

POLO-LIKE KINASE 1 INHIBITORS**FIELD OF THE INVENTION**

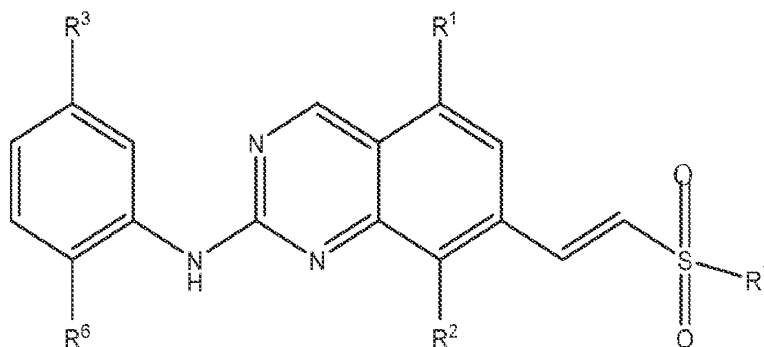
[0001] The present invention relates to inhibitors of polo-like kinase 1 ("PLK1"). In particular, the present invention relates to compounds that selectively inhibit the activity of PLK1, pharmaceutical compositions comprising a therapeutically effective amount of the compounds, and methods of use therefor, such as methods for treating PLK1-mediated diseases and disorders, such as cancer.

BACKGROUND OF THE INVENTION

[0002] *TP53* is the most frequently mutated and inactivated gene in cancer, resulting in a decrease in the levels of functional p53. Since existing approaches designed to directly target p53 have shown limited clinical success, there remains a high unmet medical need for new therapeutics to address cancers driven by changes to p53 biology.

SUMMARY OF THE INVENTION

[0003] Provided are compounds of Formula (I):



Formula (I)

wherein R¹, R², R³, R⁶, and R⁷ are as defined herein, and pharmaceutically acceptable salts thereof.

Also provided are pharmaceutical compositions comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient or elixir.

[0004] Provided are methods for treating PLK1-mediated diseases or disorders in a subject in need thereof, comprising administering a therapeutically effective amount of a compound of Formula (I) or a pharmaceutical salt thereof, or a pharmaceutical composition thereof.

[0005] Also provided herein is a use of a compound of Formula (I), or a pharmaceutically acceptable salt or thereof, as defined herein in the manufacture of a medicament for the inhibition of activity of PLK1.

[0006] Also provided herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined herein, in the manufacture of a medicament for the treatment of a PLK1-mediated disease or disorder.

DETAILED DESCRIPTION OF THE INVENTION

[0007] The present invention relates to inhibitors of polo-like kinase 1 ("PLK1"). In particular, the present invention relates to compounds that covalently inhibit the activity of PLK1, pharmaceutical compositions comprising a therapeutically effective amount of the compounds, and methods of use therefor, such as methods for treating plk1-mediated diseases and disorders, such as cancer.

PLK1

[0008] Polo-like kinase 1 (PLK1), a member of the polo subfamily of Serine/Threonine protein kinases, is important for a variety of cellular functions, including regulation of cell cycle progression and the DNA damage response (DDR). PLK1 overexpression, which undermines cellular checkpoints, thereby resulting in heightened cell proliferation, has been observed across a large spectrum of human cancers, solid tumors as well as hematologic, and has been found to be associated with poor clinical prognosis as well as resistance to chemotherapy. In contrast, PLK1 depletion or inhibition leads to mitotic arrest and DNA damage, often accompanied by cell death, and enhances the sensitivity of cancer cell viability to irradiation. The important role of PLK1 in cancer is widely accepted as unassailable.

[0009] As a component of the DDR, PLK1 plays a role in the oscillatory behavior in the activity of p53, which is a regulatory tumor suppressor protein important for DNA stability and known as the guardian of the genome. The kinase activity of PLK1 promotes proteasomal degradation of p53 through E3 ligases TOPORS and MDM2, with PLK1 depletion or inhibition resulting in elevated cellular levels of p53. In addition, active PLK1 can physically bind and inhibit p53 activity to transactivate the transcription of tumor suppressor genes. Polo-like kinase 3 (PLK3), another member of the polo subfamily of kinases, has an opposing role to PLK1 in p53 activity; PLK3-mediated phosphorylation of p53 increases its transactivation function.

[0010] While pan-PLK inhibitors can have off-setting effects on p53 function, PLK1-specific inhibitors, the PLK1-specific inhibitors of the present disclosure, can selectively increase p53 levels and activity. *TP53* is found to be mutated in ~50% of human cancers, more than any other gene, and mutations in *TP53* are among the most common emergent alterations in refractory cancers (e.g., see Hsiehchen et al., (2022) Nat. Comm. 13: 7477). Since no effective p53-based therapeutic has been successfully translated into clinical treatment, the PLK1-specific inhibitors of the present disclosure may be able to lead to therapeutic benefit by raising p53 levels in cancer cells, including but not limited to those that are p53-defective or p53-altered.

DEFINITIONS

[0011] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one skilled in the art to which this invention belongs. All patents, patent applications, and publications referred to herein are incorporated by reference to the extent they are consistent with the present disclosure. Terms and ranges have their generally defined definition unless expressly defined otherwise.

[0012] For simplicity, chemical moieties are defined and referred to throughout primarily as univalent chemical moieties (e.g., alkyl, aryl, etc.). Nevertheless, such terms may also be used to convey corresponding multivalent moieties under the appropriate structural circumstances clear to those skilled in the art. All atoms are understood to have their normal number of valences for bond formation (i.e., 4 for carbon, 3 for N, 2 for O, and 2, 4, or 6 for S, depending on the oxidation state of the S).

[0013] As used herein, a "PLK1" refers to the mammalian enzyme polo-like kinase 1.

[0014] As used herein, a "PLK1 inhibitor" refers to compounds of the present invention that are represented by Formula (I) as described herein. These compounds are capable of negatively modulating or inhibiting all or a portion of the enzymatic activity of PLK1 by forming a covalent adduct between the compound of Formula (I) and PLK1.

[0015] As used herein, the term "hydroxyl" refers to -OH.

[0016] As used herein, the term "hydroxyalkyl" refers to -alkylene-OH.

[0017] As used herein, the term "alkoxy" refers to -OC1-C3 alkyl.

[0018] The term "halogen" or "halo" as employed herein refers to chlorine, bromine, fluorine, or iodine.

[0019] The term "alkyl," as employed herein, refers to straight and branched chain aliphatic groups having from 1 to 12 carbon atoms. As such, "alkyl" encompasses C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, C₁₀, C₁₁ and C₁₂ groups. Examples of alkyl groups include, without limitation, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, and hexyl.

[0020] The term "alkylene" group is an alkyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups. Examples of alkylene groups include, without limitation, methylene, ethylene, propylene, and butylene.

[0021] The term "alkynyl," as employed herein, refers to straight and branched chain aliphatic groups comprising at least one carbon-carbon triple bond having from 2 to 6 carbon atoms. As such, "alkynyl" encompasses C₂, C₃, C₄, C₅, and C₆ groups. Examples of alkynyl groups include, without limitation, ethynyl, propynyl, butynyl, pentynyl and hexynyl.

[0022] The term "haloalkyl" refers to an alkyl chain in which one or more hydrogens have been replaced by a halogen. Exemplary haloalkyls are trifluoromethyl, difluoromethyl, fluorchloromethyl, and fluoromethyl.

[0023] The term "cycloalkyl," as employed herein, is a saturated and partially unsaturated cyclic hydrocarbon group having 3 to 12 carbons. As such, "cycloalkyl" includes C₃, C₄, C₅, C₆, C₇, C₈, C₉, C₁₀, C₁₁ and C₁₂ cyclic hydrocarbon groups. Examples of cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

[0024] An "aryl" group is a C₆-C₁₄ aromatic moiety comprising one to three aromatic rings. As such, "aryl" includes C₆, C₁₀, C₁₃, and C₁₄ cyclic hydrocarbon groups. An exemplary aryl group is a C₆-C₁₀ aryl group. Particular aryl groups include, without limitation, phenyl, naphthyl, anthracenyl, and fluorenyl. An "aryl" group also includes fused multicyclic (e.g., bicyclic) ring systems in which one or more of the fused rings is non-aromatic, provided that at least one ring is aromatic, such as indenyl.

[0025] A "heterocyclyl" or "heterocyclic" group is a mono- or bicyclic (fused or spiro) ring structure having from 3 to 12 atoms (3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 atoms), for example 4 to 8 atoms, wherein one or more ring atoms are independently -C(O)-, N, NR^A, O, or S, and the remainder of the ring atoms are quaternary or carbonyl carbons. Examples of heterocyclic groups include, without limitation, epoxy, oxiranyl, oxetanyl, azetidiny, aziridiny, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiophenyl, pyrrolidiny, piperidiny, piperaziny, imidazolidiny, thiazolidiny, thiatanyl, dithianyl, trithianyl, azathianyl, oxathianyl, dioxolanyl, oxazolidiny, oxazolidinonyl, decahydroquinoliny, piperidonyl, 4-piperidonyl, 1,4-diazapanyl, 1-methyl-1,4-diazapanyl, 1,4-dimethyl-1,4-di(11-oxidaneyl)-11,4,414-piperaziny, thiomorpholiny, dimethyl-morpholiny, and morpholiny. Specifically excluded from the scope of this term are compounds having adjacent ring O and/or S atoms.

[0026] As used herein, "L-heterocyclyl" refers to a heterocyclyl group covalently linked to another group via an alkylene linker.

[0027] As used herein, "an effective amount" of a compound is an amount that is sufficient to negatively modulate or inhibit the activity of PLK1.

[0028] As used herein, a "therapeutically effective amount" of a compound is an amount that is sufficient to ameliorate or, in some manner, reduce a symptom or stop or reverse the progression

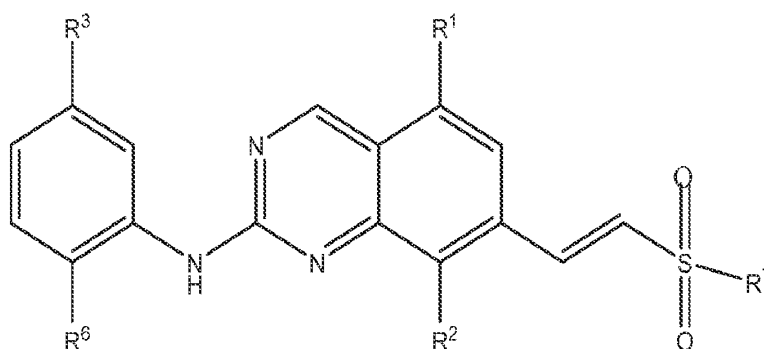
of a condition, e.g., cancer, or negatively modulate or inhibit the activity of PLK1. Such amount may be administered as a single dosage or may be administered according to a regimen, whereby it is effective.

[0029] As used herein, “treatment” means any manner in which the symptoms or pathology of a condition, disorder, or disease in a patient are ameliorated or otherwise beneficially altered.

[0030] As used herein, amelioration of the symptoms of a particular disorder by administration of a particular compound or pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient, that can be attributed to or associated with the administration of the composition.

COMPOUNDS

[0031] In certain aspects of the present disclosure, provided is a compound of Formula (I):



Formula (I)

wherein:

R¹ is hydrogen, halogen, hydroxy, aniline, C1-C6 alkyl, cycloalkyl, and haloalkyl;

R² is hydrogen, alkoxy, or -O-haloalkyl optionally substituted with one or more alkoxy groups;

R³ is hydrogen, heterocyclyl optionally substituted with one or more R⁴, -NH-L¹-N(R^AR^B), -NH-L²-cycloalkyl or -NH-L²-heterocyclyl, wherein the cycloalkyl or the heterocyclyl is optionally substituted with one or more R⁵;

R⁶ is OCF₃, SCH₃, cyclopropane, O-cyclopropane, OCH₃, CH₂CH₃, azetidine, or S(O)(O)CH₃;

R⁷ is NH₂, NHCH₃, or CH₃;

each R⁴ is independently C1-C4 alkyl, cyclopropyl, hydroxyalkyl, -L¹-N(R^AR^B), halogen, O, O-CH₃, NH₂, -C(O)O-t-butyl; -L³-aryl; or -L⁴-heterocyclyl;

each R⁵ is independently C1-C4 alkyl, N(CH₃)(CH₃), or heterocyclyl optionally substituted with aryl;

each L¹ is C1-C4 alkylene;

each L² is a bond or C1-C4 alkylene;

each L³ is -CH₂-O-CH₂-;

each L⁴ is a bond or methylene;

each R^A is hydrogen or C1-C3 alkyl;

each R^B is hydrogen or C1-C3 alkyl;

and pharmaceutically acceptable salts thereof.

[0032] In certain aspects for compounds of Formula (I), R¹ is halogen. In one embodiment, the halogen is chlorine, fluorine, or bromine.

[0033] In certain aspects for compounds of Formula (I), R¹ is hydroxy.

[0034] In certain aspects for compounds of Formula (I), R¹ is C1-C6 alkyl. In one embodiment, the C1-C6 is alkyl methyl, ethyl, or isopropyl.

[0035] In certain aspects for compounds of Formula (I), R¹ is cycloalkyl. In one embodiment, the cycloalkyl is cyclopropyl.

[0036] In certain aspects for compounds of Formula (I), R¹ is haloalkyl. In one embodiment, the haloalkyl is fluoromethyl, difluoromethyl, or trifluoromethyl.

[0037] In certain aspects for compounds of Formula (I), R^1 is aniline. In one embodiment, the aniline is NH_2 .

[0038] In certain aspects for compounds of Formula (I), R^2 is alkoxy. In one embodiment, the alkoxy is methoxy or propoxy.

[0039] In certain aspects for compounds of Formula (I), R^2 is -O-haloalkyl. In one embodiment, the haloalkyl is difluoromethyl.

[0040] In certain aspects for compounds of Formula (I), R^3 is a heterocyclyl optionally substituted with one or more R^4 .

[0041] In one embodiment, the heterocyclyl is 1,4-diazapanyl, 1-methyl-1,4-diazapanyl or 1,4-dimethyl-1,4-di(11-oxidaneyl)-114,414-piperaziny1.

[0042] In another embodiment, the heterocyclyl is pyrrolidinyl, piperidinyl, or piperaziny1, each optionally substituted with one or more R^4 , wherein R^4 is C1-C4 alkyl, hydroxyalkyl, $-L^1-N(R^A R^B)$, $-C(O)O-t-butyl$, $-L^3-aryl$, or $-L^4-heterocyclyl$.

[0043] In one embodiment, the heterocyclyl is pyrrolidinyl substituted with one R^4 , and R^4 is $L^4-heterocyclyl$, wherein L^4 is methylene, and the heterocyclyl is pyrrolidinyl.

[0044] In another embodiment, the heterocyclyl is piperidinyl substituted with one R^4 , and R^4 is $L^4-heterocyclyl$, wherein L^4 is a bond and the heterocyclyl is pyrrolidinyl. In one embodiment, the heterocyclyl is piperaziny1 and R^4 is C1-C4 alkyl, hydroxyalkyl, $-L^1-N(R^A R^B)$, $-C(O)O-t-butyl$; or $-L^3-aryl$.

[0045] In one embodiment, the piperaziny1 is substituted with one R^4 , and R^4 is C1-C4 alkyl, wherein the C1-C4 alkyl is methyl or ethyl.

[0046] In one embodiment, the piperaziny1 is substituted with one R^4 , and R^4 is $-L^1-N(R^A R^B)$.

[0047] In one embodiment, the piperaziny1 is substituted with one R^4 , and R^4 is $-C(O)O-t-butyl$.

[0048] In another embodiment, the piperaziny1 is substituted with two R^4 groups, wherein one R^4 group is C1-C4 alkyl, and the second R^4 group is hydroxyalkyl or $-L^3-aryl$.

[0049] In certain aspects for compounds of Formula (I), R^3 is $-NH-L^1-N(R^A R^B)$.

[0050] In one embodiment, L^1 is propylene, and R^A and R^B are each methyl.

[0051] In one embodiment, L^1 is propylene, and R^A and R^B are each ethyl.

[0052] In certain aspects for compounds of Formula (I), R^3 is $-NH-L^2$ -heterocyclyl, wherein the heterocyclyl is optionally substituted with one or more R^5 .

[0053] In one embodiment, L^2 is a bond, and the heterocyclyl is pyrrolidinyl optionally substituted with one or more R^5 .

[0054] In one embodiment, the pyrrolidinyl is substituted with one R^5 , wherein R^5 is ethyl or isopropyl. In another embodiment, L^2 is a C1-C4 alkylene, and the heterocyclyl is pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl, each optionally substituted with one or more R^5 .

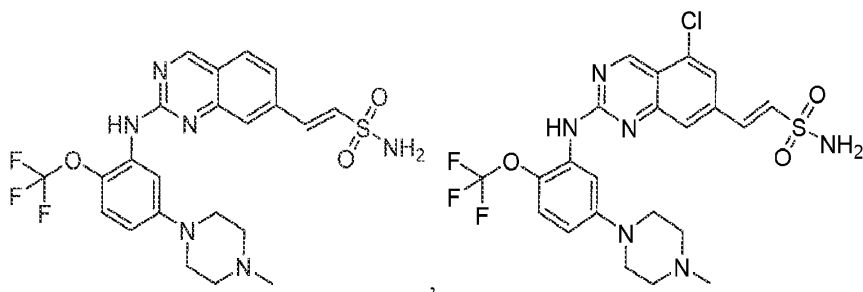
[0055] In one embodiment, L^2 is ethylene or propylene.

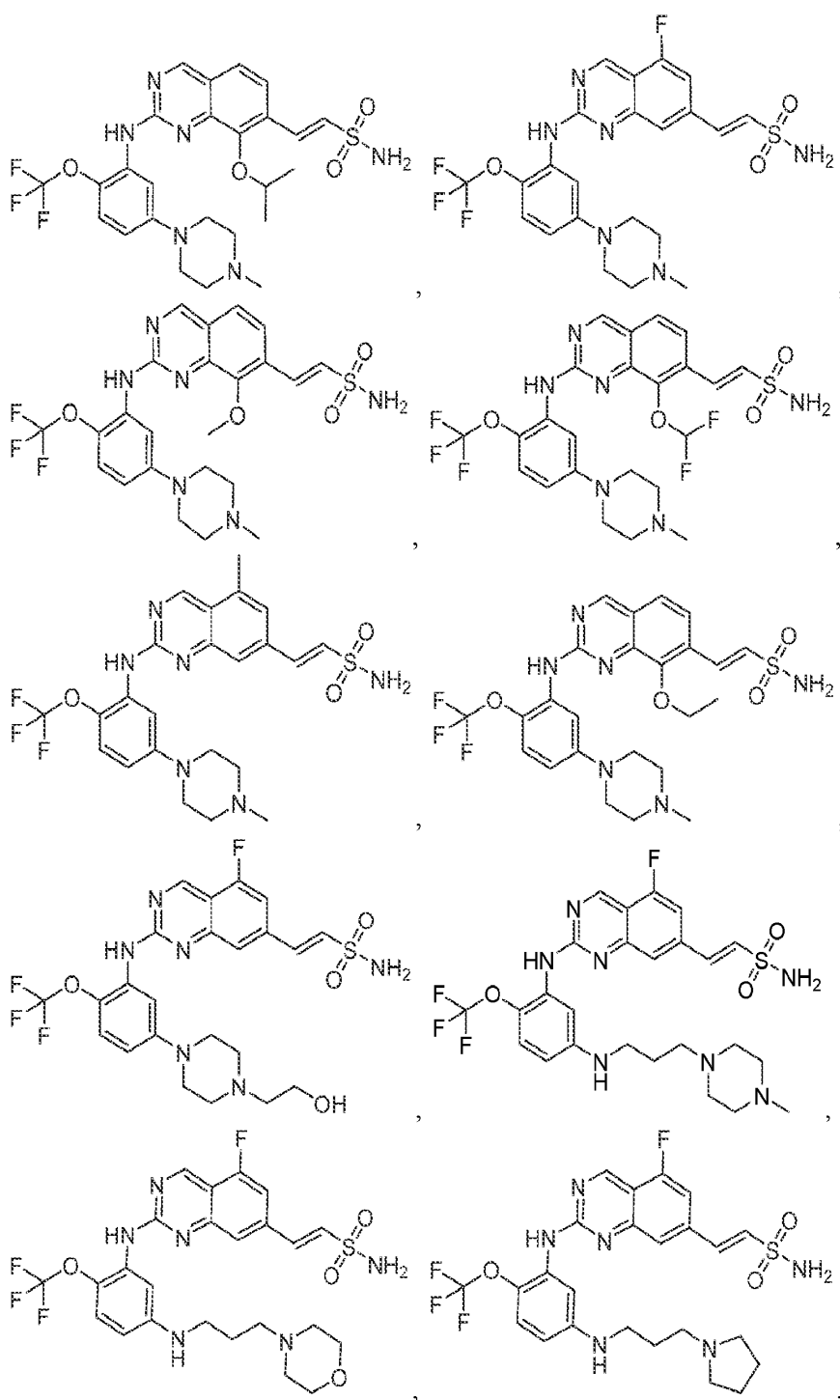
[0056] In one embodiment, the heterocyclyl is piperazinyl optionally substituted with one or more R^5 , wherein R^5 is methyl.

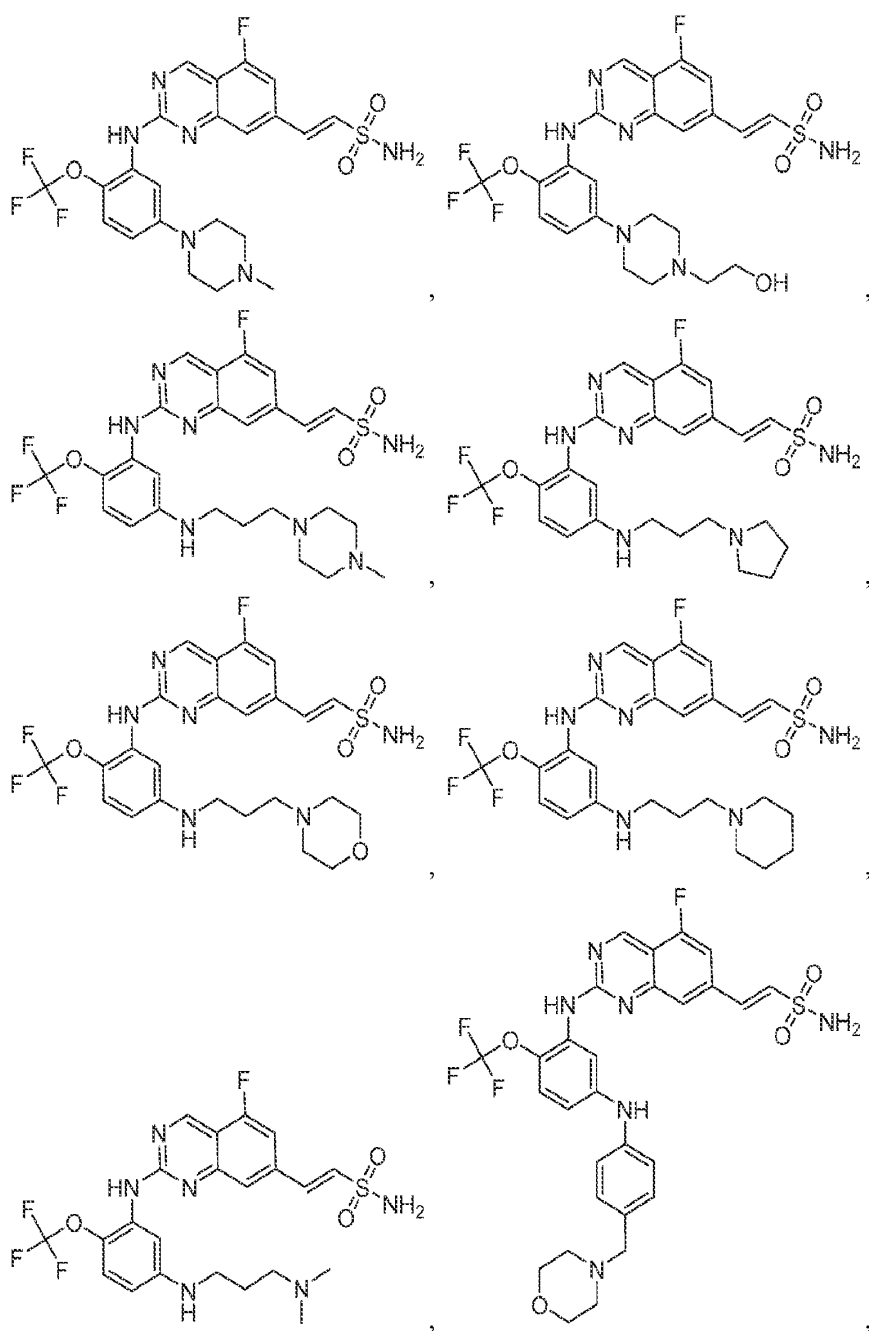
[0057] In another embodiment, L^2 is dimethylethylene, and the heterocyclyl is pyrrolidinyl, piperidinyl, or morpholinyl.

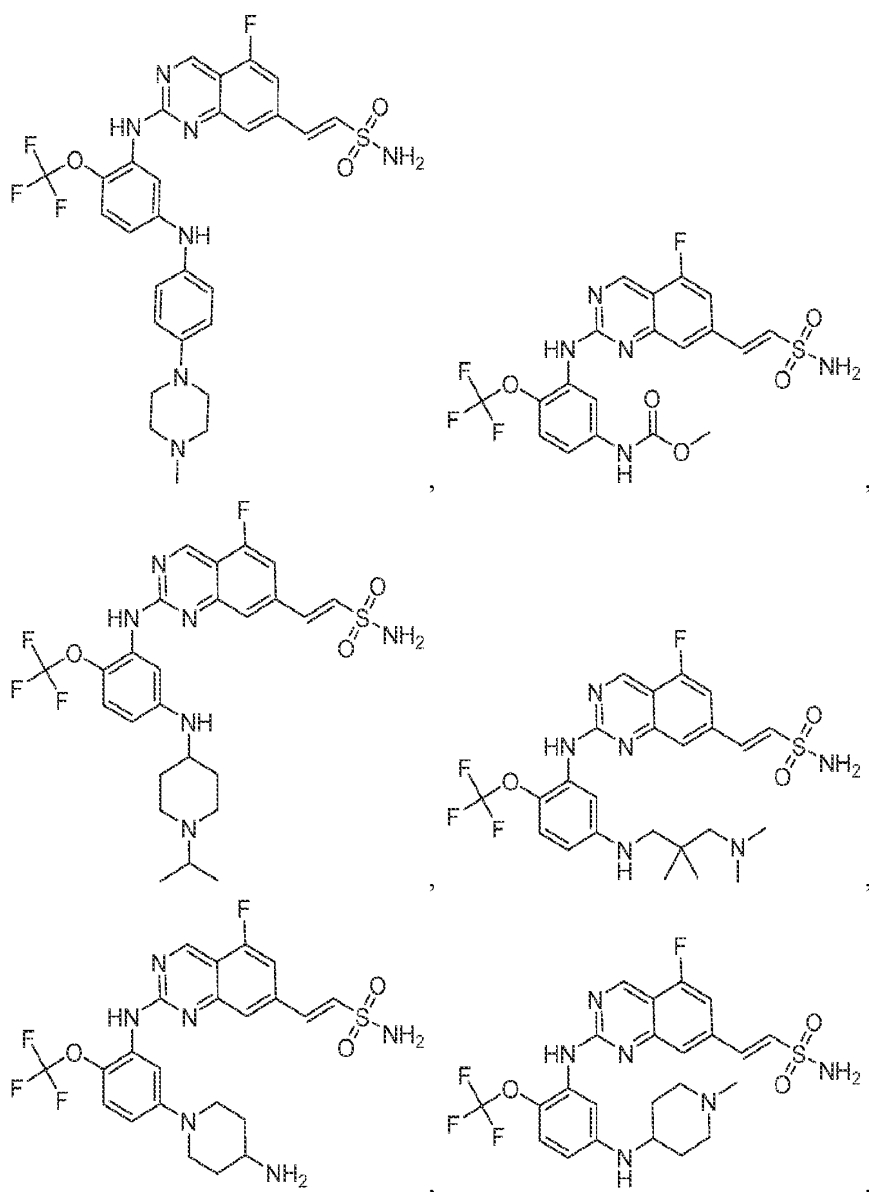
[0058] In another embodiment, L^2 is dimethylethylene, and the heterocyclyl is piperazinyl optionally substituted with one or more R^5 , wherein R^5 is methyl.

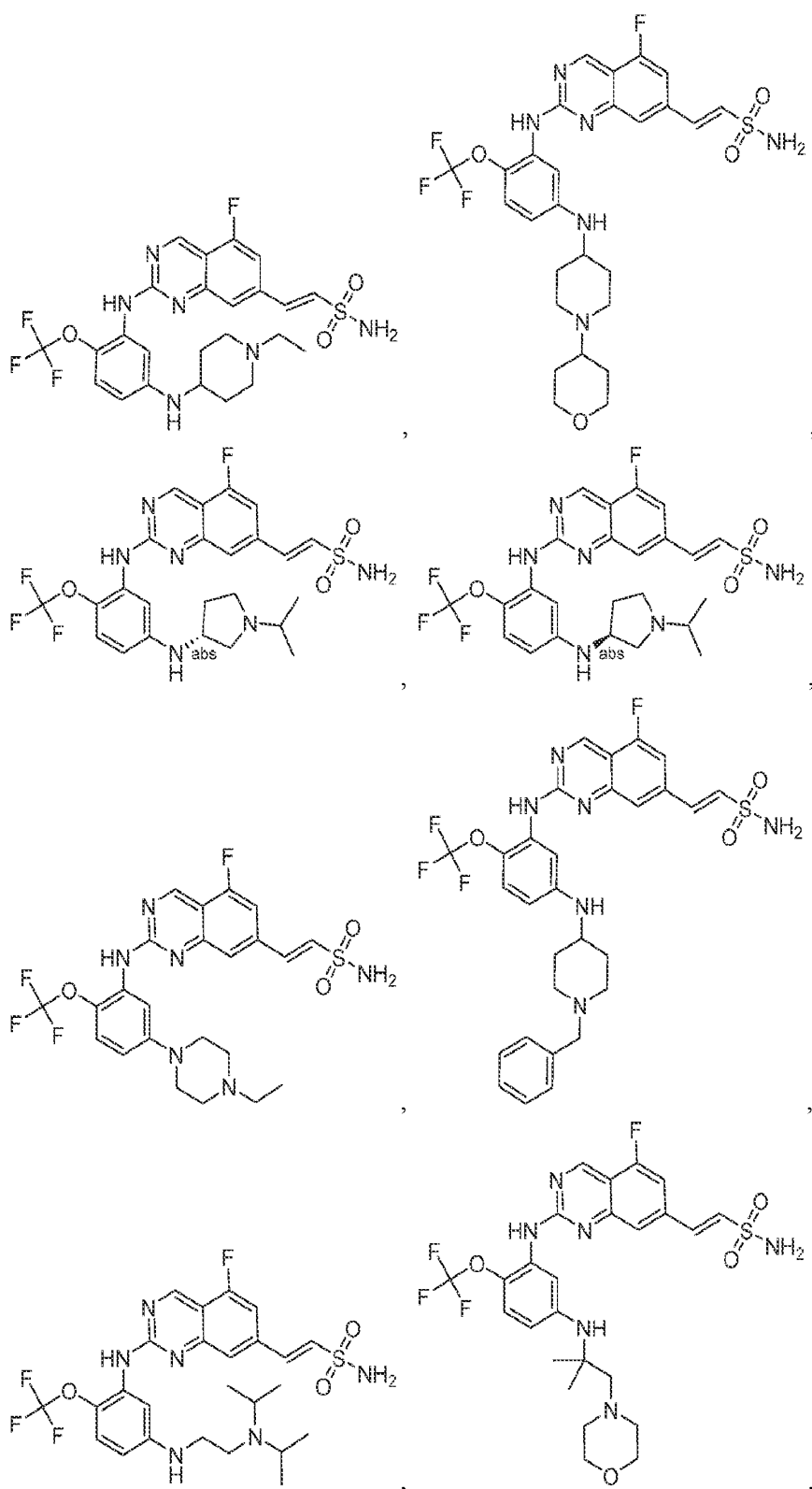
[0059] In certain aspects for compounds of Formula (I), the compound of Formula (I) is:

