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(54) Title: BIS-ARYL ETHERS CONTAINING N-ACYL AZETIDINE AS EGFR/HER2 INHIBITORS

(57) Abstract: The invention provides compounds and pharmaceutical compositions thereof, which are useful for inhibiting EGFR and erbB2 activity, as well as methods for using such compounds to treat cancer associated with mutant EGFR and erbB2 activity.

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BIS-ARYL ETHERS CONTAINING N-ACYL AZETIDINE AS EGFR/HER2 INHIBITORS

[1] This application claims the benefit of priority to United States Provisional Patent Application No. 63/023,690, filed May 12, 2020, which is hereby incorporated by reference in its entirety.

Field of the Disclosure

[2] The present invention relates to certain novel bis-aryl ethers containing N-acyl azetidine compounds, or pharmaceutically acceptable salts thereof, which possess anti-tumor activity and are accordingly useful in methods of treatment of the human or animal body. In particular, the present invention relates to compounds that bind irreversibly to Epidermal Growth Factor Receptor (EGFR), pharmaceutical compositions comprising the compounds, and methods of use therefor.

Background of the Disclosure

[3] Protein kinases are a group of enzymes that regulate diverse, important biological processes including, for example, cell growth, proliferation, survival, invasion and differentiation, organ formation, tissue repair and regeneration. Protein kinases exert their physiological functions through catalyzing the phosphorylation of protein and thereby modulating cellular activities. Because protein kinases have profound effects on cells, their activities are highly regulated. Kinases are turned on or off by phosphorylation (sometimes by autophosphorylation), by binding of activator proteins or inhibitor proteins, or small molecules, or by controlling their location in the cell relative to their substrates.

[4] EGFR is a transmembrane protein tyrosine kinase member of the erbB receptor family. Upon binding of a growth factor ligand such as epidermal growth factor (EGF), the receptor can homo-dimerize with another EGFR molecule or hetero-dimerize with another family member such as erbB2 (HER2), erbB3 (HER3), or erbB4 (HER4).

[5] Homo- and/or hetero-dimerization of erbB receptors results in the phosphorylation of key tyrosine residues in the intracellular domain and leads to the stimulation of numerous intracellular signal transduction pathways involved in cell proliferation and survival. Deregulation of erbB family signaling promotes proliferation, invasion, metastasis, angiogenesis, and tumor cell survival and has been described in many human cancers, including those of the lung, head and neck and breast.

[6] The erbB family therefore represents a rational target for anticancer drug development and a number of agents targeting EGFR or erbB2 are now clinically available, including gefitinib (IRESSA®), erlotinib (TARCEVA®) and lapatinib (TYKERB®). Detailed reviews of erbB receptor signaling and its involvement in tumorigenesis are provided in *New England Journal of Medicine* (2008) Vol. 358, 1160-74 and *Biochemical and Biophysical Research Communications* (2004) Vol. 319, 1-11.

[7] In 2004 it was reported (*Science* [2004] Vol. 304, 1497-500 and New England Journal of Medicine [2004] Vol. 350, 2129-39) that activating mutations in EGFR correlated with response to gefitinib therapy in non-small-cell lung cancer (NSCLC). The most common EGFR activating mutations, L858R and delE746_A750, result in an increase in affinity for small molecule tyrosine kinase inhibitors such as gefitinib and erlotinib and a decrease in affinity for adenosine triphosphate (ATP) relative to wild type (WT) EGFR. Ultimately, acquired resistance to therapy with gefitinib or erlotinib arises, for example

by mutation of the gatekeeper residue T790M, which is reportedly detected in 50% of clinically resistant patients. This mutation is not believed to hinder the binding of gefitinib or erlotinib to EGFR sterically, merely to alter the affinity to ATP to levels comparable to WT EGFR.

[8] In view of the importance of this mutation in resistance to existing therapies targeting EGFR, it is believed that agents which can inhibit EGFR harboring the gatekeeper mutation may be especially useful in the treatment of cancer.

[9] Exon20 insertion mutations represents the third most common erbB family activating mutations in NSCLC. EGFR exon 20 insertion mutations are collectively representing approximately 4% to 10% of all EGFR mutations. Most of EGFR exon 20 insertion mutations occur near the end of αC-helix after residue Met766, with EGFR D770_N771insSVD and V769_D770insASV accounting for about 40% of them. As EGFR exon20 insertion mutations, erbB2 exon20 insertion mutations occur in a similar prevalence in NSCLC and also in a similar position after residue Met774, with erbB2 A775_G776insYVMA accounting for about 80% of them. *See*, Jang, J. *et al.* Angew. Chem. Int. Ed. (2018) Vol. 57(36), 11629–11633.

[10] HER2 mutations are reportedly present in about 2-4% of NSCLC (*See*, Stephens *et al.* Nature (2004) Vol. 431, 525-526). The most common mutation is an in-frame insertion within exon 20. In 83% of patients having HER2 associated NSCLC, a four amino acid YVMA insertion mutation occurs at codon 775 in exon 20 of HER2. (*See*, Arcila et al. Clin Cancer Res (2012) Vol. 18, 4910-4918). The exon 20 insertion results in increased HER2 kinase activity and enhanced signaling through downstream pathways, resulting in increased survival, invasiveness, and tumorigenicity (*See*, Wang *et al.* Cancer Cell (2006) Vol. 10, 25-38). Tumors harboring the HER2 YVMA mutation are largely resistant to known EGFR inhibitors. (*See*, Arcila et al. 2012).

[11] Exon 20 insertion mutations are not restricted to lung cancer. Recent analysis of sinonasal squamous cell carcinoma (SNSCC), a rear form of head and neck cancer, demonstrated a remarkably high frequency of EGFR mutations (77% of SNSCC tumors), the majority of which were exon 20 insertions (88% of all EGFR mutations). *See*, Udager, A. M. *et al.* Cancer Res. (2015) Vol. 75, 2600–2606.

[12] Exon 20 insertion mutations rarely respond to treatment with currently approved EGFR and HER2 TKIs, such as gefitinib, erlotinib or afatinib, or chemotherapies.

[13] There remains a need for compounds that may exhibit favorable potency profiles against WT EGFR versus activating mutant forms of EGFR/erbB2 (for example the L858R EGFR mutant, or the delE746_A750 mutant or the Exon19 deletion EGFR mutant, or EGFR/erbB2 exon20 insertion mutations) and/or resistant mutant forms of EGFR (for example T790M EGFR mutant), and/or selectivity over other enzyme receptors which may make the compounds especially promising for development as therapeutic agents. In this regard, there remains a need for compounds that show a higher inhibition of certain activating or resistance mutant forms of EGFR and HER2 while at the same time showing relatively low inhibition of WT EGFR. Such compounds may be expected to be more suitable as therapeutic agents, particularly for the treatment of cancer, due to reduction of toxicology associated with WT EGFR inhibition. Such toxicologies are known to manifest themselves in man as skin rashes and/or

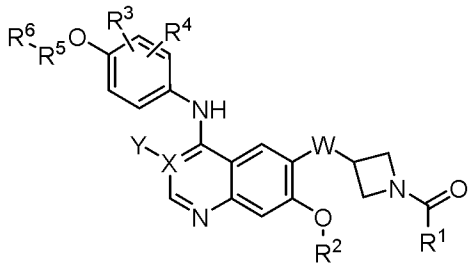
diarrhea. The inventors have found that bis-aryl ethers containing n-acyl azetidine compounds have high potency against several mutant forms of EGFR and HER2 while at the same showing relatively low inhibition of WT EGFR.

Summary of The Disclosure

[14] The invention provides compounds, compositions and methods for modulating the activity of EGFR.

[15] In one aspect, the invention provides compounds which act as inhibitors of EGFR.

[16] In some embodiments, the present disclosure is directed to a compound of Formula (I), or a tautomer, stereoisomer or a mixture of stereoisomers, or a pharmaceutically acceptable salt, or hydrate, or deuterated derivative thereof:



(I)

wherein:

R^1 is C_{1-6} alkyl, C_{1-6} alkoxyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkylene-OH, C_{1-6} alkyleneamine, or C_{1-6} alkylene-CN, each of which is substituted with 0,1, 2, or 3 R^a;

R^2 is H, C_1-C_5alkyl, deuterated C_1-C_5alkyl, C_1-C_5alkoxy, C_1-C_5haloalkyl, C_3-C_7cycloalkyl, or heterocycle, each of which is substituted with 0,1, 2, or 3 R^a;

W is O or NH;

X is C or N, wherein when X is C, Y is cyano; when X is N, Y is absent;

R^3 and R^4 are independently H, halogen, hydroxyl, cyano, C_1-C_5alkyl, C_1-C_5alkoxy, or C_1-C_5haloalkyl;

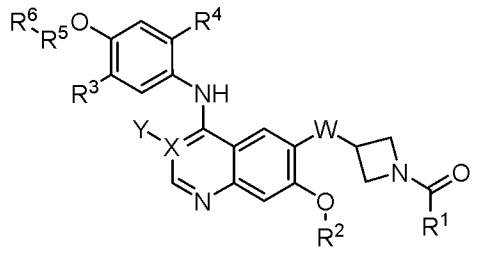
R^5 is 5- to 6-member cycloalkyl, 5- to 6-member aryl, 5- to 6-member heterocycle, or monocyclic or bicyclic 5- to 12-member heteroaryl, each of which is substituted with 0, 1, 2, or 3 R^a;

R^6 is absent, or C_1-C_5alkyl, C_1-C_5alkoxy, or C_1-C_5haloalkyl, or 5- to 6-member cycloalkyl, 5- to 6-member aryl, 5- to 6-member heterocycle, or monocyclic or bicyclic 5- to 12-member heteroaryl, each of which is substituted with 0, 1, 2, or 3 R^a;

R^a is independently hydrogen, hydroxy, halogen, amino, cyano, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, CO(O)-C_{1-4} alkyl, C_{0-3} alkylene-CN, C_{0-3} alkylene-N-(C_{1-6} alkyl)$_2$, C_{0-3} alkylene-C_{3-8} heterocycloalkyl, heterocycle, heterocycloalkyl, aryl, or heteroaryl, each of which is substituted with 0, 1, 2, or 3 R^b, and may be fully or partially deuterated; and

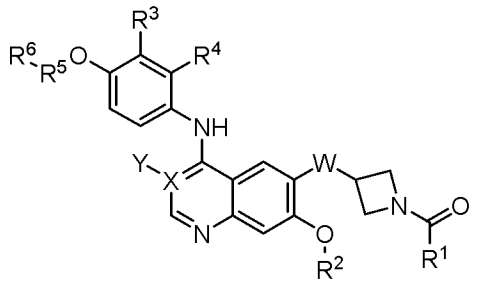
R^b is independently H, hydroxy, halogen, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, or C_{3-8} heterocycloalkyl.

[17] In some embodiments of the invention, provided herein is a compound of Formula (Ia), or a tautomer, stereoisomer or a mixture of stereoisomers, or a pharmaceutically acceptable salt, or hydrate, or deuterated derivative thereof:



(Ia).

[18] In some embodiments of the invention, provided herein is a compound of Formula (Ib), or a tautomer, stereoisomer or a mixture of stereoisomers, or a pharmaceutically acceptable salt, or hydrate, or deuterated derivative thereof:



(Ib).

[19] In another aspect, provided herein is a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more of a pharmaceutically acceptable carrier, a pharmaceutically acceptable vehicle, a pharmaceutically acceptable excipient, or combinations thereof.

[20] In another aspect, provided herein is a combination therapy comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and an additional anti-cancer agent.

[21] In another aspect, provided herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for inhibiting EGFR.

[22] In another aspect, provided herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a condition associated with EGFR or HER2 exon 20 insertion mutation.

[23] In another aspect, provided herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for treating a condition associated with EGFR or HER2 exon 20 insertion mutation.

[24] In another aspect, provided herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for treating cancer associated with EGFR or HER2 exon 20 insertion mutation, wherein the cancer is selected from breast cancer, lung cancer, pancreatic cancer, colon cancer, head and neck cancer, renal cell carcinoma, squamous cell carcinoma, thyroid cancer, gall bladder cancer, thyroid cancer, bile duct cancer, ovarian cancer, endometrial cancer, prostate cancer, or esophageal cancer.

[25] In another aspect, provided herein is a method for inhibiting EGFR, comprising administering to a system or subject a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[26] Also provided herein is a method for treating a condition associated with EGFR or HER2 exon 20 insertion mutation, comprising administering to a system or subject in need of such treatment an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION

Definitions

[27] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -CN is attached through the carbon atom.

[28] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example, "C_1-C_6 alkyl" or "C_{1-6}alkyl" is intended to encompass C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl.

[29] The term "acyl" as used herein refers to R-C(O)- groups such as, but not limited to, (alkyl)-C(O)-, (alkenyl)-C(O)-, (alkynyl)-C(O)-, (aryl)-C(O)-, (cycloalkyl)-C(O)-, (heteroaryl)-C(O)-, and (heterocyclyl)-C(O)-, wherein the group is attached to the parent molecular structure through the carbonyl functionality. In some embodiments, it is a C_{1-10} acyl radical which refers to the total number of chain or ring atoms of the, for example, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, or heteroaryl, portion plus the carbonyl carbon of acyl. For example, a C_4-acyl has three other ring or chain atoms plus carbonyl.

[30] The term "alkenyl" as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon double bond, such as a straight or branched group of 2 to 8 carbon atoms, referred to herein as C_{2-8}alkenyl. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl, 2-butenyl, and 4-(2-methyl-3-butene)-pentenyl.

[31] The term "alkyl" as used herein refers to a saturated straight or branched hydrocarbon, such as a straight or branched group of 1 to 8 carbon atoms, referred to herein as C1-8alkyl. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3 methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3 methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4 methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, and octyl. In some embodiments, "alkyl" is a straight-chain hydrocarbon. In some embodiments, "alkyl" is a branched hydrocarbon.

[32] The term "alkoxy" means a straight or branched chain saturated hydrocarbon containing 1-12 carbon atoms containing a terminal "O" in the chain, e.g., -O(alkyl). Examples of alkoxy groups include, without limitation, methoxy, ethoxy, propoxy, butoxy, t-butoxy, or pentoxy groups.

[33] The term "alkylene" as used herein referes to a divalent alkyl radical. Representative examples of C_{1-10} alkylene include, but are not limited to, methylene, ethylene, n-propylene, iso-propylene, n-butylene, sec-butylene, iso-butylene, tert-butylene, n-pentylene, isopentylene, neopentylene, n-hexylene, 3-

methylhexylene, 2,2-dimethylpentylene, 2,3-dimethylpentylene, n-heptylene, n-octylene, n-nonylene and n-decylene.

[34] The term "alkynyl" as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon triple bond, such as a straight or branched group of 2 to 8 carbon atoms, referred to herein as C_{2-8}alkynyl. Exemplary alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, 4-methyl-1-butynyl, 4-propyl-2-pentynyl, and 4-butyl-2-hexynyl.

[35] The term "aryl" as used herein refers to a mono-, bi-, or other multi carbocyclic, aromatic ring system with 5 to 14 ring atoms. The aryl group can optionally be fused to one or more rings selected from aryls, cycloalkyls, heteroaryls, and heterocyclyls. The aryl groups of this present disclosure can be substituted with groups selected from alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide, and thioketone. Exemplary aryl groups include, but are not limited to, phenyl, tolyl, anthracenyl, fluorenyl, indenyl, azulenyl, and naphthyl, as well as benzo-fused carbocyclic moieties such as 5,6,7,8-tetrahydronaphthyl. Exemplary aryl groups also include but are not limited to a monocyclic aromatic ring system, wherein the ring comprises 6 carbon atoms, referred to herein as "C_6-aryl."

[36] The term "cyano" as used herein refers to CN.

[37] The term "cycloalkyl" as used herein refers to a saturated or unsaturated cyclic, bicyclic, or bridged bicyclic hydrocarbon group of 3-16 carbons, or 3-8 carbons, referred to herein as "C_{3-8}cycloalkyl," derived from a cycloalkane. Exemplary cycloalkyl groups include, but are not limited to, cyclohexanes, cyclohexenes, cyclopentanes, and cyclopentenes. Cycloalkyl groups may be substituted with alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone. Cycloalkyl groups can be fused to other cycloalkyl (saturated or partially unsaturated), aryl, or heterocyclyl groups, to form a bicycle, tetracycle, etc. The term "cycloalkyl" also includes bridged and spiro-fused cyclic structures which may or may not contain heteroatoms.

[38] The terms "halo" or "halogen" as used herein refer to -F, -Cl, -Br, and/or -I.

[39] "Haloalkyl" means an alkyl group substituted with one or more halogens. Examples of haloalkyl groups include, but are not limited to, trifluoromethyl, difluoromethyl, pentafluoroethyl, trichloromethyl, etc.

[40] The term "heteroatoms," as used herein, refers to nitrogen (N), oxygen (O), sulfur (S) or phosphorus (P) atoms, wherein the N, S and P can optionally be oxidized to various oxidation states.

[41] The term "heteroaryl" as used herein refers to a mono-, bi-, or multi-cyclic, aromatic ring system containing one or more heteroatoms, for example 1 to 3 heteroatoms, such as nitrogen, oxygen, and sulfur. Heteroaryls can be substituted with one or more substituents including alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether,

formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone. Heteroaryls can also be fused to non-aromatic rings. Exemplary heteroaryl groups include, but are not limited to, a monocyclic aromatic ring, wherein the ring comprises 2 to 5 carbon atoms and 1 to 3 heteroatoms, referred to herein as "C_{2-5}heteroaryl." Illustrative examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, pyrimidyl, pyrazyl, triazinyl, pyrrolyl, pyrazolyl, imidazolyl, (1,2,3)- and (1,2,4)-triazolyl, pyrazinyl, pyrimidilyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, furyl, phenyl, isoxazolyl, and oxazolyl. Exemplary heteroaryl groups also include, but are not limited to, a bicyclic aromatic ring, wherein the ring comprises 5 to 14 carbon atoms and 1 to 3 heteroatoms, referred to herein as "C_{5-14}heteroaryl." Representative examples of heteroaryl include, but not limited to, indazolyl, indolyl, azaindolyl, indolinyl, benzotriazolyl, benzoxadiazolyl, imidazolyl, cinnolinyl, imidazopyridyl, pyrazolopyridyl, pyrrolopyridyl, quinolinyl, isoquinolinyl, quinazolinyl, quinazolinonyl, indolinonyl, isoindolinonyl, tetrahydronaphthyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like.

[42] The terms "heterocycle," "heterocyclyl," or "heterocyclic" as used herein each refer to a saturated or unsaturated 3- to 18-membered ring containing one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, phosphorus, and sulfur. Heterocycles can be aromatic (heteroaryls) or non-aromatic. Heterocycles can be substituted with one or more substituents including alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone. Heterocycles also include bicyclic, tricyclic, and tetracyclic groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from aryls, cycloalkyls, and heterocycles. Exemplary heterocycles include acridinyl, benzimidazolyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, biotinyl, cinnolinyl, dihydrofuryl, dihydroindolyl, dihydropyranyl, dihydrothienyl, dithiazolyl, furyl, homopiperidinyl, imidazolidinyl, imidazolinyl, imidazolyl, indolyl, isoquinolyl, isothiazolidinyl, isothiazolyl, isoxazolidinyl, isoxazolyl, morpholinyl, oxadiazolyl, oxazolidinyl, oxazolyl, piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrazinyl, pyrazolyl, pyrazolinyl, pyridazinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrrolidinyl, pyrrolidin-2-onyl, pyrrolinyl, pyrrolyl, quinolinyl, quinoxaloyl, tetrahydrofuryl, tetrahydroisoquinolyl, tetrahydropyranyl, tetrahydroquinolyl, tetrazolyl, thiadiazolyl, thiazolidinyl, thiazolyl, thienyl, thiomorpholinyl, thiopyranyl, and triazolyl.

[43] The terms "hydroxy" and "hydroxyl" as used herein refer to -OH.

[44] The terms "composition" or "pharmaceutical composition," as used herein, refers to a mixture of at least one compound, such as a compound Formula (I), or a pharmaceutically acceptable salt thereof, with at least one and optionally more than one other pharmaceutically acceptable chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients.

[45] The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of a compound described herein being administered which will relieve to some extent

one or more of the symptoms of the disease or condition being treated. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate "effective" amount in any individual case may be determined using techniques, such as a dose escalation study.

[46] The term "pharmaceutically acceptable," as used herein, refers to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compounds described herein. Such materials are administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[47] The term "carrier," as used herein, refers to chemical compounds or agents that facilitate the incorporation of a compound described herein into cells or tissues. The term "pharmaceutically acceptable carrier", as used herein, includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (e.g., antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art (see, for example, Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289-1329; Remington: The Science and Practice of Pharmacy, 21st Ed. Pharmaceutical Press 2011; and subsequent versions thereof). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.

[48] The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable vehicle" is used interchangeably and as is known to those skilled in the art, can be any and all solvents, dispersion media, Coatings, surfactants, antioxidants, preservatives (e.g., antimicrobial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drug stabilizers, binders, excipients, disintegrants, lubricant, including sweeteners, flavors, dyes, and the like, and combinations thereof (e.g., Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289-1329). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in therapeutic or pharmaceutical compositions is contemplated.

[49] The term "pharmaceutically acceptable prodrugs" as used herein represents those prodrugs of the compounds of the present disclosure that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, commensurate with a reasonable benefit / risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the present disclosure. A discussion is provided in Higuchi *et al.*, "Prodrugs as Novel Delivery Systems," ACS Symposium Series, Vol. 14, and in Roche, E.B., ed. Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

[50] The term "pharmaceutically acceptable salt(s)" refers to salts of acidic or basic groups that may be present in compounds used in the present compositions. Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, including but not limited to sulfate, citrate, matate, acetate, oxalate, chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Compounds included in the present compositions that include an amino moiety may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above. Compounds included in the present compositions, that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts and, particularly, calcium, magnesium, sodium, lithium, zinc, potassium, and iron salts.

[51] As used herein, the term "inhibit," "inhibition," or "inhibiting" refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

[52] As used herein, the term "treat," "treating," or "treatment" of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treat," "treating," or "treatment" refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, "treat," "treating," or "treatment" refers to modulating the disease or disorder, either physically (e.g., through stabilization of a discernible symptom), physiologically, (e.g., through stabilization of a physical parameter), or both. In yet another embodiment, "treat," "treating," or "treatment" refers to preventing or delaying the onset or development or progression of the disease or disorder.

[53] As used herein, "cancer" refers to diseases, disorders, and conditions that involve abnormal cell growth with the potential to invade or spread to other parts of the body. Exemplary cancers include, but are not limited to, breast cancer, lung cancer, pancreatic cancer, colon cancer, head and neck cancer, renal cell carcinoma, squamous cell carcinoma, thyroid cancer, gall bladder cancer, thyroid cancer, bile duct cancer, ovarian cancer, endometrial cancer, prostate cancer, or esophageal cancer.

[54] As used herein, the term "subject" refers to an animal. Typically, the animal is a mammal. A subject also refers to for example, primates (e.g., humans, male or female), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain embodiments, the subject is a primate. In yet other embodiments, the subject is a human.

[55] As used herein, a subject is "in need of" a treatment if such subject would benefit biologically, medically or in quality of life from such treatment.

[56] As used herein, "exon 20 insertion mutation" refers to a mutation in which one or more amino acids (preferably 1 to 7, more preferably 1 to 4) are inserted in the exon 20 region of EGFR, and includes, but is not limited to, a mutation in which amino acid sequence SVD (serine, valine, and aspartic acid in this order from the N-terminus) is inserted between the 770th aspartic acid and 771st asparagine in the exon 20 region (D770_N771insSVD); a mutation in which amino acid sequence ASV (alanine, serine, and valine in this order from the N-terminus) is inserted between the 769th alanine and 770th aspartic acid in the exon region (A769_D770insASV); and a mutation in which amino acid sequence YVMA (tyrosine, valine, methionine, and alanine in this order from the N-terminus) is inserted between the 775th alanine and 776th glycine in the exon region (A775_G776ins YVMA).

[57] The term "administration" or "administering" of the subject compound means providing a compound of the invention, a pharmaceutically acceptable salt, a pharmaceutically acceptable solvate, or solvate thereof to a subject in need of treatment.

[58] The term "combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, by way of example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and an additional anti-cancer agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, by way of example, a compound of Formula (I) or a pharmaceutically acceptable salt thereof, and an additional anti-cancer agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients.

[59] Chemical names were generated using PerkinElmer ChemDraw® Professional, version 17.

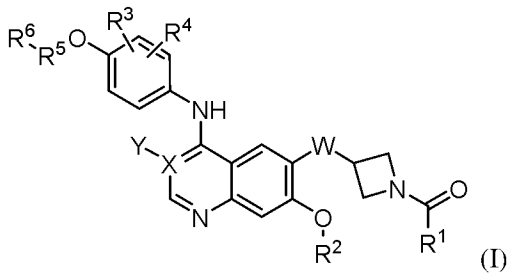
[60] Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F, ^{31}P, ^{32}P, ^{35}S, ^{36}Cl and ^{125}I respectively. The invention includes various isotopically labeled compounds as defined herein, for example those into which radioactive isotopes, such as ^{3}H, ^{13}C, and ^{14}C, are present. Such isotopically labelled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or labeled compound may be particularly desirable for PET or SPECT studies. Isotopically labeled

compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

[61] Further, substitution with heavier isotopes, particularly deuterium (i.e., ^{2}H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound of the present invention. Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Processes using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

Compounds

[62] In some embodiments, the present disclosure is directed to a compound of Formula (I), or a tautomer, stereoisomer or a mixture of stereoisomers, or a pharmaceutically acceptable salt, or hydrate, or deuterated derivative thereof:



(I)

wherein:

R^1 is C_{1-6} alkyl, C_{1-6} alkoxyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkylene-OH, C_{1-6}alkyleneamine, or C_{1-6} alkylene-CN, each of which is substituted with 0,1, 2, or 3 R^a;

R^2 is H, C_1-C_5alkyl, deuterated C_1-C_5alkyl, C_1-C_5alkoxy, C_1-C_5haloalkyl, C_3-C_7cycloalkyl, or heterocycle, each of which is substituted with 0,1, 2, or 3 R^a;

W is O or NH;

X is C or N, wherein when X is C, Y is cyano; when X is N, Y is absent;

R^3 and R^4 are independently hydrogen, halogen, hydroxyl, cyano, C_1-C_5alkyl, C_1-C_5alkoxy, or C_1-C_5haloalkyl;

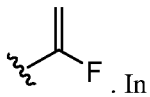
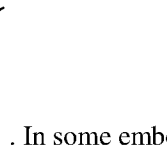
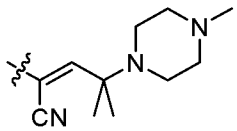
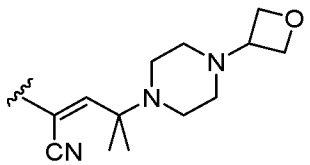
R^5 is 5- to 6-member cycloalkyl, 5- to 6-member aryl, 5- to 6-member heterocycle, or monocyclic or bicyclic 5- to 12-member heteroaryl, each of which is substituted with 0, 1, 2, or 3 R^a;

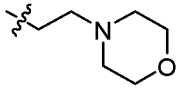
R^6 is absent, or C_1-C_5alkyl, C_1-C_5alkoxy, or C_1-C_5haloalkyl, or 5- to 6-member cycloalkyl, 5- to 6-member aryl, 5- to 6-member heterocycle, or monocyclic or bicyclic 5- to 12-member heteroaryl, each of which is substituted with 0, 1, 2, or 3 R^a;

R^a is independently hydrogen, hydroxy, halogen, amino, cyano, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, CO(O)-C_{1-4} alkyl, C_{0-3} alkylene-CN, C_{0-3} alkylene-N-(C_{1-6}

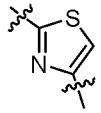
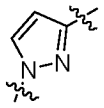
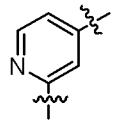
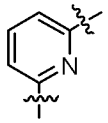
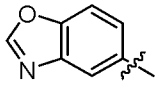
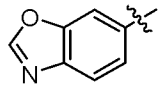
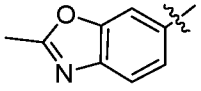
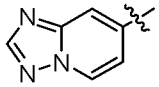
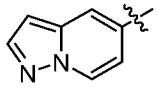
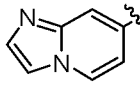
alkyl)$_2$, C_{0-3} alkylene-C_{3-8} heterocycloalkyl, heterocycle, heterocycloalkyl, aryl, or heteroaryl, each of which is substituted with 0, 1, 2, or 3 R^b, and may be fully or partially deuterated; and

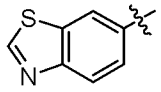
R^b is independently H, hydroxy, halogen, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, or C_{3-8} heterocycloalkyl.

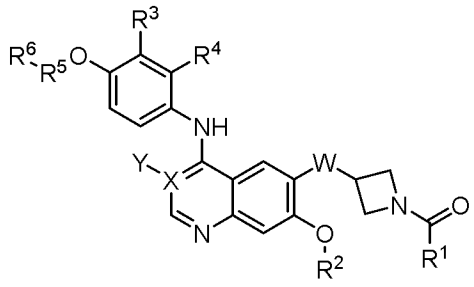
[63] In some embodiments, R^1 is C_{1-6} alkyl, C_{1-6} alkoxyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkylene-OH, C_{1-6} alkyleneamine, or C_{1-6} alkylene-CN. In a further embodiment, R^1 is vinyl substituted with 0,1, 2, or 3 R^a. In another embodiment, R^1 is 1-propynyl. In some embodiments, R^1 is vinyl. In some embodiments, R^1 is . In some embodiments, R^1 is . In some embodiments, R^1 is . In some embodiments, R^1 is .

[64] In some embodiments, R^2 is H, C_1-C_5alkyl, deuterated C_1-C_5alkyl, C_1-C_5alkoxy, C_1-C_5haloalkyl, C_3-C_7cycloalkyl, or heterocycle, each of which is substituted with 0,1, 2, or 3 R^a. In some embodiments, R^2 is C_1-C_5alkyl, each of which is substituted with 0,1, 2, or 3 R^a. In one embodiment, R^2 is methyl. In another embodiment, R^2 is ethyl. In a yet another embodiment, R^2 is deuterated methyl. In some embodiments, R^2 is . In some embodiments, R^2 is $CH_2CH_2N(CH_3)_2$.

[65] In some embodiments, R^3 and R^4 are independently hydrogen or halogen. In a further embodiment, R^3 is Cl and R^4 is H. In another embodiment, R^3 is H and R^4 is F.

[66] In some embodiments, R^5 is 5- to 6-member cycloalkyl, 5- to 6-member aryl, 5- to 6-member heterocycle, or monocyclic or bicyclic 5- to 12-member heteroaryl. In some embodiments, R^5 is . In some embodiments, R^5 is . In some embodiments, R^5 is . In some embodiments, R^5 is . In some embodiments, R^5 is . In some embodiments, R^5 is . In some embodiments, R^5 is . In some embodiments, R^5 is . In some embodiments, R^5 is . In some embodiments, R^5 is . In some embodiments, R^5

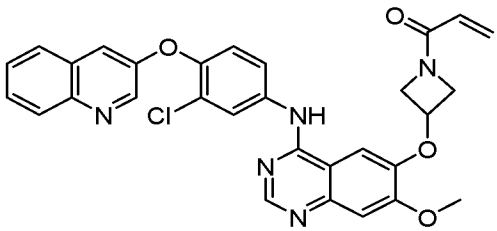
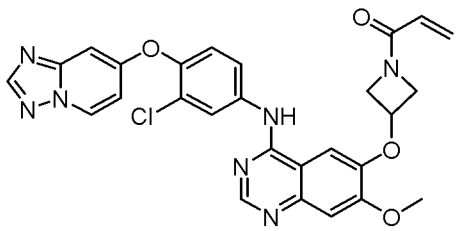
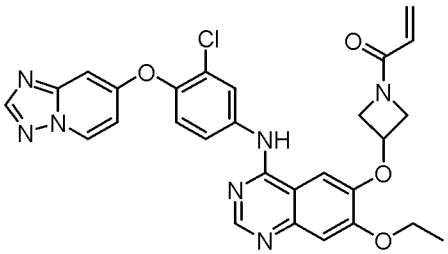
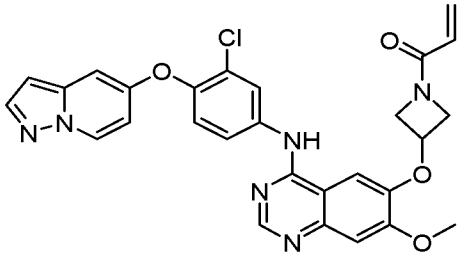
is,  . In some embodiments, R^5 is

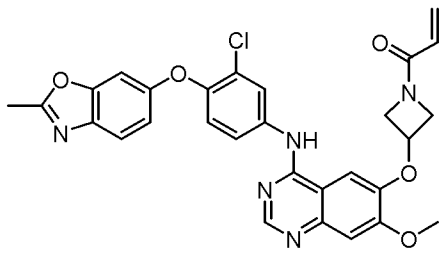
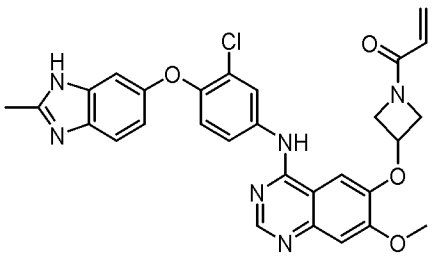
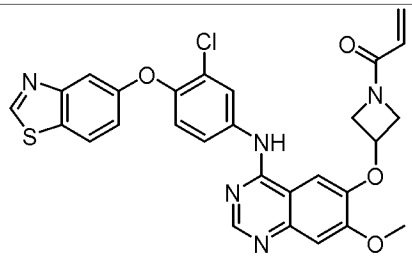
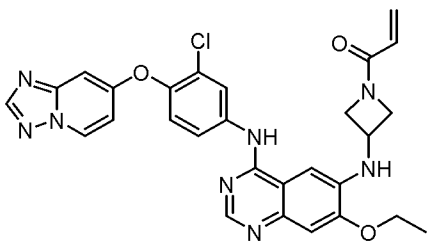
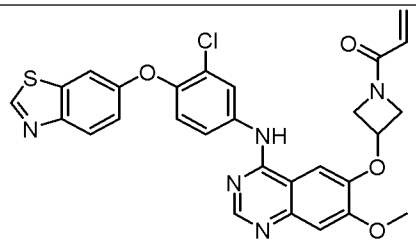
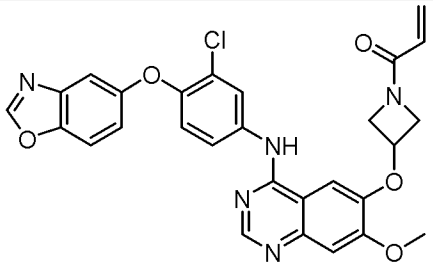


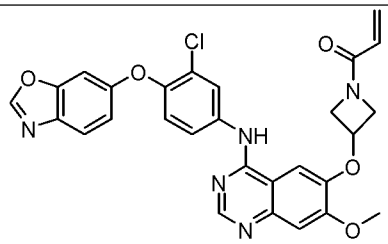
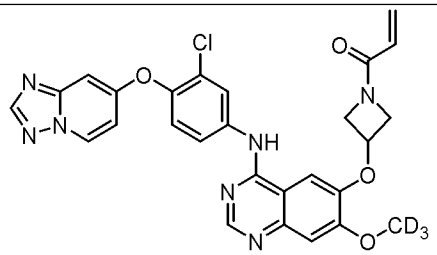
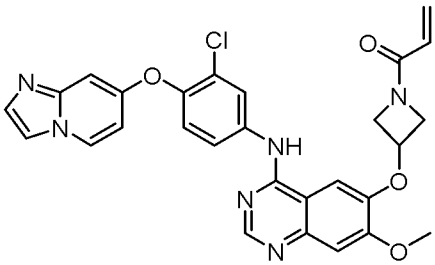
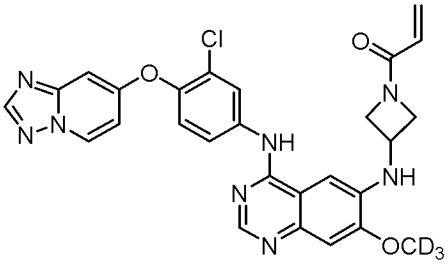
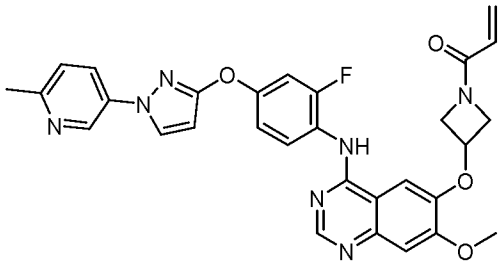
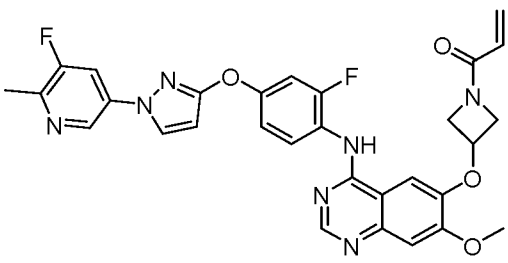
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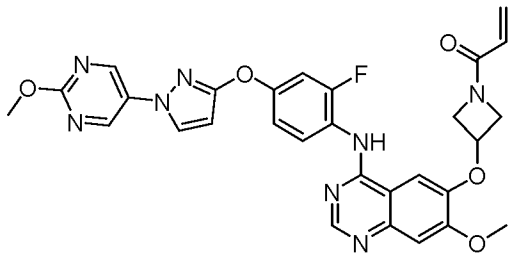
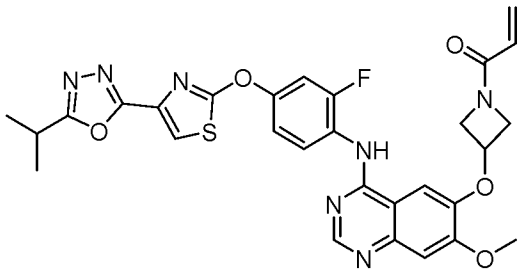
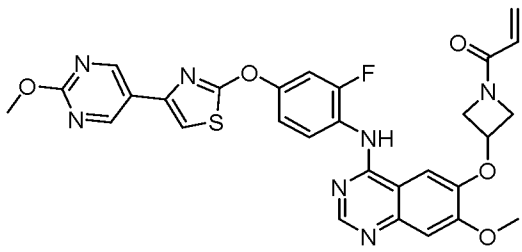
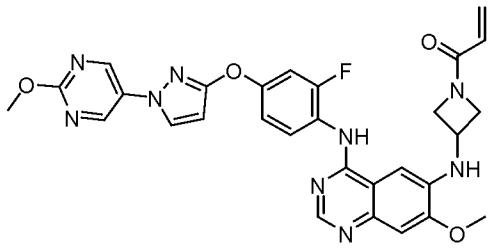
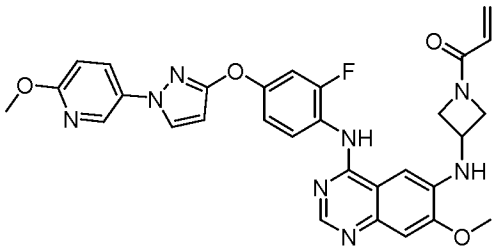
[72] In some embodiments, provided herein is a compound, or pharmaceutically acceptable salt thereof, chosen from the compounds listed in Table 1.

