method comprises administering to the subject an initial daily dose of about 1 to 500 mg of a compound of the above formula and increasing the dose by increments until clinical efficacy is achieved. Increments of about 1, 5, 10, 25, 50, 75, or 100 mg can be used to increase the dose. The dosage can be increased daily, every other day, twice per week, or once per week.

[00165] Synthesis of the Compounds

[00166] The compounds of the present application may be prepared using the methods disclosed herein and routine modifications thereof, which will be apparent given the disclosure herein and methods well known in the art. Conventional and well-known synthetic methods may be used in addition to the teachings herein. The synthesis of typical compounds described herein may be accomplished as described in the following examples. If available, reagents may be purchased commercially, *e.g.*, from Sigma Aldrich or other chemical suppliers. In general, compounds described herein are typically stable and isolatable at room temperature and pressure.

[00167] *General Synthesis*

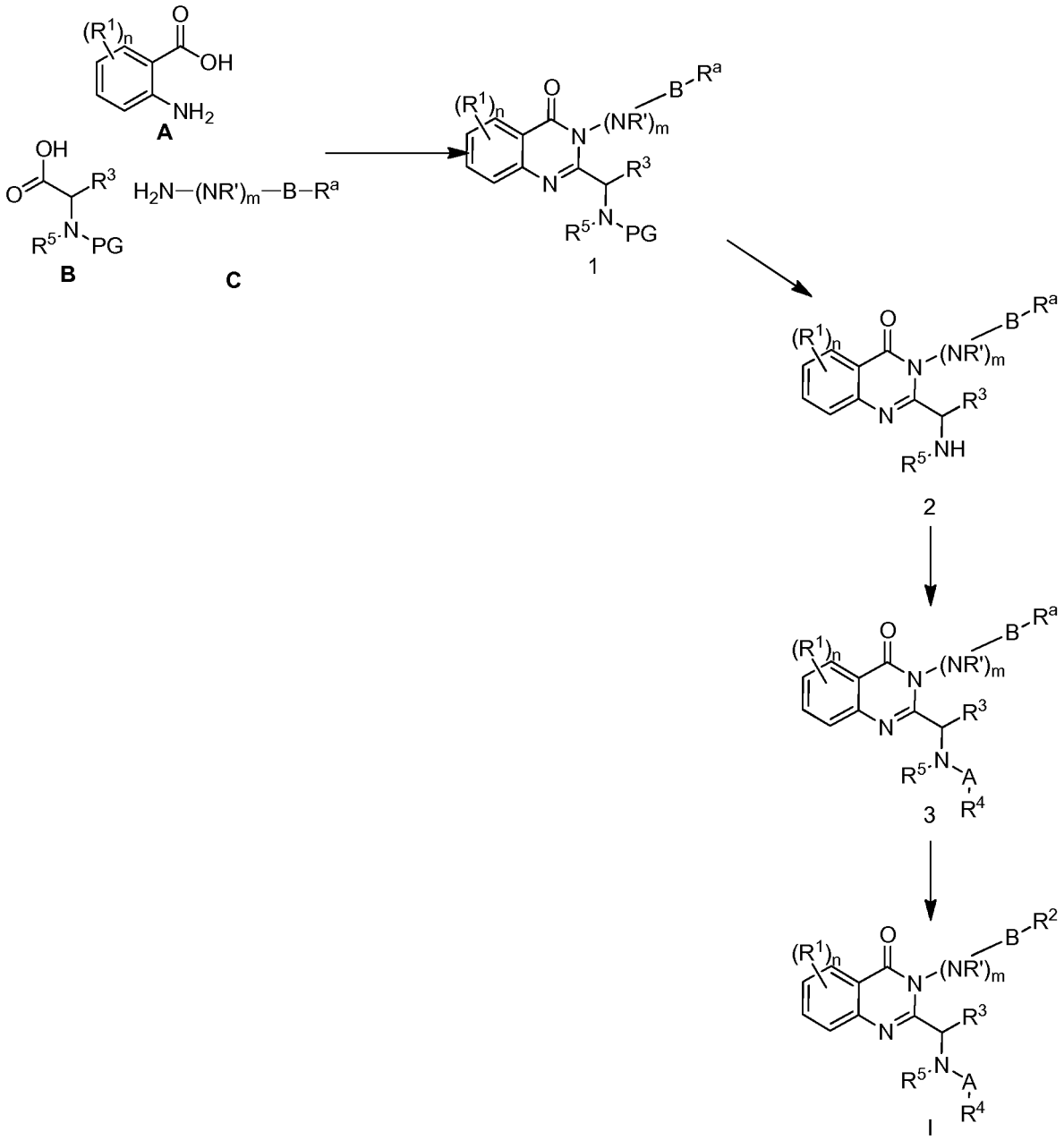
[00168] Typical embodiments of compounds described herein may be synthesized using the general reaction schemes described below. It will be apparent given the description herein that the general schemes may be altered by substitution of the starting materials with other materials having similar structures to result in products that are correspondingly different. Descriptions of syntheses follow to provide numerous examples of how the starting materials may vary to provide corresponding products. Given a desired product for which the substituent groups are defined, the necessary starting materials generally may be determined by inspection. Starting materials are typically obtained from commercial sources or synthesized using published methods. For synthesizing compounds which are embodiments described in the present disclosure, inspection of the structure of the compound to be synthesized will provide the identity of each substituent group. The identity of the final product will generally render apparent the identity of the necessary starting materials by a simple process of inspection, given the examples herein.

[00169] *Synthetic Reaction Parameters*

[00170] The terms "solvent", "inert organic solvent", or "inert solvent" refer to a solvent inert under the conditions of the reaction being described in conjunction therewith (including, for example, benzene, toluene, acetonitrile, tetrahydrofuran ("THF"), dimethylformamide ("DMF"), chloroform, methylene chloride (or dichloromethane), diethyl ether, methanol, and the like. Unless specified to the contrary, the solvents used in the reactions of the present invention are inert organic solvents, and the reactions are carried out under an inert gas, preferably nitrogen.

[00171] The compounds of formula (I) may be prepared using the method shown in Reaction Scheme I.

Reaction Scheme I



[00172] Step 1—Preparation of a compound of formula (1)

[00173] The compound of formula (1) can be made by combining compounds (A), (B) and (C) in the presence of a dehydrating agent. PG may be a protecting group such as t-

butoxycarbonyl (Boc) or fluorenylmethoxycarbonyl (Fmoc). Compounds (A), (B) and (C) are commercially available or can be made by the methods that are commonly known or used by one skilled in the art. R^1, R^5, R', and R^3 are defined as in the formula (I). R^a is either a protecting group such as NHBoc or R^2 as defined for the formula (I). Compound (A) is mixed with Compound (B) in the presence of a coupling agent such as diphenyl phosphite in a solvent such as pyridine. After stirring at a temperature between ambient and 100°C for 1 to 5 hours, compound (C) is added. The mixture is further stirred at a temperature between ambient and 100 °C for 5 to 24 hours and cooled to room temperature. To extract the compound of formula (1), an organic solvent such as ethyl acetate (EtOAc) is added. Then the reaction is washed with mild acid, water, and brine. The organic phase is concentrated to obtain the compound of formula (1). The compound of formula (1) is purified by any suitable methods known in the art, such as chromatography on silica gel. Alternatively, the compound of formula (1) is purified directly without an aqueous work-up. Alternatively, the compound of formula (1) is used in the next step without purification. In cases where it is desired to convert a nitrile to a carboxamide, reaction under conditions known to those skilled in the art may be used such as treatment with Parkins-Ghaffar catalyst. In cases where a vicinal amino alcohol is desired for -B-R^a, an olefin can be reacted with an appropriate oxidant, such as m-chloroperbenzoic acid (mCPBA) to give the epoxide, which can be subsequently reacted with an excess of the amine, R^2NH_2, in the presence of an additive, such as lithium perchlorate, to give the amino alcohol. In cases where a sulfone is desired for -B-R^2, a sulfide can be reacted with an appropriate oxidant, such as m-chloroperbenzoic acid (mCPBA) or hydrogen peroxide to give the sulfone.

[00174] Step 2—Preparation of a compound of formula (2)

[00175] The compound of formula (2) can be made by removing the protecting group(s) from the compound of formula (1). Different conditions will be used depending on the protecting group being utilized. If it is desired to remove a Boc group, the compound of formula (1) is dissolved in a suitable solvent and treated with a suitable acid. By way of example, suitable solvents include dichloromethane or dioxane, and suitable acids include trifluoroacetic acid, hydrochloric acid, or boron tribromide (BBr_3). The reaction is carried out at temperatures between -78°C to ambient temperature. After the reaction is complete, solvent is removed to obtain the compound of formula (2). If it

is desired to remove an Fmoc group the compound of formula (1) is dissolved in a suitable solvent and treated with a suitable base. By way of example, suitable solvents include dichloromethane or DMF, and suitable bases include piperidine. The reaction is carried out at temperatures between 0°C to 50°C for between 0.5 and 24 hours. After the reaction is complete, the reaction may be diluted with water and a suitable solvent for extraction such as EtOAc or dichloromethane. The solvent is removed to obtain the compound of formula (2) and used without further purification or purified via methods known, such as chromatography.

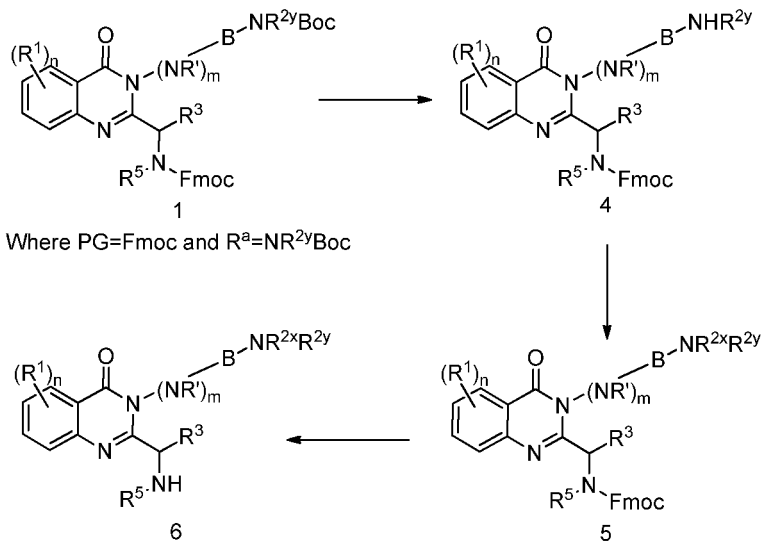
[00176] Step 3—Preparation of compounds of formulae (I) and (3)

[00177] The compound of formula (I) where A is a single bond and R^a is an R^2, can generally be prepared by coupling compound of formula (2) and an appropriately substituted R^4-X, where X is a halo, in the presence of a suitable base in a suitable solvent. An example of a suitable base is diisopropylethylamine, triethylamine or N-methylmorpholine. An example of a suitable solvent is N-methylpyrrolidone (NMP), DMF, DMSO, or isopropanol. Also, an additive such as potassium fluoride may be used. The reaction is typically performed at a temperature between 50°C to 150°C for about 30 minutes to 24 hours. Alternatively the reaction can be performed in a microwave at a temperature between 100°C to 150°C for about 30 minutes to 24 hours. The compound of formula (I) where A is C(O) and R^a is an R^2, may generally be prepared by coupling a compound of formula (2) with a suitable acid in the presence of a coupling agent, such as HATU, DCC, or carbonyl diimidazole in the presence of a base such as triethylamine or diisopropylethylamine in a suitable solvent such as dichloromethane or THF. Water can be added to quench the reaction upon completion, and the precipitate may be filtered then dissolved in an organic solvent such as dichloromethane (DCM). Alternatively, the reaction can be diluted with an appropriate solvent such as EtOAc or dichloromethane instead of filtering off the solid. The product can be isolated by methods known in the art, for example by removal of solvent under reduced pressure. The product can be purified using any suitable methods known in the art, for example, recrystallization, precipitation, or chromatography of the residue. For the compound of formula (3) where R^a is $NR^{2x}Boc$, the Boc group may be removed by methods known to one of skill in the art and described above in step 2 to give a compound of formula (I), where R^2 is NHR^{2x}. If further functionalization is desired, a compound of formula (I) where R^2 is NHR^{2x} can

be converted to an amide, R^2 is $NR^{2x}C(O)R^{2y}$ by methods known to one of skill in the art, such as reaction with an acid, $HOC(O)R^{2y}$, and a coupling agent, such as HATU, as described above. Furthermore, a compound of formula (I), where R^2 is NHR^{2x} may be alkylated by methods known to one of skill in the art through the reaction of the amine with a compound containing an aldehyde or ketone in the presence of a reducing agent, such as $NaCNBH_3$ or sodium triacetoxyborohydride, in a suitable solvent such as methanol or dichloromethane to give a compound of formula (I), where R^2 is $NR^{2x}R^{2y}$. Furthermore, a compound of formula (I), where R^2 is NHR^{2x} may be arylated or heteroarylated by methods known to one of skill such as by reaction of the amine with an activated aromatic or heteroaromatic ring in the presence of a base, such as triethylamine or diisopropylethylamine, in a suitable solvent such as DMF at a temperature between 50°C to 150°C to give a compound of formula (I), where R^2 is $NR^{2x}R^{2y}$. Furthermore, a compound of formula (I) where R^2 is CN may be converted to a compound of formula (I) where R^2 is $CONH_2$ by reaction under conditions known to those skilled in the art such as treatment with Parkins-Ghaffar catalyst. Furthermore, a compound of formula (I) where R^2 is OH may be prepared by deprotecting a compound of formula (3) where R^a is OPG, where PG is an appropriate protecting group. Appropriate protecting groups may be acetate, benzoate and the like. Such protecting groups may be removed by treatment with reagents known to those skilled in the art such as LiOH or NaOH.

[00178] The compounds of formula (I) may also be prepared using the method shown in Reaction Scheme II.

[00179] Reaction Scheme II



[00180] Preparation of a compound of formula (4)

[00181] The compound of formula (4) can be made by removing the protecting group(s) from the compound of formula (1) wherein R^a is NR^{2y}; and PG is Fmoc. The compound of formula (1) wherein R^a is NR^{2y}; and PG is Fmoc is dissolved in a suitable solvent and treated with a suitable acid. By way of example, suitable solvents include dichloromethane or dioxane, and suitable acids include trifluoroacetic acid, hydrochloric acid, or boron tribromide (BBr_3). The reaction is carried out at temperatures between -78°C to ambient temperature. After the reaction is complete, solvent is removed to obtain the compound of formula (4).

[00182] Preparation of a compound of formula (5)

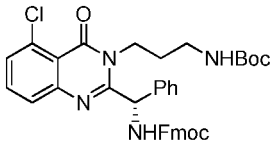
[00183] The compound of formula (5) can be made by methods known to one of skill in the art, such as reaction of the compound of formula (4) and an acid with a coupling agent, such as HATU, as described above in step 3. Furthermore, the compound of formula (4) may be alkylated by methods known to one of skill in the art through the reaction with a compound containing an aldehyde or ketone, in the presence of a reducing agent, such as $NaCNBH_3$ or sodium triacetoxyborohydride, in a suitable solvent such as methanol or dichloromethane as described above in step 3.

[00184] Preparation of a compound of formula (6)

[00185] The compound of formula (6) can be made by removing the Fmoc from the compound of formula (5) as described in step 2. The compound of formula (5) is dissolved in a suitable solvent and treated with a suitable base. By way of example, suitable solvents include dichloromethane or DMF, and suitable bases include piperidine. The reaction is carried out at temperatures between 0°C to 50°C for between 0.5 and 24 hours. After the reaction is complete, the reaction may be diluted with water and a suitable solvent for extraction such as EtOAc or dichloromethane. The solvent is removed to obtain the compound of formula (6) and used without further purification or purified via methods known, such as chromatography. It should be understood that the compounds of formula (I) can be prepared according to the methods provided in Reaction Scheme 1 or 2, starting from materials known to one of skill in the art. After synthesis, the compounds may be isolated in the form of a free base or a trifluoroacetic acid salt and further characterized by NMR. The resulting compounds and their NMR characterizations may represent either the free base or salt form. The ratio of parent compound and corresponding salt is not determined.

[00186] Example 1. Preparation of a compound of formula (1)

[00187] A. Preparation of a compound of formula (1) wherein n is 1, R^1 is chloro, m is 0, B is $(CH_2)_3$, R^a is NHBoc, R^5 is hydrogen, PG is Fmoc, and R^3 is phenyl



[00188] To a solution of 6-chloroanthranlic acid (0.92 g, 5.4 mmol) and Fmoc-L-phenylglycine (2.0 g, 5.4 mmol) in pyridine (2.7 mL) was added diphenyl phosphite (3.6 mL, 19 mmol). The mixture stirred at 40 °C for 1 h. *N*-Boc-1,3-propanediamine (0.95 g, 5.4 mmol) was added and the reaction mixture stirred overnight at 55 °C. The mixture was diluted with EtOAc, washed with 1 N HCl (aq), sat bicarbonate solution, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated onto silica gel. The crude product mixture was purified via flash chromatography (SiO_2, 0-55% EtOAc/hexanes) to give (S)-tert-butyl (3-(2-(((((9H-fluoren-9-yl)methoxy)carbonyl)amino)(phenyl)methyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)(methyl)carbamate. ES/MS 665.3 ($M+H^+$).

[00189] B. Preparation of the below compound of formula (1), using the methods described in Example 1A and Reaction Scheme I

(S)-tert-butyl (4-(2-(1-(((9H-fluoren-9-yl)methoxy)carbonylamino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)-2-methylbutan-2-yl)carbamate;

(S)-tert-butyl (2-((2-(1-(((9H-fluoren-9-yl)methoxy)carbonylamino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)(benzyl)amino)ethyl)carbamate;

(S)-tert-butyl (2-((2-(1-(((9H-fluoren-9-yl)methoxy)carbonylamino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)(methyl)amino)ethyl)carbamate;

(S)-tert-butyl (1-(5-chloro-3-(3-morpholinopropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate;

tert-butyl (2-(2-((S)-1-(((9H-fluoren-9-yl)methoxy)carbonylamino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)carbamate;

(S)-tert-butyl (1-(3-(but-3-en-1-yl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate;

tert-butyl (3-(2-((S)-1-(((9H-fluoren-9-yl)methoxy)carbonylamino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)butyl)carbamate;

tert-butyl (3-(2-((S)-1-(((9H-fluoren-9-yl)methoxy)carbonylamino)-5-chloro-4-oxoquinazolin-3(4H)-yl)-2-methylpropyl)carbamate;

(S)-tert-butyl (4-(2-(1-(((9H-fluoren-9-yl)methoxy)carbonylamino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)butyl)carbamate;

tert-butyl (3-(2-((1S)-1-(((9H-fluoren-9-yl)methoxy)carbonylamino)ethyl)-5-methyl-4-oxoquinazolin-3(4H)-yl)propyl)carbamate;

(S)-tert-butyl (1-(5-chloro-3-(3-(dimethylamino)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate;

(S)-tert-butyl (1-(5-chloro-3-(2-(dimethylamino)ethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate;

tert-butyl (3-(5-chloro-2-((1S)-1-(((9H-fluoren-9-yl)methoxy)carbonylamino)ethyl)-4-oxoquinazolin-3(4H)-yl)propyl)carbamate;

tert-butyl (3-(5-chloro-2-((1S)-1-(((9H-fluoren-9-yl)methoxy)carbonylamino)ethyl)-4-oxoquinazolin-3(4H)-yl)propyl)(methyl)carbamate;

(S)-tert-butyl (3-(2-(1-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-methylbutyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)carbamate;

(S)-tert-butyl ((5-chloro-3-(2-cyanoethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)carbamate;

(S)-tert-butyl ((5-chloro-3-(4-cyanobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)carbamate;

(S)-tert-butyl (3-(2-(1-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)(methyl)carbamate;

9H-fluoren-9-ylmethyl N-[(1S)-1-[3-[3-(tert-butoxycarbonylamino)propyl]-5-chloro-4-oxo-quinazolin-2-yl]propyl]carbamate;

tert-butyl N-[(1S)-1-[3-[3-[benzyl(methyl)amino]propyl]-5-chloro-4-oxo-quinazolin-2-yl]ethyl]carbamate;

9H-fluoren-9-ylmethyl N-[(S)-[3-[3-(tert-butoxycarbonylamino)propyl]-5-chloro-4-oxo-quinazolin-2-yl]-cyclopropyl-methyl]carbamate;

tert-butyl N-[(S)-[5-chloro-3-(3-cyanopropyl)-4-oxo-quinazolin-2-yl]-cyclopropyl-methyl]carbamate;

tert-butyl N-[3-[5-chloro-2-[(1S)-1-(9H-fluoren-9-ylmethoxycarbonylamino)ethyl]-4-oxo-quinazolin-3-yl]propyl]-N-methyl-carbamate;

9H-fluoren-9-ylmethyl N-[(1S)-1-[3-[3-(tert-butoxycarbonylamino)propyl]-5-chloro-4-oxo-quinazolin-2-yl]ethyl]carbamate;

tert-butyl N-[(S)-cyclopropyl-[5,8-dichloro-3-(3-cyanopropyl)-4-oxo-quinazolin-2-yl]methyl]carbamate;

tert-butyl N-[3-[5-chloro-2-[(S)-cyclopropyl-(9H-fluoren-9-ylmethoxycarbonylamino)methyl]-4-oxo-quinazolin-3-yl]propyl]-N-methyl-carbamate;

(S)-tert-butyl (1-(3-((1H-pyrazol-3-yl)methyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate;

(S)-tert-butyl (1-(3-((1H-pyrazol-4-yl)methyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate;

(S)-tert-butyl (1-(3-((1H-imidazol-2-yl)methyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate;

(S)-tert-butyl (1-(3-((1H-1,2,4-triazol-5-yl)methyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate;

(1R,3s)-3-(2-((S)-1-((tert-butoxycarbonyl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(S)-3-(2-(1-((tert-butoxycarbonyl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl benzoate;

3-(2-((S)-1-((tert-butoxycarbonyl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)butyl benzoate;

(1S,4r)-4-(2-((S)-1-((tert-butoxycarbonyl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)cyclohexyl benzoate;

(S)-tert-butyl 4-((2-(1-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)methyl)piperidine-1-carboxylate;

tert-butyl 2-((2-((S)-1-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)methyl)morpholine-4-carboxylate;

(S)-tert-butyl (3-(2-(1-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)cyclobutyl)carbamate;

tert-butyl 3-((2-((S)-1-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)methyl)pyrrolidine-1-carboxylate;

tert-butyl 2-((2-((S)-1-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)methyl)pyrrolidine-1-carboxylate;

tert-butyl 2-((2-((S)-1-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)methyl)piperidine-1-carboxylate;

tert-butyl 3-((2-((S)-1-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)methyl)piperidine-1-carboxylate;

(1R,3s)-3-(2-((S)-((tert-butoxycarbonyl)amino)(cyclopropyl)methyl)-5,8-dichloro-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(1S,3r)-3-(2-((S)-((tert-butoxycarbonyl)amino)(cyclopropyl)methyl)-8-chloro-6-fluoro-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(1S,3r)-3-(2-((S)-1-((tert-butoxycarbonyl)amino)ethyl)-8-chloro-6-fluoro-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(1R,3s)-3-(2-((S)-1-((tert-butoxycarbonyl)amino)ethyl)-8-chloro-6-fluoro-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(1S,3r)-3-(2-((S)-((tert-butoxycarbonyl)amino)(cyclopropyl)methyl)-5,8-dichloro-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(1S,3r)-3-(2-((S)-1-((tert-butoxycarbonyl)amino)ethyl)-5,8-dichloro-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(1R,3s)-3-(2-((S)-((tert-butoxycarbonyl)amino)(cyclopropyl)methyl)-8-chloro-6-fluoro-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(1R,3s)-3-(2-((S)-1-((tert-butoxycarbonyl)amino)ethyl)-5,8-dichloro-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(S)-tert-butyl (1-(5-chloro-3-(2-cyanoethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate;

(S)-tert-butyl (1-(5-chloro-3-(3-methoxypropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate;

(S)-tert-butyl (1-(5,8-dichloro-3-(3-methoxypropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate;

(S)-tert-butyl (1-(5,8-difluoro-3-(3-methoxypropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate;

(S)-tert-butyl (1-(5-chloro-3-(3-cyanopropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate;

(S)-tert-butyl (1-(5-chloro-3-(3-(methylsulfonyl)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate;(S)-tert-butyl ((5-chloro-3-(2-cyanoethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)carbamate;

(S)-tert-butyl ((5-chloro-3-(3-cyanopropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)carbamate;

(S)-tert-butyl ((5-chloro-3-(4-cyanobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)carbamate;

(S)-tert-butyl (1-(5-chloro-3-(3-cyanopropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamate;

(S)-tert-butyl (1-(5-chloro-3-(4-cyanobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamate;

(S)-tert-butyl (1-(5-chloro-3-(3-(methylsulfonyl)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamate;

(S)-tert-butyl ((5-chloro-3-(3-(methylsulfonyl)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)carbamate;

(S)-tert-butyl (cyclopropyl(5,8-dichloro-3-(3-(methylsulfonyl)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)carbamate;

(S)-tert-butyl ((8-chloro-6-fluoro-3-(3-(methylsulfonyl)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)carbamate;

(S)-tert-butyl ((5-chloro-3-(4-(methylthio)butyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)carbamate;

(S)-tert-butyl (1-(5-chloro-3-(2-ethoxyethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate;

(S)-tert-butyl (1-(5-chloro-3-(3-(dimethylamino)-3-oxopropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate;

(S)-tert-butyl (1-(5-chloro-3-(3-methoxy-3-methylbutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate;

(S)-tert-butyl (1-(5-chloro-3-(3-morpholinopropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate;

(S)-tert-butyl (1-(5-chloro-3-(1,3-dimethoxypropan-2-yl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate;

(S)-tert-butyl (1-(5-chloro-3-(2-(4-methylpiperazin-1-yl)ethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate;

(S)-tert-butyl (1-(5-chloro-4-oxo-3-(3-(piperidin-1-yl)propyl)-3,4-dihydroquinazolin-2-yl)ethyl)carbamate;

tert-butyl ((S)-1-(5-chloro-3-((S)-1-methoxypropan-2-yl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate;

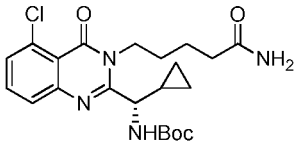
(S)-tert-butyl (1-(5-chloro-3-(3-(4-methylpiperazin-1-yl)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate;

(S)-tert-butyl (1-(5-chloro-4-oxo-3-(2-(pyrrolidin-1-yl)ethyl)-3,4-dihydroquinazolin-2-yl)ethyl)carbamate;

tert-butyl ((S)-1-(5-chloro-4-oxo-3-((S)-tetrahydrofuran-3-yl)-3,4-dihydroquinazolin-2-yl)ethyl)carbamate; and

(S)-tert-butyl (1-(3-(2-(1H-pyrazol-5-yl)ethyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate.