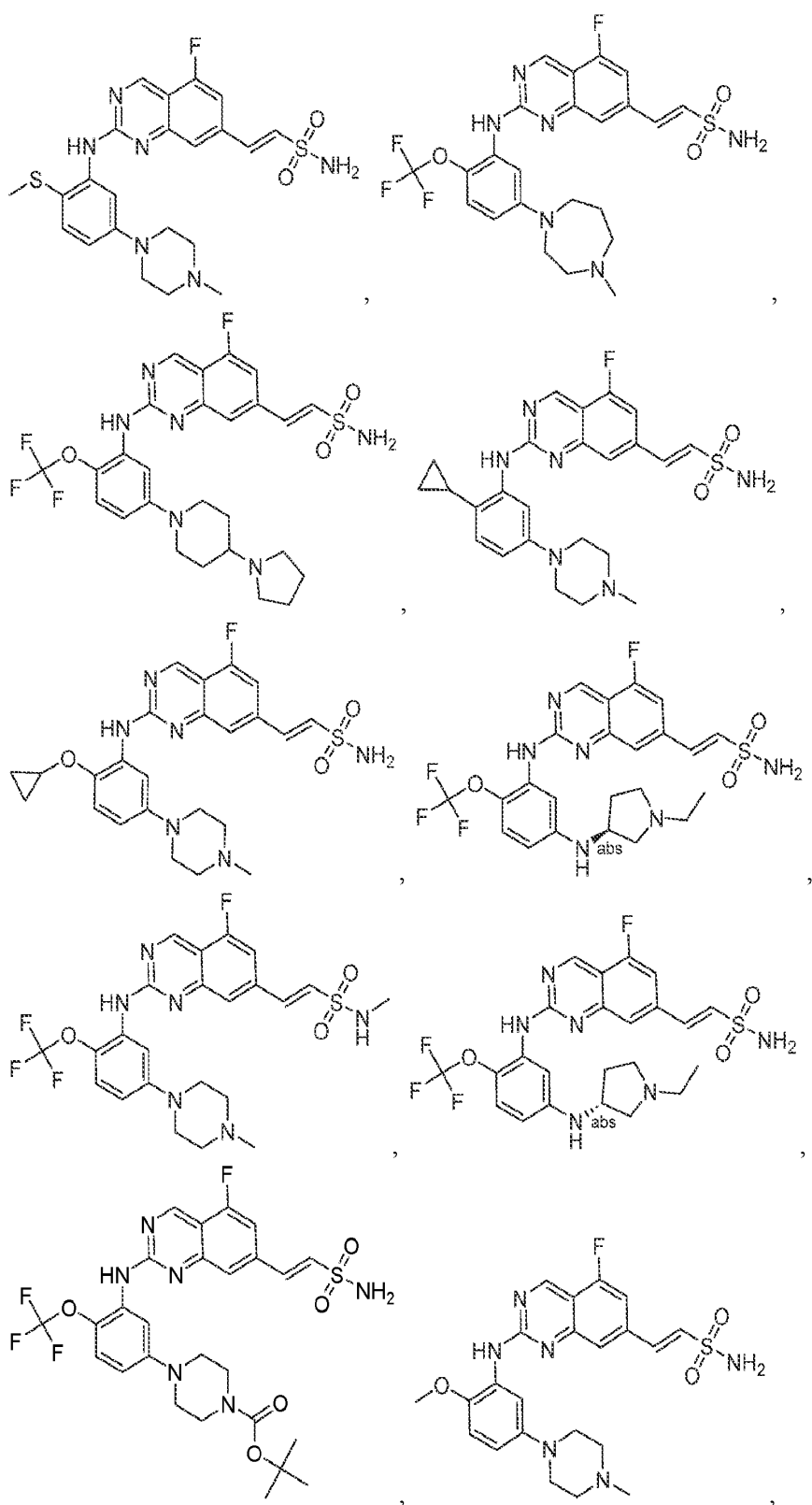


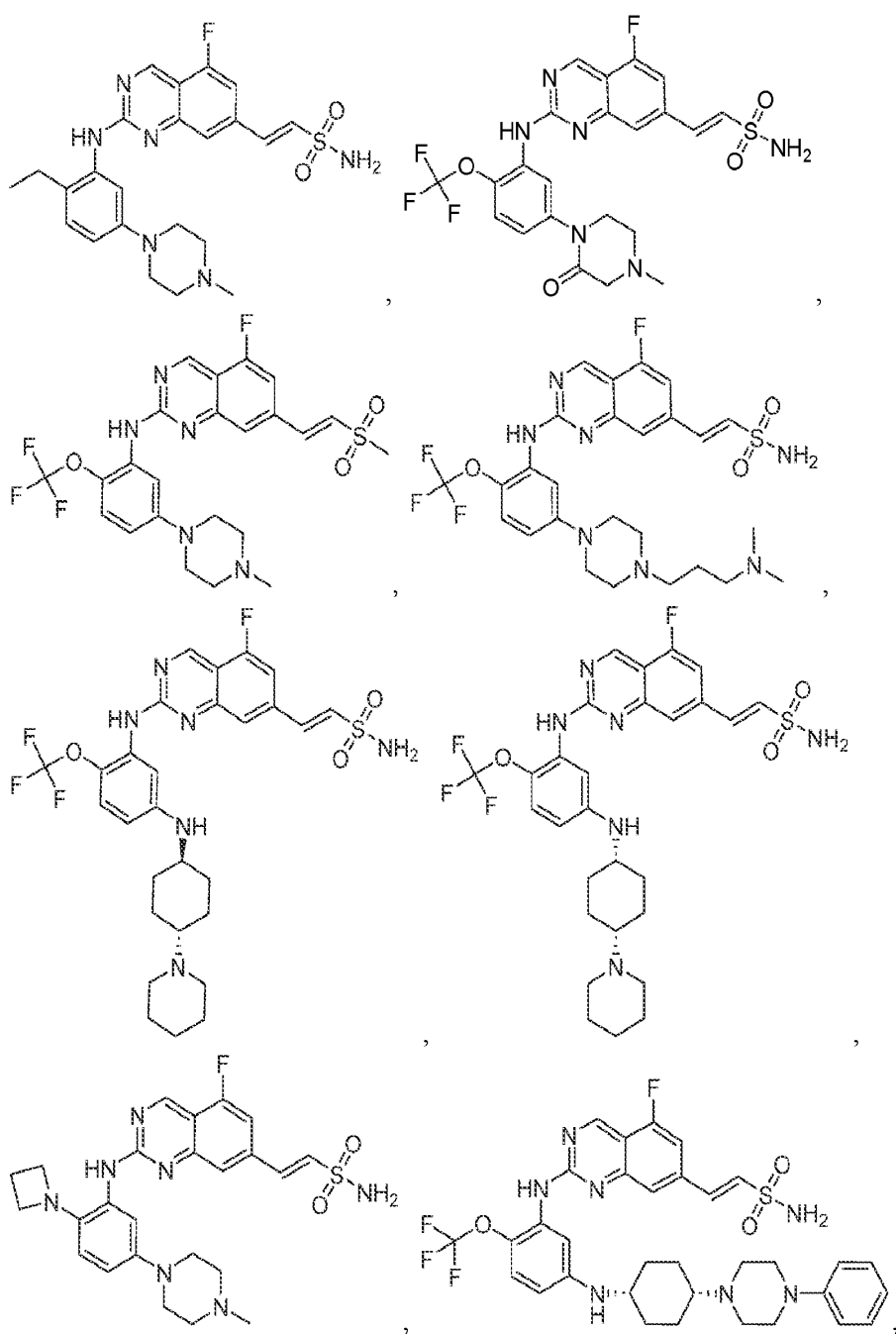


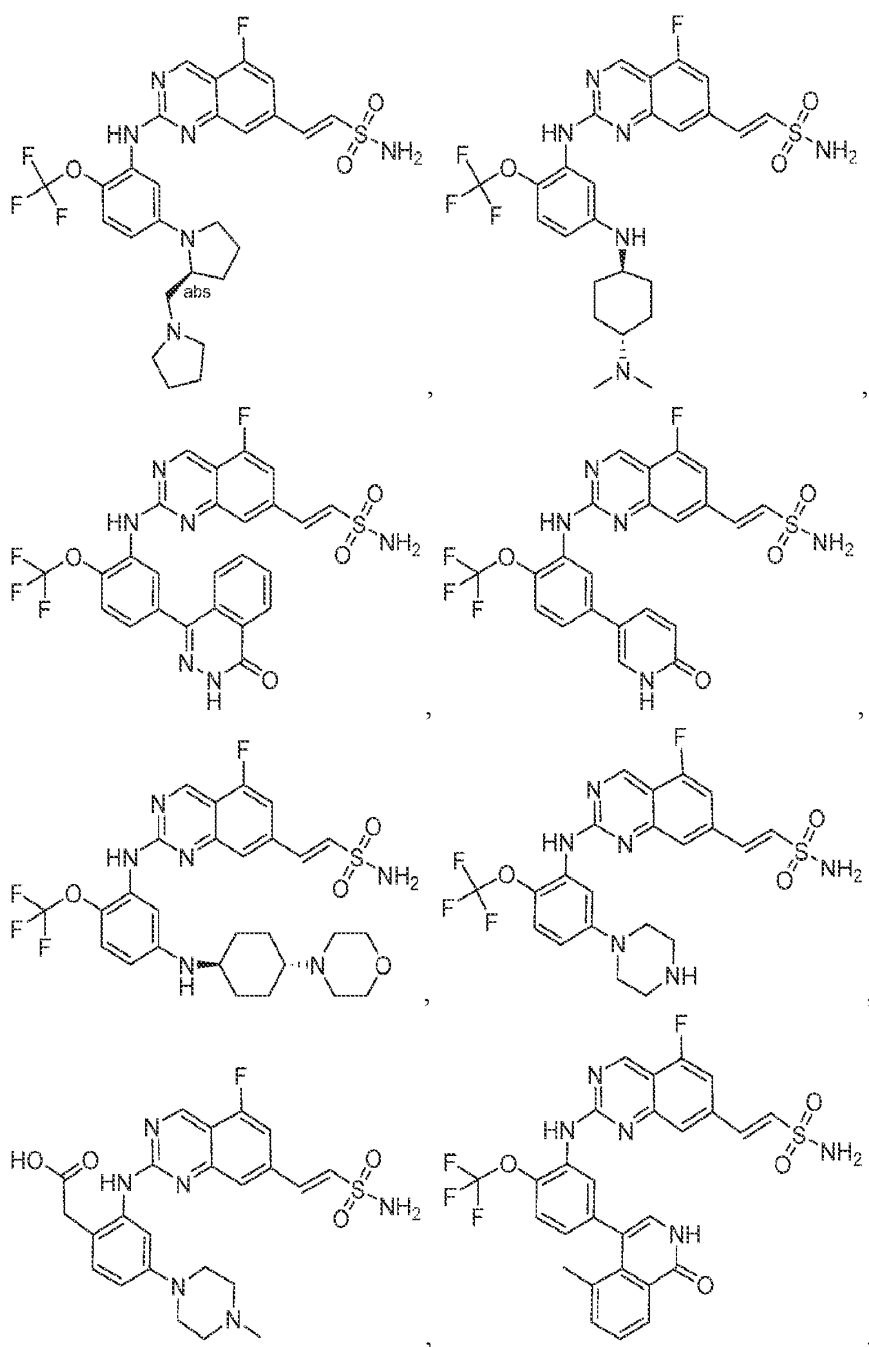


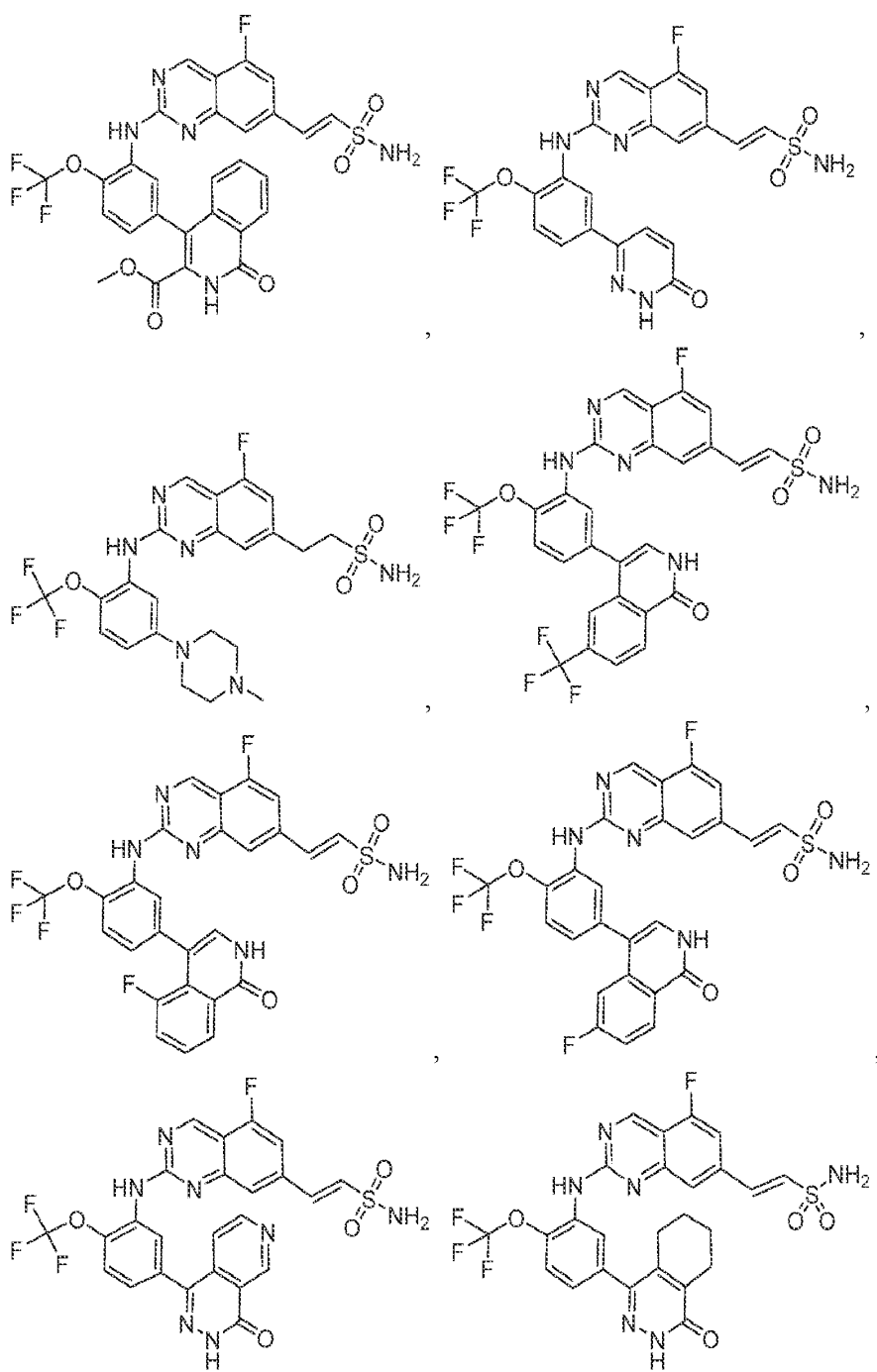


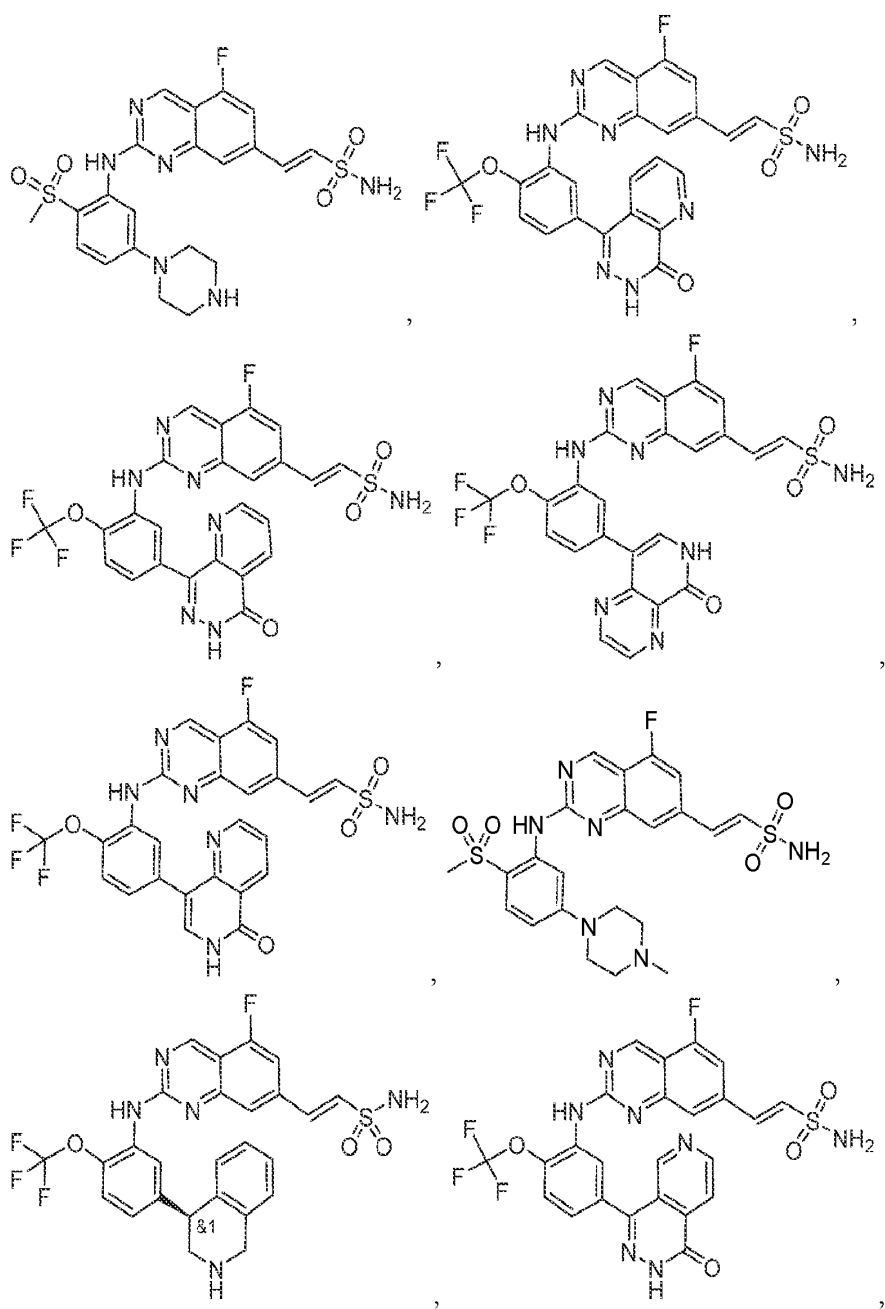


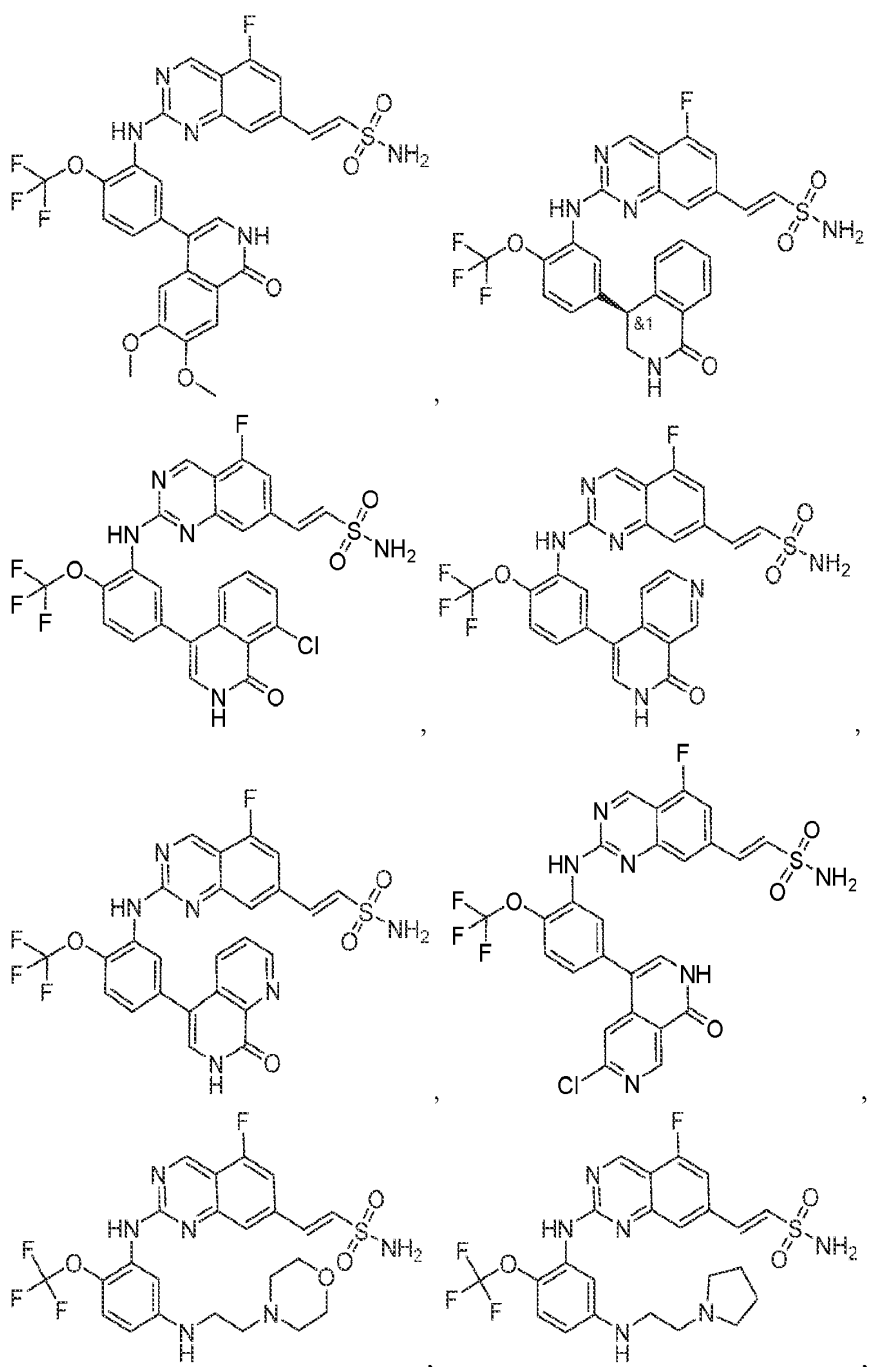


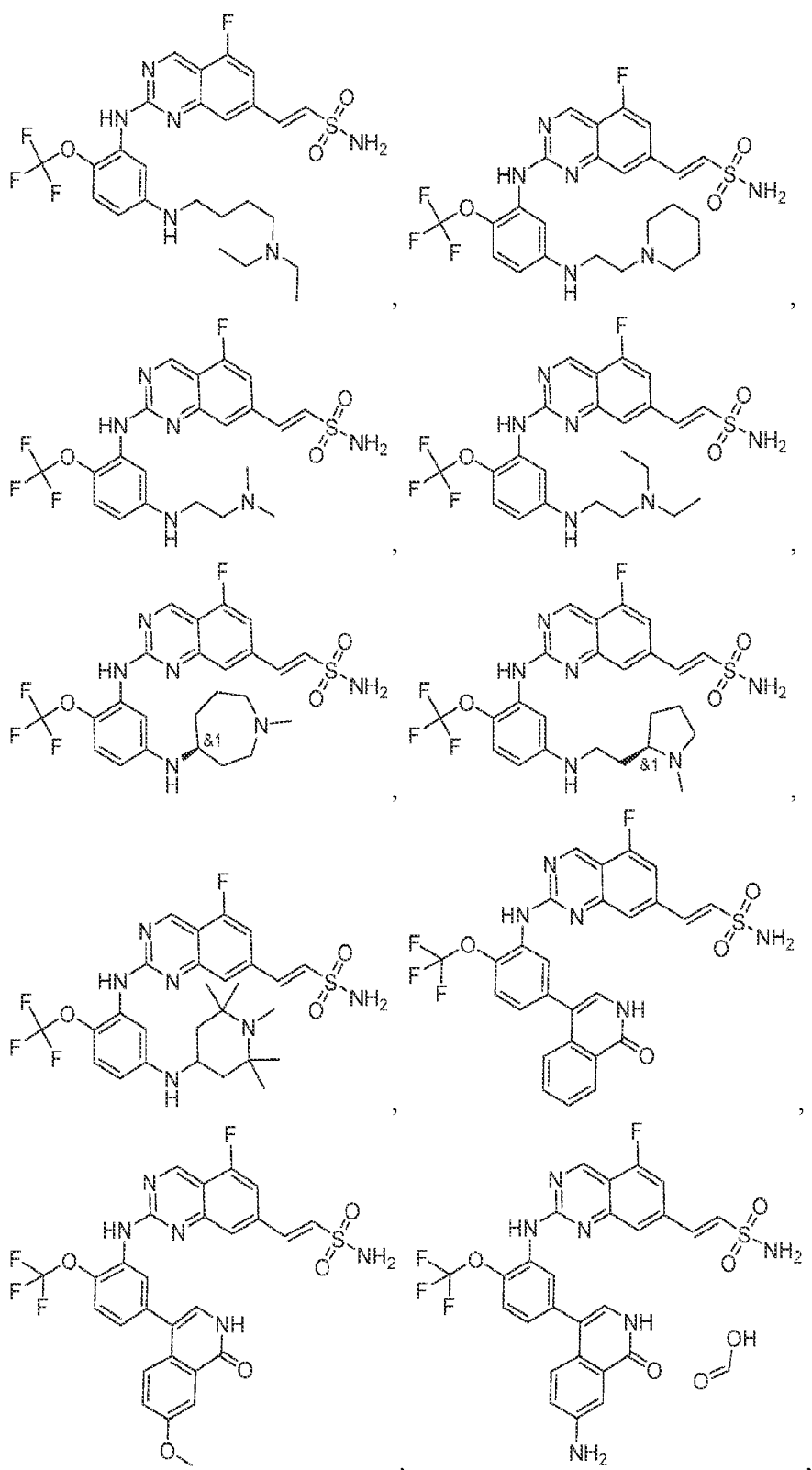


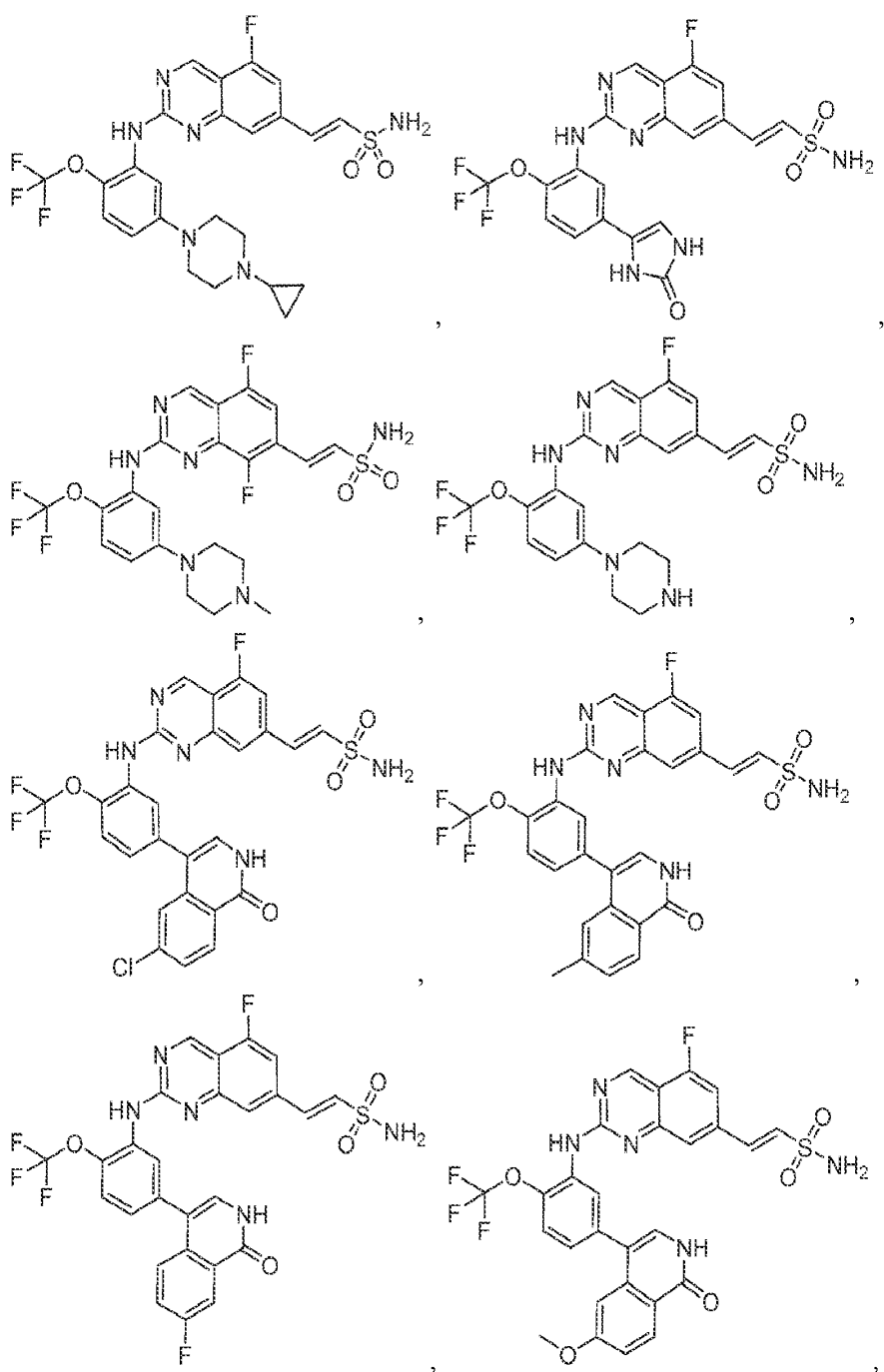


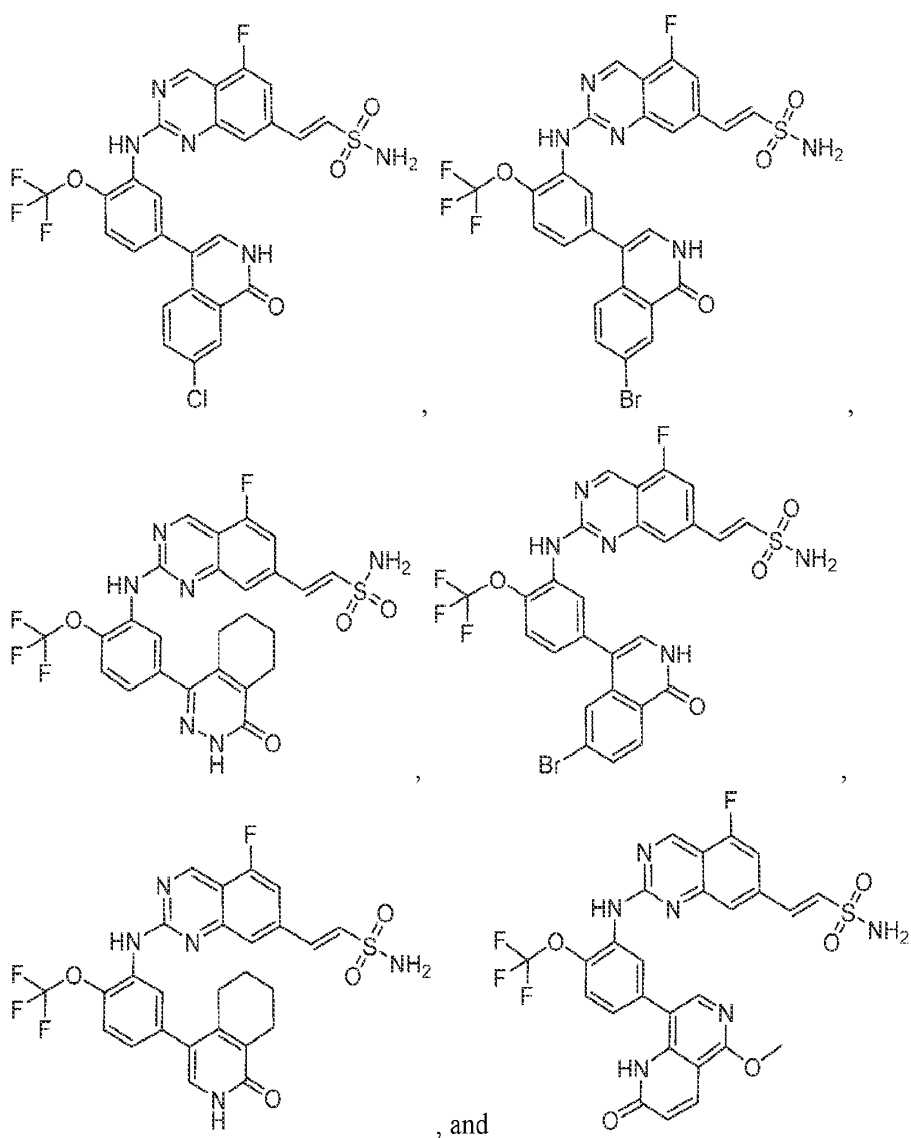












[0060] The compounds of Formula (I) and pharmaceutically acceptable salts thereof may be formulated into pharmaceutical compositions.

[0061] The invention also encompasses intermediates used in preparation of the compounds of the invention. The intermediates are disclosed in the Schemes and the Examples of the invention.

[0062] The compounds disclosed herein include all pharmaceutically acceptable isotopically-labeled compounds, in which one or more atoms of the compounds disclosed herein are replaced

by atoms having the same atomic number and an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the compounds disclosed herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, chlorine, and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , ^{123}I , and ^{125}I . Such radiolabelled compounds could be useful in determining or measuring the effectiveness of the compounds, for example, by characterizing binding affinities and kinetics of binding to PLK1 and other modes of action. Certain compounds of the disclosure, when labeled with radioactive isotopes, such as tritium, ^3H , and carbon-14, ^{14}C , could also be useful in characterizing drug distribution and in vivo tissue expression of PLK1.

[0063] When labeled with heavier isotopes such as deuterium, ^2H , compounds disclosed herein may exhibit therapeutic advantages such as greater metabolic stability, resulting in longer in-vivo half-lives, which in turn could reduce the therapeutic dosing requirements.

[0064] In order to better characterize substrate receptor occupancy or tissue expression in live specimens statically or longitudinally, replacing atoms of compounds disclosed herein with positron emitting isotopes, such as ^{11}C , ^{14}F , ^{15}O , and ^{13}N , may allow for enabling Positron Emission Tomography (PET) studies.

[0065] Isotopically-labeled compounds, as disclosed herein, can be prepared by conventional techniques known to those skilled in the art or by processes that are analogous to those described in the associated examples and schemes using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[0066] Some of the compounds disclosed herein may exist as stereoisomers. The compounds disclosed herein include all stereoisomers, both as pure individual stereoisomer preparations as well as preparations enriched of each, and both the racemic mixtures of such stereoisomers and the individual diastereomers and enantiomers that may be separated according to methods known to those skilled in the art. Additionally, the compounds disclosed herein include all individual tautomeric states of the compounds and mixtures thereof.

PHARMACEUTICAL COMPOSITIONS

[0067] In another aspect, the invention provides pharmaceutical compositions comprising a PLK1 inhibitor according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent. Compounds of the invention may be formulated by any method well known in the art and may be prepared for administration by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, subcutaneous, intranasal, intratracheal, or intrarectal. In certain embodiments, compounds of the invention are administered intravenously in a hospital setting. In certain other embodiments, administration may preferably be done by oral route.

[0068] The characteristics of the carrier will depend on the route of administration. As used herein, the term “pharmaceutically acceptable” means a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism, and that does not interfere with the effectiveness of the biological activity of the active ingredient(s). Thus, compositions according to the invention may contain, in addition to the inhibitor, diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well-known in the art. The preparation of pharmaceutically acceptable formulations is described in, e.g., Remington’s Pharmaceutical Sciences, 18th Edition, ed. A. Gennaro, Mack Publishing Co., Easton, Pa., 1990.

[0069] As used herein, the term pharmaceutically acceptable salts refers to salts that retain the desired biological activity of the above-identified compounds and exhibit minimal or no undesired toxicological effects. Examples of such salts include but are not limited to acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, and polygalacturonic acid. The compounds can also be administered as pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include the quaternary ammonium salt of the Formula NR^+Z^- , wherein R is hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate,

succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamate, mandelate, benzyloate, and diphenylacetate).

[0070] The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount without causing serious toxic effects in the patient treated. A dose of the active compound for all of the above-mentioned conditions is in the range from about 0.01 to 300 mg/kg, preferably 0.1 to 100 mg/kg per day, more generally 0.5 to about 25 mg per kilogram body weight of the recipient per day.

[0071] A typical topical dosage will range from 0.01-3 % wt/wt in a suitable carrier. The effective dosage range of the pharmaceutically acceptable derivatives can be calculated based on the weight of the parent compound to be delivered. If the derivative exhibits activity in itself, the effective dosage can be estimated as above using the weight of the derivative or by other means known to those skilled in the art.

[0072] The pharmaceutical compositions comprising compounds of the present invention may be used in the methods described herein.

METHODS OF USE

[0073] In yet another aspect, the invention provides methods for inhibiting PLK1 activity in a cell, comprising contacting the cell in which inhibition of PLK1 activity is desired with a therapeutically effective amount of a compound of Formula (I), pharmaceutically acceptable salts thereof or pharmaceutical compositions containing the compound or pharmaceutically acceptable salt thereof.

[0074] The compositions and methods provided herein are deemed particularly useful for inhibiting PLK1 activity in a cell, including cells that overexpress PLK1. In one embodiment, a cell in which inhibition of PLK1 activity is desired is contacted with an effective amount of a compound of Formula (I) to negatively modulate the activity of a PLK1 kinase. In other embodiments, a therapeutically effective amount of pharmaceutically acceptable salt or pharmaceutical compositions containing the compound of Formula (I) may be used. In certain embodiments, contacting the cell with an effective amount or a therapeutically effective amount of a compound of Formula (I) occurs in vivo. In certain embodiments, contacting the cell with an

effective amount or a therapeutically effective amount of a compound of Formula (I) occurs in vitro. In one embodiment, the therapeutically effective amount of the compound of Formula (I) is between about 0.01 to 300 mg/kg per day. In one embodiment, the therapeutically effective amount of the compound of Formula (I) is between about 0.1 to 100 mg/kg per day.

[0075] In one embodiment, methods for treating a patient having PLK1-mediated disease or disorder, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, alone or combined with a pharmaceutically acceptable carrier, excipient or diluents are provided.

[0076] In one embodiment, the PLK1-mediated disease or disorder results from overexpression of PLK1. In one embodiment, the PLK1-mediated disease or disorder is cancer. In one embodiment, the PLK1-mediated cancer is a *TP53* - or Ras-mutated cancer. In one embodiment, PLK1-mediated cancer is melanoma, non-small cell lung cancer (NSCLC), carcinomas of the head and neck, esophageal, pharynx, breast, liver, endometrium, colorectum, ovary, pancreas or prostate.

[0077] By negatively modulating the activity of PLK1, particularly in cases of cells overexpressing the PLK1 enzyme, the methods are designed to modulate the activity of PLK1, in some embodiments, to treat certain PLK1-mediated diseases or disorders, such as cancer. The cells/patient may be contacted in a single dose or multiple doses in accordance with a particular treatment regimen to induce the desired negative modulation of PLK1. For example, hematological or solid cancers may be monitored using well-known methods, including blood draws, X-rays, or other imaging techniques, such as CT scans or MRI scans, to assess the effectiveness of treatment, and dosages may be adjusted accordingly by the attending medical practitioner.

[0078] The concentration and route of administration to the patient may vary depending on the severity of the disease. The compounds, pharmaceutically acceptable salts thereof, and pharmaceutical compositions comprising such compounds and salts also may be co-administered with other compounds or used in combination with other treatments, such as surgical intervention, either as an adjuvant prior to surgery or post-operatively. The degree of PLK1

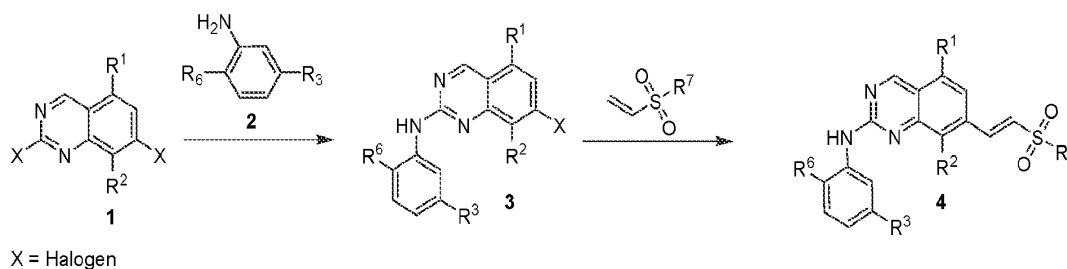
inhibition may be monitored in the patient using well-known assay methods, including those in Example A, to assess the effectiveness of treatment.

GENERAL REACTION SCHEMES AND EXAMPLES

[0079] The compounds of the present invention may be prepared using commercially available reagents using the synthetic methods and reaction schemes described herein or using other reagents and conventional methods well known to those skilled in the art.

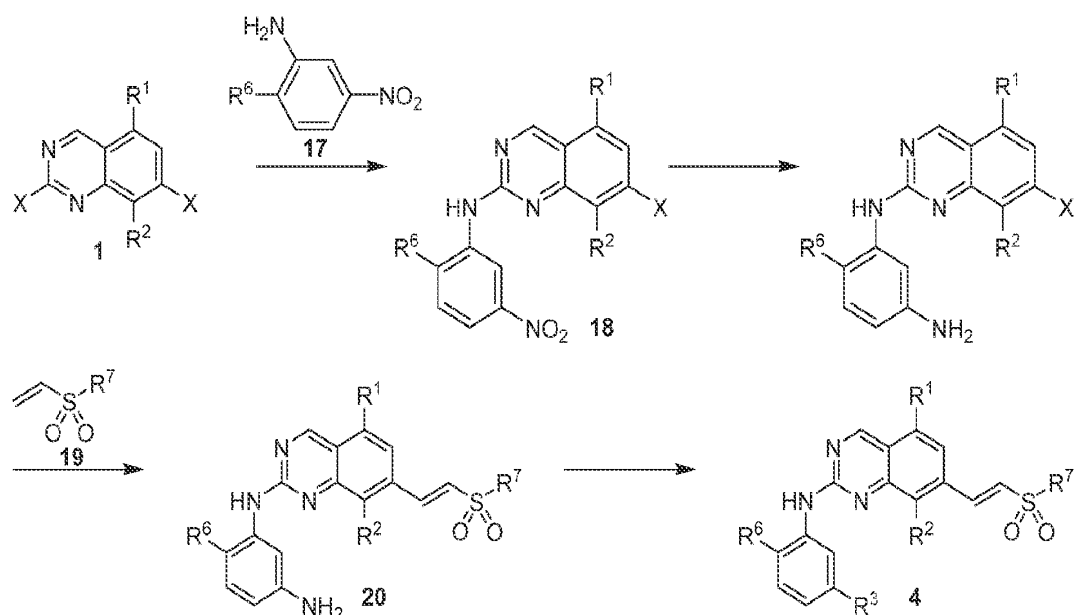
[0080] For instance, intermediates for preparing compounds and compounds of Formula (I) of the present invention may be prepared according to General Reaction Schemes I – III:

GENERAL REACTION SCHEME I



[0081] Compounds of Formula (I) wherein R^1 is hydrogen, halogen, hydroxy, C1-C6 alkyl, cycloalkyl, haloalkyl, aniline, R^2 is hydrogen, alkoxy, or -O-haloalkyl optionally substituted with one or more R^4 , and R^3 is heterocyclyl optionally substituted with one or more R^4 , -NH-L¹-N($R^A R^B$), or -NH-L²-heterocyclyl, wherein the heterocyclyl is optionally substituted with one or more R^5 may be prepared according to General Reaction Scheme I. Compound **3** is an example of Formula (I) wherein R^1 and R^2 is H and R^3 is heterocyclyl optionally substituted with one or more R^4 , -NH-L¹-N($R^A R^B$), or -NH-L²-heterocyclyl, wherein the heterocyclyl is optionally substituted with one or more R^5 . A dihaloquinazoline **1** is treated with an aniline **2**, for example, under S_NAr conditions at elevated temperature, to form anilinoquinazoline **3**, which is subjected to Pd catalyzed cross-coupling conditions, for example, Heck conditions with vinyl sulfone **19** to afford the anilinoquinazoline styryl sulfone **4**. Anilinoquinazoline styryl sulfone **4** is separated by chromatography, reverse phase HPLC to furnish the desired compound **4** of Formula (I).

GENERAL REACTION SCHEME II:



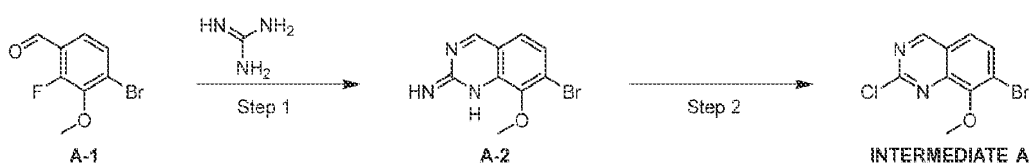
[0082] Compounds of Formula (I) wherein **R¹** is hydrogen, halogen, hydroxy, C1-C6 alkyl, cycloalkyl, haloalkyl, aniline, and **R²** is hydrogen, alkoxy, or -O-haloalkyl optionally substituted with one or more **R⁴**, **R³** is heterocyclyl optionally substituted with one or more **R⁴**, -NH-L¹-N(R^AR^B), or -NH-L²-heterocyclyl, wherein L¹, L², R^A and R^B is defined in the description and the heterocyclyl is optionally substituted with one or more **R⁵**, may be prepared according to General Reaction Scheme II. Compound **3** is an example of Formula (I) wherein **R¹** is hydrogen, halogen, hydroxy, C1-C6 alkyl, cycloalkyl, haloalkyl, aniline, and **R²** is hydrogen, alkoxy, or -O-haloalkyl optionally substituted with one or more **R⁴**. The dihaloquinazoline **1** is subjected to S_NAr conditions with, for example, nitroaniline **17** and weak acid at elevated temperature, and the resulting nitroanilinoquinazoline **18** is subjected to reducing conditions for example $Fe(III)Cl/HCl$ to furnish aminoanilinoquinazoline **20**. Aminoanilinoquinazoline **20** is subjected to Pd-catalyzed cross-coupling conditions, for example, Heck conditions with vinyl sulfone **19** to afford anilinoquinazoline styryl sulfone **20**. Styryl sulfone **20** is subjected to Buchwald cross-coupling conditions, for example, with a palladium catalyst and an aryl halide or reductive amination conditions with an alkyl halide or aldehyde for example, with sodium cyanoborohydride to provide desired product

4. The crude mixture of **4** is separated by chromatography, reverse phase HPLC to furnish the desired compound **4** of Formula (I).

INTERMEDIATES

[0083] The following intermediate may be used in the preparation of compounds of Formula (I).

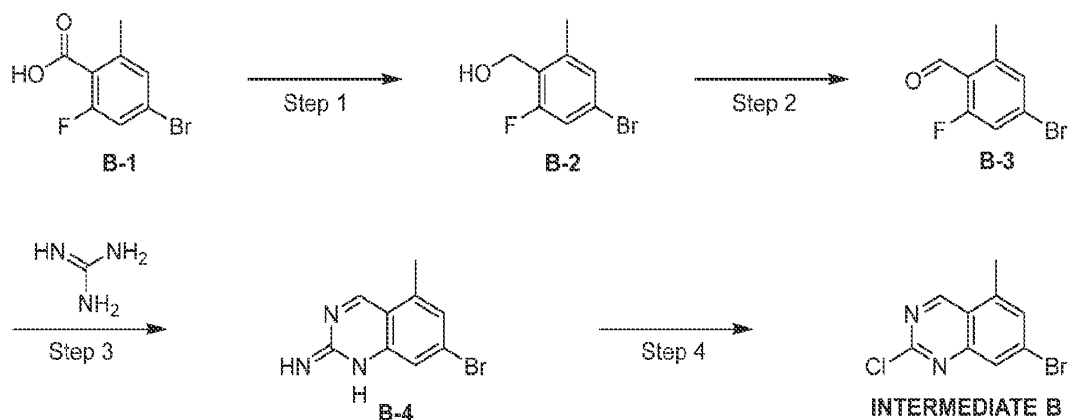
INTERMEDIATE A



[0084] **Step 1:** The solution of **A-1**, 4-bromo-2-fluoro-3-methoxybenzaldehyde (300 mg, 1.29 mmol, 1 eq) and carbonic acid; guanidine (186 mg, 1.03 mmol, 0.8 eq) in DMA (3 mL) was stirred at 140 °C for 4 h. H₂O (3 mL) was added to the mixture. The mixture was filtered, and the filter cake was dried under reduced pressure to give a residue. **A-2** 7-bromo-8-methoxy-quinazolin-2-amine (0.24 g, 945 μmol, 73% yield) was obtained as an orange solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.13 (s, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.13 (s, 2H), 3.97 (s, 3H).

[0085] **Step 2:** The mixture of **A-2** 7-bromo-8-methoxy-quinazolin-2-amine (140 mg, 551 μmol, 1 eq), TBAC (184 mg, 661 μmol, 185 μL, 1.2 eq) and TMSCl (239 mg, 2.20 mmol, 280 μL, 4 eq) in DCM (1 mL) was stirred at 20 °C under N₂. The solution of tert-butyl nitrite (171 mg, 1.65 mmol, 197 μL, 3 eq) in DMF (0.4 mL) was added to the mixture at 20 °C under N₂. The reaction was stirred at 45 °C for 4 h. The reaction mixture was quenched by adding H₂O (3 mL) and extracted with DCM (2 mL × 3). The combined organic layers were washed with brine (2 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO₂, DCM: Ethyl acetate = 40:1). 7-bromo-2-chloro-8-methoxy-quinazoline INTERMEDIATE A (60 mg, 219 μmol, 40% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.65 (s, 1H), 8.01 (d, *J* = 8.8 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 4.09 (s, 3H).

INTERMEDIATE B



[0086] **Step 1:** **B-1** (4-bromo-2-fluoro-6-methylphenyl)methanol $\text{BH}_3 \cdot \text{THF}$ (1 M, 10.7 mL, 2.5 eq) was added to the solution of 4-bromo-2-fluoro-6-methylbenzoic acid (1 g, 4.29 mmol, 1 eq) in THF (10 mL) at 0 °C under N_2 . The mixture was stirred at 50 °C for 2 h. MeOH (2 mL) was dropwise to the solution at 20 °C under N_2 . The mixture (3 batches) was concentrated under reduced pressure to give a residue. **B-2** (4-bromo-2-fluoro-6-methylphenyl)methanol (2.8 g, crude) was obtained as a white solid. ^1H NMR (400 MHz, MeOD) δ ppm 7.22 (s, 1H), 7.16-7.14 (m, 1H), 4.63 (d, $J = 2.0$ Hz, 2H), 2.43 (s, 3H).

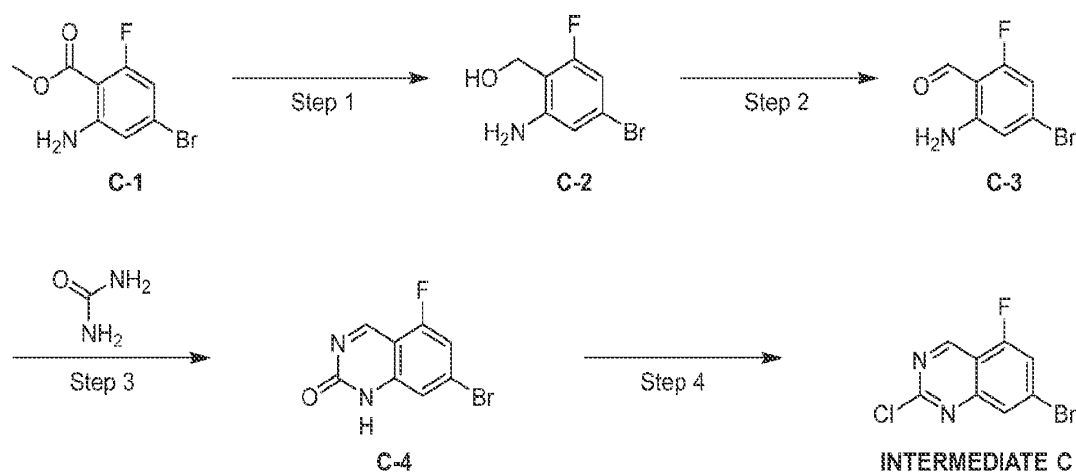
[0087] **Step 2:** The mixture of **B-2** (4-bromo-2-fluoro-6-methylphenyl)methanol (2.8 g, 12.78 mmol, 1 eq) and MnO_2 (11.11 g, 127.82 mmol, 10 eq) at DCM (30 mL) was stirred at 40 °C for 8 h. The reaction was filtered and concentrated under reduced pressure to give a residue. The residue (combined with the same scale) was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate = 1:0 to 10:1). 3.9 g of **B-3** 4-bromo-2-fluoro-6-methylbenzaldehyde was obtained as a yellow oil.

[0088] **Step 3:** The mixture of **B-3** 4-bromo-2-fluoro-6-methylbenzaldehyde (2 g, 9.22 mmol, 1 eq) and carbonic acid; guanidine (1.33 g, 7.37 mmol, 0.8 eq) in DMA (20 mL) was stirred at 140 °C for 4 h. H_2O (100 mL) was added to the reaction. The mixture was filtered, and the filter cake was dried under reduced pressure to produce a solid. **B-4** 7-bromo-5-methyl-quinazolin-2-

amine (1.5 g, crude) was obtained as a brown solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 9.22 (s, 1H), 7.43 (s, 1H), 7.17 (s, 1H), 7.00 (s, 2H), 2.59 (s, 3H).

[0089] **Step 4:** The mixture of **B-4**, 7-bromo-5-methylquinazolin-2-amine (0.5 g, 2.10 mmol, 1 eq), TBAC (700.4 mg, 2.52 mmol, 705 μL , 1.2 eq) and TMSCl (913 mg, 8.40 mmol, 1.07 mL, 4 eq) in DCM (3 mL) was stirred at 20 °C under N_2 . The solution of tert-butyl nitrite (650 mg, 6.30 mmol, 749 μL , 3 eq) in DMF (2 mL) was added to the mixture at 20 °C under N_2 . The reaction was stirred at 45 °C for 4 h. The reaction mixture (two batches) was quenched by the addition of H_2O (20 mL) and extracted with DCM (20 mL $\times$ 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , DCM: Ethyl acetate = 1:0 to 50:1). **INTERMEDIATE 4**, 7-bromo-2-chloro-5-methylquinazoline (0.100 g, 388 μmol , 10% yield) was obtained as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 9.70 (s, 1H), 8.09 (s, 1H), 7.82 (s, 1H), 2.77 (s, 3H).

INTERMEDIATE C



[0090] **Step 1:** BH_3 .THF (1 M, 10.7 mL, 2.5 eq) was added to the solution of **C-1**, 4-bromo-2-fluoro-6-methylbenzoic acid (1 g, 4.29 mmol, 1 eq) in THF (10 mL) at 0 °C under N_2 . The mixture was stirred at 50 °C for 2 h. MeOH (2 mL) was dropwise to the solution at 20 °C under N_2 . The mixture (3 batches) was concentrated under reduced pressure to give a residue. **C-2** (4-

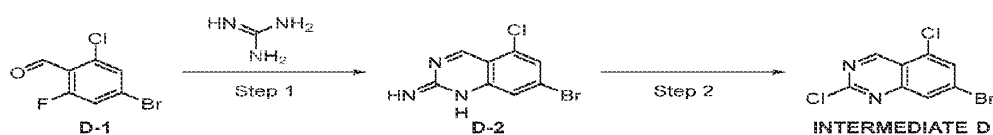
bromo-2-fluoro-6-methylphenyl)methanol (2.8 g, crude) was obtained as a white solid. ^1H NMR (400 MHz, MeOD) δ ppm 7.22 (s, 1H), 7.16-7.14 (m, 1H), 4.63 (d, $J = 2.0$ Hz, 2H), 2.43 (s, 3H).

[0091] **Step 2:** The mixture of **C-2**, (4-bromo-2-fluoro-6-methylphenyl)methanol (2.8 g, 12.78 mmol, 1 eq) and MnO_2 (11.11 g, 127.82 mmol, 10 eq) at DCM (30 mL) was stirred at 40 °C for 8 h. The reaction was filtered and concentrated under reduced pressure to give a residue. The residue (combined with the same scale) was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate = 1:0 to 10:1). 3.9 g of **C-3**, 4-bromo-2-fluoro-6-methylbenzaldehyde was obtained as a yellow oil.

[0092] **Step 3:** The mixture of **C-3**, 4-bromo-2-fluoro-6-methylbenzaldehyde (2 g, 9.22 mmol, 1 eq) and carbonic acid; guanidine (1.33 g, 7.37 mmol, 0.8 eq) in DMA (20 mL) was stirred at 140 °C for 4 h. H_2O (100 mL) was added to the reaction. The mixture was filtered, and the filter cake was dried under reduced pressure to give a residue. **C-4**, 7-bromo-5-methylquinazolin-2-amine (1.5 g, crude) was obtained as a brown solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 9.22 (s, 1H), 7.43 (s, 1H), 7.17 (s, 1H), 7.00 (s, 2H), 2.59 (s, 3H).

[0093] **Step 4:** The mixture of **C-4**, 7-bromo-5-methylquinazolin-2-amine (0.5 g, 2.10 mmol, 1 eq), TBAC (700.4 mg, 2.52 mmol, 705 μL , 1.2 eq) and TMSCl (913 mg, 8.40 mmol, 1.07 mL, 4 eq) in DCM (3 mL) was stirred at 20 °C under N_2 . The solution of tert-butyl nitrite (650.0 mg, 6.30 mmol, 749 μL , 3 eq) in DMF (2 mL) was added to the mixture at 20 °C under N_2 . The reaction was stirred at 45 °C for 4 h. The reaction mixture (two batches) was quenched by the addition of H_2O (20 mL) and extracted with DCM (20 mL $\times$ 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , DCM: Ethyl acetate = 1:0 to 50:1). **INTERMEDIATE C** 7-bromo-2-chloro-5-methylquinazoline (0.1 g, 388 μmol , 10% yield) was obtained as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 9.70 (s, 1H), 8.09 (s, 1H), 7.82 (s, 1H), 2.77 (s, 3H).

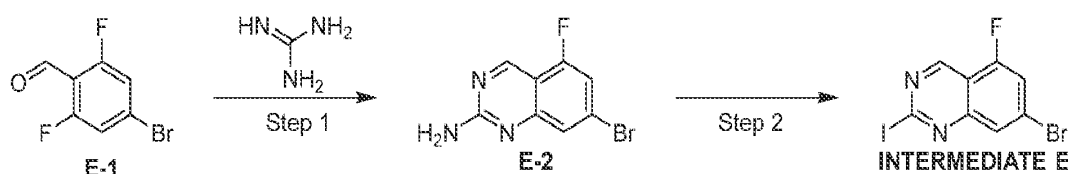
INTERMEDIATE D



[0094] Step 1: To a solution of **D-1**, 4-bromo-2-chloro-6-fluoro-benzaldehyde (400 mg, 1.68 mmol, 1 eq) in DMA (4 mL) was added carbonic acid; guanidine (243 mg, 1.35 mmol, 0.8 eq). The mixture was stirred at 140 °C for 4 hr. The residue was diluted with H₂O (20 mL), the mixture was filtered, and the filter cake was concentrated under reduced pressure to give a residue. The product was used in the next step without further purification. **D-2** 7-bromo-5-chloroquinazolin-2(1H)-imine (350 mg, 1.35 mmol, 80% yield) was obtained as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.25 (s, 1H), 7.59 (d, J = 1.4 Hz, 1H), 7.53 (d, J = 1.8 Hz, 1H), 7.34 (s, 2H).

[0095] Step 2: To a solution of **D-2** 7-bromo-5-chloro-quinazolin-2-amine (350 mg, 1.35 mmol, 1 eq), TMSCl (588 mg, 5.42 mmol, 687 μL, 4 eq) and tetrabutylammonium; chloride (452 mg, 1.62 mmol, 454 μL, 1.2 eq) in DCM (2 mL) was added tert-butyl nitrite (418.86 mg, 4.06 mmol, 483 μL, 3 eq) in DMF (2 mL). The mixture was stirred at 45 °C for 1 hr. The residue was diluted with H₂O (10 mL) and extracted with DCM (10 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether: Ethyl acetate=1:0 to 10:1). **INTERMEDIATE D** 7-bromo-2,5-dichloro-quinazoline (160 mg, 576 μmol, 43% yield) was obtained as a white solid.