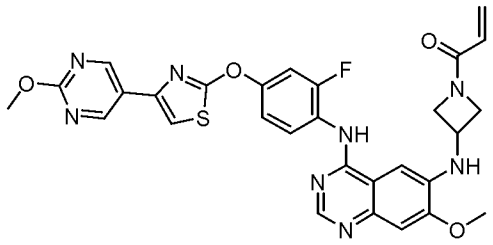
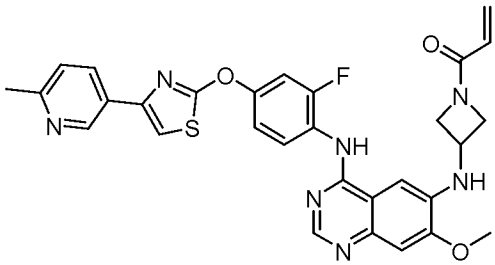
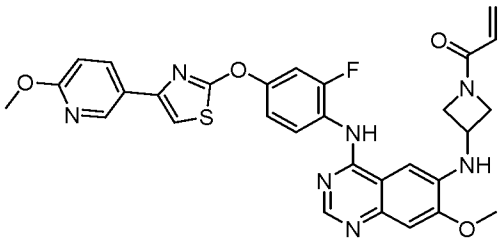
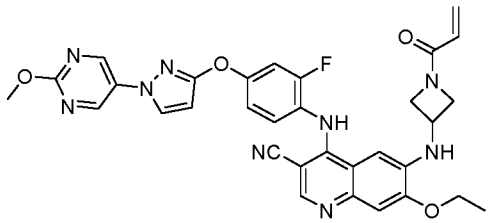
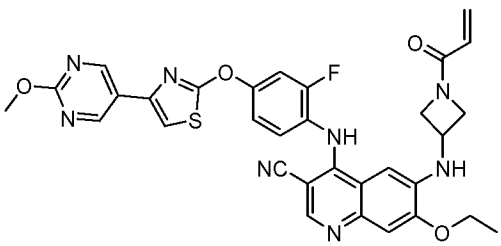
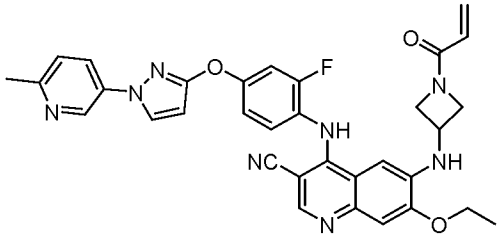
Table 1. Exemplary Compounds of the Present Disclosure

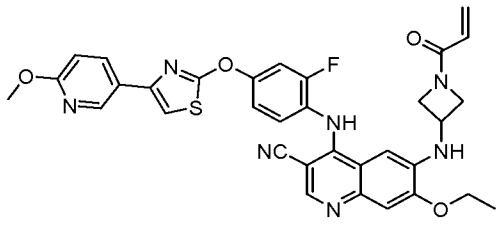
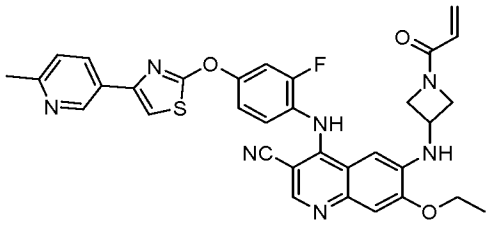
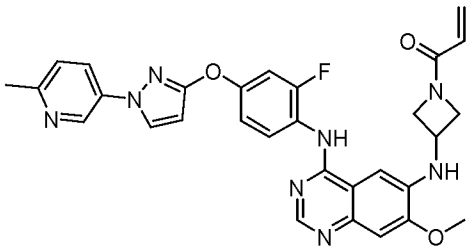
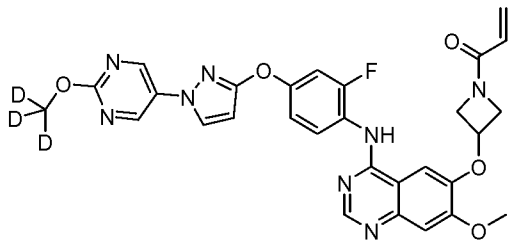
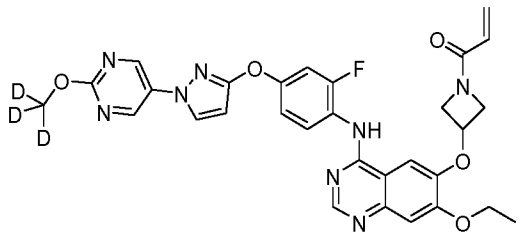
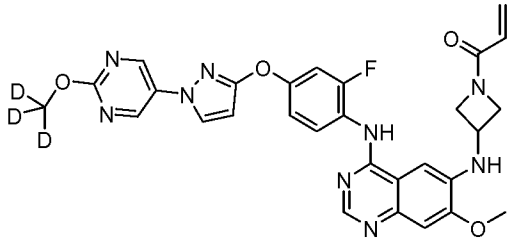
Compound No.	Chemical Structure	IUPAC Name
1		1-(3-((4-((3-chloro-4-(quinolin-3-yloxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
2		1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
3		1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-ethoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
4		1-(3-((4-((3-chloro-4-(pyrazolo[1,5-a]pyridin-5-yloxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

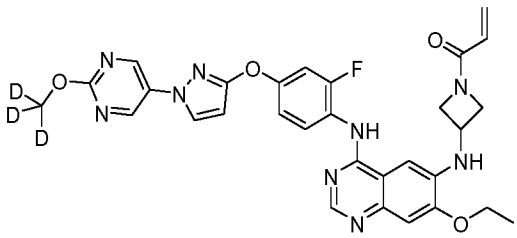
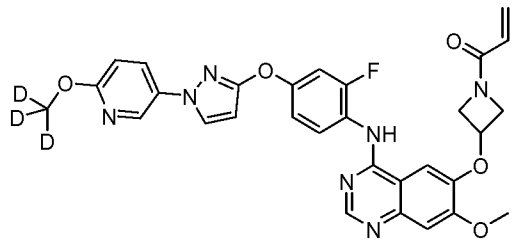
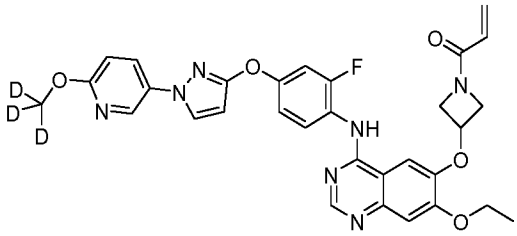
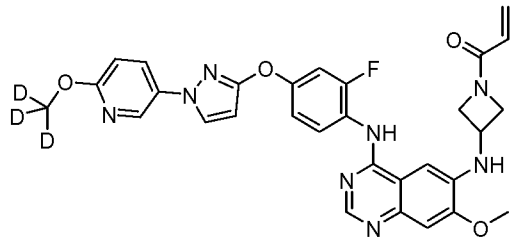
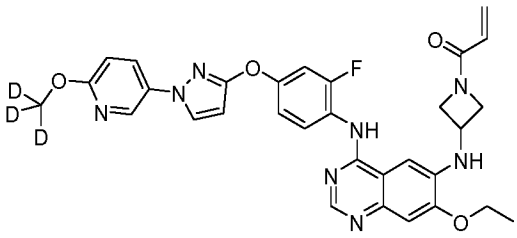
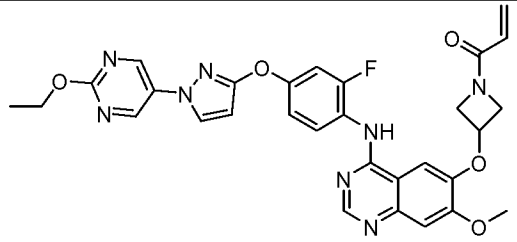
Compound No.	Chemical Structure	IUPAC Name
5		1-(3-((4-((3-chloro-4-((2-methylbenzo[d]oxazol-5-yl)methoxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
6		1-(3-((4-((3-chloro-4-((2-methyl-1H-benzo[d]imidazol-6-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
7		1-(3-((4-((4-(benzo[d]thiazol-5-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
8		1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-ethoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one
9		1-(3-((4-((4-(benzo[d]thiazol-6-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
10		1-(3-((4-((4-(benzo[d]oxazol-5-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

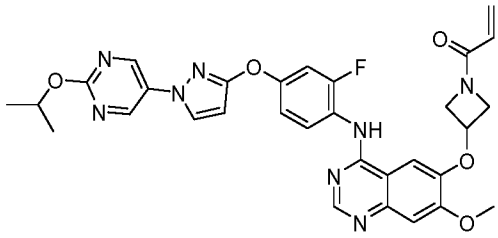
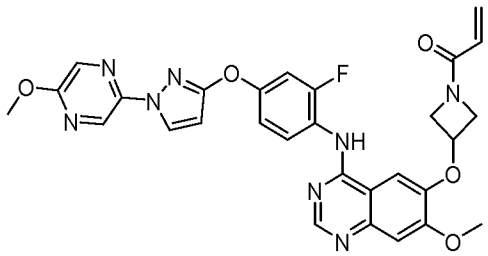
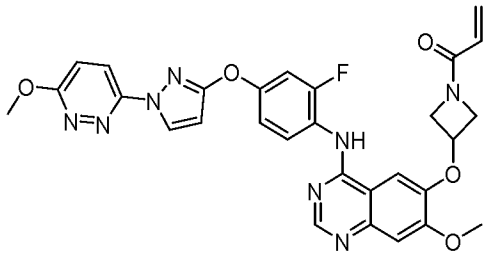
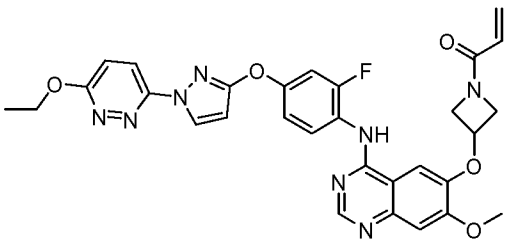
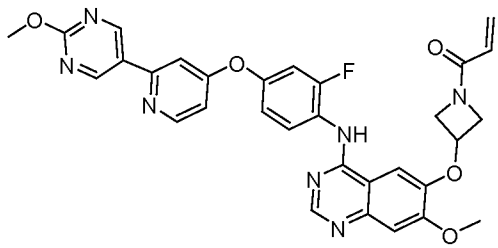
Compound No.	Chemical Structure	IUPAC Name
11		1-(3-((4-((4-(benzo[d]oxazol-6-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
12		1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-(methoxy-d3)quinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
13		1-(3-((4-((3-chloro-4-(imidazo[1,2-a]pyridin-7-yloxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
14		1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-(methoxy-d3)quinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one
15		1-(3-((4-((2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
16		1-(3-((4-((2-fluoro-4-((1-(5-fluoro-6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

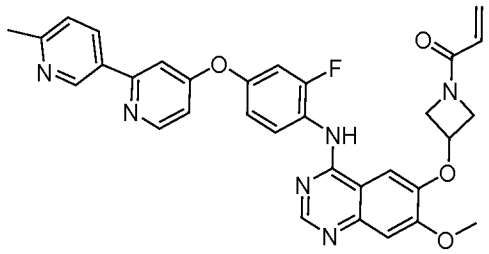
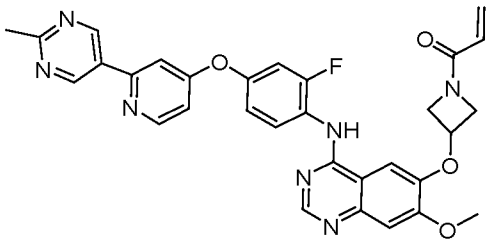
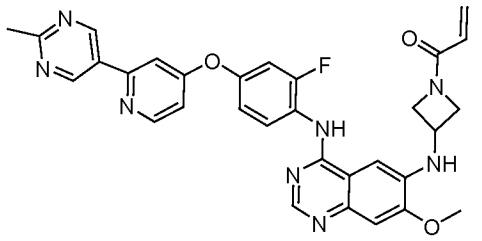
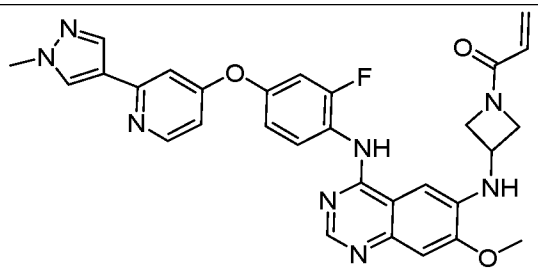
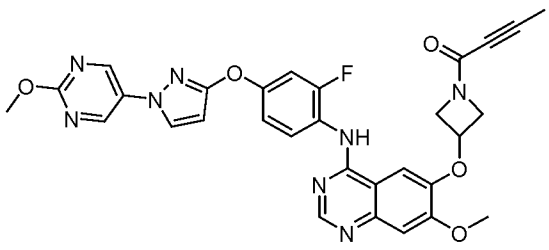
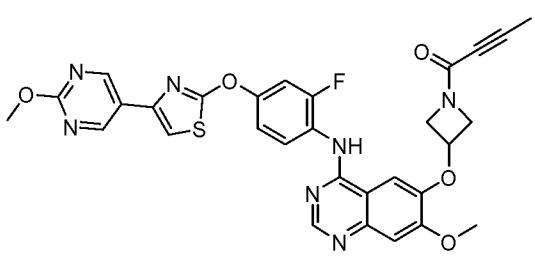
Compound No.	Chemical Structure	IUPAC Name
17		1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
18		1-(3-((4-((2-fluoro-4-((4-(5-isopropyl-1,3,4-oxadiazol-2-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
19		1-(3-((4-((2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
20		1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one
21		1-(3-((4-((2-fluoro-4-((1-(6-methoxypyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one

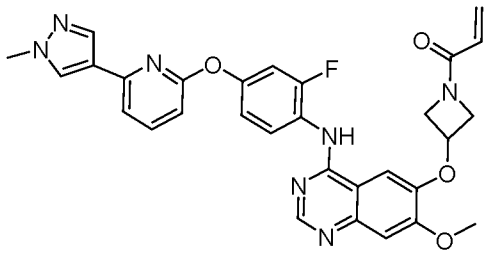
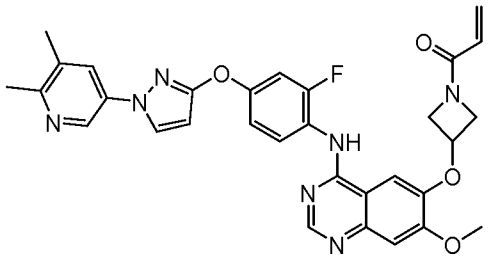
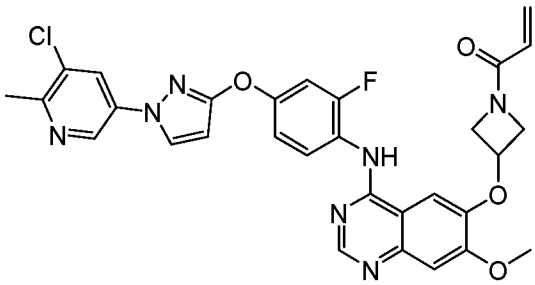
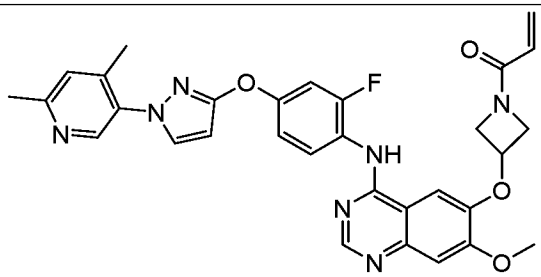
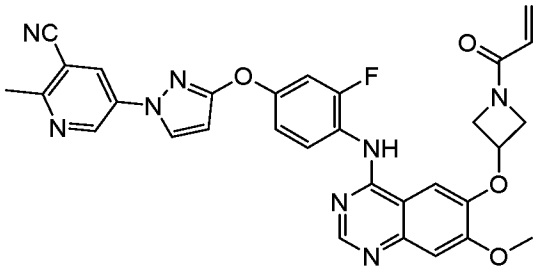
Compound No.	Chemical Structure	IUPAC Name
22		1-(3-((4-((2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one
23		1-(3-((4-((2-fluoro-4-((4-(6-methylpyridin-3-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one
24		1-(3-((4-((2-fluoro-4-((4-(6-methoxypyridin-3-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one
25		6-((1-acryloylazetidin-3-yl)amino)-7-ethoxy-4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)quinoline-3-carbonitrile
26		6-((1-acryloylazetidin-3-yl)amino)-7-ethoxy-4-((2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy)phenyl)amino)quinoline-3-carbonitrile
27		6-((1-acryloylazetidin-3-yl)amino)-7-ethoxy-4-((2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)quinoline-3-carbonitrile

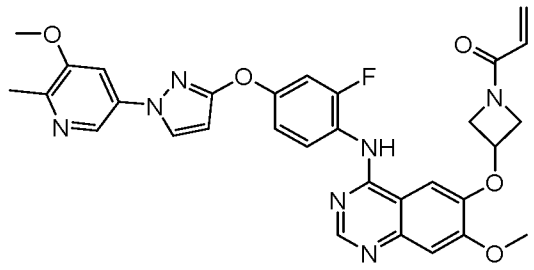
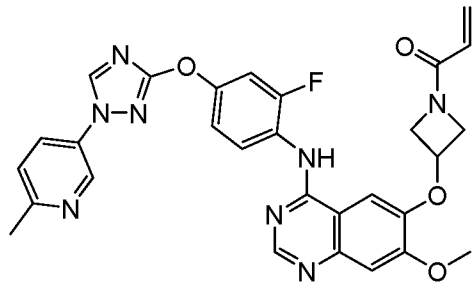
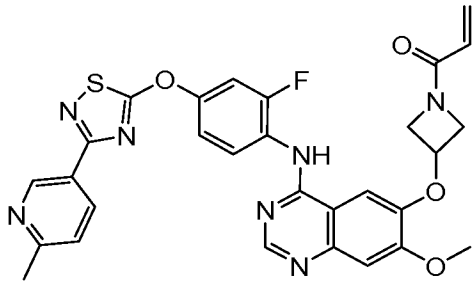
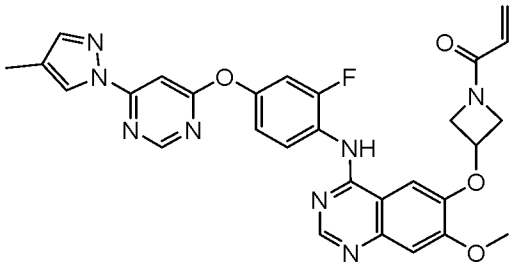
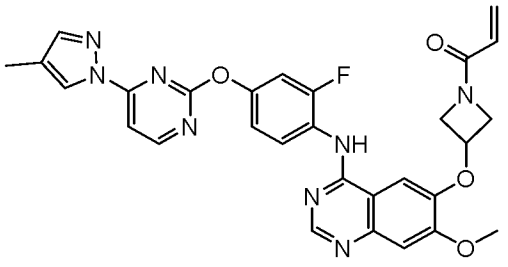
Compound No.	Chemical Structure	IUPAC Name
28		6-((1-acryloylazetidin-3-yl)amino)-7-ethoxy-4-((2-fluoro-4-((4-(6-methoxypyridin-3-yl)thiazol-2-yl)oxy)phenyl)amino)quinoline-3-carbonitrile
29		6-((1-acryloylazetidin-3-yl)amino)-7-ethoxy-4-((2-fluoro-4-((4-(6-methylpyridin-3-yl)thiazol-2-yl)oxy)phenyl)amino)quinoline-3-carbonitrile
30		1-(3-((4-((2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one
31		1-(3-((4-((2-fluoro-4-((1-(2-(methoxy-d3)pyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
32		1-(3-((7-ethoxy-4-((2-fluoro-4-((1-(2-(methoxy-d3)pyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)quinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
33		1-(3-((4-((2-fluoro-4-((1-(2-(methoxy-d3)pyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one

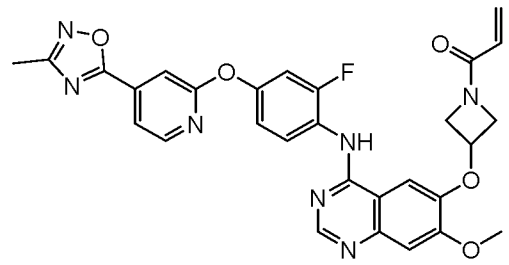
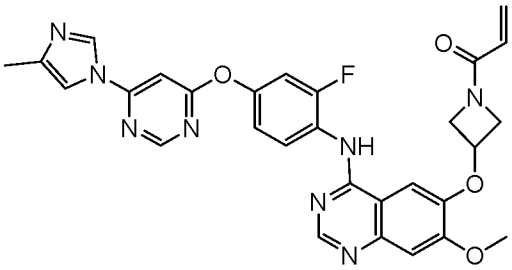
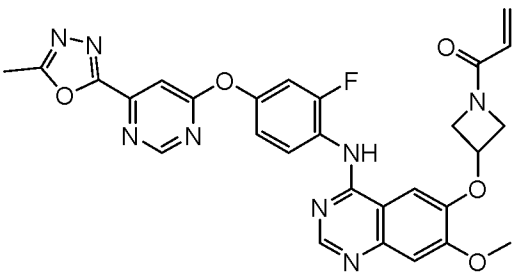
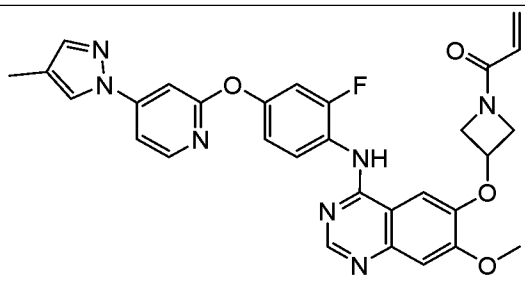
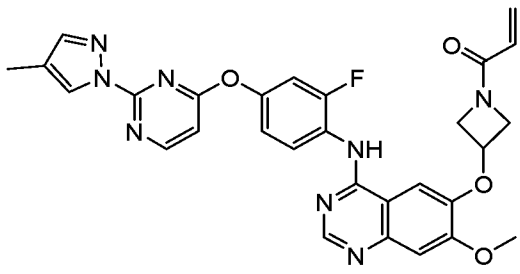
Compound No.	Chemical Structure	IUPAC Name
34		1-(3-((7-ethoxy-4-((2-fluoro-4-((1-(2-(methoxy-d3)pyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)quinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one
35		1-(3-((4-((2-fluoro-4-((1-(6-(methoxy-d3)pyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
36		1-(3-((7-ethoxy-4-((2-fluoro-4-((1-(6-(methoxy-d3)pyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)quinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
37		1-(3-((4-((2-fluoro-4-((1-(6-(methoxy-d3)pyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one
38		1-(3-((7-ethoxy-4-((2-fluoro-4-((1-(6-(methoxy-d3)pyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)quinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one
39		1-(3-((4-((4-((1-(2-ethoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-

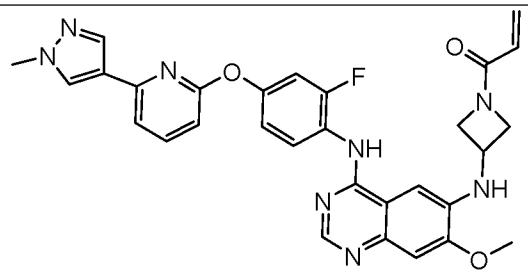
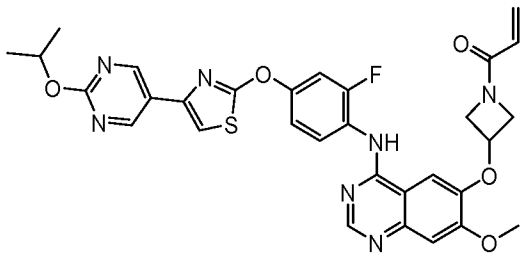
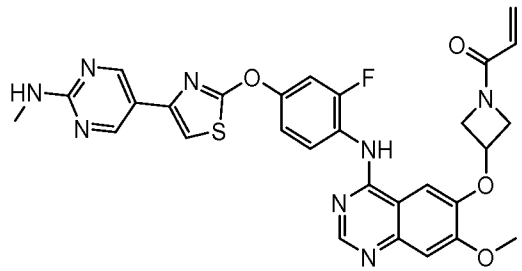
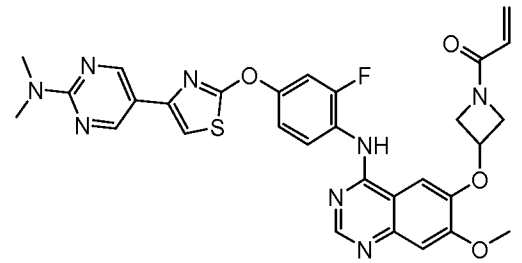
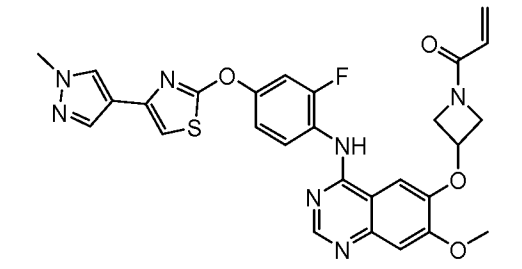
Compound No.	Chemical Structure	IUPAC Name
		yl)oxy)azetidin-1-yl)prop-2-en-1-one
40		1-(3-((4-((2-fluoro-4-((1-(2-isopropoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
41		1-(3-((4-((2-fluoro-4-((1-(5-methoxypyrazin-2-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
42		1-(3-((4-((2-fluoro-4-((1-(6-methoxypyridazin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
43		1-(3-((4-((4-((1-(6-ethoxypyridazin-3-yl)-1H-pyrazol-3-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
44		1-(3-((4-((2-fluoro-4-((2-(2-methoxypyrimidin-5-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

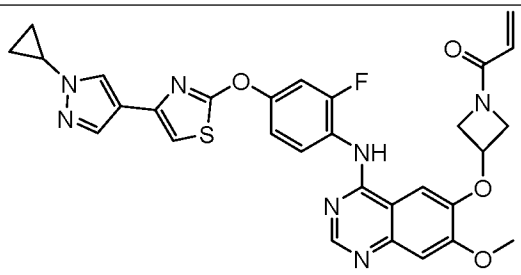
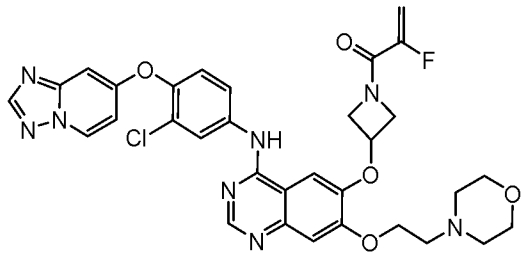
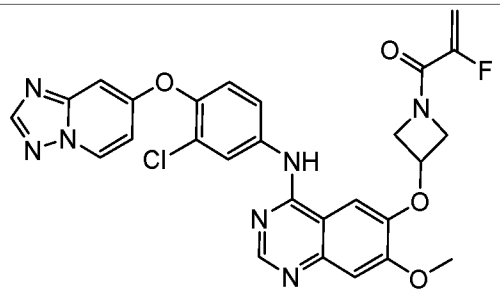
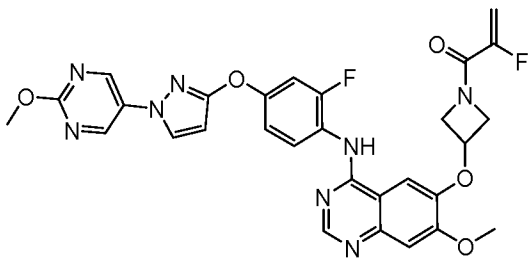
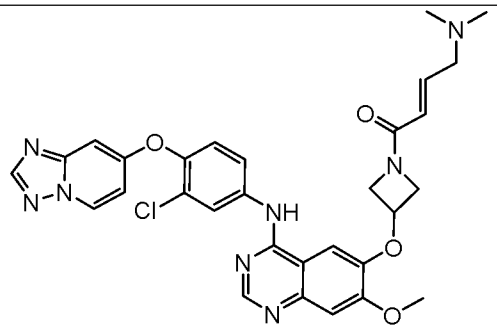
Compound No.	Chemical Structure	IUPAC Name
45		1-(3-((4-((2-fluoro-4-((6'-methyl-[2,3'-bipyridin]-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
46		1-(3-((4-((2-fluoro-4-((2-(2-methylpyrimidin-5-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
47		1-(3-((4-((2-fluoro-4-((2-(2-methylpyrimidin-5-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one
48		1-(3-((4-((2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one
49		1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)but-2-yn-1-one
50		1-(3-((4-((2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)but-2-yn-1-one

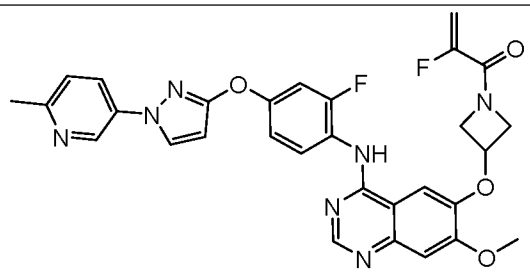
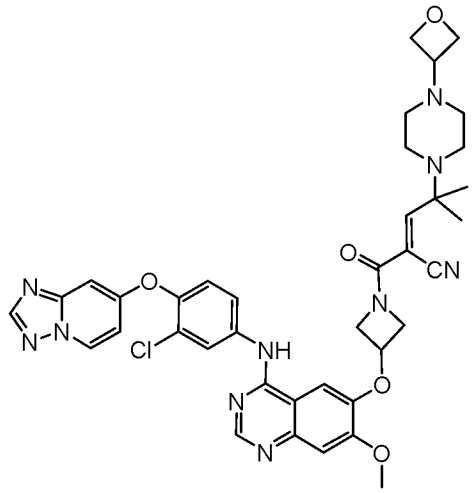
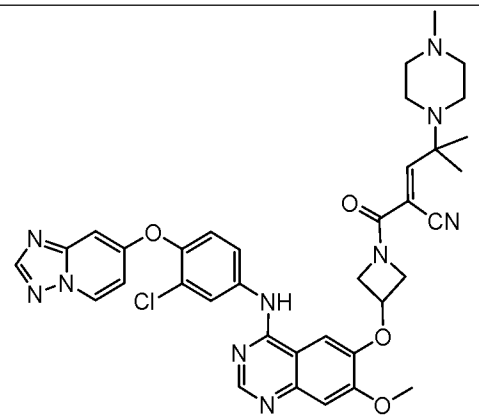
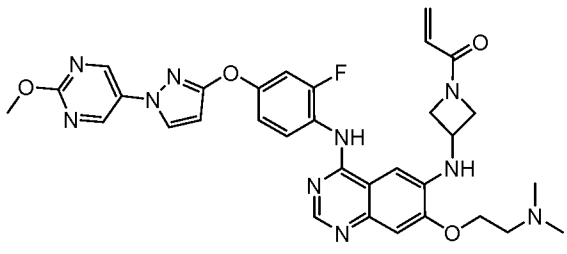
Compound No.	Chemical Structure	IUPAC Name
51		1-(3-((4-((2-fluoro-4-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
52		1-(3-((4-((4-((1-(5,6-dimethylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
53		1-(3-((4-((4-((1-(5-chloro-6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
54		1-(3-((4-((4-((1-(4,6-dimethylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
55		5-(3-(4-((6-((1-acryloylazetidin-3-yl)oxy)-7-methoxyquinazolin-4-yl)amino)-3-fluorophenoxy)-1H-pyrazol-1-yl)-2-methylnicotinonitrile

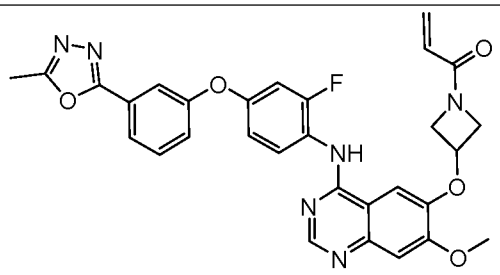
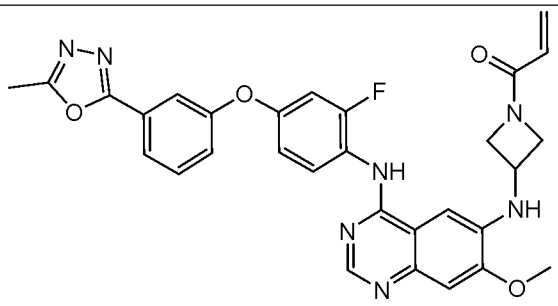
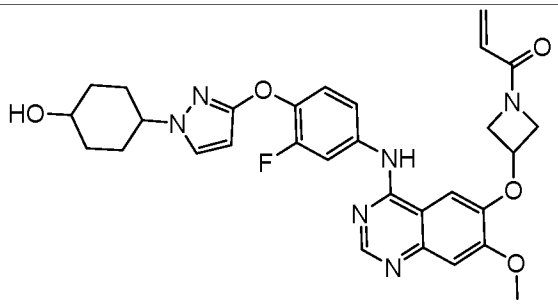
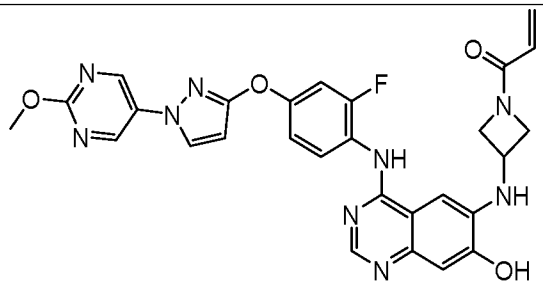
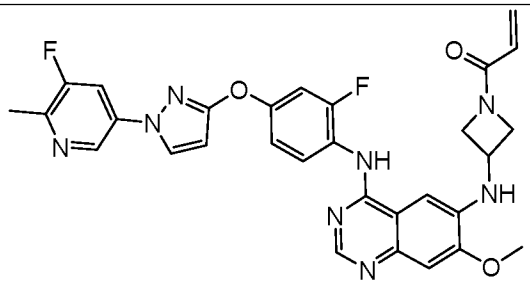
Compound No.	Chemical Structure	IUPAC Name
56		1-(3-((4-((2-fluoro-4-((1-(5-methoxy-6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
57		1-(3-((4-((2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-1,2,4-triazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
58		1-(3-((4-((2-fluoro-4-((3-(6-methylpyridin-3-yl)-1,2,4-thiadiazol-5-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
59		1-(3-((4-((2-fluoro-4-((6-(4-methyl-1H-pyrazol-1-yl)pyrimidin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
60		1-(3-((4-((2-fluoro-4-((4-(4-methyl-1H-pyrazol-1-yl)pyrimidin-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

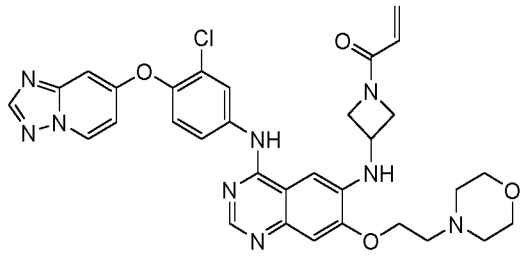
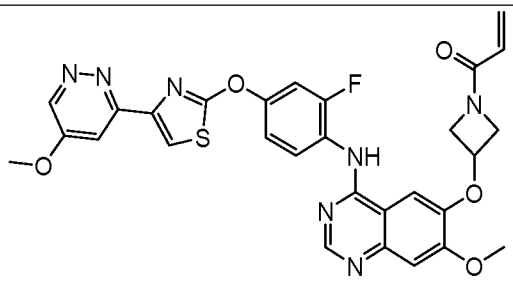
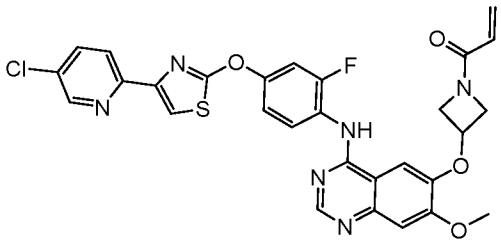
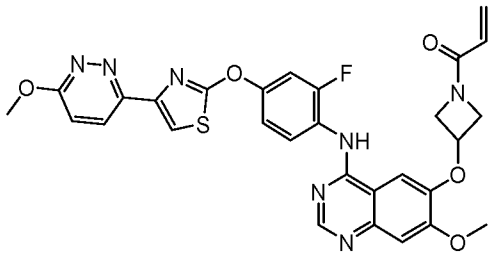
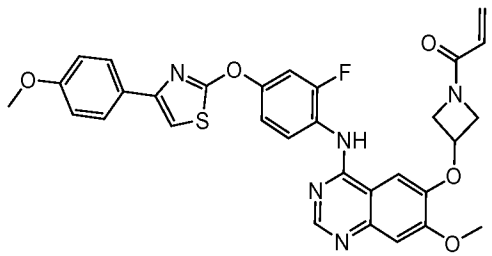
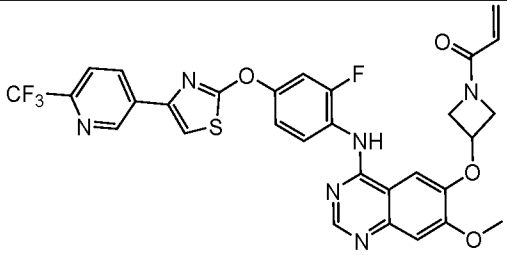
Compound No.	Chemical Structure	IUPAC Name
61		1-(3-((4-((2-fluoro-4-((4-(3-methyl-1,2,4-oxadiazol-5-yl)pyridin-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
62		1-(3-((4-((2-fluoro-4-((6-(4-methyl-1H-imidazol-1-yl)pyrimidin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
63		1-(3-((4-((2-fluoro-4-((6-(5-methyl-1,3,4-oxadiazol-2-yl)pyrimidin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
64		1-(3-((4-((2-fluoro-4-((4-(4-methyl-1H-pyrazol-1-yl)pyridin-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
65		1-(3-((4-((2-fluoro-4-((2-(4-methyl-1H-pyrazol-1-yl)pyrimidin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

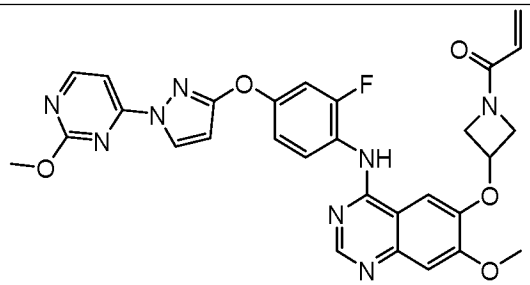
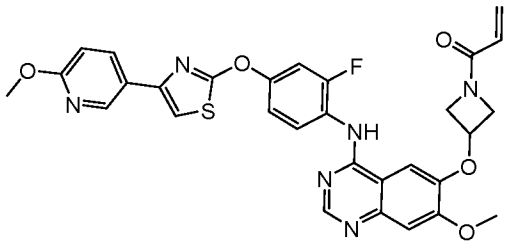
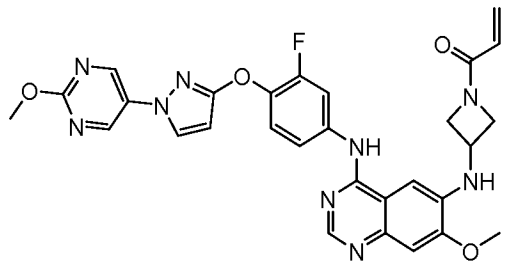
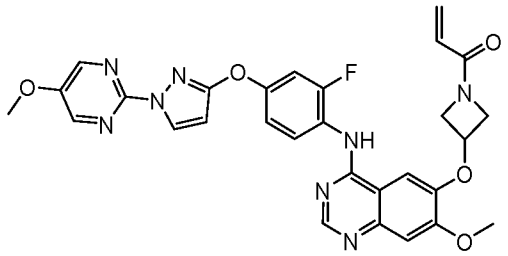
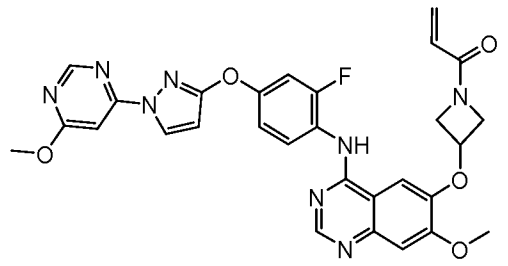
Compound No.	Chemical Structure	IUPAC Name
66		1-(3-((4-((2-fluoro-4-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one
67		1-(3-((4-((2-fluoro-4-((4-(2-isopropoxypyrimidin-5-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
68		1-(3-((4-((2-fluoro-4-((4-(2-(methylamino)pyrimidin-5-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
69		1-(3-((4-((4-((4-(2-(dimethylamino)pyrimidin-5-yl)thiazol-2-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
70		1-(3-((4-((2-fluoro-4-((4-(1-methyl-1H-pyrazol-4-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

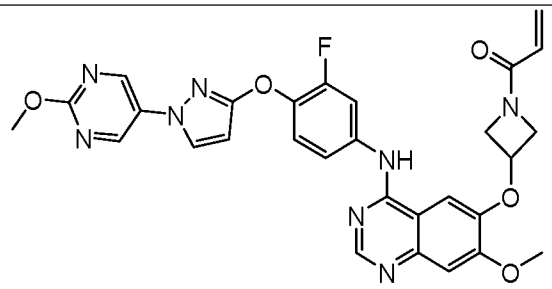
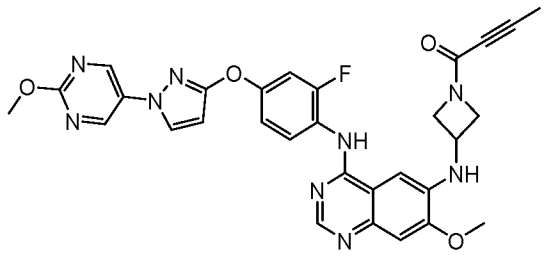
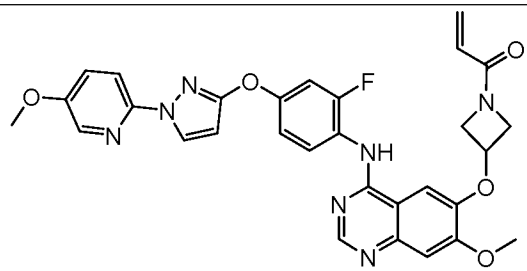
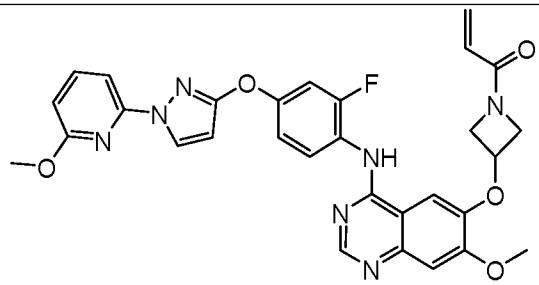
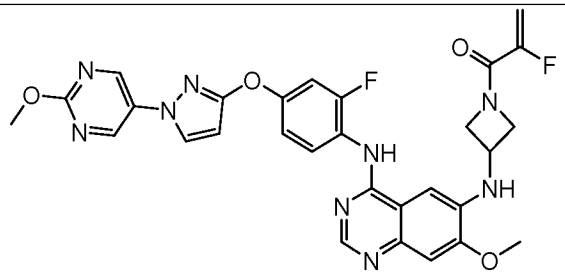
Compound No.	Chemical Structure	IUPAC Name
71		1-(3-((4-((4-((4-(1-cyclopropyl-1H-pyrazol-4-yl)thiazol-2-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
72		1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-(2-morpholinoethoxy)quinazolin-6-yl)oxy)azetidin-1-yl)-2-fluoroprop-2-en-1-one
73		1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)-2-fluoroprop-2-en-1-one
74		2-fluoro-1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
75		(E)-1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)-4-(dimethylamino)but-2-en-1-one

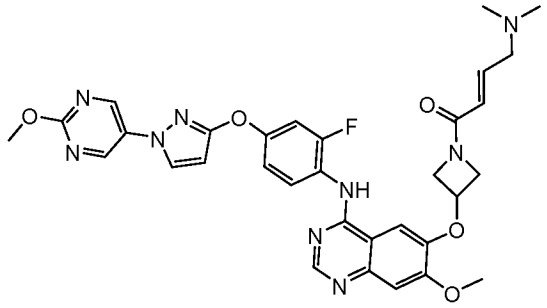
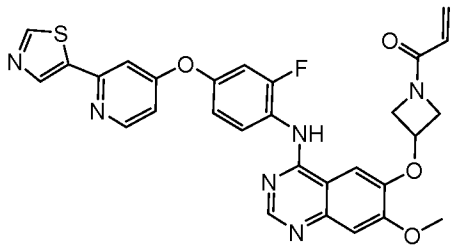
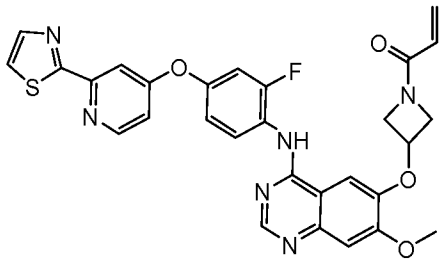
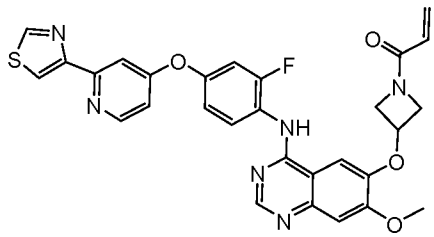
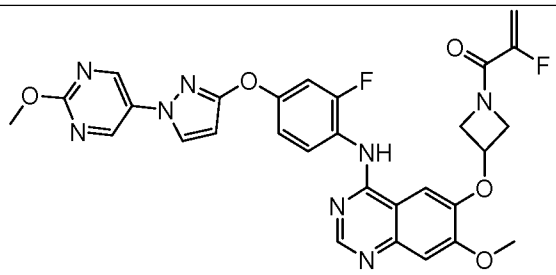
Compound No.	Chemical Structure	IUPAC Name
76		2-fluoro-1-(3-((4-((2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
77		(E)-2-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carbonyl)-4-methyl-4-(4-(oxetan-3-yl)piperazin-1-yl)pent-2-enenitrile
78		(E)-2-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carbonyl)-4-methyl-4-(4-methylpiperazin-1-yl)pent-2-enenitrile
79		1-(3-((7-(2-(dimethylamino)ethoxy)-4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)quinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one

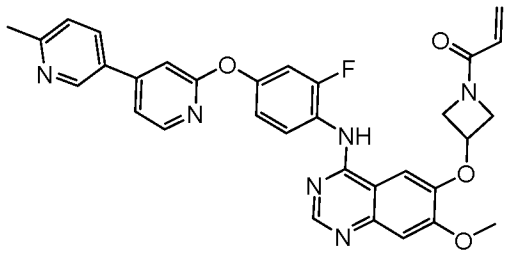
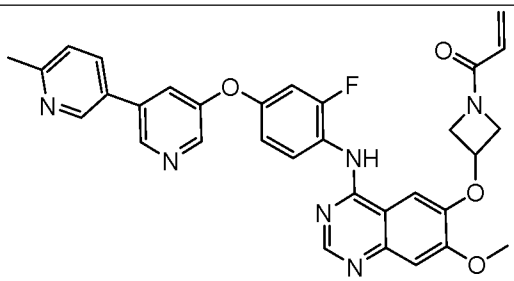
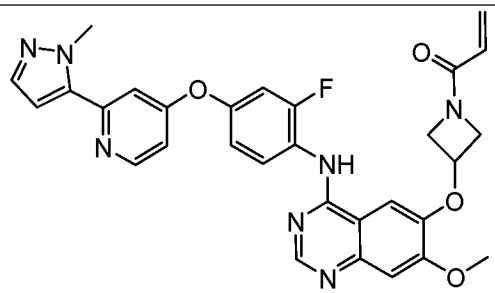
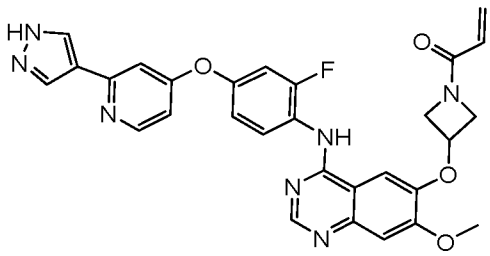
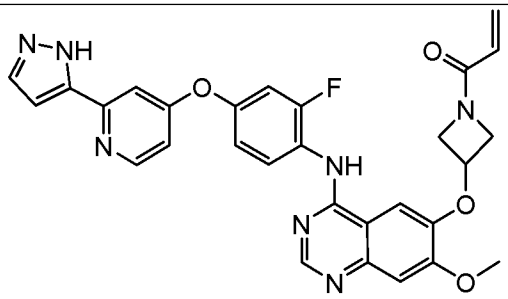
Compound No.	Chemical Structure	IUPAC Name
80		1-(3-((4-((2-fluoro-4-(3-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
81		1-(3-((4-((2-fluoro-4-(3-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one
82		1-(3-((4-((3-fluoro-4-((1-(4-hydroxycyclohexyl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
83		1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-hydroxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one
84		1-(3-((4-((2-fluoro-4-((1-(5-fluoro-6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one