[00190] C. Preparation of a compound of formula (1) wherein n is 1, R^1 is chloro, m is 0, B is $(CH_2)_4$, R^a is $CONH_2$, R^5 is hydrogen, PG is Boc, and R^3 is cyclopropyl



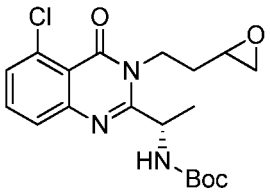
[00191] To a mixture of (*S*)-tert-butyl ((5-chloro-3-(4-cyanobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)carbamate (0.42 g, 0.97 mmol) in EtOH/H_2O (1:1, 10 mL) was added hydrido(dimethylphosphinous acid-kP)[hydrogen bis(dimethylphosphinito-kP)]platinum (II) (0.02 g, 0.05 mmol). The mixture stirred at 90 °C for 3 h. The mixture was cooled to room temperature and diluted with DCM/H_2O. The aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified via flash chromatography (SiO_2, 0-20% MeOH/EtOAc) to give (S)-tert-butyl ((3-(5-amino-5-oxopentyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)carbamate. ES/MS 449.2 ($M+H^+$).

[00192] D. Preparation of the below compound of formula (1), using the methods described in Example 1C and Reaction Scheme I:

tert-butyl N-[(S)-[3-(4-amino-4-oxo-butyl)-5,8-dichloro-4-oxo-quinazolin-2-yl]-cyclopropyl-methyl]carbamate; and

(S)-tert-butyl ((3-(4-amino-4-oxobutyl)-8-chloro-6-fluoro-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)carbamate.

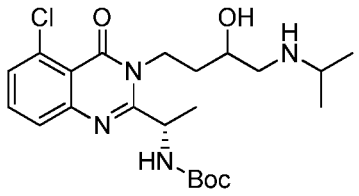
[00193] E. Preparation of a compound of formula (1) wherein n is 1, R^1 is chloro, m is 0, B is $(CH_2)_2$, R^a is oxiranyl, R^5 is hydrogen, PG is Boc, and R^3 is methyl



[00194] Solid mCPBA (1.27 g, 7.34 mmol) was added to a stirring solution of (S)-tert-butyl (1-(3-(but-3-en-1-yl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate (1.4 g, 3.67 mmol) in DCM (50 mL) at rt. The reaction mixture was stirred for 2 d then quenched with satd. $NaHCO_3$ solution and the aqueous layer was extracted with DCM (3x10 mL). Then combined organic layers were dried over Na_2SO_4

and concentrated. Chromatography of the residue afforded tert-butyl ((1S)-1-(5-chloro-3-(2-(oxiran-2-yl)ethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate. ES/MS 394.1 ($M+H^+$).

[00195] F. Preparation of a compound of formula (1) wherein n is 1, R^1 is chloro, m is 0, B is hydroxy substituted butylene, R^a is NHiPr, R^5 is hydrogen, PG is Boc, and R^3 is methyl

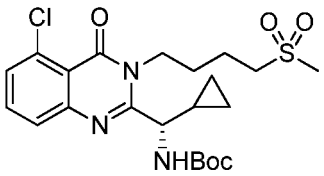


[00196] Lithium perchlorate (21 mg, 0.2 mmol) and isopropylamine (1.75 mL, 20 mmol) were added to tert-butyl ((1S)-1-(5-chloro-3-(2-(oxiran-2-yl)ethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate (400 mg, 1.0 mmol). The resulting mixture was stirred for 16 h at room temperature then diluted with EtOAc (20 mL). The organic layer was washed with water, brine, dried over Na_2SO_4, and concentrated to give crude alcohol. Chromatography afforded tert-butyl ((1S)-1-(5-chloro-3-(3-hydroxy-4-(isopropylamino)butyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate. ES/MS 453.1 ($M+H^+$).

[00197] G. Preparation of the below compound of Formula (1), using the methods described in Example 1F and reaction scheme I:

tert-butyl ((1S)-1-(3-(4-(tert-butylamino)-3-hydroxybutyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate.

[00198] H. Preparation of a compound of formula (1) wherein n is 1, R^1 is chloro, m is 0, B is $(CH_2)_4$, R^a is SO_2Me, R^5 is hydrogen, PG is Boc, and R^3 is cyclopropyl

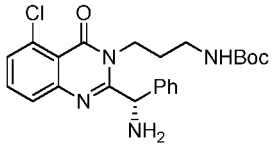


A mixture of (S)-tert-butyl ((5-chloro-3-(4-(methylthio)butyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)carbamate (0.527 g, 1 equiv) and hydrogen

peroxide (0.26 mL of 30 wt% aq, 2.2 equiv) was stirred at 75 °C for 16 h. More hydrogen peroxide (0.12 mL of 30 wt% aq, 1 equiv) was added, and the reaction mixture was stirred at 75 °C for 72 h. The mixture was cooled to rt and partitioned between DCM and H_2O. The aqueous layer was extracted 2× with DCM. The combined organic layers were dried (Na_2SO_4), filtered, concentrated onto silica gel, and purified via flash chromatography (SiO_2, 0-55% EtOAc/hexanes) to give (S)-tert-butyl ((5-chloro-3-(4-(methylsulfonyl)butyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)carbamate.

Example 2. Preparation of a compound of formula (2)

[00199] A. Preparation of a compound of formula (2) wherein n is 1, R^1 is chloro, m is 0, and R^3 is phenyl, B is $(CH_2)_3$, R^a is NHBoc, and R^5 is hydrogen, and PG is Fmoc in formula (1)



[00200] To a solution of (S)-tert-butyl (3-(2-(((((9H-fluoren-9-yl)methoxy)carbonyl)amino)(phenyl)methyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)carbamate (0.28 g, 0.42 mmol) in DMF (2 mL) was added piperidine (0.15 mL, 1.5 mmol). The mixture stirred at room temperature for 2 hours. The mixture was diluted with EtOAc/H_2O and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), decanted and concentrated. The residue was purified via flash chromatography (SiO_2, 0-20% MeOH/DCM) to give tert-butyl N-[3-[2-[(S)-amino(phenyl)methyl]-5-chloro-4-oxo-quinazolin-3-yl]propyl]carbamate. ES/MS 443.2 ($M+H^+$).

[00201] B. Preparation of the below compound of formula (2), using the methods described in Example 2A and Reaction Scheme I and PG is Fmoc in formula (1)

(S)-tert-butyl (4-(2-(1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)-2-methylbutan-2-yl)carbamate;

(S)-tert-butyl (2-((2-(1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)(benzyl)amino)ethyl)carbamate;

tert-butyl (2-(2-((S)-1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)carbamate;

(S)-tert-butyl (2-((2-(1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)(methyl)amino)ethyl)carbamate;

tert-butyl (3-(2-((S)-1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)butyl)carbamate;

(S)-tert-butyl (2-(2-(1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)ethyl)carbamate;

tert-butyl (3-(2-((S)-1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)-2-methylpropyl)carbamate;

(S)-tert-butyl (4-(2-(1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)butyl)carbamate

(S)-tert-butyl (3-(2-(1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)carbamate;

(S)-tert-butyl (3-(2-(1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)(methyl)carbamate;

(S)-tert-butyl (3-(2-(1-amino-3-methylbutyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)carbamate

tert-butyl N-[3-[2-[(1S)-1-aminopropyl]-5-chloro-4-oxo-quinazolin-3-yl]propyl]carbamate;

tert-butyl N-[3-[2-[(S)-amino(cyclopropyl)methyl]-5-chloro-4-oxo-quinazolin-3-yl]propyl]carbamate;

tert-butyl N-[3-[2-[(1S)-1-aminoethyl]-5-chloro-4-oxo-quinazolin-3-yl]propyl]-N-methyl-carbamate;

tert-butyl N-[3-[2-[(1S)-1-aminoethyl]-5-chloro-4-oxo-quinazolin-3-yl]propyl]carbamate;

tert-butyl N-[3-[2-[(S)-amino(cyclopropyl)methyl]-5-chloro-4-oxo-quinazolin-3-yl]propyl]-N-methyl-carbamate;

(S)-tert-butyl (3-(2-(1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)cyclobutyl)carbamate;

(S)-tert-butyl 4-((2-(1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)methyl)piperidine-1-carboxylate;

tert-butyl 2-((2-((S)-1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)methyl)morpholine-4-carboxylate;

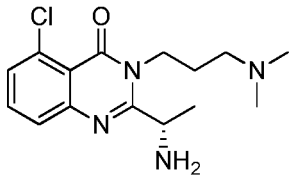
tert-butyl 3-((2-((S)-1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)methyl)pyrrolidine-1-carboxylate;

tert-butyl 2-((2-((S)-1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)methyl)pyrrolidine-1-carboxylate;

tert-butyl 2-((2-((S)-1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)methyl)piperidine-1-carboxylate; and

tert-butyl 3-((2-((S)-1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)methyl)piperidine-1-carboxylate.

[00202] C. Preparation of a compound of formula (2) wherein n is 1, R^1 is chloro, m is 0, B is $(CH_2)_3$, Ra is $-N(CH_3)_2$, R^5 is hydrogen, and R^3 is methyl and PG is Boc in formula (1)



[00203] Trifluoroacetic acid (2 mL) was added to a solution of (S)-tert-butyl (1-(5-chloro-3-(3-(dimethylamino)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate (0.5 g, 1.6 mmol) in dichloromethane (3 mL). The reaction mixture was stirred at room temperature for 1 hour. The solvents was removed *in vacuo* to afford (S)-2-(1-aminoethyl)-5-chloro-3-(3-(dimethylamino)propyl)quinazolin-4(3H)-one 2,2,2-trifluoroacetic acid salt. ES/MS *m/z* = 309.2 $(M+H)^+$

[00204] Preparation of the below compounds of formula (2), using the methods described in Example 2c and Reaction Scheme I and PG is Boc in formula (1):

(S)-2-(1-aminoethyl)-5-chloro-3-(3-morpholinopropyl)quinazolin-4(3H)-one;

2-((S)-1-aminoethyl)-5-chloro-3-(3-hydroxy-4-(isopropylamino)butyl)quinazolin-4(3H)-one;

2-((S)-1-aminoethyl)-3-(4-(tert-butylamino)-3-hydroxybutyl)-5-chloroquinazolin-4(3H)-one;

(S)-2-(1-aminoethyl)-5-chloro-3-(2-(dimethylamino)ethyl)quinazolin-4(3H)-one;

(S)-3-(2-(amino(cyclopropyl)methyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propanenitrile;

(S)-5-(2-(amino(cyclopropyl)methyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)pentanamide;

2-[(1S)-1-aminoethyl]-3-[3-[benzyl(methyl)amino]propyl]-5-chloro-quinazolin-4-one;

4-[2-[(S)-amino(cyclopropyl)methyl]-5-chloro-4-oxo-quinazolin-3-yl]butanenitrile;

5-[2-[(S)-amino(cyclopropyl)methyl]-5-chloro-4-oxo-quinazolin-3-yl]pentanamide;

4-[2-[(S)-amino(cyclopropyl)methyl]-5,8-dichloro-4-oxo-quinazolin-3-yl]butanamide;

2-[3-[2-[(S)-amino(cyclopropyl)methyl]-5-chloro-4-oxo-quinazolin-3-yl]phenyl]acetonitrile;

(S)-3-((1H-pyrazol-3-yl)methyl)-2-(1-aminoethyl)-5-chloroquinazolin-4(3H)-one;

(S)-3-((1H-pyrazol-4-yl)methyl)-2-(1-aminoethyl)-5-chloroquinazolin-4(3H)-one;

(S)-3-((1H-imidazol-2-yl)methyl)-2-(1-aminoethyl)-5-chloroquinazolin-4(3H)-one;

(S)-3-((1H-1,2,4-triazol-5-yl)methyl)-2-(1-aminoethyl)-5-chloroquinazolin-4(3H)-one;

(1R,3s)-3-(2-((S)-1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(S)-3-(2-(1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl benzoate;

3-(2-((S)-1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)butyl benzoate;

(1S,4r)-4-(2-((S)-1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)cyclohexyl benzoate;

(1R,3s)-3-(2-((S)-amino(cyclopropyl)methyl)-5,8-dichloro-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(1S,3r)-3-(2-((S)-amino(cyclopropyl)methyl)-8-chloro-6-fluoro-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(1S,3r)-3-(2-((S)-1-aminoethyl)-8-chloro-6-fluoro-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(1R,3s)-3-(2-((S)-1-aminoethyl)-8-chloro-6-fluoro-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(1S,3r)-3-(2-((S)-amino(cyclopropyl)methyl)-5,8-dichloro-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(1S,3r)-3-(2-((S)-1-aminoethyl)-5,8-dichloro-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(1R,3s)-3-(2-((S)-amino(cyclopropyl)methyl)-8-chloro-6-fluoro-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(1R,3s)-3-(2-((S)-1-aminoethyl)-5,8-dichloro-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(S)-3-(2-(1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propanenitrile;

(S)-3-(2-(1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propanenitrile;

(S)-2-(1-aminoethyl)-5,8-dichloro-3-(3-methoxypropyl)quinazolin-4(3H)-one;

(S)-2-(1-aminoethyl)-5,8-difluoro-3-(3-methoxypropyl)quinazolin-4(3H)-one;

(S)-4-(2-(1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)butanenitrile;

(S)-2-(1-aminoethyl)-5-chloro-3-(3-(methylsulfonyl)propyl)quinazolin-4(3H)-one;

(S)-3-(2-(amino(cyclopropyl)methyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propanenitrile;(S)-4-(2-(amino(cyclopropyl)methyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)butanenitrile;

(S)-5-(2-(amino(cyclopropyl)methyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)pentanenitrile;

(S)-4-(2-(1-aminopropyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)butanenitrile;

(S)-5-(2-(1-aminopropyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)pentanenitrile;

(S)-2-(1-aminopropyl)-5-chloro-3-(3-(methylsulfonyl)propyl)quinazolin-4(3H)-one;

(S)-2-(amino(cyclopropyl)methyl)-5-chloro-3-(3-(methylsulfonyl)propyl)quinazolin-4(3H)-one;

(S)-2-(amino(cyclopropyl)methyl)-5,8-dichloro-3-(3-(methylsulfonyl)propyl)quinazolin-4(3H)-one;

(S)-2-(amino(cyclopropyl)methyl)-8-chloro-6-fluoro-3-(3-(methylsulfonyl)propyl)quinazolin-4(3H)-one;

(S)-4-(2-(amino(cyclopropyl)methyl)-8-chloro-6-fluoro-4-oxoquinazolin-3(4H)-yl)butanamide;

(S)-2-(amino(cyclopropyl)methyl)-5-chloro-3-(4-(methylthio)butyl)quinazolin-4(3H)-one;

(S)-3-(2-(1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)-N,N-dimethylpropanamide;

(S)-2-(1-aminoethyl)-5-chloro-3-(2-ethoxyethyl)quinazolin-4(3H)-one;

(S)-2-(1-aminoethyl)-5-chloro-3-(3-methoxy-3-methylbutyl)quinazolin-4(3H)-one;

(S)-2-(1-aminoethyl)-5-chloro-3-(3-morpholinopropyl)quinazolin-4(3H)-one;

(S)-2-(1-aminoethyl)-5-chloro-3-(1,3-dimethoxypropan-2-yl)quinazolin-4(3H)-one;

(S)-2-(1-aminoethyl)-5-chloro-3-(2-(4-methylpiperazin-1-yl)ethyl)quinazolin-4(3H)-one;

(S)-2-(1-aminoethyl)-5-chloro-3-(3-(piperidin-1-yl)propyl)quinazolin-4(3H)-one;

2-((S)-1-aminoethyl)-5-chloro-3-((S)-1-methoxypropan-2-yl)quinazolin-4(3H)-one;

(S)-2-(1-aminoethyl)-5-chloro-3-(2-(pyrrolidin-1-yl)ethyl)quinazolin-4(3H)-one;

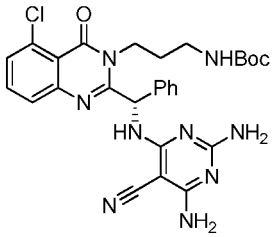
(S)-2-(1-aminoethyl)-5-chloro-3-(3-(4-methylpiperazin-1-yl)propyl)quinazolin-4(3H)-one;

2-((S)-1-aminoethyl)-5-chloro-3-((S)-tetrahydrofuran-3-yl)quinazolin-4(3H)-one; and

(S)-3-(2-(1H-pyrazol-5-yl)ethyl)-2-(1-aminoethyl)-5-chloroquinazolin-4(3H)-one.

Example 3. Preparation of compounds of formula (I) or (3)

[00205] A. Preparation of a compound of formula (3) wherein n is 1, R^1 is chloro, m is 0, B is $(CH_2)_3$, R^a is NHBoc, R^5 is hydrogen, A is a single bond, R^4 is 2,6-diamino-5-cyanopyrimidine, and R^3 is phenyl



[00206] A mixture of (*S*)-tert-butyl (3-(2-(amino(phenyl)methyl)-5-chloro-4-oxoquinazolin-3(4*H*)-yl)propyl)carbamate (71 mg, 0.16 mmol), 2,4-diamino-6-chloropyrimidine-5-carbonitrile (26 mg, 0.16 mmol), and diisopropylethylamine (42 μL, 0.24 mmol) in *i*-PrOH (1 mL) was heated in the microwave at 130 °C for 8 h. On cooling, the mixture was concentrated onto silica gel and purified via flash chromatography (SiO_2, 0-100% EtOAc/hexanes, then 0-20% MeOH/EtOAc) to give (S)-tert-butyl (3-(5-chloro-2-(((2,6-diamino-5-cyanopyrimidin-4-yl)amino)(phenyl)methyl)-4-oxoquinazolin-3(4H)-yl)propyl)carbamate. ES/MS 576.2 ($M+H^+$).

[00207] B. Preparation of the below compounds of formulae (I) or (3), using the methods described in Example 3A and Reaction Scheme I:

(S)-tert-butyl (4-(5-chloro-4-oxo-2-(1-(thiazolo[5,4-d]pyrimidin-7-ylamino)ethyl)quinazolin-3(4H)-yl)-2-methylbutan-2-yl)carbamate;

(S)-tert-butyl (4-(2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)-2-methylbutan-2-yl)carbamate;

(S)-tert-butyl (3-(5-chloro-2-(1-((2,6-diamino-5-chloropyrimidin-4-yl)amino)ethyl)-4-oxoquinazolin-3(4H)-yl)propyl)carbamate;

(S)-tert-butyl (2-(benzyl(5-chloro-2-(1-((2,6-diamino-5-cyanopyrimidin-4-yl)amino)ethyl)-4-oxoquinazolin-3(4H)-yl)amino)ethyl)carbamate;

(S)-tert-butyl (2-((5-chloro-2-(1-(imidazo[2,1-f][1,2,4]triazin-4-ylamino)ethyl)-4-oxoquinazolin-3(4H)-yl)(methyl)amino)ethyl)carbamate;

(S)-tert-butyl (2-((2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)(benzyl)amino)ethyl)carbamate;

(S)-tert-butyl (2-((5-chloro-2-(1-((2,6-diamino-5-cyanopyrimidin-4-yl)amino)ethyl)-4-oxoquinazolin-3(4H)-yl)(methyl)amino)ethyl)carbamate;

(S)-tert-butyl (2-((2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)(methyl)amino)ethyl)carbamate;

(S)-tert-butyl (3-(2-(1-(3-aminopyrazine-2-carboxamido)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)carbamate;

(S)-tert-butyl (3-(2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-methyl-4-oxoquinazolin-3(4H)-yl)propyl)carbamate;

(S)-tert-butyl (3-(2-(1-((6-amino-5-chloropyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)carbamate;

(S)-tert-butyl (3-(2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)(methyl)carbamate

tert-butyl (3-(2-((S)-1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)butyl)carbamate;

tert-butyl (2-(2-((S)-1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)carbamate;

(S)-tert-butyl (2-(2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)ethyl)carbamate;

tert-butyl (3-(2-((S)-1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)-2-methylpropyl)carbamate;

(S)-tert-butyl (4-(2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)butyl)carbamate;

(S)-tert-butyl (3-(2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)-3-methylbutyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)carbamate;

(S)-tert-butyl (3-(2-(1-aminopropyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)carbamate;

tert-butyl N-[3-[2-[(1S)-1-[(6-amino-5-cyano-pyrimidin-4-yl)amino]propyl]-5-chloro-4-oxo-quinazolin-3-yl]propyl]carbamate;

tert-butyl N-[3-[5-chloro-2-[(S)-cyclopropyl-(imidazo[2,1-f][1,2,4]triazin-4-ylamino)methyl]-4-oxo-quinazolin-3-yl]propyl]carbamate;

(S)-tert-butyl (3-(5-chloro-2-(1-((2,6-diamino-5-cyanopyrimidin-4-yl)amino)propyl)-4-oxoquinazolin-3(4H)-yl)propyl)carbamate;

(S)-tert-butyl (3-(5-chloro-2-(cyclopropyl(pyrido[3,2-d]pyrimidin-4-ylamino)methyl)-4-oxoquinazolin-3(4H)-yl)propyl)carbamate;

(S)-tert-butyl (3-(5-chloro-2-(cyclopropyl((2,6-diamino-5-chloropyrimidin-4-yl)amino)methyl)-4-oxoquinazolin-3(4H)-yl)propyl)carbamate;

tert-butyl N-[3-[5-chloro-2-[(1S)-1-[(2,6-diamino-5-cyano-pyrimidin-4-yl)amino]ethyl]-4-oxo-quinazolin-3-yl]propyl]-N-methyl-carbamate;

(S)-tert-butyl (3-(2-(((6-amino-5-cyanopyrimidin-4-yl)amino)(cyclopropyl)methyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)carbamate;

(S)-tert-butyl (3-(2-(1-((2-amino-5-cyano-6-methylpyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)(methyl)carbamate;

tert-butyl N-[3-[5-chloro-2-[(1S)-1-[(2,6-diamino-5-cyano-pyrimidin-4-yl)amino]ethyl]-4-oxo-quinazolin-3-yl]propyl]carbamate;

(S)-2-amino-4-chloro-6-(((5-chloro-3-(3-(methylamino)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile;

(S)-tert-butyl (3-(5-chloro-2-(cyclopropyl(thiazolo[5,4-d]pyrimidin-7-ylamino)methyl)-4-oxoquinazolin-3(4H)-yl)propyl)carbamate;