INTERMEDIATE E

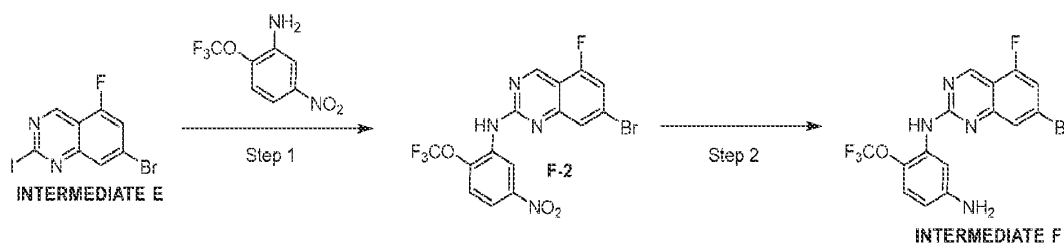


[0096] Step 1: A solution of **E1** (10 g, 45.25 mmol, 1 eq), carbonic acid, and guanidine (6.52 g, 36.20 mmol, 0.8 eq) in DMA (300 mL) was stirred at 140 °C for 4 hr. Water (1000 mL) was added and mixture was stirred at 20 °C for 0.5 hr. After such time, a yellow solid was precipitated. The solids were collected, filtered, and washed with water (1000 mL). The filter cake was dried under reduced pressure. The product was used directly in the next step without further purification. Compound 7-bromo-5-fluoro-quinazolin-2-amine (50 g, 196 mmol, 87%

yield, 95% purity) was obtained as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 9.23 (s, 1H), 7.44 (d, J = 0.8 Hz, 1H), 7.32 (s, 2H), 7.26 (dd, J = 1.6, 9.3 Hz, 1H)

[0097] Step 2: To a solution of **E2** (10 g, 41.3 mmol, 1 eq) in THF (300 mL) was added CuI (7.9 g, 41.3 mmol, 1 eq), diiodomethane (55.3 g, 206.6 mmol, 17.00 mL, 5 eq) and isopentyl nitrite (14.5 g, 124.0 mmol, 17 mL, 3 eq). The mixture was stirred at 80 °C for 2 hr. The mixture was added slowly to the ice water (100 mL) and extracted with ethyl acetate (50 mL $\times$ 3). The combined organic phase was dried with anhydrous Na_2SO_4 , filtered, and concentrated to give the residue. The residue was purified by silica gel chromatography (Petroleum ether: ethyl acetate=10:1 to 3:1). **INTERMEDIATE E** 7-bromo-5-fluoro-2-iodo-quinazoline (6 g, 16.15 mmol, 13% yield, 95% purity) was obtained as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 9.45 (s, 1H), 8.11 (s, 1H), 7.96 (dd, J = 1.5, 9.1 Hz, 1H)

INTERMEDIATE F

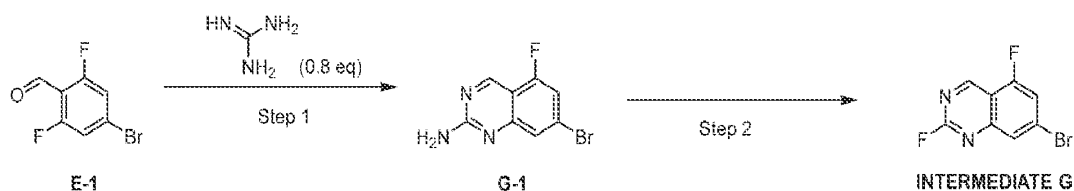


[0098] Step 1: To a solution of 5-nitro-2-(trifluoromethoxy)aniline (1 g, 4.50 mmol, 1 eq) and 7-bromo-5-fluoro-2-iodo-quinazoline (1.91 g, 5.40 mmol, 1.2 eq) in DMF (30 mL) was added NaOtBu (2 M, 4.50 mL, 2 eq) and Davephos Pd G3 (34.36 mg, 45.02 μmol , 0.01 eq). The mixture was stirred at 130 °C for 12 hr. Water (200 mL) was added, and the water layer was extracted with DCM (50 mL $\times$ 3). The combined organic phase was dried with anhydrous Na_2SO_4 , filtered, and concentrated to give a residue. The product was used for the next step without purification. 7-bromo-5-fluoro-N-[5-nitro-2-(trifluoromethoxy)phenyl]quinazolin-2-amine (4 g, crude) was obtained as a yellow solid.

[0099] Step 2: A solution of 7-bromo-5-fluoro-N-[5-nitro-2-(trifluoromethoxy)phenyl]quinazolin-2-amine (4 g, 8.95 mmol, 1 eq) in THF (30 mL), H_2O (10 mL) and Fe (4.00 g, 71.57 mmol, 8 eq) and NH_4Cl (3.83 g, 71.57 mmol, 8 eq) was stirred at 60

°C for 12 hr. The mixture was filtered, and the filtrate was concentrated to give the residue. The residue was partitioned between water (200 mL) and DCM (200 mL), and the water layer was extracted with DCM (3 x 100 mL). The combined organic phases were dried with anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (Petroleum ether: Ethyl acetate=2:1 to 0:1). INTERMEDIATE F, N3-(7-bromo-5-fluoro-quinazolin-2-yl)-4-(trifluoromethoxy)benzene-1,3-diamine (1.4 g, 3.19 mmol, 36% yield, 95% purity) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.39 (s, 1H), 9.30 (s, 1H), 7.65 (s, 1H), 7.45 (br d, J = 8.3 Hz, 1H), 7.23 (br d, J = 2.0 Hz, 1H), 7.04 (br d, J = 8.5 Hz, 1H), 6.41 (dd, J = 2.6, 8.8 Hz, 1H), 5.36 (s, 2H).

INTERMEDIATE G

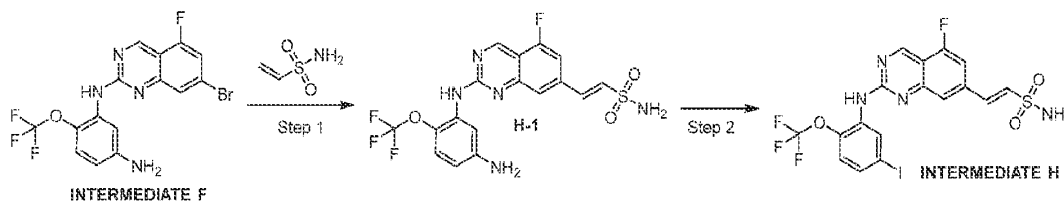


[0100] **Step 1:** To a solution of 4-bromo-2,6-difluoro-benzaldehyde (20 g, 90.50 mmol, 1 *eq*) and carbonic acid; guanidine (13.04 g, 72.40 mmol, 0.8 *eq*) in DMA (250 mL). The mixture was stirred at 140 °C for 4 hours. Water (1000 mL) was added to the mixture, and a solid was precipitated. The crude product (combined with other batches at the same scale) was filtered and washed with water (1000 mL). The solid was collected and dried under reduced pressure. The product was used in the next step without further purification. Compound 7-bromo-5-fluoro-quinazolin-2-amine (57 g, 200.17 mmol, 74% yield, 85% purity) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.23 (s, 1H), 7.44 (s, 1H), 7.32 (s, 2H), 7.27 (d, J = 9.6 Hz, 1H).

[0101] **Step 2:** To a mixture of 7-bromo-5-fluoro-quinazolin-2-amine (10 g, 41.31 mmol, 1 *eq*) in DCM (30 mL) was added pyr-HF (20 mL) dropwise at 0°C. Then t-BuONO (12.78 g, 124 mmol, 15 mL, 3 *eq*) was added to the mixture dropwise at 0°C. The mixture was stirred at 0 °C for 2 hr. The reaction mixture was poured into ice water (50 mL) and extracted with EtOAc (20 mL x 3). The combined organic phase was washed with sat. NaHCO₃ (20 mL) and brine (20 mL)

were dried over Na_2SO_4 , filtered, and concentrated under vacuum. The residue was purified by column chromatography (SiO_2 , Petroleum ether: Ethyl acetate = 100:1 to 50:1). Compound 7-bromo-2,5-difluoro-quinazoline (17.5 g, 71.42 mmol, 35% yield) was obtained as a white solid. ^1H NMR (400 MHz, CDCl_3 -*d*) δ = 9.61 (s, 1H), 8.01 (s, 1H), 7.48 (d, J = 8.8 Hz, 1H).

INTERMEDIATE H

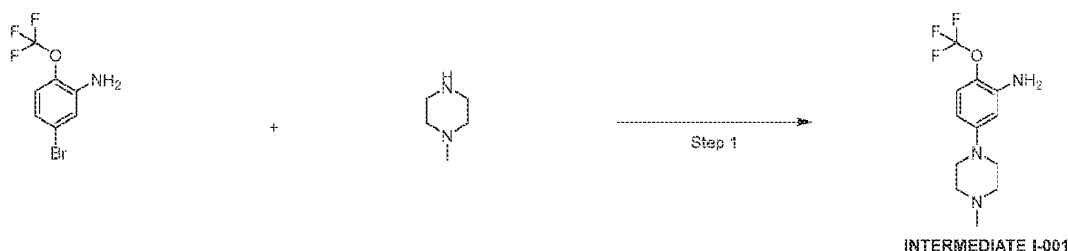


[0102] **Step 1:** A mixture of N-3-(7-bromo-5-fluoroquinazolin-2-yl)-4-(trifluoromethoxy)benzene-1,3-diamine (3 g, 7.2 mmol, 1 eq), ethenesulfonamide (925 mg, 8.63 mmol, 1.2 eq), $\text{Pd}(\text{OAc})_2$ (32.3 mg, 144 μmol , 0.02 eq), tris-*o*-tolylphosphane (88 mg, 287.66 μmol , 0.04 eq) and TEA (2.18 g, 21.57 mmol, 3.00 mL, 3 eq) in DMF (30 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 hr under N_2 atmosphere. The reaction mixture was filtered and concentrated to remove the solvent. The crude product was triturated with PE: EtOAc (5:1, 20 mL) at 20 °C for 30 min. Compound (E)-2-[2-[5-amino-2-(trifluoromethoxy)anilino]-5-fluoroquinazolin-7-yl]ethenesulfonamide (2.7 g, 6.09 mmol, 85% yield) was obtained as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 9.38 (s, 1H), 9.23 (s, 1H), 7.65 (s, 1H), 7.61 (d, J = 11.2 Hz, 1H), 7.57-7.49 (m, 1H), 7.46-7.37 (m, 1H), 7.25 (br s, 2H), 7.14 (d, J = 2.8 Hz, 1H), 7.05-7.01 (m, 1H), 6.43-6.38 (m, 1H), 5.33 (s, 2H).

[0103] **Step 2:** To a solution of (E)-2-[2-[5-amino-2-(trifluoromethoxy)anilino]-5-fluoroquinazolin-7-yl]ethenesulfonamide (500 mg, 1.13 mmol, 1 eq) and p-TsOH.H₂O (643.53 mg, 3.38 mmol, 3 eq) in ACN (12 mL) was dropwise added a solution of NaNO_2 (155.61 mg, 2.26 mmol, 2 eq) and KI (468.01 mg, 2.82 mmol, 2.5 eq) in H_2O (4 mL) at 0 °C. The mixture was stirred at 20 °C for 2 hr under N_2 . The reaction mixture was quenched by the addition of H_2O (60 mL) and aq. $\text{Na}_2\text{S}_2\text{O}_3$ (2M, 6 mL), and then extracted with EtOAc (10 mL $\times$ 3). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give a residue. The crude product was triturated with EtOAc (10 mL) at 20 °C for 20 min. (E)-2-[5-

fluoro-2-[5-iodo-2-(trifluoromethoxy)anilino]quinazolin-7-yl]ethanesulfonamide (400 mg, 722 μmol , 64% yield) was obtained as a pink solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 9.74 (s, 1H), 9.44 (s, 1H), 8.36 (d, J = 2.0 Hz, 1H), 7.74-7.64 (m, 2H), 7.64-7.59 (m, 1H), 7.55 (s, 1H), 7.51-7.44 (m, 1H), 7.28-7.21 (m, 3H).

INTERMEDIATE I-001



[0104] **Step 1:** A mixture of 5-bromo-2-(trifluoromethoxy)aniline (50 mg, 195.30 μmol , 1 eq), 1-methylpiperazine (23.47 mg, 234.36 μmol , 26.00 μL , 1.2 eq), NaOBu-t (37.54 mg, 390.59 μmol , 2 eq), [2-(2-aminophenyl)phenyl]-methylsulfonyloxy-palladium; di-tert-butyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane (15.51 mg, 19.53 μmol , 0.1 eq) in dioxane (5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 12 hr under N_2 atmosphere. The mixture was filtered through Celite, and the solvent was removed under reduced pressure to provide a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 250 $\times$ 50mm $\times$ 10 μm ; mobile phase: [water(NH_4HCO_3)-ACN]; B%: 25%-50%, 10 min. 180 mg of compound 5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)aniline, **Intermediate-001** was obtained as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 6.89 (d, J = 8.8 Hz, 1H), 6.32 (d, J = 2.8 Hz, 1H), 6.14 (dd, J = 2.8 Hz, 8.8 Hz, 1H), 5.11 (br s, 2H), 3.04 - 3.02 (m, 4H), 2.42-2.40 (m, 4H), 2.20 (s, 3H).

The Intermediates **I-002** to **I-036** shown in Table A were prepared following the teachings of the General Reaction Schemes and the method to prepare **INTERMEDIATE I-001**.

Table A

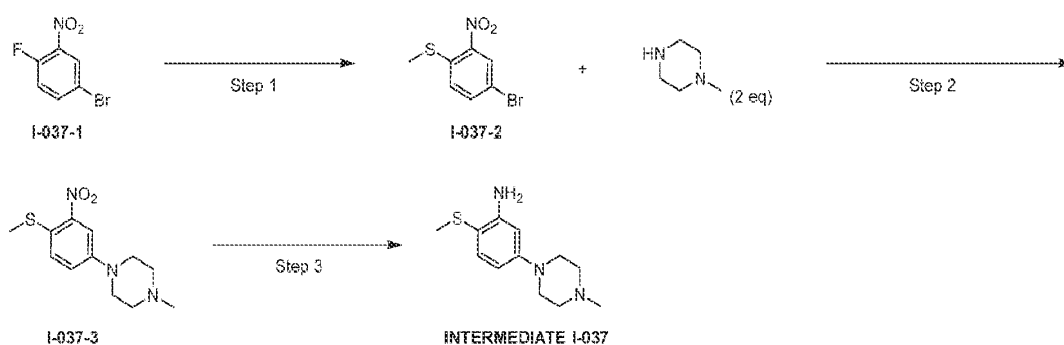
Int.	Intermediate Structure	Coupling Partner	Coupling Catalyst	Intermediate Characterization
I-002			tBuXPhos Pd G3	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 6.89 (d, J = 4.4 Hz, 1H), 6.31 (d, J = 2.8 Hz, 1H), 6.15-6.12 (m, 1H), 5.12 (s, 2H), 4.42 (s, 1H), 3.52 (s, 2H), 3.33 (s, 4H), 3.02 (s, 4H), 2.42- 2.39 (m, 2H).
I-003			tBuXPhos Pd G3	¹ H NMR (400 MHz, DMSO-d ₆) δ = 6.82 (d, J = 8.8 Hz, 1H), 5.99 (d, J = 2.6 Hz, 1H), 5.84 (dd, J = 2.5, 8.8 Hz, 1H), 5.55 (br s, 1H), 5.02 (s, 2H), 3.06- 2.93 (m, 2H), 2.39 (br t, J = 7.0 Hz, 8H), 2.20 (s, 3H), 1.71 (m, 2H). m/z (ES+) [M+H] ⁺ = 333.1
I-004			tBuXPhos Pd G3	¹ H NMR (400 MHz, CDCl ₃) δ = 6.83 (dd, J = 1.1, 8.5 Hz, 1H), 5.92- 5.82 (m, 2H), 3.67 (br s, 2H), 3.05 (t, J = 6.5 Hz, 2H), 2.50 (t, J = 6.8 Hz, 2H), 2.45- 2.42 (m, 4H), 1.75- 1.68 (m, 6H)
I-005			tBuXPhos Pd G3	¹ H NMR (400 MHz, DMSO-d ₆) δ = 6.77 (dd, J = 1.3, 8.8 Hz, 1H), 5.95 (d, J = 2.6 Hz, 1H), 5.79 (dd, J = 2.7, 8.8 Hz, 1H), 5.50 (br s, 1H), 4.97 (br s, 2H), 3.58 (t, J = 4.6 Hz, 4H), 2.95 (t, J = 6.9 Hz, 2H), 2.36 (m, 6H), 1.67 (m, 2H).
I-006			tBuXPhos Pd G3	[M+H] ⁺ = 318.1
I-007			tBuXPhos Pd G3	¹ H NMR (400 MHz, CDCl ₃) δ = 6.84 (d, J = 8.0 Hz, 1H), 5.92-5.87 (m, 2H), 4.23 (br s, 1H), 3.69 (br s, 2H), 3.04 (t, J = 6.6 Hz, 2H), 2.33 (t, J = 6.7 Hz, 2H), 2.18 (s, 6H), 1.72-1.66 (m, 2H)
I-008			tBuXPhos Pd G3	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.49 (s, 1H), 6.87-7.04 (m, 2H), 6.58-6.61 (m, 1H), 5.33 (s, 2H), 3.63 (s, 3H)
I-009			tBuXPhos Pd G3	¹ H NMR (400 MHz, DMSO-d ₆) δ = 6.91 (d, J = 8.4 Hz, 1H), 5.99- 5.95 (m, 2H), 3.73 (br s, 2H), 2.92 (s, 2H), 2.30 (s, 6H), 2.26 (s, 2H), 0.99 (s, 6H)
I-010			tBuXPhos Pd G3	¹ H NMR (400 MHz, DMSO-d ₆) δ = 6.78-6.82 (m, 1H), 6.01-6.03 (d, J = 2.6 Hz, 1H), 5.82-5.87 (dd, J = 8.8, 2.8 Hz, 1H), 5.32-5.35 (d, J = 8.0 Hz, 1H), 4.99 (s, 2H), 2.99-3.15 (m, 1H), 2.76-2.80 (d, J = 12.0 Hz, 2H), 2.21 (s, 3H), 1.97-2.06 (m, 2H), 1.85-1.94 (m, 2H), 1.35-1.48 (m, 2H).
I-011			tBuXPhos Pd G3	m/z (ES+) [M+H] ⁺ = 304.0.
I-012			tBuXPhos Pd G3	¹ H NMR (400 MHz, DMSO-d ₆) δ = 6.72 (br d, J = 7.5 Hz, 1H), 3.86 (br dd, J = 3.1, 10.9 Hz, 2H), 3.24 (br t, J = 11.3 Hz, 2H), 2.81 (br d, J = 11.4 Hz, 2H), 2.44- 2.29 (m, 1H), 2.07 (br t, J = 10.9 Hz, 2H), 1.71- 1.61 (m, 4H), 1.42- 1.30 (m, 13H).

Int.	Intermediate Structure	Coupling Partner	Coupling Catalyst	Intermediate Characterization
I-013			tBuXPhos Pd G3	m/z (ES+) [M+H] ⁺ = 306.1
I-014			tBuXPhos Pd G3	m/z (ES+) [M+H] ⁺ = 304.2
I-015			BrettPhos Pd G4	m/z (ES+) [M+H] ⁺ = 320.1
I-016			tBuXPhos Pd G3	¹ H NMR (400 MHz, DMSO-d ₆) δ = 6.89 (dd, J = 1.3, 9.0 Hz, 1H), 6.14 (d, J = 2.9 Hz, 1H), 5.95 (dd, J = 2.9, 9.1 Hz, 1H), 5.05 (s, 2H), 3.49 - 3.42 (m, 2H), 3.39 - 3.36 (m, 2H), 2.65 - 2.59 (m, 2H), 2.51 - 2.44 (m, 2H), 2.30 (s, 3H), 1.91 (quin, J = 5.8 Hz, 2H).
I-017			tBuXPhos Pd G3	m/z (ES+) [M+H] ⁺ = 330.2
I-018			tBuXPhos Pd G3	m/z (ES+) [M+H] ⁺ = 362.1; [M-55] ⁺ = 306.1
I-019			tBuXPhos Pd G3	m/z (ES+) [M-tBu] ⁺ = 306.0, m/z (ES+) [M+H] ⁺ = 362.1
I-020			tBuXPhos Pd G3	¹ H NMR (400 MHz, DMSO-d ₆) δ = 6.93 (dd, J = 11.6 Hz, 1.6 Hz, 1H), 6.34 (d, J = 2.8 Hz, 1H), 6.17 (dd, J = 9.2 Hz, 3.2 Hz, 1H), 5.15 (s, 2H), 3.42 (t, J = 4.8 Hz, 4H), 3.00 (t, J = 5.2 Hz, 4H), 1.41 (s, 9H).
I-021			tBuXPhos Pd G3	¹ H NMR (400 MHz, DMSO-d ₆) δ = 7.21 (t, J = 7.9 Hz, 2H), 6.93 (d, J = 8.0 Hz, 2H), 6.82 - 6.70 (m, 2H), 6.01 (d, J = 2.6 Hz, 1H), 5.87 (dd, J = 2.5, 8.8 Hz, 1H), 5.39 (d, J = 7.4 Hz, 1H), 4.94 (s, 2H), 3.32 (br s, 1H), 3.12 (br s, 4H), 2.62 (br s, 4H), 2.23 (br s, 1H), 1.80 - 1.67 (m, 4H), 1.54 (br s, 4H).
I-022			tBuXPhos Pd G3	¹ H NMR (400 MHz, CDCl ₃) δ = 7.77 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 7.2 Hz, 2H), 3.80-4.18 (m, 3H), 3.20-3.38 (m, 2H), 2.43 (s, 3H), 1.72-2.00 (m, 4H), 1.37 (s, 9H).

Int.	Intermediate Structure	Coupling Partner	Coupling Catalyst	Intermediate Characterization
I-023			tBuXPhos Pd G3	¹ H NMR (400 MHz, CDCl ₃) δ = 6.91 (dd, J = 0.8 Hz, 8.8 Hz, 1H), 6.04-5.85 (m, 2H), 3.77 (br s, 2H), 3.22-3.05 (m, 1H), 2.53-2.47 (m, 1H), 2.45 (s, 6H), 2.21 (d, J = 11.2 Hz, 2H), 2.19 (d, J = 12.8 Hz, 2H), 2.12-2.03 (m, 2H), 1.53-1.38 (m, 2H), 1.22-1.07 (m, 2H).
I-024			tBuXPhos Pd G3	m/z (ES ⁺) [M+H] ⁺ = 366.1
I-025			tBuXPhos Pd G3	¹ H NMR (400 MHz, CDCl ₃) δ = 6.91 (dd, J = 1.2 Hz, 8.8 Hz, 1H), 6.02-5.89 (m, 2H), 3.75 (br s, 2H), 3.39 (d, J = 7.2 Hz, 1H), 3.12-3.08 (m, 1H), 2.60 (br s, 4H), 2.39 (t, J = 11.2 Hz, 1H), 2.19 (d, J = 12.4 Hz, 2H), 2.00 (d, J = 12 Hz, 2H), 1.70-1.64 (m, 4H), 1.51-1.40 (m, 4H), 1.20-1.07 (m, 2H).
I-026			tBuXPhos Pd G3	¹ H NMR (400 MHz, CDCl ₃) δ = 6.92 (d, J=8.0 Hz, 1H), 5.99-5.94 (m, 2H), 3.74 (s, 3H), 3.52 (s, 1H), 3.54-2.5 (m, 4H), 2.31-2.23 (m, 1H), 1.93-1.90 (m, 2H), 1.74-1.71 (m, 2H), 1.65-1.56 (m, 8H), 1.48-1.45 (m, 2H). m/z (ES ⁺) [M+H] ⁺ = 358.2
I-027			tBuXPhos Pd G3	¹ H NMR (400 MHz, DMSO-d ₆) δ = 6.73-6.76 (d, J = 8.6 Hz, 1H), 5.95-5.98 (d, J = 2.2 Hz, 1H), 5.78-5.80 (m, 1H), 5.26-5.28 (d, J = 7.8 Hz, 1H), 4.92 (s, 2H), 2.94-3.07 (m, 1H), 2.71-2.78 (m, 2H), 2.62-2.70 (m, 1H), 2.09-2.27 (m, 2H), 1.80-1.93 (m, 2H), 1.19-1.41 (m, 2H), 0.89-1.02 (d, J = 6.8 Hz, 6H)
I-028			BrettPhos Pd G4	¹ H NMR (400 MHz, CDCl ₃) δ = 6.92 (d, J=8.8 Hz, 1H), 5.97-5.92 (m, 2H), 3.76~3.70 (d, J=4.4 Hz, 5H), 3.17-3.06 (m, 1H), 2.58 (d, J=4.0 Hz, 4H), 2.27-2.17 (m, 3H), 2.00 (d, J=12.8 Hz, 2H), 1.37 (dd, J=11.2 Hz, 13.2 Hz, 2H), 1.15 (dd, J=11.2 Hz, 12.8 Hz, 2H). m/z (ES ⁺) [M+H] ⁺ = 360.1
I-029			tBuXPhos Pd G3	¹ H NMR (400 MHz, CDCl ₃) δ ppm 7.01 (d, J=8.4 Hz, 1H), 6.31-6.27 (m, 2H), 4.46 (s, 1H), 3.79 (s, 2H), 3.57- 3.52(m, 2H), 2.85-2.75 (m, 2H), 2.04 (d, J=11.2 Hz, 2H), 1.58 (s, 1H), 1.51 (dd, J=12.0 Hz, J=3.6 Hz, 2H), 1.46 (s, 9H). m/z (ES ⁺) [M+H] ⁺ = 367.0.
I-030			tBuXPhos Pd G3	¹ H NMR (400 MHz, DMSO-d ₆) δ = 6.79 (br d, J = 8.8 Hz, 1H), 6.24 (d, J = 2.5 Hz, 1H), 5.98 (dd, J = 2.6, 8.8 Hz, 1H), 5.00 (s, 2H), 4.86 (br s, 1H), 3.62 - 3.58 (m, 4H), 2.57 - 2.54 (m, 2H), 2.45 (s, 2H), 1.27 (s, 6H), 1.01 (s, 2H)

Int.	Intermediate Structure	Coupling Partner	Coupling Catalyst	Intermediate Characterization
I-031			BrettPhos Pd G4	¹ H NMR (400 MHz, DMSO-d ₆) δ = 7.96 (s, 1H), 7.09-7.19 (d, J = 8.4 Hz, 2H), 6.98-7.02 (d, J = 8.4 Hz, 2H), 6.88-6.95 (m, 1H), 6.50-6.55 (d, J = 2.8 Hz, 1H), 6.18-6.25 (dd, J = 2.8, 8.8 Hz, 1H), 5.17 (br s, 2H), 3.53-3.58 (t, J = 4.4 Hz, 4H), 3.35 (s, 2H), 2.29-2.36 (m, 4H)
I-032			BrettPhos Pd G4	m/z (ES+) [M+H] ⁺ = 367.0
I-033			tBuXPhos Pd G3	¹ H NMR (400 MHz, DMSO-d ₆) δ = 6.93 (br d, J = 8.8 Hz, 1H), 6.35 (d, J = 2.7 Hz, 1H), 6.17 (dd, J = 2.7, 9.0 Hz, 1H), 5.14 (s, 2H), 3.11 - 3.01 (m, 4H), 2.51 - 2.45 (m, 4H), 2.38 (q, J = 7.1 Hz, 2H), 1.05 (t, J = 7.2 Hz, 3H).
I-034			Bromo(1,10-phenanthroline)copper(I)	¹ H NMR (400 MHz, DMSO-d ₆) δ = 7.10 (dd, J = 1.1, 8.6 Hz, 1H), 6.74 (d, J = 2.5 Hz, 1H), 6.48 (dd, J = 2.4, 8.7 Hz, 1H), 5.46 (s, 2H), 3.57 (t, J = 5.4 Hz, 2H), 3.08 (s, 2H), 2.51 (s, 2H), 2.27 (s, 3H)
I-035			Pd2(dba) ₃	¹ H NMR (400 MHz, DMSO-d ₆) δ = 7.69 (dd, J = 2.6, 9.5 Hz, 1H), 7.56 (d, J = 2.2 Hz, 1H), 7.10 (d, J = 7.8 Hz, 1H), 6.92 (d, J = 2.0 Hz, 1H), 6.70 (dd, J = 2.0, 8.5 Hz, 1H), 6.42 (d, J = 9.6 Hz, 1H), 5.41 (s, 2H), 3.94 (s, 1H).
I-036			Pd2(dba) ₃	¹ H NMR (400 MHz, DMSO-d ₆) δ = 7.69 (dd, J = 2.6, 9.5 Hz, 1H), 7.56 (d, J = 2.2 Hz, 1H), 7.10 (d, J = 7.8 Hz, 1H), 6.92 (d, J = 2.0 Hz, 1H), 6.70 (dd, J = 2.0, 8.5 Hz, 1H), 6.42 (d, J = 9.6 Hz, 1H), 5.41 (s, 2H), 3.94 (s, 1H).

INTERMEDIATE I-037



[0105] **Step 1:** To a solution of 4-bromo-1-fluoro-2-nitrobenzene, **I-037-1** (3 g, 13.64 mmol, 1.68 mL, 1 eq) in DMF (75 mL) was dropwise added the solution of NaSMc (1.05 g, 14.98

mmol, 954.55 μ L, 1.10 eq) in H₂O (25 mL) at 0 °C under N₂. The mixture was stirred at 0 °C for 1 hr under N₂. The mixture was filtered to get the filter cake and washed with H₂O (10 mL). To the residual filtrate was added the brine (20 mL), then extracted with EtOAc (10 mL $\times$ 3). The combined organic layers were dried over Na₂SO₄. The Na₂SO₄ was removed by filtration, and the filtrate was concentrated under reduced pressure to get the residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 50/1). Compound 4-bromo-1-methylsulfanyl-2-nitro-benzene (3 g, 12.09 mmol, 89% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.37 (d, *J* = 2.2 Hz, 1H), 7.91-7.95 (m, 1H), 7.53 (d, *J* = 8.6 Hz, 1H), 2.54 (s, 3H).

[0106] **Step 2:** A mixture of 4-bromo-1-methylsulfanyl-2-nitro-benzene (2 g, 8.06 mmol, 1 eq), 1-methylpiperazine (1.61 g, 16.12 mmol, 1.79 mL, 2 eq), Cs₂CO₃ (5.25 g, 16.12 mmol, 2 eq), Xantphos (466.45 mg, 806.14 μ mol, 0.1 eq) and Pd₂(dba)₃ (369.10 mg, 403.07 μ mol, 0.05 eq) in dioxane (30 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 90 °C for 12 hr under N₂ atmosphere. Filter to get the filtrate and concentrate to remove the solvent. The residue was purified by prep-HPLC (FA condition; column: Phenomenex luna C18 (250 $\times$ 70mm, 10 μ m); mobile phase: [water(FA)-ACN]; gradient: 5%-30% B over 25 min). Compound 1-methyl-4-(4-methylsulfanyl-3-nitro-phenyl)piperazine (1.5 g, 5.61 mmol, 70% yield) was obtained as a brown oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.73 (d, *J* = 2.6 Hz, 1H), 7.24-7.27 (m, 1H), 7.14-7.17 (m, 1H), 3.39 (br t, *J* = 4.6 Hz, 4H), 3.03 (br t, *J* = 4.6 Hz, 4H), 2.61 (s, 3H), 2.45 (s, 3H).

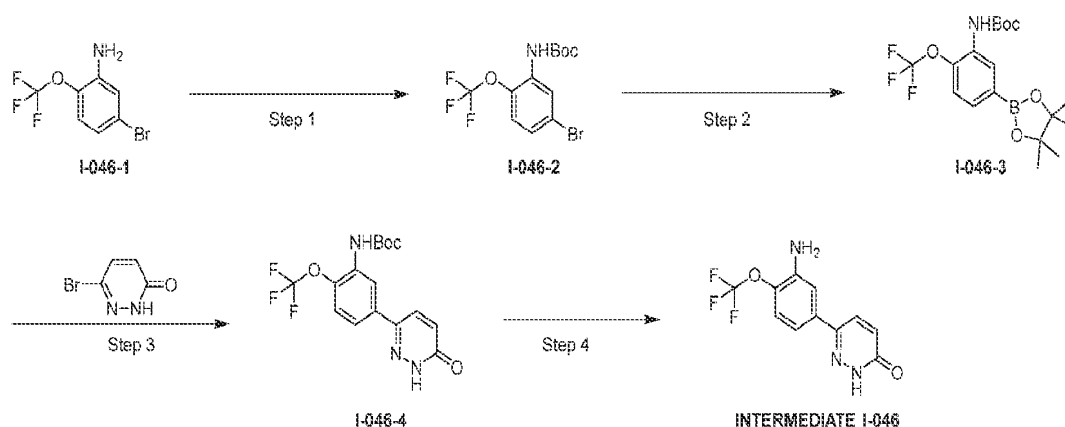
[0107] **Step 3:** To a solution of 1-methyl-4-(4-methylsulfanyl-3-nitro-phenyl)piperazine (500 mg, 1.87 mmol, 1 eq) and NH₄Cl (500.21 mg, 9.35 mmol, 5 eq) in EtOH (6 mL) and H₂O (3 mL) was added Fe (522.22 mg, 9.35 mmol, 5 eq) at 50 °C. After addition, the resulting mixture was stirred at 85 °C for 2 hr. The mixture was filtered to get the filtrate and concentrated to remove the solvent. Without further purification, it is used directly for the next step. Compound 5-(4-methylpiperazin-1-yl)-2-methylsulfanyl aniline (220 mg, crude) was obtained as a brown solid. *m/z* (ES⁺) [M+H]⁺ = 238.1.

[0108] The Intermediates I-038 to I-045 shown in Table B were prepared following the teachings of the General Reaction Schemes and the method to prepare INTERMEDIATE I-037.

Table B

Int.	Intermediate Structure	Coupling Partner	Coupling Catalyst	Intermediate Characterization
I-038			Pd(dppf)Cl ₂	¹ H NMR (400 MHz, CDCl ₃) δ = 8.23 (s, 1H), 7.03-7.01 (m, 1H), 6.96-6.94 (m, 1H), 3.36 (s, 4H), 3.04 (s, 4H), 2.61 (s, 3H), 2.29-2.15 (m, 1H), 0.92 (d, J = 8 Hz, 2H), 0.55 (d, J = 4.8 Hz, 2H).
I-039			Xantphos Pd G4	m/z (ES+) [M+H] ⁺ = 277.9
I-040			[Pd(OAc) ₂ (R-BINAP)]	¹ H NMR (400 MHz, CDCl ₃) δ = 7.43 (d, J = 2.8 Hz, 1H), 7.12-7.16 (m, 1H), 6.98-7.07 (m, 1H), 3.92 (s, 3H), 3.36 (t, J = 4.8 Hz, 4H), 3.10-3.23 (m, 4H), 2.72 (s, 3H).
I-041			Xantphos Pd G4	¹ H NMR (400 MHz, DMSO-d ₆) δ = 7.34 (d, J = 2.4 Hz, 1H), 7.32-7.26 (m, 1H), 7.26-7.18 (m, 1H), 3.29-3.06 (m, 4H), 2.67 (q, J = 7.2 Hz, 2H), 2.50-2.46 (m, 4H), 2.26 (s, 3H), 1.14 (t, J = 7.2 Hz, 3H).
I-042			Pd2(dba) ₃	m/z (ES+) [M+H] ⁺ = 333.3.
I-043			Xantphos Pd G4	m/z (ES+) [M+H] ⁺ = 306.2.
I-044			Xantphos Pd G4	¹ H NMR (400 MHz, DMSO-d ₆) δ = 7.32 (d, J = 9.2 Hz, 1H), 6.35-6.32 (m, 1H), 6.28 (d, J = 2.0 Hz, 1H), 5.80 (s, 2H), 3.49-3.38 (m, 4H), 3.28-3.16 (m, 4H), 2.99 (s, 3H), 1.42 (s, 9H).
I-045			Xantphos Pd G4	¹ H NMR (400 MHz, DMSO-d ₆) δ = 7.32 (d, J = 9.2 Hz, 1H), 6.35-6.32 (m, 1H), 6.28 (d, J = 2.0 Hz, 1H), 5.80 (s, 2H), 3.49-3.38 (m, 4H), 3.28-3.16 (m, 4H), 2.99 (s, 3H), 1.42 (s, 9H).

INTERMEDIATE I-046



[0109] **Step 1:** To a solution of 5-bromo-2-(trifluoromethoxy)aniline (2 g, 7.81 mmol, 1 eq) in THF (20 mL) was added dropwise KHMDS (1 M, 15.62 mL, 2 eq) at 0°C and stirred for 0.5 h. Then, add Boc₂O (1.70 g, 7.81 mmol, 1.79 mL, 1 eq) in portions at 0°C. The mixture was stirred at 25 °C for 2 h. The mixture was quenched with sat. NH₄Cl (50 mL) and extracted with ethyl acetate (20 mL×3). The combined organic phase was dried over anhydrous Na₂SO₄, filtered, and concentrated to give the residue. The crude product was triturated with Petroleum ether/Ethyl acetate (5:1, 10 mL) at 15 °C for 10 min, filtered, and the filter cake was dried under vacuum to give tert-butyl N-[5-bromo-2-(trifluoromethoxy)phenyl]carbamate (1.5 g, 4.21 mmol, 54% yield) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.33 (s, 1H), 7.81 (d, *J* = 2.0 Hz, 1H), 7.42- 7.38 (dd, 1H), 7.37 - 7.33 (dd, 1H), 1.50 (s, 9H).

[0110] **Step 2:** To a solution of tert-butyl N-[5-bromo-2-(trifluoromethoxy)phenyl]carbamate (1.4 g, 3.93 mmol, 1 eq) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (2.00 g, 7.86 mmol, 2 eq) in dioxane (10 mL) was added Pd(dppf)Cl₂ (287.64 mg, 393.11 μmol, 0.1 eq) and KOAc (1.16 g, 11.79 mmol, 3.5 eq). The mixture was stirred at 100 °C for 12 hr under N₂. Water (50 mL) was added to the mixture, and the mixture was extracted with ethyl acetate (10 mL×3). The combined organic phase was dried over anhydrous Na₂SO₄, filtered, and concentrated to give the residue. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=100/1, 50/1). Compound tert-butyl N-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethoxy)phenyl]carbamate (1.2 g,

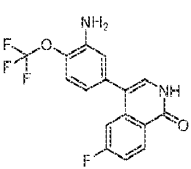
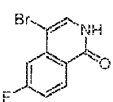
2.98 mmol, 76% yield) was obtained as a white oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 9.02 (s, 1H), 7.97 (s, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.34 (d, J = 8.2 Hz, 1H), 1.46 (s, 9H), 1.29 (s, 12H).

[0111] **Step 3:** To a solution of tert-butyl N-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethoxy)phenyl]carbamate (1 g, 2.48 mmol, 1 eq) and 3-bromo-1H-pyridazin-6-one (520.78 mg, 2.98 mmol, 1.2 eq) in dioxane (40 mL) and H_2O (4 mL) was added $\text{Pd}(\text{dppf})\text{Cl}_2$ (18.15 mg, 24.80 μmol , 0.01 eq) and K_2CO_3 (1.03 g, 7.44 mmol, 3 eq). The mixture was stirred at 100 °C for 12 hr. To the mixture was added water (50 mL), and the mixture was extracted with ethyl acetate (20 mL $\times$ 3). The combined organic phase was dried with anhydrous Na_2SO_4 , filtered, and concentrated to give the residue. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=100/1, 50/1). 600 mg of compound tert-butyl N-[5-(6-oxo-1H-pyridazin-3-yl)-2-(trifluoromethoxy)phenyl]carbamate was obtained as a white oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 13.27 (s, 1H), 9.17 (br s, 1H), 8.22 (br s, 1H), 8.00 (br dd, J = 2.8, 9.7 Hz, 1H), 7.71 - 7.62 (m, 1H), 7.45 (d, J = 6.7 Hz, 1H), 7.01 (br dd, J = 3.0, 9.8 Hz, 1H), 1.47 (s, 9H).

[0112] **Step 4:** A mixture of tert-butyl N-[5-(6-oxo-1H-pyridazin-3-yl)-2-(trifluoromethoxy)phenyl]carbamate (600 mg, 1.62 mmol, 1 eq) in HCl/EtOAc (4 M, 5 mL, 12.38 eq) was stirred at 20 °C for 1 hr. The mixture was concentrated in a vacuum. The product was used for the next step without purification. Compound 3-[3-amino-4-(trifluoromethoxy)phenyl]-1H-pyridazin-6-one (350 mg, 1.14 mmol, 70% yield, HCl salt) was obtained as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 13.20 (s, 1H), 7.89 (d, J = 9.9 Hz, 1H), 7.35 (d, J = 2.1 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 7.05 (dd, J = 2.1, 8.5 Hz, 1H), 6.97 (d, J = 9.9 Hz, 1H)

[0113] The Intermediates I-047 to I-064 shown in Table C were prepared following the teachings of the General Reaction Schemes and the method to prepare INTERMEDIATE I-046.

Table C

Int.	Intermediate Structure	Structure	Catalyst Name	Intermediate Characterization
I-047			$\text{Pd}(\text{dppf})\text{Cl}_2$	^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 11.60 (s, 1H), 8.27 (dd, J = 6.0 Hz, 8.8 Hz, 1H), 7.66 (s, 1H), 7.42-7.37 (m, 1H), 7.34 (dd, J = 2.8 Hz, 10.8 Hz, 1H). m/z (ES+) $[M+H]^+$ = 289.9.

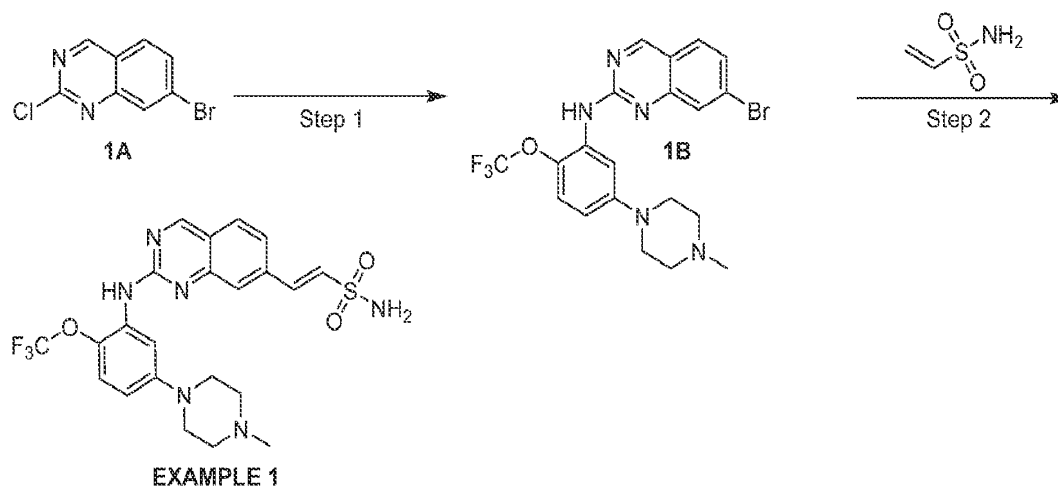
Int.	Intermediate Structure	Structure	Catalyst Name	Intermediate Characterization
I-048			Xantphos Pd G4	m/z (ES+) [M+H] ⁺ = 389.2
I-049			Pd(dtbpf)Cl ₂	¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.64 (br d, J = 5.1 Hz, 1H), 8.20 (dd, J = 1.6, 7.7 Hz, 1H), 7.64 - 7.50 (m, 2H), 7.13 (dd, J = 1.4, 8.3 Hz, 1H), 7.05 (d, J = 5.6 Hz, 1H), 6.83 (t, J = 1.8 Hz, 1H), 6.59 (td, J = 1.9, 8.3 Hz, 1H), 5.43 (s, 2H).
I-050			Pd(dppf)Cl ₂	m/z (ES+) [M+H] ⁺ = 335.0
I-051			Pd(dppf)Cl ₂	¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.43 (d, J = 6.0 Hz, 1H), 7.64-7.56 (m, 1H), 7.55-7.49 (m, 1H), 7.42 (dd, J = 1.2 Hz, 8.4 Hz, 1H), 7.19 (dd, J = 1.2 Hz, 8.0 Hz, 1H), 7.08 (d, J = 6.0 Hz, 1H), 6.82 (d, J = 2.4 Hz, 1H), 6.57 (dd, J = 2.0 Hz, 8.0 Hz, 1H).
I-052			Pd(dtbpf)Cl ₂	m/z (ES+) [M+H] ⁺ = 323.0
I-053			Pd(dppf)Cl ₂	m/z (ES+) [M+H] ⁺ = 364.0
I-054			Pd(dtbpf)Cl ₂	¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.16 (s, 1H), 9.17 (br d, J = 3.2 Hz, 1H), 8.67 (br d, J = 7.4 Hz, 1H), 7.90 (dd, J = 4.6, 7.9 Hz, 1H), 7.31 (s, 1H), 7.21 (br d, J = 8.3 Hz, 1H), 7.06 (br d, J = 8.3 Hz, 1H), 5.52 (s, 2H).
I-055			Pd(dtbpf)Cl ₂	¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.16 (s, 1H), 9.17 (br d, J = 3.2 Hz, 1H), 8.67 (br d, J = 7.4 Hz, 1H), 7.90 (dd, J = 4.6, 7.9 Hz, 1H), 7.31 (s, 1H), 7.21 (br d, J = 8.3 Hz, 1H), 7.06 (br d, J = 8.3 Hz, 1H), 5.52 (s, 2H).
I-056			Pd(dppf)Cl ₂	¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.40 (d, J = 6.0 Hz, 1H), 9.49 (s, 1H), 8.74 (d, J = 6.4 Hz, 1H), 7.72 (dd, J = 6.4 Hz, 10.4 Hz, 2H), 7.25 (dd, J = 1.2 Hz, 8.0 Hz, 1H), 6.87 (d, J = 2.4 Hz, 1H), 6.63 (dd, J = 2.0 Hz, 8.4 Hz, 1H).