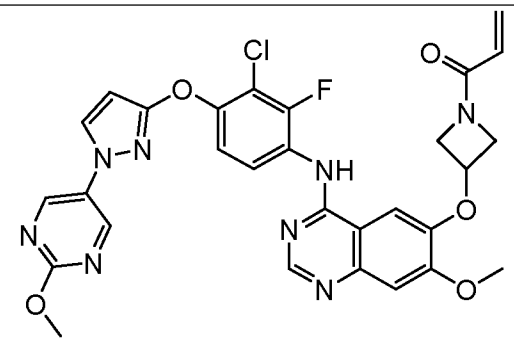
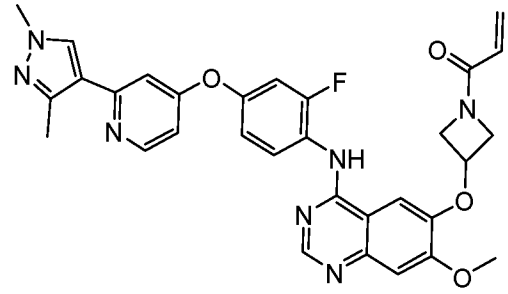
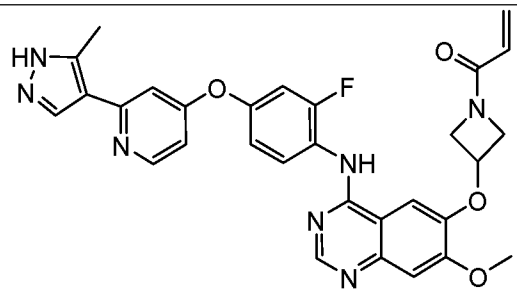
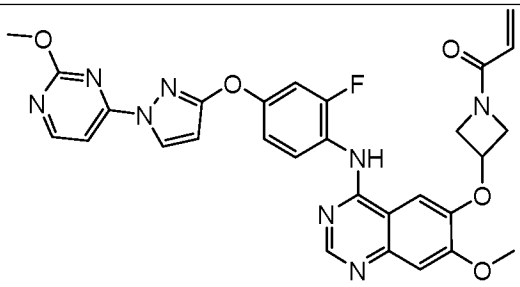
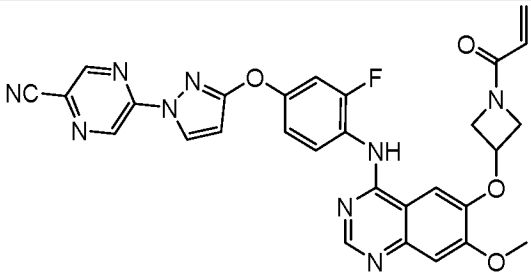
Compound No.	Chemical Structure	IUPAC Name
85		1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-(2-morpholinoethoxy)quinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one
86		1-(3-((4-((2-fluoro-4-((4-(5-methoxypyridazin-3-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
87		1-(3-((4-((4-((4-(5-chloropyridin-2-yl)thiazol-2-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
88		1-(3-((4-((2-fluoro-4-((4-(6-methoxypyridazin-3-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
89		1-(3-((4-((2-fluoro-4-((4-(4-methoxyphenyl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
90		1-(3-((4-((2-fluoro-4-((4-(6-(trifluoromethyl)pyridin-3-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-

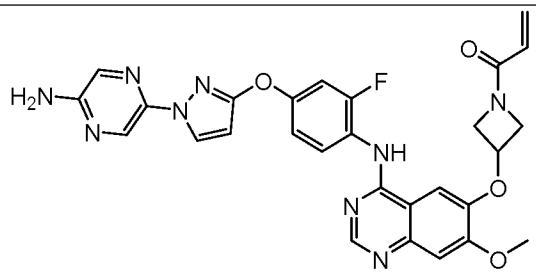
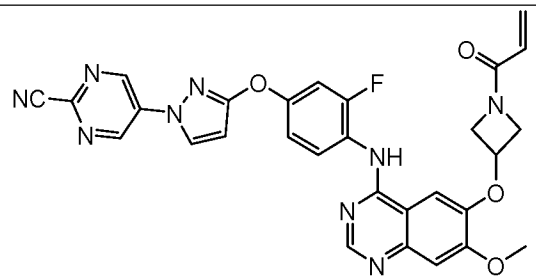
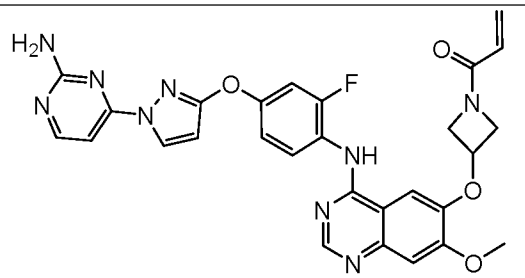
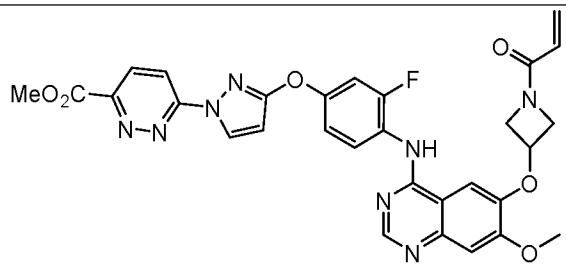
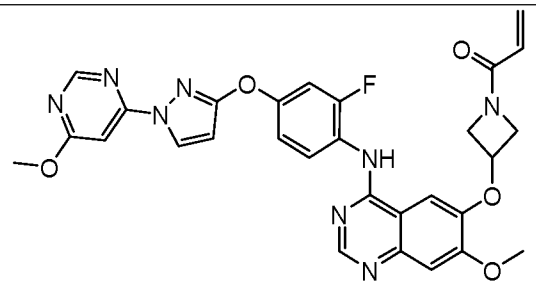
Compound No.	Chemical Structure	IUPAC Name
		yl)oxy)azetidin-1-yl)prop-2-en-1-one
91		1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-4-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
92		1-(3-((4-((2-fluoro-4-((4-(6-methoxypyridin-3-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
93		1-(3-((4-((3-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one
94		1-(3-((4-((2-fluoro-4-((1-(5-methoxypyrimidin-2-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
95		1-(3-((4-((2-fluoro-4-((1-(6-methoxypyrimidin-4-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

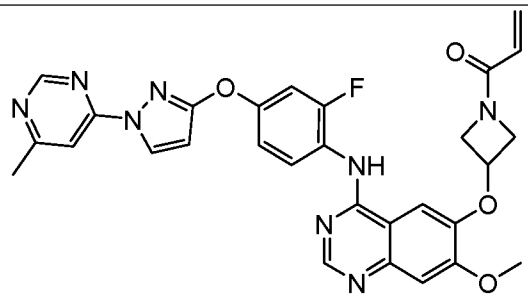
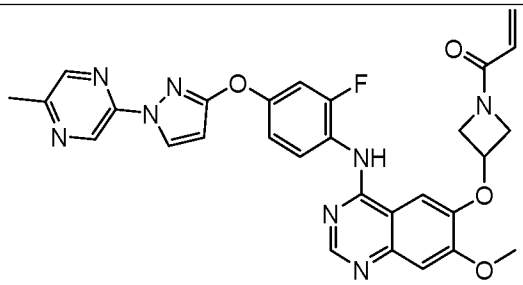
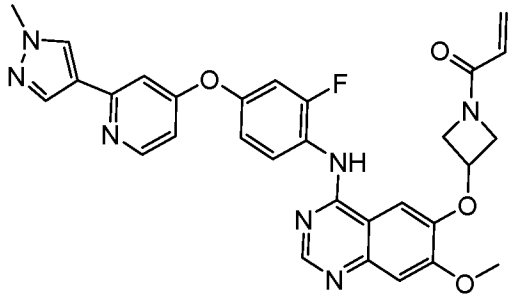
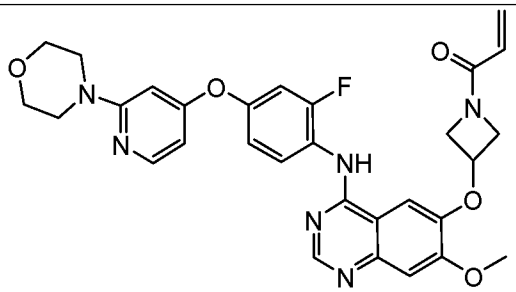
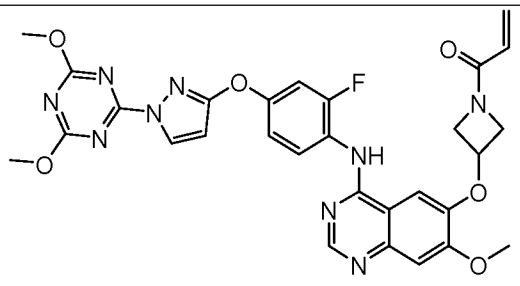
Compound No.	Chemical Structure	IUPAC Name
96		1-(3-((4-((3-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
97		1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)but-2-yn-1-one
98		1-(3-((4-((2-fluoro-4-((1-(5-methoxypyridin-2-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
99		1-(3-((4-((2-fluoro-4-((1-(6-methoxypyridin-2-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
100		2-fluoro-1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one

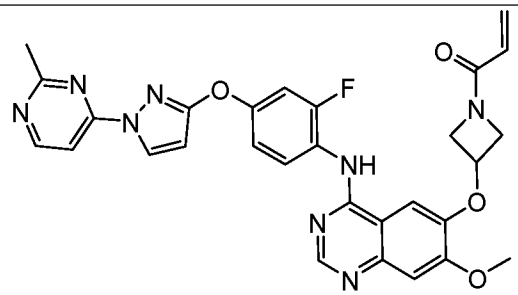
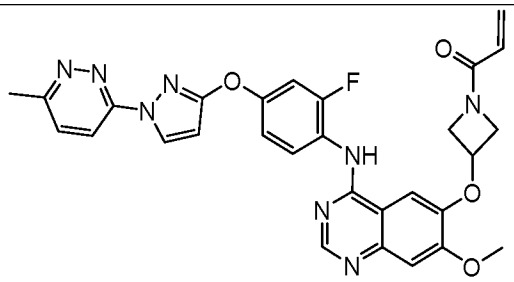
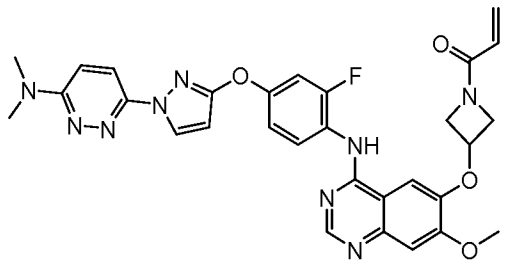
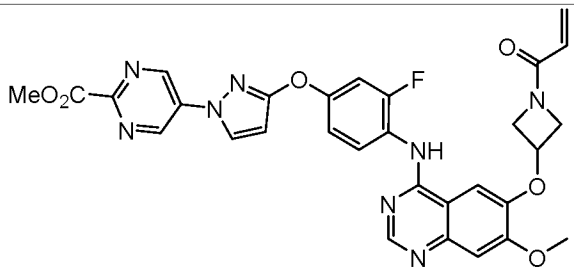
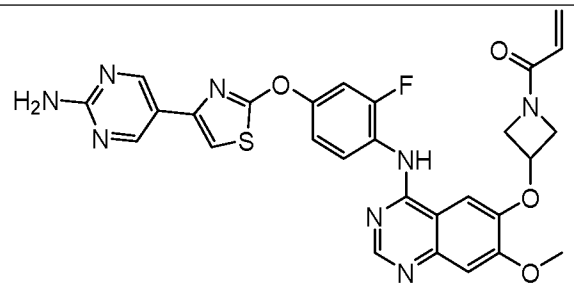
Compound No.	Chemical Structure	IUPAC Name
101		(E)-4-(dimethylamino)-1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)but-2-en-1-one
102		1-(3-((4-((2-fluoro-4-((2-(thiazol-5-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
103		1-(3-((4-((2-fluoro-4-((2-(thiazol-2-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
104		1-(3-((4-((2-fluoro-4-((2-(thiazol-4-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
105		2-fluoro-1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

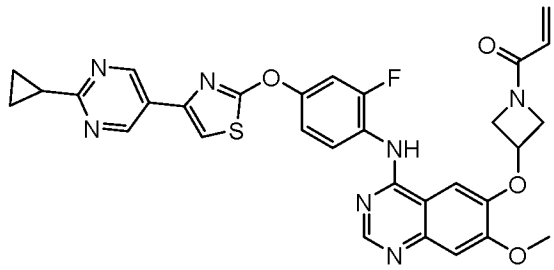
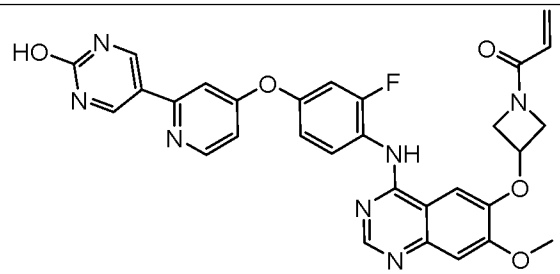
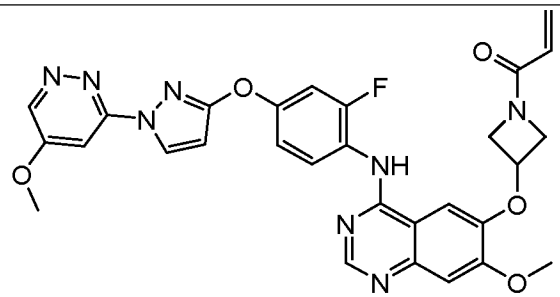
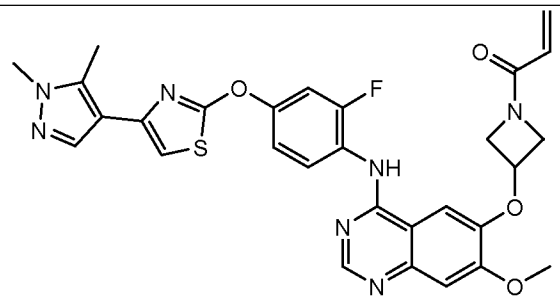
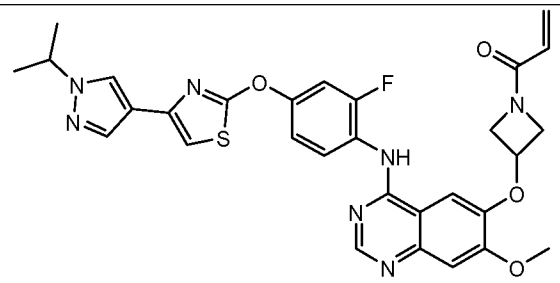
Compound No.	Chemical Structure	IUPAC Name
106		1-(3-((4-((2-fluoro-4-((6-methyl-[3,4'-bipyridin]-2'-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
107		1-(3-((4-((2-fluoro-4-((6'-methyl-[3,3'-bipyridin]-5-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
108		1-(3-((4-((2-fluoro-4-((2-(1-methyl-1H-pyrazol-5-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
109		1-(3-((4-((4-((2-(1H-pyrazol-4-yl)pyridin-4-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
110		1-(3-((4-((4-((2-(1H-pyrazol-5-yl)pyridin-4-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

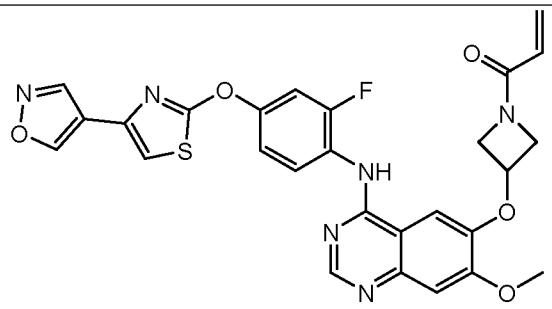
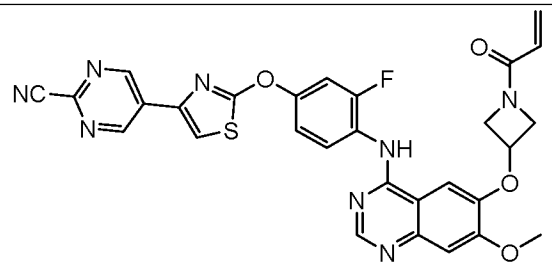
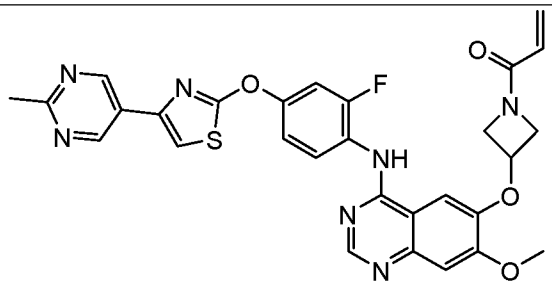
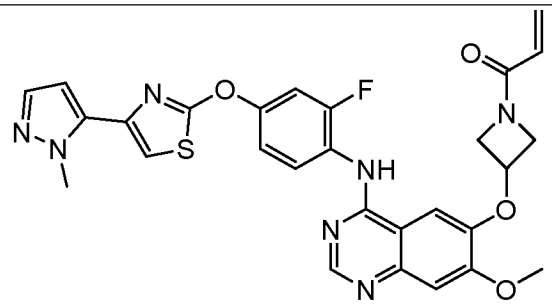
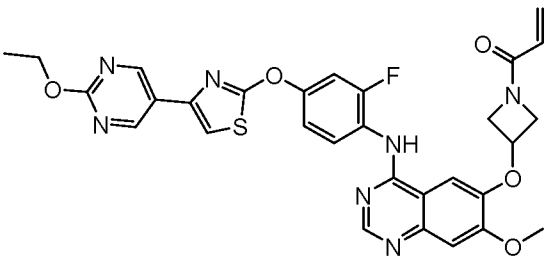
Compound No.	Chemical Structure	IUPAC Name
111		1-(3-((4-((3-chloro-2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
112		1-(3-((4-((4-((2-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
113		1-(3-((4-((2-fluoro-4-((2-(5-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
114		1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-4-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
115		5-(3-(4-((6-((1-acryloylazetidin-3-yl)oxy)-7-methoxyquinazolin-4-yl)amino)-3-fluorophenoxy)-1H-pyrazol-1-yl)pyrazine-2-carbonitrile

Compound No.	Chemical Structure	IUPAC Name
116		1-(3-((4-((4-((1-(5-aminopyrazin-2-yl)-1H-pyrazol-3-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
117		5-(3-(4-((6-((1-acryloylazetidin-3-yl)oxy)-7-methoxyquinazolin-4-yl)amino)-3-fluorophenoxy)-1H-pyrazol-1-yl)pyrimidine-2-carbonitrile
118		1-(3-((4-((4-((1-(2-aminopyrimidin-4-yl)-1H-pyrazol-3-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
119		methyl 6-(3-(4-((6-((1-acryloylazetidin-3-yl)oxy)-7-methoxyquinazolin-4-yl)amino)-3-fluorophenoxy)-1H-pyrazol-1-yl)pyridazine-3-carboxylate
120		1-(3-((4-((2-fluoro-4-((1-(6-methoxypyrimidin-4-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

Compound No.	Chemical Structure	IUPAC Name
121		1-(3-((4-((2-fluoro-4-((1-(6-methylpyrimidin-4-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
122		1-(3-((4-((2-fluoro-4-((1-(5-methylpyrazin-2-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
123		1-(3-((4-((2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
124		1-(3-((4-((2-fluoro-4-((2-morpholinopyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
125		1-(3-((4-((4-((1-(4,6-dimethoxy-1,3,5-triazin-2-yl)-1H-pyrazol-3-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

Compound No.	Chemical Structure	IUPAC Name
126		1-(3-((4-((2-fluoro-4-((1-(2-methylpyrimidin-4-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
127		1-(3-((4-((2-fluoro-4-((1-(6-methylpyridazin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
128		1-(3-((4-((4-((1-(6-(dimethylamino)pyridazin-3-yl)-1H-pyrazol-3-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
129		methyl 5-(3-(4-((6-((1-acryloylazetidin-3-yl)oxy)-7-methoxyquinazolin-4-yl)amino)-3-fluorophenoxy)-1H-pyrazol-1-yl)pyrimidine-2-carboxylate
130		1-(3-((4-((4-((4-(2-aminopyrimidin-5-yl)thiazol-2-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

Compound No.	Chemical Structure	IUPAC Name
131		1-(3-((4-((4-((4-(2-cyclopropylpyrimidin-5-yl)thiazol-2-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
132		1-(3-((4-((2-fluoro-4-((2-(2-hydroxypyrimidin-5-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
133		1-(3-((4-((2-fluoro-4-((1-(5-methoxypyridazin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
134		1-(3-((4-((4-((4-(1,5-dimethyl-1H-pyrazol-4-yl)thiazol-2-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
135		1-(3-((4-((2-fluoro-4-((4-(1-isopropyl-1H-pyrazol-4-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

Compound No.	Chemical Structure	IUPAC Name
136		1-(3-((4-((2-fluoro-4-((4-(isoxazol-4-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
137		5-(2-(4-((6-((1-acryloylazetidin-3-yl)oxy)-7-methoxyquinazolin-4-yl)amino)-3-fluorophenoxy)thiazol-4-yl)pyrimidine-2-carbonitrile
138		1-(3-((4-((2-fluoro-4-((4-(2-methylpyrimidin-5-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
139		1-(3-((4-((2-fluoro-4-((4-(1-methyl-1H-pyrazol-5-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one
140		1-(3-((4-((4-((4-(2-ethoxypyrimidin-5-yl)thiazol-2-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

Pharmaceutical Compositions

[73] Pharmaceutical compositions of the present disclosure comprise at least one compound of Formula (I), or a pharmaceutically acceptable salt thereof formulated together with one or more pharmaceutically acceptable carriers. These formulations include those suitable for oral, rectal, topical,

buccal and parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) administration. The most suitable form of administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular compound being used.

[74] Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of a compound of the present disclosure as powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. As indicated, such formulations may be prepared by any suitable method of pharmacy which includes the step of bringing into association at least one compound of the present disclosure as the active compound and a carrier or excipient (which may constitute one or more accessory ingredients). The carrier must be acceptable in the sense of being compatible with the other ingredients of the formulation and must not be deleterious to the recipient. The carrier may be a solid or a liquid, or both, and may be formulated with at least one compound described herein as the active compound in a unit-dose formulation, for example, a tablet, which may contain from about 0.05% to about 95% by weight of the at least one active compound. Other pharmacologically active substances may also be present including other compounds. The formulations of the present disclosure may be prepared by any of the well-known techniques of pharmacy consisting essentially of admixing the components.

[75] For solid compositions, conventional nontoxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talc, cellulose, glucose, sucrose, magnesium carbonate, and the like. Liquid pharmacologically administrable compositions can, for example, be prepared by, for example, dissolving or dispersing, at least one active compound of the present disclosure as described herein and optional pharmaceutical adjuvants in an excipient, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form a solution or suspension. In general, suitable formulations may be prepared by uniformly and intimately admixing the at least one active compound of the present disclosure with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet may be prepared by compressing or molding a powder or granules of at least one compound of the present disclosure, which may be optionally combined with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, at least one compound of the present disclosure in a free-flowing form, such as a powder or granules, which may be optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Molded tablets may be made by molding, in a suitable machine, where the powdered form of at least one compound of the present disclosure is moistened with an inert liquid diluent.

[76] Formulations suitable for buccal (sub-lingual) administration include lozenges comprising at least one compound of the present disclosure in a flavored base, usually sucrose and acacia or tragacanth, and pastilles comprising the at least one compound in an inert base such as gelatin and glycerin or sucrose and acacia.

[77] Formulations of the present disclosure suitable for parenteral administration comprise sterile aqueous preparations of at least one compound of Formula (I), or pharmaceutically acceptable salts thereof, which are approximately isotonic with the blood of the intended recipient. These preparations are administered intravenously, although administration may also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations may conveniently be prepared by admixing at least one compound described herein with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the present disclosure may contain from about 0.1 to about 5% w/w of the active compound.

[78] Formulations suitable for rectal administration are presented as unit-dose suppositories. These may be prepared by admixing at least one compound as described herein with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

[79] Formulations suitable for topical application to the skin may take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers and excipients which may be used include Vaseline, lanoline, polyethylene glycols, alcohols, and combinations of two or more thereof. The active compound (i.e., at least one compound of Formula (I), or pharmaceutically acceptable salts thereof) is generally present at a concentration of from about 0.1% to about 15% w/w of the composition, for example, from about 0.5 to about 2%.

[80] The amount of active compound administered may be dependent on the subject being treated, the subject's weight, the manner of administration and the judgment of the prescribing physician. For example, a dosing schedule may involve the daily or semi-daily administration of the encapsulated compound at a perceived dosage of about 1 μg to about 1000 mg. In another embodiment, intermittent administration, such as on a monthly or yearly basis, of a dose of the encapsulated compound may be employed. Encapsulation facilitates access to the site of action and allows the administration of the active ingredients simultaneously, in theory producing a synergistic effect. In accordance with standard dosing regimens, physicians will readily determine optimum dosages and will be able to readily modify administration to achieve such dosages.

[81] A therapeutically effective amount of a compound or composition disclosed herein can be measured by the therapeutic effectiveness of the compound. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being used. In one embodiment, the therapeutically effective amount of a disclosed compound is sufficient to establish a maximal plasma concentration. Preliminary doses as, for example, determined according to animal tests, and the scaling of dosages for human administration is performed according to art-accepted practices.

[82] Toxicity and therapeutic efficacy can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD_{50}/ED_{50}. Compositions that exhibit large therapeutic indices are preferable.

[83] Data obtained from the cell culture assays or animal studies can be used in formulating a range of dosage for use in humans. Therapeutically effective dosages achieved in one animal model may be converted for use in another animal, including humans, using conversion factors known in the art (see, e.g., Freireich et al., *Cancer Chemother. Reports* 50(4):219-244 (1966) and the following Table for Equivalent Surface Area Dosage Factors).

Table 2. Equivalent Surface Area Dosage Factors.

To: / From:	Mouse (20 g)	Rat (150 g)	Monkey (3.5 kg)	Dog (8 kg)	Human (60 kg)
Mouse	1	1/2	1/4	1/6	1/12
Rat	2	1	1/2	1/4	1/7
Monkey	4	2	1	3/5	1/3
Dog	6	4	3/5	1	1/2
Human	12	7	3	2	1

[84] The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. Generally, a therapeutically effective amount may vary with the subject's age, condition, and gender, as well as the severity of the medical condition in the subject. The dosage may be determined by a physician and adjusted, as necessary, to suit observed effects of the treatment.

Methods of Treatment

[85] The present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, to be administered to treat cancer in a subject in need thereof.

[86] In some embodiments, the cancer is associated with an EGFR or HER2 exon 20 insertion mutation.

[87] In some embodiments, the cancer is selected from breast cancer, lung cancer, pancreatic cancer, colon cancer, head and neck cancer, renal cell carcinoma, squamous cell carcinoma, thyroid cancer, gall bladder cancer, thyroid cancer, bile duct cancer, ovarian cancer, endometrial cancer, prostate cancer, or esophageal cancer.

[88] In some embodiments, the cancer is lung cancer. In a further embodiment, the cancer is non-small cell lung cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is colon cancer. In some embodiments, the cancer is breast cancer.

[89] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition.

[90] The concentration and route of administration to the patient will vary depending on the cancer to be treated.

[91] In one embodiment, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in combination with another therapeutic agent, e.g., chemotherapy, or used in combination

with other treatments, such as radiation or surgical intervention, either as an adjuvant prior to surgery or post-operatively.

[92] Also provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein for use in therapy.

[93] Also provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof as defined herein for use in the treatment of cancer.

[94] Also provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof for use in the inhibition of EGFR.

[95] Also provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof as defined herein, for use in the treatment of a disease or disorder associated with an EGFR or HER2 exon 20 insertion mutation.

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

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

[98] Also provided herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as defined herein, in the manufacture of a medicament for the treatment of a disease or disorder associated with an EGFR or HER2 exon 20 insertion mutation.

[99] One skilled in the art will recognize that, both in vivo and in vitro trials using suitable, known and generally accepted cell and/or animal models are predictive of the ability of a test compound to treat or prevent a given disorder.

[100] One skilled in the art will further recognize that human clinical trials including first-in-human, dose ranging and efficacy trials, in healthy patients and/or those suffering from a given disorder, may be completed according to methods well known in the clinical and medical arts.

[101] The invention also provides for a method of inhibiting EGFR kinase activity in a cell comprising contacting the cell with an effective amount of an EGFR antagonist. In one embodiment, the administered amount is a therapeutically effective amount and the inhibition of EGFR kinase activity further results in the inhibition of the growth of the cell. In a further embodiment, the cell is a cancer cell.

[102] Inhibition of cell proliferation is measured using methods known to those skilled in the art. For example, a convenient assay for measuring cell proliferation is the CellTiter-Glo™ Luminescent Cell Viability Assay, which is commercially available from Promega (Madison, Wis.). That assay determines the number of viable cells in culture based on quantitation of ATP present, which is an indication of metabolically active cells. See Crouch et al (1993) J. Immunol. Meth. 160:81-88, U.S. Pat. No. 6,602,677. The assay may be conducted in 96- or 384-well format, making it amenable to automated high-throughput screening (HTS). See Cree et al (1995) AntiCancer Drugs 6:398-404. The assay procedure involves adding a single reagent (CellTiter-Glo® Reagent) directly to cultured cells. This results in cell lysis and generation of a luminescent signal produced by a luciferase reaction. The luminescent signal is proportional to the amount of ATP present, which is directly proportional to the number of viable cells

present in culture. Data can be recorded by luminometer or CCD camera imaging device. The luminescence output is expressed as relative light units (RLU). Inhibition of cell proliferation may also be measured using colony formation assays known in the art.

[103] Furthermore, the invention provides for methods of treating a condition associated with an EGFR or HER2 exon 20 insertion mutation in a subject suffering therefrom, comprising administering to the subject a therapeutically effective amount of an EGFR antagonist. In one embodiment, the condition is a cell proliferative disease.

[104] Treatment of the cell proliferative disorder by administration of an EGFR antagonist results in an observable and/or measurable reduction in or absence of one or more of the following: reduction in the number of cancer cells or absence of the cancer cells; reduction in the tumor size; inhibition of cancer cell infiltration into peripheral organs including the spread of cancer into soft tissue and bone; inhibition of tumor metastasis; inhibition, to some extent, of tumor growth; and/or relief to some extent, one or more of the symptoms associated with the specific cancer; reduced morbidity and mortality, and improvement in quality of life issues. To the extent the EGFR antagonist may prevent growth and/or kill existing cancer cells, it may be cytostatic and/or cytotoxic. Reduction of these signs or symptoms may also be felt by the patient.

Examples

[105] The examples and preparations provided below further illustrate and exemplify the compounds as disclosed herein and methods of preparing such compounds. It is to be understood that the scope of the present disclosure is not limited in any way by the scope of the following examples and preparations.

[106] The chemical entities described herein can be synthesized according to one or more illustrative schemes herein and/or techniques well known in the art. Unless specified to the contrary, the reactions described herein take place at atmospheric pressure, generally within a temperature range from about -10° C to about 200° C. Further, except as otherwise specified, reaction times and conditions are intended to be approximate, e.g., taking place at about atmospheric pressure within a temperature range of about -10° C to about 200° C over a period that can be, for example, about 1 to about 24 hours; reactions left to run overnight in some embodiments can average a period of about 16 hours.

[107] Isolation and purification of the chemical entities and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography or thick-layer chromatography, or a combination of these procedures. See, e.g., Carey et al. Advanced Organic Chemistry, 3rd Ed., 1990 New York: Plenum Press; Mundy et al., Name Reaction and Reagents in Organic Synthesis, 2nd Ed., 2005 Hoboken, NJ: J. Wiley & Sons. Specific illustrations of suitable separation and isolation procedures are given by reference to the examples hereinbelow. However, other equivalent separation or isolation procedures can also be used.

[108] In all of the methods, it is well understood that protecting groups for sensitive or reactive groups may be employed where necessary, in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T.W. Greene and P.G.M. Wuts

(1999) Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons). These groups may be removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art.

[109] The compounds described herein can be optionally contacted with a pharmaceutically acceptable acid to form the corresponding acid addition salts. Also, the compounds described herein can be optionally contacted with a pharmaceutically acceptable base to form the corresponding basic addition salts.

[110] In some embodiments, disclosed compounds can generally be synthesized by an appropriate combination of generally well-known synthetic methods. Techniques useful in synthesizing these chemical entities are both readily apparent and accessible to those of skill in the relevant art, based on the instant disclosure. Many of the optionally substituted starting compounds and other reactants are commercially available, e.g., from Millipore Sigma or can be readily prepared by those skilled in the art using commonly employed synthetic methodology.

[111] The discussion below is offered to illustrate certain of the diverse methods available for use in making the disclosed compounds and is not intended to limit the scope of reactions or reaction sequences that can be used in preparing the compounds provided herein. The skilled artisan will understand that standard atom valencies apply to all compounds disclosed herein in genus or named compound for unless otherwise specified.

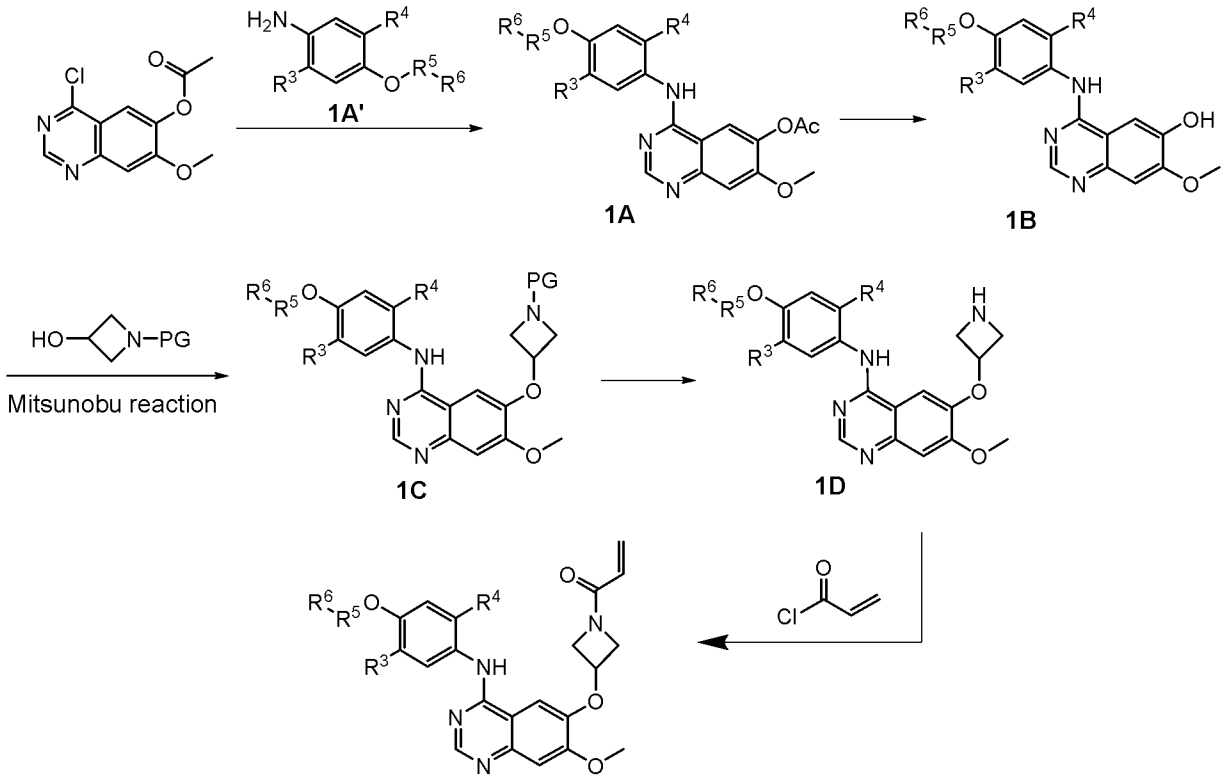
[112] The following abbreviations have the definitions set forth below:

ACN	acetonitrile
CBzCl	benzyloxycarbonyl choride
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
EA	ethyl acetate
IPA	isopropyl alcohol
LC/MS	liquid chromatography/mass spectrometry
NaHMDS	sodium hexamethyldisilylamide
NMR	nuclear magnetic resonance
Pd(dppf)Cl2	[1,1′-bis(diphenylphosphino)ferrocene]dichloro palladium(II)
PE	petroleum ether
Prep-TLC	preparative thin layer chromatography
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TsOH	p-toluenesulfonic acid

General Synthetic Schemes

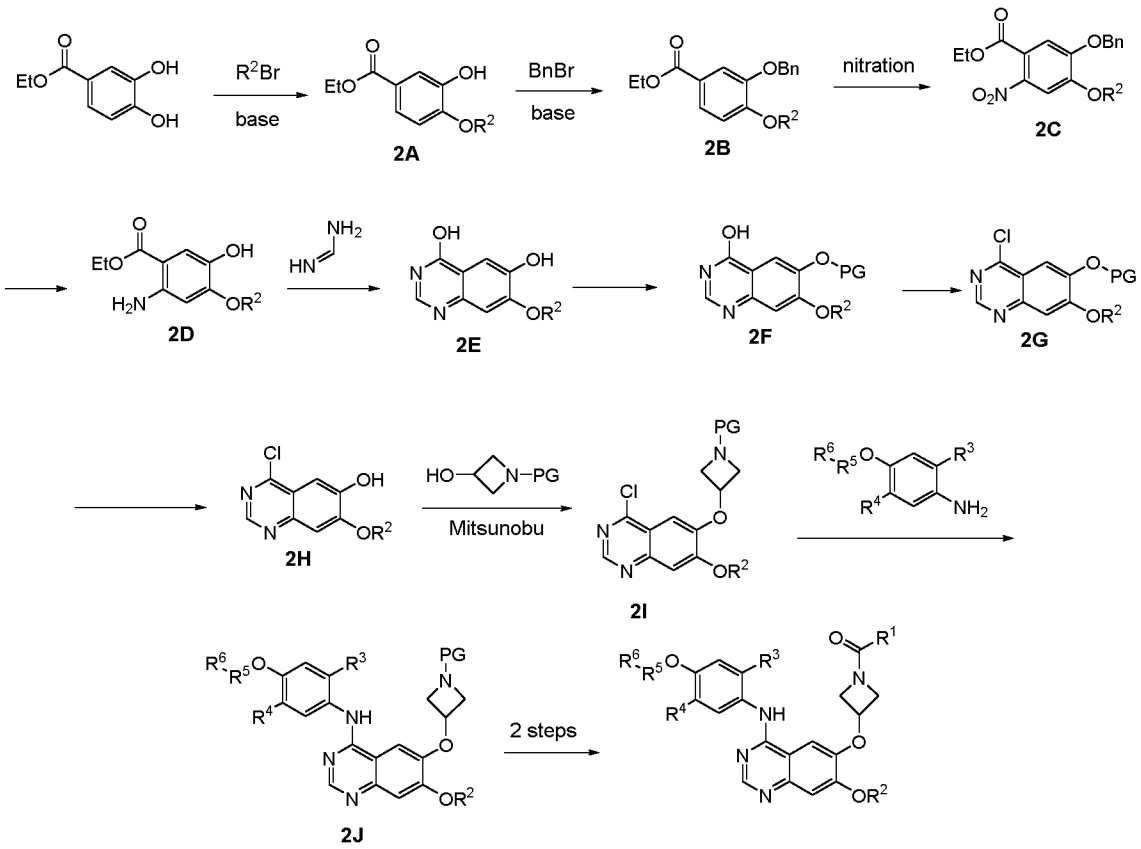
[113] The claimed compounds can be prepared according to the following schemes. The following schemes represent the general methods used in preparing these compounds. However, the synthesis of these compounds is not limited to these representative methods, as they can also be prepared through various other methods by those skilled in the art of synthetic chemistry.

Scheme 1



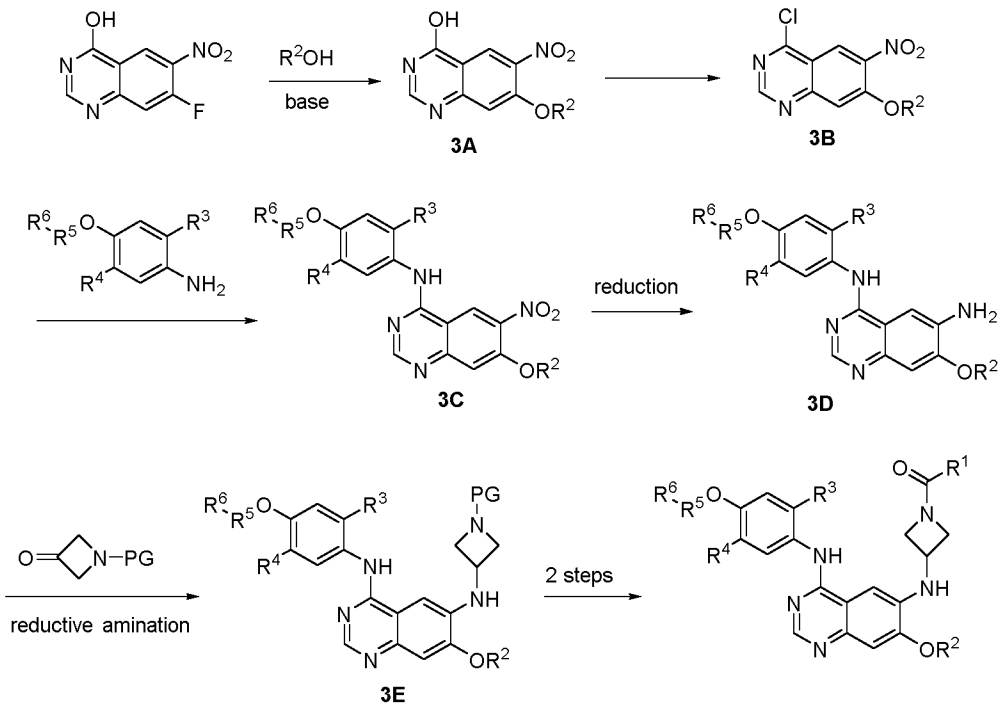
[114] Compounds with R_2 = Me can be prepared according to the synthetic sequence described in Scheme 1. Commercially available 4-Chloro-7-methoxyquinazolin-6-yl acetate can react with anilines represented as in structure **1A'**. This reaction can be assisted with acids such as HCl, p-TsOH, trifluoromethanesulfonic acid or TFA in a solvent such as isopropanol, 1,4-dioxane or DMF to provide intermediate **1A**. Removal of acetate group can be accomplished with a base such as ammonia, NaOH or an acid such as HCl. The phenol intermediate **1B** can undergo a Mitsunobu reaction with N-protected 3-hydroxylazetidine to provide intermediate **1C**. After removal of nitrogen protecting group, amino intermediate **1D** can react with acryloyl chloride to provide desired final compounds.