(S)-tert-butyl (3-(2-(((5-bromo-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)(cyclopropyl)methyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)carbamate;

tert-butyl N-[3-[5-chloro-2-[(S)-cyclopropyl-[(2,6-diamino-5-cyano-pyrimidin-4-yl)amino]methyl]-4-oxo-quinazolin-3-yl]propyl]-N-methyl-carbamate;

(S)-tert-butyl (3-(5-chloro-2-(cyclopropyl((2,6-diamino-5-cyanopyrimidin-4-yl)amino)methyl)-4-oxoquinazolin-3(4H)-yl)propyl)carbamate;

(S)-tert-butyl (3-(5-chloro-2-(((6-chloropyrido[3,2-d]pyrimidin-4-yl)amino)(cyclopropyl)methyl)-4-oxoquinazolin-3(4H)-yl)propyl)carbamate;

(S)-tert-butyl (3-(2-(((2-amino-5-cyano-6-methylpyrimidin-4-yl)amino)(cyclopropyl)methyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)carbamate;

(S)-tert-butyl (3-(5-chloro-2-(1-(imidazo[2,1-f][1,2,4]triazin-4-ylamino)ethyl)-4-oxoquinazolin-3(4H)-yl)propyl)carbamate;

(S)-tert-butyl (3-(5-chloro-4-oxo-2-(1-(thiazolo[5,4-d]pyrimidin-7-ylamino)ethyl)quinazolin-3(4H)-yl)propyl)carbamate;

(S)-tert-butyl (3-(2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)carbamate;

(1R,3s)-3-(2-((S)-1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(S)-3-(2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl benzoate;

3-(2-((S)-1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)butyl benzoate;

(1S,4r)-4-(2-((S)-1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)cyclohexyl benzoate;

(S)-tert-butyl (3-(2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)cyclobutyl)carbamate;

(S)-tert-butyl 4-((2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)methyl)piperidine-1-carboxylate;

tert-butyl 2-((2-((S)-1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)methyl)morpholine-4-carboxylate;

tert-butyl 3-((2-((S)-1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)methyl)pyrrolidine-1-carboxylate;

tert-butyl 2-((2-((S)-1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)methyl)pyrrolidine-1-carboxylate;

tert-butyl 2-((2-((S)-1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)methyl)piperidine-1-carboxylate;

tert-butyl 3-((2-((S)-1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)methyl)piperidine-1-carboxylate;

(1R,3s)-3-(5-chloro-2-((S)-1-((2,6-diamino-5-cyanopyrimidin-4-yl)amino)ethyl)-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(1R,3s)-3-(5-chloro-2-((S)-1-((2,6-diamino-5-chloropyrimidin-4-yl)amino)ethyl)-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(1R,3s)-3-(5,8-dichloro-2-((S)-cyclopropyl((2,6-diamino-5-chloropyrimidin-4-yl)amino)methyl)-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(1R,3s)-3-(5,8-dichloro-2-((S)-cyclopropyl((2,6-diamino-5-cyanopyrimidin-4-yl)amino)methyl)-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(1S,3r)-3-(8-chloro-2-((S)-cyclopropyl((2,6-diamino-5-cyanopyrimidin-4-yl)amino)methyl)-6-fluoro-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(1S,3r)-3-(8-chloro-2-((S)-1-((2,6-diamino-5-cyanopyrimidin-4-yl)amino)ethyl)-6-fluoro-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(1R,3s)-3-(8-chloro-2-((S)-1-((2,6-diamino-5-cyanopyrimidin-4-yl)amino)ethyl)-6-fluoro-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(1S,3r)-3-(5,8-dichloro-2-((S)-cyclopropyl((2,6-diamino-5-cyanopyrimidin-4-yl)amino)methyl)-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(1S,3r)-3-(5,8-dichloro-2-((S)-1-((2,6-diamino-5-cyanopyrimidin-4-yl)amino)ethyl)-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

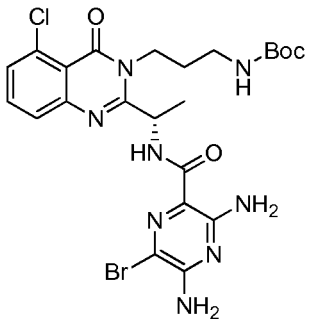
(1R,3s)-3-(8-chloro-2-((S)-cyclopropyl((2,6-diamino-5-cyanopyrimidin-4-yl)amino)methyl)-6-fluoro-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(1R,3s)-3-(5,8-dichloro-2-((S)-1-((2,6-diamino-5-cyanopyrimidin-4-yl)amino)ethyl)-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate;

(R)-tert-butyl 3-((5-chloro-2-((S)-1-((2,6-diamino-5-cyanopyrimidin-4-yl)amino)ethyl)-4-oxoquinazolin-3(4H)-yl)methyl)pyrrolidine-1-carboxylate; and

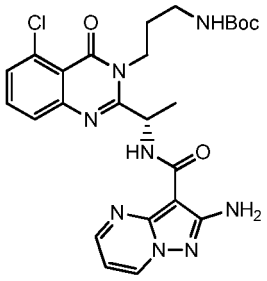
(S)-tert-butyl 3-((5-chloro-2-((S)-1-((2,6-diamino-5-cyanopyrimidin-4-yl)amino)ethyl)-4-oxoquinazolin-3(4H)-yl)methyl)piperidine-1-carboxylate.

[00208] C. Preparation of a compound of formula (3), where A is CO, n is 1, R^1 is Cl, m is 0, B is $(CH_2)_3$, R^a is NHBoc, R^5 is hydrogen, R^4 is 2,4-diamino-5-bromopyrazine, and R^3 is methyl



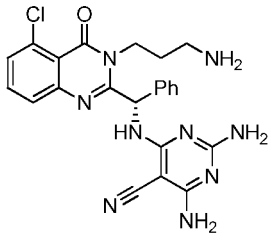
[00209] To (S)-tert-butyl (3-(2-(1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)carbamate and 3,5-diamino-6-bromopyrazine-2-carboxylic acid in DCM was added HATU and DIEA. The reaction was allowed to stir at RT for 2 hours. The reaction was monitored by LCMS. Upon completion the reaction was concentrated to dryness and purified by silica gel chromatography (20-80% EtOAc/hexanes) to give (S)-tert-butyl (3-(5-chloro-2-(1-(3,5-diamino-6-bromopyrazine-2-carboxamido)ethyl)-4-oxoquinazolin-3(4H)-yl)propyl)carbamate.

[00210] D. Preparation of the below compound of formula (3), where A is CO, n is 1, R^1 is Cl, m is 0, B is $(CH_2)_3$, R^a is NHBoc, R^5 is hydrogen, R^4 is 2-aminopyrazolo[1,5-a]pyrimidine-3-yl, and R^3 is methyl



[00211] To (S)-tert-butyl (3-(2-(1-aminoethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)carbamate (300 mg, 0.79 mmol), HATU (400 mg, 1.1mmol) and 2-aminopyrazolo[1,5-a]pyrimidine-3-carboxylic acid (196 mg, 1.1mmol) in DMF (3 mL) was added Hunig's base (0.4 mL). After stirring at room temp for 1 hour, water was added and the mixture was extracted with EtOAc (3x30 mL), dried ($MgSO_4$), and concentrated. The residue was purified on a reverse phase HPLC run from 0 to 95% ACN in water (0.1% TFA) to give (S)-tert-butyl (3-(2-(1-(2-aminopyrazolo[1,5-a]pyrimidine-3-carboxamido)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)carbamate. ES/MS 541.2 $(M+H)^+$.

[00212] E. Preparation of a compound of formula (I), where n is 1, R^1 is chloro, m is 0, B is $(CH_2)_3$, R^2 is NH_2, R^5 is hydrogen, R^4 is 2,6-diamno-5-cyanopyrimidin-4-yl, R^3 is phenyl, and R^3 is phenyl



[00213] To a solution of (*S*)-tert-butyl (3-(5-chloro-2-(((2,6-diamino-5-cyanopyrimidin-4-yl)amino)(phenyl)methyl)-4-oxoquinazolin-3(4*H*)-yl)propyl)carbamate (53 mg, 0.09 mmol) in DCM (0.5 mL) was added trifluoroacetic acid (0.5 mL). The mixture sat at room temperature 2 h. The mixture was concentrated to give (*S*)-2,4-diamino-6-(((3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)(phenyl)methyl)amino)pyrimidine-5-carbonitrile (Compound 1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (t, *J* = 8.0 Hz, 1H), 7.76 – 7.67 (m, 3H), 7.61 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.60 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.53 – 7.48 (m, 2H), 7.43 – 7.34 (m, 3H), 7.10 (br s, 2H), 6.84 (br s, 2H), 6.49 (d, *J* = 7.4 Hz, 1H), 4.18 – 4.03 (m, 1H), 3.85 – 3.76 (m, 1H), 2.91 – 2.78 (m, 2H), 2.07 – 1.94 (m, 1H), 1.79 – 1.62 (m, 1H). ES/MS 476.2 (M+H$^+$).

[00214] F. Preparation of the below compounds of formula (I), using Example 3E and Reaction Scheme I:

(S)-3-(3-amino-3-methylbutyl)-5-chloro-2-(1-(thiazolo[5,4-d]pyrimidin-7-ylamino)ethyl)quinazolin-4(3H)-one (Compound 2). 1H NMR (400 MHz, DMSO-d6) δ 9.30 (s, 1H), 8.81 (d, *J* = 6.8 Hz, 1H), 8.43 (s, 1H), 7.90 (br s, 3H), 7.68 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.57 – 7.46 (m, 2H), 5.50 (p, *J* = 6.8 Hz, 1H), 4.21 (td, *J* = 13.4, 4.2 Hz, 2H), 4.00 (td, *J* = 12.2, 4.7 Hz, 2H), 2.14 (td, *J* = 13.2, 4.8 Hz, 2H), 1.98 (td, *J* = 12.6, 4.0 Hz, 2H), 1.63 (d, *J* = 6.5 Hz, 3H), 1.24 (s, 3H), 1.23 (s, 3H). ES/MS 444.1 (M+H$^+$).

(S)-4-amino-6-((1-(3-(3-amino-3-methylbutyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 3). 1H NMR (400 MHz, DMSO-d6) δ 8.02 (s, 1H), 7.93 – 7.84 (m, 2H), 7.71 (t, *J* = 8.1 Hz, 1H), 7.60 – 7.50 (m, 2H), 5.40 (p, *J* = 6.6 Hz, 1H), 4.09 (td, *J* = 13.3, 4.8 Hz, 2H), 3.93 (td, *J* = 13.3, 4.8 Hz, 2H), 2.04 (td, *J* = 12.6, 4.7 Hz, 2H), 1.94 (td, *J* = 12.5, 4.5 Hz, 2H), 1.52 (d, *J* = 6.6 Hz, 3H), 1.26 (s, 3H), 1.25 (s, 3H). ES/MS 427.2 (M+H$^+$).

(S)-4-amino-6-((1-(3-(3-(benzylamino)propyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 6). 1H NMR (400 MHz, DMSO-

d6) δ 8.78 (br s, 2H), 7.97 (s, 1H), 7.78 (d, J = 6.8 Hz, 1H), 7.70 (dd, J = 8.4, 7.6 Hz, 1H), 7.55 – 7.35 (m, 8H), 5.34 (p, J = 6.8 Hz, 1H), 4.23 – 4.09 (m, 3H), 3.99 (p, J = 7.1 Hz, 1H), 3.03 (p, J = 7.0 Hz, 2H), 2.26 – 2.02 (m, 2H), 1.51 (d, J = 6.6 Hz, 3H). ES/MS 489.2 ($M+H^+$).

(S)-3-(3-aminopropyl)-5-chloro-2-(1-((2,6-diamino-5-chloropyrimidin-4-yl)amino)ethyl)quinazolin-4(3H)-one (Compound 7). 1H NMR (400 MHz, DMSO-d6) δ 7.79 – 7.68 (m, 3H), 7.58 (ddd, J = 7.6, 6.6, 1.2 Hz, 2H), 5.35 (p, J = 7.5 Hz, 1H), 4.18 – 4.00 (m, 2H), 2.98 – 2.86 (m, 2H), 2.07 – 1.93 (m, 2H), 1.56 (d, J = 6.5 Hz, 3H).. ES/MS 423.1 ($M+H^+$).

(S)-2,4-diamino-6-((1-(3-(3-(benzylamino)propyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 8). 1H NMR (400 MHz, DMSO-d6) δ 8.89 – 8.73 (m, 2H), 7.75 (dd, J = 8.3, 7.8 Hz, 1H), 7.58 (ddd, J = 9.9, 8.1, 1.2 Hz, 2H), 7.52 – 7.39 (m, 5H), 7.21 – 7.10 (m, 2H), 6.95 – 6.79 (m, 2H), 5.40 (p, J = 6.8 Hz, 1H), 4.19 – 4.02 (m, 4H), 3.07 (s, 2H), 2.21 – 2.02 (m, 2H), 1.53 (d, J = 6.6 Hz, 3H). ES/MS 504.2 ($M+H^+$).

(S)-2,4-diamino-6-((1-(3-((2-aminoethyl)(benzyl)amino)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 9). 1H NMR (400 MHz, DMSO-d6) δ 7.78 (t, J = 8.0 Hz, 1H), 7.72 (s, 4H), 7.61 (dd, J = 7.9, 1.1 Hz, 1H), 7.56 (dd, J = 8.1, 1.2 Hz, 1H), 7.30 (dd, J = 6.6, 2.9 Hz, 2H), 7.20 – 7.16 (m, 3H), 5.72 (p, J = 6.7 Hz, 1H), 4.63 (d, J = 12.9 Hz, 1H), 4.49 (d, J = 12.8 Hz, 1H), 3.70 – 3.53 (m, 2H), 2.89 (dt, J = 11.7, 6.3 Hz, 2H), 1.46 (d, J = 6.6 Hz, 3H). ES/MS 505.2 ($M+H^+$).

(S)-2,4-diamino-6-((1-(3-((2-aminoethyl)(benzyl)amino)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 10). 1H NMR (400 MHz, DMSO-d6) δ 7.78 (t, J = 8.0 Hz, 1H), 7.63 – 7.56 (m, 2H), 7.45 – 7.39 (m, 4H), 7.38 – 7.28 (m, 1H), 5.88 (p, J = 7.2 Hz, 1H), 4.77 (d, J = 13.7 Hz, 1H), 4.50 (d, J = 13.7 Hz, 1H), 3.70 (td, J = 11.6, 10.9, 5.4 Hz, 1H), 3.32 (td, J = 12.4, 11.9, 5.3 Hz, 1H), 2.95 (dd, J = 13.3, 7.6 Hz, 2H), 1.25 (d, J = 6.6 Hz, 3H). ES/MS 505.2 ($M+H^+$).

(S)-3-((2-aminoethyl)(methyl)amino)-5-chloro-2-(1-(imidazo[2,1-f][1,2,4]triazin-4-ylamino)ethyl)quinazolin-4(3H)-one (Compound 11). Exsists as a ~1:1 ratio of diastereomers. 1H NMR (400 MHz, DMSO-d6) δ 9.26 (d, J = 7.3 Hz, 0.5H), 9.19 (d, J = 6.8 Hz, 0.5H), 8.13 (d, J = 4.4 Hz, 1H), 8.10 (d, J = 1.1 Hz, 1H), 7.88 (s, 1.5H), 7.81 (s,

2H), 7.74 – 7.63 (m, 2H), 7.56 (q, J = 1.2 Hz, 0.5H), 7.54 (dd, J = 1.7, 1.0 Hz, 0.5H), 7.53 (dd, J = 7.9, 1.2 Hz, 0.5H), 7.48 (dd, J = 8.2, 1.2 Hz, 0.5H), 5.89 – 5.81 (m, 1H), 3.83 (dt, J = 12.3, 5.9 Hz, 0.5H), 3.68 (ddd, J = 12.9, 9.3, 6.4 Hz, 0.5H), 3.63 – 3.51 (m, 0.5H), 3.37 – 3.20 (m, 1H), 3.16 – 3.00 (m, 3.5H), 2.95 (s, 1.5H), 1.62 (d, J = 6.9 Hz, 1.5H), 1.60 (d, J = 6.9 Hz, 1.5H). ES/MS 414.1 ($M+H^+$).

(S)-4-amino-6-((1-(3-((2-aminoethyl)(benzyl)amino)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 12). 1H NMR (400 MHz, DMSO-d6) δ 8.05 (s, 1H), 7.70 (t, J = 8.0 Hz, 1H), 7.64 – 7.56 (m, 3H), 7.54 (dd, J = 7.9, 1.2 Hz, 1H), 7.51 (dd, J = 8.1, 1.2 Hz, 1H), 7.45 – 7.27 (m, 8H), 5.84 (p, J = 6.7 Hz, 1H), 4.79 (d, J = 14.0 Hz, 1H), 4.47 (d, J = 14.0 Hz, 1H), 3.70 (td, J = 13.1, 10.9, 5.8 Hz, 1H), 3.30 (td, J = 12.9, 10.6, 5.6 Hz, 1H), 3.09 – 2.94 (m, 2H), 1.27 (d, J = 6.8 Hz, 3H). ES/MS 490.2 ($M+H^+$).

(S)-4-amino-6-((1-(3-((2-aminoethyl)(benzyl)amino)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 13). 1H NMR (400 MHz, DMSO-d6) δ 8.04 (d, J = 0.5 Hz, 1H), 7.74 (t, J = 8.0 Hz, 1H), 7.68 – 7.63 (m, 4H), 7.57 (dd, J = 7.9, 1.1 Hz, 1H), 7.53 (dd, J = 8.1, 1.1 Hz, 1H), 7.34 (s, 2H), 7.27 (dd, J = 7.5, 1.9 Hz, 2H), 7.17 – 7.07 (m, 3H), 5.76 (p, J = 6.6 Hz, 1H), 4.61 (d, J = 12.6 Hz, 1H), 4.49 (d, J = 12.5 Hz, 1H), 3.67 – 3.48 (m, 2H), 2.92 – 2.72 (m, 2H), 1.45 (d, J = 6.6 Hz, 3H). ES/MS 490.2 ($M+H^+$).

(S)-2,4-diamino-6-((1-(3-((2-aminoethyl)(methyl)amino)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 14). 1H NMR (400 MHz, DMSO-d6) δ 7.80 – 7.71 (m, 3H), 7.60 (dd, J = 8.2, 1.2 Hz, 1H), 7.57 (dd, J = 7.8, 1.2 Hz, 1H), 5.62 (p, J = 7.2 Hz, 1H), 3.74 (dt, J = 12.6, 6.2 Hz, 1H), 3.30 (dt, J = 13.2, 8.2 Hz, 1H), 3.05 – 2.96 (m, 2H), 2.91 (s, 3H), 1.46 (d, J = 6.7 Hz, 3H). ES/MS 429.2 ($M+H^+$).

(S)-2,4-diamino-6-((1-(3-((2-aminoethyl)(methyl)amino)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 15). 1H NMR (400 MHz, DMSO-d6) δ 7.79 – 7.71 (m, 4H), 7.56 (ddd, J = 8.1, 4.0, 1.2 Hz, 2H), 5.64 (p, J = 6.8 Hz, 1H), 3.65 – 3.55 (m, 1H), 3.52 – 3.44 (m, 1H), 3.07 (s, 4H), 3.00 – 2.90 (m, 1H), 1.48 (d, J = 6.7 Hz, 3H). ES/MS 429.1 ($M+H^+$).

(S)-4-amino-6-((1-(3-((2-aminoethyl)(methyl)amino)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 16). 1H NMR (400 MHz, DMSO-d6) δ 8.01 (s, 1H), 7.84 (br s, 3H), 7.75 – 7.69 (m, 2H), 7.54 (ddd, J = 13.6, 8.0, 1.2 Hz, 2H), 5.68 (p, J = 6.8 Hz, 1H), 3.74 (dt, J = 12.0, 5.7 Hz, 1H), 3.24 (dt, J = 13.5, 8.2 Hz, 1H), 3.04 – 2.94 (m, 2H), 2.86 (s, 3H), 1.44 (d, J = 6.7 Hz, 3H). ES/MS 414.1 ($M+H^+$).

(S)-4-amino-6-((1-(3-((2-aminoethyl)(methyl)amino)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 17). 1H NMR (400 MHz, DMSO-d6) δ 8.00 (s, 1H), 7.72 (s, 4H), 7.68 (t, J = 8.0 Hz, 1H), 7.56 (d, J = 7.1 Hz, 1H), 7.49 (ddd, J = 8.1, 6.0, 1.2 Hz, 2H), 7.36 (s, 2H), 5.67 (p, J = 7.0 Hz, 1H), 3.62 – 3.52 (m, 1H), 3.52 – 3.43 (m, 1H), 3.14 (t, J = 13.1 Hz, 1H), 3.06 – 2.95 (m, 4H), 1.47 (d, J = 6.8 Hz, 3H). ES/MS 414.1 ($M+H^+$).

(S)-3-amino-N-(1-(3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)pyrazine-2-carboxamide (Compound 18). 1H NMR (400 MHz, DMSO-d6) δ 9.08 (d, J = 7.3 Hz, 1H), 8.23 (d, J = 2.3 Hz, 1H), 7.86 (d, J = 2.3 Hz, 1H), 7.73 – 7.67 (m, 4H), 7.57 – 7.49 (m, 2H), 5.24 (p, J = 6.7 Hz, 1H), 4.25 (ddd, J = 14.2, 8.5, 5.9 Hz, 1H), 4.00 (ddd, J = 14.7, 8.9, 6.5 Hz, 1H), 2.92 (h, J = 7.0 Hz, 2H), 2.12 – 1.92 (m, 2H), 1.53 (d, J = 6.6 Hz, 3H). ES/MS 402.1 ($M+H^+$).

(S)-4-((1-(3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)-6-methylpyrimidine-5-carbonitrile (Compound 23). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (s, 1H), 7.73 (d, J = 8.0 Hz, 3H), 7.55 (d, J = 4.7 Hz, 1H), 5.40 (m, 1H), 4.23 (s, 1H), 4.00 (s, 1H), 3.46 (brm, 2H), 2.93 (m, 2H), 2.48 (s, 3H), 2.24 – 2.11 (m, 1H), 2.07 (m, 1H), 1.58 (d, J = 6.6 Hz, 3H). ES/MS 398.1 ($M+H^+$).

4-amino-6-(((1S)-1-(3-(4-aminobutan-2-yl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 24). 1H NMR (400 MHz, DMSO-d_6) δ 8.02 (s, 1H), 7.76 (d, J = 7.1 Hz, 1H), 7.69 – 7.61 (m, 1H), 7.50 – 7.43 (m, 2H), 7.35 (s, 1H), 5.46 (t, J = 6.8, 6.8 Hz, 1H), 4.54 (m, 1H), 2.95 (m, 1H), 2.66 (m, 1H), 2,55 (m, 1H), 2.16 – 2.04 (m, 1H), 1.57 (d, J = 6.5 Hz, 3H), 1.47 (d, J = 6.7 Hz, 3H). ES/MS 413.0 ($M+H^+$).

4-amino-6-(((1S)-1-(3-(1-aminopropan-2-yl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 25). 1H NMR (400 MHz, DMSO-

d_6) δ 8.08 (s, 1H), 7.71 (t, J = 8.0, 8.0 Hz, 1H), 7.57 – 7.49 (m, 2H), 7.35 (s, 2H), 5.73 (m, 1H), 4.33 (m, 1H), 3.69 (m, 1H), 3.23 (m, 1H), 1.50 (d, J = 6.2 Hz, 3H), 1.45 (d, J = 6.4 Hz, 3H). ES/MS 398.9 ($M+H^+$).

(S)-4-amino-6-((1-(3-(2-aminoethyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 26). 1H NMR (400 MHz, DMSO-d_6) δ 7.95 (s, 1H), 7.80 (s, 2H), 7.76 (d, J = 6.6 Hz, 1H), 7.70 (t, J = 8.0, 8.0 Hz, 1H), 7.54 – 7.49 (m, 2H), 7.37 (s, 1H), 5.29 (m, 1H), 4.59 – 4.46 (m, 1H), 4.07 (m, 1H), 1.51 (d, J = 6.7 Hz, 3H). ES/MS 385.0 ($M+H^+$).

4-amino-6-(((1S)-1-(3-(3-amino-2-methylpropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 27). 1H NMR (400 MHz, DMSO-d_6) δ 8.02 (s, 1H), 7.73 – 7.68 (m, 2H), 7.63 (m, 1H), 7.56 – 7.51 (m, 2H), 5.36 (m, 1H), 4.22 (m, 1H), 4.06 – 3.95 (m, 2H), 3.01 – 2.92 (m, 1H), 2.73 (m, 1H), 1.51 (d, J = 6.6 Hz, 3H), 1.00 (dd, J = 6.8, 2.5 Hz, 3H). ES/MS 413.0 ($M+H^+$).