Int.	Intermediate Structure	Structure	Catalyst Name	Intermediate Characterization
I-057			Pd(dppf)Cl ₂	¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.22 (br s, 1H), 9.03-8.74 (m, 1H), 8.28 (d, J = 8.4 Hz, 1H), 7.93 (dd, J = 4.4 Hz, 8.4 Hz, 1H), 7.38 (s, 1H), 7.30-7.20 (m, 1H), 6.88 (d, J = 2.0 Hz, 1H), 6.63 (dd, J = 2.0 Hz, 8.4 Hz, 1H).
I-058			Pd(dtbpf)Cl ₂	¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.01 (d, J = 4.4 Hz, 1H), 8.96 (s, 1H), 8.84 (s, 1H), 7.50 (d, J = 5.6 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 6.99 (s, 1H), 6.73 (d, J = 8.4 Hz, 1H).
I-059			Pd(dtbpf)Cl ₂	¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.79 (d, J = 5.6 Hz, 1H), 8.94 (dd, J = 1.6 Hz, 4.4 Hz, 1H), 8.60 (dd, J = 2.0 Hz, 8.0 Hz, 1H), 7.57 (dd, J = 4.4 Hz, 8.0 Hz, 1H), 7.43 (d, J = 6.0 Hz, 1H), 7.22-7.13 (m, 1H), 7.08 (d, J = 2.0 Hz, 1H), 6.82 (dd, J = 1.6 Hz, 8.4 Hz, 1H).
I-060			Pd(dppf)Cl ₂	¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.36 (br s, 1H), 8.63 - 8.04 (m, 2H), 7.68 (s, 1H), 7.25 (br d, J = 8.2 Hz, 1H), 7.05 (s, 1H), 7.03 - 6.98 (m, 2H), 6.79 (br d, J = 8.3 Hz, 1H), 3.89 (s, 3H), 3.78 (s, 3H).
I-061			Pd(dppf)Cl ₂	¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.03 (br d, J = 6.3 Hz, 1H), 9.26 (s, 1H), 8.02 - 7.64 (m, 1H), 7.51 (d, J = 6.1 Hz, 1H), 7.44 (s, 1H), 7.29 (br d, J = 7.9 Hz, 1H), 6.92 (s, 1H), 6.73 - 6.65 (m, 2H).
I-062			Pd(dppf)Cl ₂	m/z (ES ⁺) [M+H] ⁺ = 379.0
I-063			Pd(dppf)Cl ₂	¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.92 (s, 1H), 9.72 (s, 2H), 7.25 (br d, J = 7.9 Hz, 1H), 7.08 (s, 1H), 6.84 (br d, J = 7.8 Hz, 1H), 2.48 - 2.41 (m, 2H), 2.40 - 2.32 (m, 2H), 1.69 (br d, J = 4.9 Hz, 2H), 1.61 (br d, J = 4.2 Hz, 2H).
I-064			Pd(dppf)Cl ₂	¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.89 (s, 1H), 8.40 (d, J = 7.2 Hz, 1H), 8.10-7.92 (m, 2H), 7.80 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.09 (d, J = 2.0 Hz, 1H), 6.82 (dd, J = 2.0 Hz, 8.4 Hz, 1H), 5.68 (s, 2H).

EXAMPLES

[0114] The following examples are intended to illustrate certain embodiments of the invention further and are not intended to limit the scope of the invention.

EXAMPLE 1

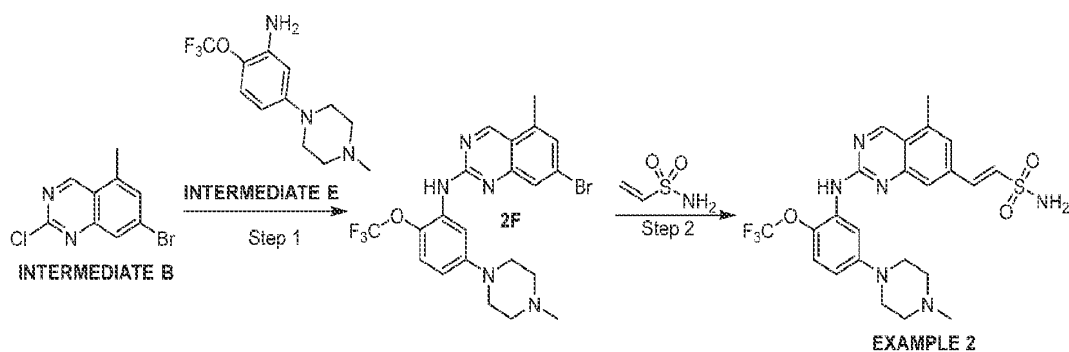


[0115] **Step 1:** To a mixture of 7-bromo-2-chloroquinazoline (663 mg, 2.72 mmol, 1.5 eq) and 5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)aniline (500 mg, 1.82 mmol, 1 eq) in DMF (6 mL) was added 4-methylbenzenesulfonic acid hydrate (415 mg, 2.18 mmol, 1.2 eq) in one portion under N₂. The mixture was stirred at 130 °C for 12 hours. To the mixture was added H₂O (60 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic phase was washed with brine (20 mL), dried with anhydrous Na₂SO₄, filtered, and concentrated in a vacuum. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate = 0/1 to Ethyl acetate/MeOH = 3/1). Compound 7-bromo-N-[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)phenyl]quinazolin-2-amine (500 mg, 1.04 mmol, 57% yield) was obtained as a white solid.

[0116] **Step 2:** To a mixture of 7-Bromo-N-[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)phenyl]quinazolin-2-amine (100 mg, 207 μmol, 1 eq), tris-*o*-tolylphosphane (25 mg, 83.0 μmol, 0.4 eq) and ethylene sulfonamide (67 mg, 622 μmol, 15.0 μL, 3 eq) in DMF (0.3 mL) was added TEA (210 mg, 2.07 mmol, 289 μL, 10 eq) and Pd(OAc)₂ (4.66 mg, 20.7

μmol , 0.1 eq) in one portion under N_2 . The mixture was stirred at $80\text{ }^\circ\text{C}$ for 12 hours. The mixture was combined with a 15 mg scale. The mixture was filtered to get filtrate and concentrated in a vacuum. Prep-HPLC purified the residue (column: Waters XBridge BEH C18 $100 \times 30\text{ mm} \times 10\text{ }\mu\text{m}$; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 35%-65%, 8 min). (E)-2-[2-[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)anilino]quinazolin-7-yl]ethylene sulfonamide (10 mg, 0.2 mmol, 10% yield 100% purity) was obtained as a white solid. ^1H NMR (400 MHz, CD_3CN) δ ppm 9.20 (s, 1H), 8.37 (d, $J = 2.8\text{ Hz}$, 1H), 7.90 (d, $J = 8.4\text{ Hz}$, 1H), 7.86 (s, 1H), 7.71 (s, 1H), 7.64-7.59 (m, 2H), 7.29 (d, $J = 8.4\text{ Hz}$, 1H), 7.24-7.21 (m, 1H), 6.70-6.67 (m, 1H), 5.58 (s, 2H), 3.27 (t, $J = 4.8\text{ Hz}$, 4H), 2.56 (t, $J = 4.8\text{ Hz}$, 4H), 2.15 (s, 3H). m/z (ES^+) $[\text{M}+1]^+ = 509.1$.

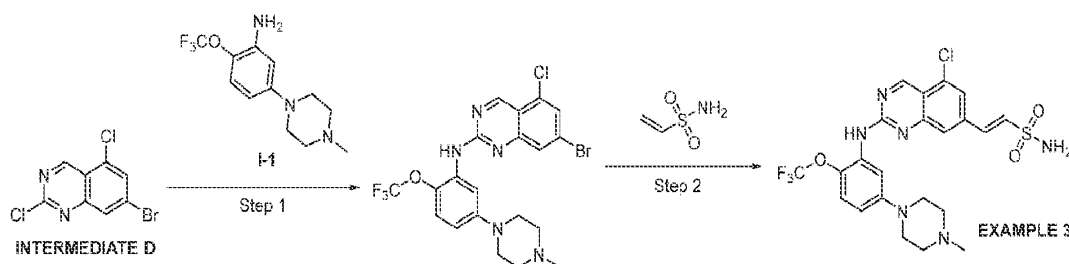
EXAMPLE 2



[0117] **Step 5:** The solution of 7-bromo-2-chloro-5-methylquinazoline (0.1 g, 388 μmol , 1 eq), 5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)aniline (107 mg, 388 μmol , 1 eq) and TFA (89 mg, 777 μmol , 58 μL , 2 eq) in $n\text{-BuOH}$ (10 mL) was stirred at $90\text{ }^\circ\text{C}$ for 12 h. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition; column: Waters XBridge Prep OBD C18 $150 \times 40\text{ mm} \times 10\text{ }\mu\text{m}$; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 45% - 75% B over 8.0 min). 7-bromo-5-methyl-N-(5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)phenyl)quinazolin-2-amine **2F** (40 mg, 81 μmol , 21% yield) was obtained as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 9.40 (s, 1H), 9.20 (s, 1H), 7.60 (d, $J = 2.8\text{ Hz}$, 2H), 7.36 (s, 1H), 7.21 (d, $J = 8.8\text{ Hz}$, 1H), 6.80-6.77 (m, 1H), 3.19-3.17 (m, 4H), 2.66 (s, 3H), 2.48-2.46 (m, 4H), 2.23 (s, 3H).

[0118] **Step 6:** Tris-o-tolylphosphane (2.45 mg, 8.1 μ mol, 0.1 eq) and Pd(OAc)₂ (1.81 mg, 8.06 μ mol, 0.1 eq) were added to the solution of 7-bromo-5-methyl-N-[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)phenyl]quinazolin-2-amine (40 mg, 81.0 μ mol, 1 eq), ethenesulfonamide (8.6 mg, 81 μ mol, 1 eq) and TEA (16 mg, 161 μ mol, 22.4 μ L, 2 eq) in DMF (1 mL) under N₂. The mixture was stirred at 100 °C for 12 h. The mixture (combined with a 60 mg scale) was concentrated in a vacuum without further workup. The residue was purified by prep-HPLC (neutral condition; column: Waters XBridge Prep OBD C18 150 $\times$ 40 mm $\times$ 10 μ m; mobile phase: [H₂O (10 mM NH₄HCO₃)-ACN]; gradient: 30% - 60% B over 8.0 min). 25 mg of (E)-2-[5-methyl-2-[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)anilino]quinazolin-7-yl]ethenesulfonamide **EXAMPLE 2** (98% purity) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.41 (s, 1H), 9.10 (s, 1H), 7.69 (d, *J* = 2.8 Hz, 1H), 7.63 (s, 1H), 7.57 (m, 1H), 7.44 (d, *J* = 4.0 Hz, 2H), 7.22-7.20 (m, 3H), 6.79-6.76 (m, 1H), 3.20-3.18 (m, 4H), 2.68-2.66 (m, 3H), 2.49-2.46 (m, 4H), 2.23 (s, 3H). *m/z* (ES⁺) [M+1]⁺ = 523.2.

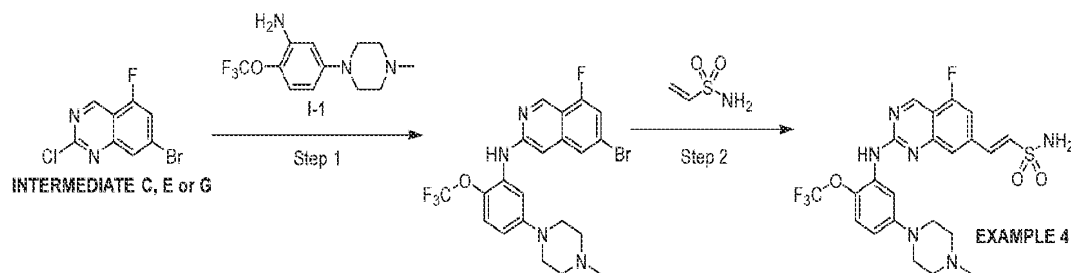
EXAMPLE 3



[0119] **Step 1:** To a solution of 7-bromo-2,5-dichloro-quinazoline (160 mg, 576 μ mol, 1 eq) and 5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)aniline (158 mg, 576 μ mol, 1 eq) in n-BuOH (10 mL) was added TFA (131.28 mg, 1.15 mmol, 86 μ L, 2 eq). The mixture was stirred at 90 °C for 12 hr. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 $\times$ 30mm 5 μ m; mobile phase: [H₂O (10mM NH₄HCO₃)-MeCN]; gradient:55%-85% B over 8.0 min). Compound 7-bromo-5-chloro-N-[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)phenyl]quinazolin-2-amine (60 mg, 116 μ mol, 20% yield) was obtained as a yellow solid. *m/z* (ES⁺) [M+1]⁺ = 516.1.

[0120] **Step 2:** A mixture of 7-bromo-5-chloro-N-[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)phenyl]quinazolin-2-amine (50 mg, 97 μ mol, 1 eq), ethenesulfonamide (12 mg, 116 μ mol, 1.2 eq), Pd(OAc)₂ (2.2 mg, 9.7 μ mol, 0.1 eq), tris-o-tolylphosphane (3.0 mg, 10.0 μ mol, 0.1 eq) and TEA (29 mg, 290 μ mol, 40 μ L, 3 eq) in DMF (1 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 80 °C for 12 hr under N₂ atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 $\times$ 40mm $\times$ 10 μ m; mobile phase: [H₂O(10mM NH₄HCO₃)-MeCN];gradient:35%-65% B over 8.0 min). Compound (E)-2-[5-chloro-2-[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)anilino]quinazolin-7-yl]ethenesulfonamide (12 mg, 20 μ mol, 21% yield, 91% purity) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.41 (s, 1H), 7.94 (s, 1H), 7.79 (s, 1H), 7.65 - 7.59 (m, 1H), 7.52 (br d, J = 2.6 Hz, 1H), 7.45 (d, J = 15.6 Hz, 1H), 7.28 - 7.18 (m, 2H), 6.82 (dd, J = 2.8, 9.1 Hz, 1H), 3.21 - 3.14 (m, 4H), 2.45 (br s, 4H), 2.22 (s, 3H). m/z (ES⁺) [M+1]⁺ = 543.1.

EXAMPLE 4



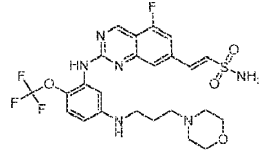
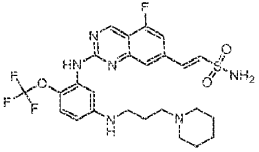
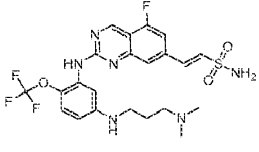
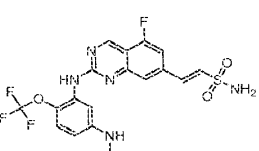
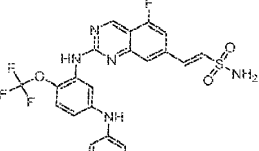
[0121] **Step 1:** To a solution of 7-bromo-2-chloro-5-fluoro-quinazoline (80 mg, 306 μ mol, 1 eq) in n-BuOH (8 mL) was added TFA (70 mg, 612 μ mol, 46 μ L, 2 eq) and 5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)aniline (84.22 mg, 305.95 μ mol, 1 eq). The mixture was stirred at 90 °C for 12 hr. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: 2_Phenomenex Gemini C18 75 $\times$ 40mm $\times$ 3 μ m; mobile phase: [H₂O(10mM NH₄HCO₃)-MeCN];gradient:40%-75% B over 8.0 min). Compound 7-bromo-5-fluoro-N-[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)phenyl]quinazolin-2-amine (30 mg, 60 μ mol, 20% yield) was obtained as a yellow solid.

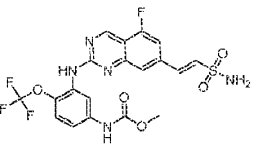
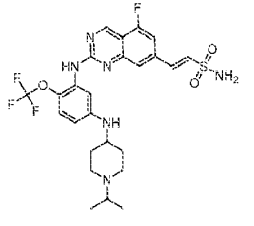
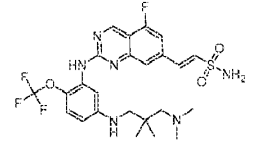
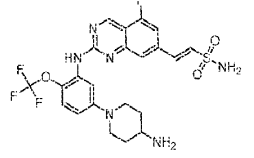
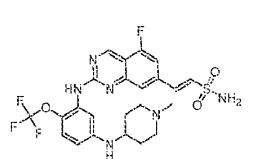
[0122] **Step 2:** To a solution of 7-bromo-5-fluoro-N-[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)phenyl] quinazolin-2-amine (30 mg, 39.98 μmol , 1 eq) and ethenesulfonamide (9 mg, 80 μmol , 2 eq) in DMF (0.1 mL) was added $\text{Pd}(\text{OAc})_2$ (898 μg , 4.00 μmol , 0.1 eq), tris-*o*-tolylphosphane (1.2 mg, 4.0 μmol , 0.1eq) and TEA (8.1 mg, 80 μmol , 11 μL , 2 eq). The mixture was stirred at 80 °C for 12 hr under N_2 . The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 $\times$ 30mm $\times$ 10 μm ; mobile phase: [H_2O (10mM NH_4HCO_3)-MeCN]; gradient: 30%-60% B over 8.0 min). Compound (E)-2-[5-fluoro-2-[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)anilino]quinazolin-7-yl]ethenesulfonamide (6 mg, 19% yield, 97% purity) was obtained as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 9.41 (br d, J = 9.6 Hz, 2H), 7.68 - 7.59 (m, 2H), 7.58 - 7.42 (m, 3H), 7.29 - 7.17 (m, 3H), 6.86 - 6.78 (m, 1H), 3.18 (br s, 4H), 2.48 - 2.43 (m, 4H), 2.23 (s, 3H). m/z (ES^+) $[\text{M}+1]^+ = 527.1$.

[0123] Following the teachings of the General Reaction Schemes and the synthesis procedure for Example 4 were prepared as shown in **Table I**:

Table I

Example	Structure	Name	Spectra	Purification
5		(E)-2-(5-fluoro-2-((5-(4-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	^1H NMR (400 MHz, DMSO- d_6) δ = 9.45 (s, 1H), 9.40 (s, 1H), 7.66 (s, 1H), 7.61 (d, J = 20.0 Hz, 1H), 7.54 (s, 1H), 7.51 (d, J = 2.0 Hz, 1H), 7.48 (s, 1H), 7.27 - 7.22 (m, 3H), 6.81 (dd, J = 2.8 Hz, J = 9.2 Hz, 1H), 4.46 (t, J = 5.2 Hz, 1H), 3.54 (q, J = 6.4 Hz, 2H), 3.19 - 3.16 (m, 4H), 2.58 - 2.56 (m, 4H), 2.44 (t, J = 6.0 Hz, 2H). m/z (ES+) $[M+H]^+$ = 557.0.	Reversed-phase HPLC neutral, column: Agela C18 250 $\times$ 50mm $\times$ 10 μ m; mobile phase: [water(NH ₄ HCO ₃) - ACN]; B%: 10-40% 30 min; 40% 20 min flowrate: 120ml/min.
6		(E)-2-(5-fluoro-2-((3-(4-methylpiperazin-1-yl)propyl)amino)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	^1H NMR (400 MHz, CDCl ₃) δ = 9.21 (s, 1H), 7.55 (d, J = 15.3 Hz, 1H), 7.46 (s, 1H), 7.19 (br d, J = 9.3 Hz, 1H), 7.04 (d, J = 15.3 Hz, 1H), 6.93 (d, J = 9.9 Hz, 1H), 6.75 (d, J = 2.2 Hz, 1H), 6.64 (dd, J = 2.3, 8.6 Hz, 1H), 4.12 - 4.03 (m, 2H), 3.97 (s, 2H), 2.73 - 2.36 (m, 10H), 2.35 (s, 3H), 1.98 - 1.92 (m, 2H). m/z (ES+) $[M+H]^+$ = 584.2.	Reversed-phase HPLC neutral, column: Agela C18 250 $\times$ 50mm $\times$ 10 μ m; mobile phase: [water(NH ₄ HCO ₃) - ACN]; B%: 40-60% 2min; 60% 10min; flowrate: 50ml/min.
7		(E)-2-(5-fluoro-2-((3-(pyrrolidin-1-yl)propyl)amino)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	^1H NMR: (400 MHz, DMSO- d_6 and a drop of D ₂ O) δ = 9.29 (s, 1H), 7.59 (s, 1H), 7.54 - 7.46 (m, 2H), 7.44 - 7.37 (m, 1H), 7.19 (d, J = 7.4 Hz, 1H), 6.79 (d, J = 2.6 Hz, 1H), 6.58 (dd, J = 2.5, 8.5 Hz, 1H), 4.11 - 4.00 (m, 2H), 3.58 - 3.48 (m, 2H), 3.27 - 3.17 (m, 2H), 3.03 - 2.91 (m, 2H), 2.08 - 1.95 (m, 4H), 1.92 - 1.83 (m, 2H). m/z (ES+) $[M+H]^+$ = 555.2.	Reversed-phase HPLC neutral, Agela C18 250 $\times$ 50mm $\times$ 10 μ m; mobile phase: [water(NH ₄ HCO ₃) - ACN]; B%: 35-65% 15 min; 65% 10min, flow rate: 130ml/min.

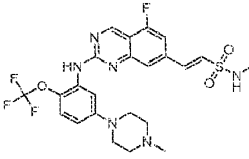
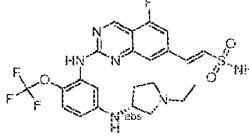
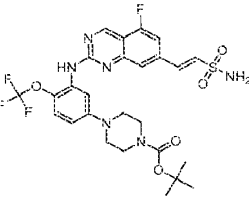
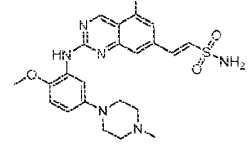
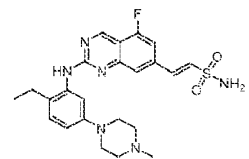
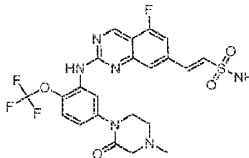
Example	Structure	Name	Spectra	Purification
8		(E)-2-(5-fluoro-2-((5-((3-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamido)propyl)amino)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 9.21 (s, 1H), 7.53 (d, J = 15.1 Hz, 1H), 7.44 (s, 1H), 7.11 (d, J = 8.6 Hz, 1H), 7.03 (d, J = 15.4 Hz, 1H), 6.93 (d, J = 9.8 Hz, 1H), 6.79 (br s, 1H), 6.65 (dd, J = 2.5, 8.6 Hz, 1H), 4.95 (br s, 2H), 4.11 (br t, J = 7.3 Hz, 2H), 4.00 (br s, 2H), 3.78 (br s, 4H), 2.55 (br s, 4H), 2.0 (br s, 2H). m/z (ES+) $[M+H]^+$ = 571.2.	Reversed-phase HPLC neutral, Agela C18 250 $\times$ 50mm $\times$ 10 μ m; mobile phase: [water(NH_4HCO_3) - ACN]; B%: 65% 20min; flowrate: 70ml/min.
9		(E)-2-(5-fluoro-2-((5-((3-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamido)piperidin-1-yl)propyl)amino)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 9.21 (s, 1H), 7.53 (br d, J = 14.9 Hz, 1H), 7.47 (s, 1H), 7.19 (br d, J = 8.2 Hz, 1H), 7.04 (br d, J = 15.3 Hz, 1H), 6.93 (br d, J = 10.0 Hz, 1H), 6.81 (br d, J = 1.4 Hz, 1H), 6.64 (br dd, J = 2.2, 8.5 Hz, 1H), 4.12 - 4.06 (m, 2H), 4.02 (br s, 2H), 2.57 - 2.49 (m, 4H), 2.06 - 1.98 (m, 2H), 1.54 - 1.46 (m, 4H), 0.93 - 0.76 (m, 2H). m/z (ES+) $[M+H]^+$ = 569.2.	Reversed-phase HPLC neutral, Agela C18 250 $\times$ 50mm $\times$ 10 μ m; mobile phase: [water(NH_4HCO_3) - ACN]; B%: 30-60% 25min; 60% 45min; flowrate: 70ml/min.
10		(E)-2-(2-((5-((3-(dimethylamino)propyl)amino)-2-(trifluoromethoxy)phenyl)amino)-5-fluoroquinazolin-7-yl)ethene-1-sulfonamido)propyl)amino)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 9.21 (s, 1H), 7.54 (d, J = 15.3 Hz, 1H), 7.47 (s, 1H), 7.19 (br d, J = 8.7 Hz, 1H), 7.03 (d, J = 15.4 Hz, 1H), 6.92 (d, J = 10.0 Hz, 1H), 6.77 (d, J = 2.4 Hz, 1H), 6.65 (dd, J = 2.4, 8.6 Hz, 1H), 4.14 - 4.04 (m, 2H), 3.98 (s, 2H), 2.48 - 2.40 (m, 2H), 2.30 (s, 6H), 1.97 - 1.91 (m, 2H). m/z (ES+) $[M+H]^+$ = 529.1.	Reversed-phase HPLC neutral, column Agela C18 250 $\times$ 50mm $\times$ 10 μ m; mobile phase: [water(NH_4HCO_3) - ACN]; B%: 25-55% 15min; 75% 10min, flowrate: 130ml/min
11		(E)-2-(5-fluoro-2-((5-((4-(morpholinomethyl)phenyl)amino)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamido)morpholin-4-yl)methyl)amino)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ = 9.47 (s, 1H), 9.41 (s, 1H), 8.37 (s, 1H), 7.77 (d, J = 2.6 Hz, 1H), 7.69 - 7.62 (m, 2H), 7.60 - 7.53 (m, 1H), 7.47 - 7.41 (m, 1H), 7.29 - 7.23 (m, 3H), 7.22 - 7.19 (m, 2H), 7.17 - 7.12 (m, 2H), 6.85 (dd, J = 2.8, 8.9 Hz, 1H), 3.54 (t, J = 4.4 Hz, 4H), 3.38 (s, 2H), 2.33 (br s, 4H). m/z (ES+) $[M+H]^+$ = 619.3.	prep-HPLC (neutral condition; column: Waters Xbridge BEH C18 150 $\times$ 25mm $\times$ 5 μ m; mobile phase: [water(NH_4HCO_3)-MeCN]; gradient: 43%-73% B over 10 min).
12		(E)-2-(5-fluoro-2-((5-((4-(4-methylpiperazin-1-yl)phenyl)amino)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamido)methyl)amino)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ = 9.42 - 9.39 (m, 1H), 9.37 (s, 1H), 8.04 (s, 1H), 7.65 (dd, J = 4.3, 6.7 Hz, 2H), 7.61 (s, 1H), 7.60 - 7.54 (m, 1H), 7.49 - 7.41 (m, 1H), 7.33 (s, 2H), 7.18 (d, J = 8.5 Hz, 1H), 7.11 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 6.69 (dd, J = 2.8, 8.9 Hz, 1H), 3.07 - 3.00 (m, 4H), 2.46 - 2.43 (m, 4H), 2.20 (s, 3H). m/z (ES+) $[M+H]^+$ = 618.0.	prep-HPLC (neutral condition; column: Waters Xbridge BEH C18 250 $\times$ 50mm $\times$ 10 μ m; mobile phase: [water(NH_4HCO_3)-ACN]; gradient: 32%-62% B over 10 min).

Example	Structure	Name	Spectra	Purification
13		methyl (E)-3-((5-fluoro-7-(2-sulfamoylvinyl)quinazolin-2-yl)amino)-4-(trifluoromethoxy)phenyl carbamate	^1H NMR (400 MHz, DMSO- d_6) δ = 9.88 (s, 1H), 9.59 (br s, 1H), 9.41 (s, 1H), 8.09 (d, J = 2.3 Hz, 1H), 7.68 - 7.62 (m, 2H), 7.58 - 7.52 (d, J = 15.2 Hz, 1H), 7.47 - 7.32 (m, 3H), 7.26 (br s, 2H), 3.69 (s, 3H). m/z (ES+) $[M+H]^+$ = 502.0.	prep-HPLC (neutral condition; column: Waters Xbridge BEH C18 250 $\times$ 50mm $\times$ 10 μm ; mobile phase: [water(NH ₄ HCO ₃)-ACN]; gradient: 22%-52% B over 10 min)
14		(E)-2-(5-fluoro-2-((5-((1-isopropylpiperidin-4-yl)amino)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	^1H NMR (400 MHz, DMSO- d_6) δ = 9.38 (s, 1H), 9.26 (s, 1H), 7.66 - 7.52 (m, 3H), 7.45 - 7.37 (m, 1H), 7.28 - 7.18 (m, 3H), 7.08 (br d, J = 8.0 Hz, 1H), 6.42 (dd, J = 2.6, 8.9 Hz, 1H), 5.79 (br d, J = 7.3 Hz, 1H), 3.20 - 3.11 (m, 1H), 2.88 - 2.77 (m, 2H), 2.75 (br dd, J = 4.7, 8.6 Hz, 1H), 2.35 - 2.20 (m, 2H), 1.98 (br d, J = 12.1 Hz, 2H), 1.45 - 1.32 (m, 2H), 0.98 (d, J = 6.5 Hz, 6H). m/z (ES+) $[M+H]^+$ = 569.2.	prep-HPLC (neutral condition; column: Waters Xbridge BEH C18 150 $\times$ 25mm $\times$ 5 μm ; mobile phase: [water(NH ₄ HCO ₃)-MeCN]; gradient:38%-68% B over 10 min)
15		(E)-2-(2-((5-((3-(dimethylamino)-2,2-dimethylpropyl)amino)-2-(trifluoromethoxy)phenyl)amino)-5-fluoroquinazolin-7-yl)ethene-1-sulfonamide	^1H NMR (400 MHz, DMSO- d_6) δ = 9.30 (s, 1H), 9.21 (s, 1H), 7.58 - 7.53 (m, 2H), 7.46 (d, J = 15.6 Hz, 1H), 7.33 (d, J = 15.6 Hz, 1H), 7.19 (br s, 2H), 7.10 (s, 1H), 7.01 (d, J = 8.3 Hz, 1H), 6.42 (dd, J = 2.1, 8.9 Hz, 1H), 5.74 - 5.68 (m, 1H), 2.81 (br d, J = 5.6 Hz, 2H), 2.16 (s, 6H), 2.12 (s, 2H), 0.86 (s, 6H). m/z (ES+) $[M+H]^+$ = 556.8	Reversed-phase HPLC neutral, column: Agela C18 250 $\times$ 50mm $\times$ 10 μm ; mobile phase: [water(NH ₄ HCO ₃)-ACN]; B%: 30-60% 25 min; 60% 45min, 70ml/min
16		(E)-2-(2-((5-(4-aminopiperidin-1-yl)-2-(trifluoromethoxy)phenyl)amino)-5-fluoroquinazolin-7-yl)ethene-1-sulfonamide	^1H NMR (400 MHz, MeOD) δ ppm 9.40 (s, 1H), 8.18 (d, J =2.8 Hz, 1H), 7.60 (s, 1H), 7.54 (d, J =15.2 Hz, 1H), 7.44-7.33 (m, 2H), 7.22 (d, J =9.2 Hz, 1H), 6.80 (dd, J =8.8 Hz, 2.8 Hz, 1H), 3.83 (d, J =13.2 Hz, 2H), 3.10-2.98 (m, 1H), 2.92 (t, J =12.0 Hz, 2H), 2.08-1.98 (m, 2H), 1.73-1.58 (m, 2H). m/z (ES+) $[M+H]^+$ = 527.0.	(Boc penultimate product) prep-HPLC (column: Waters xbridge 150 $\times$ 25mm 10 μm ; mobile phase: [water(NH ₄ HCO ₃)-ACN]; gradient:48%-78% B over 10 min).
17		(E)-2-(5-fluoro-2-((5-((1-methylpiperidin-4-yl)amino)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	^1H NMR (400 MHz, DMSO- d_6) δ = 9.38 (s, 1H), 9.27 (s, 1H), 7.68 - 7.57 (m, 2H), 7.57 - 7.51 (m, 1H), 7.44 - 7.37 (m, 1H), 7.27 (s, 2H), 7.22 (br d, J = 2.2 Hz, 1H), 7.08 (dd, J = 1.0, 9.0 Hz, 1H), 6.42 (dd, J = 2.8, 8.9 Hz, 1H), 5.79 (d, J = 7.8 Hz, 1H), 3.20 - 3.09 (m, 1H), 2.80 - 2.73 (m, 2H), 2.16 (s, 3H), 2.06 - 1.89 (m, 4H), 1.50 - 1.35 (m, 2H). m/z (ES+) $[M+H]^+$ = 541.2.	prep-HPLC (neutral condition; column: Waters Xbridge BEH C18 250 $\times$ 50mm $\times$ 10 μm ; mobile phase: [water(NH ₄ HCO ₃)-ACN]; gradient:18%-48% B over 10 min).

Example	Structure	Name	Spectra	Purification
18		(E)-2-(2-((5-((1-ethylpiperidin-4-yl)amino)-2-(trifluoromethoxy)phenyl)amino)-5-fluoroquinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.38 (s, 1H), 9.26 (s, 1H), 7.62 (d, J = 11.0 Hz, 1H), 7.59 (s, 1H), 7.56 - 7.50 (m, 1H), 7.45 - 7.36 (m, 1H), 7.26 (s, 2H), 7.21 (d, J = 2.3 Hz, 1H), 7.13 - 7.04 (m, 1H), 6.43 (dd, J = 2.8, 8.9 Hz, 1H), 5.80 (br d, J = 7.5 Hz, 1H), 3.19 (br dd, J = 3.4, 6.2 Hz, 1H), 2.90 (br d, J = 11.1 Hz, 2H), 2.38 (q, J = 7.2 Hz, 2H), 2.08 (br t, J = 10.8 Hz, 2H), 1.98 (br d, J = 11.5 Hz, 2H), 1.48 - 1.35 (m, 2H), 1.01 (t, J = 7.1 Hz, 3H). m/z (ES ⁺) [M+H] ⁺ = 555.2.	Prep-HPLC (neutral condition; column: Waters Xbridge BEH C18 250 × 50mm × 10 μm; mobile phase: [water(NH ₄ HCO ₃)-ACN]; gradient: 19%-49% B over 10 min).
19		(E)-2-(5-fluoro-2-((5-((1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl)amino)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.39 (s, 1H), 9.26 (s, 1H), 7.63 (d, J = 11.1 Hz, 1H), 7.60 - 7.50 (m, 2H), 7.47 - 7.34 (m, 1H), 7.25 (br s, 3H), 7.08 (d, J = 8.0 Hz, 1H), 6.42 (dd, J = 2.8, 9.0 Hz, 1H), 5.78 (d, J = 7.6 Hz, 1H), 3.88 (br dd, J = 2.8, 11.6 Hz, 2H), 3.30 - 3.23 (m, 2H), 3.23 - 3.09 (m, 1H), 2.90 (br d, J = 11.3 Hz, 2H), 2.46 - 2.37 (m, 1H), 2.28 - 2.17 (m, 2H), 1.99 (br d, J = 10.9 Hz, 2H), 1.67 (br d, J = 11.8 Hz, 2H), 1.48 - 1.32 (m, 4H). m/z (ES ⁺) [M+1] ⁺ = 611.2.	Silica Gel chromatography (Petroleum ether/Ethyl acetate=2:1 to 0:1).
20		(R,E)-2-(5-fluoro-2-((5-((1-isopropylpyrrolidin-3-yl)amino)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.39 (s, J = 2.2 Hz, 1H), 9.26 (s, 1H), 7.62 (s, 2H), 7.58 - 7.49 (m, 1H), 7.45 - 7.36 (m, 1H), 7.30 - 7.16 (m, 3H), 7.10 (d, J = 9.4 Hz, 1H), 6.40 (d, J = 8.8 Hz, 1H), 6.10 - 5.94 (m, 1H), 3.88 - 3.80 (m, 1H), 2.94 - 2.87 (m, 1H), 2.73 - 2.65 (m, 1H), 2.49 - 2.31 (m, 3H), 2.24 - 2.14 (m, 1H), 1.64 (dd, J = 2.4, 6.5 Hz, 1H), 1.04 (s, 6H). m/z (ES ⁺) [M+1] ⁺ = 555.2.	Prep-HPLC (neutral, column: 330g Agela C18, Solvent for sample about 5 grams of sample, dissolution: dissolved in 25 ml of MeCN; flowrate: 70ml/min, mobile phase: water, gradient B%:30-60% 25min;60% 45min; Instrument: Biotage).
21		(S,E)-2-(5-fluoro-2-((5-((1-isopropylpyrrolidin-3-yl)amino)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.39 (s, 1H), 9.27 (s, 1H), 7.60-7.66 (m, 2H), 7.50-7.57 (m, 1H), 7.38-7.45 (m, 1H), 7.26 (s, 2H), 7.19 (d, J = 2.4 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 6.40-6.42 (m, 1H), 6.05 (d, J = 6.2 Hz, 1H), 3.76-3.92 (m, 1H), 2.88-2.94 (m, 1H), 2.70-2.73 (m, 1H), 2.51-2.59 (m, 2H), 2.37-2.46 (m, 1H), 2.11-2.27 (m, 1H), 1.54-1.72 (m, 1H), 1.04 (dd, J = 6.0 Hz, 3.2 Hz, 6H). m/z (ES ⁺) [M+H] ⁺ = 555.3.	prep-HPLC (FA condition; column: Phenomenex luna C18 (250 × 70mm, 10 μm); mobile phase: [water(FA)-ACN]; gradient: 8%-38% B over 20 min).

Example	Structure	Name	Spectra	Purification
22		(E)-2-((5-(4-ethylpiperazin-1-yl)-2-(trifluoromethoxy)phenyl)amino)-5-fluoroquinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, CD ₃ CN) δ = 9.41 (s, 1H), 8.26 (d, J = 3.0 Hz, 1H), 7.85 (s, 1H), 7.70 (s, 1H), 7.60 (d, J = 15.4 Hz, 1H), 7.36 (dd, J = 1.2, 10.8 Hz, 1H), 7.33 - 7.23 (m, 2H), 6.74 (dd, J = 3.0, 9.1 Hz, 1H), 3.34 - 3.25 (m, 4H), 2.68 - 2.59 (m, 4H), 2.48 (q, J = 7.0 Hz, 2H), 1.12 (t, J = 7.3 Hz, 3H) m/z (ES ⁺) [M+1] ⁺ = 541.1	prep-HPLC (column: Waters Xbridge BEH C18 100 × 30mm × 10μm; mobile phase: [H ₂ O(10mM NH ₄ HCO ₃)-ACN]; gradient: 35%-65% B over 8.0 min).
23		(E)-2-((5-((1-benzylpiperidin-4-yl)amino)-2-(trifluoromethoxy)phenyl)amino)-5-fluoroquinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, CD ₃ CN) δ = 9.41 (s, 1H), 8.26 (d, J = 3.0 Hz, 1H), 7.85 (s, 1H), 7.70 (s, 1H), 7.60 (d, J = 15.4 Hz, 1H), 7.36 (dd, J = 1.2, 10.8 Hz, 1H), 7.33 - 7.23 (m, 2H), 6.74 (dd, J = 3.0, 9.1 Hz, 1H), 3.34 - 3.25 (m, 4H), 2.68 - 2.59 (m, 4H), 2.48 (q, J = 7.0 Hz, 2H), 1.12 (t, J = 7.3 Hz, 3H) m/z (ES ⁺) [M+1] ⁺ = 541.1	prep-HPLC (neutral condition). column: Daisogel SP ODS RPS 150 × 25mm × 5μm; mobile phase: [water(NH ₄ HCO ₃)-ACN]; gradient: 50%-80% B over 10 min.
24		(E)-2-((5-((2-(diisopropylamino)ethyl)amino)-2-(trifluoromethoxy)phenyl)amino)-5-fluoroquinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.74 (br s, 1H), 9.38 (d, J = 14.0 Hz, 2H), 7.70 (s, 1H), 7.63 (br d, J = 10.6 Hz, 1H), 7.60 - 7.54 (m, 1H), 7.46 - 7.39 (m, 1H), 7.35 - 7.20 (m, 3H), 7.17 (br d, J = 9.0 Hz, 1H), 6.48 (dd, J = 2.7, 8.8 Hz, 1H), 3.56 - 3.48 (m, 4H), 3.21 (br t, J = 6.3 Hz, 2H), 1.30 (br s, 12H). m/z (ES ⁺) [M+H] ⁺ = 571.0	prep-HPLC (neutral condition). column: Waters Xbridge BEH C18 250 × 50mm × 10μm; mobile phase: [water(NH ₄ HCO ₃)-ACN]; gradient: 53%-83% B over 10 min.
25		(E)-2-(5-fluoro-2-((5-((2-methyl-1-morpholinopropan-2-yl)amino)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, CD ₃ CN) δ = 9.41 (s, 1H), 8.17 (d, J = 2.8 Hz, 1H), 7.80 (s, 1H), 7.66 (s, 1H), 7.55 (d, J = 15.6 Hz, 1H), 7.35 (dd, J = 1.1, 10.7 Hz, 1H), 7.27 (d, J = 15.4 Hz, 1H), 7.12 (dd, J = 1.3, 8.9 Hz, 1H), 6.52 (dd, J = 2.9, 8.9 Hz, 1H), 5.63 (s, 2H), 4.72 (br d, J = 2.8 Hz, 1H), 3.69 - 3.58 (m, 4H), 2.60 - 2.56 (m, 4H), 2.56 (s, 2H), 1.42 (s, 6H). m/z (ES ⁺) [M+1] ⁺ = 585.2	prep-HPLC (column: Phenomenex Gemini-NX 80 × 30mm × 3μm; mobile phase: [H ₂ O(10mM NH ₄ HCO ₃)-ACN]; gradient: 45%-75% B over 8.0 min).
26		(E)-2-(5-fluoro-2-((5-(4-methylpiperazin-1-yl)-2-(methylthio)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.40 (s, 1H), 9.03 (s, 1H), 8.15 (s, 1H), 7.86 (br s, 1H), 7.71 (s, 1H), 7.65 (d, J = 10.8 Hz, 1H), 7.60 - 7.45 (m, 2H), 7.38 (d, J = 8.6 Hz, 1H), 7.26 (s, 2H), 6.77 (dd, J = 2.6, 8.8 Hz, 1H), 3.24 - 3.19 (m, 8H), 2.29 (s, 3H), 2.25 (s, 3H) m/z (ES ⁺) [M+H] ⁺ = 489.1	prep-HPLC (FA condition; column: Phenomenex Luna C18 (250 × 70mm, 10 μm); mobile phase: [water(FA)-ACN]; gradient: 5%-30% B over 25 min)

Example	Structure	Name	Spectra	Purification
27		(E)-2-((5-(4-methyl-1,4-diazepan-1-yl)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.40 (s, 1H), 9.32 (s, 1H), 7.66 - 7.59 (m, 2H), 7.58 - 7.52 (m, 1H), 7.49 - 7.41 (m, 1H), 7.36 (br d, J = 2.1 Hz, 1H), 7.27 (br s, 2H), 7.16 (dd, J = 1.1, 9.1 Hz, 1H), 6.54 (dd, J = 3.0, 9.1 Hz, 1H), 3.56 - 3.51 (m, 2H), 3.48 - 3.45 (m, 2H), 2.68 - 2.61 (m, 2H), 2.48 (br d, J = 5.8 Hz, 2H), 2.28 (s, 3H), 1.98 - 1.87 (m, 2H). m/z (ES+) [M+1] ⁺ = 541.2	Prep HPLC (neutral, column: 330g Agela C18, Solvent for sample about 5.00 grams of sample, dissolution: dissolved in 25 ml of MeOH; flowrate: 70ml/min, mobile phase: water, gradient B%:30-60% 25min; 60% 45min; Instrument: Biotage).
28		7-bromo-5-fluoro-N-((4-pyrrolidin-1-yl-1-piperidin-2-yl)-2-(trifluoromethoxy)phenyl)quinazolin-2-amine	¹ H NMR (400 MHz, MeOD-d ₄) δ = 9.39 (s, 1H), 8.17 (d, J = 2.0 Hz, 1H), 7.62 - 7.49 (m, 2H), 7.42 - 7.32 (m, 2H), 7.20 (d, J = 8.6 Hz, 1H), 6.77 (dd, J = 2.8, 8.8 Hz, 1H), 3.83 (d, J = 12.2 Hz, 2H), 2.94 - 2.78 (m, 2H), 2.70 (s, 4H), 2.34 - 2.22 (m, 1H), 2.10 (d, J = 12.8 Hz, 2H), 1.84 (s, 4H), 1.78 - 1.60 (m, 2H). m/z (ES+) [M+1] ⁺ = 581.2	reversed-phase HPLC (neutral, column: 800g Agela C18, Solvent for sample about 8.00 grams of sample, dissolution: dissolved in 60 ml of ACN; flowrate: 120 ml/min, mobile phase: water, gradient B%:5-35% 30 min; 35 % 20min; Instrument: Biotage).
29		(E)-2-((2-cyclopropyl-5-(4-methylpiperazin-1-yl)phenyl)amino)-5-fluoroquinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 10.79-10.75 (m, 1H), 9.38 (s, 1H), 9.20 (s, 1H), 7.64-7.57 (m, 2H), 7.51-7.48 (m, 1H), 7.45-7.41 (m, 1H), 7.31-7.23 (m, 2H), 6.97-6.95 (m, 1H), 6.78 (dd, J=2.8 Hz, 8.8 Hz, 1H), 3.79 (d, J=11.6 Hz, 2H), 3.50 (d, J=10.8 Hz, 2H), 3.17-3.09 (m, 4H), 2.82 (d, J=4.4 Hz, 3H), 1.97-1.90 (m, 1H), 1.81-0.78 (m, 2H), 0.55-0.51 (m, 2H). m/z (ES+) [M+1] ⁺ = 483.2	prep-HPLC (column: Phenomenex luna C18 (250 × 70mm, 10 μm); mobile phase: [water(FA)-ACN]; gradient: 11%-41% B over 22 min).
30		(E)-2-((2-cyclopropoxy-5-(4-methylpiperazin-1-yl)phenyl)amino)-5-fluoroquinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.36 (s, 1H), 7.94 (s, 1H), 7.66 (s, 1H), 7.58 (d, J = 11.2 Hz, 1H), 7.51-7.44 (m, 2H), 7.21 (d, J = 8.8 Hz, 1H), 6.70 (dd, J = 2.8 Hz, 8.8 Hz, 1H), 3.87-3.84 (m, 1H), 3.09-3.07 (m, 4H), 2.45-2.5 (m, 4H), 2.22 (s, 3H), 0.75-0.71 (m, 2H), 0.66-0.64 (m, 2H). m/z (ES+) [M+H] ⁺ = 499.2	prep-HPLC (column: Phenomenex luna C18 (250 × 70mm, 10 μm); mobile phase: [water(FA)-ACN]; gradient: 9%-39% B over 20 min).
31		(S,E)-2-((5-((1-ethylpyrrolidin-3-yl)amino)-2-(trifluoromethoxy)phenyl)amino)-5-fluoroquinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, CD ₃ CN -d ₃) δ = 9.36 (s, 1H), 7.96 (d, J = 2.6 Hz, 1H), 7.79 - 7.66 (m, 2H), 7.53 (d, J = 15.6 Hz, 1H), 7.32 - 7.26 (m, 2H), 7.13 (d, J = 1.4, 8.9 Hz, 1H), 6.36 (dd, J = 2.8, 8.9 Hz, 1H), 4.98 (d, J = 6.4 Hz, 1H), 4.12 - 3.92 (m, 1H), 2.98 (d, J = 6.8, 9.6 Hz, 1H), 2.92 - 2.83 (m, 1H), 2.72 - 2.58 (m, 4H), 2.46 - 2.33 (m, 3H), 1.79 - 1.71 (m, 1H), 1.13 (t, J = 7.3 Hz, 3H). m/z (ES+) [M+H] ⁺ = 541.1. 97.64% ee on SFC	reversed-phase HPLC (column: 200g Agela C18, Solvent for sample about 40 grams of sample, dissolution: dissolved in 300 ml of MeOH; flowrate: 450ml/min, mobile phase: water, gradient B%:30-60% 30min; 60% 30min; Instrument: Biotage)

Example	Structure	Name	Spectra	Purification
32		(E)-2-((5-fluoro-2-((5-(4-methylpiperazin-1-yl)-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)-N-methylethene-1-sulfonamide	¹ H NMR (400 MHz, CD ₃ CN -d ₃) δ = 9.38 (s, 1H), 8.23 (d, J = 2.8 Hz, 1H), 7.83 (s, 1H), 7.69 (s, 1H), 7.55 (d, J = 15.8 Hz, 1H), 7.35 (d, J = 10.8 Hz, 1H), 7.24 (d, J = 9.0 Hz, 1H), 7.10 (d, J = 15.6 Hz, 1H), 6.71 (dd, J = 3.0, 9.0 Hz, 1H), 5.35 - 5.24 (m, 1H), 3.29 - 3.25 (m, 4H), 2.66 (d, J = 5.2 Hz, 3H), 2.59 - 2.55 (m, 4H), 2.31 (s, 3H). m/z (ES+) [M+H] ⁺ = 541.2.	Prep-HPLC column: Waters Xbridge BEH C18 250 × 50mm × 10 μm; mobile phase: [water(NH ₄ HCO ₃)-ACN]; B%: 25%-50%, 10min.
33		(R,E)-2-((5-((1-ethylpyrrolidin-3-yl)amino)-2-(trifluoromethoxy)phenyl)amino)-5-fluoroquinazolin-7-ylethene-1-sulfonamide	¹ H NMR (400 MHz, MeCN-d ₃) δ = 9.39 (s, 1H), 7.98 (d, J = 2.3 Hz, 1H), 7.83 - 7.68 (m, 2H), 7.55 (d, J = 15.4 Hz, 1H), 7.37 - 7.26 (m, 2H), 7.15 (br d, J = 9.5 Hz, 1H), 6.38 (dd, J = 2.6, 8.9 Hz, 1H), 5.02 - 4.85 (m, 1H), 4.13 - 3.94 (m, 1H), 3.08 - 2.93 (m, 1H), 2.91 - 2.79 (m, 1H), 2.71 - 2.55 (m, 4H), 2.42 - 2.37 (m, 1H), 1.81 - 1.72 (m, 1H), 1.15 (t, J = 7.2 Hz, 3H). m/z (ES+) [M+1] ⁺ = 541.1.	flash silica gel chromatography (ISCO®; 50 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ethergradient @ 100mL/min).
34		tert-butyl (E)-4-(3-((5-fluoro-7-(2-sulfamoylvinyl)quinazolin-2-yl)amino)-4-(trifluoromethoxy)phenyl)piperazine-1-carboxylate	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.44 (s, 1H), 9.40 (s, 1H), 7.68 (s, 1H), 7.64 (d, J = 11.1 Hz, 1H), 7.56 (d, J = 15.5 Hz, 2H), 7.50 - 7.44 (m, 1H), 7.29 - 7.18 (m, 3H), 6.83 (dd, J = 2.9, 9.1 Hz, 1H), 3.52 - 3.45 (m, 4H), 3.23 - 3.10 (m, 4H), 1.42 (s, 9H). m/z (ES+) [M+H] ⁺ = 613.3.	prep-HPLC (column: Phenomenex luna C18 (250 × 70mm, 10 μm); mobile phase: [water(FA)-ACN]; gradient: 30%-60% B over 5 min).
35		(E)-2-((5-fluoro-2-((2-methoxy-5-(4-methylpiperazin-1-yl)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.42 - 9.32 (m, 1H), 8.50 (s, 1H), 8.03 (br s, 1H), 7.71 (s, 1H), 7.64 (d, J = 11.0 Hz, 1H), 7.60 - 7.54 (m, 1H), 7.53 - 7.46 (m, 1H), 7.26 (s, 2H), 6.96 (d, J = 8.9 Hz, 1H), 6.66 (dd, J = 2.9, 8.9 Hz, 1H), 3.80 (s, 3H), 3.14 - 3.06 (m, 4H), 2.50 (br s, 4H), 2.24 (s, 3H). m/z (ES+) [M+H] ⁺ = 473.1.	Phenomenex luna C18 (250 × 70mm, 10 μm); mobile phase: [water(FA)-ACN]; gradient: 5%-30% B over 25 min).
36		(E)-2-((2-((2-ethyl-5-(4-methylpiperazin-1-yl)phenyl)amino)-5-fluoroquinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.32 (s, 1H), 9.22 (s, 1H), 7.56-7.48 (m, 3H), 7.44-7.37 (m, 1H), 7.22 (s, 2H), 7.12 (d, J = 8.4 Hz, 1H), 7.07-7.03 (m, 1H), 6.79 (dd, J = 8.8 Hz, 2.8 Hz, 1H), 3.14-3.04 (m, 4H), 2.56-2.51 (m, 2H), 2.48-2.43 (m, 4H), 2.22 (s, 3H), 1.06 (t, J = 7.6 Hz, 3H). m/z (ES+) [M+H] ⁺ = 471.0.	prep-HPLC (column: Phenomenex luna C18 (250 × 70mm, 10 μm); mobile phase: [water(FA)-ACN]; gradient: 5%-35% B over 25 min).
37		(E)-2-((5-fluoro-2-((5-(4-methyl-2-oxopiperazin-1-yl)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.71 (s, 1H), 9.43 (s, 1H), 7.95 (d, J = 2.5 Hz, 1H), 7.69 - 7.63 (m, 2H), 7.59 - 7.54 (m, 1H), 7.49 - 7.42 (m, 2H), 7.31 - 7.23 (m, 3H), 3.73 (t, J = 5.3 Hz, 2H), 3.15 (s, 2H), 2.78 - 2.74 (m, 2H), 2.30 (s, 3H). m/z (ES+) [M+1] ⁺ = 541.1.	silica gel chromatography (Petroleum ether/Ethyl acetate=10/1 to 3/1).