Scheme 2



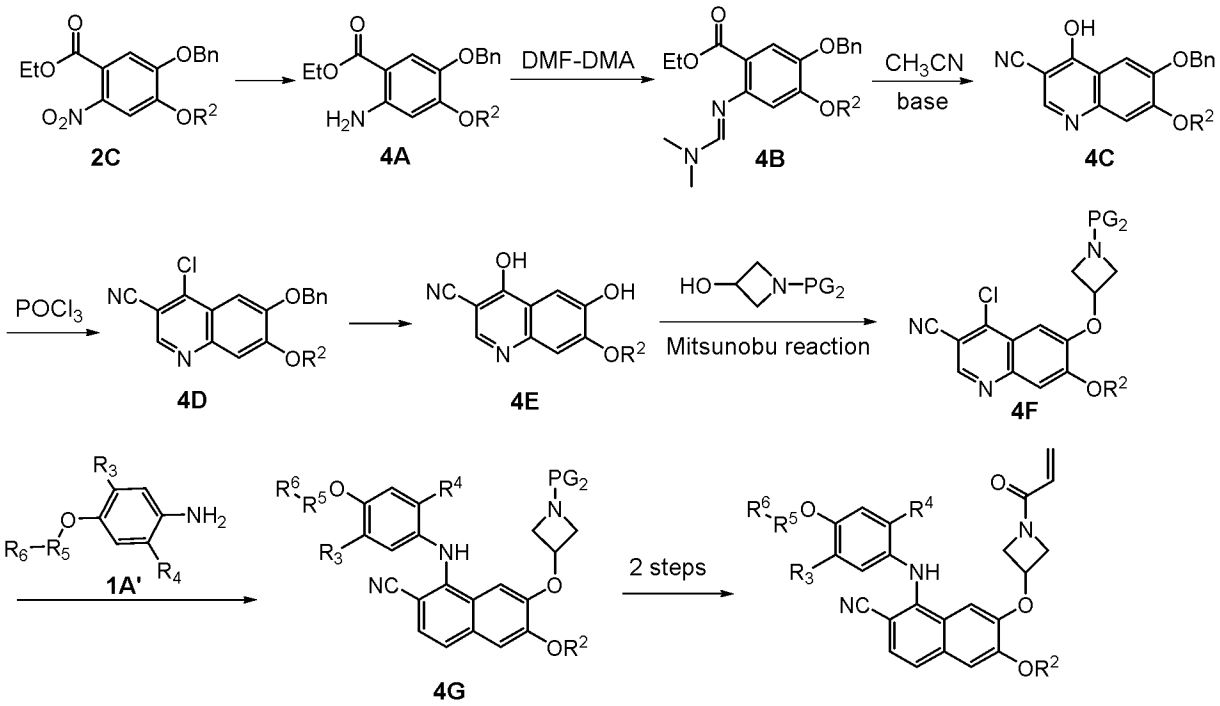
[115] Compounds with variable R_2 groups can be prepared according to the synthetic method described in Scheme 2. Selective alkylation of ethyl 3,4-dihydroxybenzoate with R_2Br in the presence of a base such as K_2CO_3 followed by protection of the phenol hydroxyl group as benzyl ether can provide intermediate **2B**. Nitration of intermediate **2B** with nitric acid followed by reduction of nitro group by hydrogenation catalyzed by Pd/C can provide intermediate **2D** with concomitant removal of Bn protecting group. Cyclization of **2D** with formamidine can provide quinazoline intermediate **2E**. The phenolic hydroxyl group can be protected as an ester such as acetate. Chlorination of intermediate **2F** can be accomplished with $POCl_3$ or $SOCl_2$. After removal of phenol protecting group, Mitsunobu reaction of intermediate **2H** with N-protected 3-hydroxylazetidine can provide intermediate **2I**. The chloro substituent of **2I** can be displaced with aniline represented as structure **1A'** to provide intermediate **2J**. After removal of nitrogen protecting group and reaction with acryloyl chloride can provide the desired final compounds.

Scheme 3



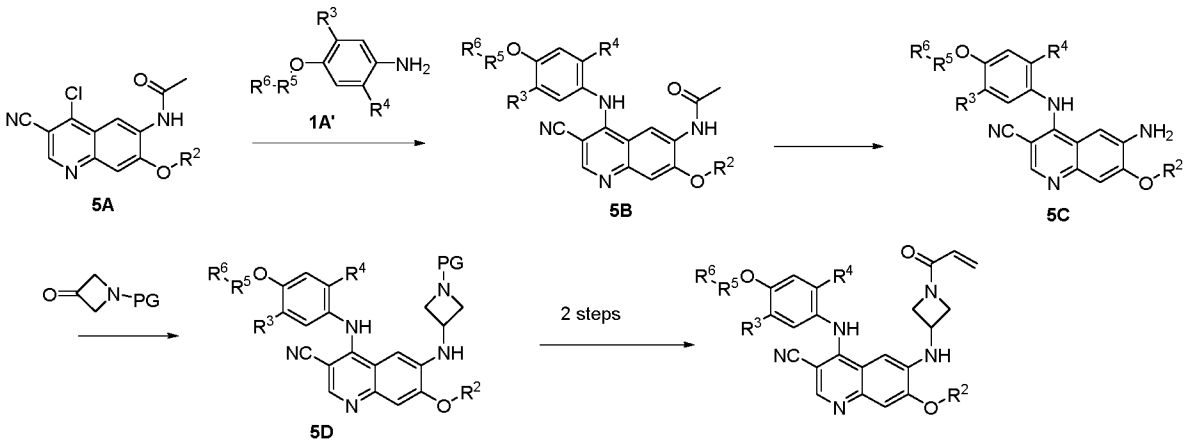
[116] Compounds of Formula 1 with W = NH can be prepared according to the synthetic method described in Scheme 3. 7-fluoro-6-nitroquinazolin-4-ol can react with alcohol R_2OH assisted with a strong base such as NaH, NaHMDS or KO^{t}Bu to provide intermediate **3A**, which can be converted to a chloro intermediate **3B** with $POCl_3$ or $SOCl_2$. Anilines represented by structure **1A'** can react with intermediate **3B** to provide intermediate **3C**, which can be reduced to amino intermediate **3D**. Reductive amination of **3D** with N-protected azetidin-3-one can generate intermediate **3E**. Removal of nitrogen protecting group followed by reaction with acryloyl chloride can provide the desired final compounds.

Scheme 4



[117] Compounds of Formula 1 with Y = CN can be prepared according to the synthetic method described in Scheme 4. Reduction of nitro group of intermediate 2C can be accomplished with reducing agents such as $SnCl_2$ to provide intermediate 4A, which can react with N,N-Dimethylformamide dimethyl acetal (DMF-DMA) to form amidine intermediate **4B**. Cyclization of intermediate 4B with acetonitrile in the presence of a strong base such as n-BuLi can provide nitrile substituted quinoline intermediate **4C**. Conversion of hydroxy group to Cl in **4C** followed by deprotection of benzyl ether can provide intermediate **4E**. Intermediate **4E** can be further converted to the desired final compound in three steps through the intermediates **4F** and **4G** according to the same sequence as described in Scheme 1.

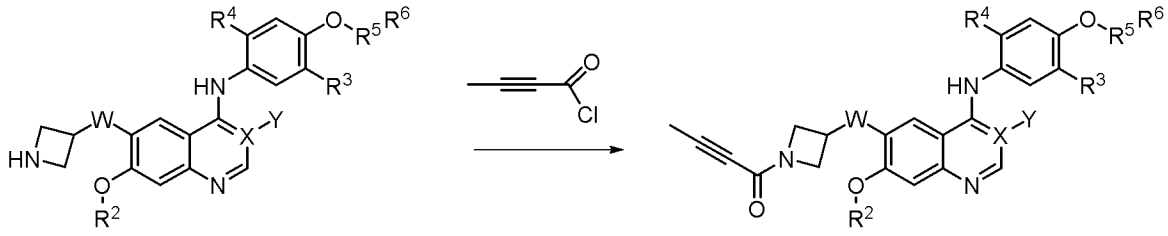
Scheme 5



[118] In the case of preparing 4-arylamino-6-alkylamino-7-alkoxyquinoline-3-carbonitrile, the commercially available **5A** can react with **1A'** under acidic condition to provide **5B**. Deprotection of acetamide can be accomplished under acidic condition to give the desired **5C**. Reductive amination of **5C**

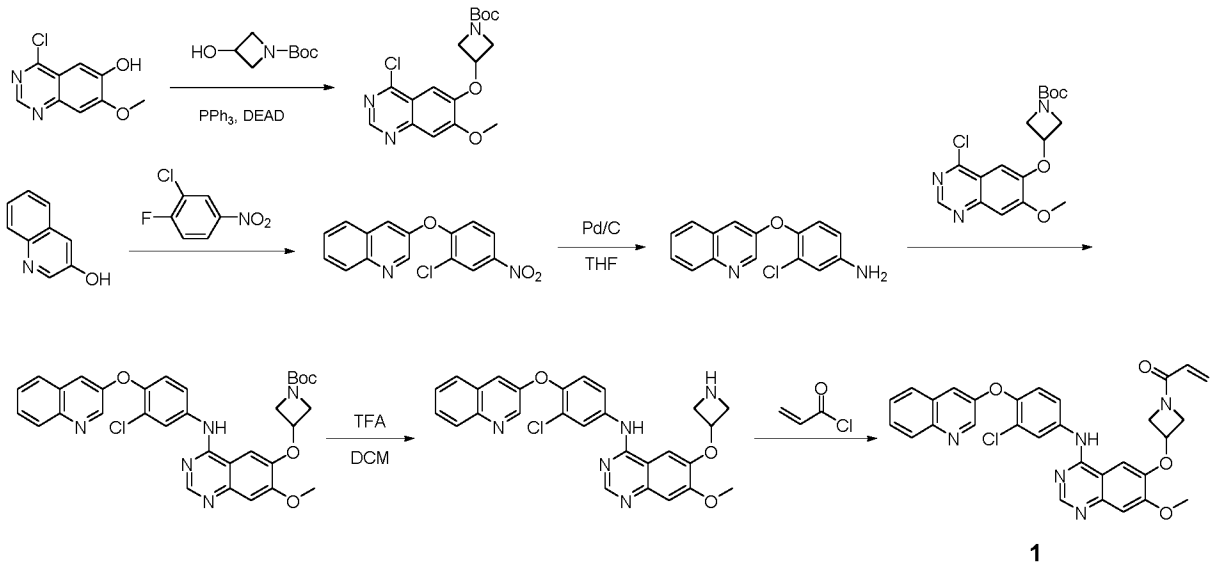
with N-protected azetidine-3-one followed N-deprotection and amide formation will result the desired compound as described in Scheme 5.

Scheme 6



[119] Finally, following scheme 6, the N-acylation of azetidine analog with but-2-tynoyl chloride will result the desired compounds such as compounds 49 and 50 in the Table 1.

Example 1: Preparation of 1-(3-((4-((3-chloro-4-(quinolin-3-yloxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (Compound 1)



Step1: Preparation of tert-butyl 3-((4-chloro-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate

[120] To the solution of 4-chloro-7-methoxyquinazolin-6-ol (5.1 g, 24.2 mmol), tert-butyl 3-hydroxyazetidine-1-carboxylate (4.2 g, 24.2 mmol) and PPh_3 (7.8 g, 29.7 mmol) in dry THF heated at 60°C was added DEAD (5 g. 28.7 mmol) portionwise under N_2. The mixture was stirred at 60°C overnight under N_2. LCMS showed the reaction completed. The mixture was concentrated and purification by flash chromatography using 0-50% EA in PE as eluent. The product was obtained as a white solid (6.0 g, 61.3%). LC/MS: 365.8 $[M+H]^+$.

Step 2: Preparation of 3-(2-chloro-4-nitrophenoxy)quinoline

[121] To a solution of quinolin-3-ol (486 mg, 6.9 mmol) and 2-chloro-1-fluoro-4-nitrobenzene (1.2 g, 6.9 mmol) in acetone (30 mL) was added K_2CO_3 (2.8 g, 20.7 mmol) and the mixture was stirred for 16 hours at room temperature. Water (30 mL) was added and the mixture was filtered, washed with water

(30 mL) and dried to afford the desired compound (2.1 g, 100%) as a yellow solid. LC/MS:300.8 $[M+H]^+$.

Step 3: Preparation of 3-chloro-4-(quinolin-3-yloxy)aniline

[122] The mixture of 3-(2-chloro-4-nitrophenoxy)quinoline (2 g, 6.7 mmol) and Pd/C (1.42 g, 1.3 mmol) in THF (20 mL) was stirred under H_2 for 16 hours at room temperature. The mixture was filtered and concentrated under vacuum to afford the titled product (1 g, 55.2%) as a white solid. LC/MS: 270.8 $[M+H]^+$.

Step 4: Preparation of tert-butyl 3-((4-((3-chloro-4-(quinolin-3-yloxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate

[123] The mixture of 3-chloro-4-(quinolin-3-yloxy)aniline (74 mg, 0.27 mmol), tert-butyl 3-[(4-chloro-7-methoxyquinazolin-6-yl)oxy]azetidine-1-carboxylate (98.7 mg, 0.27 mmol) and HCl/dioxane (1 mL) in t-BuOH (5 mL) was stirred for 16 hours at room temperature. The mixture was concentrated under vacuum to get the crude product, which was purified by flash chromatography (10% MeOH in DCM) to afford the desired compound (110 mg, 67%) as a white solid. LC/MS: 599.6 $[M+H]^+$.

Step 5: Preparation of 6-(azetidin-3-yloxy)-N-(3-chloro-4-(quinolin-3-yloxy)phenyl)-7-methoxyquinazolin-4-amine

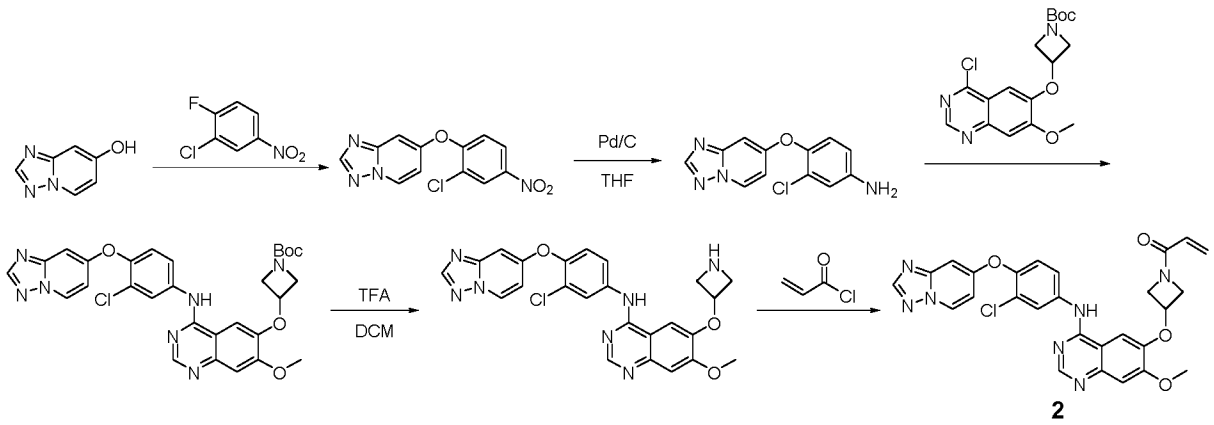
[124] The solution of tert-butyl 3-((4-((3-chloro-4-(quinolin-3-yloxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (110 mg, 0.18 mmol) in DCM (3 mL) was added TFA (1 mL). The reaction mixture was stirred for 16 hours at room temperature. The mixture was concentrated under vacuum to get the crude product (110 mg, 80% purity, 100%) as a brown oil. LC/MS: 499.7 $[M+H]^+$.

Step 6: Preparation of 1-(3-((4-((3-chloro-4-(quinolin-3-yloxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

[125] To a solution of 6-(azetidin-3-yloxy)-N-(3-chloro-4-(quinolin-3-yloxy)phenyl)-7-methoxyquinazolin-4-amine triflate (110 mg, 80% purity, 0.18 mmol) in anhydrous DCM (5 mL) stirred at -78 °C was added DIEA (116 mg, 0.9 mmol), then acryloyl chloride (16.2 mg, 0.18 mmol) in 1 mL of anhydrous DCM was added dropwise. The reaction mixture was stirred at -78°C for 2 hours. LC/MS showed the reaction completed. The mixture was quenched with 20 mL of MeOH and concentrated under vacuum to get the crude product, which was purified by flash chromatography (10% MeOH in DCM) to afford the desired compound (30 mg, 30%) as a white solid. LC/MS: 553.6 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO) δ 9.85 (brs, 1H), 8.90 (d, J = 2.8 Hz, 1H), 8.60 (s, 1H), 8.25 (d, J = 2.3 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.99 – 7.89 (m, J = 14.1, 5.2 Hz, 2H), 7.74 – 7.64 (m, 3H), 7.60 (t, J = 7.2 Hz, 1H), 7.44 (d, J = 8.9 Hz, 1H), 7.30 (s, 1H), 6.45 – 6.31 (m, 1H), 6.22 – 6.10 (m, 1H), 5.72 (dd, J = 10.3, 1.9 Hz, 1H), 5.29 (s, 1H), 4.91 – 4.78 (m, 1H), 4.64 – 4.53 (m, 1H), 4.38 – 4.26 (m, 1H), 3.99 (s, 4H).

Example 2: Preparation of 1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (Compound 2)



Step 1: Preparation of 7-(2-chloro-4-nitrophenoxy)-[1,2,4]triazolo[1,5-a]pyridine

[126] A mixture of [1,2,4]triazolo[1,5-a]pyridin-7-ol (486 mg, 3.6 mmol), 2-chloro-1-fluoro-4-nitrobenzene (631 mg, 3.6 mmol) and K_2CO_3 (1492 mg, 10.8 mmol) in acetone (10 mL) was stirred for 16 hours at room temperature. To the mixture was added water (10 mL), filtered, and the solid was washed with water (10 mL) and dried to afford the desired compound (800 mg, 75.6%) as a pale solid. LC/MS: 290.7 $[M+H]^+$.

Step 2: Preparation of 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chloroaniline

[127] The mixture of 7-(2-chloro-4-nitrophenoxy)-[1,2,4]triazolo[1,5-a]pyridine (770 mg, 2.65 mmol) and Pd/C (564 mg, 0.53 mmol) in THF (20 mL) was stirred under H_2 atmosphere for 16 hours at room temperature. The mixture was filtered and concentrated under vacuum to afford the title product (700 mg, 100%) as a pale solid. LC/MS: 260.9 $[M+H]^+$.

Step 3: Preparation of tert-butyl 3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate

[128] The mixture of 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chloroaniline (71 mg, 0.27 mmol), tert-butyl 3-[(4-chloro-7-methoxyquinazolin-6-yl)oxy]azetidine-1-carboxylate (98.7 mg, 0.27 mmol) and HCl/dioxane (1 mL) in t-BuOH (5 mL) was stirred for 16 hours at room temperature. The mixture was concentrated under vacuum to give a crude product, which was purified by flash chromatography (10% MeOH in DCM) to afford the desired compound (80 mg, 48%) as a white solid. LC/MS: 589.6 $[M+H]^+$.

Step 4: Preparation of N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)-6-(azetidin-3-yloxy)-7-methoxyquinazolin-4-amine

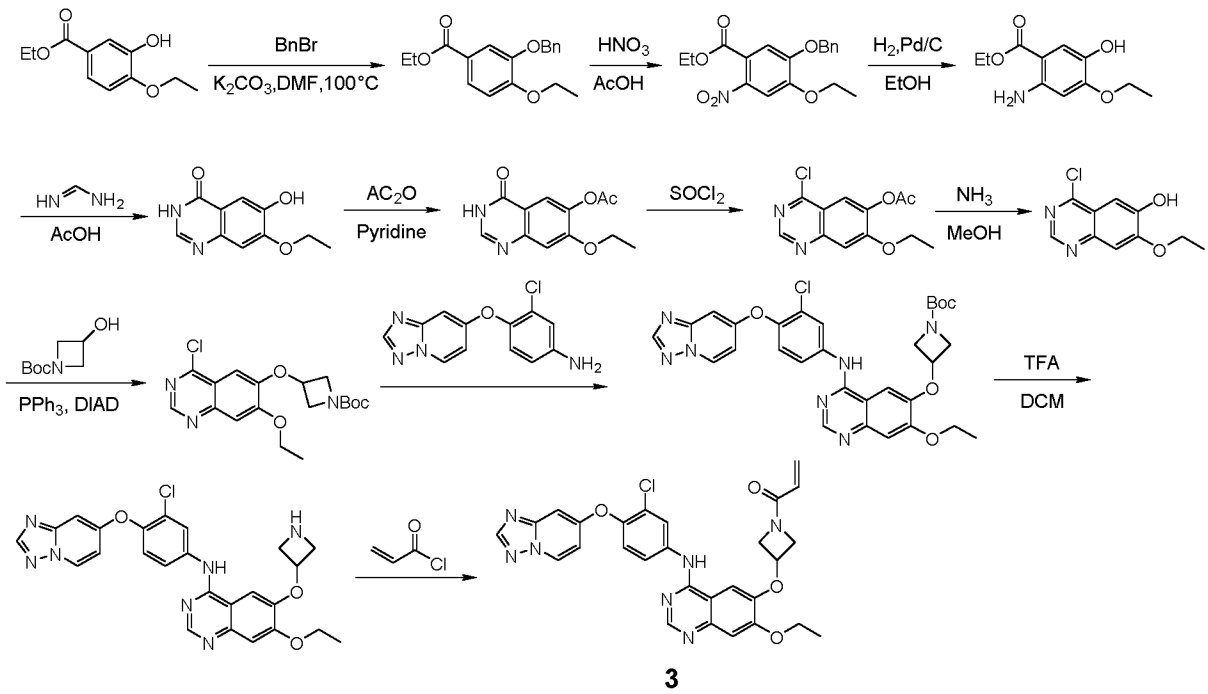
[129] To a solution of tert-butyl 3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (80 mg, 0.14 mmol) in DCM (3 mL) was added TFA (1 mL). The reaction mixture was stirred for 5 hours at room temperature. The mixture was concentrated under vacuum to get the crude product (80 mg, 85% purity, 100%) as a brown oil. LC/MS: 489.7 $[M+H]^+$.

Step 5: Preparation of 1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

[130] To a solution of N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)-6-(azetidin-3-yloxy)-7-methoxyquinazolin-4-amine triflate (80 mg, 85% purity, 0.14 mmol) in anhydrous DCM (5 mL)

stirred at -78°C was added DIEA (90 mg, 0.7 mmol). Then acryloyl chloride (12.6 mg, 0.14 mmol) in 1 mL of anhydrous DCM was added dropwise. The reaction mixture was stirred at -78 °C for 2 hours. LCMS showed the reaction completed. The mixture was quenched with 20 mL of MeOH and concentrated under vacuum to get the crude product, which was purified by flash chromatography (10% MeOH in DCM) to afford the desired compound (30 mg, 39%) as a white solid. LC/MS: 543.6 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 9.86 (brs, 1H), 8.99 (d, J = 7.5 Hz, 1H), 8.61 (s, 1H), 8.43 (s, 1H), 8.25 (d, J = 2.3 Hz, 1H), 7.95 (dd, J = 8.8, 2.4 Hz, 1H), 7.68 (s, 1H), 7.50 (d, J = 8.9 Hz, 1H), 7.30 (s, 1H), 7.09 (dd, J = 7.5, 2.6 Hz, 1H), 6.95 (d, J = 2.5 Hz, 1H), 6.39 (dd, J = 17.0, 10.3 Hz, 1H), 6.15 (dd, J = 17.0, 2.0 Hz, 1H), 5.72 (dd, J = 10.3, 2.0 Hz, 1H), 5.34 – 5.24 (m, 1H), 4.89 – 4.79 (m, 1H), 4.65 – 4.54 (m, 1H), 4.36 – 4.26 (m, 1H), 3.99 (s, 4H).

Example 3: Preparation of 1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-ethoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (Compound 3)



3

Step 1: Preparation of ethyl 3-(benzyloxy)-4-ethoxybenzoate

[131] To a solution of ethyl 4-ethoxy-3-hydroxybenzoate (4.3 g, 20.4 mmol) in 13 mL DMF was added K_2CO_3 (4.3 g, 140.1 mmol) and (bromomethyl)benzene (2.7 mL) under N_2. The resulting mixture was stirred at 100 °C overnight. LC/MS showed the reaction completed. The reaction mixture was concentrated and partitioned between EA and water. The organic phase was dried over sodium sulfate and evaporated to dryness. The crude product was purified by silica gel chromatography using 10-50% EtOAc in hexane as eluent to afford the desired compound (5.2 g, 84%). LC/MS: 300.8 $[M+H]^+$.

Step 2: Preparation of ethyl 5-(benzyloxy)-4-ethoxy-2-nitrobenzoate

[132] To a solution of 3-(benzyloxy)-4-ethoxybenzoate (5.2 g, 17.3 mmol) in HOAc (15 mL) was added HNO_3 (3.5 mL) dropwise under N_2. Then the mixture was heated at 50 °C for 2 hours. The reaction

mixture was diluted with water, and the precipitates were collected by filtration and washed with water to afford the target product as a white solid (5.0 g, 83.3%). LC/MS: 367.7 $[M+Na]^+$.

Step 3: Preparation of ethyl 2-amino-4-ethoxy-5-hydroxybenzoate

[133] To a solution of 5-(benzyloxy)-4-ethoxy-2-nitrobenzoate (5.0 g, 14.5 mmol) in EtOH (200 mL) was added Pd/C (500 mg). The mixture was stirred at room temperature overnight under H_2. LC/MS showed the reaction completed. The suspension was heated at 50 °C for a few minutes, then filtered while hot and the solid was washed with EtOH. The filtrate was concentrated to afford the desired crude compound as white solid (3.3 g). LC/MS: 225.9 $[M+H]^+$.

Step 4: Preparation of 7-ethoxy-6-hydroxyquinazolin-4(3H)-one

[134] To a suspension of ethyl 2-amino-4-ethoxy-5-hydroxybenzoate (3.3 g, 14.6 mmol) in 1,2-dimethoxyethane (50 mL) was added formamidine acetate (3.2 g, 30.7 mmol). The mixture was stirred at 80 °C overnight. LC/MS showed the reaction completed. The reaction mixture was concentrated and diluted with water. The precipitates were collected by filtration and washed with water to afford the target product as a white solid (1.7 g, 56.6%). LC/MS: 206.9 $[M+H]^+$.

Step 5: Preparation of 7-ethoxy-4-oxo-3,4-dihydroquinazolin-6-yl acetate

[135] To a suspension of 7-ethoxy-6-hydroxyquinazolin-4(3H)-one (1.7 g, 8.2 mmol) in Ac_2O (10 mL) was added pyridine (2 mL). The mixture was stirred at 110 °C for 4 hours. LC/MS showed the reaction completed. The reaction mixture was diluted with water, and the precipitates were collected by filtration and washed with water to afford the target product as a white solid (1.2 g, 60%). LC/MS: 248.9 $[M+H]^+$.

Step 6: Preparation of 4-chloro-7-ethoxyquinazolin-6-yl acetate

[136] To a solution of 7-ethoxy-4-oxo-3,4-dihydroquinazolin-6-yl acetate (1.2 g, 4.8 mmol) in $SOCl_2$ (12 mL) added dry DMF (0.2 mL). The mixture refluxed for 2 hours. LCMS showed the reaction completed. The reaction mixture was concentrated, then the residue was diluted with DCM and basified with DIEA. The product was used directly in the next step without further purification (1.5 g). LC/MS: 266.8 $[M+H]^+$.

Step 7: Preparation of 4-chloro-7-ethoxyquinazolin-6-ol

[137] A solution of 4-chloro-7-ethoxyquinazolin-6-yl acetate (1.45 g, crude) in ammonia solution (50 mL,7.0 M solution in MeOH) was stirred at room temperature for 3 hours under N_2. LC/MS showed the reaction completed. The reaction mixture was evaporated and purified with silica gel chromatography using 0-50% EA in PE as eluent to give the titled compound as a white solid (343 mg, 31.5%). LC/MS: 224.9 $[M+H]^+$.

Step 8: Preparation of tert-butyl 3-((4-chloro-7-ethoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate

[138] To a solution of 4-chloro-7-ethoxyquinazolin-6-ol (343 mg, 1.5 mmol), tert-butyl 3-hydroxyazetidine-1-carboxylate (265 mg, 1.5 mmol) and PPh_3 (481 mg, 1.8 mmol) in dry THF heated at 60°C was added DEAD (319 mg. 1.8 mmol) portionwise under N_2. The mixture was stirred overnight at 60 °C under N_2. LC/MS showed the reaction completed. The mixture was concentrated and purification by flash chromatography using 0-50% EA in PE as eluent. The product was obtained as white solid (480 mg, 82.6%). LC/MS: 379.8 $[M+H]^+$.

Step 9: Preparation of tert-butyl 3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-ethoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate

[139] The mixture containing 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chloroaniline (135 mg, 0.52 mmol), tert-butyl 3-((4-chloro-7-ethoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (198 mg, 0.52 mmol) and HCl/dioxane (0.1 mL) in i-PrOH (3 mL) was stirred for 2 hours at room temperature. The mixture was concentrated under vacuum to get the crude product, which was purified by flash column chromatography (10% MeOH in DCM) to afford the desired compound (220 mg, 70%) as a yellow solid. LC/MS: 603.7 $[M+H]^+$.

Step 10: Preparation of N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)-6-(azetidin-3-yloxy)-7-ethoxyquinazolin-4-amine

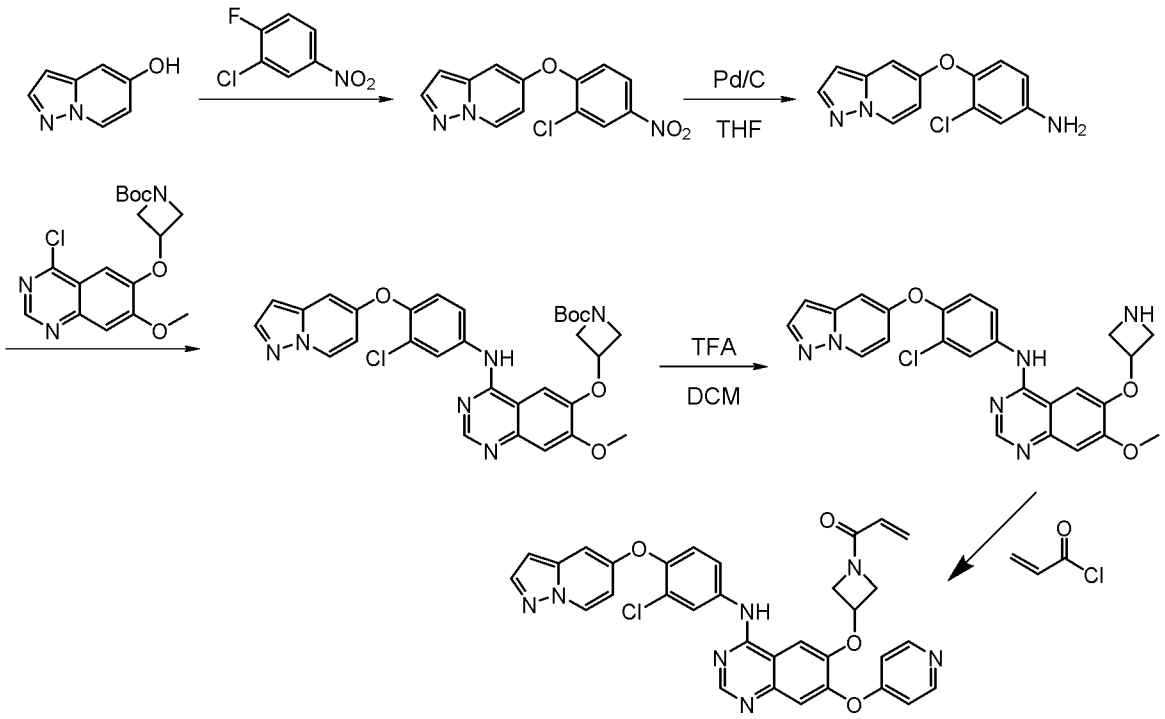
[140] To a solution of tert-butyl 3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-ethoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (220 mg, 0.36 mmol) in DCM (4 mL) was added TFA (2 mL). The reaction mixture was stirred for 5 hours at room temperature. The mixture was concentrated under vacuum to give a crude product (200 mg, 90% purity, 99%) as a yellow solid. LC/MS: 504.2 $[M+H]^+$.

Step 11: Preparation of 1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-ethoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

[141] To a solution of N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)-6-(azetidin-3-yloxy)-7-ethoxyquinazolin-4-amine triflate (200 mg, 0.36 mmol) in anhydrous DCM (5 mL) stirred at -78 °C was added DIEA (139 mg, 1.08 mmol). Then acryloyl chloride (32.4 mg, 0.36 mmol) in 1 mL of anhydrous DCM was added dropwise. The reaction mixture was stirred at -78 °C for 2 hours. LC/MS showed the reaction completed. The mixture was quenched with 20 mL of MeOH and concentrated under vacuum to get the crude product, which was purified by flash chromatography (10% MeOH in DCM) to afford the desired compound (55 mg, 27%) as a yellow solid. LC/MS: 557.6 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO) δ 10.31 (s, 1H), 8.98 (d, J = 7.5 Hz, 1H), 8.62 (s, 1H), 8.43 (s, 1H), 8.32 (d, J = 2.5 Hz, 1H), 8.03 (dd, J = 8.9, 2.5 Hz, 1H), 7.92 (s, 1H), 7.48 (d, J = 8.9 Hz, 1H), 7.28 (s, 1H), 7.08 (dd, J = 7.5, 2.7 Hz, 1H), 6.95 (d, J = 2.6 Hz, 1H), 6.44 - 6.32 (m, 1H), 6.19 - 6.10 (m, 1H), 5.71 (dd, J = 10.3, 2.1 Hz, 1H), 5.39 – 5.32 (m, 1H), 4.92 - 4.84 (m, 1H), 4.63 - 4.55 (m, 1H), 4.31 – 4.21 (m, 3H), 3.97 (dd, J = 11.1, 3.3 Hz, 1H), 1.45 (t, J = 6.9 Hz, 3H).

Example 4: Preparation of 1-(3-((4-((3-chloro-4-(pyrazolo[1,5-a]pyridin-5-yloxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (Compound 4)



Step 1: Preparation of 5-(2-chloro-4-nitrophenoxy)pyrazolo[1,5-a]pyridine

[142] A mixture of pyrazolo[1,5-a]pyridin-5-ol (185 mg, 1.38 mmol), 2-chloro-1-fluoro-4-nitrobenzene (242 mg, 1.38 mmol) and K_2CO_3 (572 mg, 4.14 mmol) in DMF (3 mL) was stirred for 16 hours at 60 °C. The mixture was added with water (5 mL), extracted with EA (10 mL x 3), washed with water (10 mL) and concentrated to afford the desired compound (375 mg, 88%) as a brown solid. LC/MS: 289.8 $[M+H]^+$.

Step 2: Preparation of 3-chloro-4-(pyrazolo[1,5-a]pyridin-5-yloxy)aniline

[143] The mixture of 5-(2-chloro-4-nitrophenoxy)pyrazolo[1,5-a]pyridine (380 mg, 1.3 mmol) and Pd/C (10%, 139 mg, 0.13 mmol) in THF (10 mL) was stirred under H_2 for 3 hours at 40 °C. The mixture was filtered and concentrated under vacuum to afford the title product (350 mg, 100%) as a brown solid. LC/MS: 259.8 $[M+H]^+$.

Step 3: Preparation of tert-butyl 3-((4-((3-chloro-4-(pyrazolo[1,5-a]pyridin-5-yloxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate

[144] The mixture of 3-chloro-4-(pyrazolo[1,5-a]pyridin-5-yloxy)aniline (57 mg, 0.22 mmol), tert-butyl 3-((4-chloro-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (80 mg, 0.22 mmol) and HCl/dioxane (0.1 mL) in i-PrOH (3 mL) was stirred for 2 hours at room temperature. The mixture was concentrated under vacuum to get the crude product, which was purified by flash column chromatography (10% MeOH in DCM) to afford the desired compound (160 mg, 75% purity, 92% yield) as a yellow solid. LC/MS: 588.7 $[M+H]^+$.

Step 4: Preparation of 6-(azetidin-3-yloxy)-N-(3-chloro-4-(pyrazolo[1,5-a]pyridin-5-yloxy)phenyl)-7-methoxyquinazolin-4-amine

[145] The solution of tert-butyl 3-((4-((3-chloro-4-(pyrazolo[1,5-a]pyridin-5-yloxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (150 mg, 0.25 mmol) in DCM (6 mL) was added

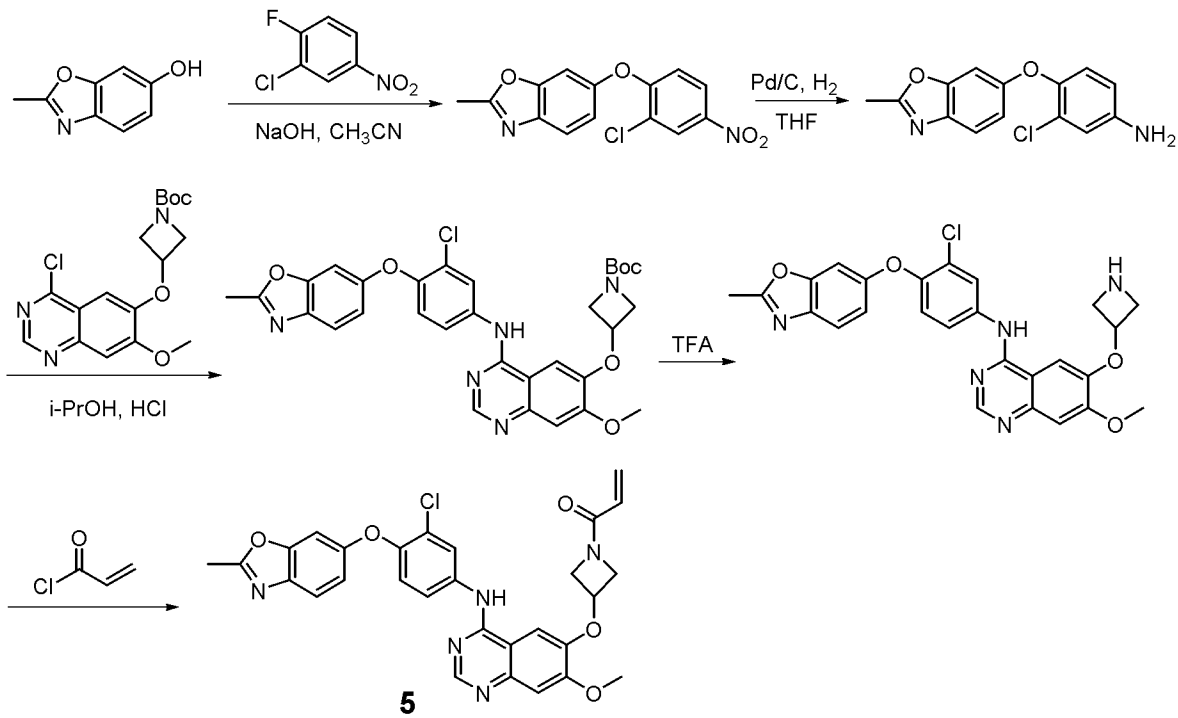
TFA (2 mL). The reaction mixture was stirred for 16 hours at room temperature. The mixture was concentrated under vacuum to get the crude product (200 mg, 60% purity, 98%) as a white solid. LC/MS: 488.7 $[M+H]^+$.

Step 5: Preparation of 1-(3-((4-((3-chloro-4-(pyrazolo[1,5-a]pyridin-5-yloxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

[146] To a solution of 6-(azetidin-3-yloxy)-N-(3-chloro-4-(pyrazolo[1,5-a]pyridin-5-yloxy)phenyl)-7-methoxyquinazolin-4-amine triflate (190 mg, 60% purity, 0.23 mmol) in anhydrous DCM (2 mL) stirred at -78°C was added DIEA (90 mg, 0.7 mmol). Then acryloyl chloride (20.7 mg, 0.14 mmol) in 1 mL of anhydrous DCM was added dropwise. The reaction mixture was stirred at -78°C for 2 hours. LCMS showed the reaction completed. The mixture was quenched with 20 mL of MeOH and concentrated under vacuum to get the crude product, which was purified by flash column chromatography (10% MeOH in DCM) to afford the desired compound (60 mg, 48%) as a white solid. LC/MS: 542.7 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO) δ 9.80 (s, 1H), 8.71 (d, J = 7.5 Hz, 1H), 8.59 (s, 1H), 8.22 (d, J = 2.4 Hz, 1H), 7.95 (d, J = 2.1 Hz, 1H), 7.92 (dd, J = 8.9, 2.5 Hz, 1H), 7.69 (s, 1H), 7.43 (d, J = 8.9 Hz, 1H), 7.30 (s, 1H), 6.85 (d, J = 2.5 Hz, 1H), 6.79 (dd, J = 7.5, 2.7 Hz, 1H), 6.49 – 6.34 (m, 2H), 6.15 (dd, J = 17.0, 2.1 Hz, 1H), 5.72 (dd, J = 10.3, 2.1 Hz, 1H), 5.34 – 5.25 (m, 1H), 4.90 – 4.79 (m, 1H), 4.62 - 4.52 (m, 1H), 4.30 (dd, J = 9.7, 3.2 Hz, 1H), 4.02 - 3.93 (m, 4H).

Example 5: Preparation of 1-(3-((4-((3-chloro-4-((2-methylbenzo[d]oxazol-5-yl)methoxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (Compound 5)



Step 1: Preparation of 6-(2-chloro-4-nitrophenoxy)-2-methylbenzo[d]oxazole

[147] The mixture of 2-methylbenzo[d]oxazol-6-ol (97 mg, 0.65 mmol), 2-chloro-1-fluoro-4-nitrobenzene (115 mg, 0.65 mmol) and NaOH (65 mg, 1.6 mmol) in acetonitrile (5 mL) was stirred at

40°C for 2 hours. LC/MS showed the reaction completed. The mixture was concentrated and partitioned between EA and water. The organic phase was dried over sodium sulfate and evaporated to dryness. The product was used directly to next step without further purification (190 mg, crude). LC/MS: 304.6 $[M+H]^+$.

Step 2: Preparation of 3-chloro-4-((2-methylbenzo[d]oxazol-6-yl)oxy)aniline

[148] To the solution of 6-(2-chloro-4-nitrophenoxy)-2-methylbenzo[d]oxazole (190 mg, crude) in dry THF (10 mL) was added Pd/C (20 mg). The mixture was stirred at 60°C for 2 hours under H_2. The suspension was filtered and the solid was washed with THF. The filtrate was concentrated to afford the desired crude compound as a white solid. The crude product was purified by Prep-TLC (30% EA in PE) to give the desired product (120 mg, 67.4%). LC/MS: 274.8 $[M+H]^+$.

Step 3: Preparation of tert-butyl 3-((4-((3-chloro-4-((2-methylbenzo[d]oxazol-5-yl)methoxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate

[149] The suspension of 3-chloro-4-((2-methylbenzo[d]oxazol-6-yl)oxy)aniline (109 mg, 0.40 mmol) and tert-butyl 3-((4-chloro-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (150 mg, 0.41 mmol) in IPA (12 mL) was added 0.1 mL HCl (4.0 M solution in 1,4-dioxane). The mixture was stirred at room temperature for 2 hours. The mixture was basified with TEA and evaporated. The crude product was purified by Prep-TLC with EA to give the desired product as brown solid (128 mg, 53.3%). LC/MS: 603.6 $[M+H]^+$.

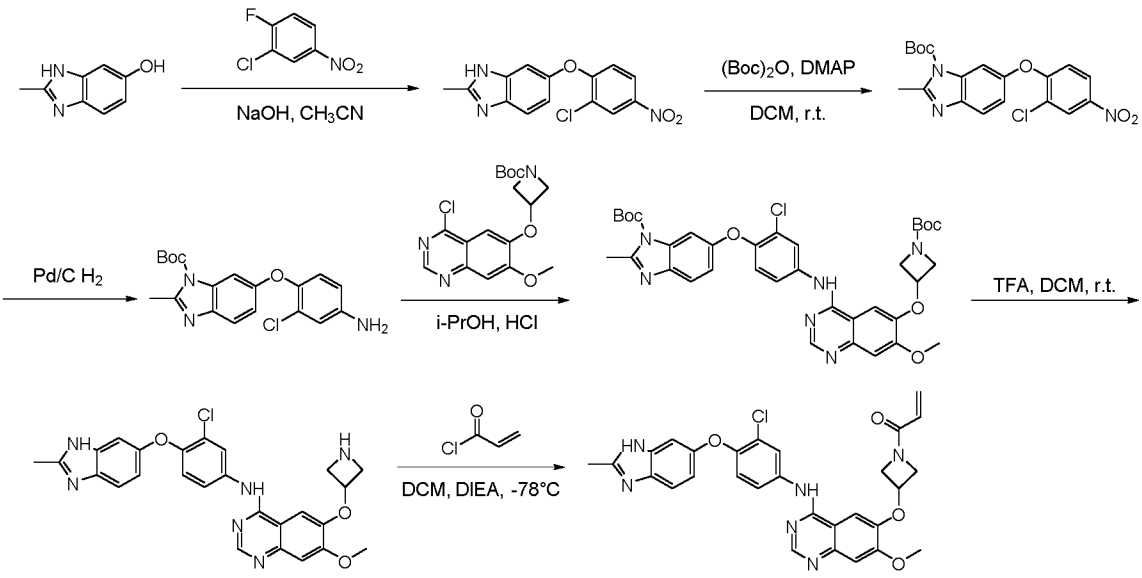
Step 4: Preparation of 6-(azetidin-3-yloxy)-N-(3-chloro-4-((2-methylbenzo[d]oxazol-5-yl)methoxy)phenyl)-7-methoxyquinazolin-4-amine

[150] To a solution of tert-butyl 3-((4-((3-chloro-4-((2-methylbenzo[d]oxazol-5-yl)methoxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (128 mg, 0.21 mmol) in DCM (4 mL) was added TFA (2 mL). The reaction mixture was stirred at room temperature for 2 hours. LC/MS showed the reaction completed. The mixture was concentrated and the product was used directly in the next step without further purification. LC/MS: 503.6 [M+H]+.