(S)-4-amino-6-((1-(3-(4-aminobutyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 28). 1H NMR (400 MHz, DMSO-d_6) δ 8.02 (s, 1H), 7.75 (m, 1H), 7.66 (m, 1H), 7.61 (s, 2H), 7.56 – 7.47 (m, 2H), 7.36 (s, 2H), 5.42 (m, 1H), 4.14 – 4.00 (m, 1H), 3.95 – 3.81 (m, 1H), 2.78 (m, 2H), 1.76 (m, 2H), 1.56 (m, 2H), 1.51 (d, J = 6.6 Hz, 3H). ES/MS 413.0 ($M+H^+$).

(S)-4-amino-6-((1-(3-(3-aminopropyl)-5-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 29). 1H NMR (400 MHz, DMSO-d6) δ 8.15 (s, 1H), 7.77 (d, J = 7.2 Hz, 1H), 7.68 – 7.57 (m, 1H), 7.49 (s, 3H), 7.41 (d, J = 8.1 Hz, 1H), 7.26 (dd, J = 7.6, 1.3 Hz, 1H),, 5.42 (p, J = 6.7 Hz, 1H), 4.23 (ddd, J = 14.4, 8.8, 5.8 Hz, 1H), 4.01 (ddd, J = 14.5, 8.7, 6.1 Hz, 1H), 2.91 (dd, J = 10.5, 4.4 Hz, 2H), 2.75 (s, 3H), 2.11 (ddq, J = 43.7, 14.1, 6.6 Hz, 2H), 1.56 (d, J = 6.6 Hz, 3H). ES/MS 379.2 ($M+H^+$).

(S)-2-(1-((6-amino-5-chloropyrimidin-4-yl)amino)ethyl)-3-(3-aminopropyl)-5-chloroquinazolin-4(3H)-one (Compound 30). 1H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.85 – 7.63 (m, 3H), 7.54 (ddt, J = 8.4, 1.8, 0.9 Hz, 1H), 7.11 (d, J = 7.1 Hz, 1H), 6.89 (s, 2H), 5.36 (p, J = 6.7 Hz, 1H), 4.26 (ddd, J = 14.2, 8.5, 5.9 Hz, 1H), 4.02 (ddd, J = 14.5, 8.9, 6.1 Hz, 1H), 2.93 (h, J = 7.0 Hz, 2H), 2.17 (dt, J = 14.7, 7.3 Hz, 1H), 2.06 (dq, J = 13.9, 7.0, 6.6 Hz, 1H), 1.55 (d, J = 6.6 Hz, 2H). ES/MS 408.1 ($M+H^+$).

(S)-4-amino-6-((1-(5-chloro-3-(3-(methylamino)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 31) 1H NMR (400 MHz, DMSO-d_6) δ 8.18 (s, 2H), 7.98 (s, 3H), 7.73 (dd, J = 8.5, 7.5 Hz, 3H), 7.65 (s, 3H), 7.59 – 7.51 (m, 2H), 5.42 (p, J = 6.7 Hz, 1H), 4.23 (ddd, J = 14.4, 8.8, 5.8 Hz, 1H), 4.01 (ddd, J = 14.5, 8.7, 6.1 Hz, 1H), 2.91 (dd, J = 10.5, 4.4 Hz, 2H), , 2.61 (t, J = 5.1 Hz, 3H), 2.11 (ddq, J = 43.7, 14.1, 6.6 Hz, 2H), 1.56 (d, J = 6.6 Hz, 3H). ES/MS 413.2 ($M+H^+$).

(S)-2-amino-N-(1-(3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (Compound 32) ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (dd, J = 6.7, 1.6 Hz, 1H), 8.64 – 8.57 (m, 2H), 7.75 – 7.66 (m, 3H), 7.55 (ddd, J = 22.8, 8.0, 1.2 Hz, 2H), 7.01 (dd, J = 6.7, 4.5 Hz, 1H), 6.49 (s, 2H), 5.38 (p, J = 6.7 Hz, 1H), 4.33 (ddd, J = 14.5, 8.6, 5.8 Hz, 1H), 4.09 – 3.97 (m, 1H), 3.00 – 2.87 (m, 2H), 2.02 (dh, J = 28.2, 6.8 Hz, 2H), 1.53 (d, J = 6.5 Hz, 3H). ES/MS 441.2 ($M+H^+$).

(*S*)-4-amino-6-((1-(3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-3-methylbutyl)amino)pyrimidine-5-carbonitrile (Compound 33). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (s, 1H), 7.79 – 7.69 (m, 4H), 7.54 (d, J = 8.2 Hz, 1H), 7.41 (br s, 2H), 5.36 (ddd, J = 10.9, 7.2, 2.8 Hz, 1H), 4.41 – 4.24 (m, 1H), 3.94 – 3.77 (m, 1H), 3.00 – 2.83 (m, 2H), 2.26 – 1.92 (m, 3H), 1.89 – 1.74 (m, 1H), 1.64 (ddd, J = 13.2, 9.7, 3.1 Hz, 1H), 0.98 (d, J = 6.5 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H). ES/MS 441.2 ($M+H^+$).

(*S*)-4-amino-6-((1-(3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)amino)pyrimidine-5-carbonitrile (Compound 34). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (s, 1H), 7.78 – 7.70 (m, 3H), 7.59 – 7.52 (m, 2H), 7.46 (br s, 2H), 5.26 (q, J = 7.1 Hz, 1H), 4.31 – 4.16 (m, 1H), 4.08 – 3.93 (m, 1H), 3.03 – 2.86 (m, 2H), 2.24 – 1.88 (m, 4H), 1.00 (t, J = 7.3 Hz, 3H). ES/MS 413.1 ($M+H^+$).

(*S*)-3-(3-aminopropyl)-5-chloro-2-(cyclopropyl(imidazo[2,1-*f*][1,2,4]triazin-4-ylamino)methyl)quinazolin-4(3*H*)-one (Compound 35). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.16 (d, J = 7.1 Hz, 1H), 8.15 (s, 1H), 8.13 (d, J = 1.1 Hz, 1H), 7.74 (dd, J = 8.2, 7.7 Hz, 1H), 7.70 (s, 2H), 7.67 (d, J = 1.1 Hz, 1H), 7.59 (dd, J = 8.2, 1.2 Hz, 1H), 7.57 (dd, J = 7.8, 1.2 Hz, 1H), 5.13 (t, J = 7.9 Hz, 1H), 4.28 – 4.05 (m, 2H), 2.99 – 2.85 (m, 2H), 2.22 – 1.94 (m, 2H), 1.81 – 1.67 (m, 1H), 0.68 – 0.57 (m, 3H), 0.56 – 0.46 (m, 1H). ES/MS 425.1 ($M+H^+$).

(*S*)-2,4-diamino-6-((1-(3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)amino)pyrimidine-5-carbonitrile (Compound 36). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 – 7.71 (m, 2H), 7.58 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.57 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.20 (br s, 2H), 5.24 (td, *J* = 7.9, 5.8 Hz, 1H), 4.20 – 4.02 (m, 2H), 2.98 – 2.88 (m, 2H), 2.08 – 1.89 (m, 4H), 0.98 (t, *J* = 7.3 Hz, 3H). ES/MS 428.2 (M+H$^+$).

(*S*)-3-(3-aminopropyl)-5-chloro-2-(cyclopropyl(pyrido[3,2-*d*]pyrimidin-4-ylamino)methyl)quinazolin-4(3*H*)-one (Compound 37). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 – 8.92 (m, 1H), 8.86 (br s, 1H), 8.65 – 8.60 (m, 1H), 8.23 – 8.18 (m, 1H), 7.98 – 7.92 (m, 1H), 7.78 – 7.67 (m, 3H), 7.60 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.57 (dd, *J* = 7.8, 1.2 Hz, 1H), 5.40 (t, *J* = 7.8 Hz, 1H), 4.37 – 4.27 (m, 1H), 4.19 – 4.09 (m, 1H), 3.01 – 2.89 (m, 2H), 2.24 – 1.95 (m, 2H), 1.81 – 1.69 (m, 1H), 0.68 – 0.59 (m, 3H), 0.52 – 0.44 (m, 1H). ES/MS 436.1 (M+H$^+$).

(*S*)-3-(3-aminopropyl)-5-chloro-2-(cyclopropyl((2,6-diamino-5-chloropyrimidin-4-yl)amino)methyl)quinazolin-4(3*H*)-one (Compound 38). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 – 7.71 (m, 3H), 7.68 – 7.55 (m, 4H), 7.45 (br s, 2H), 5.02 (t, *J* = 8.1 Hz, 1H), 4.13 – 3.91 (m, 2H), 2.96 – 2.82 (m, 2H), 2.06 – 1.83 (m, 2H), 1.75 – 1.62 (m, 1H), 0.65 – 0.38 (m, 4H). ES/MS 448.8 (M+H$^+$).

(*S*)-2,4-diamino-6-((1-(5-chloro-3-(3-(methylamino)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 39). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (br s, 2H), 7.75 (dd, *J* = 9.1, 6.9 Hz, 1H), 7.59 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.56 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.28 (br s, 1H), 6.94 (br s, 2H), 6.69 (br s, 2H), 5.47 – 5.32 (m, 1H), 4.20 – 3.98 (m, 2H), 3.12 – 2.91 (m, 2H), 2.62 – 2.55 (m, 3H), 2.15 – 1.94 (m, 2H), 1.52 (d, *J* = 6.5 Hz, 3H). ES/MS 428.2 (M+H$^+$).

(*S*)-4-amino-6-(((3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile (Compound 40). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (s, 1H), 7.75 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.72 (br s, 2H), 7.59 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.57 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.49 (br s, 1H), 5.11 (t, *J* = 7.8 Hz, 1H), 4.17 – 3.99 (m, 2H), 2.95 – 2.80 (m, 2H), 2.14 – 1.89 (m, 2H), 1.70 – 1.58 (m, 1H), 0.63 – 0.36 (m, 4H). ES/MS 425.1 (M+H$^+$).

(*S*)-2-amino-4-((1-(5-chloro-3-(3-(methylamino)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)-6-methylpyrimidine-5-carbonitrile (Compound 41). ^{1}H NMR (400 MHz,

DMSO-d_6) δ 8.39 (br s, 2H), 7.93 (br s, 1H), 7.75 (dd, J = 8.2, 7.8 Hz, 1H), 7.58 (dd, J = 8.2, 1.2 Hz, 1H), 7.56 (dd, J = 7.7, 1.2 Hz, 1H), 5.39 (p, J = 6.4 Hz, 1H), 4.15 – 3.99 (m, 2H), 3.10 – 2.92 (m, 2H), 2.58 (t, J = 5.4 Hz, 3H), 2.30 (s, 3H), 2.13 – 1.99 (m, 2H), 1.56 (d, J = 6.5 Hz, 3H). ES/MS 427.1 ($M+H^+$).

(*S*)-2,4-diamino-6-((1-(3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 42). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 – 7.71 (m, 4H), 7.59 (dd, J = 8.2, 1.1 Hz, 1H), 7.56 (dd, J = 7.8, 1.2 Hz, 1H), 7.40 (br s, 2H), 7.08 (br s, 2H), 5.40 (p, J = 6.6 Hz, 1H), 4.18 – 4.00 (m, 2H), 2.98 – 2.85 (m, 2H), 2.10 – 1.91 (m, 2H), 1.53 (d, J = 6.6 Hz, 3H). ES/MS 414.1 ($M+H^+$).

(*S*)-3-(3-aminopropyl)-2-(((5-bromo-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)(cyclopropyl)methyl)-5-chloroquinazolin-4(3*H*)-one (Compound 43). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.15 (d, J = 2.4 Hz, 1H), 8.20 (s, 1H), 7.74 (dd, J = 8.2, 7.8 Hz, 1H), 7.73 (br s, 2H), 7.64 (dd, J = 8.2, 1.2 Hz, 1H), 7.57 (dd, J = 7.8, 1.2 Hz, 1H), 7.46 (d, J = 2.6 Hz, 1H), 7.28 (d, J = 7.9 Hz, 1H), 5.72 (dd, J = 7.9, 6.2 Hz, 1H), 4.46 – 4.36 (m, 1H), 4.17 – 4.07 (m, 1H), 3.04 – 2.93 (m, 2H), 2.26 – 2.13 (m, 1H), 2.10 – 1.97 (m, 1H), 1.59 (q, J = 7.1 Hz, 1H), 0.61 – 0.51 (m, 3H), 0.42 – 0.34 (m, 1H). ES/MS 504.0 ($M+H^+$).

(*S*)-2-amino-4-(((3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)-6-chloropyrimidine-5-carbonitrile (Compound 44). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, J = 7.7 Hz, 1H), 7.84 (br s, 1H), 7.77 (t, J = 8.0 Hz, 1H), 7.74 (br s, 2H), 7.63 (dd, J = 8.2, 1.2 Hz, 1H), 7.59 (dd, J = 7.8, 1.2 Hz, 1H), 7.38 (br s, 1H), 5.01 (t, J = 8.0 Hz, 1H), 4.08 (ddd, J = 14.9, 9.5, 5.8 Hz, 1H), 3.92 (ddd, J = 14.5, 9.5, 5.7 Hz, 1H), 2.92 – 2.82 (m, 2H), 2.04 – 1.85 (m, 2H), 1.77 – 1.67 (m, 1H), 0.63 – 0.55 (m, 2H), 0.55 – 0.46 (m, 1H), 0.46 – 0.37 (m, 1H). ES/MS 458.8 ($M+H^+$).

(*S*)-3-(3-aminopropyl)-5-chloro-2-(cyclopropyl(thiazolo[5,4-*d*]pyrimidin-7-ylamino)methyl)quinazolin-4(3*H*)-one (Compound 45). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.35 (s, 1H), 8.52 (d, J = 7.4 Hz, 1H), 8.46 (s, 1H), 7.73 (dd, J = 8.2, 7.8 Hz, 1H), 7.71 (br s, 2H), 7.59 (dd, J = 8.2, 1.2 Hz, 1H), 7.56 (dd, J = 7.8, 1.2 Hz, 1H), 5.23 (t, J = 7.9 Hz, 1H), 4.28 – 4.08 (m, 2H), 2.96 – 2.85 (m, 2H), 2.23 – 1.94 (m, 2H), 1.81 – 1.64 (m, 1H), 0.65 – 0.55 (m, 3H), 0.53 – 0.45 (m, 1H). ES/MS 470.1 ($M+H^+$).

(*S*)-2,4-diamino-6-(((5-chloro-3-(3-(methylamino)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile (Compound 46). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 – 8.30 (m, 2H), 7.77 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.62 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.58 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.30 (br s, 1H), 7.22 (br s, 2H), 6.94 (br s, 2H), 5.08 (t, *J* = 8.0 Hz, 1H), 4.11 – 3.95 (m, 2H), 3.04 – 2.89 (m, 2H), 2.57 (t, *J* = 5.4 Hz, 3H), 2.09 – 1.88 (m, 2H), 1.73 – 1.61 (m, 1H), 0.61 – 0.53 (m, 2H), 0.51 – 0.36 (m, 2H). ES/MS 454.1 (M+H$^+$).

(*S*)-2,4-diamino-6-(((3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile (Compound 47). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.73 (br s, 2H), 7.62 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.58 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.37 (br s, 4H), 7.05 (br s, 2H), 5.07 (t, *J* = 8.0 Hz, 1H), 4.15 – 3.93 (m, 2H), 2.95 – 2.83 (m, 2H), 2.06 – 1.84 (m, 2H), 1.74 – 1.61 (m, 1H), 0.62 – 0.52 (m, 2H), 0.52 – 0.37 (m, 2H). ES/MS 440.2 (M+H$^+$).

(*S*)-3-(3-aminopropyl)-5-chloro-2-(((6-chloropyrido[3,2-*d*]pyrimidin-4-yl)amino)(cyclopropyl)methyl)quinazolin-4(3*H*)-one (Compound 48). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (d, *J* = 7.6 Hz, 1H), 8.59 (s, 1H), 8.23 (d, *J* = 8.8 Hz, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.75 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.71 (s, 2H), 7.61 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.57 (dd, *J* = 7.8, 1.2 Hz, 1H), 5.30 (t, *J* = 7.9 Hz, 1H), 4.30 – 4.20 (m, 1H), 4.17 – 4.07 (m, 1H), 2.97 – 2.85 (m, 2H), 2.20 – 1.94 (m, 2H), 1.83 – 1.72 (m, 1H), 0.68 – 0.57 (m, 3H), 0.55 – 0.45 (m, 1H). ES/MS 470.1 (M+H$^+$).

(*S*)-2-amino-4-(((3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)-6-methylpyrimidine-5-carbonitrile (Compound 49). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.72 (br s, 2H), 7.62 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.58 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.56 (br s, 1H), 7.41 (br s, 1H), 7.00 (br s, 1H), 5.08 (t, *J* = 8.0 Hz, 1H), 4.13 – 3.91 (m, 2H), 2.86 (d, *J* = 7.3 Hz, 2H), 2.29 (s, 3H), 2.05 – 1.85 (m, 2H), 1.76 – 1.64 (m, 1H), 0.64 – 0.52 (m, 2H), 0.52 – 0.35 (m, 2H). ES/MS 439.1 (M+H$^+$).

(S)-3,5-diamino-N-(1-(3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)-6-bromopyrazine-2-carboxamide (Compound 50). 1H NMR (400 MHz, DMSO-d6) δ 8.34 (d, J = 7.5 Hz, 1H), 7.80 - 7.69 (m, 4H), 7.61 - 7.52 (m, 2H), 7.04 (s, 2H), 5.21 (p, J = 6.7 Hz, 1H), 4.27 (ddd, J = 14.3, 8.7, 5.9 Hz, 1H), 4.03 (ddd, J = 14.5,

8.9, 6.2 Hz, 1H), 2.94 (q, J = 6.3 Hz, 2H), 2.13 - 1.91 (m, 2H), 1.53 (d, J = 6.5 Hz, 3H). ES/MS 497.1 ($M+H^+$).

(S)-3-(3-aminopropyl)-5-chloro-2-(1-(imidazo[2,1-f][1,2,4]triazin-4-ylamino)ethyl)quinazolin-4(3H)-one (Compound 71);

(S)-3-(3-aminopropyl)-5-chloro-2-(1-(thiazolo[5,4-d]pyrimidin-7-ylamino)ethyl)quinazolin-4(3H)-one (Compound 72);

(S)-4-amino-6-((1-(3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 73);

(S)-4-amino-6-((1-(3-(3-aminocyclobutyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 86). 1H NMR (400 MHz, DMSO-d6) δ 8.10 (s, 1H), 7.72 (m, 1H), 7.54 (m, 2H), 7.38 (m, 1H), 5.53 (m, 1H), 4.95 (m, 1H), 4.11 (m, 1H), 3.08 (m, 2H), 2.44 (m, 1H), 2.28 (m, 1H), 1.45 (d, J = 8 Hz, 3H). ES/MS 411.0 ($M+H^+$).

(S)-4-amino-6-((1-(5-chloro-4-oxo-3-(piperidin-4-ylmethyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 87). 1H NMR (400 MHz, DMSO-d6) δ 8.46 (m, 1H), 8.07 (s, 1H), 7.69 (m, 1H), 7.52 (m, 2H), 7.38 (m, 2H), 5.60 (m, 1H), 4.30 (m, 2H), 3.37 (m, 1H), 3.05 (m, 3H), 2.61 (m, 1H), 1.97 (m, 2H), 1.49 (d, J = 6.5 Hz, 3H). ES/MS 439.0 ($M+H^+$).

4-amino-6-(((1S)-1-(5-chloro-3-(morpholin-2-ylmethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 88). 1H NMR (400 MHz, DMSO-d6) δ 8.89 (s, 1H), 8.74 (s, 1H), 8.07 (s, 1H), 7.74 (m, 1H), 7.54 (m, 2H), 7.35 (m, 2H), 5.54 (m, 1H), 4.19 (m, 2H), 4.07 (m, 1H), 3.90 (m, 1H), 3.57 (m, 1H), 3.41 (m, 1H), 3.16 (m, 1H), 3.00 (m, 1H), 2.85 (m, 1H), 1.49 (d, J = 6.5 Hz, 3H). ES/MS 441.2 ($M+H^+$).

4-amino-6-(((1S)-1-(5-chloro-4-oxo-3-(pyrrolidin-3-ylmethyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 89). 1H NMR (400 MHz, DMSO-d6) δ 8.63 (s, 2H), 7.98 (s, 1H), 7.69 (m, 1H), 7.49 (m, 2H), 7.34 (m, 1H), 5.34 (m, 1H), 4.25 (m, 1H), 3.97 (m, 1H), 3.25 (m, 2H), 2.93 (m, 2H), 2.88 (m, 1H), 2.01 (m, 1H), 1.76 (m, 1H), 1.47 (d, J = 6.5 Hz, 3H). ES/MS 425.1 ($M+H^+$).

4-amino-6-(((1S)-1-(5-chloro-4-oxo-3-(pyrrolidin-2-ylmethyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 90). 1H NMR (400 MHz, DMSO-d6) δ 8.48 (s, 1H), 8.04 (s, 1H), 7.75 (m, 1H), 7.56 (m, 2H), 7.43 (m, 1H), 5.42 (m, 1H), 4.64 (m, 1H), 4.36 (m, 2H), 4.14 (m, 1H), 3.91 (m, 1H), 3.34 (m, 1H), 3.10 (m, 1H), 2.16 (m, 1H), 1.73 (m, 1H), 1.52 (d, J = 6.5 Hz, 3H). ES/MS 425.1 ($M+H^+$).

4-amino-6-(((1S)-1-(5-chloro-4-oxo-3-(piperidin-2-ylmethyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 91). 1H NMR (400 MHz, DMSO-d6) δ 8.60 (m, 1H), 8.37 (m, 1H), 8.07 (s, 1H), 7.70 (m, 1H), 7.55 (m, 2H), 7.43 (m, 1H), 5.24 (m, 1H), 4.63 (m, 1H), 3.94 (m, 1H), 3.84 (m, 1H), 3.29 (m, 1H), 2.67 (m, 1H), 2.02 (m, 1H), 1.78 (m, 1H), 1.68 (m, 2H), 1.51 (d, J = 6.5 Hz, 3H), 1.43 (m, 1H). ES/MS 439.2 ($M+H^+$).

4-amino-6-(((1S)-1-(5-chloro-4-oxo-3-(piperidin-3-ylmethyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 92). 1H NMR (400 MHz, DMSO-d6) δ 8.56 (m, 1H), 8.08 (s, 1H), 7.70 (m, 1H), 7.54 (m, 2H), 7.39 (m, 1H), 5.35 (m, 1H), 4.14 (m, 1H), 3.82 (m, 1H), 3.21 (m, 2H), 2.78 (m, 2H), 2.38 (m, 1H), 1.81 (m, 2H), 1.57 (m, 1H), 1.52 (d, J = 6.5 Hz, 3H), 1.38 (m, 1H). ES/MS 439.3 ($M+H^+$).

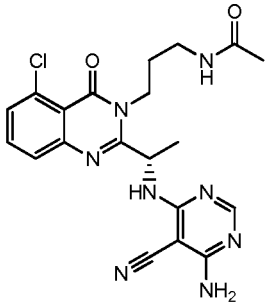
2,4-diamino-6-(((S)-1-(5-chloro-4-oxo-3-((R)-piperidin-3-ylmethyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 123). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (d, J = 11.3 Hz, 1H), 8.12 (d, J = 11.5 Hz, 1H), 7.62 – 7.50 (m, 2H), 7.40 (s, 1H), 7.04 (d, J = 81.1 Hz, 4H), 5.38 (q, J = 6.9 Hz, 1H), 4.11 (dd, J = 14.5, 8.7 Hz, 1H), 3.83 (dd, J = 14.4, 5.8 Hz, 1H), 3.25 – 3.14 (m, 3H), 2.80 (q, J = 11.8 Hz, 1H), 2.73 – 2.62 (m, 1H), 2.14 (d, J = 11.7 Hz, 1H), 1.77 (d, J = 15.4 Hz, 2H), 1.66 – 1.52 (m, 1H), 1.49 (d, J = 6.4 Hz, 3H), 1.34 (qd, J = 12.7, 12.1, 4.4 Hz, 1H). ES/MS 454.2 ($M+H^+$).