Example	Structure	Name	Spectra	Purification
38		(E)-5-fluoro-N-(5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)phenyl)-7-(2-(methylsulfonyl)vinyl)quinazolin-2-amine	^1H NMR (400 MHz, $\text{CD}_3\text{CN}-d_3$) δ = 9.39 (s, 1H), 8.21 (d, J = 2.8 Hz, 1H), 7.85 (s, 1H), 7.74 - 7.61 (m, 2H), 7.37 - 7.30 (m, 2H), 7.23 (d, J = 9.0 Hz, 1H), 6.72 (dd, J = 3.2, 9.2 Hz, 1H), 3.28 - 3.23 (m, 4H), 3.04 (s, 3H), 2.57 - 2.51 (m, 4H), 2.29 (s, 3H). m/z (ES+) $[M+H]^+$ = 526.1.	Prep-HPLC column: Waters Xbridge BEH C18 250 $\times$ 50mm $\times$ 10 μm ; mobile phase: [water(NH_4HCO_3)-ACN]; B%: 25%-50%, 10min.
39		(E)-2-((5-(4-(3-(dimethylamino)propyl)piperazin-1-yl)-2-(trifluoromethoxy)phenyl)amino)-5-fluoroquinazolin-7-yl)ethene-1-sulfonamide	^1H NMR (400 MHz, MeOD) δ = 9.42 (s, 1H), 8.21 (d, J =2.8Hz, 1H), 7.65-7.56 (m, 2H), 7.43-7.37 (m, 2H), 7.26-7.24 (m, 1H), 6.82 (dd, J =3.2 Hz, 9.2 Hz, 1H), 2.74-2.71 (m, 4H), 2.52-2.43 (m, 4H), 2.32 (s, 6H), 1.82-1.78 (m, 2H). ^1H NMR (400 MHz, CDCl_3) δ = 9.34 (s, 1H), 8.78 (br s, 1H), 7.71 (br d, J = 13.0 Hz, 2H), 7.60 (d, J = 15.3 Hz, 1H), 7.38 (br d, J = 15.3 Hz, 1H), 7.18 (br d, J = 9.0 Hz, 2H), 7.03 (br d, J = 9.6 Hz, 1H), 6.63 (dd, J = 2.7, 8.8 Hz, 1H), 3.44 - 3.34 (m, 4H), 3.02 (br d, J = 7.4 Hz, 2H), 2.74 (br s, 10H), 2.54 (br t, J = 6.4 Hz, 2H), 2.10 - 2.05 (m, 2H). m/z (ES+) $[M+H]^+$ = 598.3	prep-HPLC (column: CD07-Daisogel SP-100-8-ODS-PK 150 $\times$ 25 $\times$ 10 μm ;mobile phase: [water(NH_4HCO_3)-ACN];gradient:37%-57% B over 10 min).
40		(E)-2-(5-fluoro-2-(((1r,4r)-4-(piperidin-1-yl)cyclohexyl)amino)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	^1H NMR (400 MHz, DMSO- d_6) δ = 9.38 (s, 1H), 9.27 (s, 1H), 7.68-7.57 (m, 2H), 7.56-7.50 (m, 1H), 7.45-7.36 (m, 1H), 7.25 (s, 2H), 7.15 (d, J = 2.0 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 6.40 (dd, J = 2.8 Hz, 9.2 Hz, 1H), 5.73 (d, J = 7.6 Hz, 1H), 3.12-3.04 (m, 1H), 2.47-2.42 (m, 4H), 2.31-2.25 (m, 1H), 2.08 (d, J = 11.2 Hz, 2H), 1.79 (d, J = 11.2 Hz, 2H), 1.52-1.42 (m, 4H), 1.40-1.32 (m, 4H), 1.21-1.11 (m, 2H). m/z (ES+) $[M+H]^+$ = 609.2.	prep-HPLC (column: Phenomenex luna C18 150 $\times$ 25mm $\times$ 10 μm ;mobile phase: [water(HCl)-ACN];gradient:25%-55% B over 14 min) and then by prep-HPLC (Neutral condition; column: CD07-Daisogel SP-100-8-ODS-PK 150 $\times$ 25 $\times$ 10 μm ;mobile phase: [water(NH_4HCO_3)-ACN];gradient:45%-75% B over 10 min).

Example	Structure	Name	Spectra	Purification
41		(E)-2-(5-fluoro-2-(((1s,4s)-4-(piperidin-1-yl)cyclohexyl)amino)-2-(trifluoromethoxy)phenyl)aminoquinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, MeOD) δ = 9.38 (s, 1H), 7.85 (d, J=2.4 Hz, 1H), 7.63 (s, 1H), 7.55-7.52 (m, 1H), 7.40-7.34 (m, 2H), 7.09-7.07 (m, 1H), 6.45 (dd, J=2.8 Hz, 8.8 Hz, 1H), 3.64 (s, 1H), 2.71 (s, 4H), 2.13 (d, J=11.6 Hz, 2H), 1.78-1.66 (m, 11H), 1.52-1.51 (m, 2H). ¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.37 (s, 1H), 9.27 (s, 1H), 7.59 (br t, J = 14.1 Hz, 2H), 7.52 (s, 1H), 7.46 - 7.38 (m, 1H), 7.26 (s, 2H), 7.14 (br d, J = 1.9 Hz, 1H), 7.07 (br d, J = 8.6 Hz, 1H), 6.47 (dd, J = 2.6, 8.9 Hz, 1H), 5.80 (br d, J = 7.3 Hz, 1H), 3.43 (br s, 1H), 2.46 (br s, 4H), 1.84 - 1.67 (m, 4H), 1.63 - 1.45 (m, 9H), 1.37 (br d, J = 4.5 Hz, 2H). m/z (ES+) [M+H] ⁺ = 609.3	prep-HPLC (column: CD07-Daisogel SP-100-8-ODS-PK 150 × 25 × 10 μ m; mobile phase: [water(NH ₄ HCO ₃)-ACN]; gradient: 40%-60% B over 10 min).
42		(E)-2-(2-((2-(azetidin-1-yl)-5-(4-methylpiperazin-1-yl)phenyl)amino)-5-fluoroquinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, MeOD) δ = 9.26 (s, 1H), 7.49-7.42 (m, 3H), 7.29-7.22 (m, 2H), 6.79 (dd, J=2.4 Hz, 8.4 Hz, 1H), 6.68 (d, J=8.8 Hz, 1H), 3.73 (t, J=6.8 Hz, 4H), 3.09 (t, J=4.8 Hz, 4H), 2.58 (t, J=4.8 Hz, 4H), 2.30 (s, 3H), 2.19-2.12 (m, 2H). m/z (ES+) [M+H] ⁺ = 498.2	prep-HPLC (neutral condition). column: CD07-Daisogel SP-100-8-ODS-PK 150 × 25 × 10 μ m; mobile phase: [water(NH ₄ HCO ₃)-ACN]; gradient: 22%-52% B over 10 min.
43		(E)-2-(5-fluoro-2-(((1s,4s)-4-(4-phenylpiperazin-1-yl)cyclohexyl)amino)-2-(trifluoromethoxy)phenyl)aminoquinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.38 (s, 1H), 9.29 (s, 1H), 7.65 - 7.58 (m, 2H), 7.57 - 7.51 (m, 1H), 7.42 (br d, J = 15.1 Hz, 1H), 7.27 (s, 2H), 7.23 - 7.13 (m, 3H), 7.08 (br d, J = 8.3 Hz, 1H), 6.92 (br d, J = 8.3 Hz, 2H), 6.76 (t, J = 7.1 Hz, 1H), 6.52 - 6.45 (m, 1H), 5.85 (br d, J = 7.1 Hz, 1H), 3.45 (br d, J = 3.8 Hz, 1H), 3.18 - 3.06 (m, 4H), 2.63 (br s, 4H), 2.30 - 2.19 (m, 1H), 1.85 - 1.71 (m, 4H), 1.68 - 1.52 (m, 4H). m/z (ES+) [M+H] ⁺ = 686.2.	silica gel chromatography (Petroleum ether/Ethyl acetate=10/1, 3/1).
44		(S,E)-2-(5-fluoro-2-(((5-(2-(pyrrolidin-1-yl)methyl)pyrrolidin-1-yl)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.39 (s, 1H), 9.35 (s, 1H), 7.60-7.69 (m, 2H), 7.40-7.57 (m, 2H), 7.23-7.30 (m, 3H), 7.19 (dd, J = 9.2 Hz, 1.2 Hz, 1H), 6.38 (dd, J = 9.2 Hz, 2.8 Hz, 1H), 3.73-3.91 (m, 1H), 3.37-3.46 (m, 1H), 3.03-3.16 (m, 1H), 2.54-2.61 (m, 2H), 2.34-2.48 (m, 4H), 1.90-2.08 (m, 4H), 1.47-1.63 (m, 4H). m/z (ES+) [M+H] ⁺ = 581.3.	Silica Gel Chromatography (SiO ₂ , Petroleum ether/ Ethyl acetate= 8/1 to 5/1).

Example	Structure	Name	Spectra	Purification
45		(E)-2-((5-(((1r,4r)-4-(dimethylamino)cyclohexyl)amino)-2-(trifluoromethoxy)phenyl)amino)-5-fluoroquinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.38 (s, 1H), 9.25 (s, 1H), 7.72-7.46 (m, 3H), 7.44-7.36 (m, 1H), 7.34-7.13 (m, 3H), 7.07 (d, J = 8.8 Hz, 1H), 6.40 (dd, J = 2.8 Hz, 9.2 Hz, 1H), 5.74 (br d, J = 7.6 Hz, 1H), 3.18-3.05 (m, 1H), 2.46-2.40 (m, 1H), 2.17 (s, 6H), 2.12-2.03 (m, 2H), 1.84 (br d, J = 11.6 Hz, 2H), 1.37-1.08 (m, 4H). m/z (ES+) [M+H] = 569.2.	prep-HPLC (column: Phenomenex luna C18 (250 × 70mm, 10 μm); mobile phase: [water(NH ₄ HCO ₃)-ACN]; gradient: 28%-58% B over 20 min).
46		(E)-2-((5-fluoro-2-((5-(4-oxo-3,4-dihydrophthalazin-1-yl)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.94 (s, 1H), 9.88 (s, 1H), 9.45 (s, 1H), 8.37 (d, J = 7.6 Hz, 1H), 8.23 (d, J = 2.0 Hz, 1H), 8.04-7.88 (m, 3H), 7.68-7.49 (m, 5H), 7.47-7.40 (m, 1H), 7.27 (br s, 2H). m/z (ES+) [M+H] = 573.0.	prep-HPLC (column: CD02-Waters Xbridge BEH C18 150 × 25 × 10μm; mobile phase: [water(NH ₄ HCO ₃)-ACN]; gradient: 34%-64% B over 10 min).
47		(E)-2-((5-fluoro-2-((5-(6-oxo-1,6-dihydropyridin-3-yl)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.82 (br s, 1H), 9.71 (s, 1H), 9.43 (s, 1H), 8.11 (d, J = 1.4 Hz, 1H), 7.86 (dd, J = 2.8, 9.5 Hz, 1H), 7.76 (s, 1H), 7.68 - 7.62 (m, 2H), 7.59 - 7.53 (m, 1H), 7.47 - 7.42 (m, 3H), 7.33 - 7.19 (m, 2H), 6.46 (d, J = 9.6 Hz, 1H). m/z (ES+) [M+H] = 522.0	prep-HPLC (column: CD07-Daisogel SP-100-8-ODS-PK 150 × 25 × 10μm; mobile phase: [water(NH ₄ HCO ₃)-ACN]; gradient: 25%-55% B over 15 min.)
48		(E)-2-((5-fluoro-2-(((1r,4r)-4-morpholinocyclohexyl)amino)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.44 (s, 1H), 7.94 (s, 1H), 7.73 (s, 1H), 7.67 (d, J=10.8 Hz, 1H), 7.58-7.54 (m, 1H), 7.45-7.41 (m, 1H), 7.36-7.34 (d, J=8.0 Hz, 1H), 6.90 (d, J=6.4 Hz, 1H), 3.98-3.95 (m, 2H), 3.82 (t, J=12 Hz, 2H), 3.40-3.33 (m, 3H), 3.25-3.19 (m, 1H), 3.10-3.05 (m, 2H), 2.21 (t, J=11.2 Hz, 4H), 1.65-1.56 (m, 2H), 1.50-1.41 (m, 2H). m/z (ES+) [M+H] = 611.3	prep-HPLC (column: Welch Ultimate C18 150 × 25mm × 5μm; mobile phase: [water(HCl)-ACN]; gradient: 20%-50% B over 10 min).
49		(E)-2-((5-fluoro-2-((5-(piperazin-1-yl)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.50-9.33 (m, 2H), 7.70-7.60 (m, 2H), 7.59-7.51 (m, 1H), 7.50-7.38 (m, 2H), 7.34-7.09 (m, 3H), 6.80 (dd, J = 9.2 Hz, 2.4 Hz, 1H), 3.14-2.98 (m, 4H), 2.95-2.71 (m, 4H). ¹ H NMR (400 MHz, CD ₃ OD) δ = 9.40 (s, 1H), 8.22-8.15 (m, 1H), 7.63 (s, 1H), 7.58-7.51 (m, 1H), 7.45-7.33 (m, 2H), 7.24 (d, J = 7.6 Hz, 1H), 6.82-6.76 (m, 1H), 3.28-3.24 (m, 4H), 3.09-3.04 (m, 4H). m/z (ES+) [M+H] = 513.1	prep-HPLC (column: CD02-Waters Xbridge BEH C18 150 × 25 × 10μm; mobile phase: [water(NH ₄ HCO ₃)-ACN]; gradient: 26%-56% B over 10 min).

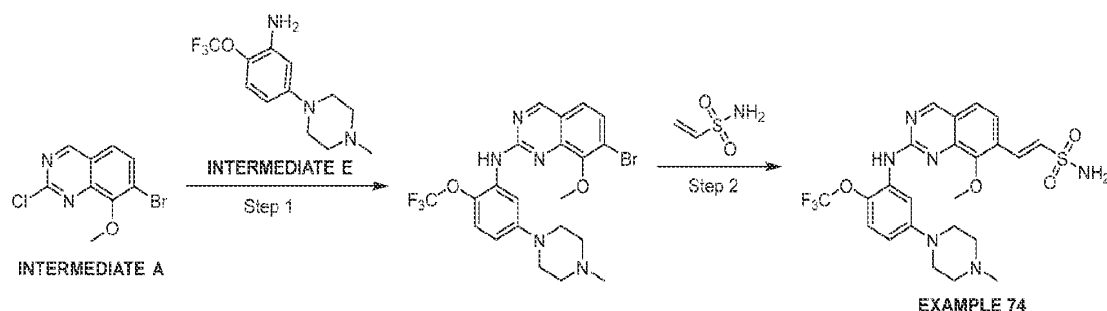
Example	Structure	Name	Spectra	Purification
50		(E)-2-(2-((5-fluoro-7-(2-sulfamoylvinyl)quinazolin-2-yl)amino)-4-(4-methylpiperazin-1-yl)phenyl)acetic acid	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.82-9.57 (m, 1H), 9.34 (s, 1H), 7.59-7.53 (m, 2H), 7.51 (s, 1H), 7.46-7.39 (m, 1H), 7.31 (s, 1H), 7.24 (s, 2H), 7.11 (d, J = 8.8 Hz, 1H), 6.74 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 3.47 (s, 2H), 3.15-3.08 (m, 4H), 2.48-2.46 (m, 4H), 2.23 (s, 3H). m/z (ES+) [M+H] ⁺ = 501.1.	prep-HPLC (column: CD20-Waters Xbridge BEH C18 250 × 25 × 10μm; mobile phase: [water(NH ₄ HCO ₃)-ACN]; gradient: 5%-35% B over 15 min).
51		(E)-2-(5-fluoro-2-((5-methyl-1-oxo-1,2-dihydroisoquinolin-4-yl)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.48 (s, 1H), 9.77 (s, 1H), 9.41 (s, 1H), 8.23 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 2.0 Hz, 1H), 7.63 (d, J = 11.0 Hz, 1H), 7.57-7.53 (m, 1H), 7.51-7.38 (m, 5H), 7.31-7.23 (m, 3H), 7.04 (d, J = 5.4 Hz, 1H), 2.08 (s, 3H). m/z (ES+) [M+H] ⁺ = 586.0	prep-HPLC (column: Waters Xbridge Prep OBD C18 150 × 40mm × 10μm; mobile phase: [H ₂ O(10mM NH ₄ HCO ₃)-ACN]; gradient: 45%-70% B over 8.0 min).
52		methyl (E)-4-(3-((5-fluoro-7-(2-sulfamoylvinyl)quinazolin-2-yl)amino)-4-(trifluoromethoxy)phenyl)-1-oxo-1,2-dihydroisoquinoline-3-carboxylate	¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.52 (br s, 1H), 9.80 (s, 1H), 9.42 (s, 1H), 8.41-8.31 (m, 1H), 7.92 (d, J = 2.0 Hz, 1H), 7.87-7.82 (m, 1H), 7.71-7.62 (m, 2H), 7.59-7.51 (m, 3H), 7.45-7.37 (m, 2H), 7.28 (s, 2H), 7.20 (dd, J = 2.1, 8.4 Hz, 1H), 3.60 (s, 3H). m/z (ES+) [M+H] ⁺ = 630.1	prep-HPLC (column: Waters Xbridge Prep OBD C18 150 × 40mm × 10μm; mobile phase: [H ₂ O(10mM NH ₄ HCO ₃)-ACN]; gradient: 45%-70% B over 8.0 min).
53		(E)-2-(5-fluoro-2-((6-oxo-1,6-dihydropyridazin-3-yl)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.23 (br s, 1H), 9.83 (br s, 1H), 9.44 (s, 1H), 8.46 (d, J = 1.6 Hz, 1H), 8.06 (d, J = 9.9 Hz, 1H), 7.77 (dd, J = 2.1, 8.7 Hz, 1H), 7.70-7.64 (m, 2H), 7.60-7.52 (m, 2H), 7.48-7.41 (m, 1H), 7.38-7.15 (m, 2H), 7.03 (d, J = 9.9 Hz, 1H). m/z (ES+) [M+H] ⁺ = 523.0.	prep-HPLC (column: Waters Xbridge BEH C18 100 × 30mm × 10μm; mobile phase: [H ₂ O(10mM NH ₄ HCO ₃)-ACN]; gradient: 25%-60% B over 8.0 min).
54		2-(5-fluoro-2-((5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethane-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆ , added a drop of D ₂ O) δ = 9.34 (s, 1H), 7.55 (br s, 1H), 7.27 (s, 1H), 7.22 (br d, J = 8.9 Hz, 1H), 7.12 (br d, J = 11.0 Hz, 1H), 6.83-6.76 (m, 1H), 3.40-3.33 (m, 2H), 3.20-3.09 (s, 6H), 2.46 (br s, 4H), 2.20 (s, 3H). m/z (ES+) [M+H] ⁺ = 529.1.	prep-HPLC (column: Waters Xbridge BEH C18 100 × 25mm × 10μm; mobile phase: [H ₂ O (10mM NH ₄ HCO ₃)-ACN]; gradient: 35%-65% B over 8.0 min)
55		(E)-2-[5-fluoro-2-[5-[1-oxo-6-(trifluoromethyl)-2H-isoquinolin-4-yl]-2-(trifluoromethoxy)anilino]quinazolin-7-yl]ethenesulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.79 (s, 1H), 9.41 (s, 1H), 8.52 (d, J = 8.3 Hz, 1H), 8.10 (d, J = 1.5 Hz, 1H), 7.92-7.85 (m, 2H), 7.65 (d, J = 10.4 Hz, 1H), 7.60-7.56 (m, 2H), 7.56-7.50 (m, 1H), 7.42 (s, 1H), 7.41-7.35 (m, 3H). m/z (ES+) [M+H] ⁺ = 640.1.	prep-HPLC (column: Waters Xbridge BEH C18 100 × 30mm × 10μm; mobile phase: [H ₂ O(10mM NH ₄ HCO ₃)-ACN]; gradient: 40%-75% B over 8.0 min)

Example	Structure	Name	Spectra	Purification
56		(E)-2-[5-fluoro-2-[5-(trifluoromethoxy)amino]quinazolin-7-yl]ethenesulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.71 (br s, 1H), 9.43 (s, 1H), 8.19 (dd, J = 1.9, 7.2 Hz, 1H), 7.98 (s, 1H), 7.65 (d, J = 11.1 Hz, 1H), 7.61 (s, 1H), 7.60 - 7.55 (m, 2H), 7.54 (s, 1H), 7.46 (s, 1H), 7.44 - 7.41 (m, 1H), 7.30 (td, J = 2.2, 8.4 Hz, 2H), 7.16 (s, 1H). m/z (ES+) [M+H] ⁺ = 590.1.	prep-HPLC (column: Waters Xbridge BEH C18 100 × 30mm × 10μm; mobile phase: [H ₂ O(10mM NH ₄ HCO ₃)-ACN]; gradient: 35%-70% B over 8.0 min).
57		(E)-2-(5-fluoro-2-((5-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.64 (s, 1H), 9.83 (s, 1H), 9.43 (s, 1H), 8.39 (dd, J = 6.4 Hz, 9.2 Hz, 1H), 8.07 (d, J = 2.0 Hz, 1H), 7.67 (d, J = 11.2 Hz, 1H), 7.62 (s, 1H), 7.56 - 7.54 (m, 1H), 7.51 (s, 1H), 7.48 (dd, J = 2.4 Hz, 8.8 Hz, 1H), 7.44 - 7.42 (m, 1H), 7.38 - 7.32 (m, 3H), 7.28 (s, 2H). m/z (ES+) [M+H] ⁺ = 590.2.	prep-HPLC (column: CD02-Waters Xbridge BEH C18 150 × 25 × 10μm; mobile phase: [water(NH ₄ HCO ₃)-ACN]; gradient: 44%-74% B over 10 min).
58		(E)-2-(5-fluoro-2-((4-oxo-3,4-dihydropyrido[3,4-d]pyridazin-1-yl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.52 - 12.91 (m, 1H), 9.90 (s, 1H), 9.55 (s, 1H), 9.46 (s, 1H), 9.09 (d, J = 5.6 Hz, 1H), 8.26 (d, J = 2.0 Hz, 1H), 7.84 (d, J = 5.6 Hz, 1H), 7.69 - 7.61 (m, 3H), 7.59 - 7.52 (m, 2H), 7.49 - 7.40 (m, 1H), 7.26 (s, 2H). m/z (ES+) [M+H] ⁺ = 574.1	prep-HPLC (column: Waters xbridge 150 × 25mm 10μm; mobile phase: [H ₂ O(10mM NH ₄ HCO ₃)-ACN]; gradient: 30%-60% B over 8.0 min).
59		(E)-2-(5-fluoro-2-((4-oxo-3,4,5,6,7,8-hexahydrophthalazin-1-yl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.44 (s, 1H), 8.08 (d, J = 1.6 Hz, 1H), 7.66 (br d, J = 11.0 Hz, 1H), 7.61 (s, 1H), 7.59 - 7.53 (m, 1H), 7.51 (br d, J = 8.4 Hz, 1H), 7.46 - 7.40 (m, 1H), 7.37 (dd, J = 2.0, 8.4 Hz, 1H), 2.50 - 2.44 (m, 4H), 1.82 - 1.61 (m, 4H). ¹ H NMR (400 MHz, MeOD-d ₄) δ = 9.43 (br s, 1H), 8.66 (br s, 1H), 7.60 (br s, 1H), 7.56 - 7.46 (m, 2H), 7.44 - 7.26 (m, 3H), 2.75 - 2.62 (m, 4H), 1.97 - 1.74 (m, 4H). m/z (ES+) [M+H] ⁺ = 577.1.	prep-HPLC (column: Waters xbridge 150 × 25mm 10μm; mobile phase: [H ₂ O(10mM NH ₄ HCO ₃)-ACN]; gradient: 35%-65% B over 8.0 min).
60		(E)-2-(5-fluoro-2-((2-(methylsulfonyl)-5-(piperazin-1-yl)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.78 (s, 1H), 9.50 (s, 1H), 9.25 (br s, 1H), 8.52 (d, J = 2.4 Hz, 1H), 7.86 (s, 1H), 7.79 (d, J = 10.8 Hz, 1H), 7.72 (d, J = 9.2 Hz, 1H), 7.65 - 7.50 (m, 2H), 7.30 (s, 2H), 6.90 (dd, J = 2.4 Hz, 9.2 Hz, 1H), 3.71 - 3.64 (m, 4H), 3.30 - 3.26 (m, 4H), 3.21 (s, 3H). m/z (ES+) [M+H] ⁺ = 507.2.	(Boc penultimate product) prep-HPLC (column: CD07-Daisogel SP-100-8-ODS-PK 150 × 25 × 10μm; mobile phase: [water(NH ₄ HCO ₃)-ACN]; gradient: 40%-70% B over 11 min). Residue was diluted with H ₂ O (5 mL) and washed with EtOAc (10 mLx2). Aqueous phase adjusted pH to 7 with NH ₃ ·H ₂ O isolated as filter cake.

Example	Structure	Name	Spectra	Purification
61		(E)-2-(5-fluoro-2-((5-(8-oxo-7,8-dihydropyrido[2,3-d]pyridazin-5-yl)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.93 (s, 1H), 9.49 (s, 1H), 9.16 (br d, J = 3.2 Hz, 1H), 8.38 (br d, J = 7.9 Hz, 1H), 8.26 (s, 1H), 7.99 (br dd, J = 4.5, 7.5 Hz, 1H), 7.72 - 7.66 (m, 3H), 7.63 (br d, J = 13.1 Hz, 1H), 7.58 - 7.54 (m, 2H), 7.50 - 7.43 (d, 1H), 7.38 - 7.22 (m, 2H). m/z (ES+) [M+H] ⁺ = 574.1.	prep-HPLC (column: Waters Xbridge BEH C18 100 × 30mm × 10μm; mobile phase: [H ₂ O(10mM NH ₄ HCO ₃)-ACN]; gradient: 35%-65% B over 8.0 min).
62		(E)-2-(5-fluoro-2-((5-(5-oxo-5,6-dihydropyrido[2,3-d]pyridazin-8-yl)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.21 (s, 1H), 9.81 (s, 1H), 9.43 (s, 1H), 9.19 (dd, J = 1.8, 4.6 Hz, 1H), 8.70 (dd, J = 1.8, 8.1 Hz, 1H), 8.40 (d, J = 2.0 Hz, 1H), 7.92 (dd, J = 4.5, 8.0 Hz, 1H), 7.84 (dd, J = 2.1, 8.5 Hz, 1H), 7.66 - 7.61 (m, 2H), 7.59 - 7.52 (m, 2H), 7.45 - 7.39 (m, 1H), 7.25 (br s, 2H). m/z (ES+) [M+H] ⁺ = 574.1.	prep-HPLC (column: Waters Xbridge BEH C18 100 × 30mm × 10μm; mobile phase: [H ₂ O(10mM NH ₄ HCO ₃)-ACN]; gradient: 33%-67% B over 8.0 min).
63		(E)-2-(5-fluoro-2-((5-(5-oxo-5,6-dihydropyrido[3,4-b]pyrazin-8-yl)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.04 (s, 1H), 9.72 (s, 1H), 9.41 (s, 1H), 8.99 (d, J = 2.0 Hz, 1H), 8.87 (d, J = 2.0 Hz, 1H), 8.12 (s, 1H), 7.68 (s, 1H), 7.65 - 7.59 (m, 2H), 7.55 - 7.47 (m, 3H), 7.45 - 7.38 (m, 1H), 7.23 (br s, 2H). m/z (ES+) [M+H] ⁺ = 574.0.	prep-HPLC column: CD20-Waters Xbridge BEH C18 250 × 25 × 10μm; mobile phase: [water(NH ₄ HCO ₃)-ACN]; gradient: 25%-55% B over 15 min).
64		(E)-2-(5-fluoro-2-((5-(5-oxo-5,6-dihydro-1,6-naphthyridin-8-yl)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.80 (br s, 1H), 9.72 (d, J = 2.4 Hz, 1H), 9.41 (s, 1H), 9.02 - 8.88 (m, 1H), 8.67 - 8.54 (m, 1H), 8.10 (d, J = 1.6 Hz, 1H), 7.65 - 6.98 (m, 10H). m/z (ES+) [M+H] ⁺ = 573.0.	prep-HPLC (column: CD20-Waters Xbridge BEH C18 250 × 25 × 10μm; mobile phase: [water(NH ₄ HCO ₃)-ACN]; gradient: 28%-58% B over 15 min).
65		(E)-2-[5-fluoro-2-[5-(4-methylpiperazin-1-yl)-2-methylsulfonylanilino]quinazolin-7-yl]ethenesulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.75 (s, 1H), 9.49 (s, 1H), 8.46 (d, J = 2.0 Hz, 1H), 7.82 (s, 1H), 7.77 (d, J = 10.8 Hz, 1H), 7.65 (d, J = 9.2 Hz, 1H), 7.62 - 7.50 (m, 2H), 7.27 (s, 2H), 6.83 (dd, J = 2.4 Hz, 9.2 Hz, 1H), 3.47 - 3.38 (m, 4H), 3.33 - 3.30 (m, 4H), 3.18 (s, 3H), 2.25 (s, 3H). m/z (ES+) [M+H] ⁺ = 521.1.	prep-HPLC (column: CD02-Waters Xbridge BEH C18 150 × 25 × 10μm; mobile phase: [water(NH ₄ HCO ₃)-ACN]; gradient: 20%-50% B over 13 min).
67		(E)-2-(5-fluoro-2-((5-(1-oxo-1,2-dihydropyrido[3,4-d]pyridazin-4-yl)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.29 (s, 1H), 10.03 (s, 1H), 9.72 (s, 1H), 9.48 (s, 1H), 9.12 (d, J = 4.9 Hz, 1H), 8.51 (s, 1H), 8.23 (d, J = 5.0 Hz, 1H), 8.05 (s, 1H), 7.76 (d, J = 15.6 Hz, 1H), 7.66 - 7.56 (m, 3H), 7.46 (d, J = 15.4 Hz, 1H), 7.39 (s, 2H). m/z (ES+) [M+1] ⁺ = 574.0	prep-HPLC (column: Phenomenex luna C18 100 × 40mm × 5 μm; mobile phase: [H ₂ O(0.04% HCl)-ACN]; gradient: 30%-60% B over 8.0 min).

Example	Structure	Name	Spectra	Purification
68		(E)-2-(2-((5-(6,7-dimethoxy-1-oxo-1,2-dihydroisoquinolin-4-yl)-2-(trifluoromethoxy)phenyl)amino)-5-fluoroquinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.43 (s, 1H), 9.83 (s, 1H), 9.44 (s, 1H), 8.11 (d, J = 1.9 Hz, 1H), 7.72 (s, 1H), 7.67 (d, J = 10.6 Hz, 1H), 7.60 - 7.55 (m, 2H), 7.54 (s, 1H), 7.46 - 7.43 (m, 1H), 7.42 (br d, J = 2.5 Hz, 1H), 7.37 - 7.18 (m, 2H), 7.14 (s, 1H), 7.12 (s, 1H), 3.92 (s, 3H), 3.78 (s, 3H). m/z (ES+) [M+H] ⁺ = 632.1.	(Boc penultimate product) prep-TLC (SiO ₂ , Petroleum ether/Ethyl acetate= 0:1).
70		(E)-2-(2-((5-(8-chloro-1-oxo-1,2-dihydroisoquinolin-4-yl)-2-(trifluoromethoxy)phenyl)amino)-5-fluoroquinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.55 (d, J = 4.4 Hz, 1H), 9.66 (s, 1H), 8.06-7.93 (m, 2H), 7.71-7.65 (m, 1H), 7.64-7.57 (m, 2H), 7.56-7.51 (m, 4H), 7.38 (d, J = 7.6 Hz, 1H), 7.31 (s, 2H), 7.19 (d, J = 3.2 Hz, 1H), 1.47 (s, 9H).	p-HPLC (column: XPT C18 150 × 30 7μm; mobile phase: [H ₂ O(10mM NH ₄ HCO ₃)-ACN];gradient:15%-45% B over 8.0 min).
71		(E)-2-(5-fluoro-2-((5-(1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.83 (br s, 1H), 9.82 (s, 1H), 9.43 (m, 2H), 8.79 (d, J = 5.6 Hz, 1H), 8.05 (d, J = 2.0 Hz, 1H), 7.69-7.63 (m, 3H), 7.60-7.55 (m, 1H), 7.55-7.52 (m, 2H), 7.48-7.42 (m, 1H), 7.37 (dd, J = 2.0 Hz, 8.4 Hz, 1H), 7.35-6.98 (m, 2H). m/z (ES+) [M+H] ⁺ = 573.1.	prep-HPLC (column: CD07-Daisogel SP-100-8-ODS-PK 150 × 25 × 10μm;mobile phase: [water(NH ₄ HCO ₃)-ACN];gradient:24%-54% B over 10 min).
72		(E)-2-(5-fluoro-2-((5-(8-oxo-7,8-dihydro-1,7-naphthyridin-5-yl)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.80 (br s, 1H), 9.83 (s, 1H), 9.44 (s, 1H), 8.84 (dd, J = 1.6 Hz, 4.4 Hz, 1H), 8.18 (dd, J = 1.2 Hz, 8.4 Hz, 1H), 8.05 (d, J = 1.6 Hz, 1H), 7.77 (dd, J = 4.4 Hz, 8.4 Hz, 1H), 7.64 (t, J = 6.0 Hz, 2H), 7.59-7.51 (m, 2H), 7.47-7.40 (m, 1H), 7.38-7.33 (m, 2H), 7.28 (s, 2H). m/z (ES+) [M+H] ⁺ = 573.2.	prep-HPLC (column: CD02-Waters Xbridge BEH C18 150 × 25 × 10μm;mobile phase: [water(NH ₄ HCO ₃)-ACN];gradient:26%-56% B over 10 min).
73		(E)-2-(2-((5-(6-chloro-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2-(trifluoromethoxy)phenyl)amino)-5-fluoroquinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.87 (s, 1H), 9.47 (s, 1H), 9.25 (s, 1H), 8.08 (d, J = 1.6 Hz, 1H), 7.71 - 7.66 (m, 2H), 7.63 (s, 1H), 7.62 - 7.61 (m, 1H), 7.55 (s, 1H), 7.57 - 7.54 (m, 1H), 7.47 - 7.41 (m, 1H), 7.41 - 7.37 (m, 2H), 7.36 - 7.19 (m, 2H). m/z (ES+) [M+H] ⁺ = 607.0, 609.0.	prep-HPLC (column: Waters Xbridge BEH C18 100 × 30mm × 10μm;mobile phase: [H ₂ O(10mM NH ₄ HCO ₃)-ACN];gradient:35%-70% B over 8.0 min).

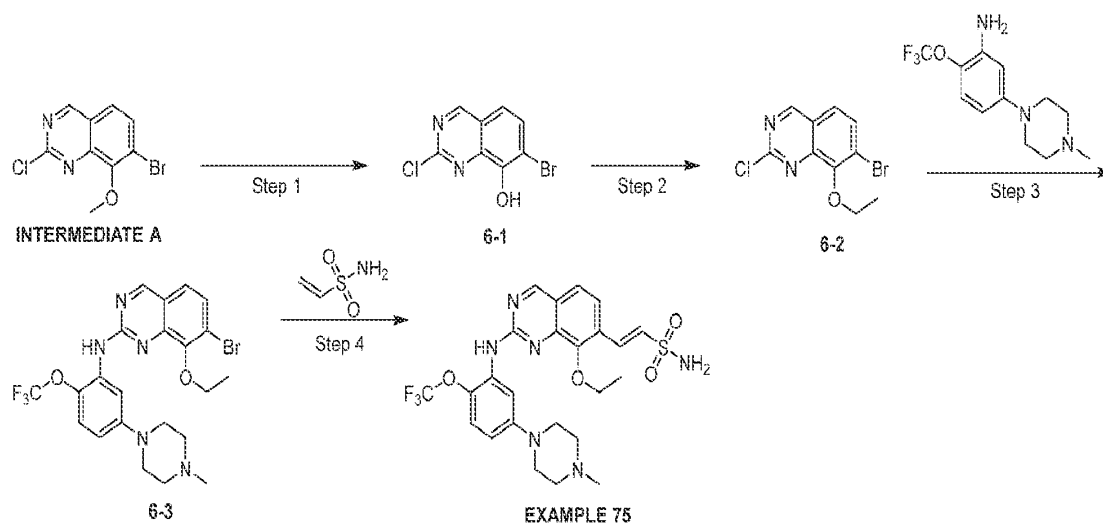
EXAMPLE 74



[0124] **Step 1:** The solution of 7-bromo-2-chloro-8-methoxyquinazoline (60 mg, 219 μmol , 1 eq), 5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)aniline (60 mg, 219 μmol , 1 eq) and TFA (50 mg, 439 μmol , 32.6 μL , 2 eq) in n-BuOH (6 mL) was stirred at 90 °C for 12 h. The mixture (combined with a 15 mg scale) was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition; column: Waters XBridge Prep OBD C18 150 $\times$ 40 mm $\times$ 10 μm ; mobile phase: [H₂O (10 mM NH₄HCO₃)-ACN]; gradient: 40%-70% B over 8.0 min). 20 mg of 7-bromo-8-methoxy-N-(5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy) phenyl)quinazolin-2-amine **5-2** (39 μmol) was obtained as a brown oil.

[0125] **Step 2:** Tris-o-tolylphosphane (1.2 mg, 4 μmol , 0.1 eq) and Pd(OAc)₂ (876 μg , 3.9 μmol , 0.1 eq) were added to the solution of 7-bromo-8-methoxy-N-(5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)phenyl)quinazolin-2-amine (20 mg, 39 μmol , 1 eq), ethene sulfonamide (4 mg, 39 μmol , 1 eq) and TEA (8 mg, 78 μmol , 11 μL , 2 eq) in DMF (0.5 mL) under N₂. The mixture was stirred at 100 °C for 12 h under N₂. The reaction (combined with a 40 mg scale) was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition; column: Waters XBridge Prep OBD C18 150 $\times$ 40 mm $\times$ 10 μm ; mobile phase: [H₂O (10 mM NH₄HCO₃)-ACN]; gradient: 30%-60% B over 8.0 min). 17 mg of (E)-2-(8-methoxy-2-((5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide (29 μmol , 93% purity) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.32 (s, 1H), 9.19 (s, 1H), 7.89 (s, 1H), 7.74-7.68 (m, 3H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.25-7.22 (m, 3H), 6.78-6.75 (m, 1H), 4.02 (s, 3H), 3.21-3.19 (m, 4H), 2.48-2.43 (m, 4H), 2.23 (s, 3H). *m/z* (ES⁺) [M+1]⁺ = 539.2.

EXAMPLE 75



[0126] **Step 1:** The solution of BBr₃ (586 mg, 2.34 mmol, 225 μ L, 4 eq) in DCM (3 mL) was added to the mixture of 7-bromo-2-chloro-8-methoxyquinazoline (0.16 g, 585 μ mol, 1 eq) in DCM (1.6 mL) at 0 °C under N₂. The mixture was stirred at 20 °C for 12 h. The solution of DCM/MeOH (6 mL, 5:1) was added to the reaction at 0 °C. The mixture was concentrated under reduced pressure to give a residue. 7-bromo-2-chloro-quinazolin-8-ol, **6-1** (0.2 g, crude) was obtained as a brown solid. m/z (ES⁺) [M+1]⁺ = 259.0.

[0127] **Step 2:** The mixture of 7-bromo-2-chloroquinazolin-8-ol (0.2 g, 771 μmol , 1 eq), K_2CO_3 (213.04 mg, 1.54 mmol, 2 eq), and iodoethane (240 mg, 1.54 mmol, 123 μL , 2 eq) in DMF (2 mL) was stirred at 60 $^\circ\text{C}$ for 2 h. The reaction mixture was quenched by adding H_2O (5 mL) and extracted with EtOAc (5 mL $\times$ 3). The combined organic layers were washed with brine (3 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2 , Petroleum ether/Ethyl acetate = 5:1). 7-bromo-2-chloro-8-ethoxy-quinazoline **6-2** (0.15 g, 475 μmol , 62% yield) was obtained as a yellow solid. m/z (ES^+) $[\text{M}+1]^+ = 287.2$.

[0128] **Step 3:** The mixture of 7-bromo-2-chloro-8-ethoxyquinazoline (90 mg, 313 μmol , 1 eq), 5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)aniline (86 mg, 313 μmol , 1 eq) and TFA (71 mg, 626 μmol , 46.50 μL , 2 eq) in n-BuOH (1 mL) was stirred at 90 °C for 12 h. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition; column: Waters XBridge Prep OBD C18 150 $\times$ 40 mm $\times$ 10 μm ; mobile

phase: [H₂O (10 mM NH₄HCO₃)-ACN]; gradient: 45%-75% B over 8.0 min). 7-bromo-8-ethoxy-N-(5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)phenyl)quinazolin-2-amine **6-3** (60 mg, 112 μmol, 36% yield, 98% purity) was obtained as a brown solid. m/z (ES⁻) [M+1]⁺ = 526.1.