Step 5: Preparation of 1-(3-((4-((3-chloro-4-((2-methylbenzo[d]oxazol-5-yl)methoxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

[151] To a solution of 6-(azetidin-3-yloxy)-N-(3-chloro-4-((2-methylbenzo[d]oxazol-5-yl)methoxy)phenyl)-7-methoxyquinazolin-4-amine triflate (crude) in anhydrous DCM (5 mL) stirred at -78°C was added DIEA (55 mg, 0.43 mmol). Then acryloyl chloride (19 mg, 0.21 mmol) in 1 mL of anhydrous DCM was added dropwise. The reaction mixture was stirred at -78°C for 1 hour. The mixture was quenched with 2 mL of MeOH and concentrated under vacuum. The crude product was purified by Prep-TLC with 10% MeOH in DCM to give the desired product (40 mg, 33.9%). LC/MS: 557.6 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 9.89 (s, 1H), 8.61 (s, 1H), 8.13 (d, J = 2.4 Hz, 1H), 7.77 (dd, J = 8.9, 2.5 Hz, 1H), 7.70 – 7.65 (m, 2H), 7.37 (d, J = 2.3 Hz, 1H), 7.29 (s, 1H), 7.21 (d, J = 8.9 Hz, 1H), 7.00 (dd, J = 8.7, 2.3 Hz, 1H), 6.39 (dd, J = 17.0, 10.3 Hz, 1H), 6.15 (dd, J = 17.0, 2.1 Hz, 1H), 5.72 (dd, J = 10.3, 2.1 Hz, 1H), 5.29 – 5.24 (m, 1H), 4.85 – 4.80 (m, 1H), 4.58 (dd, J = 10.9, 6.0 Hz, 1H), 4.33 – 4.27 (m, 1H), 3.99 (s, 3H), 3.98 – 3.93 (m, 1H), 2.60 (s, 3H).

Example 6: Preparation of 1-(3-((4-((3-chloro-4-((2-methyl-1H-benzo[d]imidazol-6-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (Compound 6)



6

Step1: Preparation of 6-(2-chloro-4-nitrophenoxy)-2-methyl-1H-benzo[d]imidazole

[152] To a solution of 2-methyl-1H-benzo[d]imidazol-6-ol (250 mg, 1.69 mmol) in 10 mL ACN was added 2-chloro-1-fluoro-4-nitrobenzene (297 mg, 1.69 mmol) and NaOH (700 mg, 5.07 mmol). The reaction was stirred at 40 °C for 3 hours. After the evaporation of solvent, the residue was purified by flash column chromatography with PE: EA = 1: 2 to afford the desired product. (375 mg, 73%). LC/MS: 303.8 $[M+H]^+$.

Step 2: Preparation of tert-butyl 6-(2-chloro-4-nitrophenoxy)-2-methyl-1H-benzo[d]imidazole-1-carboxylate

[153] To a solution of 6-(2-chloro-4-nitrophenoxy)-2-methyl-1H-benzo[d]imidazole (300 mg, 0.99 mmol) in 15 mL DCM was added $(Boc)_2O$ (238 mg, 1.09 mmol) and DMAP (24 mg, 0.198 mmol). The reaction was stirred at room temperature for 6 hours. The solvent was removed, the residue was purified by flash column chromatography with PE : EA = 1 : 1 to afford the desired product. (300 mg, 74%). LC/MS: 348.1 $[M+H\text{-}t\text{-}Bu]^+$.

Step 3: Preparation of tert-butyl 6-(4-amino-2-chlorophenoxy)-2-methyl-1H-benzo[d]imidazole-1-carboxylate

[154] To a solution of tert-butyl 6-(2-chloro-4-nitrophenoxy)-2-methyl-1H-benzo[d]imidazole-1-carboxylate (300 mg, 0.75 mmol) in 20 mL EA was added Pd/C (80 mg, palladium 10% on carbon, wetted with ca. 55% water). The reaction was stirred at room temperature for 6 hours under H_2. The mixture was filtered out and the solvent was removed to afford the desired product (300 mg, crude). LC/MS: 317.9 $[M+H\text{-}t\text{-}Bu]^+$.

Step 4: Preparation of tert-butyl 6-(4-((6-((1-(tert-butoxycarbonyl)azetidin-3-yl)oxy)-7-methoxyquinazolin-4-yl)amino)-2-chlorophenoxy)-2-methyl-1H-benzo[d]imidazole-1-carboxylate

[155] To a solution of tert-butyl 6-(4-amino-2-chlorophenoxy)-2-methyl-1H-benzo[d]imidazole-1-carboxylate (150 mg, 0.4 mmol) in 5 mL i-PrOH was added tert-butyl 3-((4-chloro-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (161 mg, 0.44 mmol) and 0.1 mL HCl (12 M in H_2O). The reaction was stirred at room temperature for 2 hours. The mixture was adjusted to pH about 7 and the solvent was evaporated. The residue was purified by flash column chromatography with DCM : MeOH = 10 : 1 to afford the desired product (200 mg, 71%), LC/MS: 702.6 $[M+H]^+$.

Step 5: Preparation of 6-(azetidin-3-yloxy)-N-(3-chloro-4-((2-methyl-1H-benzo[d]imidazol-6-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine

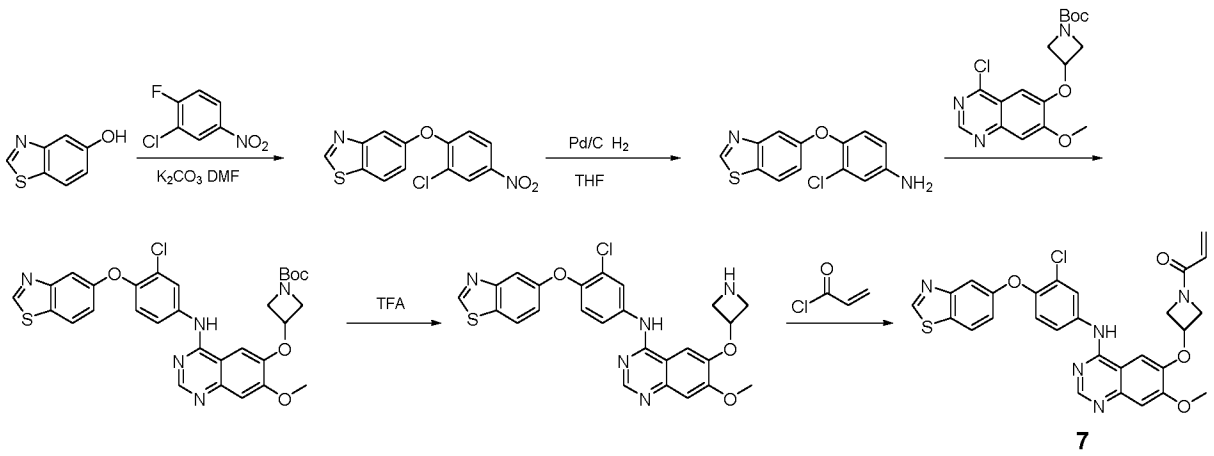
[156] To a solution of tert-butyl 6-(4-((6-((1-(tert-butoxycarbonyl)azetidin-3-yl)oxy)-7-methoxyquinazolin-4-yl)amino)-2-chlorophenoxy)-2-methyl-1H-benzo[d]imidazole-1-carboxylate (200 mg, 0.28 mmol) in 3 mL of DCM was added 1 mL of TFA. The reaction was stirred at room temperature for 1 hour. The solvent was removed to afford the desired product (200 mg, crude). LC/MS: 502.7 $[M+H]^+$.

Step 6: Preparation of 1-(3-((4-((3-chloro-4-((2-methyl-1H-benzo[d]imidazol-6-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

[157] To a solution of 6-(azetidin-3-yloxy)-N-(3-chloro-4-((2-methyl-1H-benzo[d]imidazol-6-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine triflate (200 mg, 0.397 mmol) in 5 mL anhydrous DCM was added DIEA (135 mg, 1.044 mmol) at -78 °C. Then acryloyl chloride (31 mg, 0.397 mmol) was added. The reaction was stirred at -78 °C for 30 minutes under Ar. The solvent was removed and the residue was purified by Prep-TLC with DCM : MeOH = 10 : 1 to afford the desired product. (12.5 mg, 5.6 %). LC/MS: 556.6 [M+H]+.

^{1}H NMR (400 MHz, DMSO) δ 12.28 (s, 1H), 9.54 (s, 1H), 8.51 (s, 1H), 8.08 (d, J = 2.5 Hz, 1H), 7.69 (dd, J = 8.9, 2.6 Hz, 1H), 7.57 (s, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.27 (s, 1H), 7.13 – 6.96 (m, 2H), 6.86 (dd, J = 8.6, 2.3 Hz, 1H), 6.38 (dd, J = 17.0, 10.3 Hz, 1H), 6.14 (dd, J = 17.0, 2.1 Hz, 1H), 5.71 (dd, J = 10.3, 2.1 Hz, 1H), 5.24 (s, 1H), 4.84 – 4.77 (m, 1H), 4.56 (dd, J = 11.0, 6.5 Hz, 1H), 4.29 (d, J = 6.8 Hz, 1H), 3.94 – 3.99 (m, 4H), 2.47 (s, 3H).

Example 7: Preparation of 1-(3-((4-((4-(benzo[d]thiazol-5-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (Compound 7)



Step 1: Preparation of 5-(2-chloro-4-nitrophenoxy)benzo[d]thiazole

[158] The mixture of benzo[d]thiazol-5-ol (130 mg, 0.86 mmol), 2-chloro-1-fluoro-4-nitrobenzene (151 mg, 0.86 mmol) and K_2CO_3 (238 mg, 1.7 mmol) in DMF (5 mL) was stirred at room temperature overnight. LCMS showed the reaction completed. The mixture was concentrated under vacuum. The crude product was purified by Prep-TLC (10% EA in PE) to give the desired product as a brown solid (200 mg, 75.7%). LC/MS: 306.7 $[M+H]^+$.

Step 2: Preparation of 4-(benzo[d]thiazol-5-yloxy)-3-chloroaniline

[159] To the solution 5-(2-chloro-4-nitrophenoxy)benzo[d]thiazole (200 mg, 0.65 mmol) in dry THF (10 mL) was added Pd/C (20 mg). The mixture was stirred at 60 °C for 2 hours under H_2. LCMS showed the reaction completed. The suspension was filtered and the solid was washed with THF. The filtrate was concentrated to afford the desired crude compound. The crude materail was purified by Prep-TLC (30% EA in PE) to give the desired product (130 mg, 72.2%). LC/MS: 277.1 $[M+H]^+$.

Step 3: Preparation of tert-butyl 3-((4-((4-(benzo[d]thiazol-5-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate

[160] The suspension of 4-(benzo[d]thiazol-5-yloxy)-3-chloroaniline (105 mg, 0.38 mmol) and tert-butyl 3-((4-chloro-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (138 mg, 0.38 mmol) in IPA (8 mL) was added 0.1 mL HCl (4.0 M solution in 1,4-dioxane). The mixture was stirred at room temperature for 2 hours. The mixture was basified with TEA and evaporated. The crude product was purified by Prep-TLC with EA to give the desired product as a brown solid (130 mg, 56.5%). LC/MS: 605.4 $[M+H]^+$.

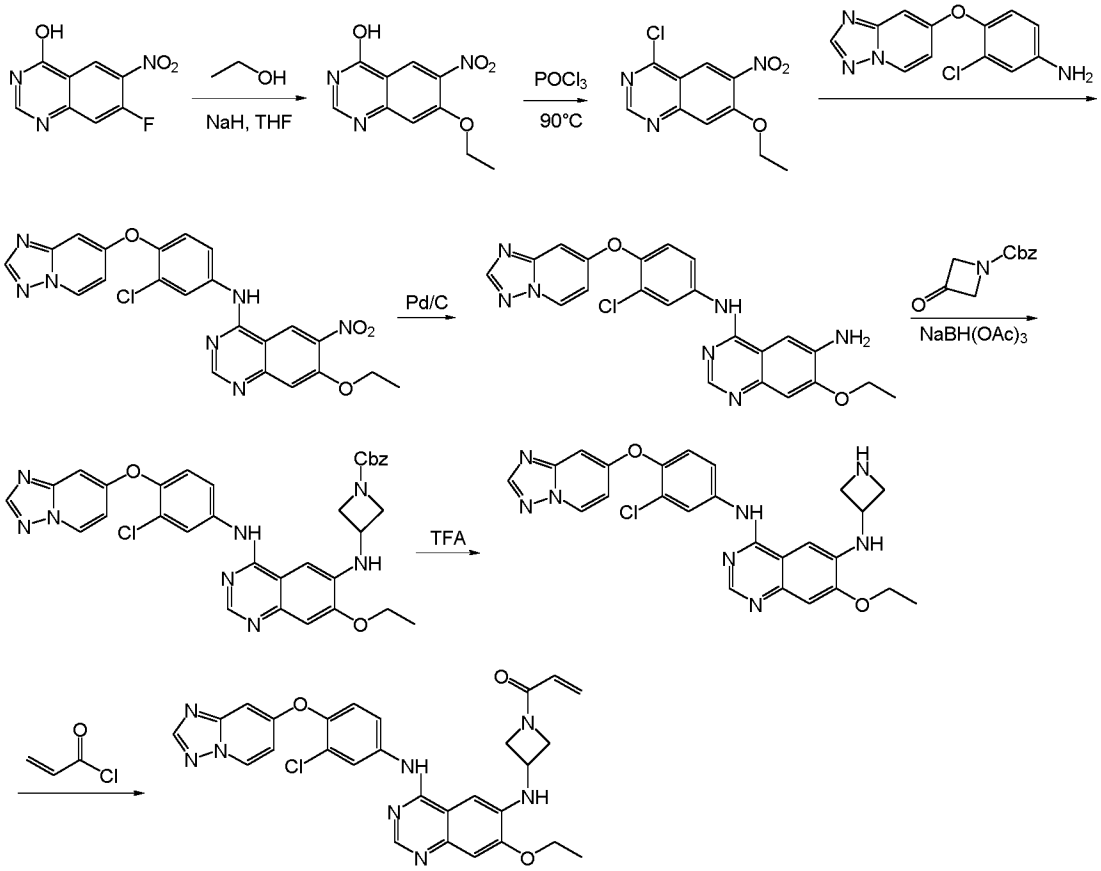
Step 4: Preparation of 6-(azetidin-3-yloxy)-N-(4-(benzo[d]thiazol-5-yloxy)-3-chlorophenyl)-7-methoxyquinazolin-4-amine

[161] To a solution containing tert-butyl 3-((4-((4-(benzo[d]thiazol-5-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (130 mg, 0.21 mmol) in DCM (6 mL) was added TFA (2 mL). The reaction mixture was stirred for 2 hours at room temperature. LCMS showed the reaction completed. The mixture was concentrated and the crude product was used directly in the next step without further purification. LC/MS: 506.1 $[M+H]^+$.

Step 5: Preparation of 1-(3-((4-((4-(benzo[d]thiazol-5-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

[162] To a solution of 6-(azetidin-3-yloxy)-N-(4-(benzo[d]thiazol-5-yloxy)-3-chlorophenyl)-7-methoxyquinazolin-4-amine triflate (crude) in anhydrous DCM (5 mL) stirred at -78 °C was added DIEA (55 mg, 0.43 mmol). Then acryloyl chloride (19 mg, 0.21 mmol) in 1 mL of anhydrous DCM was added dropwise. The reaction mixture was stirred at -78 °C for 1 hour. The mixture was quenched with 2 mL of MeOH and concentrated under vacuum. The crude product was purified via Prep-TLC using DCM/MeOH (10:1) as eluent to give the title compound (60 mg, 50%). LC/MS: 559.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 9.89 (s, 1H), 9.45 (s, 1H), 8.63 (s, 1H), 8.24 – 8.12 (m, 2H), 7.79 (d, J = 7.1 Hz, 1H), 7.58 (d, J = 28.1 Hz, 2H), 7.30 (t, J = 10.1 Hz, 3H), 6.40 (dd, J = 17.0, 10.3 Hz, 1H), 6.16 (d, J = 16.2 Hz, 1H), 5.73 (d, J = 10.3 Hz, 1H), 5.25 (s, 1H), 4.91 – 4.75 (m, 1H), 4.65 – 4.51 (m, 1H), 4.31 (d, J = 6.7 Hz, 1H), 4.00 (s, 4H).

Example 8: Preparation of 1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-ethoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one (Compound 8)



Step 1: Preparation of 7-ethoxy-6-nitroquinazolin-4-ol

[163] To a solution of ethanol (0.24 g, 5.3 mmol) in THF (20 mL) was added NaH (286 mg, 7.2 mmol) at 0 °C. After stirring for 0.5 hours, a solution of 7-fluoro-6-nitroquinazolin-4-ol (1 g, 4.8 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated, diluted with water, adjusted pH to 3 with 1N HCl. The precipitates were collected by filtration and washed with 15 mL of water to afford the target product as a white solid. (1.1 g, 95%). LC/MS:235.9 $[M-H]^+$.

Step 2: Preparation of 4-chloro-7-ethoxy-6-nitroquinazoline

[164] A solution of 7-ethoxy-6-nitroquinazolin-4-ol (150 mg, 0.64 mmol) in $POCl_3$ (5 mL) was stirred overnight at 90 °C. The reaction solution was concentrated under vacuum to afford the target product was a yellow solid (160 mg, 93%). LC/MS: 249.9 $[M+H]^+$.

Step 3: Preparation of N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)-7-ethoxy-6-nitroquinazolin-4-amine

[165] To a solution of 4-chloro-7-ethoxy-6-nitroquinazoline (200 mg, 0.79 mmol) and HCl/dioxane (0.1 mL) in i-PrOH (4 mL) stirred at room temperature was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chloroaniline (205 mg, 0.79 mmol). The reaction mixture was stirred overnight at room temperature. The resulting solution was concentrated under vacuum. The residue was purified with silica gel column (12 g) with MeOH/DCM (1/10) as eluent to afford target product as a yellow solid. (180 mg, 47%) LC/MS:477.6 $[M+H]^+$.

Step 4: Preparation of N-4-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)-7-ethoxyquinazoline-4,6-diamine

[166] The mixture of N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)-7-ethoxy-6-nitroquinazolin-4-amine (170 mg, 0.36 mmol) and Pd/C (10%, 76 mg, 0.072 mmol) in THF (2 mL) was stirred at 40 °C under H_2 atmosphere for 3 hours. The mixture was filtered. The filtrate was concentrated under vacuum to afford the target product as a yellow solid. (140 mg, 85%). LC/MS: 447.7 $[M+H]^+$.

Step 5: Preparation of benzyl 3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-ethoxyquinazolin-6-yl)amino)azetidine-1-carboxylate

[167] A solution of N-4-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)-7-ethoxyquinazoline-4,6-diamine (140 mg, 0.31 mmol) and benzyl 3-oxoazetidine-1-carboxylate (76.3 mg, 0.37 mmol) in TFA (3 mL) was stirred for 30 minutes. Then sodium triacetoxyborohydride (68.5 mg, 0.32 mmol) was added. The mixture was stirred for 2 hours at room temperature, then 4 mL of water was added dropwise. The resulting solution was extracted with ethyl acetate (3x10 mL). The organic layers were combined, washed with water (3x10 mL), dried and concentrated under vacuum to afford the desired product as a yellow solid (55 mg, 27%). LC/MS: 636.6 $[M+H]^+$.

Step 6: Preparation of N-4-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)-N-6-(azetidin-3-yl)-7-ethoxyquinazoline-4,6-diamine

[168] A solution of benzyl 3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-ethoxyquinazolin-6-yl)amino)azetidine-1-carboxylate (50 mg, 0.08 mmol) in TFA (2 mL) was stirred at 90 °C overnight. The reaction solution was concentrated under vacuum to afford desired product as a yellow solid. (40 mg, 98%), LC/MS: 502.7 $[M+H]^+$.

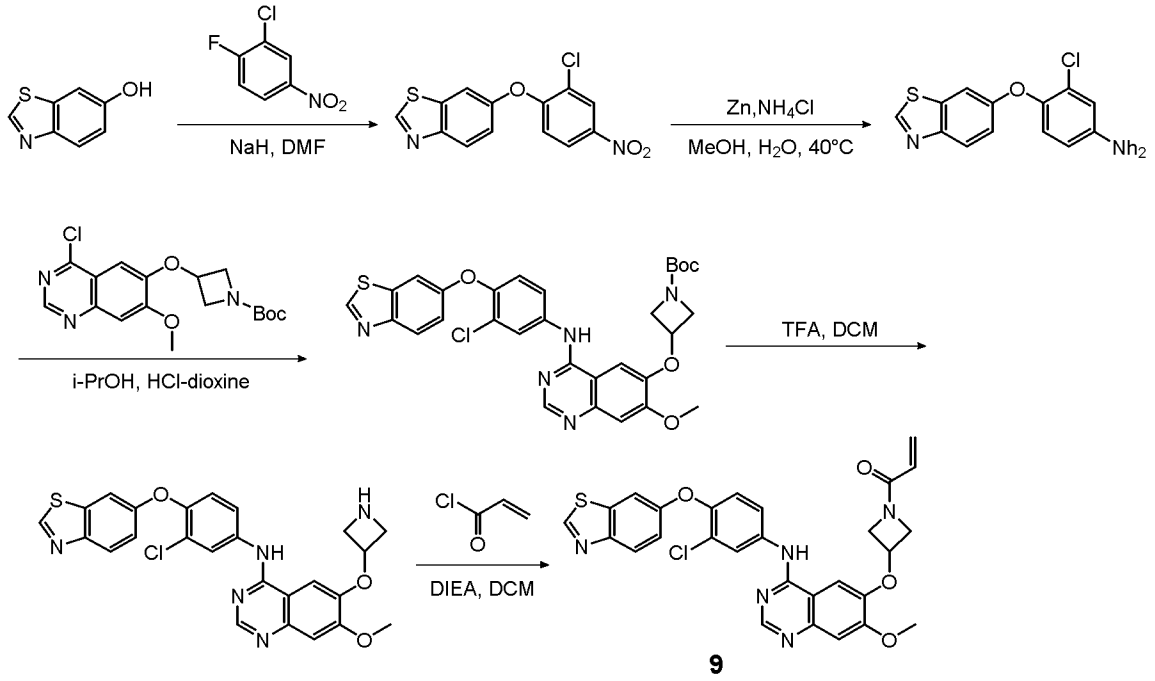
Step 7: Preparation of 1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-ethoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one

[169] To a solution of N-4-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)-N-6-(azetidin-3-yl)-7-ethoxyquinazoline-4,6-diamine triflate (40 mg, 0.08 mmol) and DIEA (31 mg, 0.24 mmol) in DCM (2 mL) stirred at -78 °C was added prop-2-enoyl chloride (7.2 mg, 0.08 mmol) dropwise. The reaction

mixture was extracted with water (3x15 mL), dried with Na_2SO_4 and concentrated under vacuum. The residue was purified by Prep-TLC (MeOH/DCM=1/10) to afford the desired product as a yellow solid. (10 mg, 21%), LC/MS:556.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 10.71 (brs, 1H), 8.99 (d, J = 7.4 Hz, 1H), 8.66 (s, 1H), 8.43 (s, 1H), 8.23 (d, J = 2.4 Hz, 1H), 7.95 (dd, J = 8.9, 2.4 Hz, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.22 (s, 1H), 7.09 (dd, J = 7.5, 2.6 Hz, 1H), 6.97 (d, J = 2.5 Hz, 1H), 6.56 (d, J = 6.7 Hz, 1H), 6.43 – 6.33 (m, 1H), 6.20 – 6.09 (m, 1H), 5.70 (dd, J = 10.3, 2.1 Hz, 1H), 4.79 (t, J = 8.0 Hz, 1H), 4.69 – 4.61 (m, 1H), 4.52 – 4.44 (m, 1H), 4.37 – 4.25 (m, 2H), 4.22 – 4.15 (m, 1H), 3.99 (dd, J = 10.0, 5.2 Hz, 1H), 1.50 (t, J = 6.9 Hz, 3H).

Example 9: Preparation of 1-(3-((4-((4-(benzo[d]thiazol-6-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (Compound 9)



9

Step 1: Preparation of 6-(2-chloro-4-nitrophenoxy)-1,3-benzothiazole

[170] 1,3-Benzothiazol-6-ol (480 mg, 3.1 mmol) was added to a slurry of sodium hydride (160 mg of a 60% dispersion in oil, 4 mmol) in DMF (15 mL) at 0 °C. After stirring for 5 minutes, 2-chloro-1-fluoro-4-nitrobenzene (500 mg, 2.85 mmol) was added and the reaction mixture was warmed to room temperature. The reaction mixture was first stirred at room temperature for 3 hours, and then stirred at 60 °C for 16 hours. After cooling to room temperature, the mixture was evaporated in vacuo. The crude product was purified by flash column chromatography with hexane: EtOAc= 1:1. The title product was obtained as yellow solid (860 mg, 78%). LC/MS: 306.7 $[M+H]^+$.

Step 2: Preparation of 4-(1,3-benzothiazol-6-yloxy)-3-chloroaniline

[171] Zn powder (664 mg, 10.16 mmol) was added to a mixture of 2-(2-chloro-4-nitrophenoxymethyl)-1,3-thiazole (780 mg, 2.54 mmol) in 3:1 MeOH: saturated aqueous NH_4Cl solution (20 mL). After stirring for 2 hours, the reaction mixture was filtered and the filtrate was concentrated. The crude product was

purified by flash column chromatography with hexane: EtOAc= 1:1. The title product was obtained as yellow solid (657 mg, 93%). LC/MS: 276.8 $[M+H]^+$.

Step 3: Preparation of tert-butyl 3-((4-((4-(benzo[d]thiazol-6-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate

[172] A round-bottom flask containing a mixture of 4-(1,3-benzothiazol-6-yloxy)-3-chloroaniline (80 mg, 0.29 mmol), tert-butyl 3-((4-chloro-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (106 mg, 0.29 mmol) and i-PrOH (10 mL) was stirred at room temperature, then HCl in dioxane (0.3 mL, 4 N) was added to the mixture. The mixture was continuously stirred at room temperature for 1 hour. The mixture was filtered and concentrated in vacuo. The crude product was purified by flash column chromatography with DCM: MeOH= 10:1. The title product was obtained as yellow solid (164 mg, 93%). LC/MS: 605.5 $[M+H]^+$.

Step 4: Preparation of 6-(azetidin-3-yloxy)-N-[4-(1,3-benzothiazol-6-yloxy)-3-chlorophenyl]-7-methoxyquinazolin-4-amine

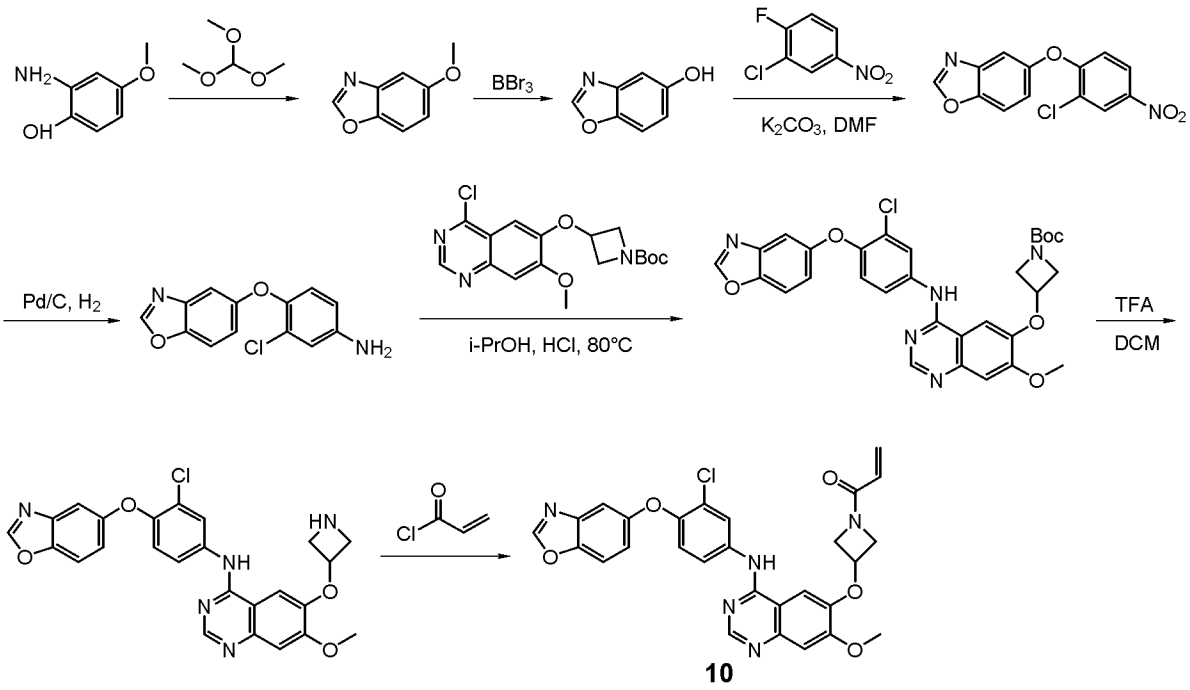
[173] A solution of tert-butyl 3-((4-((4-(benzo[d]thiazol-6-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (134 mg, 0.22 mmol), TFA (3 mL) and DCM (9 mL) was stirred at room temperature for 2 hours. The mixture was evaporated in vacuo and used directly in the subsequent step without further purification. LC/MS: 505.6 $[M+H]^+$.

Step 5: Preparation of 1-{3-[(4-{[4-(1,3-benzothiazol-6-yloxy)-3-chlorophenyl]amino}-7-methoxyquinazolin-6-yl)oxy]azetidin-1-yl}prop-2-en-1-one

[174] A solution of 6-(azetidin-3-yloxy)-N-[4-(1,3-benzothiazol-6-yloxy)-3-chlorophenyl]-7-methoxyquinazolin-4-amine triflate (180 mg, 0.36 mmol) and DIEA (140 mg, 1.08 mmol) in DCM (10 mL) is cooled to -78 °C in a dry ice-EA bath under argon. To the stirred solution was added prop-2-enoyl chloride (33 mg, 0.36 mmol). The mixture was stirred for 0.5 hours and warmed to room temperature. The mixture was evaporated in vacuo and purified by Prep-HPLC. The title product was obtained as yellow solid (10.4 mg, 5.06%). LC/MS: 559.6 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO) δ 10.83 (brs, 1H), 9.34 (s, 1H), 8.85 (brs, 1H), 8.13 (d, J = 8.9 Hz, 1H), 8.06 (d, J = 2.3 Hz, 1H), 7.83 (d, J = 2.4 Hz, 1H), 7.81 – 7.74 (m, 1H), 7.71 (dd, J = 8.9, 2.3 Hz, 1H), 7.41 – 7.35 (m, 1H), 7.32 – 7.26 (m, 2H), 6.43 – 6.33 (m, 1H), 6.15 (dd, J = 17.0, 1.9 Hz, 1H), 5.72 (dd, J = 10.3, 1.9 Hz, 1H), 5.27 (s, 1H), 4.86 – 4.81 (m, 1H), 4.62 – 4.57 (m, 1H), 4.34 – 4.29 (m, 1H), 4.03 (s, 3H), 3.99 – 3.94 (m, 1H).

Example 10: Preparation of 1-(3-((4-((4-(benzo[d]oxazol-5-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (Compound 10)



Step 1: Preparation of 5-methoxybenzo[d]oxazole

[175] A mixture of 2-amino-4-methoxyphenol (500 mg, 3.6 mmol) in trimethoxymethane (36 mL) was stirred at 110 °C overnight. The mixture was evaporated. The crude product was purified by silica gel chromatography using 10-30% EtOAc in hexane as eluent to afford the desired compound (398 mg, 74.2%). LC/MS: 150.0 $[M+H]^+$.

Step 2: Preparation of benzo[d]oxazol-5-ol

[176] To a solution of 5-methoxybenzo[d]oxazole (450 mg, 3.0 mmol) in DCM (20 mL) was added of tribromoborane (4.2 g, 1.5 mmol) dropwise at 0 °C. The mixture was stirred at room temperature overnight. LCMS showed the reaction was complete. The mixture was evaporated. The crude product was purified by silica gel chromatography using 0-10% MeOH in DCM as eluent to afford the desired compound (300 mg, 74.1%). LC/MS: 136.0 $[M+H]^+$.

Step 3: Preparation of 5-(2-chloro-4-nitrophenoxy)benzo[d]oxazole

[177] To a solution of benzo[d]oxazol-5-ol (300 mg, 2.22 mmol), 2-chloro-1-fluoro-4-nitrobenzene (388.5 mg, 2.22 mmol) and in DCM (10 mL) was added K_2CO_3 (919 mg, 6.66 mmol). The mixture was stirred at room temperature overnight. LCMS showed the reaction completed. The mixture was evaporated and the crude product was purified by silica gel column chromatography using 0-10% MeOH in DCM as eluent to afford the desired compound (500 mg, 77.7%). LC/MS: 290.8 $[M+H]^+$.

Step 4: Preparation of 4-(benzo[d]oxazol-5-yloxy)-3-chloroaniline

[178] To a solution of 5-(2-chloro-4-nitrophenoxy)benzo[d]oxazole (580 mg, 2.0 mmol) in THF (20 mL) was added Pd/C (200 mg) portion-wise. The reaction mixture was stirred under hydrogen at room temperature for 1 hour. The reaction mixture was filtered and evaporated in vacuo to give the desired product as a yellow solid (290 mg, 55.8 %). LC/MS: 260.9 $[M+H]^+$.

Step 5: Preparation of tert-butyl 3-((4-((4-(benzo[d]oxazol-5-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate

[179] To a solution of 4-(benzo[d]oxazol-5-yloxy)-3-chloroaniline (260 mg, 1.0 mmol), tert-butyl 3-((4-chloro-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (366 mg, 1.0 mmol) in i-PrOH (30 mL) was added two drops of HCl-dioxane. The mixture was stirred at room temperature for 1.5 hours. The mixture was evaporated, and the crude product was purified by Prep-TLC using with DCM:MeOH = 10 :1 to afford the desired compound (320 mg, 54.2%). LC/MS: 589.7 $[M+H]^+$.

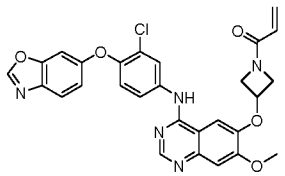
Step 6: Preparation of 6-(azetidin-3-yloxy)-N-(4-(benzo[d]oxazol-5-yloxy)-3-chlorophenyl)-7-methoxyquinazolin-4-amine

[180] To a solution of tert-butyl 3-((4-((4-(benzo[d]oxazol-5-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (300 mg, 0.51 mmol) in DCM (10 mL) was added TFA (3 mL). The mixture was stirred at room temperature for 1 hour. The residue was concentrated in vacuum to afford the desired compound (150.0 mg, 60%). LC/MS: 489.7 $[M+H]^+$.

Step 7: Preparation of 1-(3-((4-((4-(benzo[d]oxazol-5-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

[181] To a solution of 6-(azetidin-3-yloxy)-N-(4-(benzo[d]oxazol-5-yloxy)-3-chlorophenyl)-7-methoxyquinazolin-4-amine triflate (150 mg, 0.31 mmol) and DIEA (120.0 mg, 0.93 mmol) in DCM (30 mL) was added acryloyl chloride (28.1 mg, 0.31 mmol) dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 1 hour. LC/MS showed the reaction completed. The resulting mixture was treated with MeOH. The residue was concentrated in vacuum, and the crude product was purified by Prep-TLC using DCM : MeOH = 10:1 to afford the desired compound (34.2 mg, 20.4%). LC/MS: 543.6 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO) δ 9.61 (s, 1H), 8.79 (s, 1H), 8.54 (s, 1H), 8.14 (d, J = 2.5 Hz, 1H), 7.82 (d, J = 8.9 Hz, 1H), 7.78 (dd, J = 8.9, 2.5 Hz, 1H), 7.59 (s, 1H), 7.36 (d, J = 2.5 Hz, 1H), 7.28 (s, 1H), 7.20 (d, J = 8.9 Hz, 1H), 7.15 (dd, J = 8.9, 2.5 Hz, 1H), 6.39 (dd, J = 17.0, 10.3 Hz, 1H), 6.15 (dd, J = 17.0, 2.1 Hz, 1H), 5.71 (dd, J = 10.3, 2.1 Hz, 1H), 5.27 – 5.22 (m, 1H), 4.82 (dd, J = 9.3, 6.8 Hz, 1H), 4.57 (dd, J = 11.0, 6.5 Hz, 1H), 4.30 (dd, J = 9.8, 3.4 Hz, 1H), 3.99-3.92 (m, 4H).

Example 11: Preparation of 1-(3-((4-((4-(benzo[d]oxazol-6-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one. (Compound 11)



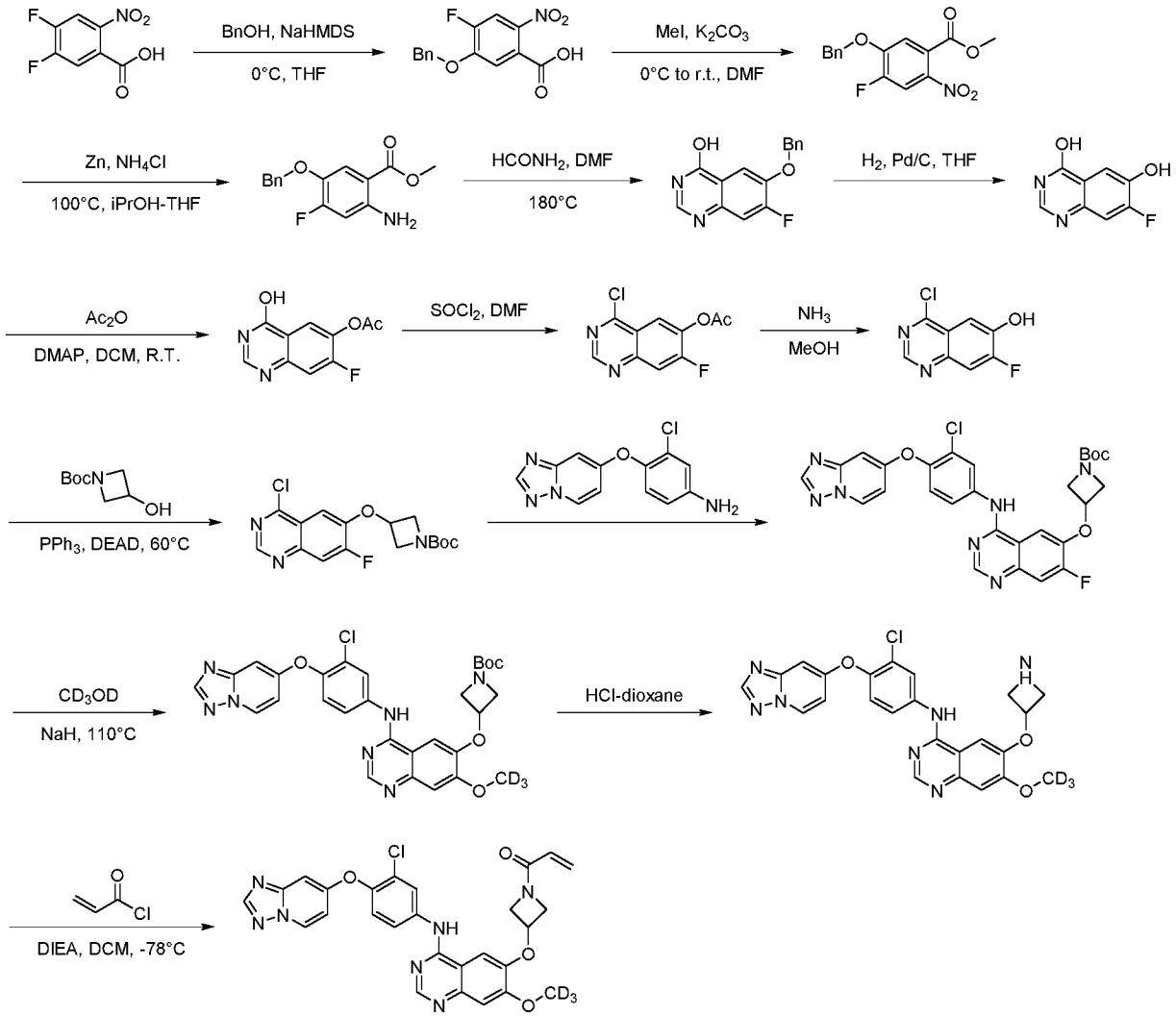
[182] Compound **11** was prepared according to the procedures described for the preparation of Compound **7** by replacing benzo[d]thiazol-5-ol with benzo[d]oxazol-6-ol in step 1.

LC/MS: 543.6$[M+H]^+$.

1H NMR (400 MHz, DMSO) δ 8.61 (s, 1H), 8.08 (s, 1H), 7.91 (s, 1H), 7.74 (d, J = 8 Hz, 1H), 7.66-7.63 (m, 1H), 7.56 (s, 1H), 7.34 (s, 1H), 7.16 (d, J = 4 Hz, 1H), 7.10-7.07 (m, 1H), 7.00 (d, J = 8 Hz, 1H),

6.36-6.27 (m, 2H), 5.75 (d, J = 12 Hz, 1H), 5.32-5.24 (m, 1H), 4.84-4.74 (m, 2H), 4.53-4.50 (m, 1H), 4.26-4.22 (m, 1H),4.02 (s, 3H).

Example 12: Preparation of 1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-(methoxy-d3)quinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (Compound 12)



Step 1: Preparation of 5-(benzyloxy)-4-fluoro-2-nitrobenzoic acid

[183] Benzyl alcohol (26.3 g, 243.8 mmol) was added to a suspension of 4,5-difluoro-2-nitrobenzoic acid (22.5 g, 110.8 mmol) in anhydrous THF (320 mL). The mixture was cooled to 0°C and NaHMDS (2.0 M in THF, 175 mL, 354.5 mmol) was added dropwise over 45 minutes. The mixture was stirred at 0 °C for 1 hour and then quenched with 2N HCl dropwise to pH=1~2. The mixture was then diluted with EA and the aqueous phase was extracted with EA for 3 times. The organic phase was combined and dried over Na_2SO_4. After concentration under reduced pressure, a crude product was obtained as a dark brown oil (49.0 g, ~60% purity). LC/MS: 291.9 $[M+H]^+$.

Step 2: Preparation of methyl 5-(benzyloxy)-4-fluoro-2-nitrobenzoate

[184] Potassium carbonate (40.9 g, 297 mmol) was added to a suspension of crude product of 5-(benzyloxy)-4-fluoro-2-nitrobenzoic acid (48.0 g, 99 mmol) in DMF (280 mL) at 0 °C followed by the

addition of methyl iodide (18.4 mL, 297 mmol). This mixture was warmed to room temperature and stirred for 2 hours. The mixture was quenched with cold water and extracted with EA 4 times. The organic phase was combined and washed with water, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by chromatography on silica-gel column eluted with PE/EA (20/1) to afford the desired product as a yellow solid (28.7 g, ~80% purity). LC/MS:327.9 $[M+Na]^+$.