2,4-diamino-6-(((S)-1-(5-chloro-4-oxo-3-((S)-piperidin-3-ylmethyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 124). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (d, J = 11.4 Hz, 1H), 8.11 (d, J = 11.5 Hz, 1H), 7.79 – 7.67 (m, 1H), 7.63 – 7.50 (m, 2H), 7.39 – 7.26 (m, 1H), 7.16 (s, 2H), 7.06 – 6.81 (m, 2H), 5.54 – 5.40 (m, 1H), 3.95 (dq, J = 15.8, 7.3 Hz, 2H), 3.20 (t, J = 16.3 Hz, 2H), 2.77 (dt, J = 21.9, 10.9 Hz, 2H), 2.15 (s, 1H), 1.82 – 1.65 (m, 2H), 1.47 (d, J = 6.5 Hz, 3H), 1.29 (td, J = 12.8, 12.4, 9.2 Hz, 1H). ES/MS 454.2 ($M+H^+$).

2,4-diamino-6-(((S)-1-(5-chloro-4-oxo-3-((S)-pyrrolidin-3-ylmethyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 125). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 – 8.50 (m, 2H), 7.72 (t, J = 8.0 Hz, 1H), 7.60 – 7.46 (m, 2H), 7.35 (s, 1H), 7.09 (s, 1H), 6.84 (s, 1H), 5.41 (p, J = 6.8 Hz, 1H), 4.17 (dd, J = 14.7, 8.1 Hz, 1H), 4.08 (dd, J = 14.6, 5.8 Hz, 1H), 3.73 (t, J = 5.3 Hz, 1H), 3.13 – 2.97 (m, 2H), 2.74 – 2.60 (m, 1H), 2.10 (dtd, J = 11.7, 7.2, 4.2 Hz, 1H), 1.69 (dt, J = 12.8, 8.8 Hz, 1H), 1.61 (q, J = 5.9, 4.5 Hz, 1H), 1.56 – 1.52 (m, 1H), 1.49 (d, J = 6.5 Hz, 3H). ES/MS 440.2 (M+H$^+$).

2,4-diamino-6-(((S)-1-(5-chloro-4-oxo-3-((R)-pyrrolidin-3-ylmethyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 126). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (d, J = 23.6 Hz, 2H), 7.72 (t, J = 8.0 Hz, 1H), 7.55 (ddd, J = 12.7, 8.0, 1.2 Hz, 2H), 7.35 (d, J = 12.2 Hz, 1H), 7.13 (s, 2H), 6.87 (s, 2H), 5.44 (p, J = 6.7 Hz, 1H), 4.24 – 4.03 (m, 2H), 3.12 – 2.90 (m, 2H), 2.74 – 2.57 (m, 1H), 1.99 (dtd, J = 12.4, 7.3, 4.8 Hz, 1H), 1.73 (dq, J = 12.9, 8.4 Hz, 1H), 1.48 (d, J = 6.5 Hz, 3H). ES/MS 440.2 (M+H$^+$).

[00215] G. Preparation of a compound of formula (I) wherein n is 1, R^1 is chloro, m is 0, B is $(CH_2)_3$, R^2 is $NHCOCH_3$, R^3 is methyl, R^4 is 4-amino-5-cyanopyrimidin-2-yl, and R^5 is hydrogen



[00216] To (S)-4-amino-6-((1-(3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile(200 mg, 0.502 mmol), HATU (285 mg, 0.75mmol) and acetic acid (45 mg, 0.75 mmol) in DMF (2 mL) was added Hunig's base (0.3 mL). After stirring at room temp for 1 hour, water was added and the mixture was extracted with EtOAc (3x20 mL), dried ($MgSO_4$), and concentrated. The residue was purified on a reverse phase HPLC run from 0 to 95% ACN in water (0.1% TFA) to give (S)-N-(3-(2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)acetamide (Compound 51). 1H NMR (400

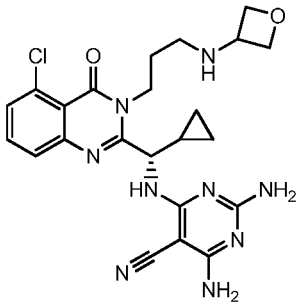
MHz, DMSO-d_6) δ 8.06 (s, 1H), 7.94 (t, J = 5.8 Hz, 1H), 7.87 (d, J = 6.9 Hz, 1H), 7.71 (t, J = 8.0 Hz, 1H), 7.54 (ddd, J = 7.8, 5.5, 1.2 Hz, 2H), 7.48 (s, 2H), 5.42 (p, J = 6.7 Hz, 1H), 4.13 (ddd, J = 14.5, 9.9, 5.7 Hz, 1H), 3.89 (ddd, J = 14.5, 10.1, 5.6 Hz, 1H), 3.11 (q, J = 6.5 Hz, 2H), 1.88 (ddt, J = 23.2, 10.5, 7.0 Hz, 2H), 1.80 (s, 3H), 1.54 (d, J = 6.6 Hz, 3H). ES/MS 441.2 ($M+H^+$).

[00217] H. Preparation of the below compounds of formula (I), using Example 3G and Reaction Scheme I:

(S)-N-(3-(5-chloro-2-(cyclopropyl((2,6-diamino-5-cyanopyrimidin-4-yl)amino)methyl)-4-oxoquinazolin-3(4H)-yl)propyl)pivalamide (Compound 52). 1H NMR (400 MHz, DMSO-d_6) δ 7.87 (t, J = 5.9 Hz, 1H), 7.73 (dd, J = 8.3, 7.7 Hz, 1H), 7.55 (ddd, J = 7.8, 5.3, 1.2 Hz, 2H), 6.73 (s, 2H), 6.58 (s, 2H), 6.40 (d, J = 8.7 Hz, 1H), 5.30 (t, J = 7.9 Hz, 1H), 4.19 (t, J = 10.6 Hz, 1H), 3.94 (t, J = 11.8 Hz, 1H), 3.04 (dd, J = 13.3, 7.2 Hz, 1H), 2.05 – 1.90 (m, 1H), 1.73 (d, J = 6.5 Hz, 1H), 1.51 (h, J = 7.8 Hz, 2H), 1.12 (s, 9H), 0.60 – 0.49 (m, 2H), 0.48 – 0.39 (m, 1H), 0.38 – 0.26 (m, 1H). ES/MS 524.2 ($M+H^+$).

(S)-N-(3-(5-chloro-2-(cyclopropyl((2,6-diamino-5-cyanopyrimidin-4-yl)amino)methyl)-4-oxoquinazolin-3(4H)-yl)propyl)acetamide (Compound 53). 1H NMR (400 MHz, DMSO-d_6) δ 8.12 (t, J = 6.0 Hz, 1H), 7.75 (dd, J = 8.3, 7.7 Hz, 1H), 7.58 (ddd, J = 10.9, 8.0, 1.2 Hz, 5H), 5.16 (t, J = 8.0 Hz, 1H), 4.09 – 3.85 (m, 2H), 3.22 (dd, J = 13.1, 6.7 Hz, 1H), 3.04 (dt, J = 13.4, 6.6 Hz, 1H), 1.83 (d, J = 0.9 Hz, 3H), 1.76 (s, 1H), 1.69 – 1.56 (m, 2H), 0.57 (dt, J = 8.1, 4.2 Hz, 3H), 0.43 (p, J = 4.8 Hz, 3H). ES/MS 482.2 ($M+H^+$).

[00218] I. Preparation of a compound of formula (I) wherein n is 1, R^1 is chloro, m is 0, R^3 is methyl, B is $(CH_2)_3$, R^2 is NHoxetanyl, R^3 is cyclopropyl, R^4 is 2,6-diamino-5-cyanopyrimidin-2-yl, and R^5 is hydrogen



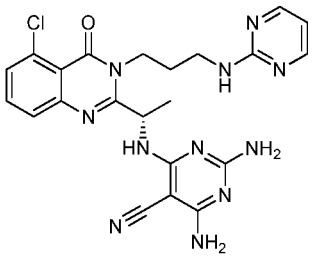
[00219] To (S)-2,4-diamino-6-(((3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile (100 mg, 0.23 mmol) in MeOH (5mL), was added 3-oxetanone (82 mg, 1.15mmlo). After stirring at room temp for 12 hour, sodium triacetoxyborohydride (964 mg, 4.5mmol) was added. After stirring for 3 hour at room temperature saturated sodium bicarbonate solution (30 mL) was added and the mixture was extracted with EtOAc (3x30 mL) and concentrated. The residue was purified on a reverse phase HPLC run from 0 to 95% ACN in water (0.1% TFA) to (S)-2,4-diamino-6-(((5-chloro-3-(3-(oxetan-3-ylamino)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile (Compound 55). 1H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 2H), 7.83 – 7.69 (m, 1H), 7.67 – 7.47 (m, 2H), 7.12 (s, 2H), 6.84 (s, 2H), 5.10 (t, J = 7.9 Hz, 1H), 4.73 (dd, J = 8.2, 6.7 Hz, 2H), 4.60 (q, J = 6.7 Hz, 2H), 4.35 (d, J = 7.0 Hz, 1H), 4.06 (t, J = 7.5 Hz, 2H), 2.95 (s, 2H), 1.99 (s, 2H), 1.74 – 1.58 (m, 1H), 0.57 (dd, J = 8.4, 4.2 Hz, 2H), 0.51 – 0.31 (m, 2H). ES/MS 496.2 ($M+H^+$).

[00220] J. Preparation of the below compounds of formula (I), using Example 3I and Reaction Scheme I:

(S)-2,4-diamino-6-(((5-chloro-3-(3-(cyclobutylamino)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile (Compound 54). 1H NMR (400 MHz, DMSO-d_6) δ 8.65 (s, 2H), 7.88 – 7.70 (m, 1H), 7.66 – 7.53 (m, 2H), 7.18 (d, J = 34.9 Hz, 2H), 6.88 (s, 2H), 5.09 (t, J = 8.0 Hz, 1H), 4.03 (t, J = 7.7 Hz, 2H), 3.72 – 3.57 (m, 1H), 2.99 – 2.74 (m, 2H), 2.23 – 2.05 (m, 3H), 1.98 (dq, J = 16.0, 8.1, 7.6 Hz, 2H), 1.78 (td, J = 9.9, 7.1 Hz, 2H), 1.67 (dq, J = 8.0, 4.1, 3.0 Hz, 1H), 1.32 – 1.13 (m, 1H), 0.56 (dd, J = 8.2, 4.6 Hz, 2H), 0.50 – 0.43 (m, 1H), 0.43 – 0.33 (m, 1H). ES/MS 494.2 ($M+H^+$).

(S)-2,4-diamino-6-(((5-chloro-3-(3-((4,4-difluorocyclohexyl)amino)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile (Compound 56). 1H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, J = 47.0 Hz, 2H), 7.85 – 7.70 (m, 1H), 7.68 – 7.51 (m, 2H), 7.20 (s, 2H), 6.93 (s, 1H), 5.13 (t, J = 8.0 Hz, 1H), 4.06 (t, J = 7.5 Hz, 2H), 3.18 (s, 1H), 3.01 (s, 2H), 2.21 – 1.75 (m, 9H), 1.67 (dtd, J = 13.2, 8.1, 5.1 Hz, 1H), 1.61 – 1.44 (m, 2H), 0.62 – 0.52 (m, 2H), 0.52 – 0.42 (m, 1H), 0.42 – 0.30 (m, 1H). ES/MS 558.2 ($M+H^+$).

[00221] K. Preparation of a compound of formula (I) wherein n is 1, R^1 is chloro, m is 0, B is $(CH_2)_3$, R^2 is NH(pyrimidin-2-yl), R^3 is methyl, R^4 is 2,6-diamino-5-cyanopyrimidin-2-yl, and R_5 is hydrogen

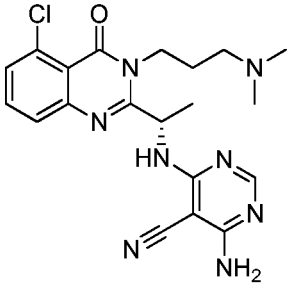


[00222] A solution of (S)-2,4-diamino-6-((1-(3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (80 mg, 0.19 mmol, 1 equiv) and 2-chloropyrimidine (22 mg, 0.193) in isopropyl alcohol (2 mL) was stirred at 85 °C for seven days. The reaction was concentrated and purified by Prep HPLC to give (S)-2,4-diamino-6-((1-(5-chloro-4-oxo-3-(3-(pyrimidin-2-ylamino)propyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 4). 1H NMR (400 MHz, DMSO-d6) δ 8.27 (d, *J* = 4.8 Hz, 2H), 8.04 (br s, 2H), 7.81 (br s, 2H), 7.74 (t, *J* = 8.0 Hz, 1H), 7.57 (ddd, *J* = 9.1, 8.0, 1.2 Hz, 2H), 7.32 (br s, 2H), 6.59 (t, *J* = 4.8 Hz, 1H), 5.50 – 5.37 (m, 1H), 4.11 – 3.97 (m, 2H), 3.41 – 3.32 (m, 2H), 2.01 – 1.90 (m, 1H), 1.50 (d, *J* = 6.5 Hz, 3H). ES/MS 492.2 ($M+H^+$).

[00223] L. Preparation of the below compounds of formula (I), using Example 3K and Reaction Scheme I:

(S)-2,4-diamino-6-((1-(5-chloro-4-oxo-3-(3-(pyridin-2-ylamino)propyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 5). 1H NMR (400 MHz, DMSO-d6) δ 7.99 (d, *J* = 23.6 Hz, 4H), 7.74 (t, *J* = 8.2 Hz, 1H), 7.58 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.55 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.36 (s, 2H), 7.05 (s, 2H), 5.42 (p, *J* = 7.0 Hz, 1H), 4.04 (t, *J* = 7.8 Hz, 1H), 3.60 – 3.46 (m, 1H), 3.45 – 3.33 (m, 1H), 2.03 – 1.88 (m, 2H), 1.54 (s, 3H), 1.52 (s, 3H). ES/MS 490.2 ($M+H^+$).

[00224] M. Preparation of a compound of formula (I) wherein n is 1, R^1 is chloro, m is 0, B is $(CH_2)_3$, R^2 is $N(CH_3)_2$, R^3 is methyl, R^4 is 4-amino-5-cyanopyrimidin-2-yl, and R_5 is hydrogen



[00225] To (S)-2-(1-aminoethyl)-5-chloro-3-(3-(dimethylamino)propyl)quinazolin-4(3H)-one (200 mg, 0.65 mmol) and 4-amino-6-chloropyrimidine-5-carbonitrile (100 mg, 0.65 mmol) in IPA (2 mL) was added Hunig's base (0.3 mL). After stirring at 90 °C for 4 hours in a microwave reactor, water was added and the mixture was extracted with EtOAc (3x50 mL), dried ($MgSO_4$), and concentrated. The residue was purified on a reverse phase system run from 0 to 95% ACN in water (0.1% TFA) to give (S)-4-amino-6-((1-(5-chloro-3-(3-(dimethylamino)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 57). 1H NMR (400 MHz, DMSO-d_6) δ 8.18 (s, 1H), 8.16 (d, J = 6.1 Hz, 1H), 7.98 (s, 1H), 7.73 (dd, J = 8.5, 7.5 Hz, 2H), 7.65 (s, 1H), 7.59 – 7.51 (m, 1H), 5.42 (p, J = 6.7 Hz, 1H), 4.23 (ddd, J = 14.4, 8.8, 5.8 Hz, 1H), 4.01 (ddd, J = 14.5, 8.7, 6.1 Hz, 1H), 2.91 (dd, J = 10.5, 4.4 Hz, 2H), 2.58 (s, 6H) 2.11 (ddq, J = 43.7, 14.1, 6.6 Hz, 2H), 1.56 (d, J = 6.6 Hz, 3H). ES/MS 427.2 ($M+H^+$).

[00226] N. Preparation of the below compounds of formula (I), using Example 3M and Reaction Scheme I:

(S)-2,4-diamino-6-((1-(5-chloro-3-(2-(dimethylamino)ethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 58). 1H NMR (400 MHz, DMSO-d_6) δ 8.37 (d, J = 10.8 Hz, 2H), 7.75 (dd, J = 9.0, 7.0 Hz, 1H), 7.57 (m, 1H), 7.29 (d, J = 11.9 Hz, 1H), 6.94 (s, 2H), 6.68 (s, 2H), 5.39 (q, J = 6.9 Hz, 1H), 4.06 (dd, J = 21.6, 14.1 Hz, 3H), 2.40 (s, 6H), 2.06 (d, J = 13.5 Hz, 2H), 1.52 (d, J = 6.4 Hz, 2H). ES/MS 428.2 ($M+H^+$).

(S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-chloro-3-(3-morpholinopropyl)quinazolin-4(3H)-one (Compound 19). 1H NMR (400 MHz, DMSO-d6) δ 9.79 (s, 1H), 8.45 (s, 1H), 8.38 – 8.25 (m, 2H), 7.68 (t, J = 8.0 Hz, 1H), 7.56 – 7.47 (m, 1H), 5.63 – 5.46 (m, 1H), 4.38 – 4.22 (m, 1H), 4.10 – 3.90 (m, 3H), 3.70 – 3.55 (m, 2H), 3.41 (t, J = 15.2 Hz, 2H),

3.30 – 3.18 (m, 2H), 3.13 – 2.96 (m, 2H), 2.39 – 2.26 (m, 1H), 2.25 – 2.12 (m, 1H), 1.63 (d, J = 6.5 Hz, 3H).ES/MS 469.1 ($M+H^+$).

2,4-diamino-6-(((1S)-1-(5-chloro-3-(3-hydroxy-4-(isopropylamino)butyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 74). ^1H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 2H), 7.79 – 7.67 (m, 1H), 7.62 – 7.50 (m, 3H), 7.27 – 7.21 (m, 2H), 6.94 (s, 2H), 5.55 (s, 1H), 5.44 (q, J = 6.8 Hz, 1H), 4.11 (t, J = 7.8 Hz, 1H), 3.91 – 3.77 (m, 1H), 3.33 – 3.24 (m, 1H), 3.05 – 2.97 (m, 1H), 2.86 – 2.81 (m, 1H), 1.90 (q, J = 7.3 Hz, 2H), 1.60 – 1.49 (m, 3H), 1.28 – 1.17 (m, 6H). ES/MS 486.2 ($M+H^+$).

2,4-diamino-6-(((1S)-1-(3-(4-(tert-butylamino)-3-hydroxybutyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 75). ^1H NMR (400 MHz, DMSO-d_6) δ 8.32 – 8.24 (m, 1H), 8.23 – 8.18 (m, 1H), 7.80 – 7.64 (m, 2H), 7.63 – 7.51 (m, 2H), 7.34 (s, 2H), 7.03 (s, 2H), 5.63 – 5.39 (m, 2H), 4.38 – 3.93 (m, 1H), 3.79 (d, J = 10.3 Hz, 1H), 3.01 (d, J = 10.6 Hz, 1H), 2.81 – 2.71 (m, 1H), 1.98 – 1.88 (m, 2H), 1.61 – 1.51 (m, 3H), 1.27 (s, 9H). ES/MS 500.2 ($M+H^+$).

(*S*)-5-(5-chloro-2-(cyclopropyl((2,6-diamino-5-chloropyrimidin-4-yl)amino)methyl)-4-oxoquinazolin-3(4*H*)-yl)pentanamide (Compound 59). ^1H NMR (400 MHz, DMSO-d_6) δ 7.72 (dd, J = 8.2, 7.8 Hz, 1H), 7.58 (dd, J = 8.2, 1.2 Hz, 1H), 7.54 (dd, J = 7.8, 1.2 Hz, 1H), 7.29 (br s, 1H), 6.77 (br s, 1H), 6.17 (d, J = 8.7 Hz, 1H), 6.12 (br s, 2H), 5.77 (br s, 2H), 5.20 (dd, J = 8.8, 7.4 Hz, 1H), 4.15 – 3.86 (m, 2H), 2.16 – 2.05 (m, 2H), 1.78 – 1.44 (m, 5H), 0.57 – 0.32 (m, 4H). ES/MS 491.1 ($M+H^+$).

(*S*)-2,4-diamino-6-((1-(3-(3-(benzyl(methyl)amino)propyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 60). ^1H NMR (400 MHz, DMSO-d_6) δ 7.88 – 6.98 (m, 8H), 6.82 – 6.57 (m, 2H), 6.43 (br s, 2H), 5.55 – 5.30 (m, 1H), 4.51 – 3.77 (m, 3H), 3.55 – 2.98 (m, 2H), 2.75 – 2.57 (m, 1H), 2.46 – 1.82 (m, 5H), 1.51 (d, J = 6.3 Hz, 3H). ES/MS 518.2 ($M+H^+$).

(*S*)-2-amino-4-((1-(3-(3-(benzyl(methyl)amino)propyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)-6-methylpyrimidine-5-carbonitrile (Compound 61). ^1H NMR (400 MHz, DMSO-d_6) δ 9.49 (br s, 1H), 7.83 – 7.11 (m, 8H), 6.85 (br s, 1H), 5.59 – 5.27 (m, 1H), 4.52 – 3.78 (m, 4H), 3.59 – 3.03 (m, 2H), 2.77 – 2.62 (m, 2H), 2.46 – 1.81 (m, 6H), 1.55 (d, J = 6.3 Hz, 3H). ES/MS 517.2 ($M+H^+$).

(*S*)-2,4-diamino-6-((1-(5-chloro-3-(3-(methyl(2,2,2-trifluoroethyl)amino)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 62). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (t, *J* = 8.1 Hz, 1H), 7.57 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.53 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.64 (br s, 2H), 5.52 – 5.40 (m, 1H), 4.18 – 4.02 (m, 1H), 3.94 – 3.78 (m, 1H), 3.23 – 3.09 (m, 2H), 2.62 – 2.53 (m, 2H), 2.35 (s, 3H), 1.99 – 1.80 (m, 2H), 1.50 (d, *J* = 6.5 Hz, 3H). ES/MS 510.1 (M+H$^+$).

(*S*)-3-(5-chloro-2-(cyclopropyl((2,6-diamino-5-chloropyrimidin-4-yl)amino)methyl)-4-oxoquinazolin-3(4*H*)-yl)propanenitrile (Compound 63). ^{1}H NMR (DMSO-d_6) δ 7.78 (t, *J* = 8.0 Hz, 1H), 7.64 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.60 (dd, *J* = 7.7, 1.1 Hz, 1H), 5.04 (t, *J* = 8.1 Hz, 1H), 4.36 – 4.22 (m, 1H), 4.17 – 4.05 (m, 1H), 3.14 – 3.01 (m, 1H), 2.85 – 2.72 (m, 1H), 1.74 – 1.62 (m, 1H), 0.66 – 0.41 (m, 4H). ES/MS 445.1 (M+1$^+$).

(*S*)-5-(5-chloro-2-(cyclopropyl((2,6-diamino-5-cyanopyrimidin-4-yl)amino)methyl)-4-oxoquinazolin-3(4*H*)-yl)pentanamide (Compound 64). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (t, *J* = 8.0 Hz, 1H), 7.59 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.55 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.29 (br s, 1H), 6.79 (br s, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 6.69 (br s, 2H), 6.53 (br s, 2H), 5.21 (t, *J* = 8.1 Hz, 1H), 3.96 (t, *J* = 7.5 Hz, 2H), 2.18 – 2.02 (m, 2H), 1.73 – 1.43 (m, 5H), 0.61 – 0.39 (m, 3H), 0.40 – 0.28 (m, 1H). ES/MS 482.2 (M+H$^+$).

(*S*)-4-(5,8-dichloro-2-(cyclopropyl((2,6-diamino-5-cyanopyrimidin-4-yl)amino)methyl)-4-oxoquinazolin-3(4*H*)-yl)butanamide (Compound 65). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, *J* = 8.5 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.44 (br s, 1H), 6.92 (br s, 1H), 6.73 (br s, 2H), 6.58 (br s, 2H), 6.27 (d, *J* = 8.7 Hz, 1H), 5.48 (dd, *J* = 8.5, 7.2 Hz, 2H), 4.28 – 4.16 (m, 1H), 3.97 – 3.86 (m, 1H), 2.29 – 2.15 (m, 3H), 1.94 – 1.78 (m, 1H), 1.60 – 1.43 (m, 1H), 0.62 – 0.45 (m, 3H), 0.37 – 0.27 (m, 1H). ES/MS 502.1 (M+H$^+$).

(*S*)-4-(5-chloro-2-(cyclopropyl((2,6-diamino-5-cyanopyrimidin-4-yl)amino)methyl)-4-oxoquinazolin-3(4*H*)-yl)butanamide (Compound 66). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (t, *J* = 8.0 Hz, 1H), 7.59 – 7.53 (m, 2H), 7.46 (br s, 1H), 6.93 (br s, 1H), 5.33 – 5.21 (m, 1H), 4.27 – 4.08 (m, 1H), 4.02 – 3.83 (m, 1H), 2.27 – 2.07 (m, 3H), 1.92 – 1.75 (m, 1H), 1.64 – 1.49 (m, 1H), 0.62 – 0.46 (m, 3H), 0.42 – 0.30 (m, 1H). ES/MS 468.2 (M+H$^+$).