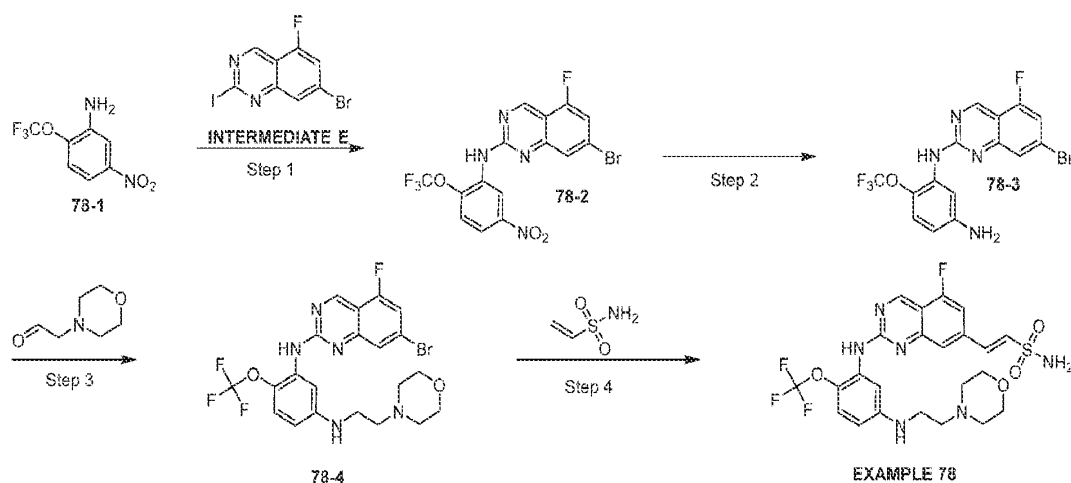
[0129] **Step 4:** Tris-*o*-tolylphosphane (3.68 mg, 12.09 μmol, 0.1 eq) and Pd(OAc)₂ (2.71 mg, 12.1 μmol, 0.1 eq) were added to the solution of 7-bromo-8-ethoxy-N-(5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)phenyl)quinazolin-2-amine (60 mg, 114 μmol, 0.943 eq), ethenesulfonamide (13 mg, 121 μmol, 1 eq) and TEA (25 mg, 242 μmol, 34 μL, 2 eq) in DMF (1 mL) under N₂. The mixture was stirred at 100 °C for 12 h. The reaction was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition; column: Waters XBridge Prep OBD C18 150 × 40 mm × 10 μm; mobile phase: [H₂O (10 mM NH₄HCO₃)-ACN]; gradient: 30%-60% B over 8.0 min). (E)-2-(8-ethoxy-2-((5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethane -1-sulfonamide **EXAMPLE 75** (15 mg, 27.15 μmol, 22.5% yield, 100% purity) was obtained as a yellow solid. ¹H NMR (400 MHz, CD₃CN) δ ppm 9.19 (s, 1H), 8.16 (d, J = 2.8 Hz, 1H), 7.89 (d, J = 15.6 Hz, 1H), 7.73 (s, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.28-7.23 (m, 2H), 6.72-6.69 (m, 1H), 5.54 (s, 2H), 4.45-4.40 (m, 2H), 3.23 (t, J = 4.8 Hz, 4H), 2.52 (t, J = 4.8 Hz, 4H), 2.28 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H). m/z (ES⁺) [M+1]⁺ = 553.2.

[0130] Following the teachings of the General Reaction Schemes and the synthesis procedure for Example **6** were prepared as shown in **Table I** (below):

Table I cont.

Example	Structure	Name	Characterization	Purification
76		(E)-2-(8-isopropoxy-2-((5-(4-(trifluoromethoxy)phenyl)amino)quinazolin-2-yl)methylpiperazin-1-yl)-2-(trifluoromethoxy)phenyl)sulfonamide	¹ H NMR (400 MHz, CD ₃ CN) δ ppm 9.17 (s, 1H), 7.90 (d, J = 16.0 Hz, 1H), 7.82 (d, J = 2.8 Hz, 1H), 7.68 (s, 1H), 7.60-7.53 (m, 2H), 7.25-7.21 (m, 2H), 6.76-6.73 (m, 1H), 5.53 (s, 2H), 5.11-5.07 (m, 1H), 3.20 (t, J =	prep-HPLC (neutral condition; column: Waters Xbridge Prep OBD C18 150 × 40 mm × 10 μm; mobile phase: [H ₂ O (10 mM NH ₄ HCO ₃)-ACN]; gradient: 30%-60% B over 8.0 min).
77		(E)-2-(8-(difluoromethoxy)-2-((5-(4-(trifluoromethoxy)phenyl)amino)quinazolin-2-yl)methylpiperazin-1-yl)-2-(trifluoromethoxy)phenyl)sulfonamide	¹ H NMR (400 MHz, CD ₃ CN) δ ppm 9.24 (s, 1H), 7.89-7.80 (m, 4H), 7.64 (d, J = 8.4 Hz, 1H), 7.42-7.04 (m, 3H), 6.76-6.73 (m, 1H), 5.63 (s, 2H), 3.21 (t, J = 4.8 Hz, 4H), 2.51 (t, J = 5.2 Hz, 4H), 2.27 (s, 3H). m/z (ES ⁺)	prep-HPLC (neutral condition; column: Waters Xbridge Prep OBD C18 150 × 40 mm × 10 μm; mobile phase: [H ₂ O (10 mM NH ₄ HCO ₃)-ACN]; gradient: 20%-50% B over 8.0 min).

EXAMPLE 78



[0131] **Step 1:** A mixture of 5-nitro-2-(trifluoromethoxy)aniline **7-1**, (1.3 g, 5.85 mmol, 1 eq), 7-bromo-5-fluoro-2-iodo-quinazoline **INTERMEDIATE E** (2.07 g, 5.85 mmol, 1 eq), Davephos Pd G3 (44.67 mg, 58.53 μmol, 0.01 eq), NaOtBu (2 M, 5.85 mL, 2 eq) in dioxane (25 mL) was degassed and purged with N₂ 3 times, and the mixture was stirred at 60 °C for 12 hr under N₂ atmosphere. The mixture was filtered, and the filtrate was concentrated under reduced pressure to remove the solvent. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=50:1 to 10:1). 0.9 g of 7-bromo-5-fluoro-N-[5-nitro-2-(trifluoromethoxy)phenyl]quinazolin-2-amine was obtained as a yellow solid. m/z (ES⁻) [M+H]⁺ = 446.9.

[0132] **Step 2:** To a solution of 7-bromo-5-fluoro-N-[5-nitro-2-(trifluoromethoxy)phenyl]quinazolin-2-amine (0.9 g, 2.01 mmol, 1 eq) and NH₄Cl (538.34 mg, 10.06 mmol, 5 eq) in H₂O (2 mL) and EtOH (4 mL) was added Fe (562.02 mg, 10.06 mmol, 5 eq) at 50 °C. After addition, the resulting mixture was stirred at 85 °C for 2 hr. The mixture was filtered to get the filtrate and concentrated to remove the solvent. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=50/1 to 10/1). Compound N3-(7-bromo-5-fluoro-quinazolin-2-yl)-4-(trifluoromethoxy)benzene-1,3-diamine (0.4 g, 958.88 μmol, 48% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.44 (s, 1H), 9.34 (s, 1H), 7.71 (s, 1H), 7.50 (d, *J* = 9.6 Hz, 1H), 7.28 (d, *J* = 1.6 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 1H), 6.43-6.48 (m, 1H), 5.41 (s, 2H).

[0133] **Step 3:** To a solution of N3-(7-bromo-5-fluoro-quinazolin-2-yl)-4-(trifluoromethoxy)benzene-1,3-diamine (100 mg, 239.72 μmol, 1 eq), 4A MS (100 mg) and 2-morpholinoacetaldehyde (46.44 mg, 359.58 μmol, 1.5 eq) in MeOH (2 mL) was added NaBH₃CN (30.13 mg, 479.44 μmol, 2 eq). The mixture was stirred at 25 °C for 12 hr. The mixture was filtered to get the filtrate and concentrated to remove the solvent. The residue was purified by prep-TLC (SiO₂, PE: EtOAc = 1:1). Compound N3-(7-bromo-5-fluoro-quinazolin-2-yl)-N1-(2-morpholinoethyl)-4-(trifluoromethoxy)benzene-1,3-diamine (60 mg, 113.14 μmol, 47% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.39 (s, 1H), 9.35 (s, 1H), 7.63 (s, 1H), 7.44-7.47 (m, 1H), 7.26 (d, *J*=2.2 Hz, 1H), 7.10 (d, *J*=8.0 Hz, 1H), 6.43 (dd, *J*=2.8, 8.8 Hz, 1H), 5.82 (t, *J*=5.6 Hz, 1H), 3.58 (t, *J*=4.8 Hz, 4H), 3.13-3.19 (m, 2H), 2.52-2.54 (m, 2H), 2.40-2.44 (m, 4H).

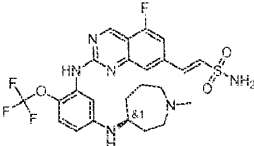
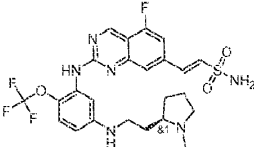
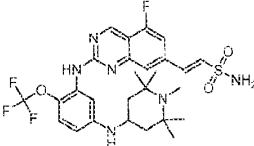
[0134] **Step 4:** A mixture of N3-(7-bromo-5-fluoro-quinazolin-2-yl)-N1-(2-morpholinoethyl)-4-(trifluoromethoxy)benzene-1,3-diamine (50 mg, 94.28 μmol, 1 eq), ethenesulfonamide (15.15 mg, 141.43 μmol, 1.5 eq), diacetoxypalladium (423.35 μg, 1.89 μmol, 0.02 eq), tris-*o*-tolylphosphane (1.15 mg, 3.77 μmol, 0.04 eq) and TEA (28.62 mg, 282.85 μmol, 39.37 μL, 3 eq) in DMF (2 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 12 hr under N₂ atmosphere. The mixture was filtered and concentrated to remove the solvent. The residue was purified by prep-HPLC (neutral condition; column: CD07-Daisogel SP-100-8-ODS-PK 150 × 25 × 10 μm; mobile phase: [water (NH₄HCO₃)-ACN]; gradient: 32%-62% B over 10 min). Compound (E)-2-[5-fluoro-2-[5-(2-morpholinoethylamino)-2-

(trifluoromethoxy)anilino]quinazolin-7-yl]ethanesulfonamide (4 mg, 7.19 μ mol, 8% yield) was obtained as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ = 9.38 (s, 1H), 9.28 (s, 1H), 7.58-7.69 (m, 2H), 7.49-7.58 (m, 1H), 7.38-7.46 (m, 1H), 7.25 (br s, 2H), 7.18 (d, J = 1.6 Hz, 1H), 7.10 (d, J = 9.4 Hz, 1H), 6.42-6.46 (m, 1H), 5.78 (t, J = 5.2 Hz, 1H), 3.57 (t, J = 4.4 Hz, 4H), 3.13-3.20 (m, 2H), 2.52-2.55 (m, 2H), 2.40-2.44 (m, 4H). m/z (ES^+) $[\text{M}+\text{H}]^+$ = 557.2.

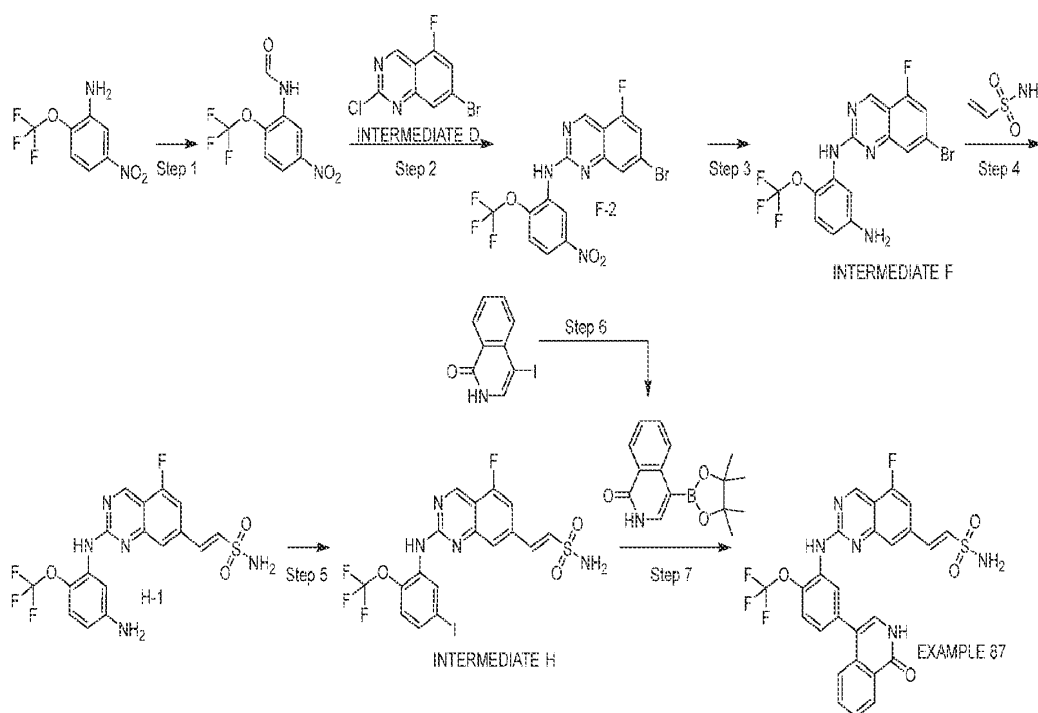
[0135] Following the teachings of the General Reaction Schemes and the synthesis procedure for Example 78 were prepared as shown in **Table I**:

Table I cont.

Example	Structure	Name	Characterization	Purification
79		(E)-2-((5-fluoro-2-((2-(pyrrolidin-1-yl)ethyl)amino)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, MeOD-d ₄) δ = 9.39 (s, 1H), 7.90 (d, J = 2.6 Hz, 1H), 7.68 (s, 1H), 7.56 - 7.50 (m, 1H), 7.40 (s, 1H), 7.37 (d, J = 6.2 Hz, 1H), 7.11 (br d, J = 8.9 Hz, 1H), 6.42 (dd, J = 2.7, 9.0 Hz, 1H), 3.37 (t, J = 6.9 Hz, 2H), 2.87 (br t, J = 7.1 Hz, 2H), 2.77 - 2.68 (m, 4H), 1.87 (br s, 4H). m/z (ES+) [M+H] ⁺ = 541.2.	prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um; mobile phase: [H ₂ O(10mM NH ₄ HCO ₃)-ACN]; gradient: 29%-65% B over 8.0 min).
80		(E)-2-((5-((4-(diethylamino)butyl)amino)-2-(trifluoromethoxy)phenyl)amino)-5-fluoroquinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.38 (s, 1H), 9.28 (s, 1H), 7.66-7.58 (m, 2H), 7.58-7.50 (m, 1H), 7.46-7.38 (m, 1H), 7.26 (s, 2H), 7.17-7.04 (m, 2H), 6.40 (dd, J = 2.4 Hz, 9.2 Hz, 1H), 5.93 (t, J = 5.2 Hz, 1H), 3.05-2.98 (m, 2H), 2.46-2.34 (m, 6H), 1.65-1.39 (m, 4H), 0.91 (t, J = 7.2 Hz, 6H). m/z (ES+) [M+H] ⁺ = 571.2.	prep-HPLC (column: CD02-Waters Xbridge BEH C18 150*25*10um; mobile phase: [water(NH ₄ HCO ₃)-ACN]; gradient: 35%-55% B over 10 min).
81		(E)-2-((5-fluoro-2-((2-(piperidin-1-yl)ethyl)amino)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.38 (s, 1H), 9.28 (s, 1H), 7.66 - 7.59 (m, 2H), 7.58 - 7.49 (m, 1H), 7.47 - 7.38 (m, 1H), 7.26 (s, 2H), 7.18 (d, J = 2.6 Hz, 1H), 7.09 (dd, J = 1.2, 8.8 Hz, 1H), 6.43 (dd, J = 2.8, 8.9 Hz, 1H), 5.75 (br t, J = 5.4 Hz, 1H), 3.19 - 3.09 (m, 2H), 2.49 - 2.45 (m, 2H), 2.37 (br s, 4H), 1.48 (quin, J = 5.5 Hz, 4H), 1.37 (br d, J = 4.9 Hz, 2H). m/z (ES+) [M+H] ⁺ = 555.2.	prep-HPLC (neutral condition; column: CD07-Daisogel SP-100-8-ODS-PK 150*25*10um; mobile phase: [water(NH ₄ HCO ₃)-ACN]; gradient: 40%-70% B over 10 min).
82		(E)-2-((5-((2-(dimethylamino)ethyl)amino)-2-(trifluoromethoxy)phenyl)amino)-5-fluoroquinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.39 (s, 1H), 9.31 (s, 1H), 7.68-7.60 (m, 2H), 7.58-7.51 (m, 1H), 7.45-7.38 (m, 1H), 7.28 (s, 2H), 7.22 (d, J = 2.0 Hz, 1H), 7.12-7.07 (m, 1H), 6.44 (dd, J = 2.8 Hz, 9.2 Hz, 1H), 5.77 (t, J = 5.2 Hz, 1H), 3.15-3.10 (m, 2H), 2.49-2.44 (m, 2H), 2.20 (s, 6H). m/z (ES+) [M+H] ⁺ = 515.0.	prep-HPLC (neutral condition; column: CD07-Daisogel SP-100-8-ODS-PK 150*25*10um; mobile phase: [water(NH ₄ HCO ₃)-ACN]; gradient: 32%-62% B over 10 min).
83		(E)-2-((5-((2-(diethylamino)ethyl)amino)-2-(trifluoromethoxy)phenyl)amino)-5-fluoroquinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.38 (s, 1H), 9.31 (s, 1H), 7.65-7.60 (m, 2H), 7.58-7.51 (m, 1H), 7.45-7.38 (m, 1H), 7.28 (s, 2H), 7.18 (d, J = 2.8 Hz, 1H), 7.12-7.07 (m, 1H), 6.43 (dd, J = 2.8 Hz, 9.2 Hz, 1H), 5.74 (t, J = 5.6 Hz, 1H), 3.15-3.04 (m, 2H), 2.59 (t, J = 6.8 Hz, 2H), 2.55-2.51 (m, 4H), 0.95 (t, J = 7.2 Hz, 6H). m/z (ES+) [M+H] ⁺ = 543.4.	prep-HPLC (neutral condition; column: CD07-Daisogel SP-100-8-ODS-PK 150*25*10um; mobile phase: [water(NH ₄ HCO ₃)-ACN]; gradient: 38%-68% B over 10 min).

Example	Structure	Name	Characterization	Purification
84		rac-(R,E)-2-((5-fluoro-2-((5-((1-methylazepan-4-yl)amino)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, MeOD-d ₄) δ = 7.41 (d, J = 4.4 Hz, 1H), 7.38 (s, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.28 (d, J = 1.2 Hz, 1H), 7.24 (s, 1H), 6.83-6.79 (m, 2H), 5.93 (s, 1H), 3.86-3.68 (m, 2H), 3.60-3.42 (m, 4H), 3.20-3.10 (m, 1H), 2.92 (s, 3H), 2.41-2.16 (m, 4H). m/z (ES+) [M+H] ⁺ = 555.2.	prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(HCl)-ACN];gradient:25%-45% B over 10 min column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(HCl)-ACN];gradient:25%-45% B over 10 min).
85		rac-(R,E)-2-((5-fluoro-2-((5-((2-(1-methylpyrrolidin-2-yl)ethyl)amino)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 10.2 (br s, 1H), 9.39 (s, 1H), 9.32 (s, 1H), 7.72 - 7.60 (m, 2H), 7.59 - 7.51 (m, 1H), 7.48 - 7.39 (m, 1H), 7.29 - 7.12 (m, 5H), 6.47 (dd, J = 2.7, 8.8 Hz, 1H), 3.23 - 3.10 (m, 3H), 3.07 - 2.98 (m, 1H), 2.84 - 2.59 (m, 4H), 2.37 - 2.15 (m, 2H), 2.02 - 1.82 (m, 3H), 1.78 - 1.62 (m, 1H). m/z (ES+) [M+1] ⁺ = 555.2	prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(HCl)-ACN];gradient:18%-48% B over 10 min).
86		(E)-2-((5-fluoro-2-((5-((1,2,2,6,6-pentamethylpiperidin-4-yl)amino)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.39 (s, 1H), 9.30 (s, 1H), 7.66-7.59 (m, 2H), 7.57-7.50 (m, 1H), 7.44-7.35 (m, 1H), 7.28 (s, 2H), 7.18 (d, J = 2.8 Hz, 1H), 7.14-7.05 (m, 1H), 6.42 (dd, J = 2.8 Hz, 9.2 Hz, 1H), 5.71 (t, J = 7.6 Hz, 1H), 3.59-3.44 (m, 1H), 2.18 (s, 3H), 1.91-1.82 (m, 2H), 1.25 (t, J = 12.4 Hz, 2H), 1.10 (br s, 6H), 1.04 (br s, 6H). m/z (ES+) [M+H] ⁺ = 597.3.	prep-HPLC (column: CD07-Daisogel SP-100-8-ODS-PK 150*25*10um;mobile phase: [water (NH ₄ HCO ₃)-ACN];gradient:40%-70% B over 10 min).

EXAMPLE 87



[0136] **Step 1:** A mixture of 5-nitro-2-(trifluoromethoxy)aniline (5 g, 22.51 mmol, 1 eq) in HCOOH (50 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 1hr under N₂ atmosphere. The mixture was concentrated to remove the solvent and used for the next step directly without further purification. Compound N-[5-nitro-2-(trifluoromethoxy)phenyl]formamide (5 g, 19.99 mmol, 89% yield) was obtained as a dark brown solid. m/z (ES⁺) [M+H]⁺ = 251.0.

[0137] **Step 2:** To a solution of N-[5-nitro-2-(trifluoromethoxy)phenyl]formamide (5 g, 19.99 mmol, 1 eq) in THF (60 mL) was portionwise added NaH (11.99 g, 299.84 mmol, 60% purity, 15 eq) at 0°C under N₂. The mixture was stirred at 20°C for 0.5 hr under N₂. Then 7-bromo-2-chloro-5-fluoro-quinazoline (6.27 g, 23.99 mmol, 1.2 eq) was portionwise added to the mixture at 0°C under N₂, then the mixture was stirred at 20°C for 47.5 hr under N₂. The reaction mixture was quenched with sat. NH₄Cl (20 mL) and extracted with EtOAc (10 mL * 3). The combined organic layers were dried over Na₂SO₄ and filtered, and the filtrate was concentrated under reduced pressure to create a residue. The crude was used for the next step directly without

purification. Compound 7-bromo-5-fluoro-N-[5-nitro-2-(trifluoromethoxy)phenyl]quinazolin-2-amine (6 g, crude) was obtained as a yellow solid. m/z (ES+) $[M+H]^+ = 447.0, 449.0$.

[0138] **Step 3:** To a solution of 7-bromo-5-fluoro-N-[5-nitro-2-(trifluoromethoxy)phenyl]quinazolin-2-amine (6 g, 13.42 mmol, 1 eq) and NH_4Cl (3.59 g, 67.09 mmol, 5 eq) in H_2O (20 mL) and EtOH (40 mL) was added portionwise Fe (3.75 g, 67.09 mmol, 5 eq) at 50 °C. After addition, the resulting mixture was stirred at 85 °C for 2 hr. The reaction mixture was filtered, and the filtrate was concentrated to remove the solvent. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=10/1 to 5/1). Compound N3-(7-bromo-5-fluoro-quinazolin-2-yl)-4-(trifluoromethoxy)benzene-1,3-diamine (3 g, 7.19 mmol, 54% yield) was obtained as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 9.44 (s, 1H), 9.34 (s, 1H), 7.71 (s, 1H), 7.50 (d, J = 9.6 Hz, 1H), 7.28 (d, J = 1.6 Hz, 1H), 7.09 (d, J = 8.8 Hz, 1H), 6.46 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 5.41 (s, 2H).

[0139] **Step 4:** A mixture of N3-(7-bromo-5-fluoro-quinazolin-2-yl)-4-(trifluoromethoxy)benzene-1,3-diamine (3 g, 7.19 mmol, 1 eq), ethenesulfonamide (924.53 mg, 8.63 mmol, 1.2 eq), $\text{Pd}(\text{OAc})_2$ (32.29 mg, 143.83 μmol , 0.02 eq), tris-*o*-tolylphosphane (87.55 mg, 287.66 μmol , 0.04 eq) and TEA (2.18 g, 21.57 mmol, 3.00 mL, 3 eq) in DMF (30 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 hr under N_2 atmosphere. The reaction mixture was filtered and concentrated to remove the solvent. The crude product was triturated with petroleum ether: EtOAc (5:1, 20 mL) at 20 °C for 30 min. Compound (E)-2-[2-[5-amino-2-(trifluoromethoxy)anilino]-5-fluoro-quinazolin-7-yl]ethenesulfonamide (2.7 g, 6.09 mmol, 85% yield) was obtained as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 9.38 (s, 1H), 9.23 (s, 1H), 7.65 (s, 1H), 7.61 (d, J = 11.2 Hz, 1H), 7.57-7.49 (m, 1H), 7.46-7.37 (m, 1H), 7.25 (br s, 2H), 7.14 (d, J = 2.8 Hz, 1H), 7.05-7.01 (m, 1H), 6.43-6.38 (m, 1H), 5.33 (s, 2H).

[0140] **Step 5:** To a solution of (E)-2-[2-[5-amino-2-(trifluoromethoxy)anilino]-5-fluoro-quinazolin-7-yl]ethenesulfonamide (500 mg, 1.13 mmol, 1 eq) and $p\text{-TsOH}\cdot\text{H}_2\text{O}$ (643.53 mg,

3.38 mmol, 3 eq) in ACN (12 mL) was dropwise added a solution of NaNO₂ (155.61 mg, 2.26 mmol, 2 eq) and KI (468.01 mg, 2.82 mmol, 2.5 eq) in H₂O (4 mL) at 0 °C. The mixture was stirred at 20 °C for 2 hr under N₂. The reaction mixture was quenched by the addition of H₂O (60 mL) and aq. Na₂S₂O₃ (2M, 6 mL), and then extracted with EtOAc (10 mL * 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The crude product was triturated with EtOAc (10 mL) at 20 °C for 20 min. (E)-2-[5-fluoro-2-[5-iodo-2-(trifluoromethoxy)anilino]quinazolin-7-yl]ethenesulfonamide (400 mg, 721.69 µmol, 64% yield) was obtained as a pink solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.74 (s, 1H), 9.44 (s, 1H), 8.36 (d, *J* = 2.0 Hz, 1H), 7.74-7.64 (m, 2H), 7.64-7.59 (m, 1H), 7.55 (s, 1H), 7.51-7.44 (m, 1H), 7.28-7.21 (m, 3H).

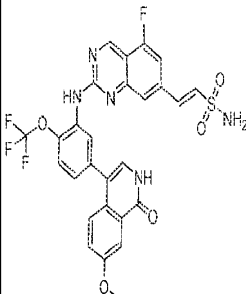
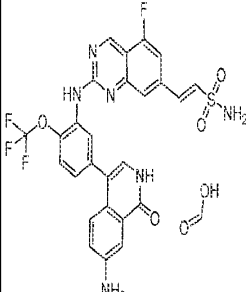
[0141] **Step 6:** A mixture of 4-bromo-2H-isoquinolin-1-one (400 mg, 1.79 mmol, 1 eq), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (2.72 g, 10.71 mmol, 6 eq), Pd₂(dba)₃ (163.48 mg, 178.53 µmol, 0.1 eq), tricyclohexylphosphane (100.13 mg, 357.06 µmol, 0.2 eq) and AcOK (525.64 mg, 5.36 mmol, 3 eq) in dioxane (20 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 110 °C for 12 hr under N₂ atmosphere. The reaction mixture was filtered to get the filtrate and concentrated to remove the solvent. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 1/1). Compound 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-isoquinolin-1-one (300 mg, 1.11 mmol, 62% yield) was obtained as a white solid. *m/z* (ES+) [M+H]⁺ = 272.1.

[0142] **Step 7:** A mixture of (E)-2-[5-fluoro-2-[5-iodo-2-(trifluoromethoxy)anilino]quinazolin-7-yl]ethenesulfonamide (50 mg, 90.21 µmol, 1 eq), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-isoquinolin-1-one (36.69 mg, 135.32 µmol, 1.5 eq), Pd(dppf)Cl₂·CH₂Cl₂ (7.37 mg, 9.02 µmol, 0.1 eq), Na₂CO₃ (23.90 mg, 225.53 µmol, 2.5 eq) in THF (2 mL), and H₂O (0.2 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 70 °C for 12 hr under N₂ atmosphere. The reaction mixture was filtered and washed with DMF (3 mL), and the filtrate was concentrated to remove the solvent. The residue was purified by prep-HPLC (column: CD07-Daisogel SP-100-8-ODS-PK 150*25*10µm; mobile phase: [water(NH₄HCO₃)-

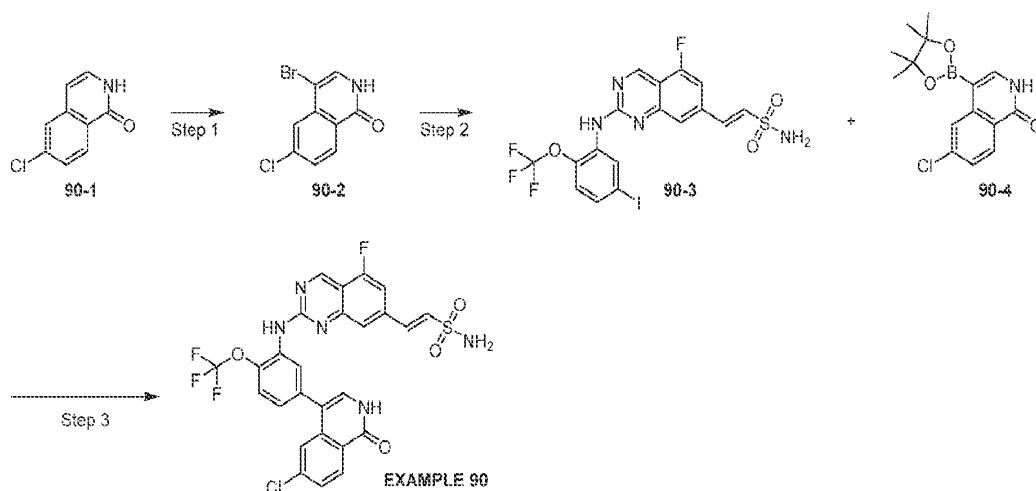
ACN]; gradient:35%-65% B over 15 min). Compound (E)-2-[5-fluoro-2-[5-(1-oxo-2H-isoquinolin-4-yl)-2-(trifluoromethoxy)anilino]quinazolin-7-yl]ethenesulfonamide (3 mg, 5.25 μ mol, 6% yield) was obtained as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 11.53 (br s, 1H), 9.80 (s, 1H), 9.43 (s, 1H), 8.32 (d, J = 8.0 Hz, 1H), 8.05 (s, 1H), 7.82-7.73 (m, 2H), 7.65-7.61 (m, 2H), 7.60-7.52 (m, 3H), 7.47-7.40 (m, 1H), 7.38-7.33 (m, 1H), 7.30-7.19 (m, 3H). m/z (ES+) $[M+H]^+ = 572.1$.

[0143] Following the teachings of the General Reaction Schemes and the synthesis procedure for Example 87 were prepared as shown in Table I:

Table I cont.

Example	Structure	Name	Characterization	Purification
88		(E)-2-[5-fluoro-2-[5-(7-methoxy-1-oxo-2H-isoquinolin-4-yl)-2-(trifluoromethoxy)anilino]quinazolin-7-yl]ethenesulfonamide	^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 11.49 (s, 1H), 9.79 (s, 1H), 9.43 (s, 1H), 8.00 (s, 1H), 7.76-7.60 (m, 4H), 7.58-7.49 (m, 2H), 7.47-7.38 (m, 2H), 7.37-7.30 (m, 1H), 7.30-7.20 (m, 2H), 7.11 (s, 1H), 3.89 (s, 3H). m/z (ES+) $[M+H]^+ = 602.2$.	prep-HPLC (column: CD01-Phenomenex luna C18 150*25*10 μ m; mobile phase: [water(FA)-ACN];gradient:40%-70% B over 8 min).
89		(E)-2-[2-((5-(7-amino-1-oxo-1,2-dihydroisoquinolin-4-yl)-2-(trifluoromethoxy)phenyl)amino)-5-fluoroquinazolin-7-yl]ethenesulfonamide	^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 11.11 (d, J = 6.0 Hz, 1H), 9.76 (s, 1H), 9.42 (s, 1H), 7.97 (d, J = 2.0 Hz, 1H), 7.65-7.62 (m, 2H), 7.57-7.54 (m, 1H), 7.51 (dd, J = 0.8 Hz, 8.0 Hz, 1H), 7.46-7.42 (m, 3H), 7.31 (dd, J = 2.0 Hz, 8.4 Hz, 1H), 7.25 (s, 2H), 7.05 (dd, J = 2.4 Hz, 8.4 Hz, 1H), 6.86 (d, J = 5.6 Hz, 1H), 5.59 (s, 2H). m/z (ES+) $[M+H]^+ = 587.2$.	prep-HPLC (column: CD01-Phenomenex luna C18 150*25*10 μ m; mobile phase: [water(FA)-ACN];gradient:32%-62% B over 8 min).

EXAMPLE 90



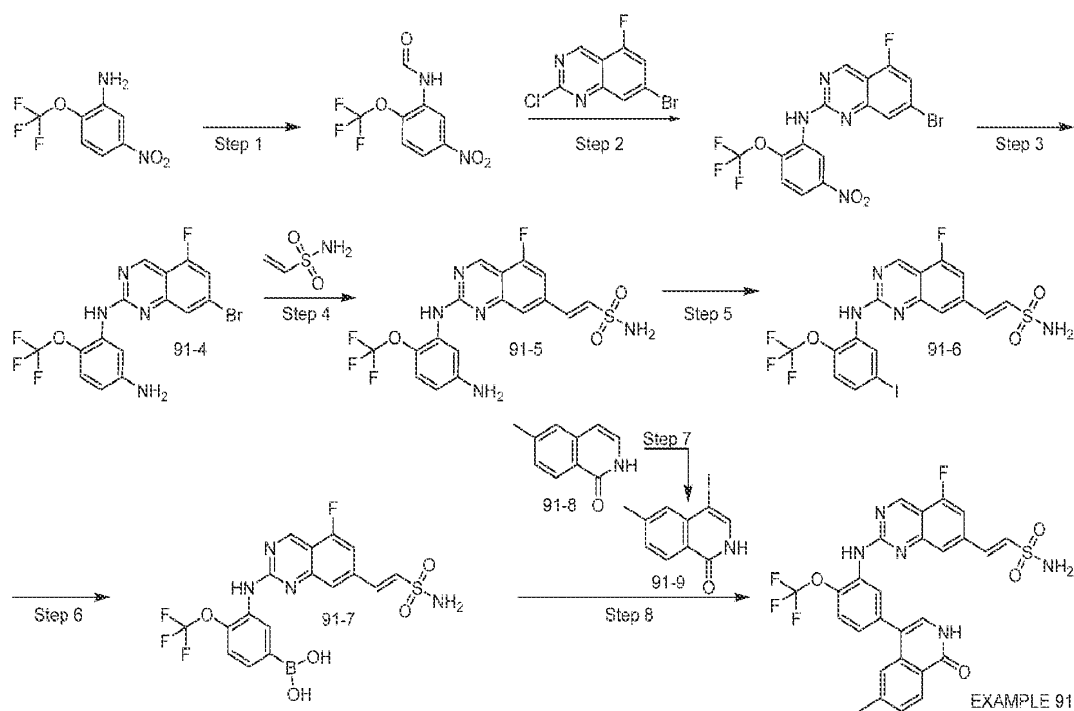
[0144] **Step 1:** To a solution of 6-chloro-2H-isoquinolin-1-one (500 mg, 2.78 mmol, 1 eq) in THF (9 mL) and DCM (6 mL) was added NBS (495.49 mg, 2.78 mmol, 1 eq) in portions at 0 °C. The mixture was stirred at 20 °C for 12 hr under N₂. The reaction mixture was quenched by the addition of H₂O (20 mL), extracted with CH₂Cl₂ (10 mLx3), and washed with brine 30 mL (10 mLx3). Then, the organic phase was combined, dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue. The crude product was triturated with DCM (10 mL) at 20 °C for 20 min. Compound 4-bromo-6-chloro-2H-isoquinolin-1-one (450 mg, 1.74 mmol, 63% yield) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 11.73 (s, 1H), 8.22 (d, J = 8.8 Hz, 1H), 7.71 (d, J = 2.0 Hz, 1H), 7.67-7.60 (m, 2H).

[0145] **Step 2:** A mixture of 4-bromo-6-chloro-2H-isoquinolin-1-one (400 mg, 1.55 mmol, 1 eq), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (707.30 mg, 2.79 mmol, 1.8 eq), Pd₂(dba)₃ (141.70 mg, 154.74 μmol, 0.1 eq), tricyclohexylphosphane (86.79 mg, 309.48 μmol, 0.2 eq) and KOAc (455.59 mg, 4.64 mmol, 3 eq) in dioxane (10 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 110 °C for 12 hr under N₂ atmosphere. The reaction mixture was filtered to get the filtrate and concentrated to remove the solvent. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 1/1). Compound 6-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-isoquinolin-1-one (360 mg, 1.18 mmol, 76% yield) was obtained as a white solid. m/z (ES⁺) [M+H]⁺ = 306.1, 308.0.

[0146] Step 3: To a solution of (E)-2-[5-fluoro-2-[5-iodo-2-(trifluoromethoxy)anilino]quinazolin-7-yl]ethenesulfonamide (100 mg, 180.42 μmol , 1 eq) in THF (2 mL) and water (0.2 mL) was added 6-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-isoquinolin-1-one (106.02 mg, 270.63 μmol , 1.5 eq), Pd(dppf)Cl₂.CH₂Cl₂ (14.73 mg, 18.04 μmol , 0.1 eq) and Na₂CO₃ (47.81 mg, 451.05 μmol , 2.5 eq). The mixture was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 70 °C for 12 hr under N₂ atmosphere.

[0147] The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (column: CD07-Daisogel SP-100-8-ODS-PK 150*25*10um; mobile phase: [water(NH₄HCO₃)-ACN]; gradient: 40%-70% B over 15 min). Compound (E)-2-[2-[5-(6-chloro-1-oxo-2H-isoquinolin-4-yl)-2-(trifluoromethoxy)anilino]-5-fluoro-quinazolin-7-yl]ethenesulfonamide (4 mg, 6.46 μmol , 98% purity) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 11.83-11.49 (m, 1H), 9.82(s, 1H), 9.44(s, 1H), 8.32 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 2.0 Hz, 1H), 7.69-7.60 (m, 4H), 7.58-7.50 (m, 2H), 7.44-7.38 (m, 1H), 7.35 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.33-7.16 (m, 3H). m/z (ES+) [M+H]⁺ = 606.0, 608.0.

EXAMPLE 91



[0148] **Step 1:** To a solution of 6-methyl-2H-isoquinolin-1-one (1 g, 6.28 mmol, 1 eq) and NIS (2.12 g, 9.42 mmol, 1.5 eq) in DCE (6 mL) was added TsOH (216.35 mg, 1.26 mmol, 0.2 eq) under N₂. The mixture was stirred at 25 °C for 12 hr. The reaction mixture was quenched by the addition of H₂O (20 mL) and then extracted with DCM (20 mL x 2). The combined organic layers were dried over Na₂SO₄ and filtered, and the filtrate was concentrated under reduced pressure to create a residue. The crude product was triturated with DCM (10 mL) for 15 min. Compound 4-iodo-6-methyl-2H-isoquinolin-1-one (400 mg, 1.40 mmol, 22% yield) as a yellow solid was obtained. ¹H NMR (400 MHz, DMSO-d₆) δ = 11.41 (s, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 4.4 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 2H), 2.54 (s, 3H). *m/z* (ES⁺) [M+H]⁺ = 285.9

[0149] **Step 2:** A mixture of 5-nitro-2-(trifluoromethoxy)aniline (5 g, 22.51 mmol, 1 eq) in HCOOH (100 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 1 hr under N₂ atmosphere. Compound N-[5-nitro-2-

(trifluoromethoxy)phenyl]formamide (16 g, 63.97 mmol, 95% yield) was obtained as a brown solid. m/z (ES+) $[M+H]^+ = 251.0$.

[0150] **Step 3:** To a solution of N-[5-nitro-2-(trifluoromethoxy)phenyl]formamide (5 g, 19.99 mmol, 1 eq) in THF (60 mL) was portionwise added NaH (11.99 g, 299.84 mmol, 60% purity, 15 eq) at 0 °C under N₂. The mixture was stirred at 20 °C for 0.5 hr under N₂. Then 7-bromo-2-chloro-5-fluoro-quinazoline (5.75 g, 21.99 mmol, 1.1 eq) was portionwise added to the mixture at 0 °C under N₂, then the mixture was stirred at 20 °C for 47.5 hr under N₂. The reaction mixture was quenched with sat. NH₄Cl (60 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na₂SO₄ and filtered, and the filtrate was concentrated under reduced pressure to create a residue. The obtained compound is used directly for the next step without further purification. Compound 7-bromo-5-fluoro-N-[5-nitro-2-(trifluoromethoxy)phenyl]quinazolin-2-amine (4 g, crude) was obtained as a yellow solid. It was used for the next step directly without any purification.

[0151] **Step 4:** To a solution of 7-bromo-5-fluoro-N-[5-nitro-2-(trifluoromethoxy)phenyl]quinazolin-2-amine (2 g, 4.47 mmol, 1 eq) and NH₄Cl (1.20 g, 22.36 mmol, 5 eq) in H₂O (20 mL) and EtOH (40 mL) was added portionwise Fe (1.25 g, 22.36 mmol, 5 eq) at 85 °C. After addition, the resulting mixture was stirred at 85 °C for 2 hr. The mixture was filtered by celite, and the filtrate was concentrated to remove the solvent. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 5/1). Compound N3-(7-bromo-5-fluoro-quinazolin-2-yl)-4-(trifluoromethoxy)benzene-1,3-diamine (3 g, 7.19 mmol, 54% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 9.44 (s, 1H), 9.34 (s, 1H), 7.71 (s, 1H), 7.50 (d, J = 9.6 Hz, 1H), 7.28 (d, J = 1.6 Hz, 1H), 7.09 (d, J = 8.8 Hz, 1H), 6.46 (dd, J = 2.4 Hz, 8.4 Hz, 1H), 5.41 (s, 2H).

[0152] **Step 5:** A mixture of N3-(7-bromo-5-fluoro-quinazolin-2-yl)-4-(trifluoromethoxy)benzene-1,3-diamine (3.0 g, 7.20 mmol, 1 eq), ethenesulfonamide (924.54 mg, 8.62 mmol, 1.2 eq), Pd(OAc)₂ (32.3 mg, 143.84 μ mol, 0.02 eq), tris-o-tolylphosphane (87.56 mg, 287.66 μ mol, 0.04 eq) and TEA (2.18 g, 21.58 mmol, 3.00 mL, 3 eq) in DMF (60 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 12 hr under N₂ atmosphere. The mixture was filtered to get the filtrate and concentrated under reduced

pressure to get the residue. The crude product was triturated with PE: EtOAc (5:1, 20 mL) at 20 °C for 30 min and filtered to afford (E)-2-[2-[5-amino-2-(trifluoromethoxy)anilino]-5-fluoroquinazolin-7-yl]ethanesulfonamide (2.7 g, 6.09 mmol, 85% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 9.38 (s, 1H), 9.23 (s, 1H), 7.65 (s, 1H), 7.61 (d, J = 11.2 Hz, 1H), 7.57-7.49 (m, 1H), 7.46-7.37 (m, 1H), 7.25 (br s, 2H), 7.14 (d, J = 2.8 Hz, 1H), 7.03 (dd, J = 1.2 Hz, 8.8 Hz, 1H), 6.41 (dd, J = 2.8 Hz, 8.8 Hz, 1H), 5.33 (s, 2H).

[0153] **Step 6:** To a solution of (E)-2-[2-[5-amino-2-(trifluoromethoxy)anilino]-5-fluoroquinazolin-7-yl]ethanesulfonamide (1 g, 2.26 mmol, 1 eq) and p-TsOH.H₂O (1.29 g, 6.77 mmol, 3 eq) in ACN (18 mL) was dropwise added NaNO₂ (311.23 mg, 4.51 mmol, 2 eq) and KI (936.02 mg, 5.64 mmol, 2.5 eq) in H₂O (6 mL) at 0 °C. The mixture was stirred at 20 °C for 2 hr. The reaction mixture was quenched by the addition of H₂O (120 mL) and aq. Na₂S₂O₃ (2 M, 10 mL), and then extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na₂SO₄ and filtered, and the filtrate was concentrated under reduced pressure to yield a residue. The crude product was triturated with EtOAc: PE (5:1, 20 mL) at 20 °C for 30 min and filtered to afford (E)-2-[5-fluoro-2-[5-iodo-2-(trifluoromethoxy)anilino]quinazolin-7-yl]ethanesulfonamide (700 mg, 1.26 mmol, 28% yield) as a dark red solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 9.74 (s, 1H), 9.44 (s, 1H), 8.36 (dd, J = 2.0 Hz, 1H), 7.74-7.64 (m, 2H), 7.64-7.59 (m, 1H), 7.56 (s, 1H), 7.53 (m, 1H), 7.28-7.21 (m, 3H).

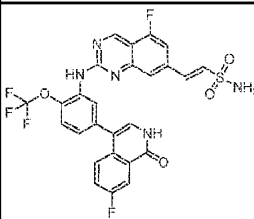
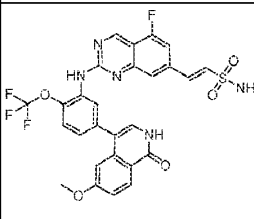
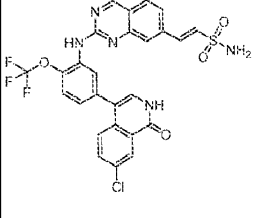
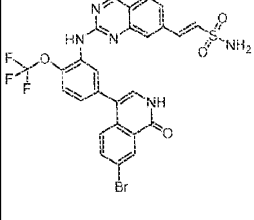
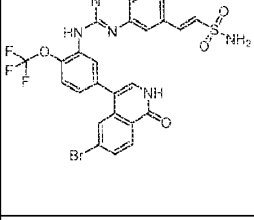
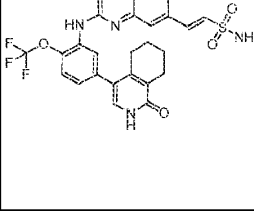
[0154] **Step 7:** A mixture of (E)-2-[5-fluoro-2-[5-iodo-2-(trifluoromethoxy)anilino]quinazolin-7-yl]ethanesulfonamide (500 mg, 902.11 μmol, 1 eq), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (458.16 mg, 1.80 mmol, 2 eq), cataCXiumA Pd G3 (65.70 mg, 90.21 μmol, 0.1 eq) and AcOK (265.61 mg, 2.71 mmol, 3 eq) in dioxane (10 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 90 °C for 12 hr under N₂ atmosphere. The mixture was filtered to get the filtrate and concentrated under reduced pressure to get the residue. The residue was purified by prep-HPLC (neutral condition; column: CD02-Waters Xbridge BEH C18 150*25*10um; mobile phase: [water(NH₄HCO₃)-ACN]; gradient: 52%-72% B over 15 min). Compound [3-[[5-fluoro-7-[(E)-2-sulfamoylvinyl]quinazolin-2-yl]amino]-4-(trifluoromethoxy)phenyl]boronic acid (150 mg, 317.68 μmol, 35% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ =

9.64 (s, 1H), 9.39 (s, 1H), 8.21 (s, 2H), 8.09 (d, J = 1.2 Hz, 1H), 7.72 (dd, J = 1.6 Hz, 8.4 Hz, 1H), 7.62-7.57 (m, 2H), 7.52 (s, 1H), 7.44 (s, 1H), 7.40-7.36 (m, 1H), 7.24 (s, 2H).