Step 3: Preparation of methyl 2-amino-5-(benzyloxy)-4-fluorobenzoate

[185] Zn powder (22.0 g, 344 mmol) was added to a solution of methyl 5-(benzyloxy)-4-fluoro-2-nitrobenzoate (21.0 g, 68.8 mmol) in iPrOH (240 mL) and THF (40 mL), and the mixture was heated to 100°C. Water (16 mL) and NH_4Cl (16 g) was added to the mixture and stirred at 100°C for 12 hours. The mixture was filtered and the filtrate was washed with water and ether, dried over Na_2SO_4, and concentrated to afford the desired product as a white solid (7.95 g, 42% yield). LC/MS: 276.0 $[M+H]^+$.

Step 4: Preparation of 6-(benzyloxy)-7-fluoroquinazolin-4-ol

[186] A mixture of methyl 2-amino-5-(benzyloxy)-4-fluorobenzoate (8.38 g, 30.5 mmol), $HCONH_2$ (50 mL) and DMF (1 mL) was heated to 180°C for 2.5 hours. The mixture was then cooled to room temperature and diluted with water and DCM. After phase separation, the aqueous phase was extracted with DCM 3 times. The organic phase was combined and dried over Na_2SO_4, then concentrated and the resulted solid was washed with water and ether to afford 6-(benzyloxy)-7-fluoroquinazolin-4-ol as a yellow solid (5.8 g, 70% yield). LC/MS: 271.9 $[M+H]^+$.

Step 5: Preparation of 7-fluoroquinazoline-4,6-diol

[187] To a suspension of 6-(benzyloxy)-7-fluoroquinazolin-4-ol (5.8 g, 21.4 mmol) in THF (250 mL) was added Pd/C (100 mg) and the mixture was stirred under H_2 atmosphere at room temperature for 16 hours. The mixture was then filtered through membrane and concentrated to afford 7-fluoroquinazoline-4,6-diol as a white solid (2.0 g, 52% yield). LC/MS: 181.0$[M+H]^+$.

Step 6: Preparation of 7-fluoro-4-hydroxyquinazolin-6-yl acetate

[188] Acetic anhydride (1.38 g, 13.3 mmol) was added to a suspension of 7-fluoroquinazoline-4,6-diol (2.0 g, 11.1 mmol) in DCM (100 mL) followed by DMAP (14 mg). The mixture was stirred at room temperature for 12 hours. The mixture was concentrated under vacuum, washed with water and dried to afford 7-fluoro-4-hydroxyquinazolin-6-yl acetate as a white solid (2.28 g, 92% yield). LC/MS: 223.0$[M+H]^+$.

Step 7: Preparation of 4-chloro-7-fluoroquinazolin-6-yl acetate

[189] DMF (1 mL) was added to a solution of 7-fluoro-4-hydroxyquinazolin-6-yl acetate (2.2 g, 10 mmol) in $SOCl_2$ (40 mL) and the mixture was stirred at 80°C for 15 hours. The mixture was cooled to room temperature and concentrated under vacuum. The residue was diluted with sat. $NaHCO_3$ (aq.) and EA. The aqueous phase was extracted with EA, the organic phase was combined and dried over Na_2SO_4. This organic solution was directly used for the next step without further purification as the desired product was not stable while stored as solid. LC/MS: 240.9$[M+H]^+$.

Step 8: Preparation of 4-chloro-7-fluoroquinazolin-6-ol

[190] NH_3-MeOH (7N, 30 mL) was added to half of the ethyl acetate solution of 4-chloro-7-fluoroquinazolin-6-yl acetate and the mixture was stirred at room temperature for 20 hours. The mixture was concentrated under vacuum and was purified by column chromatography eluted with DCM to DCM/EA (2/1) to afford 4-chloro-7-fluoroquinazolin-6-ol as white solid (610 mg, ~60% for 2 steps). LC/MS: 199.0$[M+H]^+$.

Step 9: Preparation of tert-butyl 3-((4-chloro-7-fluoroquinazolin-6-yl)oxy)azetidine-1-carboxylate

[191] DEAD (1.06 g, 5.76 mmol) was added to a solution containing 4-chloro-7-fluoroquinazolin-6-ol (760 mg, 3.84 mmol), tert-butyl 3-hydroxyazetidine-1-carboxylate (798 mg, 4.6 mmol) and PPh_3 (1.50 g, 5.76 mmol) in anhydrous THF (30 mL). The mixture was stirred at 60°C for additional 3 hours. The mixture was cooled to room temperature and was used directly for the next step without workup. The desired compounds was detected by LC/MS: 354.1$[M+H]^+$.

Step 10: Preparation of tert-butyl 3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-fluoroquinazolin-6-yl)oxy)azetidine-1-carboxylate

[192] The crude reaction mixture of tert-butyl 3-((4-chloro-7-fluoroquinazolin-6-yl)oxy)azetidine-1-carboxylate (250 mg, 0.71 mmol) was diluted with iPrOH (5 mL). Then 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chloroaniline (185 mg, 0.71 mmol) was added followed by 2 drops of HCl in dioxane. The mixture was stirred at room temperature for 2 hours and then concentrated under vacuum. The crude mixture was purified by chromatography on silica-gel column eluted with DCM to DCM/MeOH (10/1) to afford the desired product as a yellow solid (200 mg, 48%). LC/MS: 577.6$[M+H]^+$.

Step 11: Preparation of tert-butyl 3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-(methoxy-d3)quinazolin-6-yl)oxy)azetidine-1-carboxylate

[193] NaH (60%, 210 mg, 3.5 mmol) was added to CD_3OD (2 mL) in a sealed tube at room temperature. After stirring for 30 minutes, tert-butyl 3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-fluoroquinazolin-6-yl)oxy)azetidine-1-carboxylate (200 mg, 0.35 mmol) was added and the reaction mixture was heated to 110°C for 16 hours. The reaction was quenched with sat. $NaHCO_3$ (aq.) and extracted with DCM, dried over Na_2SO_4. The crude mixture was purified with chromatography on silica-gel column eluted with DCM/MeOH (10/1) to afford the desired product as a white solid (100 mg, 47% yield). LC/MS: 594.6$[M+H]^+$.

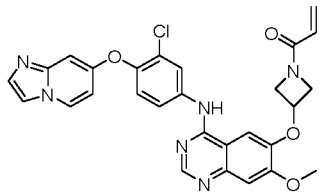
Step 12: Preparation of N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)-6-(azetidin-3-yloxy)-7-(methoxy-d3)quinazolin-4-amine

[194] The above tert-butyl 3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-(methoxy-d3)quinazolin-6-yl)oxy)azetidine-1-carboxylate (90 mg, 0.14 mmol) was dissolved in TFA/DCM (1:3, 4 mL) and was stirred at room temperature for 16 hours. The mixture was directly concentrated to afford the crude product (90 mg, 95% purity, 100%) as a yellow solid. LC/MS: 494.1$[M+H]^+$.

Step 13: Preparation of 1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-(methoxy-d3)quinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

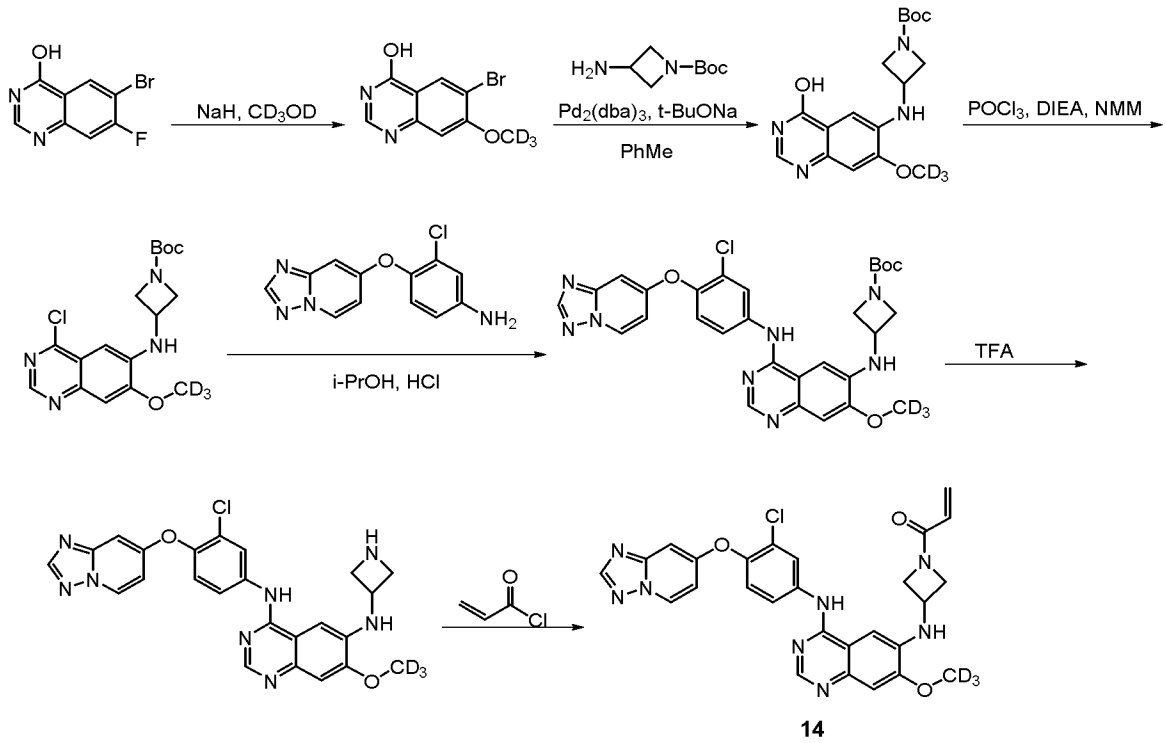
[195] To a solution of N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)-6-(azetidin-3-yloxy)-7-(methoxy-d3)quinazolin-4-amine triflate (90 mg, 95% purity, 0.17 mmol) in anhydrous DCM (2 mL) stirred at -78°C was added DIEA (116 mg, 0.9 mmol). Then acryloyl chloride (16 mg, 0.17 mmol) in 1 mL of anhydrous DCM was added dropwise. The reaction mixture was stirred at -78°C for 2 hours. LCMS showed the reaction completed. The mixture was quenched with 5 mL of MeOH and concentrated under vacuum. The crude product was purified by flash column chromatography (10% MeOH in DCM) to afford the desired compound (30 mg, 32%) as a pale yellow solid. LC/MS: 547.7 $[M+H]^+$.
^{1}H NMR (400 MHz, DMSO) δ 9.67 (s, 1H), 8.98 (t, J = 3.7 Hz, 1H), 8.59 (s, 1H), 8.43 (s, 0.5H), 8.24 (d, J = 2.5 Hz, 1H), 7.93 (dd, J = 8.9, 2.5 Hz, 1H), 7.61 (s, 1H), 7.50 (d, J = 8.9 Hz, 1H), 7.30 (s, 1H), 7.09 (d, J = 7.5 Hz, 0.5H), 6.94 (s, 0.5H), 6.39 (dd, J = 17.0, 10.3 Hz, 1H), 6.15 (dd, J = 17.0, 2.1 Hz, 1H), 5.72 (dd, J = 10.3, 2.1 Hz, 1H), 5.29 – 5.23 (m, 1H), 4.86 – 4.79 (m, 1H), 4.62 – 4.53 (m, 1H), 4.34 – 4.27 (m, 1H), 4.02 – 3.95 (m, 1H).

Example 13: Preparation of 1-(3-((4-((3-chloro-4-(imidazo[1,2-a]pyridin-7-yloxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (Compound 13)



[196] Compound **13** was prepared according to the procedures described for the preparation of compound **7** by replacing benzo[d]thiazol-5-ol with imidazo[1,2-a]pyridin-7-ol in step 1 of the sequence. LCMS m/z 543.1 $[M+1]^+$.
^{1}H NMR (400 MHz, DMSO) δ = 9.80 (s, 1H), 8.68 – 8.49 (m, 2H), 8.45 – 8.38 (s, 2H), 8.23 (s, 1H), 7.93 – 7.87 (m, 1H), 7.67 (s, 1H), 7.58 – 7.35 (m, 2H), 7.29 (s, 1H), 6.84 (d, J=7.1, 1H), 6.66 (s, 1H), 6.42 – 6.35 (m, 1H), 6.15 (d, J=16.9, 1H), 5.71 (d, J=10.3, 1H), 5.28 – 5.21 (s, 1H), 4.89 – 4.78 (m, 1H), 4.57 – 4.52 (m, 1H), 4.29 – 4.23(m, 1H), 3.98 (s, 3H).

Example 14: Preparation of 1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-(methoxy-d3)quinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one (Compound 14)



14

Step 1: Preparation of 6-bromo-7-(methoxy-d3)quinazolin-4-ol

[197] NaH (960 mg, 40 mmol) was added to a solution of THF (20 mL) and CD_3OD (2 mL) at 0°C. After stirring for 30 minutes, 6-bromo-7-fluoroquinazolin-4-ol (1 g, 4.11 mmol) was added. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with water and the pH was adjusted to 6-7. After concentration under reduced pressure, the crude product was purified with chromatography using DCM/MeOH=20/1 to afford 6-bromo-7-(methoxy-d3)quinazolin-4-ol (700 mg, 2.7 mmol, 66.0%) as a white solid.

LC/MS: 258.0 $[M+H]^+$.

Step 2: Preparation of tert-butyl 3-((4-hydroxy-7-(methoxy-d3)quinazolin-6-yl)amino)azetidine-1-carboxylate

[198] A mixture of 6-bromo-7-(methoxy-d3)quinazolin-4-ol (700 mg, 2.7 mmol), tert-butyl 3-aminoazetidine-1-carboxylate (557 mg, 3.2 mmol), $Pd_2(dba)_3$ (0.5 mg, 0.00054mmol) and t-BuONa (518.4 mg，5.4mmol) were stirred in toluene under the protection of nitrogen at 100 °C for 16 hours. The reaction mixture was filtered, and the filtrate was concentrated. The crude product was purified by chromatography eluted by DCM/MeOH (50:1) to afford tert-butyl 3-((4-hydroxy-7-(methoxy-d3)quinazolin-6-yl)amino)azetidine-1-carboxylate (200 mg, 0.57 mmol, 21.1%) as a white solid. LC/MS: 350.2 $[M+H]^+$.

Step 3: Preparation of tert-butyl 3-((4-chloro-7-(methoxy-d3)quinazolin-6-yl)amino)azetidine-1-carboxylate

[199] To a solution of tert-butyl 3-((4-hydroxy-7-(methoxy-d3)quinazolin-6-yl)amino)azetidine-1-carboxylate (170 mg, 0.49 mmol), DIEA (632 mg, 4.9 mmol) and NMM (495 mg, 4.9 mmol) in MeCN 20 mL stirred at room temperature was added $POCl_3$ (749 mg, 4.9 mmol). The reaction mixture was

stirred overnight at room temperature. After concentration under vacuum, the residue was purified with column chromatography (12 g silica gel) using MeOH/DCM (1/50) as eluent to afford the target product as a yellow solid (75 mg, 0.20 mmol 41.7%). LC/MS: 368.2 $[M+H]^+$.

Step 4: Preparation of tert-butyl 3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-(methoxy-d3)quinazolin-6-yl)amino)azetidine-1-carboxylate

[200] To a solution of tert-butyl 3-((4-chloro-7-(methoxy-d3)quinazolin-6-yl)amino)azetidine-1-carboxylate (75 mg, 0.20 mmol) and 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chloroaniline (53 mg, 0.20mmol) in i-PrOH (10 mL) was added HCl (0.05 ml, 4.0 N in dioxane). The mixture was stirred at room temperature for 1 hour. After evaporation of solvent under reduce pressure, the product was obtained as a white solid (55 mg, 0.093 mmol, 45.6%), which was used without further purification. LC/MS: 592.0 $[M+H]^+$.

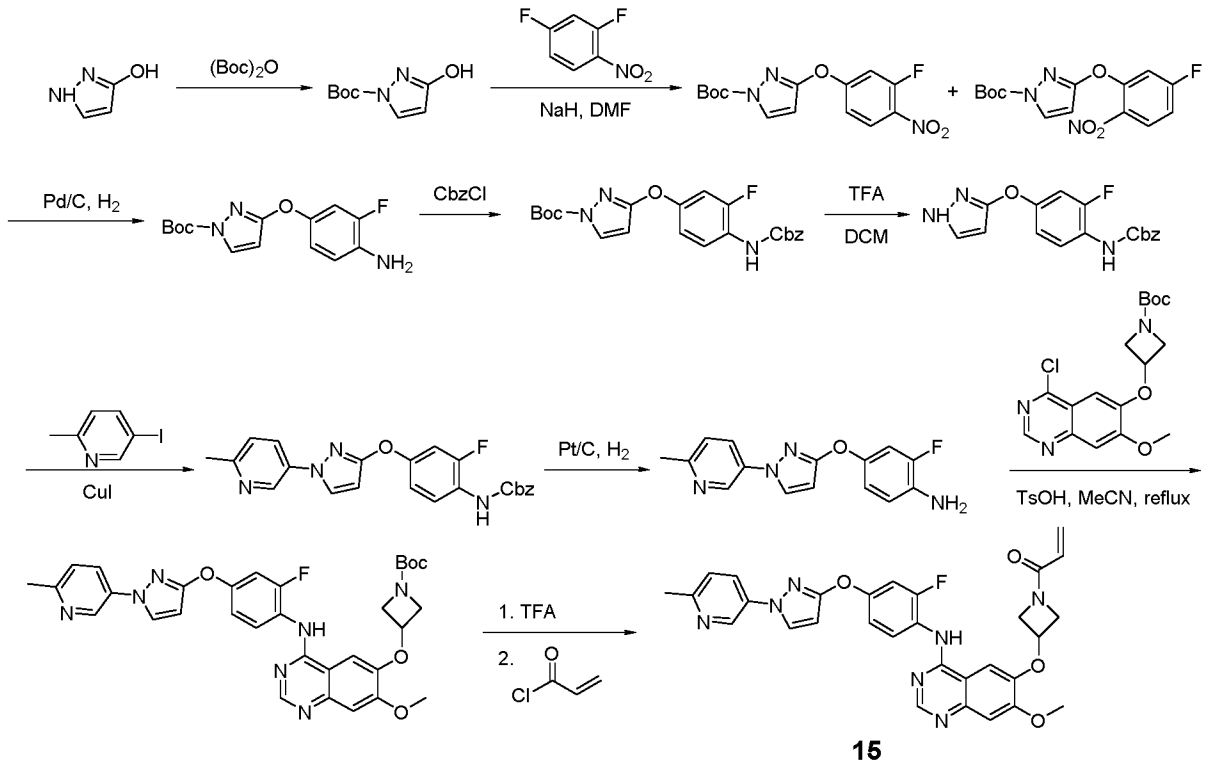
Step 5: Preparation of N4-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)-N6-(azetidin-3-yl)-7-(methoxy-d3)quinazoline-4,6-diamine

[201] A solution of tert-butyl 3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-(methoxy-d3)quinazolin-6-yl)amino)azetidine-1-carboxylate (55 mg, 0.093 mmol) in a solvent of DCM (5 mL) and TFA (1 mL) was stirred at 5°C for 1 hour. The reaction solution was concentrated under vacuum to afford desired product as a yellow solid (41.3 mg, 0.084 mmol, 90%). LC/MS: 492.1 $[M+H]^+$.

Step 6: Preparation of 1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-(methoxy-d3)quinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one

[202] To a solution of N4-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)-N6-(azetidin-3-yl)-7-(methoxy-d3)quinazoline-4,6-diamine (41 mg, 0.084 mmol) and DIEA (21.6 mg, 0.168 mmol) in DCM (2 mL) stirred at -78 °C was added prop-2-enoyl chloride (7.6 mg, 0.084 mmol). The reaction mixture was stirred at -78 °C for 1 hour. The reaction mixture was extracted with water (3x15 mL), dried with Na_2SO_4 and concentrated under vacuum. The residue was purified by Prep-TLC (MeOH/DCM=1/10) to afford the desired product as a yellow solid (20 mg, 0.037 mmol, 44.0%). LC/MS: 546.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO) δ 9.41 (s, 1H), 8.98 (d, J = 7.5 Hz, 1H), 8.44 (d, J = 12.6 Hz, 2H), 8.26 (d, J = 2.5 Hz, 1H), 7.96 (dd, J = 8.9, 2.5 Hz, 1H), 7.47 (d, J = 8.9 Hz, 1H), 7.15 (s, 1H), 7.12 – 7.00 (m, 2H), 6.93 (d, J = 2.6 Hz, 1H), 6.47 – 6.33 (m, 2H), 6.13 (dd, J = 17.0, 2.2 Hz, 1H), 5.69 (dd, J = 10.3, 2.2 Hz, 1H), 4.74 (t, J = 7.9 Hz, 1H), 4.56 – 4.42 (m, 2H), 4.19 – 4.13 (m, 1H), 4.01 – 3.95 (m, 1H).

Example 15: Preparation of 1-(3-((4-((2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (Compound 15)



15

Step 1: Preparation of tert-butyl 3-hydroxy-1H-pyrazole-1-carboxylate

[203] To a solution of 1H-pyrazol-3-ol (10 g, 119 mmol) and Et_3N (18.06 g, 178.5 mmol) in DCM (100 mL) stirred at room temperature was added Boc_2O (28.57 g, 130.9 mmol) portion-wise. The reaction mixture was stirred at room temperature for 12 hours. The mixture was diluted with 100 mL of DCM, washed with water, brine, dried and concentrated under vacuum to give a crude product, which was purified by flash column chromatography (PE/EtOAc = 1:1) to give the desired product (18 g, 82.1%) as a yellow solid. LC/MS: 391.1 $[2M+Na]^+$.

^1H NMR (400 MHz, $CDCl_3$) δ = 11.59 (s, 1H), 7.84 (s, 1H), 5.92 (d, *J*= 3.2 Hz, 1H), 1.64 (s, 9H).

Step 2: Preparation of tert-butyl 3-(3-fluoro-4-nitrophenoxy)-1H-pyrazole-1-carboxylate and tert-butyl 3-(5-fluoro-2-nitrophenoxy)-1H-pyrazole-1-carboxylate

[204] To a solution of tert-butyl 3-hydroxy-1H-pyrazole-1-carboxylate (5 g, 27.2 mmol) in DMF (50 mL) stirred at 0 °C was added NaH (2.2 g, 60%, 54.28 mmol) portion-wise. The mixture was stirred at 0 °C for 30 minutes. A solution of 2,4-difluoro-1-nitrobenzene (4.32 g, 27.14 mmol) was added and the mixture was stirred at room temperature for 1 hour. The mixture was poured into 50 mL of ice water, extracted with EtOAc (100 mL×2). The combined organic layers were washed with brine (200 mL), dried and concentrated under vacuum to provide the crude product which was purified by flash column chromatography (10% MeOH in DCM) to give the desired product (4 g, 45.6%) as a mixture two regio-isomers. LC/MS: 346.1 $[M+Na]^+$.

Step 3: Preparation of tert-butyl 3-(4-amino-3-fluorophenoxy)-1H-pyrazole-1-carboxylate

[205] To a solution of the above regio-isomers (3.9 g, 12.06 mmol) in THF (40 mL) stirred at room temperature was added Pd/C (1.28 g, 12.06 mmol). The reaction mixture was stirred at 60 °C under H_2 for 9.5 hours and then stirred at room temperature for 12 hours. LC/MS indicated the reaction completed. The

mixture was filtered and the filtrate was concentrated under vacuum to provide a crude product, which was purified by flash column chromatography (PE/EtOAc= 2:1) to give the desired product (715 mg, 20.2%), LC/MS: 609.0 $[2M+H]^+$.

^1H NMR (400 MHz, $CDCl_3$) δ = 7.96 (d, *J*= 2.8 Hz, 1H), 6.93 (dd, *J*= 11.6, 2.8 Hz, 1H), 6.83-6.83 (m, 1H), 6.79 (t, *J*= 8.8 Hz, 1H), 5.91 (d, *J*= 3.2 Hz, 1H), 3.16 (s, 2H), 1.65 (s, 9H).

Step 4: Preparation of tert-butyl 3-(4-(((benzyloxy)carbonyl)amino)-3-fluorophenoxy)-1H-pyrazole-1-carboxylate

[206] To a solution of [3-(4-amino-3-fluorophenoxy)pyrazol-1-yl] tert-butyl formate (650 mg, 2.21 mmol) in THF/H_2O (4 mL, 1:1) stirred at 0 °C was added Na_2CO_3 (468 mg, 4.42 mmol) and CbzCl (422 mg, 2.47 mmol). The reaction mixture was stirred at room temperature for 12 hours. The mixture was diluted with 20 mL of water, extracted with EtOAc (25 mL×2). The combined organic layers were washed with brine, dried and concentrated under vacuum to give a crude product, which was purified by flash column chromatography (PE/EtOAc= 1:1) to afford the desired product (430 mg, 45.4%). LC/MS: 450.0 $[M+Na]^+$.

Step 5: Preparation of benzyl (4-((1H-pyrazol-3-yl)oxy)-2-fluorophenyl)carbamate

[207] Tert-butyl {3-[3-fluoro-4-({3-[(formyloxy)methyl]phenyl}amino)phenoxy]pyrazol-1-yl} formate (400 mg, 0.94 mmol) was stirred in TFA/DCM (1:5, 3mL) at room temperature for 1 hour. The mixture was concentrated under vacuum to give a brown oil which was dissolved in 10 mL of DCM. Then Et_3N (1 mL) was added and the mixture was concentrated under vacuum. The residue was purified by flash column chromatography (DCM/MeOH= 10:1) to give the desired product (290 mg, 94.3%). LC/MS: 328.0 $[M+H]^+$.

Step 6: Preparation of benzyl (2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)carbamate

[208] To a solution of benzyl (4-((1H-pyrazol-3-yl)oxy)-2-fluorophenyl)carbamate (160 mg, 0.49 mmol) in THF (5 mL) stirred at room temperature was added 5-iodo-2-methylpyridine (161 mg, 0.74 mmol), K_3PO_4 (208 mg, 0.98 mmol), (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (140 mg, 0.49 mmol) and CuI (93 mg, 0.49 mmol). The reaction mixture was stirred at 80 °C under argon for 3 hours. LC/MS showed the reaction completed. The mixture was poured into H_2O (20 mL), extracted with EtOAc (20 mL×3). The combined organic layers were washed with brine (50 mL), dried and concentrated under vacuum to give a crude product, which was purified by flash column chromatography (DCM/MeOH= 10:1) to provide the desired product (100 mg, 48.8%). LC/MS: 419.0 $[M+H]^+$.

Step 7: Preparation of 2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)aniline

To a solution of benzyl (2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)carbamate (90 mg, 0.22 mmol) in THF (5 mL) stirred at room temperature was added Pd/C (23 mg, 0.22 mmol). The reaction mixture was stirred at room temperature under H_2 for 1 hour. LC/MS showed the reaction completed. The mixture was filtered and the filtrate was concentrated under vacuum to give the desired product (64 mg, 100%), LC/MS: 285.0 $[M+H]^+$.

Step 8: Preparation of tert-butyl 3-((4-((2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate

[209] To a solution of 2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)aniline (44 mg, 0.15 mmol) in ACN (5 mL) stirred at room temperature was added tert-butyl 3-((4-chloro-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (57 mg, 0.15 mmol) and TsOH (8 mg, 0.045 mmol). The reaction mixture was stirred at 80 °C for 3 hours. LC/MS showed the reaction completed. After evaporation under vacuum, water (30 mL) was added and the mixture was extracted with EtOAc (30 mL×2). The combined organic layers were washed with brine (50 mL), dried and concentrated under vacuum to get the crude product, which was purified by flash column chromatography (DCM/MeOH= 10:1) to afford tert-butyl 3-((4-((2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (60 mg, 65.2%). LC/MS: 614.1 $[M+H]^+$.

Step 9: Preparation of 6-(azetidin-3-yloxy)-N-(2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine

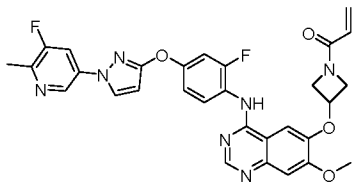
[210] Tert-butyl 3-((4-((2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (60 mg, 0.1 mmol) was stirred in TFA/DCM (1:5, 3mL) at room temperature for 1 hour. The mixture was concentrated under vacuum to give the crude product (80 mg). LC/MS: 514.1 $[M+H]^+$.

Step 10: Preparation of 1-(3-((4-((2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

To a solution of 6-(azetidin-3-yloxy)-N-(2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine triflate (80 mg) in DCM (5 mL) stirred at -78 °C was added Et_3N (20 mg, 0.2 mmol) and acryloyl chloride (10 mg, 0.11 mmol). The reaction mixture was stirred at -78 °C for 1 hour. The mixture was diluted with DCM (15 mL) and quenched with water (20 mL). The organic layer was washed with brine, dried and concentrated under vacuum to give the crude product, which was purified by Prep-TLC (DCM/MeOH= 10:1) to afford the desired product (9 mg, 15.8% yield of two step). LC/MS: 568.0 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ = 9.56 (s, 1H), 8.91 (d, *J*= 2.4 Hz, 1H), 8.58 (d, *J*= 2.4 Hz, 1H), 8.39 (s, 1H), 8.06 (dd, J= 8.0, 2.4 Hz, 1H), 7.57-7.48 (m, 2H), 7.40 (d, *J*= 4.4 Hz, 1H), 7.33-7.25 (m, 2H), 7.12 (d, *J*= 8.0 Hz, 1H), 6.40 (t, *J*= 8.0 Hz, 1H), 6.36 (d, *J*= 2.8 Hz, 1H), 6.15 (d, *J*= 16.8 Hz, 1H), 5.71 (d, *J*= 10.4 Hz, 1H), 5.23 – 5.17 (m, 1H), 4.85-4.77 (m, 1H), 4.62-4.53 (m, 1H), 4.32-4.24 (m, 1H), 3.97 (s, 4H), 2.52 (s, 3H).

Example 16: Preparation of 1-(3-((4-((2-fluoro-4-((1-(5-fluoro-6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (Compound 16)

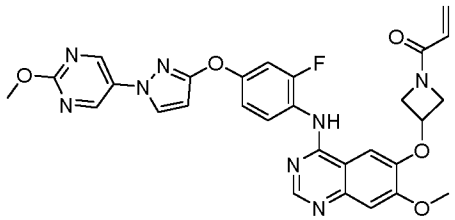


[211] Compound **16** was prepared according to the procedures described for compound **15** by replacing 5-iodo-2-methylpyridine with 5-bromo-3-fluoro-2-methylpyridine in step 6.

LC/MS: 585.6 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO) δ 9.64 (s, 1H), 8.82 (d, *J* = 1.7 Hz, 1H), 8.63 (d, *J* = 2.7 Hz, 1H), 8.41 (s, 1H), 8.11 (dd, *J* = 10.8, 2.1 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.31 – 7.25 (m, 2H), 7.14 (dd, *J* = 8.8, 1.9 Hz, 1H), 6.39 (dt, *J* = 17.0, 7.8 Hz, 2H), 6.14 (dd, *J* = 17.0, 2.1 Hz, 1H), 5.70 (dd, *J* = 10.3, 2.1 Hz, 1H), 5.20 (ddd, *J* = 10.5, 6.4, 4.1 Hz, 1H), 4.81 (dd, *J* = 9.6, 6.7 Hz, 1H), 4.57 (dd, *J* = 11.1, 6.4 Hz, 1H), 4.30 (dd, *J* = 10.0, 3.5 Hz, 1H), 4.02-3.90 (m, 4H), 2.48 (d, *J* = 2.9 Hz, 3H).

Example 17: Preparation of 1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (Compound 17)

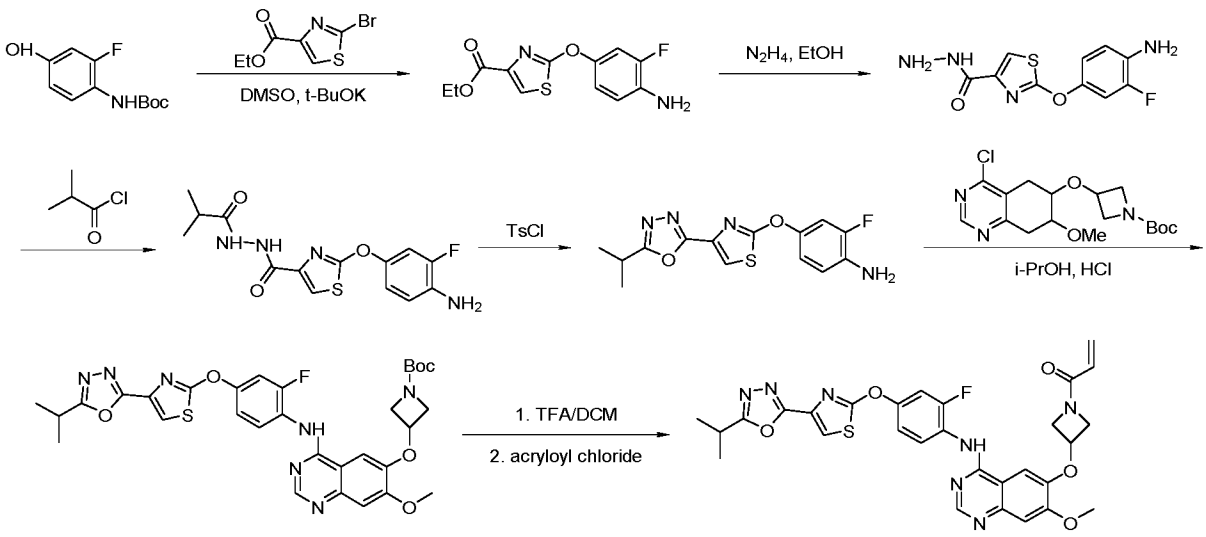


[212] Compound **17** was prepared according to the procedures described for compound **15** by replacing 5-iodo-2-methylpyridine with 5-bromo-2-methoxypyrimidine in step 6.

LC/MS: 584.8 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO) δ 9.57 (s, 1H), 9.04 (s, 2H), 8.53 (d, *J* = 2.6 Hz, 1H), 8.39 (s, 1H), 7.53 (t, *J* = 8.7 Hz, 2H), 7.30 – 7.24 (m, 2H), 7.15 – 7.10 (m, 1H), 6.39 (q, *J* = 12.3 Hz, 2H), 6.14 (dd, *J* = 17.0, 1.9 Hz, 1H), 5.71 (dd, *J* = 10.3, 1.9 Hz, 1H), 5.20 (s, 1H), 4.80 (d, *J* = 6.7 Hz, 1H), 4.60 – 4.53 (m, 1H), 4.29 (br, 1H), 3.97 (br, 7H).

Example 18: 1-(3-((4-((2-fluoro-4-((4-(5-isopropyl-1,3,4-oxadiazol-2-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one. (Compound 18)



Step 1: Preparation of ethyl 2-(4-amino-3-fluorophenoxy)thiazole-4-carboxylate

[213] To a solution of tert-butyl (2-fluoro-4-hydroxyphenyl)carbamate (2.00 g, 8.77 mmol) in anhydrous THF (25 mL) was added potassium t-butoxide (2.00 g, 17.86 mmol). The reaction mixture was stirred at 70 °C for 1 hour. The reaction mixture was evaporated to dryness, then dissolved in DMSO. Ethyl 2-bromothiazole-4-carboxylate (2.3 g, 9.75 mmol) was added to the reaction mixture and stirred at 85 °C for 12 hours. LC/MS showed the reaction completed. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layers were dried with anhydrous sodium sulfate and evaporated to dryness to afford the crude product, which was purified by column chromatography (EA : PE=1:1) to obtain the desired product as a yellow oil. (600 mg, 24% yield). LC/MS: 282.8$[M+H]^+$.

Step 2: Preparation of 2-(4-amino-3-fluorophenoxy)thiazole-4-carbohydrazide

[214] To a solution of ethyl 2-(4-amino-3-fluorophenoxy)thiazole-4-carboxylate (600 mg, 2.12 mmol) in EtOH (15 mL) was added hydrazine hydrate (1.60 g, 31.96 mmol). The reaction mixture was stirred at 60 °C for 12 hours. The LC/MS showed the reaction completed., The reaction mixture was concentrated in vacuum to give the desired compound as a light-yellow oil, which was used directly in the next step (550 mg, 96% yield). LC/MS: 268.8$[M+H]^+$

Step 3: Preparation of 2-(4-amino-3-fluorophenoxy)-N'-isobutyrylthiazole-4-carbohydrazide

[215] To a solution of 2-(4-amino-3-fluorophenoxy)thiazole-4-carbohydrazide (300 mg, 1.12 mmol) and TEA (339 mg, 3.36 mmol) in DCM (8 mL) was added isobutyryl chloride (135 mg, 1.12 mmol) under nitrogen. The reaction mixture was stirred at room temperature for 2 hours. LC/MS showed the reaction was completed. The reaction solution was quenched by water and extracted with DCM. The organic phase was dried over sodium sulfate and concentrated in vacuum to give the desired compound as a lightly yellow oil, which was used directly in the next step (200 mg, 53 % yield). LC/MS: 338.9$[M+H]^+$.

Step 4: Preparation of 2-fluoro-4-((4-(5-isopropyl-1,3,4-oxadiazol-2-yl)thiazol-2-yl)oxy)aniline.

[216] To a solution of 2-(4-amino-3-fluorophenoxy)-N'-isobutyrylthiazole-4-carbohydrazide (200 mg, 0.59 mmol) and TEA (179 mg, 1.77 mmol) in DCM (5 mL) was added 4-methylbenzenesulfonyl chloride

(337 mg, 1.77 mmol) under nitrogen. The reaction mixture was stirred at room temperature for 12 hours. LC/MS showed the reaction was completed. The reaction mixture was concentrated in vacuum to dryness and extracted with water (50 mL) and ethyl acetate (100 mL x 3). The combined organic layers were dried with anhydrous sodium sulfate and evaporated to dryness to afford the crude product, which was purified by column chromatography (DCM : MeOH=10:1) to obtain the desired product as a yellow oil (150 mg, 24% yield). LC/MS: 320.9$[M+H]^+$.

Step 5: Preparation of tert-butyl 3-((4-((2-fluoro-4-((4-(5-isopropyl-1,3,4-oxadiazol-2-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate.

[217] To a solution of 2-fluoro-4-((4-(5-isopropyl-1,3,4-oxadiazol-2-yl)thiazol-2-yl)oxy)aniline (65 mg, 0.20 mmol) and tert-butyl 3-((4-chloro-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (89 mg, 0.24 mmol) in ACN (5 mL) was added TsOH (17.5 mg, 0.1 mmol) under nitrogen. The reaction mixture was stirred at 80 °C for 3 hours. LC/MS showed the reaction was completed. The reaction mixture was concentrated in vacuum to dryness and purified by silica gel column chromatography (DCM : MeOH=10:1) to obtain the desired product as a white solid (45 mg, 34% yield). LC/MS: 649.8$[M+H]^+$.

Step 6: Preparation of 6-(azetidin-3-yloxy)-N-(2-fluoro-4-((4-(5-isopropyl-1,3,4-oxadiazol-2-yl)thiazol-2-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine

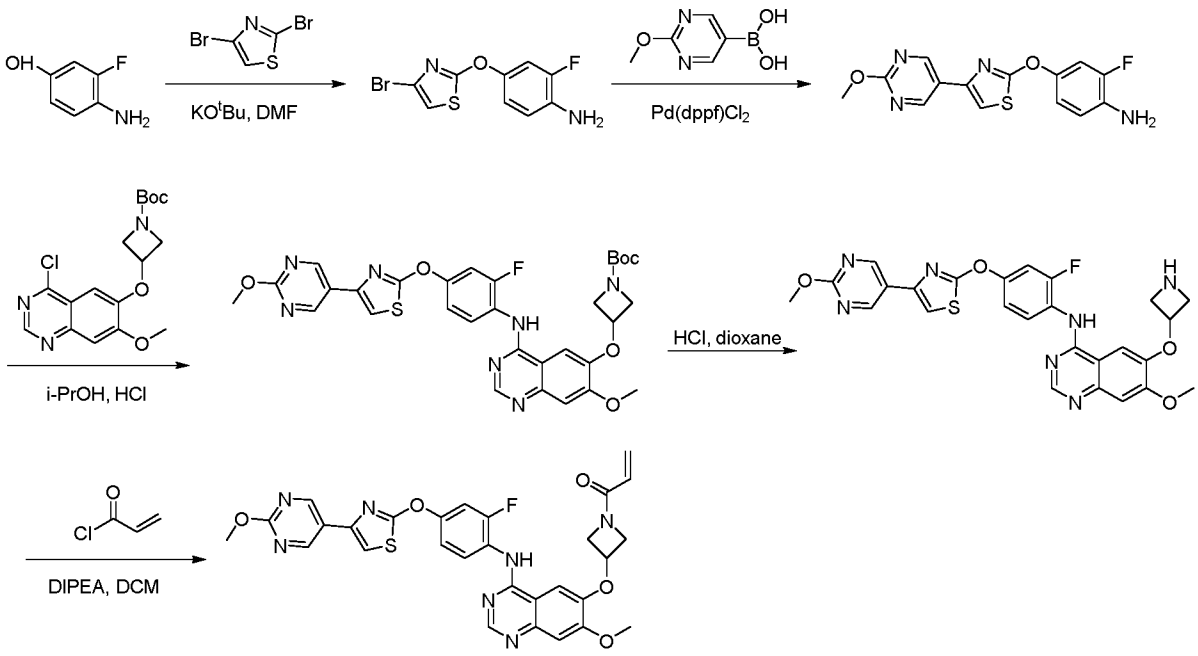
[218] A solution of tert-butyl 3-((4-((2-fluoro-4-((4-(5-isopropyl-1,3,4-oxadiazol-2-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (45 mg, 0.07 mmol) in DCM (4 mL) was added TFA (1 mL) under nitrogen. The reaction mixture was stirred at room temperature for 2 hours. LC/MS showed the reaction was completed. The reaction mixture was concentrated in vacuum to give the desired compound (38 mg) which was used directly in the next step. LC/MS: 549.8$[M+H]^+$.

Step 7: Preparation of 1-(3-((4-((2-fluoro-4-((4-(5-isopropyl-1,3,4-oxadiazol-2-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one.

[219] To a solution of 6-(azetidin-3-yloxy)-N-(2-fluoro-4-((4-(5-isopropyl-1,3,4-oxadiazol-2-yl)thiazol-2-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine triflate (38 mg, 0.07 mmol) and DIEA (27 mg, 0.21 mmol) in DCM (5 mL) was added acryloyl chloride (6.3 mg, 0.07 mmol) at -70 °C. The reaction was stirred at -70 °C for 1 hour. LC/MS showed the reaction was completed. The mixture was evaporated to dryness, and the residue was purified by silica gel column chromatography (DCM : MeOH=10:1) to afford the desired product as a white solid (20 mg, 47%). LC/MS: 603.8$[M+H]^+$.

^{1}H NMR (400 MHz, DMSO) δ 9.57 (s, 1H), 8.41 (s, 1H), 8.11 (s, 1H), 7.68 (t, J = 8.7 Hz, 1H), 7.62 (dd, J = 10.8, 2.6 Hz, 1H), 7.51 (s, 1H), 7.38 (dd, J = 8.7, 1.9 Hz, 1H), 7.27 (s, 1H), 6.39 (dd, J = 17.0, 10.3 Hz, 1H), 6.14 (dd, J = 17.0, 2.1 Hz, 1H), 5.71 (dd, J = 10.3, 2.1 Hz, 1H), 5.21 (s, 1H), 4.86 – 4.76 (m, 1H), 4.58 (dd, J = 11.0, 6.4 Hz, 1H), 4.30 (d, J = 6.5 Hz, 1H), 4.01-3.90 (m, 4H), 3.31 – 3.22 (m, 1H), 1.35 (d, J = 7.0 Hz, 6H).