2-[3-[5-chloro-2-[(S)-cyclopropyl-[(2,6-diamino-5-chloro-pyrimidin-4-yl)amino]methyl]-4-oxo-quinazolin-3-yl]phenyl]acetonitrile.

(S)-4-((1-(3-((1H-pyrazol-3-yl)methyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)-2,6-diaminopyrimidine-5-carbonitrile (Compound 76). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.68 (s, 1H), 7.81 – 7.59 (m, 2H), 7.52 (ddd, J = 8.0, 1.2 Hz, 2H), 6.91 (d, J = 6.8 Hz, 1H), 6.61 (s, 2H), 6.39 (br s, 2H), 6.20 (d, J = 2.2 Hz, 1H), 5.62 – 5.16 (m, 3H), 1.25 (d, J = 6.5 Hz, 3H). ES/MS 437.1 (M+H$^+$).

(S)-4-((1-(3-((1H-pyrazol-3-yl)methyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)-6-aminopyrimidine-5-carbonitrile (Compound 77). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.65 (s, 1H), 7.97 (s, 1H), 7.77 – 7.67 (m, 1H), 7.63 (br s, 1H), 7.59 (br d, J = 6.7 Hz, 1H), 7.57 – 7.48 (m, 2H), 7.44 – 7.04 (br m, 2H), 6.17 (d, J = 2.2 Hz, 1H), 5.61 – 5.48 (m, 1H), 5.44 – 5.19 (m, 2H), 1.35 (d, J = 6.5 Hz, 3H). ES/MS 422.1 (M+H$^+$).

(S)-3-((1H-pyrazol-3-yl)methyl)-5-chloro-2-(1-(imidazo[2,1-f][1,2,4]triazin-4-ylamino)ethyl)quinazolin-4(3H)-one (Compound 78). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.66 (s, 1H), 9.09 (br s, 1H), 8.14 – 8.00 (m, 2H), 7.74 – 7.41 (m, 5H), 6.20 (d, J = 2.2 Hz, 1H), 5.76 – 5.56 (m, 1H), 5.56 – 5.28 (m, 2H), 1.45 (d, J = 6.5 Hz, 3H). ES/MS 422.1 (M+H$^+$).

(S)-4-((1-(3-((1H-pyrazol-4-yl)methyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)-2,6-diaminopyrimidine-5-carbonitrile (Compound 79). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (br s, 1H), 7.94 - 7.23 (br m, 2H), 7.85 (br s, 2H), 7.71 (dd, J = 8.3, 7.7 Hz, 1H), 7.62 (s, 2H), 7.57 – 7.48 (m, 2H), 5.59 – 5.41 (m, 1H), 5.22 (d, J = 15.6 Hz, 1H), 5.01 (d, J = 15.6 Hz, 1H), 1.37 (d, J = 6.5 Hz, 3H). ES/MS 437.1 (M+H$^+$).

(S)-4-((1-(3-((1H-imidazol-2-yl)methyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)-2,6-diaminopyrimidine-5-carbonitrile (Compound 80). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 – 7.76 (m, 1H), 7.65 (dd, J = 8.2, 1.2 Hz, 1H), 7.59 (dd, J = 7.8, 1.2 Hz, 1H), 7.55 (s, 2H), 7.33 – 6.81 (br m, 5H), 5.55 – 5.33 (m, 3H), 1.43 (d, J = 6.4 Hz, 3H). ES/MS 437.1 (M+H$^+$).

(S)-4-((1-(3-((1H-1,2,4-triazol-3-yl)methyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)-2,6-diaminopyrimidine-5-carbonitrile (Compound 81). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (br s, 1H), 8.10 (br s, 1H), 7.84 (br s, 2H), 7.78 – 7.68 (m, 1H), 7.62 – 7.49 (m, 2H), 7.60 - 7.22 (br m, 2H), 5.49 (d, J = 16.8 Hz, 1H), 5.41 – 5.34 (m, 1H), 5.31 (d, J = 16.8 Hz, 1H), 1.39 (d, J = 6.5 Hz, 3H). ES/MS 438.1 (M+H$^+$).

(S)-2,4-diamino-6-((1-(5-chloro-3-(2-cyanoethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 104). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (td, J = 8.1, 1.1 Hz, 1H), 7.57 (ddt, J = 7.8, 4.5, 1.3 Hz, 2H), 5.54 – 5.29 (m, 1H), 4.36 (dt, J = 14.6, 7.6 Hz, 2H), 4.16 (dt, J = 14.1, 6.8 Hz, 2H), 1.52 (d, J = 6.5 Hz, 3H). ES/MS 410.1 (M+H$^+$).

((S)-4-amino-6-((1-(5-chloro-3-(3-methoxypropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 105). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (s, 1H), 7.81 (d, J = 7.1 Hz, 1H), 7.69 (t, J = 8.0 Hz, 1H), 7.51 (td, J = 8.0, 1.2 Hz, 2H), 7.42 (s, 1H), 5.45 (p, J = 6.6 Hz, 1H), 4.13 (ddd, J = 14.5, 8.7, 6.4 Hz, 1H), 3.84 (dt, J = 14.3, 6.9 Hz, 1H), 3.32 (td, J = 6.1, 1.9 Hz, 2H), 1.94 (ddt, J = 12.8, 9.5, 4.7 Hz, 2H), 1.50 (d, J = 6.6 Hz, 3H). ES/MS 414.1 (M+H$^+$).

(S)-4-amino-6-((1-(5,8-dichloro-3-(3-methoxypropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 106). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, J = 0.5 Hz, 1H), 8.00 – 7.79 (m, 1H), 7.61 – 7.35 (m, 2H), 5.66 – 5.36 (m, 1H), 4.09 (dd, J = 14.4, 6.7 Hz, 3H), 3.29 (t, J = 6.0 Hz, 2H), 3.25 – 3.04 (m, 3H), 1.90 (s, 2H), 1.52 (d, J = 6.5 Hz, 3H). ES/MS 449.1 (M+H$^+$).

(S)-2,4-diamino-6-((1-(5,8-dichloro-3-(3-methoxypropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 107). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 – 7.84 (m, 1H), 7.79 – 7.26 (m, 3H), 5.73 – 5.15 (m, 1H), 4.23 – 3.78 (m, 2H), 3.53 – 3.28 (m, 2H), 3.32 – 3.04 (m, 3H), 2.04 – 1.74 (m, 2H), 1.63 – 1.31 (m, 3H). ES/MS 464.1 (M+H$^+$).

(S)-4-amino-6-((1-(5,8-difluoro-3-(3-methoxypropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 108). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (d, J = 7.1 Hz, 1H), 7.77 – 7.56 (m, 1H), 7.41 (s, 1H), 7.25 (ddd, J = 10.5, 9.0, 3.6 Hz, 2H), 5.48 (p, J = 6.7 Hz, 1H), 4.14 (dt, J = 14.3, 7.5 Hz, 2H), 3.87 (dt, J = 14.4, 7.5 Hz, 2H), 3.31 (td, J = 6.2, 1.7 Hz, 2H), 3.15 (s, 3H), 1.94 (p, J = 7.0 Hz, 2H), 1.51 (d, J = 6.5 Hz, 3H). ES/MS 431.1 (M+H$^+$). ES/MS 416.1 (M+H$^+$).

(S)-2,4-diamino-6-((1-(5,8-difluoro-3-(3-methoxypropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 109). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.81 – 7.44 (m, 3H), 7.42 – 6.84 (m, 3H), 5.45 (q, J = 6.8 Hz,

1H), 3.91 (dq, *J* = 14.5, 6.9, 6.2 Hz, 4H), 3.22 – 3.06 (m, 3H), 2.16 – 1.76 (m, 2H), 1.50 (d, *J* = 6.3 Hz, 3H). ES/MS 431.1 ($M+H^+$).

(S)-2,4-diamino-6-((1-(5-chloro-3-(3-cyanopropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 110). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (s, 1H), 7.81 – 7.58 (m, 2H), 7.53 (ddt, *J* = 8.6, 7.7, 1.0 Hz, 2H), 5.37 (t, *J* = 6.8 Hz, 1H), 3.94 (q, *J* = 7.9, 7.3 Hz, 3H), 2.79 – 2.55 (m, 2H), 1.99 (tt, *J* = 14.9, 6.5 Hz, 2H), 1.50 (d, *J* = 6.4 Hz, 3H). ES/MS 424.1 ($M+H^+$).

(S)-2,4-diamino-6-((1-(5-chloro-3-(3-(methylsulfonyl)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 111). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 – 7.61 (m, 1H), 7.65 – 7.35 (m, 2H), 7.19 (s, 2H), 5.41 (p, *J* = 6.8 Hz, 1H), 4.21 (ddd, *J* = 14.8, 9.7, 5.5 Hz, 1H), 4.08 – 3.85 (m, 1H), 3.44 – 3.06 (m, 2H), 2.97 (s, 3H), 2.15 (d, *J* = 34.6 Hz, 2H), 1.50 (d, *J* = 6.6 Hz, 3H). ES/MS 477.1 ($M+H^+$).

(*S*)-2,4-diamino-6-(((5-chloro-3-(2-cyanoethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile (Compound 112). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (t, *J* = 8.0 Hz, 1H), 7.64 – 7.56 (m, 2H), 5.09 (t, *J* = 8.2 Hz, 1H), 4.37 – 4.09 (m, 2H), 3.14 – 2.98 (m, 1H), 2.97 – 2.80 (m, 1H), 2.95 – 2.79 (m, 1H), 1.74 – 1.56 (m, 1H), 0.64 – 0.52 (m, 2H), 0.51 – 0.41 (m, 2H). ES/MS 436.1 ($M+1^+$).

(*S*)-2,4-diamino-6-(((5-chloro-3-(3-cyanopropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile (Compound 113). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.59 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.55 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.76 – 6.67 (m, 3H), 6.46 (br s, 3H), 5.16 (t, *J* = 7.9 Hz, 1H), 4.21 – 4.11 (m, 1H), 4.07 – 3.97 (m, 1H), 2.64 – 2.57 (m, 2H), 2.06 – 1.95 (m, 2H), 1.66 – 1.56 (m, 1H), 0.59 – 0.52 (m, 2H), 0.46 – 0.40 (m, 2H). ES/MS 450.1 ($M+1^+$).

(*S*)-2,4-diamino-6-(((5-chloro-3-(4-cyanobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile (Compound 114). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.60 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.55 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.70 (br s, 2H), 6.47 (br s, 2H), 5.15 (t, *J* = 8.0 Hz, 1H), 4.04 – 3.92 (m, 2H), 1.81 – 1.49 (m, 5H), 0.59 – 0.46 (m, 3H), 0.41 – 0.31 (m, 1H). ES/MS 464.2 ($M+1^+$).

(*S*)-2,4-diamino-6-((1-(5-chloro-3-(3-cyanopropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)amino)pyrimidine-5-carbonitrile (Compound 115). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (dd, *J* = 8.3, 7.7 Hz, 1H), 7.55 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.53 (dd, *J* = 7.7, 1.2 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.67 (br s, 2H), 5.34 – 5.15 (m, 1H), 4.43 – 3.87 (m, 2H), 2.26 – 1.69 (m, 6H), 0.99 (t, *J* = 7.5 Hz, 3H). ES/MS 438.1 (M+1$^+$).

(S)-2,4-diamino-6-((1-(5-chloro-3-(4-cyanobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)amino)pyrimidine-5-carbonitrile (Compound 116). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.56 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.54 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.67 (br s, 2H), 5.35 – 5.26 (m, 1H), 4.18 – 3.95 (m, 2H), 2.61 – 2.54 (m, 2H), 2.13 – 1.56 (m, 6H), 0.96 (t, *J* = 7.2 Hz, 3H). ES/MS 452.2 (M+1$^+$).

(*S*)-2,4-diamino-6-((1-(5-chloro-3-(3-(methylsulfonyl)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)amino)pyrimidine-5-carbonitrile (Compound 117). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (dd, *J* = 8.3, 7.7 Hz, 1H), 7.54 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.54 (dd, *J* = 7.7, 1.2 Hz, 1H), 6.91 (br s, 2H), 5.33 – 5.23 (m, 1H), 4.43 – 4.32 (m, 1H), 4.05 – 3.94 (m, 1H), 3.41 – 3.26 (m, 2H), 3.02 (s, 3H), 2.40 – 2.22 (m, 1H), 2.22 – 2.06 (m, 1H), 1.98 – 1.84 (m, 2H), 1.01 (t, *J* = 7.3 Hz, 3H). ES/MS 491.1 (M+1$^+$).

(*S*)-2,4-diamino-6-(((5-chloro-3-(3-(methylsulfonyl)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile (Compound 118). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (dd, *J* = 8.2, 7.7 Hz, 1H), 7.57 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.55 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.73 (br s, 2H), 6.53 (d, *J* = 8.3 Hz, 1H), 5.26 (t, *J* = 7.9 Hz, 1H), 4.32 – 4.21 (m, 1H), 4.12 – 3.99 (m, 1H), 3.33 (s, 3H), 3.32 – 3.20 (m, 2H), 2.31 – 2.20 (m, 1H), 2.19 – 2.04 (m, 1H), 1.63 – 1.51 (m, 1H), 0.60 – 0.52 (m, 2H), 0.51 – 0.43 (m, 1H), 0.41 – 0.32 (m, 1H). ES/MS 503.1 (M+1$^+$).

(*S*)-2,4-diamino-6-((cyclopropyl(5,8-dichloro-3-(3-(methylsulfonyl)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)amino)pyrimidine-5-carbonitrile (Compound 119). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (d, *J* = 8.5 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 6.75 (br s, 2H), 6.42 (d, *J* = 8.7 Hz, 1H), 5.42 (dd, *J* = 8.7, 7.2 Hz, 1H), 4.33 – 4.22 (m, 1H), 4.10 – 3.99 (m, 1H), 3.32 – 3.21 (m, 2H), 2.99 (s, 3H), 2.31 – 2.06 (m, 2H), 1.62 – 1.51 (m, 1H), 0.65 – 0.43 (m, 3H), 0.43 – 0.30 (m, 1H). ES/MS 537.1 (M+1$^+$).

(*S*)-2,4-diamino-6-(((8-chloro-6-fluoro-3-(3-(methylsulfonyl)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile (Compound 120). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (dd, *J* = 8.5, 2.9 Hz, 1H), 7.81 (dd, *J* = 8.3, 2.9 Hz, 1H), 6.75 (br s, 2H), 6.46 (d, *J* = 8.7 Hz, 1H), 5.42 (dd, *J* = 8.5, 7.3 Hz, 1H), 4.38 – 4.24 (m, 1H), 4.17 – 4.04 (m, 1H), 3.32 – 3.24 (m, 2H), 2.31 – 2.08 (m, 2H), 1.65 – 1.53 (m, 1H), 0.61 – 0.43 (m, 3H), 0.40 – 0.32 (m, 1H). ES/MS 521.1 (M+1$^+$).

(*S*)-4-(8-chloro-2-(cyclopropyl((2,6-diamino-5-cyanopyrimidin-4-yl)amino)methyl)-6-fluoro-4-oxoquinazolin-3(4H)-yl)butanamide (Compound 121). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (dd, *J* = 8.5, 2.9 Hz, 1H), 7.79 (dd, *J* = 8.3, 2.9 Hz, 1H), 7.43 (s, 1H), 6.92 (s, 1H), 6.73 (s, 2H), 6.57 (s, 2H), 6.29 (d, *J* = 8.7 Hz, 1H), 5.52 – 5.45 (m, 1H), 4.35 – 4.17 (m, 1H), 4.07 – 3.89 (m, 1H), 2.30 – 1.74 (m, 4H), 1.62 – 1.48 (m, 1H), 0.63 – 0.26 (m, 4H). ES/MS 486.1 (M+1$^+$).

(*S*)-2,4-diamino-6-(((5-chloro-3-(4-(methylsulfonyl)butyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile (Compound 122). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.60 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.55 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.71 (br s, 2H), 5.16 (t, *J* = 8.0 Hz, 1H), 4.04 – 3.94 (m, 2H), 3.19 – 3.09 (m, 2H), 2.95 (s, 3H), 1.85 – 1.59 (m, 5H), 0.60 – 0.43 (m, 3H), 0.43 – 0.31 (m, 1H). ES/MS 517.1 (M+1$^+$).

(S)-2,4-diamino-6-((1-(5-chloro-3-(3-morpholinopropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 127). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 7.75 (q, *J* = 8.0 Hz, 1H), 7.65 – 7.50 (m, 2H), 7.43 (s, 2H), 7.23 – 6.98 (s, 2H), 5.40 (p, *J* = 6.6 Hz, 1H), 4.14 – 4.02 (m, 2H), 3.99 (d, *J* = 13.0 Hz, 2H), 3.64 (t, *J* = 12.3 Hz, 2H), 3.42 (s, 2H), 3.22 (d, *J* = 10.1 Hz, 2H), 3.08 (s, 2H), 2.12 (p, *J* = 7.8 Hz, 2H), 1.54 (d, *J* = 6.5 Hz, 3H).). ES/MS 484.2(M+H$^+$).

(S)-3-(5-chloro-2-(1-((2,6-diamino-5-cyanopyrimidin-4-yl)amino)ethyl)-4-oxoquinazolin-3(4H)-yl)-N,N-dimethylpropanamide (Compound 128). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.61 – 7.48 (m, 2H), 7.07 (d, *J* = 7.2 Hz, 1H), 6.63 (s, 2H), 6.44 (s, 2H), 5.41 (p, *J* = 6.7 Hz, 1H), 4.40 (ddd, *J* = 14.1, 9.7, 6.1 Hz, 1H), 4.04 – 3.89 (m, 1H), 2.95 (s, 3H), 2.89 – 2.81 (m, 1H), 2.79 (s, 3H), 1.51 (d, *J* = 6.5 Hz, 3H). ES/MS 456.2(M+H$^+$).

(S)-2,4-diamino-6-((1-(5-chloro-3-(3-methoxy-3-methylbutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 129). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (dd, J = 8.2, 7.8 Hz, 1H), 7.61 – 7.48 (m, 2H), 7.14 (d, J = 7.4 Hz, 1H), 6.64 (s, 2H), 6.35 (s, 2H), 5.46 – 5.34 (m, 1H), 4.08 (dd, J = 12.1, 6.4 Hz, 1H), 3.97 – 3.82 (m, 1H), 3.15 (s, 3H), 1.87 (tt, J = 12.9, 6.2 Hz, 2H), 1.52 (d, J = 6.5 Hz, 3H), 1.13 (d, J = 8.1 Hz, 7H). ES/MS 456.2(M+H$^+$).

(S)-2,4-diamino-6-((1-(5-chloro-3-(2-ethoxyethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 130). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (dd, J = 8.2, 7.8 Hz, 1H), 7.56 (ddd, J = 10.8, 8.0, 1.2 Hz, 2H), 6.91 (d, J = 7.3 Hz, 1H), 6.65 (s, 2H), 6.45 (s, 2H), 5.52 (t, J = 6.8 Hz, 1H), 4.52 – 4.39 (m, 1H), 4.19 – 4.07 (m, 1H), 3.76 – 3.55 (m, 2H), 3.41 (dd, J = 7.0, 3.9 Hz, 1H), 1.50 (d, J = 6.5 Hz, 3H), 1.01 (t, J = 7.0 Hz, 3H). ES/MS 429.2(M+H$^+$).

(S)-2,4-diamino-6-((1-(5-chloro-3-(1,3-dimethoxypropan-2-yl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 131). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (dd, J = 8.2, 7.8 Hz, 1H), 7.65 – 7.50 (m, 2H), 7.17 (d, J = 7.3 Hz, 1H), 6.63 (s, 2H), 6.51 (s, 2H), 5.50 (p, J = 6.5 Hz, 1H), 4.44 (s, 1H), 4.08 – 3.95 (m, 1H), 3.91 (dd, J = 9.7, 6.6 Hz, 1H), 3.72 (ddd, J = 22.3, 9.9, 4.9 Hz, 2H), 3.24 (s, 3H), 3.17 (s, 3H), 1.99 (s, 0H), 1.51 (d, J = 6.3 Hz, 3H). ES/MS 459.2(M+H$^+$).

2,4-diamino-6-(((S)-1-(5-chloro-3-((S)-1-methoxypropan-2-yl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 132). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 – 7.68 (m, 1H), 7.60 – 7.50 (m, 2H), 7.18 (d, J = 7.0 Hz, 1H), 6.71 – 6.59 (m, 2H), 6.49 (d, J = 13.0 Hz, 2H), 5.45 (p, J = 6.5 Hz, 1H), 4.45 (d, J = 10.9 Hz, 1H), 3.93 – 3.76 (m, 2H), 3.22 (s, 0H), 3.17 (s, 3H), 1.54 (d, J = 6.7 Hz, 3H), 1.49 (d, J = 6.5 Hz, 3H), 1.45 (d, J = 6.7 Hz, 1H). ES/MS 429.2 (M+H$^+$).

(S)-4-amino-6-((1-(5-chloro-3-(3-(4-methylpiperazin-1-yl)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 133). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.1 (d, J = 1.2 Hz, 1H), 7.92 (d, J = 7.0 Hz, 1H), 7.75 (td, J = 8.0, 1.2 Hz, 1H), 7.61 (ddt, J = 7.5, 5.2, 1.2 Hz, 2H), 7.47 (d, J = 24.2 Hz, 2H), 5.49 (p, J = 6.5 Hz, 1H), 4.26 – 4.10 (m, 1H), 4.01 – 3.83 (m, 1H), 3.8 – 3.32 (m, 6H), 3.31–2.96(m, 2H), 2.86 (s, 3H), 1.59 (dd, J = 6.5, 1.3 Hz, 3H). ES/MS 468.2 (M+H$^+$).

(S)-4-amino-6-((1-(5-chloro-4-oxo-3-(3-(piperidin-1-yl)propyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 134). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (s, 1H), 8.05 (d, J = 1.8 Hz, 1H), 7.83 (dd, J = 6.7, 1.8 Hz, 1H), 7.74 (td, J = 8.0, 1.9 Hz, 1H), 7.56 (dddd, J = 7.7, 5.4, 2.1, 1.2 Hz, 2H), 7.44 (s, 1H), 5.42 (td, J = 6.8, 2.1 Hz, 1H), 4.19 (dt, J = 14.5, 6.5 Hz, 1H), 3.96 (ddd, J = 14.3, 8.7, 5.6 Hz, 1H), 3.43 (t, J = 10.2 Hz, 2H), 3.28 – 3.05 (m, 2H), 2.87 (p, J = 10.1 Hz, 2H), 2.19 (ddt, J = 32.8, 16.5, 8.0 Hz, 2H), 1.82 (d, J = 14.3 Hz, 2H), 1.65 (dd, J = 26.6, 13.8 Hz, 2H), 1.55 (dd, J = 6.6, 1.9 Hz, 3H), 1.39 (t, J = 12.5 Hz, 1H), 1.31 – 1.17 (m, 1H). ES/MS 467.2 (M+H$^+$).

(S)-4-amino-6-((1-(5-chloro-3-(3-(4-methylpiperazin-1-yl)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 135). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, J = 1.2 Hz, 1H), 7.81 (d, J = 7.0 Hz, 1H), 7.73 (td, J = 8.0, 1.2 Hz, 1H), 7.55 (ddt, J = 7.5, 5.2, 1.2 Hz, 2H), 7.40 (d, J = 24.2 Hz, 2H), 5.45 (p, J = 6.5 Hz, 1H), 4.26 – 4.10 (m, 1H), 4.01 – 3.83 (m, 1H), 3.66 – 2.96 (m, 6H), 2.80 (s, 3H), 2.04 (dd, J = 19.8, 11.2 Hz, 2H), 1.55 (dd, J = 6.5, 1.3 Hz, 3H), 1.32 – 1.19 (m, 1H). ES/MS 482.2 (M+H$^+$).

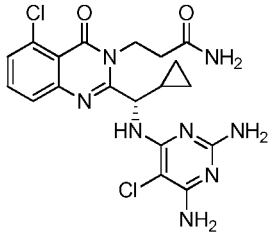
(S)-4-amino-6-((1-(5-chloro-4-oxo-3-(2-(pyrrolidin-1-yl)ethyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 136). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (s, 1H), 8.05 (d, J = 1.8 Hz, 1H), 7.74 (td, J = 8.0, 1.9 Hz, 1H), 7.56 (dddd, J = 7.7, 5.4, 2.1, 1.2 Hz, 2H), 7.44 (s, 2H), 5.42 (td, J = 6.8, 2.1 Hz, 1H), 4.35 (qt, J = 14.5, 6.8 Hz, 2H), 3.67 (d, J = 11.7 Hz, 2H), 3.60 – 3.49 (m, 2H), 3.14 (dp, J = 23.8, 7.9 Hz, 2H), 2.04 (s, 2H), 1.89 (q, J = 11.4, 9.4 Hz, 2H), 1.53 (d, J = 6.5 Hz, 3H). ES/MS 439.2 (M+H$^+$).