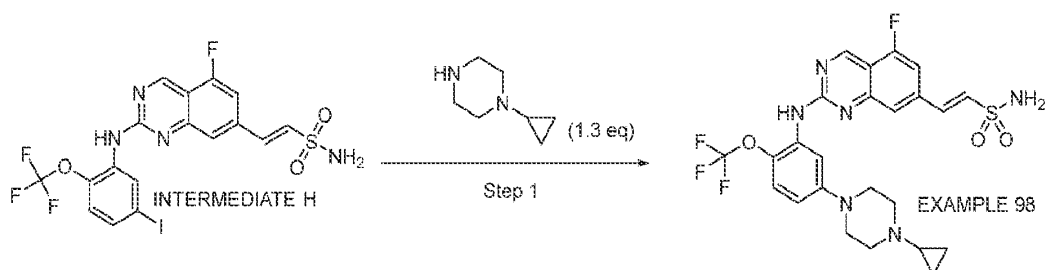
[0155] **Step 8:** To a solution of [3-[[5-fluoro-7-[(E)-2-sulfamoylvinyl]quinazolin-2-yl]amino]-4-(trifluoromethoxy)phenyl]boronic acid (62.11 mg, 131.54 μ mol, 1.5 eq) and 4-iodo-6-methyl-2H-isoquinolin-1-one (25 mg, 87.69 μ mol, 1 eq) in THF (1 mL) and H₂O (0.1 mL) was added Pd(dppf)Cl₂·CH₂Cl₂ (7.16 mg, 8.77 μ mol, 0.1 eq) and Na₂CO₃ (27.88 mg, 263.08 μ mol, 3 eq) under N₂. The mixture was stirred at 75 °C for 6 hr. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to provide a residue. The residue was purified by prep-HPLC (column: CD03-Welch Xtimate C18 150*25*5 μ m; mobile phase: [water(HCl)-ACN]; gradient: 40%-70% B over 10 min). Compound (E)-2-[5-fluoro-2-[5-(6-methyl-1-oxo-2H-isoquinolin-4-yl)-2-(trifluoromethoxy)anilino]quinazolin-7-yl]ethanesulfonamide (8 mg, 12.86 μ mol, 15% yield, HCl salt) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 11.45 (d, J=6.0 Hz, 1H), 9.79 (s, 1H), 9.43 (s, 1H), 8.22 (d, J=8.0 Hz, 1H), 8.027 (d, J=2.0 Hz, 1H), 7.65-7.59 (m, 2H), 7.55-7.51 (m, 2H), 7.47 (s, 1H), 7.43-7.41 (m, 1H), 7.39 (s, 1H), 7.36 (dd, J=2.0 Hz, 8.4 Hz, 1H), 7.26 (s, 2H), 7.19 (d, J=6.0 Hz, 1H), 2.42 (s, 3H). m/z (ES+) [M+H]⁺ = 586.1

[0156] Following the teachings of the General Reaction Schemes and the synthesis procedure for **Example 91** were prepared as shown in **Table I**:

Table I cont.

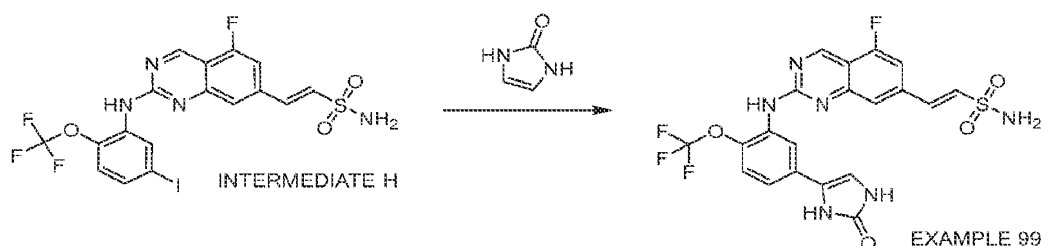
Example	Structure	Name	Characterization	Purification
92		(E)-2-((5-(7-fluoro-1-oxo-1,2-dihydroisoquinolin-4-yl)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 11.68 (s, 1H), 9.81 (s, 1H), 9.44 (s, 1H), 8.02 (d, J = 1.6 Hz, 1H), 7.97 (dd, J = 9.2 Hz, 2.8 Hz, 1H), 7.83-7.76 (m, 1H), 7.73-7.61 (m, 3H), 7.59-7.52 (m, 2H), 7.47-7.40 (m, 1H), 7.36 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.24 (d, J = 7.2 Hz, 3H). m/z (ES+) [M+H] ⁺ = 590.0.	prep-HPLC (column: CD02-Waters Xbridge BEH C18 150*25*10um; mobile phase: [water(NH ₄ HCO ₃)-ACN]; gradient: 40%-70% B over 10 min).
93		(E)-2-((5-(6-methoxy-1-oxo-1,2-dihydroisoquinolin-4-yl)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 11.34 (br s, 1H), 9.79 (br s, 1H), 9.43 (s, 1H), 8.27 (d, J=8.8 Hz, 1H), 8.10 (d, J=1.2 Hz, 1H), 7.67 (d, J=10.8 Hz, 1H), 7.57-7.51 (m, 3H), 7.42-7.35 (m, 2H), 7.24-7.15 (m, 4H), 3.82 (s, 3H). m/z (ES+) [M+1] ⁺ = 602.1	prep-HPLC (column: CD07-Daisogel SP-100-8-ODS-PK 150*25*10um; mobile phase: [water(NH ₄ HCO ₃)-ACN]; gradient:40%-70% B over 15 min).
94		(E)-2-((5-(7-chloro-1-oxo-1,2-dihydroisoquinolin-4-yl)-2-(trifluoromethoxy)phenyl)amino)-5-fluoroquinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 11.73 (s, 1H), 9.81 (s, 1H), 9.44 (s, 1H), 8.24 (d, J = 2.4 Hz, 1H), 8.02 (d, J = 2.0 Hz, 1H), 7.89-7.81 (m, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.68-7.62 (m, 2H), 7.59-7.52 (m, 2H), 7.47-7.41 (m, 1H), 7.35 (dd, J = 2.0 Hz, 8.4 Hz, 1H), 7.29-7.22 (m, 3H). m/z (ES+) [M+H] ⁺ = 606.0.	prep-HPLC (column: CD07-Daisogel SP-100-8-ODS-PK 150*25*10um;mobile phase: [water(NH ₄ HCO ₃)-ACN];gradient:39%-69% B over 10 min).
95		(E)-2-((5-(7-bromo-1-oxo-1,2-dihydroisoquinolin-4-yl)-2-(trifluoromethoxy)phenyl)amino)-5-fluoroquinazolin-7-yl)ethenesulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 9.75 (s, 1H), 9.44 (s, 1H), 8.39 (d, J=2.0 Hz, 1H), 8.02 (d, J=2.0 Hz, 1H), 7.97 (dd, J=2.4 Hz, 8.8 Hz, 1H), 7.68-7.64 (m, 3H), 7.57-7.53 (m, 2H), 7.48-7.42 (m, 1H), 7.36 (dd, J=2.0 Hz, 10.4 Hz, 1H), 7.30 (s, 1H). m/z (ES+) [M+H] ⁺ = 650.0.	prep-HPLC (column: CD07-Daisogel SP-100-8-ODS-PK 150*25*10um;mobile phase: [water(NH ₄ HCO ₃)-ACN];gradient:42%-72% B over 15 min).
96		(E)-2-((5-(6-bromo-1-oxo-1,2-dihydroisoquinolin-4-yl)-2-(trifluoromethoxy)phenyl)amino)-5-fluoroquinazolin-7-yl)ethenesulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 9.82 (s, 1H), 9.45 (s, 1H), 8.25 (d, J=8.4 Hz, 1H), 8.07 (d, J=2.0 Hz, 1H), 7.80 (d, J=1.6 Hz, 1H), 7.76 (dd, J=2.0 Hz, 8.8 Hz, 1H), 7.66-7.63 (m, 2H), 7.57-7.51 (m, 3H), 7.44-7.40 (m, 1H), 7.35 (dd, J=2.4 Hz, 8.4 Hz, 1H), 7.29-7.27 (m, 3H). m/z (ES+) [M+H] ⁺ = 650.1, 651.9	prep-HPLC (column: CD07-Daisogel SP-100-8-ODS-PK 150*25*10um;mobile phase: [water(NH ₄ HCO ₃)-ACN]; gradient:45%-75% B over 10 min).
97		(E)-2-((5-(1-oxo-1,2,5,6,7,8-hexahydroisoquinolin-4-yl)-2-(trifluoromethoxy)phenyl)amino)quinazolin-7-yl)ethene-1-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 11.49 (s, 1H), 9.70 (s, 1H), 9.42 (s, 1H), 7.88 (d, J = 2.0 Hz, 1H), 7.64 (d, J = 11.0 Hz, 1H), 7.59 - 7.51 (m, 2H), 7.43 (s, 1H), 7.42 - 7.38 (m, 1H), 7.26 (s, 2H), 7.19 (m, 1H), 7.12 (s, 1H), 2.48 - 2.44 (m, 2H), 2.44 - 2.38 (m, 2H), 1.74 - 1.59 (m, 4H). m/z (ES+) [M+H] ⁺ = 576.1	prep-HPLC (column: WePure Biotech XP tC18 150*40*10um;mobile phase: [H ₂ O(10mM NH ₄ HCO ₃)-ACN];gradient:40%-70% B over 8.0 min).

EXAMPLE 98



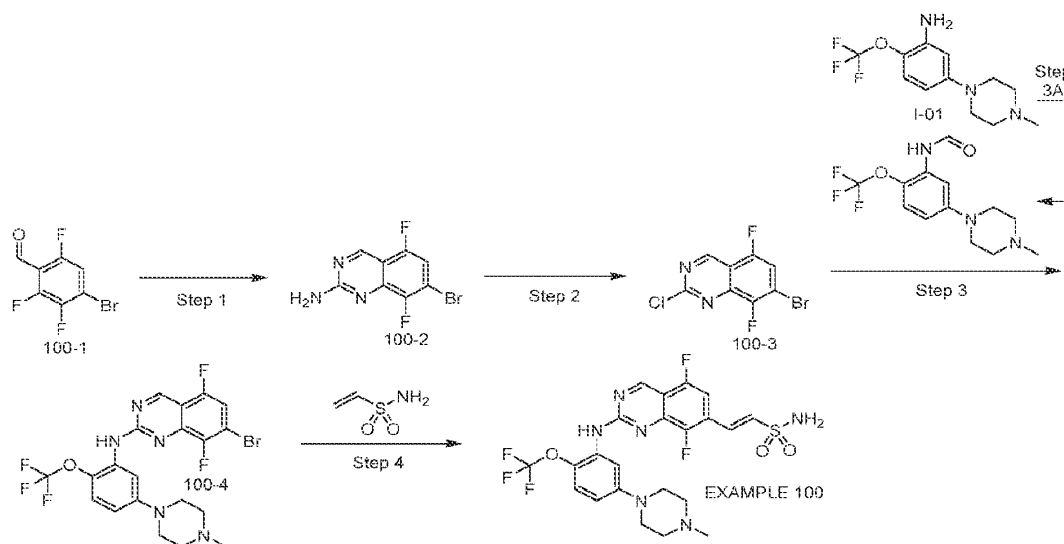
[0157] **Step 1:** A mixture of (E)-2-[5-fluoro-2-[5-iodo-2-(trifluoromethoxy)anilino]quinazolin-7-yl]ethenesulfonamide, Intermediate H (80 mg, 144.34 μ mol, 0.7 eq), 1-cyclopropylpiperazine (39.03 mg, 309.29 μ mol, 1.3 eq), Pd-PEPSI-IHept-Cl (20.06 mg, 20.62 μ mol, 0.1 eq), t-BuONa (2 M, 309.29 μ L, 3 eq) in 2-methylbutan-2-ol (2 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 90 °C for 12 hr under N₂ atmosphere. The mixture was filtered and concentrated under reduced pressure to get the residue. The residue was purified by prep-HPLC (column: CD07-Daisogel SP-100-8-ODS-PK 150*25*10 μ m; mobile phase: [water(NH₄HCO₃)-ACN]; gradient: 44%-74% B over 11 min). Compound (E)-2-[2-[5-(4-cyclopropylpiperazin-1-yl)-2-(trifluoromethoxy)anilino]-5-fluoro-quinazolin-7-yl]ethenesulfonamide (12 mg, 20.68 μ mol, 96% yield, 95.24% purity) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.42 (s, 1H), 9.40 (s, 1H), 7.69-7.60 (m, 2H), 7.59-7.42 (m, 3H), 7.29-7.19 (m, 3H), 6.81 (dd, *J* = 2.8 Hz, 9.2 Hz, 1H), 3.14 (t, *J* = 4.4 Hz, 4H), 2.69 (t, *J* = 1.2 Hz, 4H), 1.73-1.61 (m, 1H), 0.50-0.39 (m, 2H), 0.39-0.29 (m, 2H). *m/z* (ES⁺) [M+H]⁺ = 553.3.

EXAMPLE 99



[0158] **Step 1:** A mixture of (E)-2-[5-fluoro-2-[5-iodo-2-(trifluoromethoxy)anilino]quinazolin-7-yl]ethenesulfonamide (80.10 mg, 144.51 μmol , 1.5 eq), 1,3-dihydroimidazol-2-one (8.1 mg, 96.34 μmol , 1 eq), $\text{Pd}(\text{OAc})_2$ (1.08 mg, 4.82 μmol , 0.05 eq), NaOAc (23.71 mg, 289.02 μmol , 3 eq) in DMSO (3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 $^\circ\text{C}$ for 12 hr under N_2 atmosphere. The reaction mixture was filtered to get the filtrate and concentrated to remove the solvent. The residue was purified by prep-HPLC (column: CD02-Waters Xbridge BEH C18 150*25*10um; mobile phase: [water(NH_4HCO_3)-ACN]; gradient: 22%-52% B over 10 min). Compound (E)-2-[5-fluoro-2-[5-(2-oxo-1,3-dihydroimidazol-4-yl)-2-(trifluoromethoxy)anilino]quinazolin-7-yl]ethenesulfonamide (5 mg, 9.40 μmol , 6.0% yield, 96% purity) as a yellow solid was obtained. ^1H NMR (400 MHz, DMSO- d_6) δ = 10.55 (s, 1H), 10.14 (s, 1H), 9.64 (s, 1H), 9.41 (s, 1H), 7.99 (s, 1H), 7.69 (s, 1H), 7.65 (d, J =10.8 Hz, 1H), 7.58 (m, 1H), 7.43 (m, 3H), 7.24 (s, 2H), 6.96-6.95 (m, 1H). ^1H NMR (400 MHz, DMSO- d_6 and a drop of D_2O) δ = 9.39 (s, 1H), 7.99 (s, 1H), 7.63 (br d, J = 6.3 Hz, 1H), 7.55 - 7.49 (m, 1H), 7.48 - 7.44 (m, 1H), 7.40-7.34 (m, 1H), 7.38 (br s, 2H), 6.96 - 6.88 (m, 1H). m/z (ES+) $[M+H]^+$ = 511.0

EXAMPLE 100



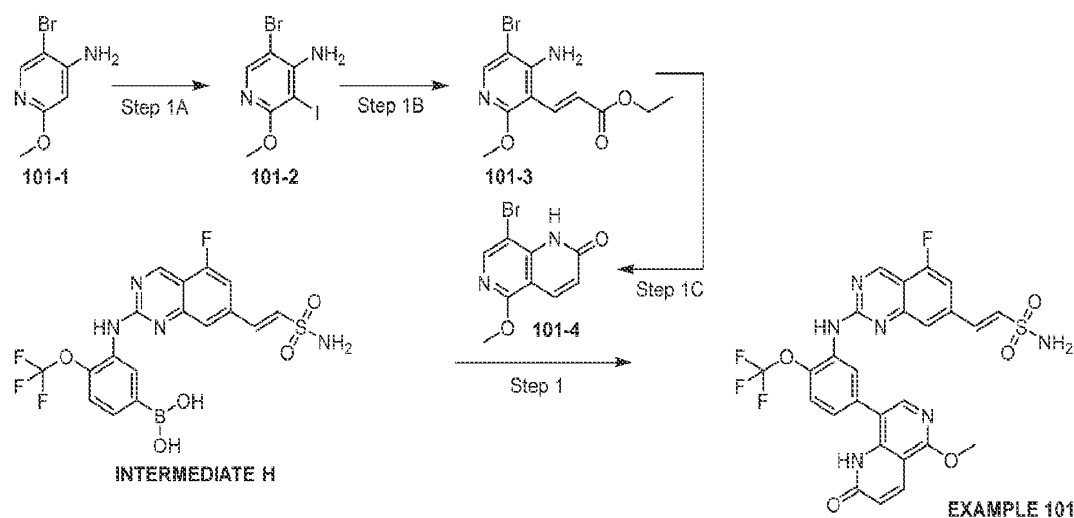
[0159] Step 1: To a solution of 4-bromo-2,3,6-trifluoro-benzaldehyde (1.8 g, 7.53 mmol, 1 eq) and carbonic acid guanidine (1.09 g, 6.03 mmol, 0.8 eq) in DMA (20 mL). The mixture was stirred at 140 °C for 4 hr. Water (50 mL) was added to the mixture, and the mixture was filtered to provide the filter cake. The filter cake was dried under a vacuum to give the desired product. The product was used for the next step without purification. Compound 7-bromo-5,8-difluoro-quinazolin-2-amine (1.3 g, 5.00 mmol, 66% yield) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 9.28 (d, J = 1.0 Hz, 1H), 7.62 (br s, 2H), 7.36 (dd, J = 4.8, 8.8 Hz, 1H).

[0160] Step 2: To a solution of 7-bromo-5,8-difluoro-quinazolin-2-amine (800 mg, 3.08 mmol, 1 eq) in DCM (8 mL) and DMF (1 mL) was added tetrabutylammonium chloride (1.03 g, 3.69 mmol, 1.03 mL, 1.2 eq) at 0 °C for 0.5 h. Then, to the mixture was added chloro(trimethyl)silane (1.34 g, 12.31 mmol, 1.56 mL, 4 eq) and tert-butyl nitrite (951.74 mg, 9.23 mmol, 1.10 mL, 3 eq). The mixture was stirred at 45 °C for 4.5 h. The reaction mixture was poured into ice water (50 mL) and extracted with EtOAc (20 mL x 3). The combined organic phase was washed with sat. NaHCO₃ (20 mL) and brine (20 mL) were dried over Na₂SO₄, filtered, and concentrated in vacuum. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=10/1, 3/1). Compound 7-bromo-2-chloro-5,8-difluoro-quinazoline (320 mg, 1.15 mmol, 37% yield) was obtained as a yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ = 9.78 (s, 1H), 8.12 (br dd, J = 4.4, 8.8 Hz, 1H).

[0161] Step 3: To a solution of N-[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)phenyl]formamide (130.22 mg, 429.39 μmol, 1.2 eq) and 7-bromo-2-chloro-5,8-difluoro-quinazoline (100 mg, 357.82 μmol, 1 eq) in THF (1 mL) was added NaH (161.00 mg, 5.37 mmol, 1.34 mL, 80% purity, 15 eq) at 0 °C in portions under N₂. The mixture was stirred at 25 °C for 48 hr. To the mixture was added sat. NH₄Cl (20 mL). The mixture was extracted with ethyl acetate (10 mL*3). The combined organic phase was dried with anhydrous Na₂SO₄, filtered, and concentrated to give the residue. The product was used for the next step without purification. Compound 7-bromo-5,8-difluoro-N-[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)phenyl]quinazolin-2-amine (20 mg, 38.59 μmol, 11% yield) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 9.80 (s, 1H), 9.45 (d, J = 1.0 Hz, 1H), 7.72 (br

s, 1H), 7.57 (dd, J = 4.6, 8.9 Hz, 1H), 7.24 (dd, J = 1.1, 9.0 Hz, 1H), 6.83 (dd, J = 2.9, 9.1 Hz, 1H), 3.22 - 3.17 (m, 4H), 2.48 (br s, 4H), 2.25 (s, 3H).

[0162] Step 4: To a solution of 7-bromo-5,8-difluoro-N-[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)phenyl]quinazolin-2-amine (70 mg, 135.06 μ mol, 1 eq) and ethenesulfonamide (17.36 mg, 162.08 μ mol, 1.2 eq) in DMF (1 mL) was added TEA (41.00 mg, 405.19 μ mol, 56.40 μ L, 3 eq), Pd(OAc)₂ (606.45 μ g, 2.70 μ mol, 0.02 eq) and tris-o-tolylphosphane (1.64 mg, 5.40 μ mol, 0.04 eq). The mixture was stirred at 100 °C for 12 hr under N₂. The mixture was filtered, and the filtrate was concentrated to produce the residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um; mobile phase: [H₂O(10mM NH₄HCO₃)-ACN];gradient:45%-75% B over 8.0 min). Compound (E)-2-[5,8-difluoro-2-[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)anilino]quinazolin-7-yl]ethenesulfonamide (1.2 mg, 2.19 μ mol, 2% yield, 99% purity) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 9.73 (s, 1H), 9.45 (s, 1H), 7.77 (s, 1H), 7.73 - 7.68 (m, 1H), 7.67 - 7.61 (m, 1H), 7.59 - 7.52 (m, 1H), 7.38 (s, 2H), 7.24 (br d, J = 8.9 Hz, 1H), 6.82 (dd, J = 2.6, 9.1 Hz, 1H), 3.20 (br s, 4H), 2.48 (br s, 4H), 2.24 (s, 3H). m/z (ES+) [M+H]⁺ = 545.1.



EXAMPLE 101

[0163] Step 1: To a solution of 5-bromo-2-methoxy-pyridin-4-amine (1 g, 4.93 mmol, 1 eq) in ACN (20 mL) was added TsOH.H₂O (65.58 mg, 344.77 μ mol, 0.07 eq) and NIS (1.86 g, 8.27 mmol, 1.68 eq). The mixture was stirred at 70 °C for 12 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was triturated with EtOAc (20 mL) at 25 °C for 20 min, filtered, and the filter cake was dried in a vacuum. Compound 5-bromo-3-iodo-2-methoxy-pyridin-4-amine (1.37 g, 4.16 mmol, 84% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 7.89 (s, 1H), 6.09 (s, 2H), 3.80 (s, 3H). m/z (ES+) [M+H]⁺ = 328.8, 330.9.

[0164] Step 2: To a solution of 5-bromo-3-iodo-2-methoxy-pyridin-4-amine (1.37 g, 4.16 mmol, 1 eq), ethyl prop-2-enoate (750.56 mg, 7.50 mmol, 814.94 μ L, 1.8 eq), TEA (632.18 mg, 6.25 mmol, 869.57 μ L, 1.5 eq) and tris-*o*-tolylphosphane (126.77 mg, 416.50 μ mol, 0.1 eq) in DMF (14 mL) was added Pd(OAc)₂ (46.75 mg, 208.25 μ mol, 0.05 eq) under N₂. The mixture was stirred at 100 °C for 12 hr under N₂. The reaction mixture was quenched by addition aq. NaClO (30 mL) is concentrated under reduced pressure to create a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 5/1). Compound ethyl (E)-3-(4-amino-5-bromo-2-methoxy-3-pyridyl)prop-2-enoate (0.9 g, 2.99 mmol, 72% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 7.95 (s, 1H), 7.72 (d, *J*=4.0 Hz, 1H), 6.63-6.56 (m, 3H), 4.18 (dd, *J*=6.8 Hz, 14.4 Hz, 2H), 3.86 (s, 3H), 1.25 (t, *J*=6.8 Hz, 3H). m/z (ES+) [M+H]⁺ = 301.0, 302.8.

[0165] Step 3: To a solution of ethyl (E)-3-(4-amino-5-bromo-2-methoxy-3-pyridyl)prop-2-enoate (900 mg, 2.99 mmol, 1 eq) in EtOH (10 mL) was added NaSMc (230.42 mg, 3.29 mmol, 209.47 μ L, 1.1 eq) under N₂. The mixture was stirred at 25 °C for 2 hr. The reaction mixture was quenched by the addition of H₂O (30 mL) at 0 °C and then extracted with DCM (30 mL * 2). The combined organic layers were dried over Na₂SO₄ and filtered, and the filtrate was concentrated under reduced pressure to create a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 8/1). Compound 8-bromo-5-methoxy-1H-1,6-naphthyridin-2-one (230 mg, 901.72 μ mol, 30% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 11.14 (s, 1H), 8.30 (s, 1H), 7.99 (d, *J*=8.8 Hz, 1H), 6.60 (d, *J*=8.8 Hz, 1H), 3.98 (s, 3H). m/z (ES+) [M+H]⁺ = 255.0, 257.0.

[0166] Step 4: To a solution of (E)-2-[5-fluoro-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethoxy)anilino]quinazolin-7-yl]ethenesulfonamide (50 mg, 90.20 μmol , 1 *eq*), 8-bromo-5-methoxy-1H-1,6-naphthyridin-2-one (20.71 mg, 81.18 μmol , 0.9 *eq*) and Na_2CO_3 (28.68 mg, 270.60 μmol , 3 *eq*) in THF (2 mL) and H_2O (0.4 mL) was added $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (7.37 mg, 9.02 μmol , 0.1 *eq*) under N_2 . The mixture was stirred at 75 °C for 6 hr under N_2 . The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: CD24-XPT C18 150*25*7 μm ; mobile phase: [water(NH_4HCO_3)-ACN]; gradient: 35%-65% B over 10 min). Compound (E)-2-[5-fluoro-2-[5-(5-methoxy-2-oxo-1H-1,6-naphthyridin-8-yl)-2-(trifluoromethoxy)anilino]quinazolin-7-yl]ethenesulfonamide (16 mg, 26.56 μmol , 30% yield) was obtained as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 10.63 (s, 1H), 9.83 (s, 1H), 9.49 (s, 1H), 8.19 (d, J =1.6 Hz, 1H), 8.11-8.10 (m, 2H), 7.79 (s, 1H), 7.64-7.58 (m, 2H), 7.56-7.54 (m, 1H), 7.46-7.42 (m, 1H), 7.33 (dd, J =1.2 Hz, 8.8 Hz, 1H), 7.27 (s, 2H), 6.63 (d, J =9.6 Hz, 1H), 4.04 (s, 3H). m/z (ES^+) [$\text{M}+\text{H}$] $^+$ = 603.1.

EXAMPLE A

[0167] This example illustrates that exemplary compounds of the present invention inhibit PLK1 enzymatic activity.

[0168] Compounds were solubilized in DMSO to produce 10 mM stock solutions and diluted to 100 μM working solutions in DMSO. A series of 10, three-fold dilutions of each compound working solution was dispensed (Tecan D300e digital dispenser) on a 384-well white ProxiPlate (PerkinElmer, #6008280) in two technical replicates, yielding dilution series with final concentrations in 10 μL total reaction volume ranging from 0.05 to 1000 nM. Volasertib (MedChemExpress, #HY-12137) & GSK461364 (MedChemExpress, #HY-50877) were used as positive controls (1.0 μM final concentration, 5 technical replicates each). The volume was made up to 4 μL using a kinase buffer (PerkinElmer, HTRF® KinEASE-STK S1 kit # 62ST1PEB), supplemented with 1.0 mM DTT & 5.0 mM MgCl_2 , and that same assay buffer without compounds was used as a negative control. DMSO was normalized to 1% final concentration across all wells.

[0169] All subsequent assay components were diluted using the kinase buffer supplemented with 1 mM DTT & 5 mM MgCl₂. A 25 nM PLK1 protein (Carna Biosciences, #05-157) working solution was prepared, and 2 µL was dispensed into each well, resulting in a 5 nM final concentration. A 10 µM STK substrate 1-biotin solution (PerkinElmer, HTRF® KinEASE-STK S1 kit #62ST1PEB) was prepared according to manufacturer's instructions, and 2 µL was dispensed into each well, resulting in a 2 µM final concentration. Finally, a 100 µM ATP solution (Sigma-Aldrich, #A7699) was prepared, and 2 µL was added to each well, resulting in a 20 µM final concentration, initiating the kinase reaction. The plate was sealed, shaken briefly to mix the reaction contents well, centrifuged, and incubated for 90 min at 37 °C.

[0170] After the kinase reaction finished, the plate seal was removed, 0.5 µM Streptavidin-XL665 (PerkinElmer, HTRF® KinEASE-STK S1 kit #62ST1PEB) working solution was prepared according to manufacturer's instructions in the detection buffer (PerkinElmer, HTRF® KinEASE-STK S1 kit #62ST1PEB) and 5 µL was dispensed into each well, resulting in 0.125 µM final concentration. Then, 5 µL of the Antibody-cryptate (PerkinElmer, HTRF® KinEASE-STK S1 kit #62ST1PEB) solution was added to each well. The plate was sealed again, shaken briefly, centrifuged, and incubated for 60 minutes at room temperature (25 °C). The FRET signal was then read on a PHERAstar® FSX microplate reader (BMG LABTECH) using 620 nm / 665 nm wavelengths for excitation/emission, respectively. Signal values were normalized for the background signal, and the acceptor/donor signal ratio was calculated and plotted against compound concentrations using GraphPad Prism™ software to generate semi-log concentration-response curves (CRCs). IC₅₀ values were determined using nonlinear regression of a variable slope model.

Table II

Example	PLK1 HTRF CRC/IC ₅₀ (nM)	Example	PLK1 HTRF CRC/IC ₅₀ (nM)	Example	PLK1 HTRF CRC/IC ₅₀ (nM)
1	14.7	35	5.3	69	125.5
2	12.2	36	4.6	70	325.9
3	7	37	404.6	71	> 1000
4	1.8	38	55.9	72	115
5	14.4	39	35.1	73	N/A
6	> 1000	40	59.8	74	9.3
7	> 1000	41	67.7	75	50.9
8	951	42	53.8	76	133
9	> 1000	43	153.5	77	6.3
10	> 1000	44	> 1000	78	60.4
11	17	45	391.6	79	20.9
12	351	46	> 1000	80	232.4
13	300	47	> 1000	81	12.8
14	75.9	48	131.7	82	13.7
15	18.6	49	12.2	83	30.2
16	71.9	50	790.2	84	20.4
17	11.5	51	821.4	85	50.8
18	27.2	52	> 1000	86	175.8
19	55.1	53	30.3	87	> 1000
20	13.3	54	> 1000	88	> 1000
21	11	55	> 1000	89	78.7
22	5.5	56	> 1000	90	> 1000
23	47.6	57	226.9	91	> 1000
24	32	58	34.8	92	> 1000
25	282.7	59	76.3	93	> 1000
26	0.7	60	509.2	94	> 1000

Table II cont.

Example	PLK1 HTRF CRC/IC ₅₀ (nM)	Example	PLK1 HTRF CRC/IC ₅₀ (nM)	Example	PLK1 HTRF CRC/IC ₅₀ (nM)
27	23.7	61	559.1	95	> 1000
28	65.9	62	257.3	96	N/A
29	3.5	63	456	97	176
30	1.9	64	> 1000	98	9.8
31	11.6	65	> 1000	99	130.2
32	178.2	66	29.7	100	4.4
33	10.4	67	2.4	101	> 1000
34	> 1000	68	N/A		

EXAMPLE B

[0171] This example illustrates the reactivity of glutathione in the reduced state (GSH) at pH 7.5 with exemplary compounds of the present invention.

Analyses of compound reactivity with GSH (USP, catalog # 1294820) were performed in a time-dependent experiment through the use of Liquid Chromatography-Mass Spectrometry (LC-MS) detection. The peak area of the compound normalized with the peak area of the internal standard (IS), Rhodamine B (Sigma Aldrich, catalog # R6626), was calculated in order to determine the half-life ($t_{1/2}$).

[0172] Compounds were solubilized in DMSO to obtain 10 mM concentrations. Dilutions of each compound were made in acetonitrile (LC-MS grade) to obtain 100 μ M concentrations. An assay buffer, 50 mM Tris pH 7.5 with 150 mM NaCl, was deoxidized prior to testing by keeping it under a nitrogen stream for approximately 1 hour. GSH and the IS were solubilized in the assay buffer to obtain 1.2 mM and 25 μ M concentrations, respectively.

[0173] To 86 μ L of 1.2 mM GSH solution, 4 μ L of 25 μ M Rhodamine B solution was added into a glass vial with an insert. To initiate the reaction, 10 μ L of the 100 μ M compound solution was added to the vial, and the reaction mixtures were immediately injected into an LC-MS system, followed by repeated injections at fixed time intervals up to 24 hours. An autosampler temperature was set to 25°C to maintain a steady incubation temperature. Compounds were separated on an ACQUITY UPLC® HSS T3 1.8 μ m, 2.1x100 mm column (Waters) at temperature 40°C with a 10–95% gradient of 0.1% formic acid in

acetonitrile for 5.5 min at a flow rate of 0.25 mL/min using the ultra-high-performance liquid chromatography Dionex UltiMate 3000 system (Thermo Scientific) and analyzed using a Q Exactive™ Plus mass spectrometer equipped with an electrospray ionization ion source (Thermo Scientific). The mass spectrometer was operated in a standard Full MS mode in a scan range of 200 to 600 m/z.

Table III

Example	GSH t½ (min)	Example	GSH t½ (min)	Example	GSH t½ (min)
1	>1440	35	>1440	69	>1440
2	>1440	36	>1440	70	433
3	770	37	>1440	71	403
4	>1440	38	630	72	598
5	>1440	39	>1440	73	806
6	>1440	40	>1440	74	>1440
7	>1440	41	>1440	75	>1440
8	>1440	42	>1440	76	>1440
9	>1440	43	17	77	>1440
10	>1440	44	>1440	78	>1440
11	100	45	>1440	79	>1440
12	277	46	976	80	>1440
13	>1200	47	>1440	81	>1440
14	>1200	48	>1440	82	>1440
15	>1260	49	>1440	83	>1440
16	>1260	50	>1440	84	>1440
17	>1260	51	>1440	85	>1440
18	>1260	52	1195	86	>1440
19	>1080	53	>1440	87	770
20	>1080	54	>1440	88	630
21	>1080	55	730	89	529
22	>1080	56	>1440	90	1118
23	630	57	889	91	>1440
24	>1440	58	>1440	92	1386
25	>1440	59	1195	93	>1440
26	>1440	60	>1440	94	686
27	>1440	61	608	95	912
28	>1440	62	>1440	96	>1440
29	1155	63	1100	97	138
30	>1440	64	118	98	210
31	>1440	65	>1440	99	>1320

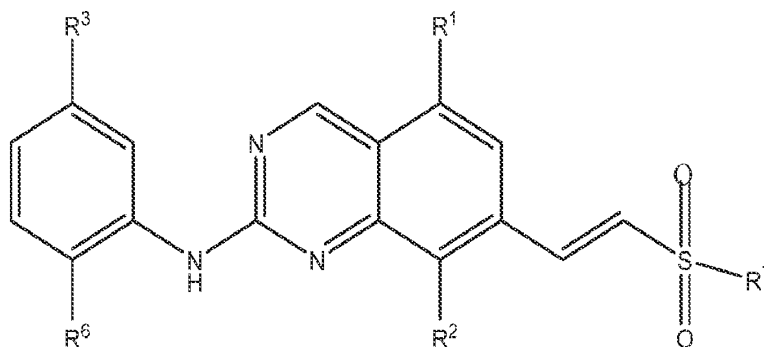
Table III cont.

Example	GSH t _{1/2} (min)	Example	GSH t _{1/2} (min)	Example	GSH t _{1/2} (min)
32	>1440	66	>1440	100	950
33	>1440	67	131	101	182
34	71	68	630		

[0174] From the obtained chromatograms, peak areas of the test compounds and the internal standard (IS) were integrated using the Chromeleon™ Chromatography Data System, and the area ratios between the test compounds and IS and a natural logarithm (ln) from the obtained area ratios were calculated. The t_{1/2} value for each compound was determined from the plot curve of ln (area ratio) versus time and the equation $t_{1/2} = \ln 2 / (-\text{slope})$.

We claim:

1. A compound of Formula (I):



Formula (I)

wherein:

R^1 is hydrogen, halogen, hydroxy, C1-C6 alkyl, cycloalkyl, haloalkyl, or aniline;

R^2 is hydrogen, alkoxy, or -O-haloalkyl optionally substituted with one or more alkoxy groups,

R^3 is hydrogen, heterocyclyl optionally substituted with one or more R^4 , -NH- L^1 -N($R^A R^B$), -NH- L^2 -cycloalkyl or -NH- L^2 -heterocyclyl, wherein the cycloalkyl or the heterocyclyl is optionally substituted with one or more R^5 ;

R^6 is OCF₃, SCH₃, cyclopropane, O-cyclopropane, OCH₃, CH₂CH₃, azetidine, or S(O)(O)CH₃;

R^7 is NH₂, NHCH₃, or CH₃;

each R^4 is independently C1-C4 alkyl, cyclopropyl, hydroxyalkyl, - L^1 -N($R^A R^B$), halogen, O, O-CH₃, NH₂, -C(O)O-t-butyl; - L^3 -aryl; or - L^4 -heterocyclyl;

each R^5 is independently C1-C4 alkyl, N(CH₃)(CH₃), or heterocyclyl optionally substituted with aryl;

each L^1 is C1-C4 alkylene;

each L^2 is a bond or C1-C4 alkylene;

each L^3 is $-\text{CH}_2\text{-O-CH}_2-$;

each L^4 is a bond or methylene;

each R^A is hydrogen or C1-C3 alkyl;

each R^B is hydrogen or C1-C3 alkyl;

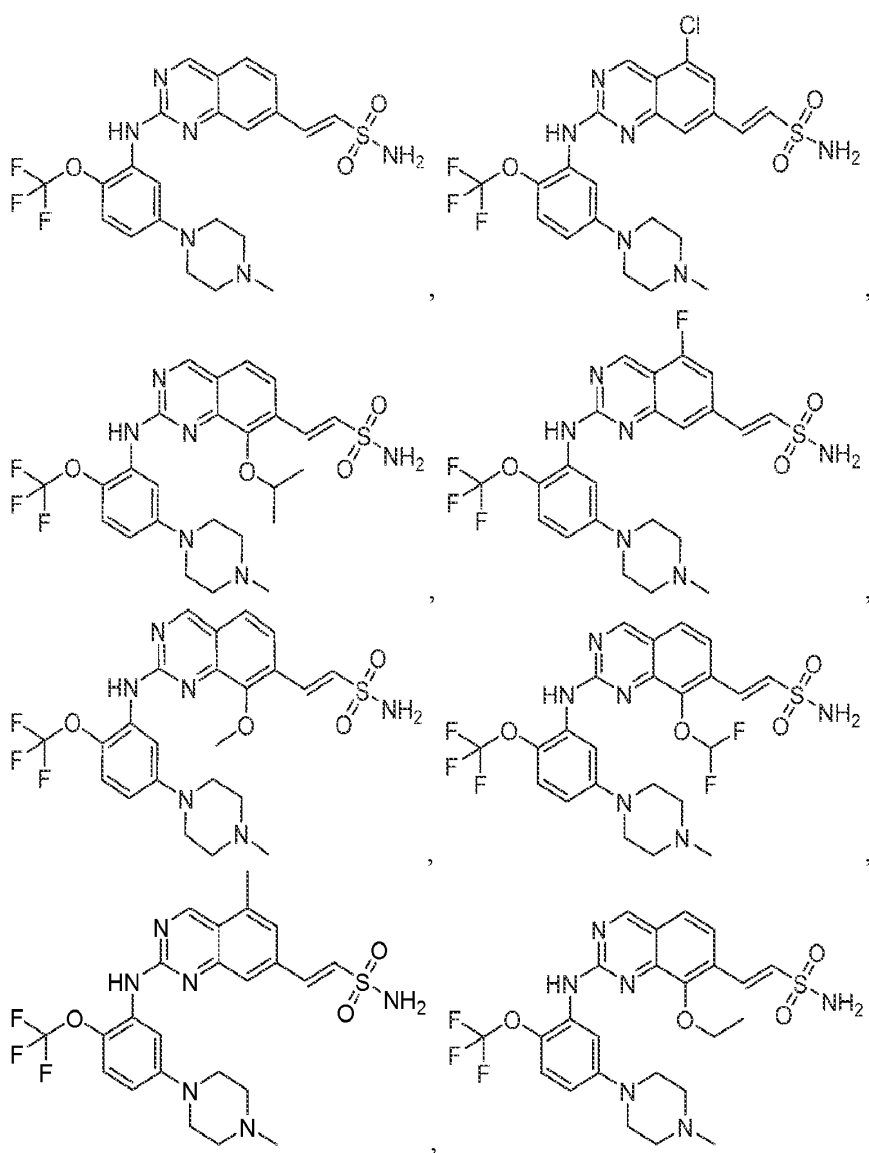
and pharmaceutically acceptable salts thereof.

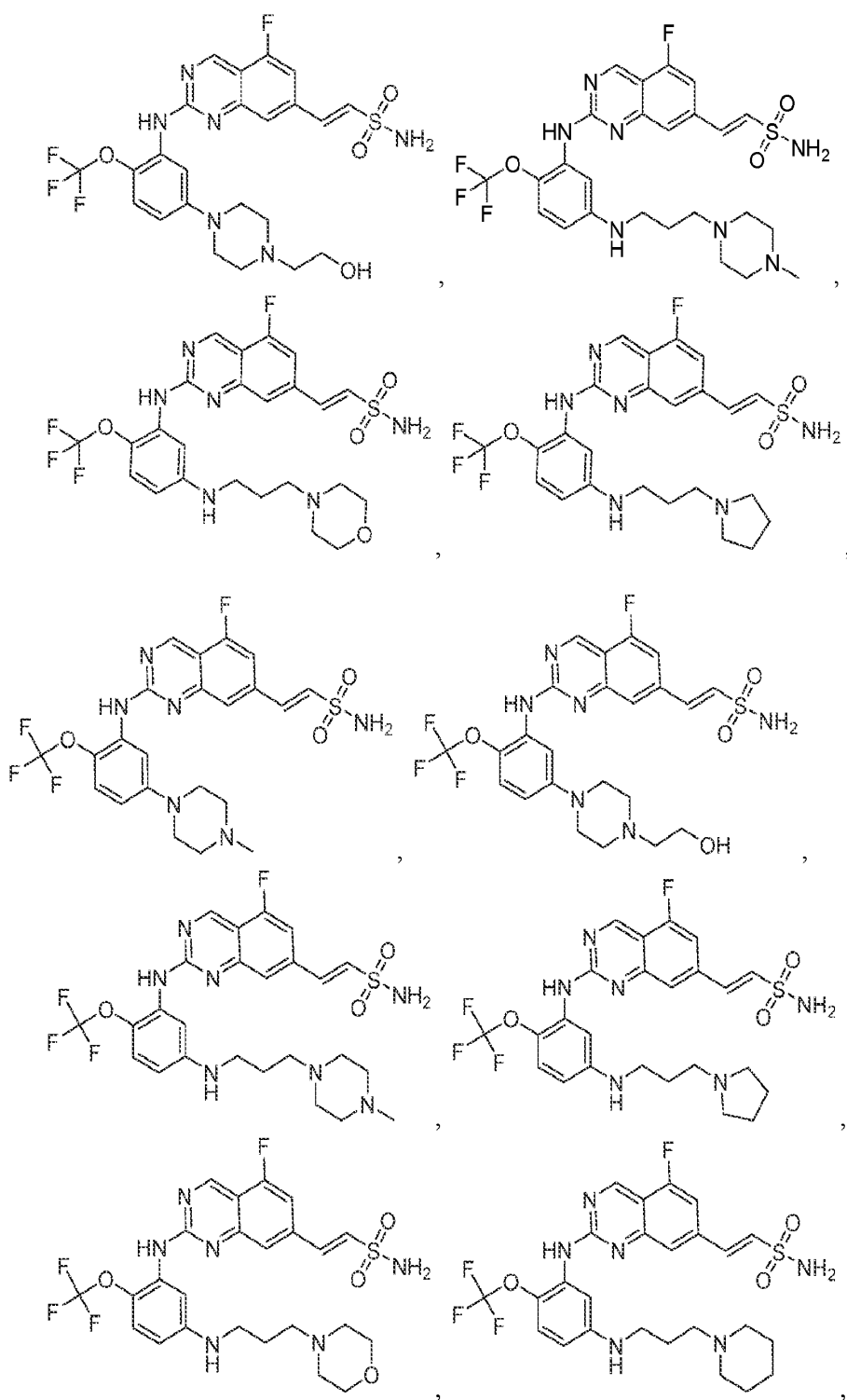
2. The compound of claim 1, wherein R^1 is halogen.
3. The compound of claim 2, wherein the halogen is chlorine, fluorine, or bromine.
4. The compound of claim 1, wherein R^1 is hydroxy.
5. The compound of claim 1, wherein R^1 is C1-C6 alkyl.
6. The compound of claim 5, wherein the C1-C6 is alkyl, is methyl, ethyl, or isopropyl.
7. The compound of claim 1, wherein R^1 is cycloalkyl.
8. The compound of claim 7, wherein the cycloalkyl is cyclopropyl.
9. The compound of claim 1, wherein R^1 is haloalkyl.
10. The compound of claim 9, wherein the haloalkyl is fluoromethyl, difluoromethyl, or trifluoromethyl.
11. The compound of claim 1, wherein R^1 is aniline.
12. The compound of claim 11, wherein the aniline is NH_2 .
13. The compound of any of claims 1-12, wherein R^2 is alkoxy or -O-haloalkyl.