Example 19: Preparation of 1-(3-((4-((2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (Compound 19)



Step 1: Preparation of 4-((4-bromothiazol-2-yl)oxy)-2-fluoroaniline

[220] A mixture of 4-amino-3-fluorophenol (2.54 g, 20 mmol), 2,4-dibromothiazole (4.86 g, 20 mmol), and potassium t-butoxide (4.49 g, 40 mmol) in DMF (20 mL) was stirred under N_2 at 50 °C for 5 hours. The mixture was diluted with water and extracted with EtOAc. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by silica gel column chromatography to give the desired product (1.0 g, yield: 17%) as a yellow solid. LC/MS: 288.9 $[M+H]^+$.

Step 2: Preparation of 2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy)aniline

[221] Under nitrogen protection, $Pd(dppf)Cl_2$ (205 mg, 0.28 mmol) was added to a degassed mixture of 4-((4-bromothiazol-2-yl)oxy)-2-fluoroaniline (800 mg, 2.8 mmol), (2-methoxypyrimidin-5-yl)boronic acid (431 mg, 2.8 mmol) and K_2CO_3 (773 mg, 5.6 mmol) in dioxane (12 mL)/water (2 mL). The mixture was stirred at 90 °C for 4 hours. LC/MS showed the reaction completed. The solvent was concentrated in vacuo and the crude residue was purified by chromatography to afford 2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy)aniline (800 mg, yield: 85%) as yellow solid. LC/MS: 319.0 $[M+H]^+$.

Step 3: Preparation of tert-butyl 3-((4-((2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate

[222] A mixture of 2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy)aniline (95 mg. 0.3 mmol), tert-butyl 3-((4-chloro-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (109 mg, 0.3 mmol), HCl (a few drops) in i-PrOH (10 mL) was stirred at room temperature for 8 hours. The reaction mixture was concentrated in vacuum to give the desired compound (130 mg, 67% yield). LC/MS: 647.8 $[M+H]^+$.

Step 4: 6-(azetidin-3-yloxy)-N-(2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy) phenyl)-7-methoxyquinazolin-4-amine

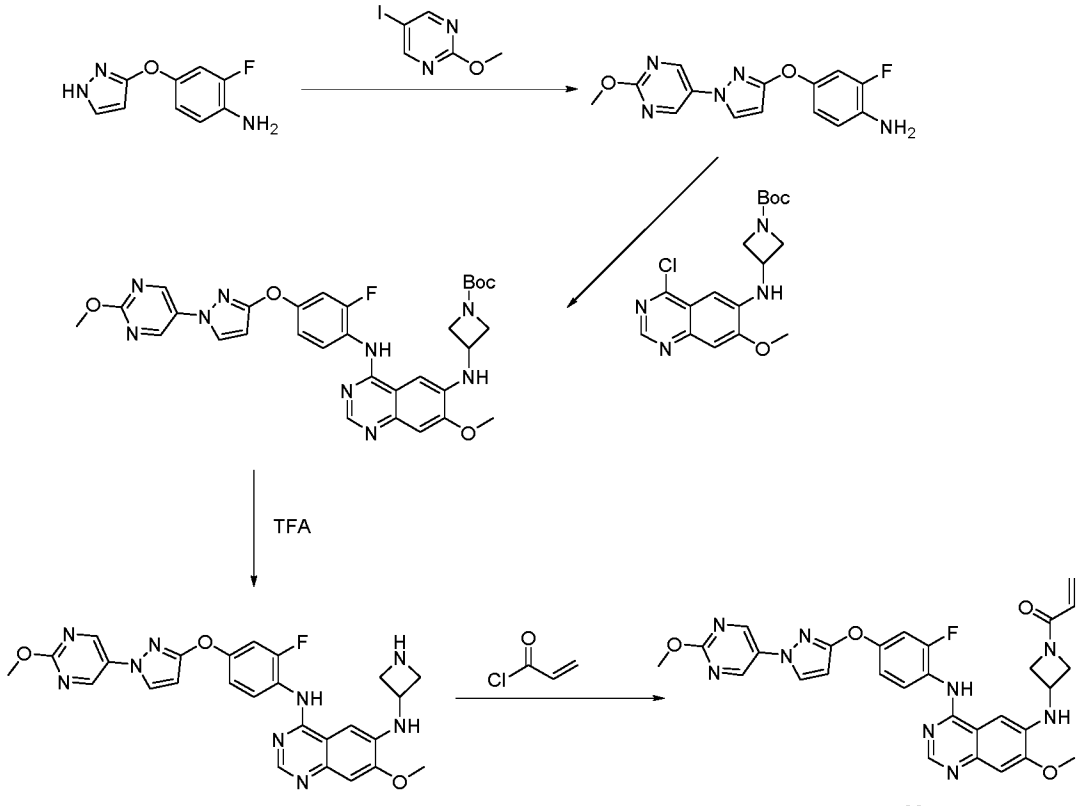
[223] A solution of tert-butyl 3-((4-((2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (130 mg, 0.2 mmol) in 4 M

HCl/dioxane (5 mL) was stirred at room temperature for 1 hour. The reaction mixture was concentrated in vacuum to afford the desired compound (110 mg crude, 80% on LCMS). LC/MS: 547.7 $[M+H]^+$.

Step 5: Preparation of 1-(3-((4-((2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

[224] To a solution of 6-(azetidin-3-yloxy)-N-(2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine (110 mg crude) and DIEA (77 mg, 0.6 mmol) in DCM (10 mL) was added acryloyl chloride (18 mg, 0.1 mmol) dropwise at -40 °C. The resulting mixture was stirred at -40 °C for 10 minutes. LC/MS showed the reaction completed. The resulting mixture was quenched with MeOH and concentrated in vacuum. The crude product was purified by Prep-HPLC to provide 1-(3-((4-((2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (17 mg, 14%). LC/MS: 601.8 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO) δ 9.56 (s, 1H), 9.04 (s, 2H), 8.40 (s, 1H), 8.18 (s, 1H), 7.80 (s, 1H), 7.72 – 7.60 (m, 2H), 7.52 (s, 1H), 7.41 (dd, J = 8.7, 1.8 Hz, 1H), 7.27 (s, 1H), 6.39 (dd, J = 17.0, 10.3 Hz, 1H), 6.14 (dd, J = 17.0, 2.1 Hz, 1H), 5.71 (dd, J = 10.3, 2.1 Hz, 1H), 5.19 (d, J = 10.6 Hz, 1H), 4.90 – 4.75 (m, 1H), 4.58 (dd, J = 10.9, 6.7 Hz, 1H), 4.35 – 4.25 (m, 1H), 3.99-3.91 (m, 7H).

Example 20: 1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one (Compound 20)



Step 1: Preparation of 2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)aniline

[225] To a suspension of 4-((1H-pyrazol-3-yl)oxy)-2-fluoroaniline (800 mg, 4.14 mmol), 5-iodo-2-methoxypyrimidine (1.17 g, 4.967 mmol) and K_2CO_3 (1.14 g, 8.28 mmol) in DMSO (15 mL) was added CuI (788 mg, 4.14 mmol) and (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (589 mg, 4.14 mmol). The mixture was stirred at 100 °C for 1 hour under N_2 atmosphere. The mixture was diluted with water (20 mL) and extracted with EA (20 mL*3). The organic layer was concentrated and purified by flash Chromatography (PE: EA = 0 – 50 %) to afford the title compound (770 mg, 61.7 % yield) as a white solid. LC/MS: 302.0$[M+H]^+$.

Step 2: Preparation of tert-butyl 3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidine-1-carboxylate

[226] To a solution of 2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)aniline (150 mg, 0.5 mmol) and tert-butyl {3-[(4-chloro-7-methoxyquinazolin-6-yl)amino]azetidin-1-yl}formate (183 mg, 0.5 mmol) in IPA (10 mL) was added HCl/Dioxane (4N, 0.2 mL). The mixture was stirred at 25 °C for 16 hours. The mixture was concentrated and purified by flash Chromatography (DCM: MeOH = 0 – 10 %) to afford the title compound (91 mg, 28.8 % yield) as a yellow solid. LC/MS: 630.1$[M+H]^+$.

Step 3: Preparation of N6-(azetidin-3-yl)-N4-(2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)-7-methoxyquinazoline-4,6-diamine

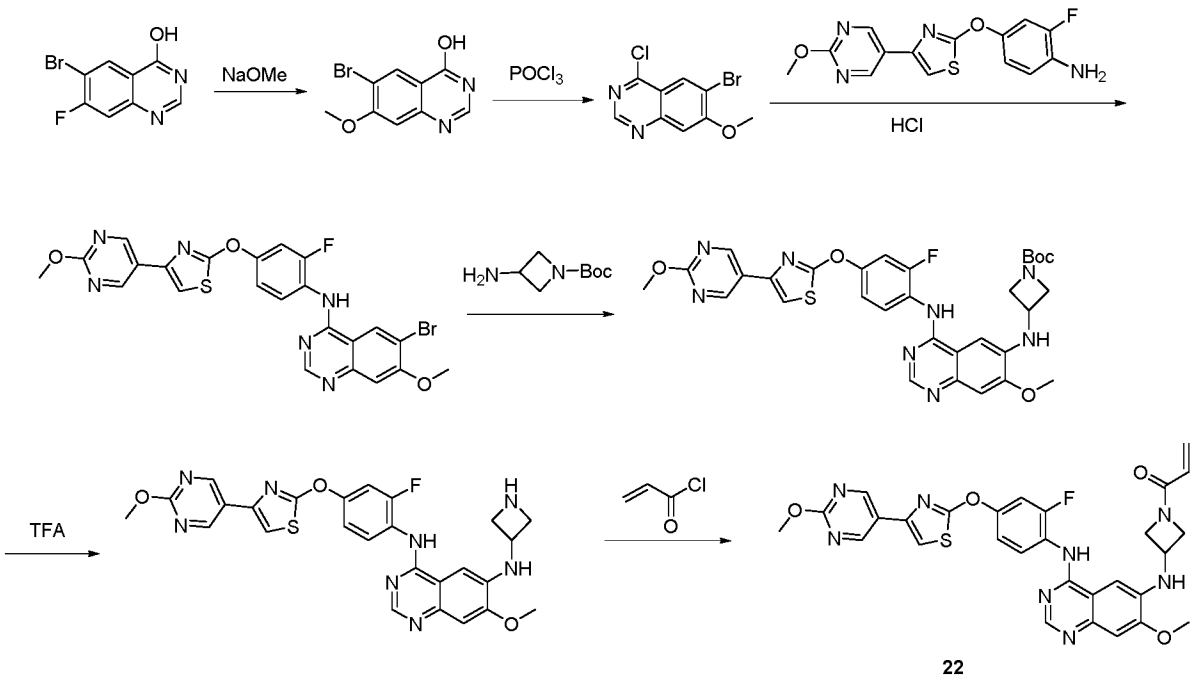
[227] To a solution of tert-butyl 3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy) phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidine-1-carboxylate (91 mg, 0.14 mmol) in DCM (3 mL) was added TFA (1 mL). The mixture was stirred at 25 °C for 3 hours. The mixture was concentrated to afford the title compound (80 mg, TFA salt, 91.2 % yield) as a yellow oil. LC/MS: 530.0$[M+H]^+$.

Step 4: Preparation of 1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy) phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one

[228] To a solution of N6-(azetidin-3-yl)-N4-(2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)-7-methoxyquinazoline-4,6-diamine (80 mg, 0.13 mmol) and DIPEA (58 mg, 0.45 mmol) in DCM (5 mL) was added acryloyl chloride (13 mg, 0.15 mmol) slowly at -40 °C . The mixture was stirred at -40 °C for 15 minutes. The mixture was quenched with MeOH (1 mL) and concentrated. The residue was purified by Prep-HPLC to afford the title compound (35.8 mg, 46.1 % yield) as a yellow solid. LC/MS: 584.0$[M+H]^+$.

^{1}H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 9.04 (s, 2H), 8.73 (s, 1H), 8.55 (d, J = 2.6 Hz, 1H), 7.58 (t, J = 8.8 Hz, 1H), 7.37 (dd, J = 11.2, 2.7 Hz, 1H), 7.25 - 7.17 (m, 3H), 7.03 - 6.96 (m, 1H), 6.42 (d, J = 2.6 Hz, 1H), 6.37 (dd, J = 17.0, 10.3 Hz, 1H), 6.13 (dd, J = 17.0, 2.2 Hz, 1H), 5.69 (dd, J = 10.3, 2.2 Hz, 1H), 4.75 - 4.69 (m, 1H), 4.48 - 4.39 (m, 2H), 4.24 - 4.17 (m, 1H), 4.07 (s, 3H), 3.98 - 3.89 (m, 4H).

Example 21: 1-(3-((4-((2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one (Compound 22)



22

Step 1: Preparation of 6-bromo-7-methoxyquinazolin-4-ol

[229] To a solution of sodium methanolate (10.8 g, 201 mmol) in MeOH (150 mL) was added 6-bromo-7-fluoroquinazolin-4-ol (5 g, 20.1 mmol) at 0 °C. The mixture was stirred at 80 °C overnight. The solvent was evaporated in vacuum and the residue was dissolved with water (50 mL). The mixture was adjusted pH to 5 with HCl and the solid was filtrated. The solid was dried in vacuum to give the title product (7.6 g, 60 % purity, 89 % yield) which was used in the next step without further purification. LC/MS: 254.9$[M+H]^+$.

Step 2: Preparation of 6-bromo-4-chloro-7-methoxyquinazoline

[230] The mixture of 6-bromo-7-methoxyquinazolin-4-ol (4 g, 60 % purity) in $POCl_3$ (50 mL) was stirred at 90 °C overnight. The solvent was evaporated in vacuum and the residue was quenched with TEA (10 mL). The crude product was purified by silica gel chromatography with 20 – 40 % EA in PE to afford the desired compound (2 g, 77.7 % yield) as a brown solid. LC/MS: 273.0$[M+H]^+$.

Step 3: Preparation of 6-bromo-N-(2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy) phenyl)-7-methoxyquinazolin-4-amine

[231] To a mixture of 6-bromo-4-chloro-7-methoxyquinazoline (173 mg, 0.63 mmol) and 2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy)aniline (200 mg, 0.63 mmol) in IPA (30 mL) was added HCl in dioxane (4 M, 0.1 mL). The mixture was stirred at room temperature overnight. The mixture was quenched with TEA (2 mL). The solvent was evaporated in vacuum and the residue was purified by Prep-TLC with MeOH: DCM = 10: 1 to afford the desired compound (160 mg, 45.7 % yield) as a white solid. LC/MS: 554.9 $[M+H]^+$.

Step 4: Preparation of tert-butyl 3-((4-((2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy) phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidine-1-carboxylate

[232] The mixture of 6-bromo-N-(2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine (130 mg, 0.23 mmol), tert-butyl 3-aminoazetidine-1-carboxylate (48 mg,

0.28 mmol), BrettPhos-Pd-G3 (21 mg, 0.023 mmol) and t-BuONa (33 mg, 0.34 mmol) in dioxane (10 mL) was stirred at 75 °C for overnight. The mixture was diluted with water (15 mL) and extracted with DCM (30 mL). The organic phase was concentrated in vacuum and the residue was purified by Prep-TLC with MeOH: DCM = 20: 1 to afford the desired compound (40 mg, 26.8 % yield) as a white solid. LC/MS: 647.1 $[M+H]^+$.

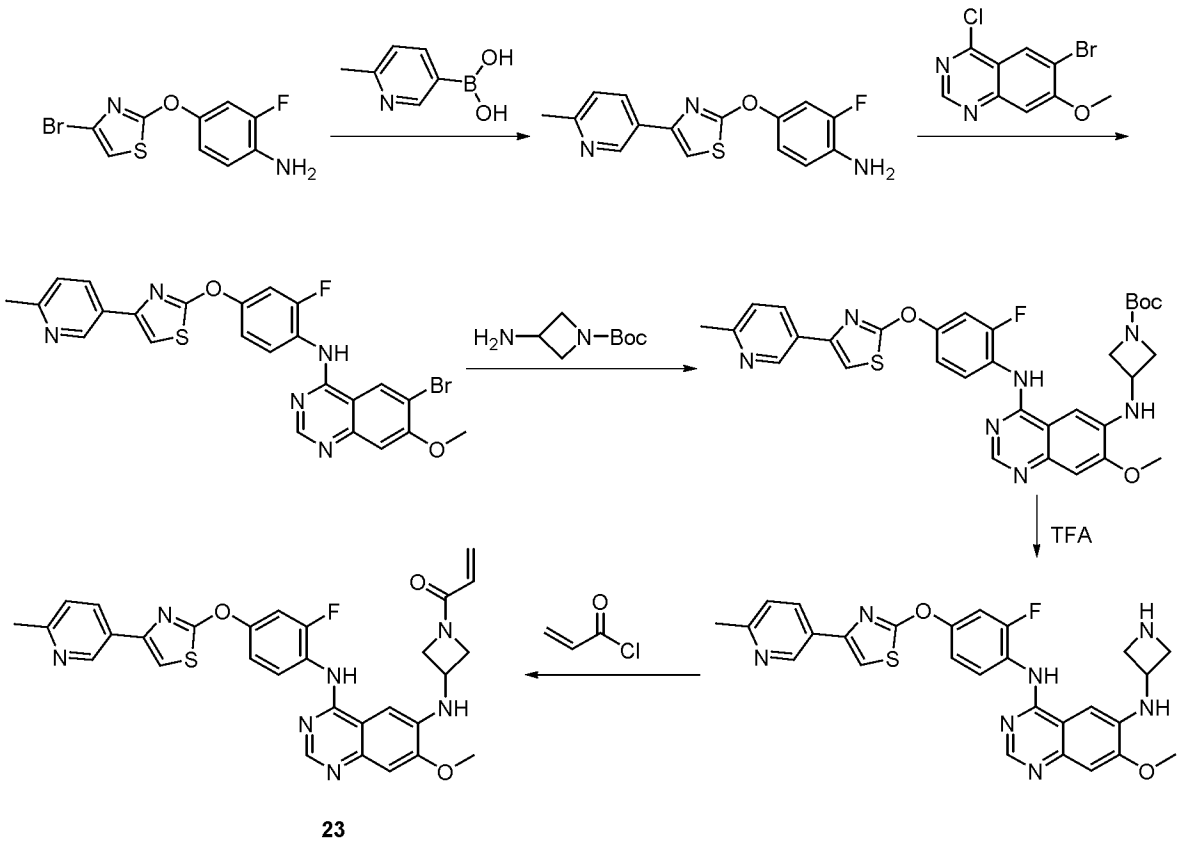
Step 5: Preparation of N^6-(azetidin-3-yl)-N^4-(2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy)phenyl)-7-methoxyquinazoline-4,6-diamine

[233] The solution of tert-butyl 3-((4-((2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy) phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidine-1-carboxylate (60 mg, 0.09 mmol) in DCM/TFA (5:1, 6 mL) was stirred at room temperature for 2 hours. The mixture was concentrated in vacuum to give the desired compound (60 mg, TFA salt, 100 % yield) as a brown solid. LC/MS: 547.0 $[M+H]^+$.

Step 6: Preparation of 1-(3-((4-((2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy) phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one

[234] To a solution of N^6-(azetidin-3-yl)-N^4-(2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy)phenyl)-7-methoxyquinazoline-4,6-diamine (60 mg, TFA salt, 0.09 mmol) and DIEA (24 mg, 0.19 mmol) in dry DCM (5 mL) was added acryloyl chloride (9 mg, 0.099 mmol) at -70 °C. The mixture was stirred at -70 °C for 0.5 hours. The mixture was quenched with water (1 mL) and extracted with DCM (10 mL). The organic phase was concentrated in vacuum and the crude product was purified by Prep-TLC with MeOH: DCM = 10: 1 to afford the desired compound (12 mg, 22.2 % yield). LC/MS: 601.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO): δ 9.56 (s, 1H), 9.04 (s, 2H), 8.35 (s, 1H), 7.80 (s, 1H), 7.70 - 7.60 (m, 2H), 7.40 (dd, J = 8.7, 1.9 Hz, 1H), 7.15 - 7.07 (m, 2H), 6.48 - 6.33 (m, 2H), 6.12 (dd, J = 17.0, 2.2 Hz, 1H), 5.68 (dd, J = 10.3, 2.2 Hz, 1H), 4.76 - 4.69 (m, 1H), 4.47 - 4.39 (m, 2H), 4.19 - 4.14 (m, 1H), 4.02 - 3.93 (m, 7H).

Example 22: 1-(3-((4-((2-fluoro-4-((4-(6-methylpyridin-3-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxy quinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one (Compound 23)



23

Step 1: Preparation of 2-fluoro-4-{[4-(6-methylpyridin-3-yl)-1,3-thiazol-2-yl]oxy}aniline

[235] To a suspension of 4-((4-bromothiazol-2-yl)oxy)-2-fluoroaniline (140 mg, 0.48 mmol), (6-methyl pyridin-3-yl)boranediol (99 mg, 0.72 mmol) and K_2CO_3 (200 mg, 1.44 mmol) in dioxane (5 mL) and H_2O (0.5 mL), $Pd(PPh_3)_4$ (55 mg, 0.048 mmol) was added under N_2 atmosphere. The mixture was stirred at 90 °C for 5 hours. The mixture was evaporated and purified by flash Chromatography (EA: PE = 0 -60 %) to afford the title compound (155 mg, 90 % purity, 95% yield) as a yellow solid. LC/MS: 302.0$[M+H]^+$.

Step 2: Preparation of 6-bromo-N-(2-fluoro-4-{[4-(6-methylpyridin-3-yl)-1,3-thiazol-2-yl]oxy} phenyl)-7-methoxyquinazolin-4-amine

[236] To a solution of 2-fluoro-4-{[4-(6-methylpyridin-3-yl)-1,3-thiazol-2-yl]oxy}aniline (154 mg, 90 % purity, 0.46 mmol) and 6-bromo-4-chloro-7-methoxyquinazoline (140 mg, 0.51 mmol) in IPA (10 mL) HCl/dioxane (0.2 mL) was added. The mixture was stirred at 50 °C for 4 hours. The mixture was evaporated in vacuum to afford the title compound (242 mg, 98% yield) as a light yellow solid. LC/MS: 537.8$[M+H]^+$

Step 3: Preparation of tert-butyl 3-((4-((2-fluoro-4-((4-(6-methylpyridin-3-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidine-1-carboxylate

[237] To a solution of 6-bromo-N-(2-fluoro-4-{[4-(6-methylpyridin-3-yl)-1,3-thiazol-2-yl]oxy} phenyl) -7-methoxyquinazolin-4-amine (242 mg, 0.45 mmol), (3-aminoazetidin-1-yl) tert-butyl formate (101 mg, 0.583 mmol) in dioxane (10 mL) NaOtBu (153 mg, 1.59 mmol) and BrettPhos-Pd-G3 (48 mg, 0.1 mmol) was added under N_2 atmosphere. The mixture was stirred at 100 °C for 10 hours. The mixture was

evaporated and purified by flash Chromatography (MeOH: DCM = 0 - 10%) to afford the title compound (160 mg, 56.3 % yield) as yellow solid. LC/MS: 630.0[M+H]$^+$.

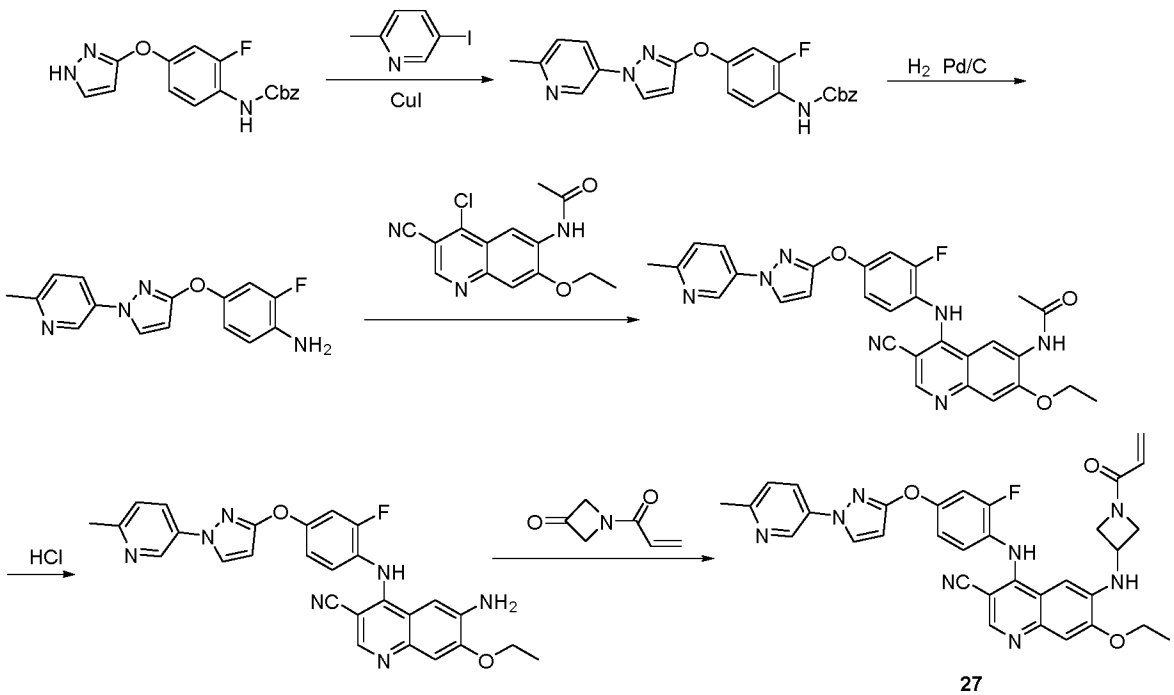
Step 4: Preparation of N6-(azetidin-3-yl)-N4-(2-fluoro-4-((4-(6-methylpyridin-3-yl)thiazol-2-yl)oxy)phenyl)-7-methoxyquinazoline-4,6-diamine

[238] To a solution of tert-butyl AB-4-110-3 (160 mg, 0.25 mmol) in DCM (3 mL) was added TFA (1 mL). The mixture was stirred at 20 °C for 4 hours. The mixture was evaporated to afford the title compound (130 mg, TFA salt, 82.9 % yield) as a brown oil. LC/MS: 530.1[M+H]$^+$.

Step 5: Preparation of 1-(3-((4-((2-fluoro-4-((4-(6-methylpyridin-3-yl)thiazol-2-yl)oxy)phenyl) amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one.

[239] To a solution of N6-(azetidin-3-yl)-N4-(2-fluoro-4-((4-(6-methylpyridin-3-yl)thiazol-2-yl)oxy) phenyl)-7-methoxyquinazoline-4,6-diamine (130 mg, 0.21 mmol) and DIPEA (97 mg, 0.75 mmol) in DCM (9 mL) was added prop-2-enoyl chloride (23 mg, 0.25 mmol) in DCM (1 mL) at -40 °C slowly. The mixture was stirred at -40 °C for 15 minutes. The reaction was quenched by adding water (5 mL). The phase was separated and the organic layer was evaporated. The residue was purified by Prep-TLC (DCM: MeOH = 10: 1) to afford the title compound (34.2 mg, 27.7 % yield). LC/MS: 584.0[M+H]$^+$. ^{1}H NMR (400 MHz, DMSO) δ 9.28 (s, 1H), 8.93 (d, J = 2.1 Hz, 1H), 8.28 (s, 1H), 8.08 (dd, J = 8.1, 2.3 Hz, 1H), 7.78 (s, 1H), 7.66 (t, J = 8.8 Hz, 1H), 7.59 (dd, J = 10.8, 2.7 Hz, 1H), 7.37 (dd, J = 8.7, 1.9 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.13 (s, 1H), 7.03 (s, 1H), 6.42 - 6.33 (m, 2H), 6.12 (dd, J = 17.0, 2.2 Hz, 1H), 5.68 (dd, J = 10.3, 2.3 Hz, 1H), 4.75 - 4.69 (m, 1H), 4.49 - 4.38 (m, 2H), 4.15 (dd, J = 8.9, 4.0 Hz, 1H), 3.99 (s, 3H), 3.98 - 3.93 (m, 1H), 2.49 (s, 3H).

Example 23: Preparation of 6-((1-acryloylazetidin-3-yl)amino)-7-ethoxy-4-((2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)quinoline-3-carbonitrile (Compound 27)



27

Step 1: Preparation of benzyl (2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl) carbamate

[240] To a solution of benzyl (4-((1H-pyrazol-3-yl)oxy)-2-fluorophenyl)carbamate (100 mg, 0.31 mmol) in THF (5 mL) stirred at room temperature was added 5-iodo-2-methylpyridine (80 mg, 0.37 mmol), K_3PO_4 (130 mg, 0.61 mmol), (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (87 mg, 0.61 mmol) and CuI (58 mg, 0.31 mmol). The reaction mixture was stirred at 80 °C under Argon for 12 hours. The mixture was poured into H_2O (20 mL) and extracted with EtOAc (20 mL*3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated under vacuum to give a crude product. The crude product was purified by Flash Chromatography (DCM/MeOH= 10:1) to give the desired product (100 mg, 77%). LC/MS: 419.1 $[M+H]^+$.

Step 2: Preparation of benzyl 2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)aniline

[241] To a solution of benzyl (2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl) carbamate (100 mg, 0.24 mmol) in THF (5 mL) stirred at room temperature was added Pd/C (23 mg, 0.22 mmol). The reaction mixture was stirred at room temperature under H_2 for 1 hour. The mixture filtered and the filtrate was concentrated under vacuum to give the desired product (68 mg, 100%). LC/MS: 285.1 $[M+H]^+$.

Step 3: Preparation of N-(3-cyano-7-ethoxy-4-((2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyra zol-3-yl)oxy)phenyl)amino)quinolin-6-yl)acetamide

[242] To a solution of benzyl 2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)aniline (75 mg, 0.26 mmol) in CH_3CN (5 mL) stirred at room temperature was added N-(4-chloro-3-cyano-7-ethoxyquinolin-6-yl)acetamide (92 mg, 0.32 mmol) and TsOH (13.6 mg, 0.08 mmol). The reaction mixture was stirred at 80 °C for 3 hours. The mixture was concentrated in vacuum then dissolved with EA (60 mL) and washed with water (20 mL). The organic layer was washed with brine (50 mL), dried over Na_2SO_4, and concentrated under vacuum to give a crude product. The crude product was purified by Flash Chromatography (DCM/MeOH= 10:1) to give the desired product (115 mg, 82 %). LC/MS: 538.1 $[M+H]^+$.

Step 4: Preparation of 6-amino-7-ethoxy-4-((2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)quinoline-3-carbonitrile

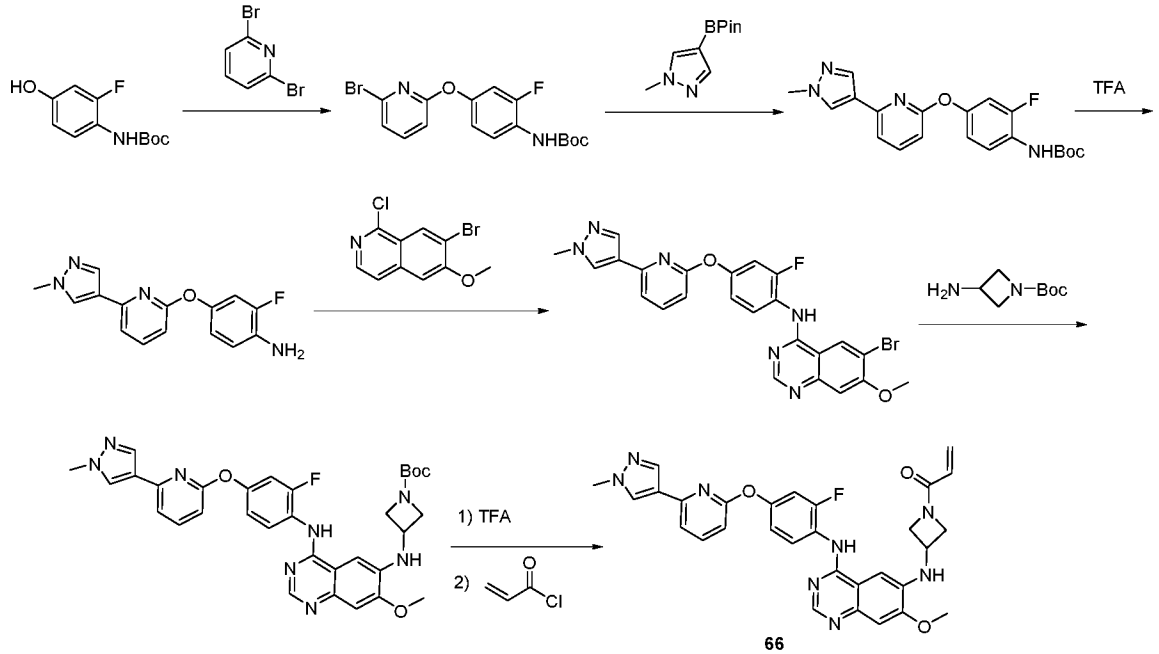
[243] A solution of N-(3-cyano-7-ethoxy-4-((2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl) oxy) phenyl)amino)quinolin-6-yl)acetamide (115 mg, 0.21 mmol) in HCl/H_2O (3:1, 6 mL) was stirred at room temperature for 1 hour. The mixture was concentrated under vacuum to give the crude product (90 mg). LC/MS: 496.1 $[M+H]^+$.

Step 5: Preparation of 6-((1-acryloylazetidin-3-yl)amino)-7-ethoxy-4-((2-fluoro-4-((1-(6-methyl pyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)quinoline-3-carbonitrile

[244] To a solution of 6-amino-7-ethoxy-4-((2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)quinoline-3-carbonitrile (85 mg, crude) , 1-acryloylazetidin-3-one (107 mg, 0.85 mmol) in TFA (5 ml) stirred at 0°C was added STAB (91 mg, 0.43 mmol) slowly. The reaction mixture was stirred at room temperature for 5 hours. The reaction mixture was concentrated then diluted with

DCM (20 mL). The suspension was washed with water (20 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum to give a crude product. The crude product was purified by Prep-TLC (DCM/MeOH= 10:1) to afford the desired product (40 mg, 38% yield). LC/MS: 604.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 9.14 (s, 1H), 8.90 (d, J = 2.7 Hz, 1H), 8.56 (d, J = 2.7 Hz, 1H), 8.28 (s, 1H), 8.06 (dd, J = 8.4, 2.8 Hz, 1H), 7.49 (t, J = 9.0 Hz, 1H), 7.39 (d, J = 8.5 Hz, 1H), 7.32 (dd, J = 11.4, 2.7 Hz, 1H), 7.22 (s, 1H), 7.14 (dd, J = 8.7, 2.0 Hz, 1H), 7.05 (s, 1H), 6.37 (dd, J = 17.0, 10.3 Hz, 1H), 6.32 (d, J = 6.9 Hz, 1H), 6.23 (d, J = 2.6 Hz, 1H), 6.12 (dd, J = 17.0, 2.2 Hz, 1H), 5.67 (dd, J = 10.3, 2.2 Hz, 1H), 4.67 (t, J = 8 Hz, 1H), 4.48 – 4.38 (m, 2H), 4.27 (q, J = 7.0 Hz, 2H), 4.18 - 4.07 (m, 1H), 4.05 - 3.90 (m, 1H), 1.47 (t, J = 7.0 Hz, 3H).

Example 24: Preparation of 1-(3-((4-((2-fluoro-4-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one (Compound 66)



Step 1: Preparation of tert-butyl (4-((6-bromopyridin-2-yl)oxy)-2-fluorophenyl)carbamate

[245] To a solution of tert-butyl N-(2-fluoro-4-hydroxyphenyl)carbamate (454 mg, 2 mmol) in DMF (5 mL) was added NaH (120 mg, 3 mmol) slowly at 0 °C. The mixture was stirred at 0 °C for 30 minutes then 2,6-dibromopyridine (521 mg, 2.2 mmol) was added. The mixture was stirred at 70 °C for 1 hour. The reaction was quenched with water (5 mL) and extracted by EA (5 mL×3). The organic layer was concentrated in vacuum and the residue was purified by flash Chromatography with PE in EA = 0 ~ 10 % to afford the title compound (212 mg, 27.6% yield) as a white solid. LC/MS: 382.8 $[M+H]^+$.

Step 2: Preparation of tert-butyl(2-fluoro-4-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)oxy) phenyl) carbamate

[246] To a solution of tert-butyl (4-((6-bromopyridin-2-yl)oxy)-2-fluorophenyl)carbamate (200 mg, 0.52 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (163 mg, 0.78 mmol) and

K_2CO_3 (216 mg, 1.56 mmol) in dioxane (10 mL) and water (1 mL) was added $Pd(PPh_3)_4$ (60 mg, 0.05 mmol). The mixture was stirred at 90 °C for 3 hours under N_2 atmosphere. The mixture was concentrated in vacuum and the residue was purified by flash Chromatography with PE in EA = 0 ~ 40 % to afford the title compound (184 mg, 92 % yield) as a yellow oil. LC/MS: 385.0$[M+H]^+$.

Step 3: Preparation of 2-fluoro-4-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)oxy)aniline

[247] A solution of tert-butyl(2-fluoro-4-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)oxy)phenyl) carbamate (184 mg, 0.48 mmol) in HCl/dioxane (7 N, 10 mL) was stirred at 20 °C for 2 hours. The mixture was concentrated in vacuum to afford the title compound (136 mg, 100% yield) as a brown solid. LC/MS: 285.0$[M+H]^+$.

Step 4: Preparation of 6-bromo-N-(2-fluoro-4-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)oxy) phenyl)-7-methoxyquinazolin-4-amine

[248] To a solution of 2-fluoro-4-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)oxy)aniline (200 mg, 0.7 mmol) and 6-bromo-4-chloro-7-methoxyquinazoline (190 mg, 0.7 mmol) in IPA (10 mL) was added HCl/dioxane (0.5 mL). The mixture was stirred at 50 °C for 16 hours. The mixture was concentrated in vacuum to afford the title compound (450 mg, 60 % purity, 74 % yield) as a brown solid. LC/MS: 520.9$[M+H]^+$.

Step 5: Preparation of tert-butyl 3-((4-((2-fluoro-4-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl) oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidine-1-carboxylate

[249] To a solution of 6-bromo-N-(2-fluoro-4-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)oxy) phenyl)-7-methoxyquinazolin-4-amine (390 mg, 60 % purity 0.45 mmol), (3-aminoazetidin-1-yl) tert-butylformate (130 mg, 0.75 mmol) and t-BuONa (216 mg, 2.25 mmol) in dioxane (10 mL) was added BrettPhos-Pd-G3 (68 mg, 0.075 mmol) under N_2 atmosphere. The mixture was stirred at 100 °C for 10 hours. The mixture was concentrated in vacuum and the residue was purified by flash Chromatography with MeOH in DCM = 0 ~ 8 % to afford the title compound (220 mg, 79.6 % yield) as a yellow solid. LC/MS: 613.2$[M+H]^+$.

Step 6: Preparation of N6-(azetidin-3-yl)-N4-(2-fluoro-4-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)oxy)phenyl)-7-methoxyquinazoline-4,6-diamine

[250] A solution of tert-butyl-3-((4-((2-fluoro-4-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)oxy) phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidine-1-carboxylate (220 mg, 0.36 mmol) in DCM/TFA (3:1, 4 mL)was stirred at 20 °C for 3 hours. The mixture was concentrated in vacuum to afford the title compound (220 mg, TFA salt, 100 % yield) as a yellow oil. LC/MS: 513.1$[M+H]^+$.

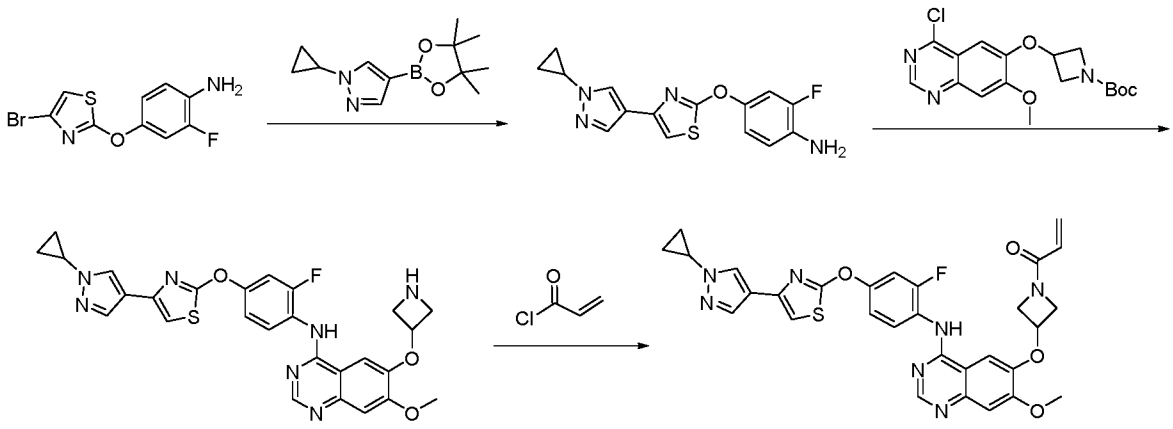
Step 7: Preparation of 1-(3-((4-((2-fluoro-4-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)oxy) phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one

[251] To a solution of N6-(azetidin-3-yl)-N4-(2-fluoro-4-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)oxy)phenyl)-7-methoxyquinazoline-4,6-diamine (220 mg, TFA salt, 0.36 mmol) and DIPEA (159 mg, 1.23 mmol) in DCM (9 mL) was added acryloyl chloride (37 mg, 0.41 mmol at -40 °C. The mixture was stirred at -40 °C for 15 minutes. The mixture was quenched with MeOH (0.5 mL) and concentrated in

vacuum. The residue was purified by Prep-TLC (DCM: MeOH = 10:1) to afford the title compound (67 mg, 32.8 % yield) as a white solid. LC/MS: 567.1[M+H]$^+$.

^{1}H NMR (400 MHz, DMSO) δ 9.30 (s, 1H), 8.28 (s, 1H), 8.12 (s, 1H), 7.89 - 7.83 (m, 2H), 7.56 (t, J = 8.8 Hz, 1H), 7.45 - 7.42 (m, 1H), 7.24 (dd, J = 11.3, 2.6 Hz, 1H), 7.12 (s, 1H), 7.11 - 7.07 (m, 1H), 7.06 (s, 1H), 6.83 (d, J = 7.6 Hz, 1H), 6.43 - 6.33 (m, 2H), 6.12 (dd, J = 17.0, 2.2 Hz, 1H), 5.68 (dd, J = 10.3, 2.3 Hz, 1H), 4.75 - 4.68 (m, 1H), 4.44 (d, J = 6.5 Hz, 2H), 4.19 - 4.12 (m, 1H), 3.99 (s, 3H), 3.96 (d, J = 4.7 Hz, 1H), 3.86 (s, 3H).

Example 25: Preparation of 1-(3-((4-((4-((4-(1-cyclopropyl-1H-pyrazol-4-yl)thiazol-2-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (Compound 71)



71

Step 1: Preparation of 4-((4-(1-cyclopropyl-1H-pyrazol-4-yl)thiazol-2-yl)oxy)-2-fluoroaniline

[252] To a solution of 4-[(4-bromo-1,3-thiazol-2-yl)oxy]-2-fluoroaniline (200 mg, 0.69 mmol) and 1-cyclopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (194mg, 0.82mmol) in dioxane/H2O (5:1, 10 mL) stirred under argon at room temperature was added Pd(dppf)Cl2DCM (28.17mg, 0.034mmol) and K_2CO_3 (286 mg, 2.07 mmol). The reaction mixture was stirred at 90 °C for 2 hours. The solvent was removed in vacuum to give a crude product. The crude product was purified by chromatography eluted with PE/EA (1/1) to afford the title compound (150 mg, 90 % purity, 61.7% yield) as a yellow solid. .LC/MS: 317.0 [M+H]$^+$.