(S)-2,4-diamino-6-((1-(5-chloro-4-oxo-3-(2-(pyrrolidin-1-yl)ethyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 137). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1H), 7.83 – 7.72 (m, 1H), 7.64 – 7.54 (m, 2H), 7.38 – 7.20 (m, 2H), 6.98 (s, 2H), 5.30 (p, J = 6.6 Hz, 1H), 4.35 (qt, J = 14.5, 6.8 Hz, 2H), 3.67 (d, J = 11.7 Hz, 2H), 3.60 – 3.49 (m, 2H), 3.14 (dp, J = 23.8, 7.9 Hz, 2H), 2.04 (s, 2H), 1.89 (q, J = 11.4, 9.4 Hz, 2H), 1.53 (d, J = 6.5 Hz, 3H). ES/MS 454.0 (M+H$^+$).

(S)-4-((1-(3-(2-(1H-pyrazol-5-yl)ethyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)-2,6-diaminopyrimidine-5-carbonitrile (Compound 140). ^{1}H NMR (400

MHz, DMSO-d_6) δ 7.80 – 7.70 (m, 1H), 7.63 – 7.51 (m, 4H), 6.09 (d, J = 2.1 Hz, 1H), 5.38 (t, J = 6.9 Hz, 1H), 4.59 (m, 1H), 4.39 – 4.27 (m, 2H), 4.06 (dd, J = 14.5, 7.9 Hz, 2H), 3.05 (q, J = 6.6, 5.1 Hz, 2H), 1.47 (d, J = 6.5 Hz, 2H), 1.26 (d, J = 5.9 Hz, 2H). ES/MS 451.1 ($M+H^+$).

[00227] O. Preparation of a compound of formula (I) wherein n is 1, R^1 is chloro, m is 0, B is $(CH_2)_2$, R^2 is $CONH_2$, R^3 is cyclopropyl, R^4 is 2,6-diamino-5-chloropyrimidin-4-yl, and R^5 is hydrogen



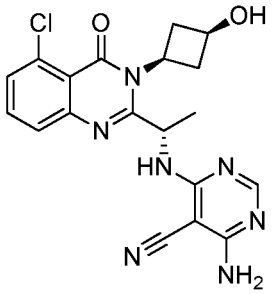
[00228] To a mixture of (*S*)-3-(5-chloro-2-(cyclopropyl((2,6-diamino-5-chloropyrimidin-4-yl)amino)methyl)-4-oxoquinazolin-3(4*H*)-yl)propanenitrile (46 mg, 0.10 mmol) in EtOH/H_2O (1:1, 2 mL) was added hydrido(dimethylphosphinous acid-kP)[hydrogen bis(dimethylphosphinito-kP)]platinum (II) (6 mg, 0.01 mmol). The mixture stirred at 90 °C for 1 h. The mixture was cooled to room temperature and diluted with DCM/H_2O and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified via flash chromatography (SiO_2, 0-50% MeOH/EtOAc) to give (*S*)-3-(5-chloro-2-(cyclopropyl((2,6-diamino-5-chloropyrimidin-4-yl)amino)methyl)-4-oxoquinazolin-3(4*H*)-yl)propanamide (Compound 68). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (t, J = 8.1 Hz, 1H), 7.56 (dd, J = 8.2, 1.2 Hz, 1H), 7.54 (dd, J = 7.8, 1.2 Hz, 1H), 7.49 (br s, 1H), 6.99 (br s, 1H), 6.18 – 6.00 (m, 3H), 5.66 (br s, 2H), 5.23 (t, J = 7.8 Hz, 1H), 4.58 – 4.37 (m, 1H), 4.24 – 4.07 (m, 1H), 2.78 – 2.63 (m, 1H), 2.63 – 2.53 (m, 1H), 1.63 – 1.47 (m, 1H), 0.59 – 0.42 (m, 3H), 0.39 – 0.30 (m, 1H). ES/MS 463.1 ($M+H^+$).

[00229] P. Preparation of the below compounds of Formula (I), using Example 3O and Reaction Scheme I:

(*S*)-4-(5-chloro-2-(cyclopropyl((2,6-diamino-5-chloropyrimidin-4-yl)amino)methyl)-4-oxoquinazolin-3(4*H*)-yl)butanamide (Compound 69). ^{1}H NMR (400 MHz, DMSO-d_6) δ

7.70 (t, *J* = 8.1 Hz, 1H), 7.54 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.52 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.43 (br s, 1H), 6.90 (br s, 1H), 6.10 (s, 2H), 5.90 (d, *J* = 8.9 Hz, 1H), 5.79 (s, 2H), 5.30 (dd, *J* = 8.9, 7.3 Hz, 1H), 4.33 – 4.23 (m, 1H), 3.97 – 3.87 (m, 1H), 2.35 – 2.18 (m, 3H), 1.91 – 1.78 (m, 1H), 1.56 – 1.46 (m, 1H), 0.57 – 0.47 (m, 3H), 0.34 – 0.27 (m, 1H). ES/MS 477.1 ($M+H^+$).

[00230] Q. Preparation of a compound of formula (I) wherein n is 1, R^1 is chloro, m is 0, B is cyclobutyl, R^2 is OH, R^3 is methyl, R^4 is 2,6-diamino-5-cyanopyrimidin-4-yl, and R^5 is hydrogen



A solution of (1R,3s)-3-(2-((S)-1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)cyclobutyl benzoate (27 mg, 0.052 mmol) dissolved in tetrahydrofuran (700 µL) and methanol (300 µL) was treated with lithium hydroxide (7 mg, 0.16 mmol) dissolved in water. The reaction mixture was stirred at room temperature for 1h and concentrated *in vacuo*. The residue was suspended in EtOAc and washed with 1N HCl solution. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give a light-yellow solid. The solid was dissolved in DMF and purified by HPLC to give 4-amino-6-(((S)-1-(5-chloro-3-((1S,3R)-3-hydroxycyclobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 82). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (s, 1H), 7.76 (m, 1H), 7.69 (m, 1H), 7.50 (d, J = 8 Hz, 2H), 7.39 (m, 1H), 5.55 (m, 1H), 4.12 (m, 1H), 3.73 (m, 1H), 2.80 (m, 2H), 2.57 (m, 1H), 2.47 (m, 1H), 1.46 (d, J = 6.4 Hz, 3H). ES/MS 412.0 ($M+H^+$).

[00231] R. Preparation of the below compounds of formula (I), using Example 3Q and Reaction Scheme I:

(S)-4-amino-6-((1-(5-chloro-3-(3-hydroxypropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 83). 1H NMR (400 MHz, DMSO-

d_6) δ 8.00 (s, 1H), 7.70 (m, 1H), 7.52 (m, 1H), 7.34 (m, 1H), 5.46 (m, 1H), 4.21 (m, 2H), 3.92 (m, 2H), 1.88 (m, 2H), 1.52 (d, J = 6.8 Hz, 3H). ES/MS 400.1 ($M+H^+$).

4-amino-6-(((1S)-1-(5-chloro-3-(4-hydroxybutan-2-yl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 84). 1H NMR (400 MHz, DMSO-d_6) δ 8.04 (s, 1H), 7.69 (m, 1H), 7.59 (m, 1H), 7.52 (m, 2H), 5.65 (m, 1H), 4.40 (m, 1H), 3.38 (m, 1H), 3.15 (m, 1H), 2.24 (m, 1H), 1.96 (m, 1H), 1.52 (d, J = 8 Hz, 3H), 1.47 (d, J = 8 Hz, 3H). ES/MS 414.1 ($M+H^+$).

(S)-4-amino-6-((1-(5-chloro-3-(4-hydroxycyclohexyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 85). 1H NMR (400 MHz, DMSO-d_6) δ 8.03 (s, 1H), 7.71 (m, 1H), 7.67 (m, 1H), 7.49 (m, 1H), 5.70 (m, 1H), 3.85 (m, 1H), 1.73 (m, 1H), 1.70 (m, 1H), 1.62 (m, 1H), 1.50 (d, J = 8 Hz, 3H). ES/MS 440.1 ($M+H^+$).

2,4-diamino-6-(((S)-1-(5-chloro-3-((cis)-3-hydroxycyclobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 93). 1H NMR (400 MHz, DMSO-d6) δ 7.72 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.56 – 7.52 (m, 2H), 5.52 (p, *J* = 6.7 Hz, 1H), 4.14 (p, *J* = 8.2 Hz, 1H), 3.85 – 3.74 (m, 1H), 2.80 – 2.61 (m, 4H), 1.49 (d, *J* = 6.5 Hz, 3H). ES/MS 427.1 ($M+H^+$).

5-chloro-2-((S)-1-((2,6-diamino-5-chloropyrimidin-4-yl)amino)ethyl)-3-((cis)-3-hydroxycyclobutyl)quinazolin-4(3H)-one (Compound 94). 1H NMR (400 MHz, DMSO-d6) δ 7.72 (t, *J* = 8.2 Hz, 1H), 7.59 – 7.52 (m, 2H), 5.53 – 5.44 (m, 1H), 4.13 (p, *J* = 8.2 Hz, 1H), 3.81 (p, *J* = 7.0 Hz, 1H), 2.81 – 2.60 (m, 4H), 1.50 (d, *J* = 6.5 Hz, 3H). ES/MS 436.1 ($M+H^+$).

5,8-dichloro-2-((S)-cyclopropyl((2,6-diamino-5-chloropyrimidin-4-yl)amino)methyl)-3-((cis)-3-hydroxycyclobutyl)quinazolin-4(3H)-one (Compound 95). 1H NMR (400 MHz, DMSO-d6) δ 7.93 (d, *J* = 8.5 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 5.27 (t, *J* = 7.7 Hz, 1H), 4.21 – 4.09 (m, 1H), 3.81 (t, *J* = 7.1 Hz, 1H), 2.84 – 2.63 (m, 4H), 1.61 – 1.47 (m, 1H), 0.64 – 0.39 (m, 4H). ES/MS 496.1 ($M+H^+$).

2,4-diamino-6-(((S)-cyclopropyl(5,8-dichloro-3-((cis)-3-hydroxycyclobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)amino)pyrimidine-5-carbonitrile (Compound 96). 1H NMR (400 MHz, DMSO-d6) δ 7.89 (d, *J* = 8.5 Hz, 1H), 7.51 (d, *J* = 8.3 Hz, 1H), 5.27 (t,

J = 7.7 Hz, 1H), 4.12 (t, *J* = 8.3 Hz, 1H), 3.76 (p, *J* = 7.3 Hz, 1H), 2.80 – 2.57 (m, 4H), 1.52 (dt, *J* = 8.0, 6.4 Hz, 1H), 0.62 – 0.32 (m, 4H). ES/MS 487.1 ($M+H^+$).

2,4-diamino-6-(((S)-(8-chloro-6-fluoro-3-((trans)-3-hydroxycyclobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile (Compound 97). 1H NMR (400 MHz, DMSO-d6) δ 8.04 (dd, *J* = 8.5, 2.9 Hz, 1H), 7.79 (dd, *J* = 8.3, 2.9 Hz, 1H), 5.38 (t, *J* = 7.2 Hz, 1H), 5.03 – 4.95 (m, 1H), 4.55 – 4.48 (m, 2H), 3.23 – 3.03 (m, 2H), 2.21 – 1.98 (m, 2H), 1.51 – 1.43 (m, 1H), 0.60 – 0.31 (m, 4H). ES/MS 471.1 ($M+H^+$).

2,4-diamino-6-(((S)-1-(8-chloro-6-fluoro-3-((trans)-3-hydroxycyclobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 98). 1H NMR (400 MHz, DMSO-d6) δ 8.05 (dd, *J* = 8.5, 2.9 Hz, 1H), 7.80 (dd, *J* = 8.3, 2.9 Hz, 1H), 5.57 (t, *J* = 6.7 Hz, 1H), 4.92 – 4.82 (m, 1H), 4.54 – 4.47 (m, 1H), 3.21 – 3.05 (m, 2H), 2.20 – 2.09 (m, 1H), 2.09 – 2.00 (m, 1H), 1.48 (d, *J* = 6.4 Hz, 3H). ES/MS 445.1 ($M+H^+$).

2,4-diamino-6-(((S)-1-(8-chloro-6-fluoro-3-((cis)-3-hydroxycyclobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 99). 1H NMR (400 MHz, DMSO-d6) δ 8.03 (dd, *J* = 8.5, 2.9 Hz, 1H), 7.77 (dd, *J* = 8.3, 2.9 Hz, 1H), 5.59 (p, *J* = 7.1, 6.6 Hz, 1H), 4.14 (p, *J* = 8.4, Hz, 1H), 3.76 (p, *J* = 7.1 Hz, 1H), 2.94 – 2.77 (m, 2H), 2.61 – 2.51 (m, 1H), 2.45 – 2.39 (m, 1H), 1.48 (d, *J* = 6.4 Hz, 3H). ES/MS 445.1 ($M+H^+$).

2,4-diamino-6-(((S)-cyclopropyl(5,8-dichloro-3-((trans)-3-hydroxycyclobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)amino)pyrimidine-5-carbonitrile (Compound 100). 1H NMR (400 MHz, DMSO-d6) δ 7.89 (d, *J* = 8.5 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 5.35 (t, *J* = 7.4 Hz, 1H), 4.99 – 4.89 (m, 1H), 4.53 – 4.45 (m, 1H), 3.16 – 2.99 (m, 2H), 2.21 – 2.11 (m, 1H), 2.09 – 1.98 (m, 1H), 1.52 – 1.41 (m, 1H), 0.60 – 0.31 (m, 4H). ES/MS 487.1 ($M+H^+$).

2,4-diamino-6-(((S)-1-(5,8-dichloro-3-((trans)-3-hydroxycyclobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 101). 1H NMR (400 MHz, DMSO-d6) δ 7.89 (dd, *J* = 8.5, 0.7 Hz, 1H), 7.51 (dd, *J* = 8.5, 0.9 Hz, 1H), 5.52 (t, *J* = 7.0 Hz, 1H), 4.89 – 4.80 (m, 1H), 4.52 – 4.44 (m, 1H), 3.14 – 3.01 (m,

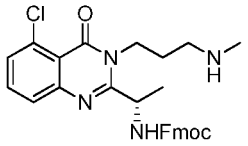
2H), 2.19 – 2.10 (m, 1H), 2.10 – 2.01 (m, 1H), 1.46 (d, *J* = 6.3 Hz, 3H). ES/MS 461.1 ($M+H^+$).

2,4-diamino-6-(((S)-(8-chloro-6-fluoro-3-((cis)-3-hydroxycyclobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile (Compound 102). 1H NMR (400 MHz, DMSO-d6) δ 8.03 (dd, *J* = 8.7, 2.9 Hz, 1H), 7.77 (dd, *J* = 8.3, 2.5 Hz, 1H), 5.30 (t, *J* = 7.8 Hz, 1H), 4.18 (p, *J* = 8.6 Hz, 1H), 3.79 – 3.69 (m, 1H), 2.92 (q, *J* = 8.7 Hz, 1H), 2.83 (q, *J* = 9.2 Hz, 1H), 2.60 – 2.51 (m, 1H), 2.41-2.31 (m, 1H), 1.58 – 1.49 (m, 1H), 0.60 – 0.31 (m, 4H). ES/MS 471.1 ($M+H^+$).

2,4-diamino-6-(((S)-1-(5,8-dichloro-3-((cis)-3-hydroxycyclobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile (Compound 103). 1H NMR (400 MHz, DMSO-d6) δ 7.88 (d, *J* = 8.5 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 5.52 (p, *J* = 6.8 Hz, 1H), 4.08 (p, *J* = 8.3 Hz, 1H), 3.82 – 3.73 (m, 1H), 2.76 – 2.56 (m, 4H), 1.47 (d, *J* = 6.4 Hz, 3H). ES/MS 461.1 ($M+H^+$).

Example 4. Preparation of a compound of formula (4)

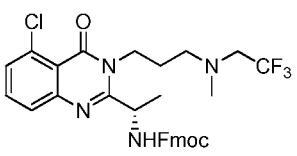
[00232] A. Preparation of a compound of formula (4) wherein n is 1, R^1 is chloro, m is 0, B is $(CH_2)_3$, R^{2y} is methyl, R^3 is methyl, and R^5 is hydrogen



(S)-(9H-fluoren-9-yl)methyl (1-(5-chloro-3-(3-(methylamino)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate was prepared as described above from (S)-tert-butyl (3-(2-(1-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)(methyl)carbamate.

Example 5. Preparation of a compound of formula (5)

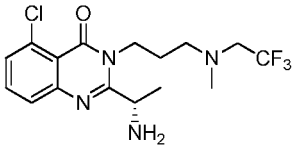
[00233] A. Preparation of a compound of formula (5) wherein n is 1, R^1 is chloro, m is 0, B is $(CH_2)_3$, R^{2y} is methyl, R^{2x} is trifluoroethyl, R^3 is methyl, and R^5 is hydrogen



[00234] To a mixture of (*S*)-(9*H*-fluoren-9-yl)methyl (1-(5-chloro-3-(3-(methylamino)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate (0.21 g, 0.40 mmol) and potassium carbonate (0.33 g, 2.4 mmol) in MeCN (8 mL) was added 2,2,2-trifluoroethyltriflate (70 μL, 0.49 mmol). The mixture was heated to 55 °C overnight. The mixture was filtered and the filtrate was concentrated. The residue was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), decanted and concentrated. The residue was carried forward without purification to give (S)-(9H-fluoren-9-yl)methyl (1-(5-chloro-3-(3-(methyl(2,2,2-trifluoroethyl)amino)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate.

Example 6. Preparation of a compound of formula (6)

[00235] A. Preparation of a Compound of Formula (6) wherein n is 1, R^1 is chloro, m is 0, B is $(CH_2)_3$, R^{2y} is methyl, R^{2x} is trifluoroethyl, R^3 is methyl, and R^5 is hydrogen



[00236] (S)-2-(1-aminoethyl)-5-chloro-3-(3-(methyl(2,2,2-trifluoroethyl)amino)propyl)quinazolin-4(3H)-one was prepared as described above from (S)-(9H-fluoren-9-yl)methyl (1-(5-chloro-3-(3-(methyl(2,2,2-trifluoroethyl)amino)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate.

[00237] Biological Examples

[00238] The compounds of formula (I) were characterized for their enzymatic activity against the PI3K isoforms. The activities were measured using a time-resolved fluorescence resonance energy transfer (TR-FRET) assay. TR-FRET monitored the formation of 3,4,5-inositol triphosphate molecule that competed with fluorescently labeled PIP3 for binding to the GRP-1 pleckstrin homology domain protein. An increase in phosphatidylinositide 3-phosphate product resulted in a decrease in TR-FRET signal as the labeled fluorophore was displaced from the GRP-1 protein binding site.

[00239] Class I PI3K isoforms were expressed and purified as heterodimeric recombinant proteins. All assay reagents and buffers for the TR-FRET assay were

purchased from Millipore. PI3K isoforms were assayed under initial rate conditions in the presence of 25 mM Hepes (pH 7.4), and 2× Km ATP (75-500 μM), 2 μM PIP2, 5% glycerol, 5 mM $MgCl_2$, 50 mM NaCl, 0.05% (v/v) Chaps, 1 mM dithiothreitol, and 1% (v/v) DMSO at the following concentrations for each isoform: PI3Kα, PI3Kβ, and PI3Kδ between 25 and 50 pM, and PI3Kγ at 2 nM. The compounds of Table 1 and Compound X, ((S)-2,4-diamino-6-((1-(5-chloro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile) were added to the assay solution and incubated for 30 minutes at 25°C. The reactions were terminated with a final concentration of 10 mM EDTA, 10 nM labeled-PIP3, and 35 nM Europium labeled GRP-1 detector protein before reading TR-FRET on an Envision plate reader (Ex: 340 nm; Em: 615/665 nm; 100 μs delay and 500 μs read window).

[00240] The results were normalized based on positive (1 μM wortmanin) and negative (DMSO) controls, and the IC_{50} values for PI3K α, β, δ, and γ were calculated from the fit of the dose-response curves to a four-parameter equation. These assays generally produced results within 3-fold of the reported mean.

[00241] Table 2 summarizes the IC_{50} (nM) values for PI3K isoforms β, δ, and γ. The results indicate that certain compounds of formula (I) inhibit both PI3Kδ and PI3Kβ. Also, Compound X exhibited PI3Kδ IC_{50} of 0.2 nM, a PI3Kβ IC_{50} of 11 nM, and a PI3Kγ IC_{50} of 7 nM. The PI3Kγ/PI3Kβ ratio for Compound X and compound 47 is 0.6 and 230, respectively. The results indicate that certain compounds have greater selectivity for PI3Kβ over PI3Kγ compared to compound X. Compounds in Table 1a were analyzed using the same assay, and the results are summarized in Table 2a.

[00242] **Table 2.** The IC_{50} values (nM) for PI3K isoforms β, δ, and γ.

Compound	IC_{50} (β)	IC_{50} (δ)	IC_{50} (γ)
1	27	9	≥10000
2	1500	27	≥10000
3	1300	15	≥10000
4	420	5	660
5	930	5	2200
6	250	9	≥10000

7	140	35	≥10000
8	68	5	1700
9	170	77	≥10000
10	840	480	≥10000
11	93	37	≥10000
12	300	52	≥10000
13	6800	3300	≥10000
14	9	2	1900
15	2	3	1700
16	42	7	≥10000
17	69	11	≥10000
18	360	370	≥10000
19	1300	14	≥10000
23	90	25	≥10000
24	51	6	≥10000
25	1300	100	≥10000
26	740	150	≥10000
27	200	7	≥10000
28	100	3	≥10000
29	47	7	≥10000
30	110	11	≥10000
31	47	6	≥10000
32	44	92	3200
33	2100	210	≥10000
34	250	79	≥10000
35	110	21	≥10000
36	71	27	8200
37	57	16	4800
38	44	12	≥10000
39	25	3	2400
40	21	9	≥10000
41	15	3	1800

42	15	2	1400
43	7	6	3400
44	8	11	6000
45	7	4	2100
46	6	3	2500
47	5	3	1100
48	4	4	900
49	1	1	750
50	75	71	4600
52	29	4	1200
51	110	8	5500
53	9	2	190
54	5	0.4	830
55	4	0.5	280
56	4	0.4	540
57	480	6	≥10000
58	460	24	6600
59	500	8	2200
60	150	4	6400
61	140	7	6600
62	320	4	960
63	640	2	800
64	12	1	110
65	7	1	470
66	4	1	97
68	520	5	1000
69	49	2	1300
71	240	34	≥10000
72	35	12	7900
73	21	6	9400
74	17	1	1620
75	19	1	2300

[00243] **Table 2a.** The IC_{50} values (nM) for PI3K isoforms β, δ, and γ.

Compound	IC_{50} (β)	IC_{50} (δ)	IC_{50} (γ)
76	46	2	160
77	860	33	7000
78	920	49	3000
79	40	2	380
80	1100	27	2400
81	47	5	320
82	150	5	2300
83	180	6	2900
84	260	4	2900
85	92	3	1200
86	620	24	≥10000
87	150	4	≥10000
88	250	42	≥10000
89	54	3	≥10000
90	2800	37	≥10000
91	1700	95	≥10000
92	320	7	≥10000
93	4	1	158
94	190	14	1587
95	720	16	≥10000
96	10	2	960
97	58	8	2800
98	330	20	3200
99	290	9	2400
100	44	3	2900
101	140	12	3200
102	66	2	1100
103	21	5	2600
104	58	9	78
105	820	9	8400

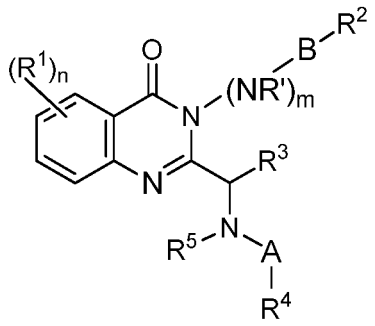
106	590	8	>10000
107	82	3	1700
108	2000	39	≥10000
109	520	14	2185
110	42	4	180
111	40	3	530
112	8	3	62
113	17	1	59
114	12	0.8	130
115	190	9	190
116	150	5	540
117	250	21	3000
118	13	2	570
119	8	2	1100
120	30	8	1900
121	9	2	760
122	23	0.7	120
123	79	3	1300
124	88	2	3200
125	49	3	2300
126	24	0.9	2500
127	130	2	720
128	530	15	280
129	290	2	530
130	120	3	410
131	210	13	1400
132	58	2	330
133	340	11	≥10000
134	550	4	≥10000
135	640	6	≥10000
136	990	25	≥10000
137	760	27	≥10000

140	410	6	590
142	527	87	≥10000
143	374	34	4236

[00244] All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification are incorporated herein by reference, in their entirety to the extent not inconsistent with the present description. From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the present application.