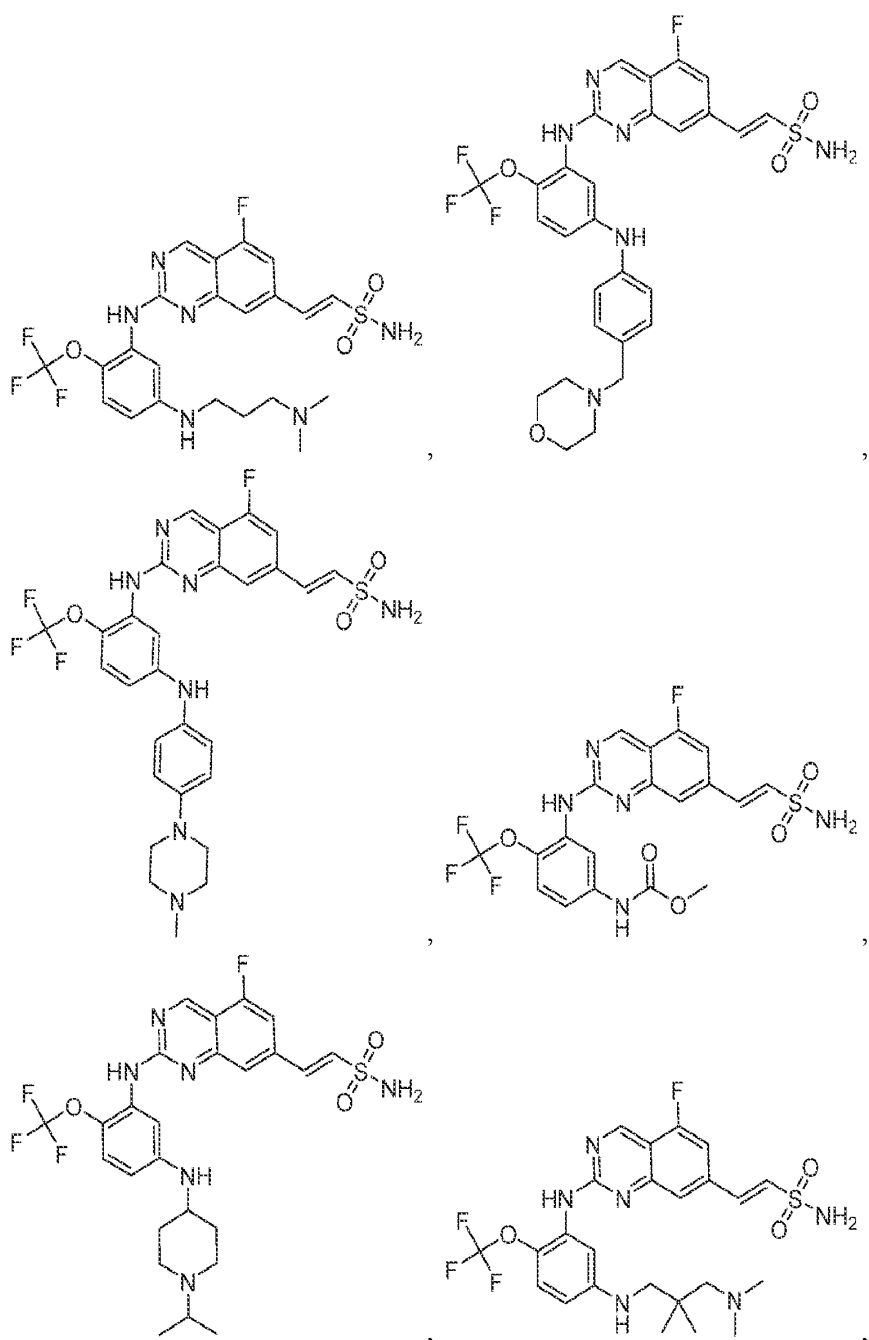
14. The compound of claim 13, wherein R^2 is alkoxy.
15. The compound of claim 14, wherein the alkoxy is methoxy or propoxy.
16. The compound of claim 13, wherein R^2 is -O-haloalkyl.
17. The compound of claim 16, wherein the haloalkyl is difluoromethyl.
18. The compound of any of claims 1-17, wherein R^6 is OCF_3 .
19. The compound of any of claims 1-18, wherein R^7 is NH_2 .
20. The compound of any of claims 1-19, wherein R^3 is heterocyclyl optionally substituted with one or more R^4 , $-NH-L^1-N(R^A R^B)$, $-NH-L^2$ -cycloalkyl or $-NH-L^2$ -heterocyclyl, wherein the cycloalkyl or the heterocyclyl is optionally substituted with one or more R^5 .
21. The compound of claim 20, wherein R^3 is heterocyclyl optionally substituted with one or more R^4 .
22. The compound of claim 21, wherein the heterocyclyl is 1,4-diazapanyl, 1-methyl-1, 4-diazapanyl or 1, 4-dimethyl-1,4-di(11-oxidaneyl)-114,414-piperaziny1.
23. The compound of claim 21, wherein the heterocyclyl is pyrrolidinyl, piperidinyl, or piperaziny1, each optionally substituted with one or more R^4 , wherein R^4 is C1-C4 alkyl, hydroxyalkyl, $-L^1-N(R^A R^B)$, $-C(O)O$ -t-butyl, $-L^3$ -aryl, or $-L^4$ -heterocyclyl.
24. The compound of claim 23, wherein the heterocyclyl is pyrrolidinyl substituted with one R^4 , and R^4 is L^4 -heterocyclyl, wherein L^4 is methylene, and the heterocyclyl is pyrrolidinyl.

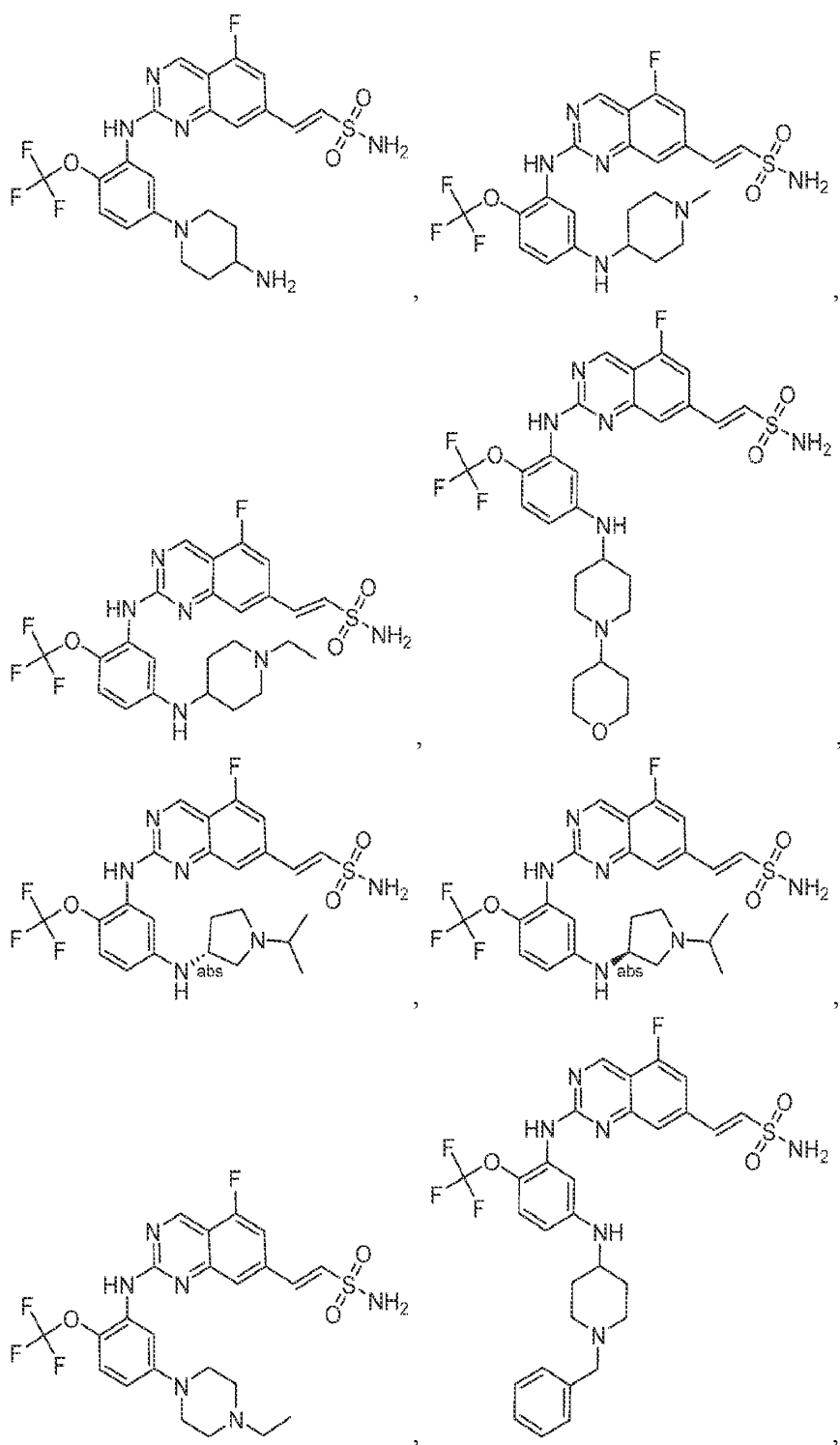
25. The compound of claim 23, wherein the heterocyclyl is piperidinyl substituted with one R^4 , and R^4 is L^4 -heterocyclyl, wherein L^4 is a bond, and the heterocyclyl is pyrrolidinyl.
26. The compound of claim 23, wherein the heterocyclyl is piperazinyl, and R^4 is C1-C4 alkyl, hydroxyalkyl, $-L^1-N(R^A R^B)$, $-C(O)O$ -t-butyl; or $-L^3$ -aryl.
27. The compound of claim 26, wherein the piperazinyl is substituted with one R^4 , and R^4 is C1-C4 alkyl, wherein the C1-C4 alkyl is methyl or ethyl.
28. The compound of claim 26, wherein the piperazinyl is substituted with one R^4 , and R^4 is $-L^1-N(R^A R^B)$.
29. The compound of claim 26, wherein the piperazinyl is substituted with one R^4 , and R^4 is $-C(O)O$ -t-butyl.
30. The compound of claim 26, wherein the piperazinyl is substituted with two R^4 groups, wherein one R^4 group is C1-C4 alkyl and the second R^4 group is hydroxyalkyl or $-L^3$ -aryl.
31. The compound of claim 20, wherein R^3 is $-NH-L^1-N(R^A R^B)$.
32. The compound of claim 31, wherein L^1 is propylene and R^A and R^B are each methyl.
33. The compound of claim 31, wherein L^1 is propylene and R^A and R^B are each ethyl.
34. The compound of claim 20, wherein R^3 is $-NH-L^2$ -heterocyclyl, wherein the heterocyclyl is optionally substituted with one or more R^5 .
35. The compound of claim 20, wherein R^3 is $NH-L^2$ -cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more R^5 .

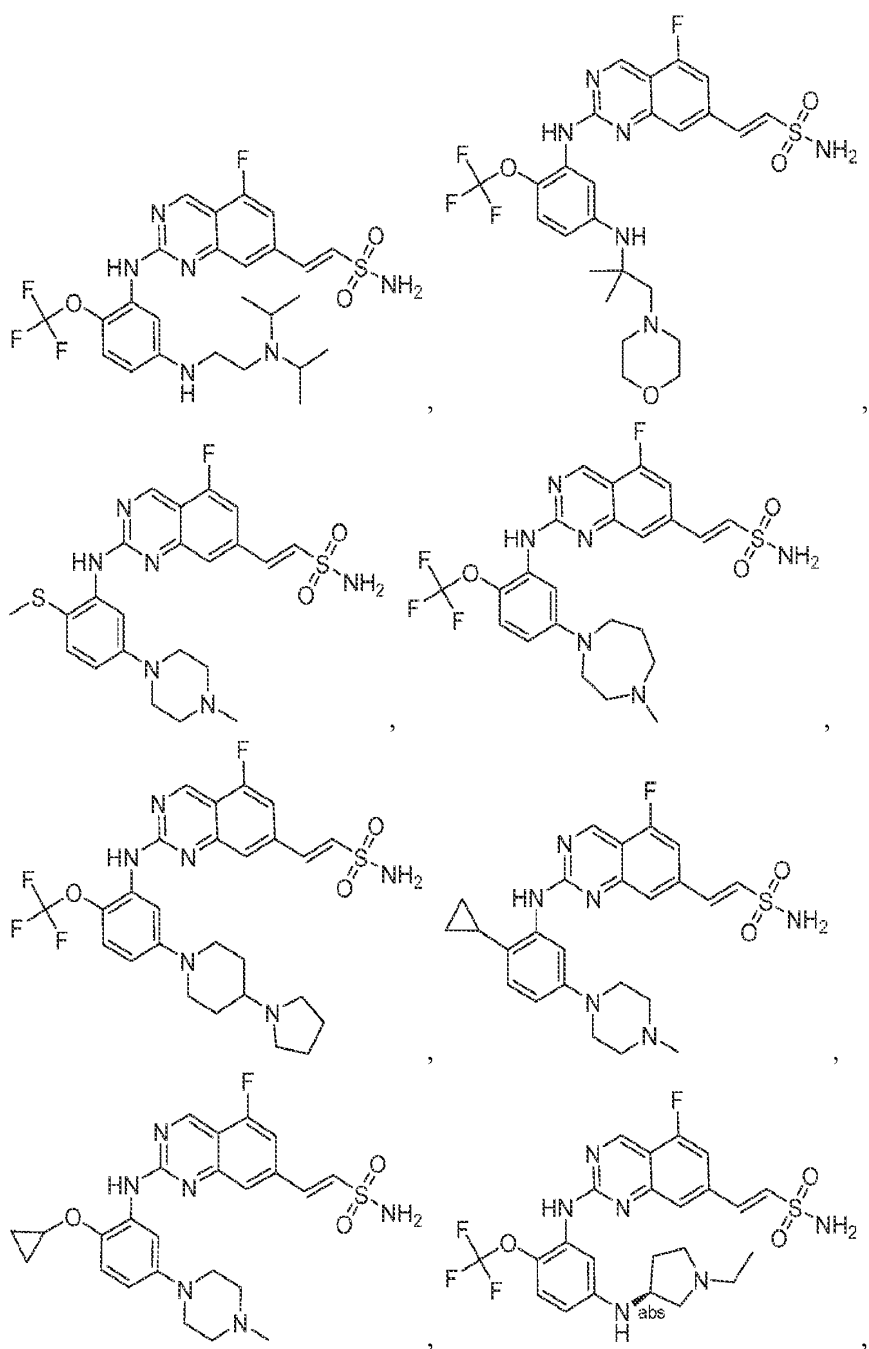
36. The compound of claim 34, wherein L^2 is a bond, and the heterocyclyl is pyrrolidinyl optionally substituted with one or more R^5 .
37. The compound of claim 36, wherein the pyrrolidinyl is substituted with one R^5 , wherein R^5 is ethyl or isopropyl.
38. The compound of claim 34, wherein L^2 is a C1-C4 alkylene, and the heterocyclyl is pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl, each optionally substituted with one or more R^5 .
39. The compound of claim 38, wherein L^2 is ethylene or propylene.
40. The compound of claim 39, wherein the heterocyclyl is piperazinyl optionally substituted with one or more R^5 , wherein R^5 is methyl.
41. The compound of claim 34, wherein L^2 is dimethylethylene, and the heterocyclyl is pyrrolidinyl, piperidinyl, or morpholinyl.
42. The compound of claim 38, wherein L^2 is dimethylethylene, and the heterocyclyl is piperazinyl optionally substituted with one or more R^5 , wherein R^5 is methyl.
43. A compound of Formula (I), wherein the compound is:

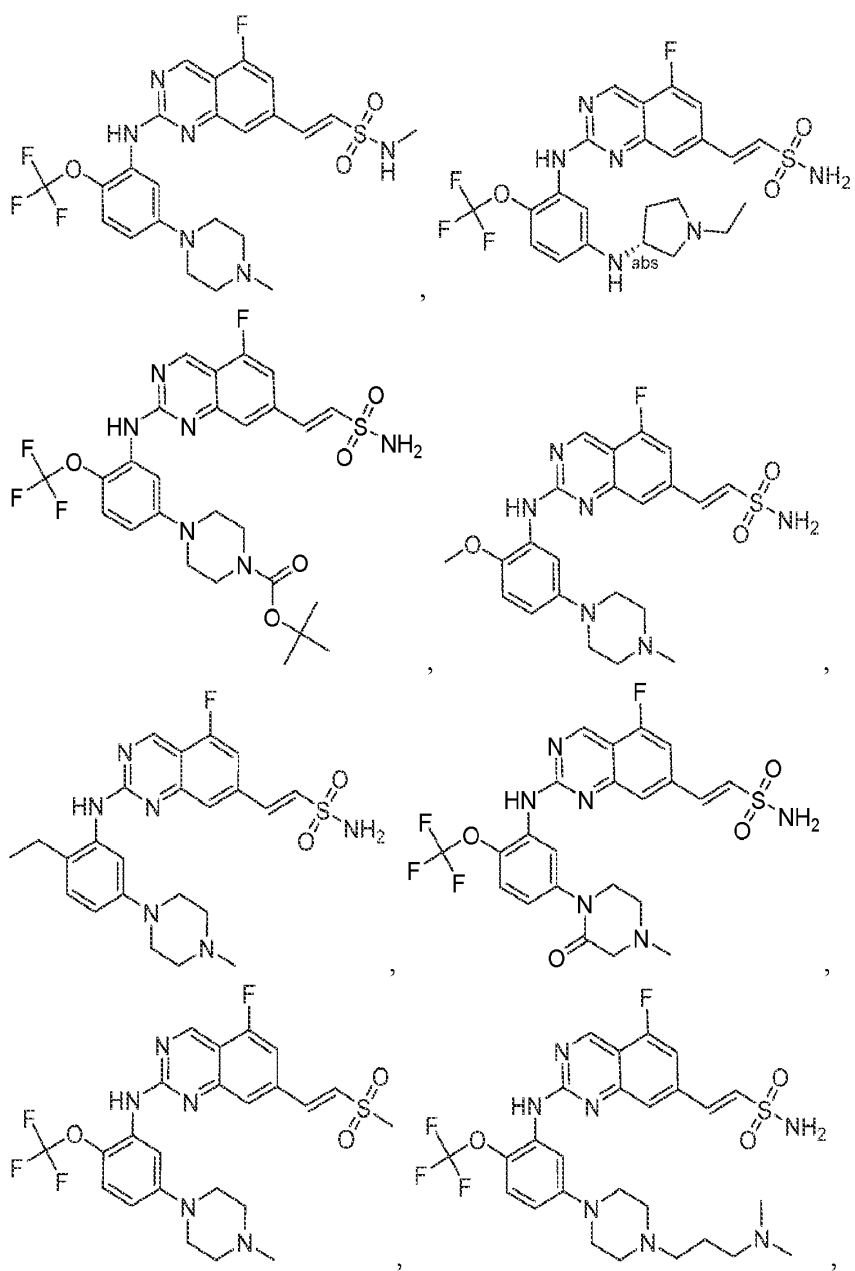


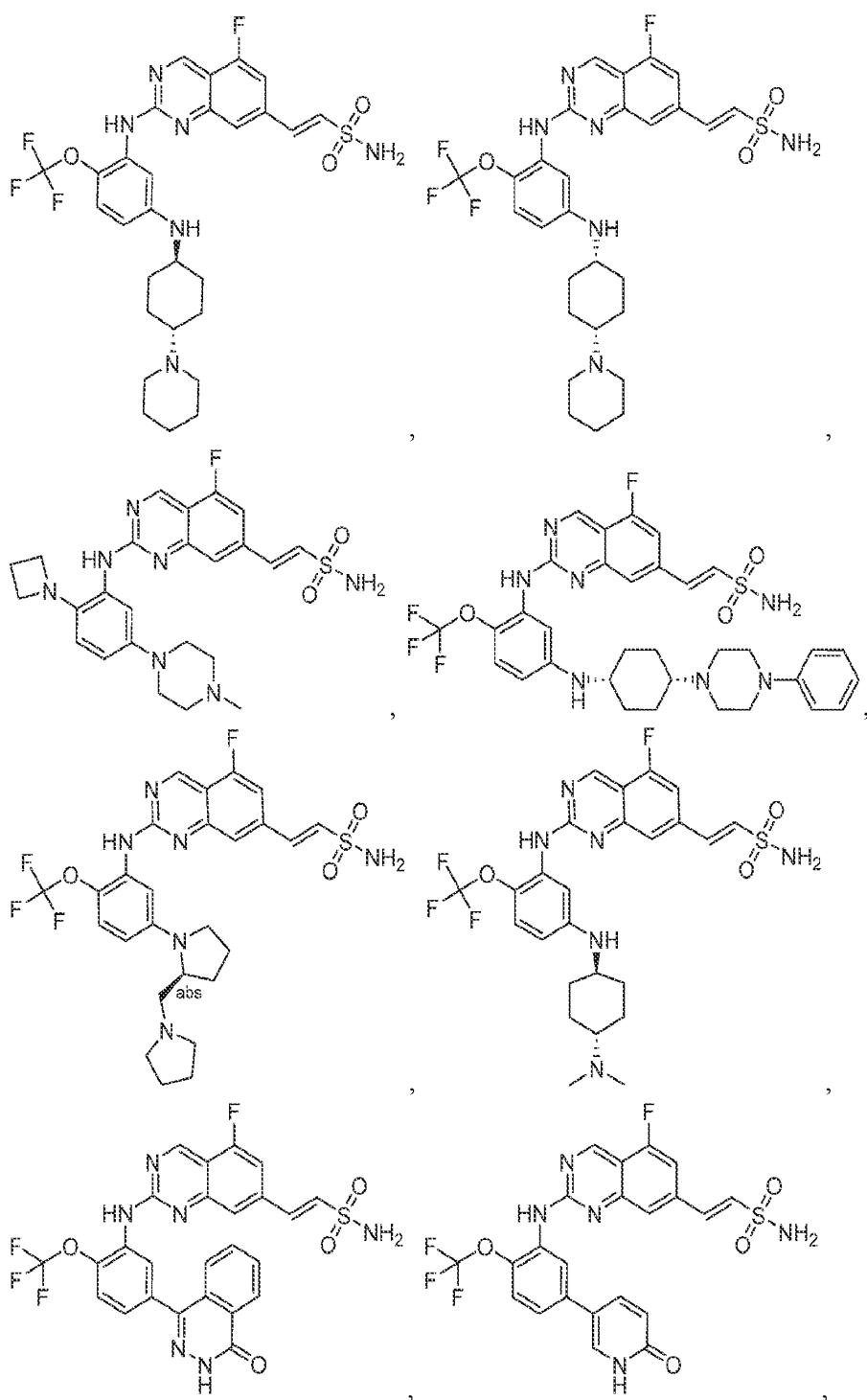


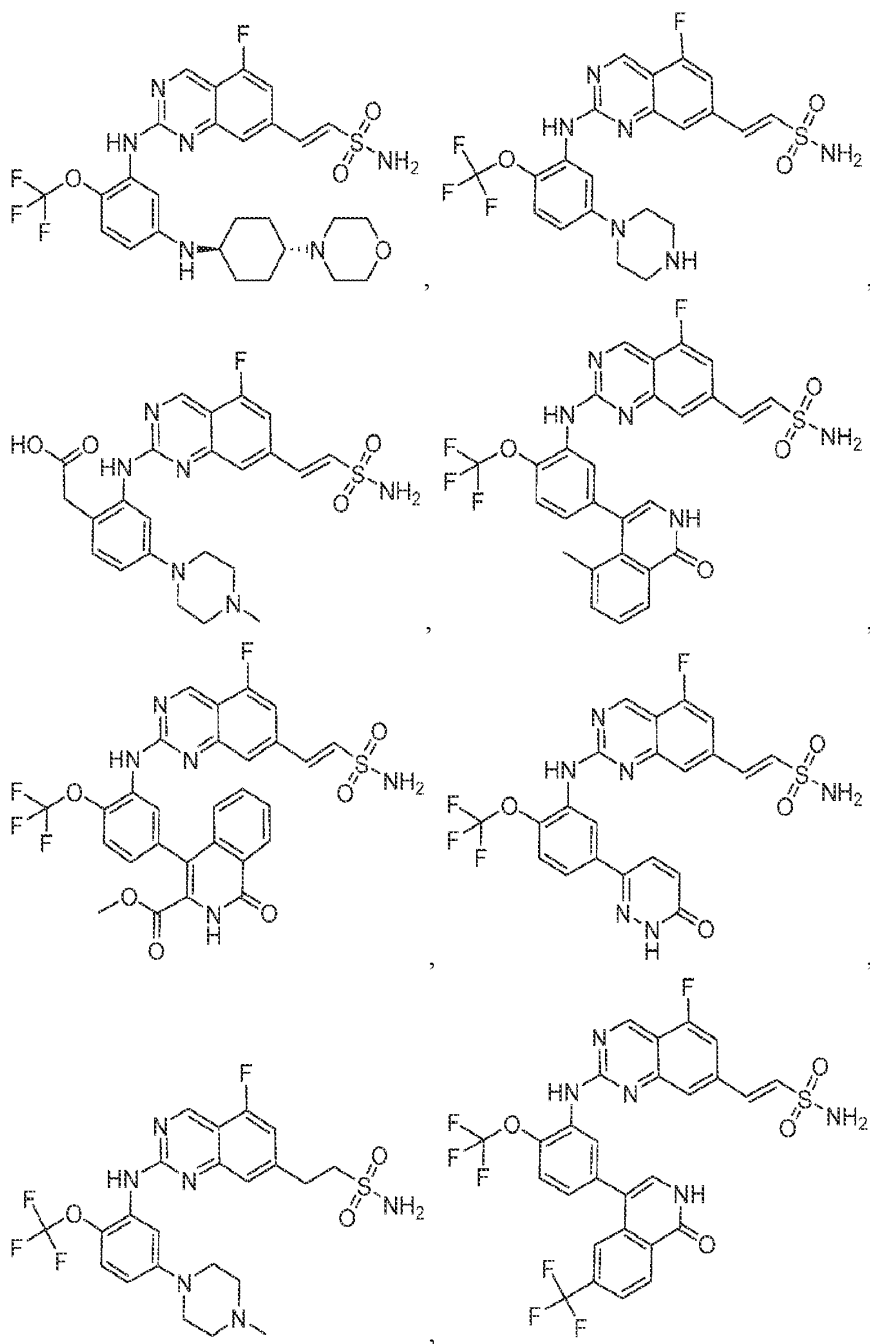


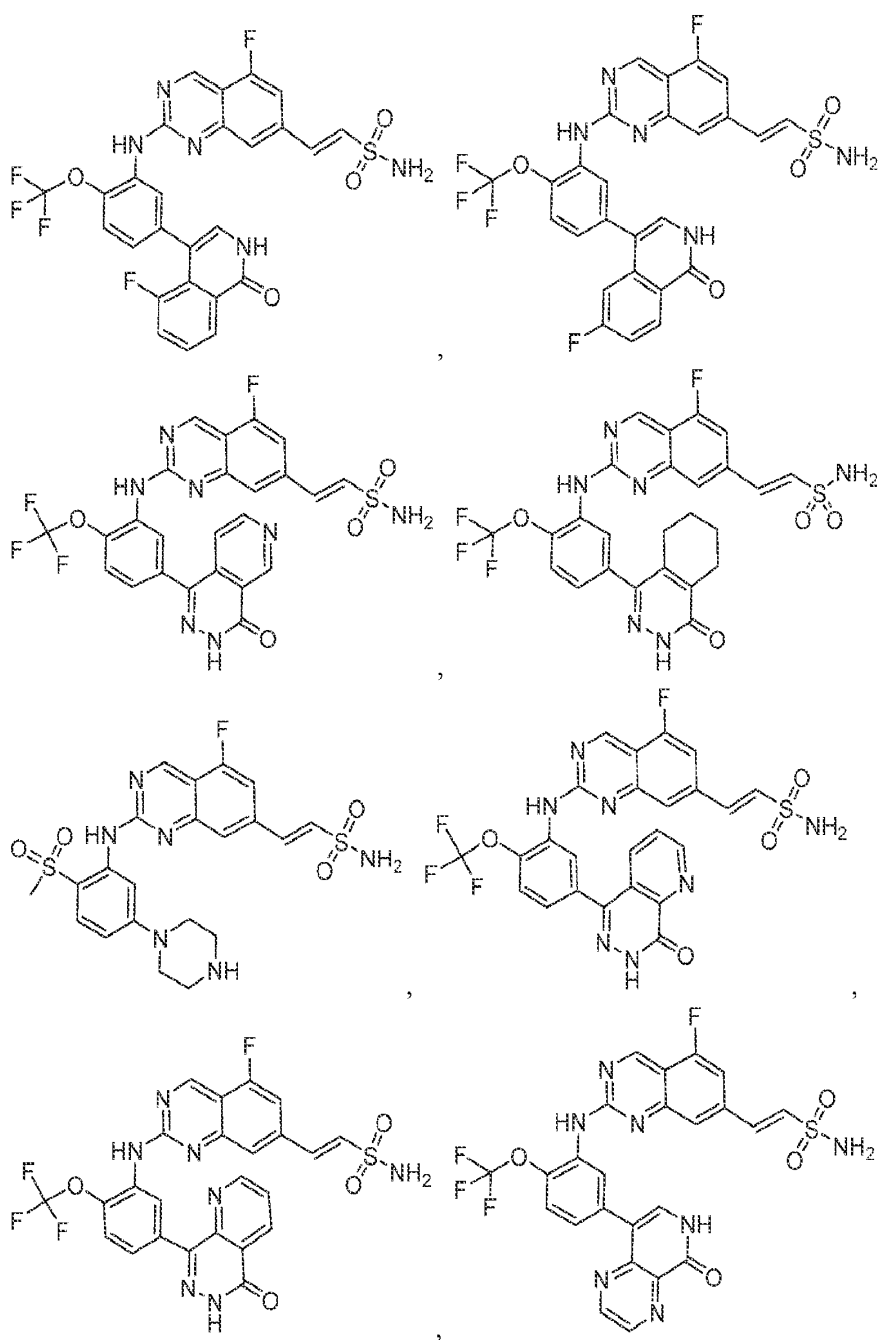


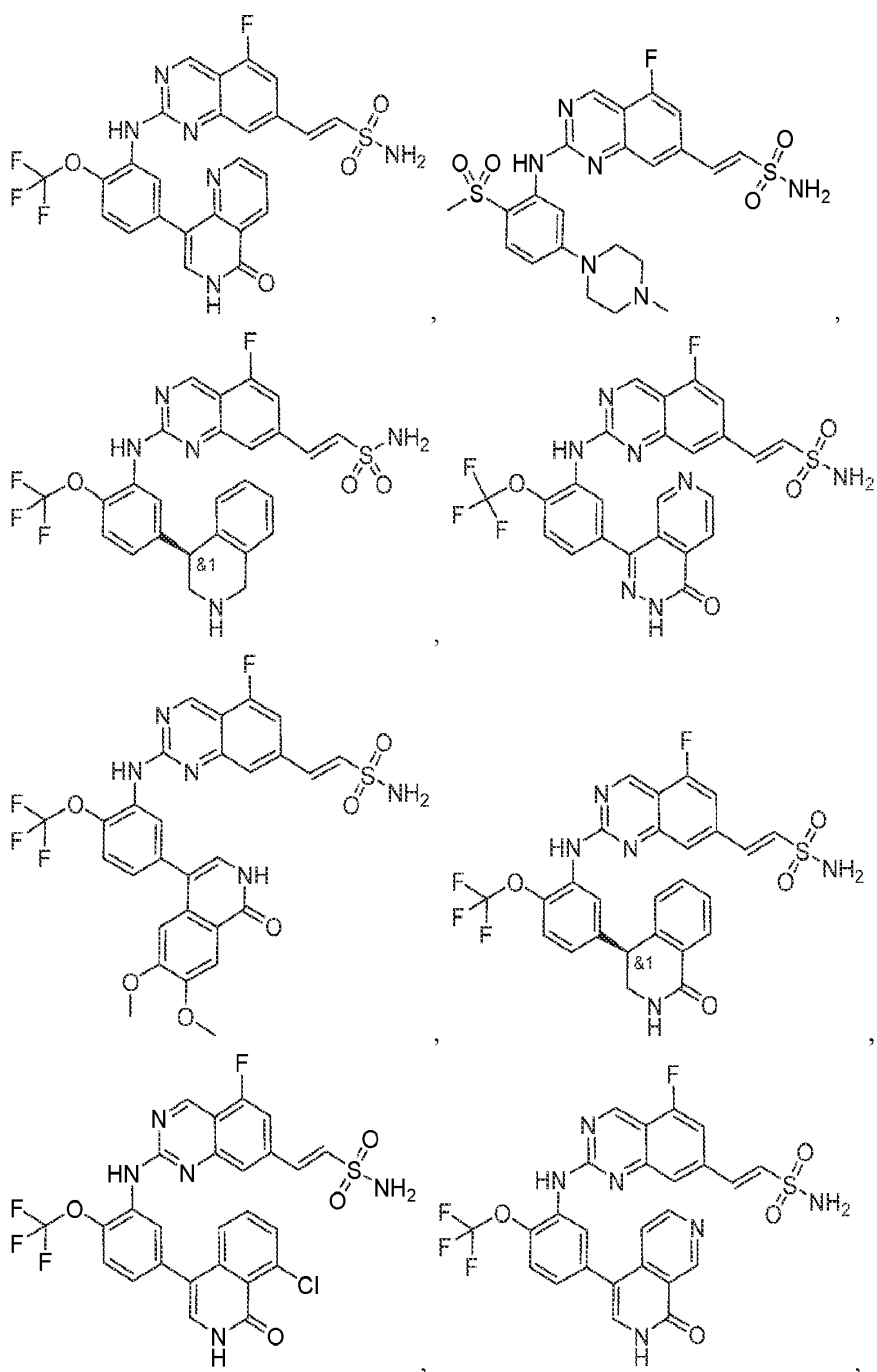


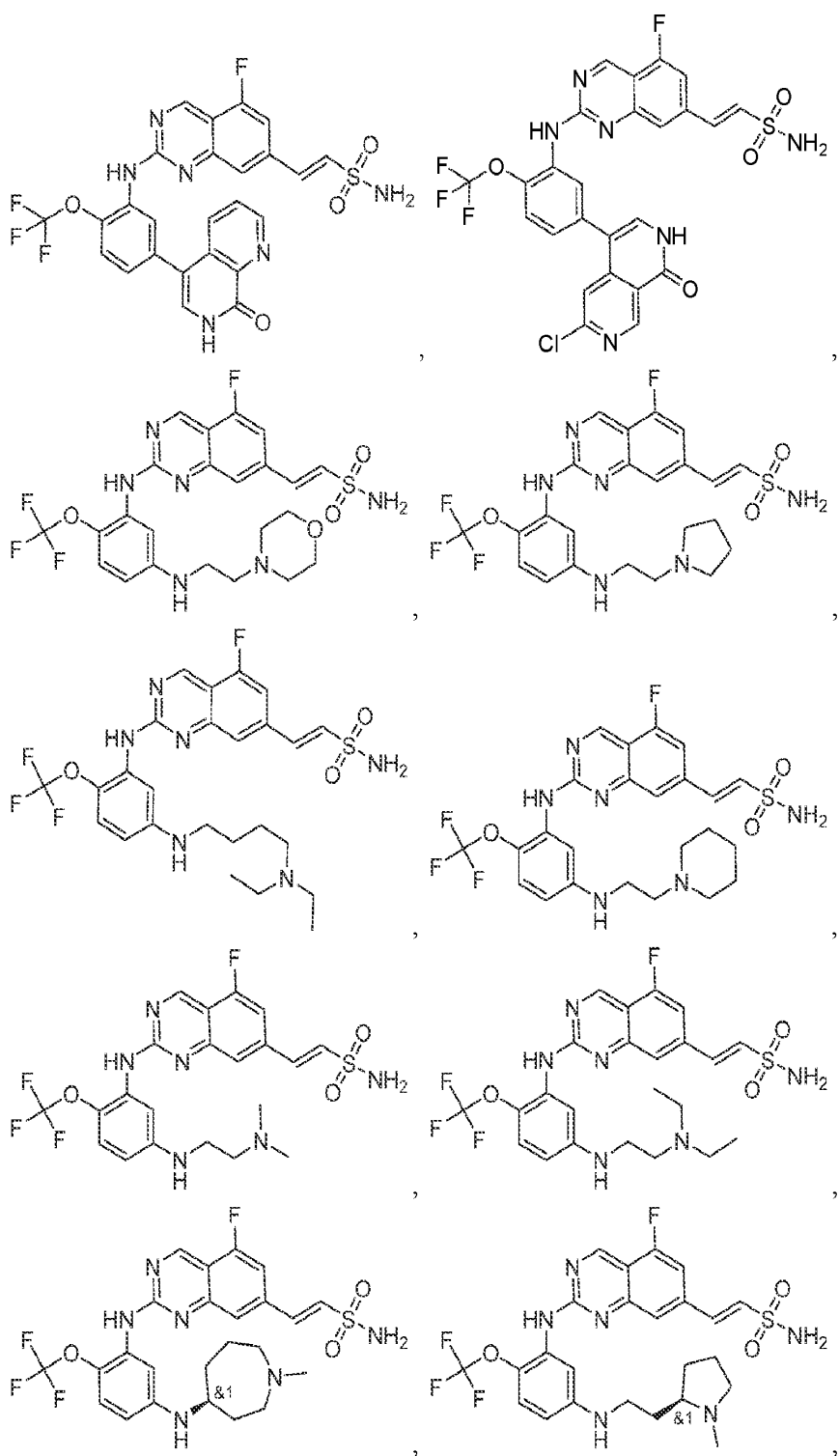


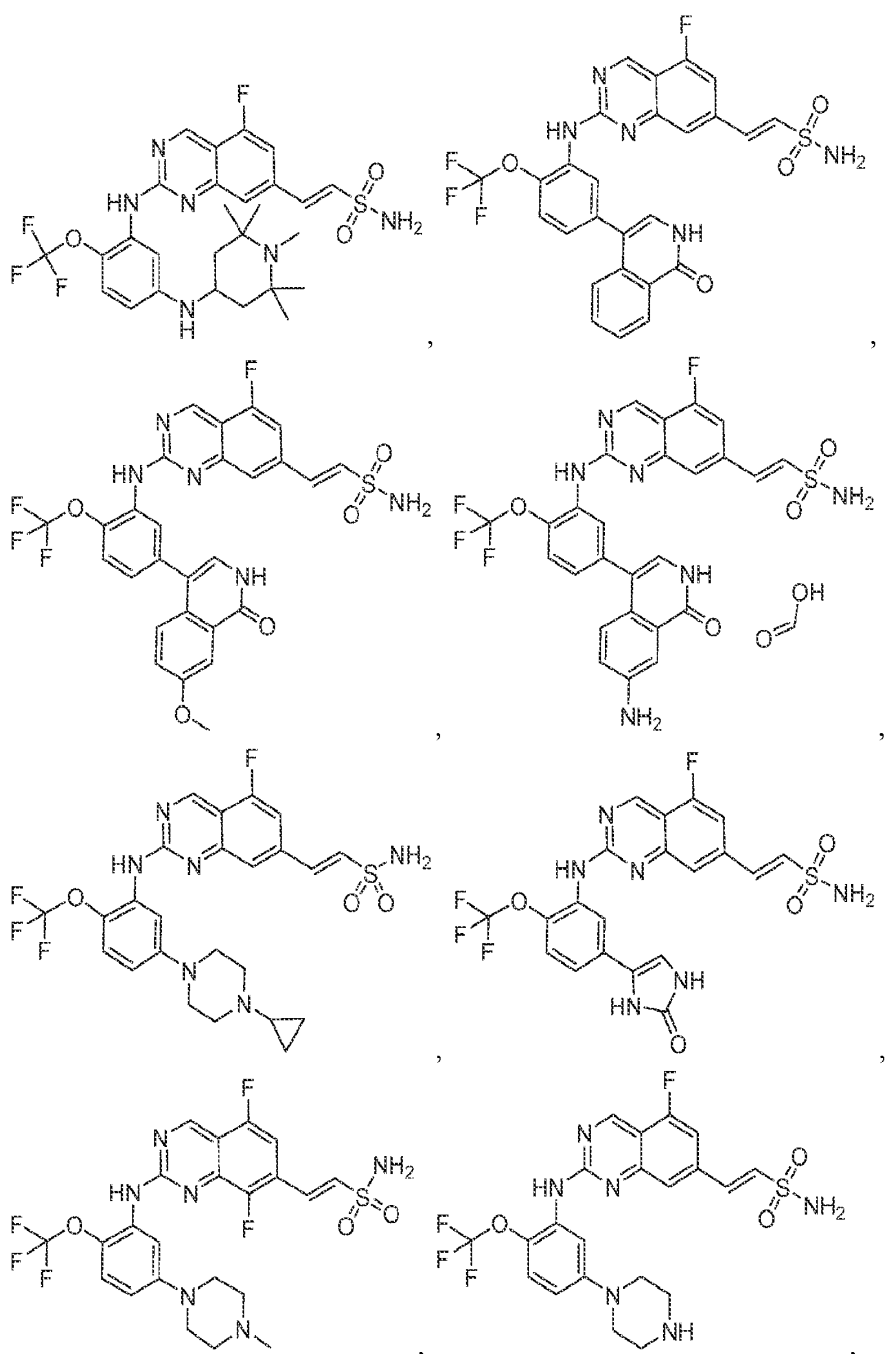


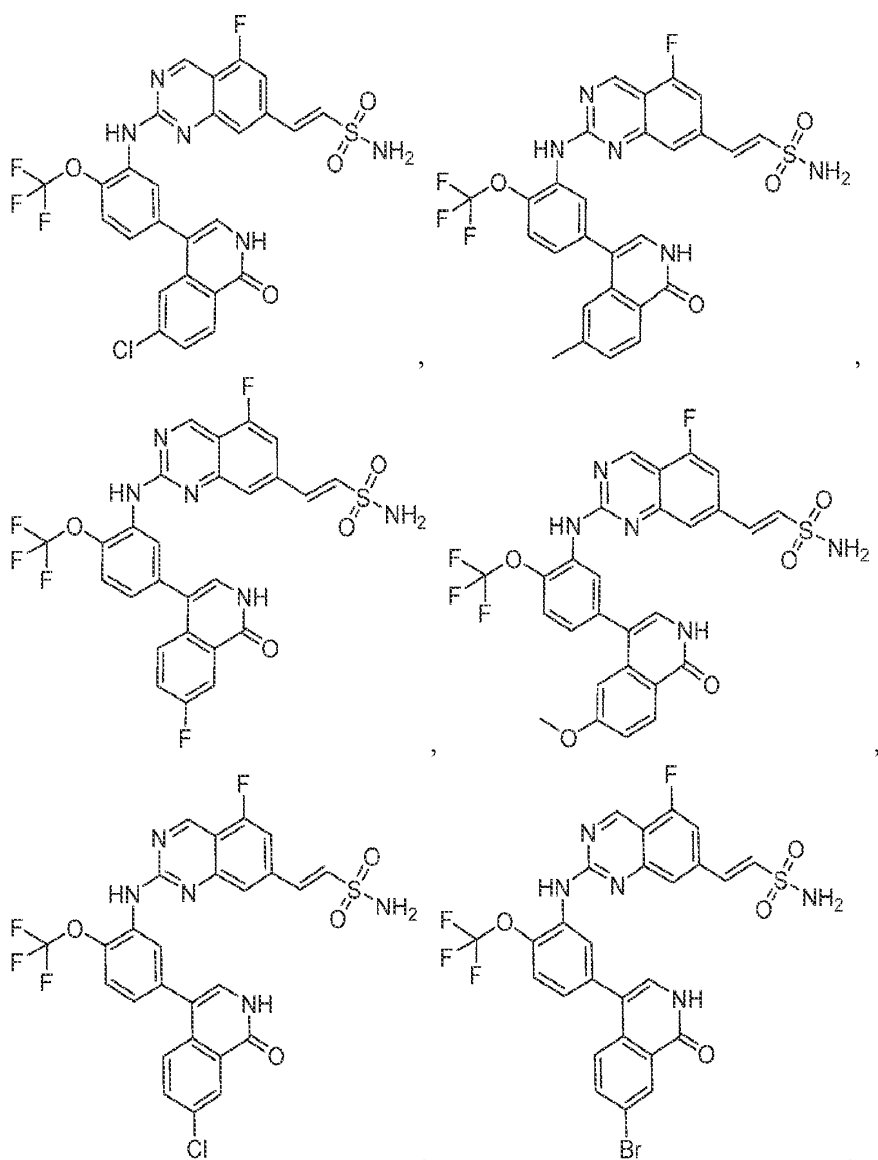


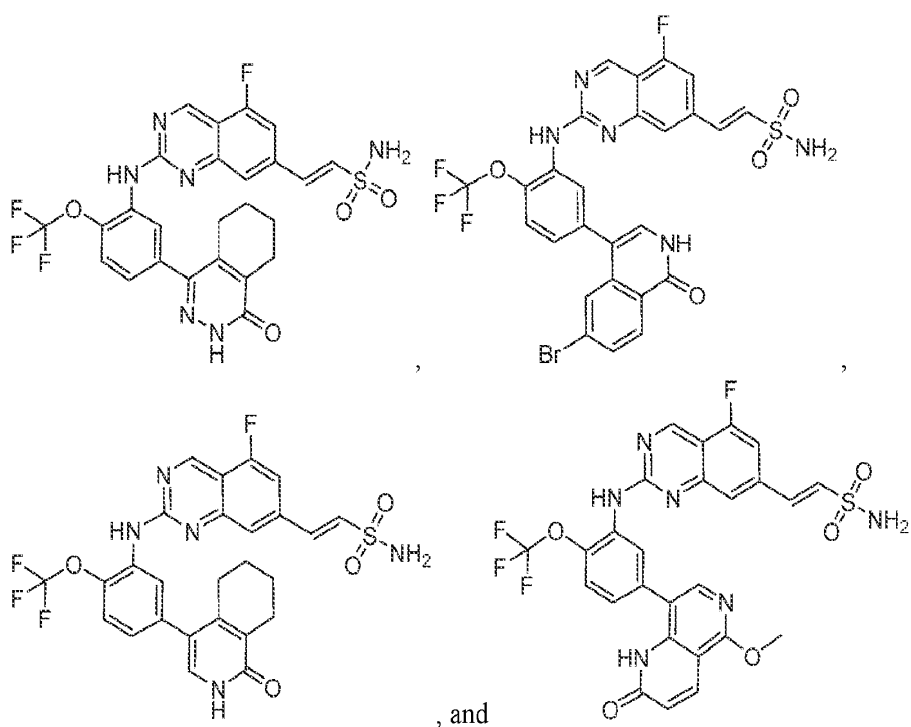












44. A pharmaceutical composition comprising a compound of Formula (I), a pharmaceutically acceptable salt, and at least one pharmaceutically acceptable excipient or elixir.
45. A method of treating a PLK1-mediated disease or disorder in a subject in need thereof, comprising administering a therapeutically effective amount of a compound of claims 1-43 or a pharmaceutical salt thereof, or a pharmaceutical composition of claim 44.
46. The method of claim 45, wherein the PLK1-mediated disease or disorder is cancer.
47. The method of claim 46, wherein the PLK1-mediated cancer is melanoma, non-small cell lung cancer (NSCLC), carcinomas of the head and neck, esophageal, pharynx, breast, liver, endometrium, colorectum, ovary, pancreas or prostate.