What is claimed:

1. A compound having the structure of formula (IVa):



(IVa)

wherein:

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

m is 0 or 1;

A is a single bond or C(O);

B is C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} heteroalkyl, or C_{3-8} heterocycloalkyl wherein each of the alkyl, cycloalkyl, and heterocycloalkyl moieties is optionally substituted with hydroxyl or C_{1-6} alkoxy;

R′ is hydrogen or optionally substituted C_{1-6} alkyl;

each R^1 is independently selected from halo, cyano, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} haloalkyl, optionally substituted C_{1-6} alkoxy, optionally substituted sulfonyl, optionally substituted C_{1-6} alkylsulfonyl, optionally substituted C_{3-8} aryl, optionally substituted C_{3-8} heteroaryl, optionally substituted C_{3-8} cycloalkyl, and optionally substituted C_{2-8} heterocycloalkyl;

R^2 is hydrogen, cyano, optionally substituted C_{3-8} heterocycloalkyl, optionally substituted C_{3-8} heteroaryl, $-NR^{2x}R^{2x}$, $-NR^{2y}C(O)R^{2x}$, $-C(O)NR^{2x}R^{2y}$, $-OR^{2y}$, or $-SO_2R^{2z}$,

where R^{2x} is hydrogen, optionally substituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{2-8} heterocycloalkyl, C_{4-8} heteroaryl;

wherein R^{2y} is independently selected from hydrogen and C_{1-6} alkyl; and wherein R^{2z} is C_{1-6} alkyl;

R^3 is hydrogen, optionally substituted C_{1-6} alkyl, C_{3-8} cycloalkyl, or C_{6-10} aryl;

R^4 is a six- to twelve-membered heteroaryl having at least one aromatic group and at least two heteroatoms selected from N, O, or S, wherein the heteroaryl is optionally substituted with one, two, or three members independently selected from halo, cyano, optionally substituted haloalkyl, optionally substituted C_{1-6} alkyl, and $-NH_2$; and

R^5 is hydrogen or optionally substituted C_{1-6} alkyl, wherein R^5 and R^3 together with the atoms to which they are attached optionally form a four- or eight-membered heterocyclic ring;

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

2. The compound of claim 1, wherein

n is 0, 1, 2 or 3;

m is 0 or 1;

A is a single bond or C(O);

B is C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} heteroalkyl or C_{3-8} heterocycloalkyl wherein each of the alkyl, cycloalkyl, heteroalkyl, and heterocycloalkyl moieties is optionally substituted with hydroxyl or C_{1-6} alkoxy;

R′ is hydrogen or C_{1-6} alkyl optionally substituted with C_{6-10} aryl;

each R^1 is independently selected from halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} alkylsulfonyl;

R^2 is hydrogen, cyano, morpholinyl, $-NR^{2x}R^{2x}$, $-NR^{2y}C(O)R^{2x}$, $-C(O)NR^{2x}R^{2y}$, $-OR^{2y}$, or $-SO_2R^{2z}$, pyrrolidinyl , piperidinyl, optionally substituted piperazinyl, phenyl, pyrazolyl, or triazolyl.

where R^{2x} is hydrogen, optionally substituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{2-8} heterocycloalkyl, C_{4-8} heteroaryl;

wherein R^{2y} is independently selected from hydrogen and C_{1-6} alkyl; and wherein R^{2z} is C_{1-6} alkyl;

R^3 is hydrogen, optionally substituted C_{1-6} alkyl, C_{3-8} cycloalkyl, or C_{6-10} aryl;

R^4 is a six- to twelve-membered heteroaryl having at least one aromatic group and at least two heteroatoms selected from N, O, or S, wherein the heteroaryl is optionally substituted with one, two, or three members independently selected from halo, cyano, optionally substituted haloalkyl, optionally substituted C_{1-6} alkyl, and $-NH_2$; and

R^5 is hydrogen or optionally substituted C_{1-6} alkyl, wherein R^5 and R^3 together with the atoms to which they are attached optionally form a four- or eight-membered heterocyclic ring;

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

3. The compound of claims 1-2, wherein m is 0.

4. The compound of claim 3, wherein the compound is select from the group consisting of:

(S)-2,4-diamino-6-(((3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)(phenyl)methyl)amino)pyrimidine-5-carbonitrile;

(S)-3-(3-amino-3-methylbutyl)-5-chloro-2-(1-(thiazolo[5,4-d]pyrimidin-7-ylamino)ethyl)quinazolin-4(3H)-one;

(S)-4-amino-6-((1-(3-(3-amino-3-methylbutyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-((1-(5-chloro-4-oxo-3-(3-(pyrimidin-2-ylamino)propyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-((1-(5-chloro-4-oxo-3-(3-(pyridin-2-ylamino)propyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-4-amino-6-((1-(3-(3-(benzylamino)propyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-3-(3-aminopropyl)-5-chloro-2-(1-((2,6-diamino-5-chloropyrimidin-4-yl)amino)ethyl)quinazolin-4(3H)-one;

(S)-2,4-diamino-6-((1-(3-(3-(benzylamino)propyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-3-amino-N-(1-(3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)pyrazine-2-carboxamide;

(S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-chloro-3-(3-morpholinopropyl)quinazolin-4(3H)-one (Compound 19);

(S)-4-((1-(3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)-6-methylpyrimidine-5-carbonitrile;

4-amino-6-(((1S)-1-(3-(4-aminobutan-2-yl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

4-amino-6-(((1S)-1-(3-(1-aminopropan-2-yl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-4-amino-6-((1-(3-(2-aminoethyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

4-amino-6-(((1S)-1-(3-(3-amino-2-methylpropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-4-amino-6-((1-(3-(4-aminobutyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-4-amino-6-((1-(3-(3-aminopropyl)-5-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-2-(1-((6-amino-5-chloropyrimidin-4-yl)amino)ehyl)-3-(3-aminopropyl)-5-chloroquinazolin-4(3H)-one;

(S)-4-amino-6-((1-(5-chloro-3-(3-(methylamino)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-2-amino-N-(1-(3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(S)-4-amino-6-((1-(3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-3-methylbutyl)amino)pyrimidine-5-carbonitrile;

(S)-4-amino-6-((1-(3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)amino)pyrimidine-5-carbonitrile;

(S)-3-(3-aminopropyl)-5-chloro-2-(cyclopropyl(imidazo[2,1-f][1,2,4]triazin-4-ylamino)methyl)quinazolin-4(3H)-one;

(S)-2,4-diamino-6-((1-(3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)amino)pyrimidine-5-carbonitrile;

(S)-3-(3-aminopropyl)-5-chloro-2-(cyclopropyl(pyrido[3,2-d]pyrimidin-4-ylamino)methyl)quinazolin-4(3H)-one;

(S)-3-(3-aminopropyl)-5-chloro-2-(cyclopropyl((2,6-diamino-5-chloropyrimidin-4-yl)amino)methyl)quinazolin-4(3H)-one;

(S)-2,4-diamino-6-((1-(5-chloro-3-(3-(methylamino)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-4-amino-6-(((3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile;

(S)-2-amino-4-((1-(5-chloro-3-(3-(methylamino)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)-6-methylpyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-((1-(3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-3-(3-aminopropyl)-2-(((5-bromo-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)(cyclopropyl)methyl)-5-chloroquinazolin-4(3H)-one;

(S)-2-amino-4-(((3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)-6-chloropyrimidine-5-carbonitrile;

(S)-3-(3-aminopropyl)-5-chloro-2-(cyclopropyl(thiazolo[5,4-d]pyrimidin-7-ylamino)methyl)quinazolin-4(3H)-one;

(S)-2,4-diamino-6-(((5-chloro-3-(3-(methylamino)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-(((3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile;

(S)-3-(3-aminopropyl)-5-chloro-2-(((6-chloropyrido[3,2-d]pyrimidin-4-yl)amino)(cyclopropyl)methyl)quinazolin-4(3H)-one;

(S)-2-amino-4-(((3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)-6-methylpyrimidine-5-carbonitrile;

(S)-3,5-diamino-N-(1-(3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)-6-bromopyrazine-2-carboxamide;

(S)-N-(3-(2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)acetamide;

(S)-N-(3-(5-chloro-2-(cyclopropyl((2,6-diamino-5-cyanopyrimidin-4-yl)amino)methyl)-4-oxoquinazolin-3(4H)-yl)propyl)pivalamide;

(S)-N-(3-(2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-5-chloro-4-oxoquinazolin-3(4H)-yl)propyl)acetamide;

(S)-2,4-diamino-6-(((5-chloro-3-(3-(cyclobutylamino)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-(((5-chloro-3-(3-(oxetan-3-ylamino)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-(((5-chloro-3-(3-((4,4-difluorocyclohexyl)amino)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile;

(S)-4-amino-6-((1-(5-chloro-3-(3-(dimethylamino)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-((1-(5-chloro-3-(2-(dimethylamino)ethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-5-(5-chloro-2-(cyclopropyl((2,6-diamino-5-chloropyrimidin-4-yl)amino)methyl)-4-oxoquinazolin-3(4H)-yl)pentanamide;

(S)-2,4-diamino-6-((1-(3-(3-(benzyl(methyl)amino)propyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-2-amino-4-((1-(3-(3-(benzyl(methyl)amino)propyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)-6-methylpyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-((1-(5-chloro-3-(3-(methyl(2,2,2-trifluoroethyl)amino)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-3-(5-chloro-2-(cyclopropyl((2,6-diamino-5-chloropyrimidin-4-yl)amino)methyl)-4-oxoquinazolin-3(4H)-yl)propanenitrile;

(S)-5-(5-chloro-2-(cyclopropyl((2,6-diamino-5-cyanopyrimidin-4-yl)amino)methyl)-4-oxoquinazolin-3(4H)-yl)pentanamide;

(S)-4-(5,8-dichloro-2-(cyclopropyl((2,6-diamino-5-cyanopyrimidin-4-yl)amino)methyl)-4-oxoquinazolin-3(4H)-yl)butanamide;

(S)-4-(5-chloro-2-(cyclopropyl((2,6-diamino-5-cyanopyrimidin-4-yl)amino)methyl)-4-oxoquinazolin-3(4H)-yl)butanamide;

(S)-3-(5-chloro-2-(cyclopropyl((2,6-diamino-5-chloropyrimidin-4-yl)amino)methyl)-4-oxoquinazolin-3(4H)-yl)propanamide;

(S)-4-(5-chloro-2-(cyclopropyl((2,6-diamino-5-chloropyrimidin-4-yl)amino)methyl)-4-oxoquinazolin-3(4H)-yl)butanamide;

(S)-3-(3-aminopropyl)-5-chloro-2-(1-(imidazo[2,1-f][1,2,4]triazin-4-ylamino)ethyl)quinazolin-4(3H)-one;

(S)-3-(3-aminopropyl)-5-chloro-2-(1-(thiazolo[5,4-d]pyrimidin-7-ylamino)ethyl)quinazolin-4(3H)-one;

(S)-4-amino-6-((1-(3-(3-aminopropyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

2,4-diamino-6-(((1S)-1-(5-chloro-3-(3-hydroxy-4-(isopropylamino)butyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

2,4-diamino-6-(((1S)-1-(3-(4-(tert-butylamino)-3-hydroxybutyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-4-((1-(3-((1H-pyrazol-3-yl)methyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)-2,6-diaminopyrimidine-5-carbonitrile;

(S)-4-((1-(3-((1H-pyrazol-3-yl)methyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)-6-aminopyrimidine-5-carbonitrile;

(S)-3-((1H-pyrazol-3-yl)methyl)-5-chloro-2-(1-(imidazo[2,1-f][1,2,4]triazin-4-ylamino)ethyl)quinazolin-4(3H)-one;

(S)-4-((1-(3-((1H-pyrazol-4-yl)methyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)-2,6-diaminopyrimidine-5-carbonitrile;

(S)-4-((1-(3-((1H-imidazol-2-yl)methyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)-2,6-diaminopyrimidine-5-carbonitrile;

(S)-4-((1-(3-((1H-1,2,4-triazol-3-yl)methyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)-2,6-diaminopyrimidine-5-carbonitrile;

4-amino-6-(((S)-1-(5-chloro-3-((1S,3R)-3-hydroxycyclobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;
(S)-4-amino-6-((1-(5-chloro-3-(3-hydroxypropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

4-amino-6-(((1S)-1-(5-chloro-3-(4-hydroxybutan-2-yl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-4-amino-6-((1-(5-chloro-3-(4-hydroxycyclohexyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-4-amino-6-((1-(3-(3-aminocyclobutyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-4-amino-6-((1-(5-chloro-4-oxo-3-(piperidin-4-ylmethyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

4-amino-6-(((1S)-1-(5-chloro-3-(morpholin-2-ylmethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

4-amino-6-(((1S)-1-(5-chloro-4-oxo-3-(pyrrolidin-3-ylmethyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

4-amino-6-(((1S)-1-(5-chloro-4-oxo-3-(pyrrolidin-2-ylmethyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

4-amino-6-(((1S)-1-(5-chloro-4-oxo-3-(piperidin-2-ylmethyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

4-amino-6-(((1S)-1-(5-chloro-4-oxo-3-(piperidin-3-ylmethyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

2,4-diamino-6-(((S)-1-(5-chloro-3-((cis)-3-hydroxycyclobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

5-chloro-2-((S)-1-((2,6-diamino-5-chloropyrimidin-4-yl)amino)ethyl)-3-((cis)-3-hydroxycyclobutyl)quinazolin-4(3H)-one;

5,8-dichloro-2-((S)-cyclopropyl((2,6-diamino-5-chloropyrimidin-4-yl)amino)methyl)-3-((cis)-3-hydroxycyclobutyl)quinazolin-4(3H)-one;

2,4-diamino-6-(((S)-cyclopropyl(5,8-dichloro-3-((cis)-3-hydroxycyclobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)amino)pyrimidine-5-carbonitrile;

2,4-diamino-6-(((S)-(8-chloro-6-fluoro-3-((trans)-3-hydroxycyclobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile;

2,4-diamino-6-(((S)-1-(8-chloro-6-fluoro-3-((trans)-3-hydroxycyclobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

2,4-diamino-6-(((S)-1-(8-chloro-6-fluoro-3-((cis)-3-hydroxycyclobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

2,4-diamino-6-(((S)-cyclopropyl(5,8-dichloro-3-((trans)-3-hydroxycyclobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)amino)pyrimidine-5-carbonitrile;

2,4-diamino-6-(((S)-1-(5,8-dichloro-3-((trans)-3-hydroxycyclobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

2,4-diamino-6-(((S)-(8-chloro-6-fluoro-3-((cis)-3-hydroxycyclobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile;

2,4-diamino-6-(((S)-1-(5,8-dichloro-3-((cis)-3-hydroxycyclobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-((1-(5-chloro-3-(2-cyanoethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

((S)-4-amino-6-((1-(5-chloro-3-(3-methoxypropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-4-amino-6-((1-(5,8-dichloro-3-(3-methoxypropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-((1-(5,8-dichloro-3-(3-methoxypropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-4-amino-6-((1-(5,8-difluoro-3-(3-methoxypropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-((1-(5,8-difluoro-3-(3-methoxypropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-((1-(5-chloro-3-(3-cyanopropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-((1-(5-chloro-3-(3-(methylsulfonyl)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-(((5-chloro-3-(2-cyanoethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-(((5-chloro-3-(3-cyanopropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-(((5-chloro-3-(4-cyanobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-((1-(5-chloro-3-(3-cyanopropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-((1-(5-chloro-3-(4-cyanobutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-((1-(5-chloro-3-(3-(methylsulfonyl)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-(((5-chloro-3-(3-(methylsulfonyl)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-((cyclopropyl(5,8-dichloro-3-(3-(methylsulfonyl)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-(((8-chloro-6-fluoro-3-(3-(methylsulfonyl)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile;

(S)-4-(8-chloro-2-(cyclopropyl((2,6-diamino-5-cyanopyrimidin-4-yl)amino)methyl)-6-fluoro-4-oxoquinazolin-3(4H)-yl)butanamide;

(S)-2,4-diamino-6-(((5-chloro-3-(4-(methylsulfonyl)butyl)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)amino)pyrimidine-5-carbonitrile;

2,4-diamino-6-(((S)-1-(5-chloro-4-oxo-3-((R)-piperidin-3-ylmethyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

2,4-diamino-6-(((S)-1-(5-chloro-4-oxo-3-((S)-piperidin-3-ylmethyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

2,4-diamino-6-(((S)-1-(5-chloro-4-oxo-3-((S)-pyrrolidin-3-ylmethyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

2,4-diamino-6-(((S)-1-(5-chloro-4-oxo-3-((R)-pyrrolidin-3-ylmethyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-((1-(5-chloro-3-(3-morpholinopropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-3-(5-chloro-2-(1-((2,6-diamino-5-cyanopyrimidin-4-yl)amino)ethyl)-4-oxoquinazolin-3(4H)-yl)-N,N-dimethylpropanamide;

(S)-2,4-diamino-6-((1-(5-chloro-3-(3-methoxy-3-methylbutyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-((1-(5-chloro-3-(2-ethoxyethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-((1-(5-chloro-3-(1,3-dimethoxypropan-2-yl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

2,4-diamino-6-(((S)-1-(5-chloro-3-((S)-1-methoxypropan-2-yl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-4-amino-6-((1-(5-chloro-3-(3-(4-methylpiperazin-1-yl)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-4-amino-6-((1-(5-chloro-4-oxo-3-(3-(piperidin-1-yl)propyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-4-amino-6-((1-(5-chloro-3-(3-(4-methylpiperazin-1-yl)propyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-4-amino-6-((1-(5-chloro-4-oxo-3-(2-(pyrrolidin-1-yl)ethyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-((1-(5-chloro-4-oxo-3-(2-(pyrrolidin-1-yl)ethyl)-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-4-((1-(3-(2-(1H-pyrazol-5-yl)ethyl)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)-2,6-diaminopyrimidine-5-carbonitrile;

4-amino-6-(((S)-1-(5-chloro-3-((R)-2,3-dihydroxypropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

4-amino-6-(((S)-1-(5-chloro-3-((S)-2,3-dihydroxypropyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

5. The compound of claims 1-2, wherein m is 1.

6. The compound of claim 5, wherein the compound is select from the group consisting of:

(S)-2,4-diamino-6-((1-(3-((2-aminoethyl)(benzyl)amino)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-((1-(3-((2-aminoethyl)(benzyl)amino)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-3-((2-aminoethyl)(methyl)amino)-5-chloro-2-(1-(imidazo[2,1-f][1,2,4]triazin-4-ylamino)ethyl)quinazolin-4(3H)-one;

(S)-4-amino-6-((1-(3-((2-aminoethyl)(benzyl)amino)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-4-amino-6-((1-(3-((2-aminoethyl)(benzyl)amino)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-((1-(3-((2-aminoethyl)(methyl)amino)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-2,4-diamino-6-((1-(3-((2-aminoethyl)(methyl)amino)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-4-amino-6-((1-(3-((2-aminoethyl)(methyl)amino)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

(S)-4-amino-6-((1-(3-((2-aminoethyl)(methyl)amino)-5-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidine-5-carbonitrile;

or a pharmaceutically acceptable salt, isomer, or a mixture thereof.

7. The compound of any of claims 1-6, wherein B is methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, each of which is optionally substituted with methoxy, ethoxy, or hydroxyl.

8. The compound of any of claims 1-7, wherein R′ is methyl, ethyl, propyl, phenylmethyl, phenylethyl, or phenylpropyl.

9. The compound of any of claims 1-8, wherein each R^1 is independently selected from chloro, fluoro, bromo, iodo, methyl, ethyl, propyl, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoroethyl, difluoroethyl, and fluoroethyl.

10. The compound of any of claims 1-9, wherein each R^2 is selected from cyano, morpholinyl, $-NH_2$, $-NHR^{2x}$, $-NR^{2x}R^{2x}$, $-NHC(O)R^{2y}$, $-NR^{2x}C(O)R^{2y}$, $-C(O)NHR^{2y}$, $-C(O)NR^{2x}R^{2y}$, $-OH$, $-OR^{2y}$, or $-SO_2R^{2z}$; wherein each R^{2x} is independently methyl, ethyl, propyl, butyl, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoroethyl, difluoroethyl, fluoroethyl, phenyl, phenylmethyl, phenylethyl, pyridinyl, pyrimidinyl, cyclopropyl, cyclobutyl, cyclohexyl, or oxetanyl, each of R^{2x} is optionally substituted with one, two, or three members selected from fluoro, chloro, bromo, or iodo; wherein each R^{2y} is independently hydrogen, methyl, ethyl, propyl, butyl; and wherein each R^{2z} is independently methyl, ethyl, propyl, or butyl.

11. The compound of any of claims 1-10, wherein R^3 is selected from hydrogen, methyl, ethyl, propyl, butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, or phenyl.

12. The compound of any of claims 1-11, wherein R^5 is hydrogen, methyl, ethyl, or propyl.

13. The compound of any of claims 1-12, R^5 and R^3 together with the atoms to which they are attached optionally form pyrrolidinyl.

14. The compound of any of claims 1-13, wherein R^4 is a monocyclic heteroaryl having at least two nitrogen atoms, wherein R^4 is optionally substituted with two or three

members independently selected from bromo, chloro, fluoro, cyano, methyl, ethyl, propyl, and -NH_2.

15. The compound of any of claims 1-14, wherein R^4 is bicyclic heteroaryl having at least one aromatic ring, at least two nitrogen atoms, and at least one additional heteroatom selected from N, O, or S; wherein R^4 is optionally substituted with two or three members independently selected from bromo, chloro, fluoro, cyano, methyl, ethyl, propyl, and -NH_2.

16. The compounds of any of claims 1-15, wherein the compound is an atropisomer.

17. A pharmaceutical composition comprises the compound of any of claims 1-16 and at least one pharmaceutically acceptable vehicle.

18. A method of treating a disease or condition in a human in need thereof comprises the administering to the human a therapeutically effective amount of the compound of any of claims 1-16, wherein the disease or condition is selected from cancer, hematologic malignancies, leukemias, lymphomas, myeloproliferative disorders, myelodysplastic syndromes, plasma cell neoplasms, solid tumor, inflammation, fibrosis, autoimmune disorders, allergic conditions, hypersensitivity, cardiovascular diseases, neurodegenerative diseases, renal disorders, viral infections, obesity, and autoimmune diseases.

19. The method of claim 18, wherein the disease or condition is selected from rheumatoid arthritis, osteoarthritis, atherosclerosis, psoriasis, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel disease, asthma, chronic obstructive airways disease, pneumonitis, dermatitis, alopecia, nephritis, vasculitis, atherosclerosis, Alzheimer's disease, hepatitis, primary biliary cirrhosis, sclerosing cholangitis, diabetes (including type I diabetes), acute rejection of transplanted organs, lymphomas, multiple myelomas, leukemias, pancreatic cancer, bladder cancer, colorectal cancer, breast cancer, prostate cancer, renal cancer, hepatocellular cancer, lung cancer, ovarian cancer, cervical cancer, rectum cancer, liver cancer, kidney cancer, stomach cancer, skin cancer, gastric cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancers, CNS cancers (e.g., neuroblastoma), brain tumors (*e.g.*, glioma, anaplastic oligodendroglioma, adult glioblastoma multiforme, and adult anaplastic astrocytoma), bone cancer, or soft tissue sarcoma. In some embodiments, the solid

tumor is non-small cell lung cancer, small-cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, pancreatic cancer, prostate cancer, and breast cancer.

20. A method of inhibiting the activity of a phosphatidylinositol 3-kinase polypeptide by contacting the polypeptide with the compound of any of claims 1-16.

21. A method of inhibiting excessive or destructive immune reactions or growth or a proliferation of cancer cells, comprising administering an effective amount of the compound of any of claims 1-16.

22. A kit comprises the compound of any of claims 1-16 or a label and/or instructions for use.

23. The compound, a pharmaceutically acceptable salt, isomer, or a mixture thereof of any of claims 1-16 for use in therapy.

24. The compound, a pharmaceutically acceptable salt, isomer, or a mixture thereof of any of claims 1-16 for use in a method of treating of any of claims 18-19.

25. Use of the compound, a pharmaceutically acceptable salt, isomer, or a mixture thereof of any of claims 1-16 for the manufacture of a medicament for treatment of a disease or condition of any of claims 18-19.