Step 2: Preparation of 6-(azetidin-3-yloxy)-N-(4-((4-(1-cyclopropyl-1H-pyrazol-4-yl)thiazol-2-yl)oxy)-2-fluorophenyl)-7-methoxyquinazolin-4-amine

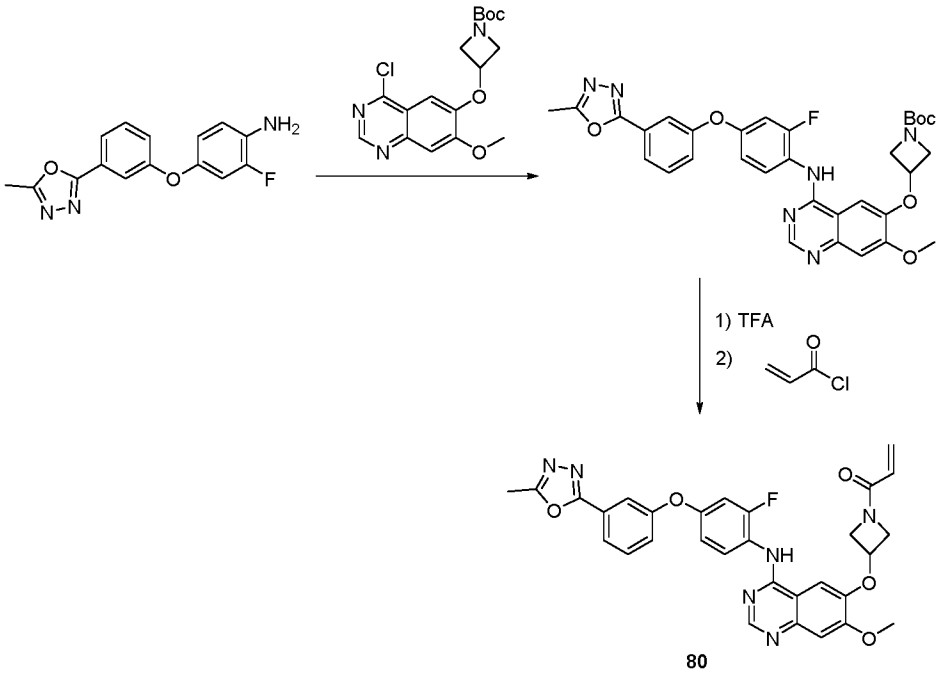
[253] A solution of 4-{[4-(1-cyclopropylpyrazol-4-yl)-1,3-thiazol-2-yl]oxy}-2-fluoroaniline （100 mg ，90 % purity, 0.29 mmol） and tert-butyl {3-[(4-chloro-7-methoxyquinazolin-6-yl)oxy] azetidine-1-yl}formate (117 mg, 0.32 mmol) in i-PrOH/HCl（10:1, 10 mL） was stirred at 50 °C for 4 hours. The solvent was removed in vacuum to give a crude product. The crude product was purified by Prep-TLC with MeOH/DCM (1/10) to afford the title compound (110 mg, 90 % purity, 62.0 % yield) as a white solid. LC/MS: 547. 0[M+H]$^+$.

Step 3: Preparation of 1-(3-((4-((4-((4-(1-cyclopropyl-1H-pyrazol-4-yl)thiazol-2-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

[254] To a solution of 6-(azetidin-3-yloxy)-N-(4-{[4-(1-cyclopropylpyrazol-4-yl)-1,3-thiazol-2-yl]oxy} -2-fluorophenyl)-7-methoxyquinazolin-4-amine (70 mg, 90 % purity, 0.12mmol) and TEA (20 mg, 0.19mmol) in DCM (15 mL) was added prop-2-enoyl chloride (9.4 mg， 0.104mmol) in batches at -78 °C.The reaction mixture was stirred at -78 °Cfor 15 minutes then quenched by adding MeOH (2 mL). The solvent was removed in vacuum to give a crude product. The crude product was purified by Prep-TLC with MeOH/DCM (1/10) to afford the title compound (21 mg, 29.1 % yield) as a white solid. LC/MS: 599.63 [M+H]+ .

^{1}H NMR (400 MHz, DMSO) δ 9.56 (s, 1H), 8.40 (s, 1H), 8.11 (s, 1H), 7.76 (s, 1H), 7.64 (t, J = 8.8 Hz, 1H), 7.58 - 7.48 (m, 2H), 7.33 (dd, J = 8.8, 1.9 Hz, 1H), 7.29 - 7.23 (m, 2H), 6.44 - 6.33 (m, 1H), 6.14 (dd, J = 17.0, 2.1 Hz, 1H), 5.71 (dd, J = 10.3, 2.1 Hz, 1H), 5.25 - 5.15 (s, 1H), 4.87 - 4.76 (m, 1H), 4.63 - 4.53 (m, 1H), 4.34 - 4.26 (m, 1H), 4.05 - 3.93 (s, 4H), 3.80 - 3.70 (m, 1H), 1.09 - 1.01 (m, 2H), 1.00 - 0.92 (m, 2H).

Example 26: Preparation of 1-(3-((4-((2-fluoro-4-(3-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy)phenyl)amino)-7-methoxy quinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (Compound 80)



Step 1: Preparation of tert-butyl 3-((4-((2-fluoro-4-(3-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy) phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate

[255] To a solution of 2-fluoro-4-[3-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy]aniline (190 mg, 0.66 mmol) and tert-butyl 3-((4-chloro-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (244 mg, 0.66 mmol) in dioxane (20 mL) stirred under nitrogen at 25 °C was added HCl/dioxane (0.3 mL). The reaction mixture was stirred at 25 °C for 5 hours. The reaction mixture was evaporated in vacuum to give a crude product. The crude product was purified by flash chromatography with DCM: MeOH = 100:1 ~ 10:1 to give the desired product (200 mg, 49.3 % yield). LC/MS: 615.2 $[M+1]^+$.

Step 2: Preparation of 6-(azetidin-3-yloxy)-N-(2-fluoro-4-(3-(5-methyl-1,3,4-oxadiazol-2-yl) phenoxy)phenyl)-7-methoxyquinazolin-4-amine

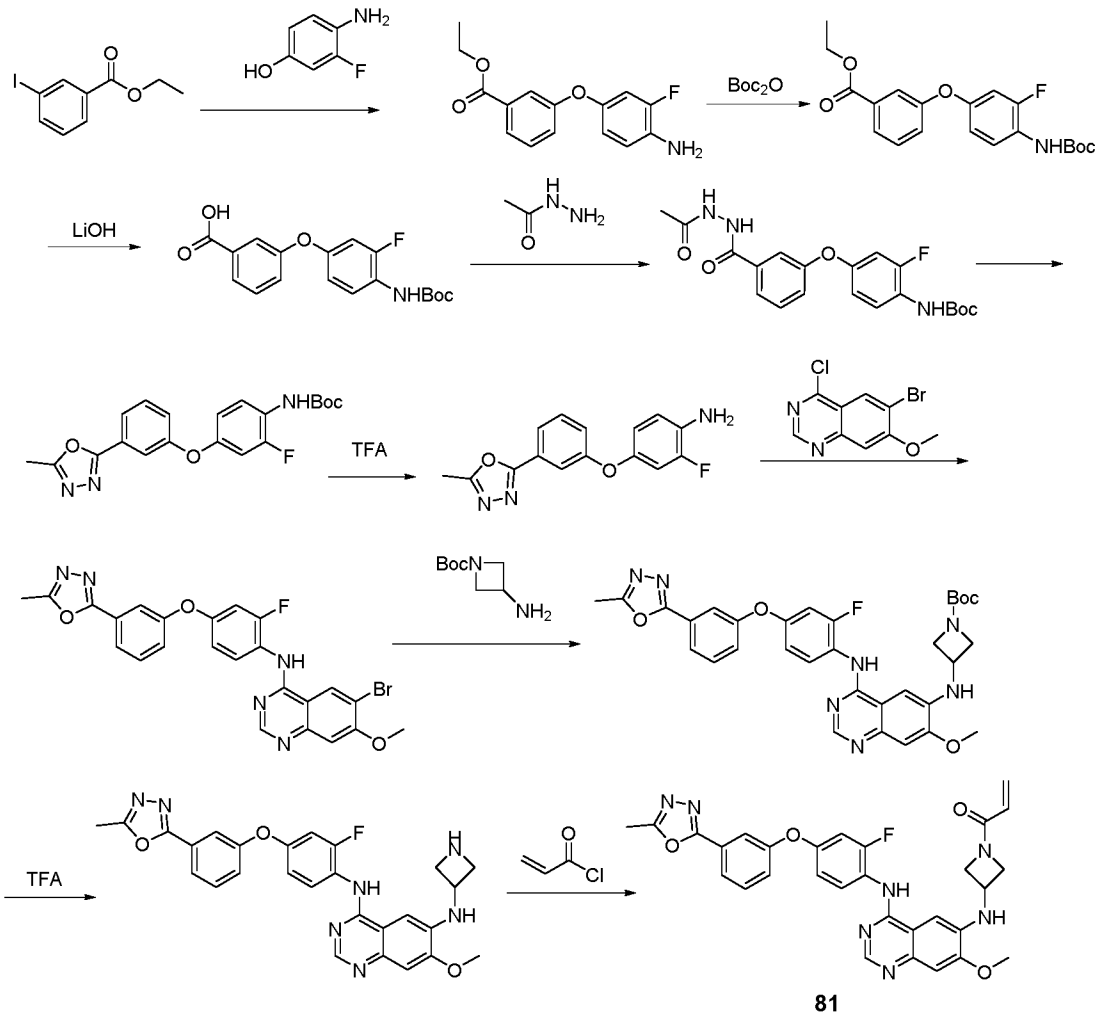
[256] A solution of tert-butyl 3-((4-((2-fluoro-4-(3-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy)phenyl) amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (200 mg, 0.32 mmol) in TFA/ DCM (1:3, 20 mL) was stirred under nitrogen at 25 °C for 2 hours. The reaction mixture was evaporated in vacuum to give the desired product (200 mg, TFA salt, 100 % yield) as a brown solid. LC/MS: 515.0 $[M+H]^+$.

Step 3: Preparation of 1-(3-((4-((2-fluoro-4-(3-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy)phenyl) amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

[257] To a solution of 6-(azetidin-3-yloxy)-N-{2-fluoro-4-[3-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy] phenyl}-7-methoxyquinazolin-4-amine (200 mg, TFA salt, 0.32 mmol) and triethylamine (100 mg, 0.99 mmol) in DCM (20 mL) stirred under nitrogen at -78 °C was added prop-2-enoyl chloride (36 mg, 0.36 mmol). The reaction mixture was stirred at -78 °C for 10 minutes then quenched with water (10 mL), extracted with DCM (50 mL), dried over sodium sulphate and evaporated in vacuum to give a crude product. The crude product was purified by flash chromatography with DCM: MeOH = 100:1 ~ 10:1 to give the desired product (50 mg, 27.4 % yield) as a white solid. LC/MS: 569.2 $[M+1]^+$.

^{1}H NMR (400 MHz, DMSO) δ 9.49 (s, 1H), 8.39 (s, 1H), 7.79 (d, J = 7.7 Hz, 1H), 7.67 (t, J = 8.0 Hz, 1H), 7.61 - 7.54 (m, 2H), 7.51 (s, 1H), 7.42 - 7.39 (m, 1H), 7.25 (s, 1H), 7.23 - 7.19 (m, 1H), 7.05 - 6.99 (m, 1H), 6.43 - 6.33 (m, 1H), 6.17 - 6.11 (m, 1H), 5.73 - 5.68 (m, 1H), 5.22 - 5.19 (m, 1H), 4.85 - 4.78 (m, 1H), 4.58 - 4.55 (m, 1H), 4.32 - 4.29(m, 1H), 3.98 - 3.95 (m, 4H), 2.58 (s, 3H).

Example 27: Preparation of 1-(3-((4-((2-fluoro-4-(3-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy)phenyl)amino)-7-methoxy quinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one (Compound 81)



Step 1: Preparation of ethyl 3-(4-amino-3-fluorophenoxy)benzoate

[258] To a solution of ethyl 3-iodobenzoate (19.0 g, 68.8 mmol) in ACN (500 mL) stirred under argon at room temperature was added 4-amino-3-fluorophenol (17.5 g, 137.6 mmol), K_2CO_3 (42.79 g, 309.6 mmol), trans-N,N'-Dimethyl-cyclohexane-1,2-diamine (2.0 g, 13.7 mmol) and Copper(I) iodide (0.66 g, 3.44 mmol). The reaction mixture was stirred at 60 °C for 86 hours. The solid was filtered off and washed with ACN (100 mL×3). The combined solution was evaporated in vacuum to give a crude product. The crude product was purified by flash chromatography with PE: EA=10:1 ~ 1:1 to give the desired product (2.10 g, 11.0 %) as a yellow oil. LC/MS: 276.1 $[M+1]^+$.

Step 2: Preparation of ethyl 3-(4-((tert-butoxycarbonyl)amino)-3-fluorophenoxy)benzoate

[259] To a solution of ethyl 3-(4-amino-3-fluorophenoxy)benzoate (2.10 g, 7.63 mmol) in 1,4-Dioxane (50 mL) stirred under argon at room temperature was added $(Boc)_2O$ (1.83 g, 8.39 mmol). The reaction mixture was stirred at 100 °C for 12 hours. The reaction mixture was evaporated in vacuum to give a crude product. The crude product was purified by flash chromatography (0 ~ 10 % MeOH in DCM) to give the desired product (2.60 g, 90.7 %) as a white solid. LC/MS: 398.0 $[M+Na]^+$.

Step 3: Preparation of 3-(4-((tert-butoxycarbonyl)amino)-3-fluorophenoxy)benzoic acid

[260] To a solution of ethyl 4-{3-[(tert-butyldimethylsilyl)oxy]propyl}benzoate (1.0 g, 2.66 mmol) in THF/ Water (50 mL, 9:1) stirred under argon at room temperature was added Lithium hydroxide

monohydrate (0.87 g, 20.77 mmol). The reaction mixture was stirred at room temperature for 10 hours. The reaction mixture was dissolved with EA (200 mL) and adjusted pH to 7 with HCl (2 M). The mixture was dried by freezing drier to give the desired product (2.0 g, crude, mixed with LiCl) as a grey solid. LC/MS: 370.0 $[M+Na]^+$.

Step 4: Preparation of tert-butyl (4-(3-(2-acetylhydrazine-1-carbonyl)phenoxy)-2-fluorophenyl) carbamate

[261] To a solution of 3-(4-{[(tert-butoxy)carbonyl]amino}-3-fluorophenoxy)benzoic acid (2.0 g, crude, mixed with LiCl) in DCM (50 mL) stirred under argon at room temperature was added HATU (1.3 g, 3.45 mmol), DIEA (1.3 g, 10.35 mmol) and acetohydrazide (0.6 g, 7.98 mmol). The reaction mixture was stirred at room temperature for 10 hours. The reaction mixture was partitioned between EA (500 mL) and Water (50 mL). The organic layer was washed with saturated sodium chloride solution (50 mL), dried over sodium sulphate, and evaporated to give a crude product. The crude product was purified by flash Chromatography with MeOH: DCM = 0:1 ~ 1:10 to give the desired product (0.35 g, 32.6 % yield) as a white solid. LC/MS: 425.8 $[M+Na]^+$.

Step 5: Preparation of tert-butyl (2-fluoro-4-(3-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy)phenyl) carbamate

[262] To a solution of tert-butyl N-{4-[3-(N'-acetylhydrazinecarbonyl)phenoxy]-2-fluorophenyl}carbamate (320 mg, 0.79 mmol) and triethylamine (401 mg, 3.96 mmol) in DCM (20 mL) stirred under nitrogen at 0 °C was added TsCl (227 mg, 1.18 mmol). The reaction mixture was stirred at 25 °C for 5 hours. The reaction was quenched by adding water (20 ml). The organic layer was washed with saturated sodium chloride solution (10 mL) and dried over sodium sulphate. The solvent was removed in vacuum and the residue was purified by flash Chromatography with PE: EA = 10:1 ~ 0:1 to give the desired product (250 mg, 82.1 % yield) as a white solid. LC/MS: 408.1 $[M+Na]^+$.

Step 6: Preparation of 2-fluoro-4-(3-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy)aniline

[263] A solution of tert-butyl N-{2-fluoro-4-[3-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy]phenyl}carbamate (250 mg, 0.64 mmol) in TFA/DCM (1:3, 15 mL) was stirred at 25 °C for 1 hour. The reaction mixture was evaporated in vacuum to give the desired product (150 mg, 82.4 % yield). LC/MS: 285.9 $[M+1]^+$.

Step 7: Preparation of 6-bromo-N-(2-fluoro-4-(3-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy)phenyl) -7-methoxyquinazolin-4-amine

[264] To a solution of 2-fluoro-4-[3-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy]aniline (200 mg, 0.70 mmol) and 6-bromo-4-chloro-7-methoxyquinazoline (192 mg, 0.70 mmol) in dioxane (15 mL) stirred under nitrogen at 25 °C was added HCl/dioxane (0.5 mL). The reaction mixture was stirred at 25 °C for 5 hours. The reaction mixture was evaporated in vacuum to give a crude product. The crude product was purified by flash Chromatography with DCM: MeOH = 100:1 ~ 10:1 to give the desired product (200 mg, 54.7 % yield). LC/MS: 522.1 $[M+1]^+$.

Step 8: Preparation of tert-butyl 3-((4-((2-fluoro-4-(3-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy) phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidine-1-carboxylate

[265] To a suspension of 6-bromo-N-{2-fluoro-4-[3-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy]phenyl}-7-methoxyquinazolin-4-amine (200 mg, 0.38 mmol), (3-aminoazetidin-1-yl) tert-butylformate (332 mg, 1.91 mmol) and Cs_2CO_3 (374 mg, 1.15 mmol) in dioxane (20 mL) stirred under nitrogen at 25 °C was added Brettphos-Pd-G3 (35 mg, 0.04 mmol). The reaction mixture was stirred at 90 °C for 8 hours. The solid was filtered off and washed with EA (10 mL*2). The combined solution was evaporated in vacuum to give a crude product. The crude product was purified by flash Chromatography with DCM: MeOH = 1:0 ~ 10:1 to give the desired product (120 mg, 51.3 % yield). LC/MS: 614.3 $[M+1]^+$.

Step 9: Preparation of N6-(azetidin-3-yl)-N4-(2-fluoro-4-(3-(5-methyl-1,3,4-oxadiazol-2-yl) phenoxy)phenyl)-7-methoxyquinazoline-4,6-diamine

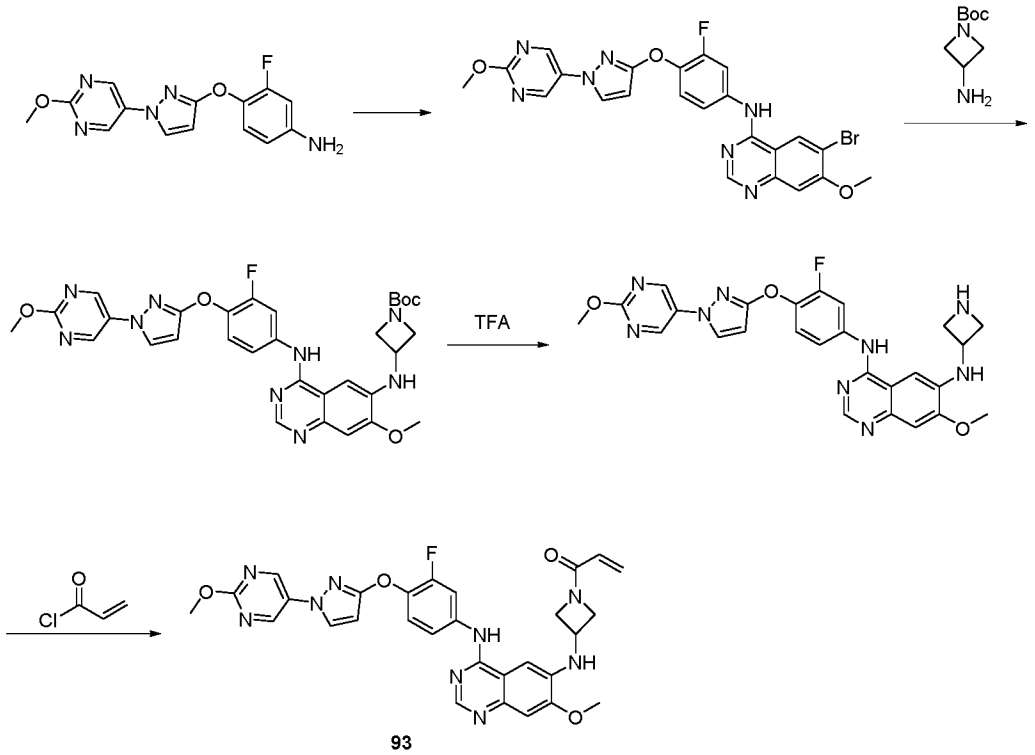
[266] A solution of tert-butyl 3-((4-((2-fluoro-4-(3-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy) phenyl) amino)-7-methoxyquinazolin-6-yl)amino)azetidine-1-carboxylate (120 mg, 0.19 mmol) in TFA/ DCM (1:3, 15 mL) was stirred at 25 °C for 2 hours. The reaction mixture was evaporated in vacuum to give the desired product (120 mg, TFA salt, 100 % yield). LC/MS: 514.2 $[M+1]^+$.

Step 10: Preparation of 1-(3-((4-((2-fluoro-4-(3-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy)phenyl) amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one

[267] To a solution of 6-N-(azetidin-3-yl)-4-N-{2-fluoro-4-[3-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy] phenyl}-7-methoxyquinazoline-4,6-diamine (120 mg, TFA salt, 0.19 mmol) and triethylamine (53 mg, 0.52 mmol) in DCM (10 mL) stirred under nitrogen at -78 °C was added prop-2-enoyl chloride (19 mg, 0.19 mmol). The reaction mixture was stirred at -78 °C for 20 minutes. The reaction mixture was quenched with water (10 mL), extracted with DCM (50 mL), dried over sodium sulphate and evaporated in vacuum to give a crude product. The crude product was purified by flash Chromatography with DCM: MeOH = 1:0 ~10:1 to give the desired product (15 mg, 13.9 % yield). LC/MS: 568.2 $[M+1]^+$.

^{1}H NMR (400 MHz, DMSO) δ 9.23 (s, 1H), 8.26 (s, 1H), 7.80 - 7.76 (m, 1H), 7.69 - 7.63 (m, 1H), 7.60 - 7.52 (m, 2H), 7.42 - 7.35 (m, 1H), 7.24 - 7.16 (m, 1H), 7.11 (s, 1H), 7.05 - 6.98 (m, 2H), 6.41 - 6.34 (m, 2H), 6.15 - 6.07 (m, 1H), 5.70 - 5.65 (m, 1H), 4.72 (t, J = 7.6 Hz, 1H), 4.50 - 4.37 (m, 2H), 4.16 - 4.12 (m, 1H), 3.99 (s, 3H), 3.97 - 3.91 (m, 1H), 2.58 (s, 3H).

Example 28: Preparation of 1-(3-((4-((3-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one (Compound 93)



93

Step 1: Preparation of 6-bromo-N-(3-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine

[268] To a solution of 3-fluoro-4-{[1-(2-methoxypyrimidin-5-yl)pyrazol-3-yl]oxy}aniline (397 mg, 1.3 mmol) and 6-bromo-4-chloro-7-methoxyquinazoline (300 mg, 1.1 mmol) in IPA/DCM (1/10, 10 mL) was added HCl/Dioxane (4N, 1 mL). The mixture was stirred at 25 °C for 3 hours. The mixture was concentrated in vacuum and purified by flash Chromatography (MeOH in DCM = 0 – 10 %) to afford the title compound (300 mg, 90 % purity, 45.5 % yield) as a yellow solid. LC/MS: 537.5$[M+H]^+$.

Step 2: Preparation of tert-butyl 3-((4-((3-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidine-1-carboxylate

[269] To a solution of 6-bromo-N-(3-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy) phenyl)-7-methoxyquinazolin-4-amine (220 mg, 90 % purity, 0.37 mmol) and (3-aminoazetidin-1-yl) tert-butyl formate (77 mg, 0.44 mmol) in dioxane (10 mL) was added Brett Phos-Pd-G3 (50 mg, 0.06 mmol) and t-BuONa (89 mg, 0.83 mmol). The mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. The reaction was quenched by adding water (20 mL) and extracted with EA (20 mL×3). The organic layer was washed with brine and concentrated in vacuum. The residue was purified by flash Chromatography (MeOH in DCM = 0 – 10 %) to afford the title compound (100 mg, 90 % purity, 38.6 % yield) as a white solid. LC/MS: 630.3$[M+H]^+$.

Step 3: Preparation of N6-(azetidin-3-yl)-N4-(3-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)-7-methoxyquinazoline-4,6-diamine

[270] To a solution of tert-butyl 3-((4-((3-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidine-1-carboxylate (100 mg, 90 % purity, 0.14 mmol) in DCM (9 mL) was added TFA (3 mL). The mixture was stirred at 25 °C for 1 hour. The

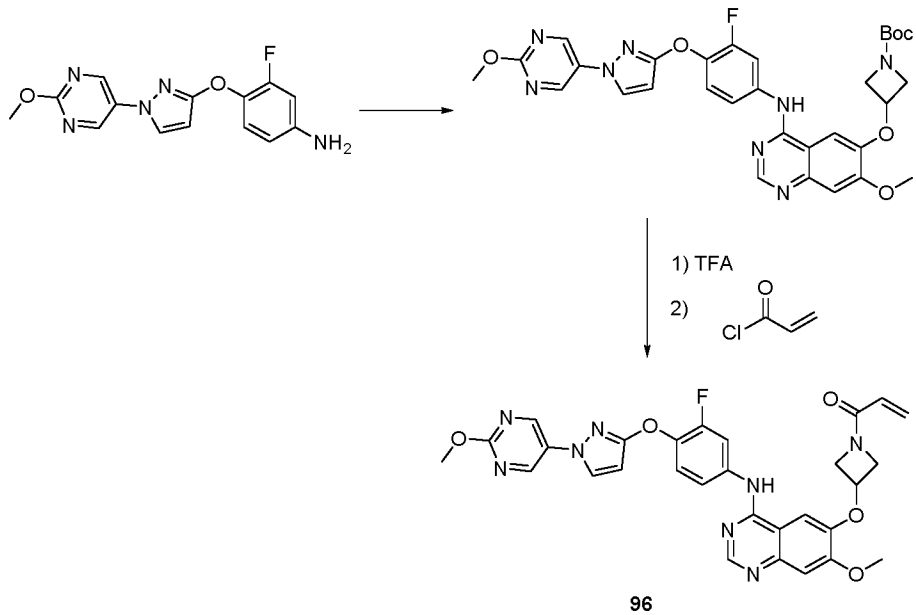
mixture was concentrated to afford the title compound (90 mg, TFA salt, 100 % yield) as a yellow oil. LC/MS: 529.7[M+H]$^+$.

Step 4: Preparation of 1-(3-((4-((3-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one

[271] To a solution of N6-(azetidin-3-yl)-N4-(3-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)-7-methoxyquinazoline-4,6-diamine (90 mg, TFA salt, 0.14 mmol) and DIPEA (73 mg, 0.57 mmol) in DCM (10 mL) was added acryloyl chloride (13 mg, 0.15 mmol) slowly at -78 °C . The mixture was stirred at -78 °C for 15 minutes. The mixture was quenched with MeOH (1 mL) and concentrated. The residue was purified by Prep-TLC with MeOH: DCM = 1: 10 to afford the title compound (15 mg, 18.3 % yield) as a yellow solid. LC/MS: 583.6[M+H]$^+$.

^{1}H NMR (400 MHz, DMSO) δ 10.67 (s, 1H), 8.98 (s, 2H), 8.76 (s, 1H), 8.48 (d, J = 2.5 Hz, 1H), 7.86 (d, J = 12.8 Hz, 1H), 7.59 - 7.47 (m, 2H), 7.23 (d, J = 5.1 Hz, 2H), 6.96 - 6.86 (m, 1H), 6.42 - 6.25 (m, 2H), 6.13 (d, J = 17.0 Hz, 1H), 5.70 (d, J = 10.3 Hz, 1H), 4.72 (d, J = 7.3 Hz, 1H), 4.53 - 4.40 (m, 2H), 4.23 - 4.15 (m, 1H), 4.06 (s, 3H), 4.01 - 3.91 (m, 4H).

Example 29: Preparation of 1-(3-((4-((3-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (Compound 96)



Step 1: Preparation of tert-butyl 3-((4-((3-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate

[272] A solution of 3-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)aniline （400 mg ，1.33 mmol） and tert-butyl {3-[(4-chloro-7-methoxyquinazolin-6-yl)oxy] azetidine-1-yl} formate (534 mg, 1.46 mmol) in DCM/i-PrOH/HCl（8:1:1, 10 mL） was stirred at room temperature for 4 hours. The solvent was removed in vacuum to give a crude product. The crude product was purified by Prep-TLC with MeOH/DCM (1/10) to afford the title compound (400 mg, 95 % purity, 45.3 % yield) as a white solid. LC/MS: 630. 6[M+H]$^+$.

Step 2: Preparation of methyl 6-(azetidin-3-yloxy)-N-(3-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine

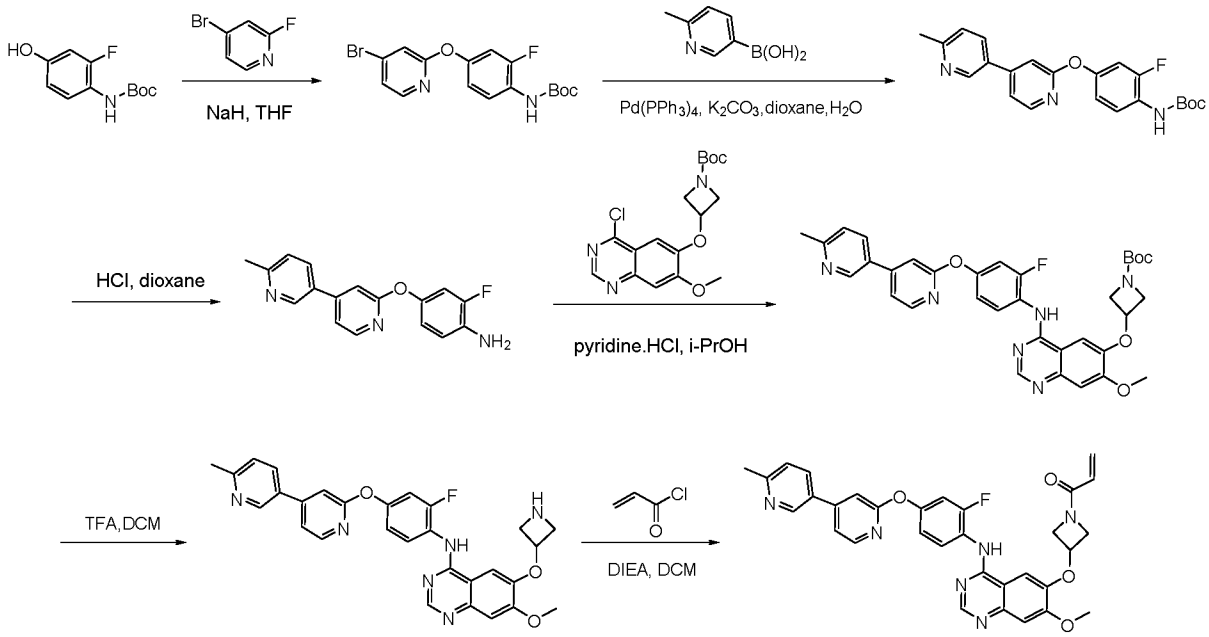
[273] A solution of tert-butyl 3-((4-((3-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy) phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (400 mg, 0.60 mmol) in DCM (7.5 mL) and TFA (2.5 mL) was stirred at room temperature for 2 hours. The solvent was removed in vacuum to give the title compound (400 mg, TFA salt, 100 % yield) as a brown solid. LC/MS: 530.7 $[M+H]^+$.

Step 3: Preparation of 1-(3-((4-((3-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy) phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

[274] To a solution of 6-(azetidin-3-yloxy)-N-(3-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine (400 mg, TFA salt, 0.60 mmol) and DIEA (254 mg, 2.3 mmol) in DMF (10 mL) was added prop-2-enoyl chloride (82 mg， 0.1 mmol) in batches at -30 °C.The reaction mixture was stirred at -30 °C for 60 minutes then quenched by adding MeOH (10 mL). The reaction was quenched by adding water (10 mL). The mixture was extracted with EA (10 ml×3). The residue was purified by silica gel chromatography with MeOH: DCM = 0:1 ~ 1:10 to afford the title compound (130 mg, 29.1 % yield) as a yellow solid. LC/MS: 584.6 [M+H]+ .

^{1}H NMR (400 MHz, DMSO) δ 9.83 (s, 1H), 8.97 (s, 2H), 8.60 (s, 1H), 8.46 (d, J = 2.6 Hz, 1H), 7.99 (dd, J = 13.1, 2.4 Hz, 1H), 7.65 - 7.53 (m, 2H), 7.47 (t, J = 9.0 Hz, 1H), 7.28 (s, 1H), 6.38 (dd, J = 17.0, 10.3 Hz, 1H), 6.24 (d, J = 2.5 Hz, 1H), 6.15 (dd, J = 17.0, 2.1 Hz, 1H), 5.71 (dd, J = 10.3, 2.0 Hz, 1H), 5.28 - 5.20 (m, 1H), 4.85 - 4.77 (m, 1H), 4.61 - 4.52 (m, 1H), 4.34 - 4.26 (m, 1H), 4.03 - 3.93 (m, 7H).

Example 30: Preparation of 1-(3-((4-((2-fluoro-4-((6-methyl-[3,4'-bipyridin]-2'-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (Compound 106)



106

Step 1: Preparation of tert-butyl (4-((4-bromopyridin-2-yl)oxy)-2-fluorophenyl)carbamate

[275] To a solution of tert-butyl (2-fluoro-4-hydroxyphenyl)carbamate (1 g, 4.4 mmol) in THF (30 mL) was added NaH (264 mg, 6.6 mmol, 60%). The solution was stirred at 25 °C for 0.5 hour. And then 4-bromo-2-fluoropyridine (774 mg, 4.4 mmol) was added. The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into ice water. The water layer was extracted with CH_2Cl_2 (100 mL × 3). The organic layer was combined, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified with Combi-flash (MeOH/DCM=1:19) to afford tert-butyl (4-((4-bromopyridin-2-yl)oxy)-2-fluorophenyl)carbamate (824 mg, 49%) as a light yellow solid. LC/MS: 383 $[M+H]^+$.

Step 2: Preparation of tert-butyl (2-fluoro-4-((6-methyl-[3,4'-bipyridin]-2'-yl)oxy)phenyl)carbamate

[276] To a solution of tert-butyl (4-((4-bromopyridin-2-yl)oxy)-2-fluorophenyl)carbamate (500 mg, 1.31 mmol) in dioxane/H_2O (10 mL/2.5 mL) was added (6-methylpyridin-3-yl)boronic acid (500 mg, 1.31 mmol), $Pd(PPh_3)_4$ (150 mg, 0.13 mmol) and K_2CO_3 (362 mg, 2.62 mmol). The mixture was stirred at 80 °C for 6 hours. The reaction mixture was concentrated and purified by Combi-flash (CH_2Cl_2/MeOH = 13:1) to afford tert-butyl (2-fluoro-4-((6-methyl-[3,4'-bipyridin]-2'-yl)oxy)phenyl)carbamate (383 mg, 74%) as an off-white solid. LC/MS: 396 $[M+H]^+$.

Step 3: Preparation of 2-fluoro-4-((6-methyl-[3,4'-bipyridin]-2'-yl)oxy)aniline

[277] A solution of tert-butyl (2-fluoro-4-((6-methyl-[3,4'-bipyridin]-2'-yl)oxy)phenyl)carbamate (373 mg, 0.94 mmol) in HCl/dioxane (8 mL) was stirred at room temperature for 1 hour. The reaction mixture was concentrated in vacuo to afford 2-fluoro-4-((6-methyl-[3,4'-bipyridin]-2'-yl)oxy)aniline (277 mg, crude) as a light yellow solid. LC/MS: 296 $[M+H]^+$.

Step 4: Preparation of tert-butyl 3-((4-((2-fluoro-4-((6-methyl-[3,4'-bipyridin]-2'-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate

[278] To a solution of 2-fluoro-4-((6-methyl-[3,4'-bipyridin]-2'-yl)oxy)aniline (100 mg, 0.34 mmol) in i-PrOH (10 mL) was added tert-butyl 3-((4-chloro-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (124 mg, 0.34 mmol) and pyridine hydrochloride (59 mg, 0.51 mmol). The reaction mixture was stirred at 80 °C for 2 hours. The reaction mixture was concentrated and purified by Combi-flash (DCM/MeOH=11/1) to afford tert-butyl 3-((4-((2-fluoro-4-((6-methyl-[3,4'-bipyridin]-2'-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (120 mg, 57%) as a light yellow solid. LC/MS: 625 $[M+H]^+$.

Step 5: Preparation of 6-(azetidin-3-yloxy)-N-(2-fluoro-4-((6-methyl-[3,4'-bipyridin]-2'-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine

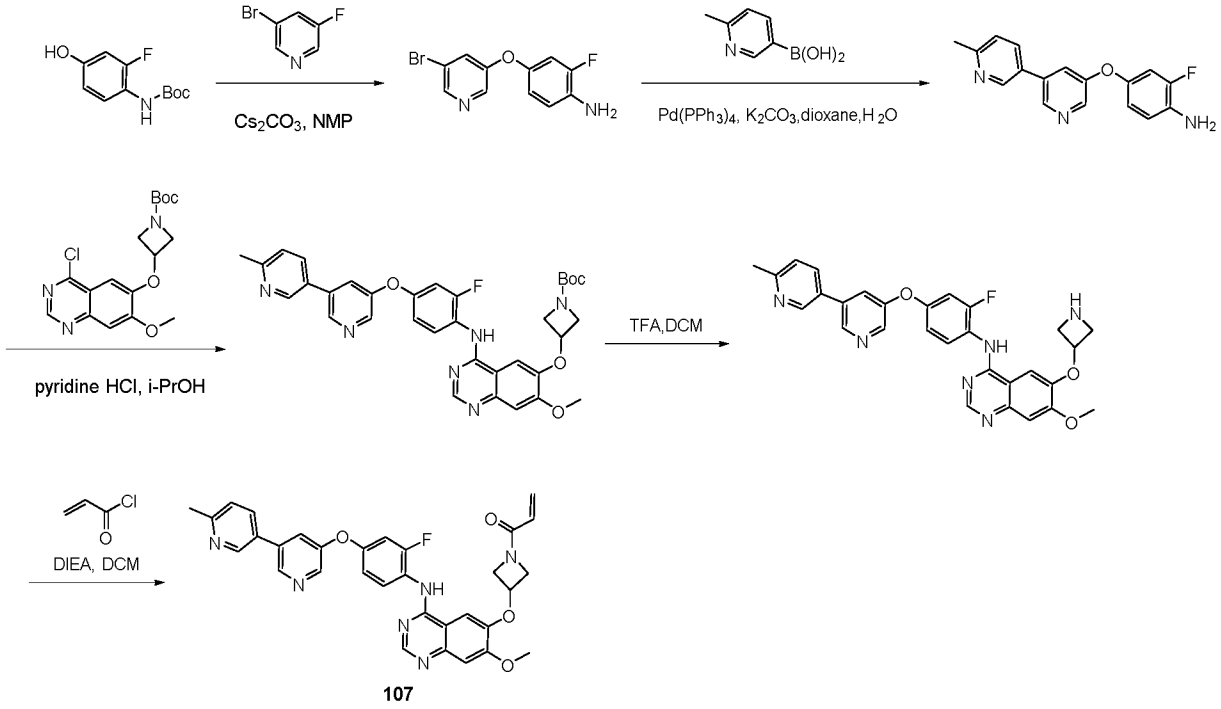
[279] A solution of tert-butyl 3-((4-((2-fluoro-4-((6-methyl-[3,4'-bipyridin]-2'-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (115 mg, 0.18 mmol) in DCM/TFA (6 mL/2 mL) was stirred at room temperature for 1 hour. The reaction solution was poured into water (60 mL) and extracted with CH_2Cl_2 (50 mL × 3). The organic layer was combined, dried over Na_2SO_4 and concentrated in vacuo to afford 6-(azetidin-3-yloxy)-N-(2-fluoro-4-((6-methyl-[3,4'-bipyridin]-2'-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine (80 mg, crude) as an off-white solid. LC/MS: 525 $[M+H]^+$.

Step 6: Preparation of 1-(3-((4-((2-fluoro-4-((6-methyl-[3,4'-bipyridin]-2'-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

[280] To a solution of 6-(azetidin-3-yloxy)-N-(2-fluoro-4-((6-methyl-[3,4'-bipyridin]-2'-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine (75 mg, 0.14 mmol) in CH_2Cl_2 (10 mL) was added DIEA (36 mg, 0.28 mmol) and acryloyl chloride (13 mg, 0.14 mmol) at -78 °C. The reaction was stirred at -78 °C for 3 min. The reaction mixture was concentrated and purified by prep-HPLC (CH_3CN/H_2O = 60:40) to afford AB-BD-12-26 (22.4 mg, 27 %) as a white solid. LC/MS: 579 $[M+H]^+$.

^1H NMR (400 MHz, CD_3OD) δ 9.13 (s, 1H), 8.76-8.73 (m, 1H), 8.70 (s, 1H), 8.35 (d, J = 5.2 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.71 (s, 1H), 7.66 – 7.52 (m, 3H), 7.34 (s, 1H), 7.23-7.20 (m, 1H), 7.19 – 7.13 (m, 1H), 6.40-6.38 (m, 1H), 6.29-6.27 (m, 1H), 5.79-5.77 (m, 1H), 5.34 – 5.27 (m, 1H), 4.91 – 4.86 (m, 1H), 4.64-4.63 (m, 1H), 4.46-4.43 (m, 1H), 4.23 – 4.07 (m, 4H), 2.83 (s, 3H).

Example 31: Preparation of 1-(3-((4-((2-fluoro-4-((6'-methyl-[3,3'-bipyridin]-5-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (Compound 107)



107

Step 1: Preparation of 4-((5-bromopyridin-3-yl)oxy)-2-fluoroaniline

[281] To a solution of tert-butyl (2-fluoro-4-hydroxyphenyl)carbamate (1 g, 4.4 mmol) in NMP (20 mL) was added 3-bromo-5-fluoropyridine (774 mg, 4.4 mmol) and Cs_2CO_3 (1.4 g, 8.8 mmol). The solution was stirred at 100 °C for 3 hours. The reaction mixture was poured into water and extracted with EA (200 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified with Combi-flash (MeOH/DCM = 1:13) to afford 4-((5-bromopyridin-3-yl)oxy)-2-fluoroaniline (396 mg, 32%) as a light yellow solid. LC/MS: 283 $[M+H]^+$.

Step 2: Preparation of 2-fluoro-4-((6'-methyl-[3,3'-bipyridin]-5-yl)oxy)

[282] To a solution of 4-((5-bromopyridin-3-yl)oxy)-2-fluoroaniline (386 mg, 1.36 mmol) in dioxane/H_2O (8 mL/2 mL) was added (6-methylpyridin-3-yl)boronic acid (186 mg, 1.36 mmol), $Pd(PPh_3)_4$ (161 mg, 0.14 mmol) and K_2CO_3 (375 mg, 2.72 mmol). The mixture was stirred at 80 °C for 6 hours. The reaction mixture was concentrated and purified by Combi-flash (CH_2Cl_2/MeOH=13:1) to afford 2-fluoro-4-((6'-methyl-[3,3'-bipyridin]-5-yl)oxy)aniline (396 mg, 98%) as an off-white solid. LC/MS: 396 $[M+H]^+$.

Step 3: Preparation of tert-butyl 3-((4-((2-fluoro-4-((6'-methyl-[3,3'-bipyridin]-5-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate

[283] To a solution of 2-fluoro-4-((6-methyl-[3,4'-bipyridin]-2'-yl)oxy)aniline (100 mg, 0.34 mmol) in i-PrOH (10 mL) was added tert-butyl 3-((4-chloro-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (124 mg, 0.34 mmol) and pyridine hydrochloride (79 mg, 0.68 mmol). The reaction mixture was stirred at 80 °C for 2 hours. The reaction mixture was concentrated and purified by Combi-flash (DCM/MeOH=11/1) to afford tert-butyl 3-((4-((2-fluoro-4-((6'-methyl-[3,3'-bipyridin]-5-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (70 mg, 33%) as a light yellow solid. LC/MS: 625 $[M+H]^+$.

Step 4: Preparation of 6-(azetidin-3-yloxy)-N-(2-fluoro-4-((6'-methyl-[3,3'-bipyridin]-5-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine

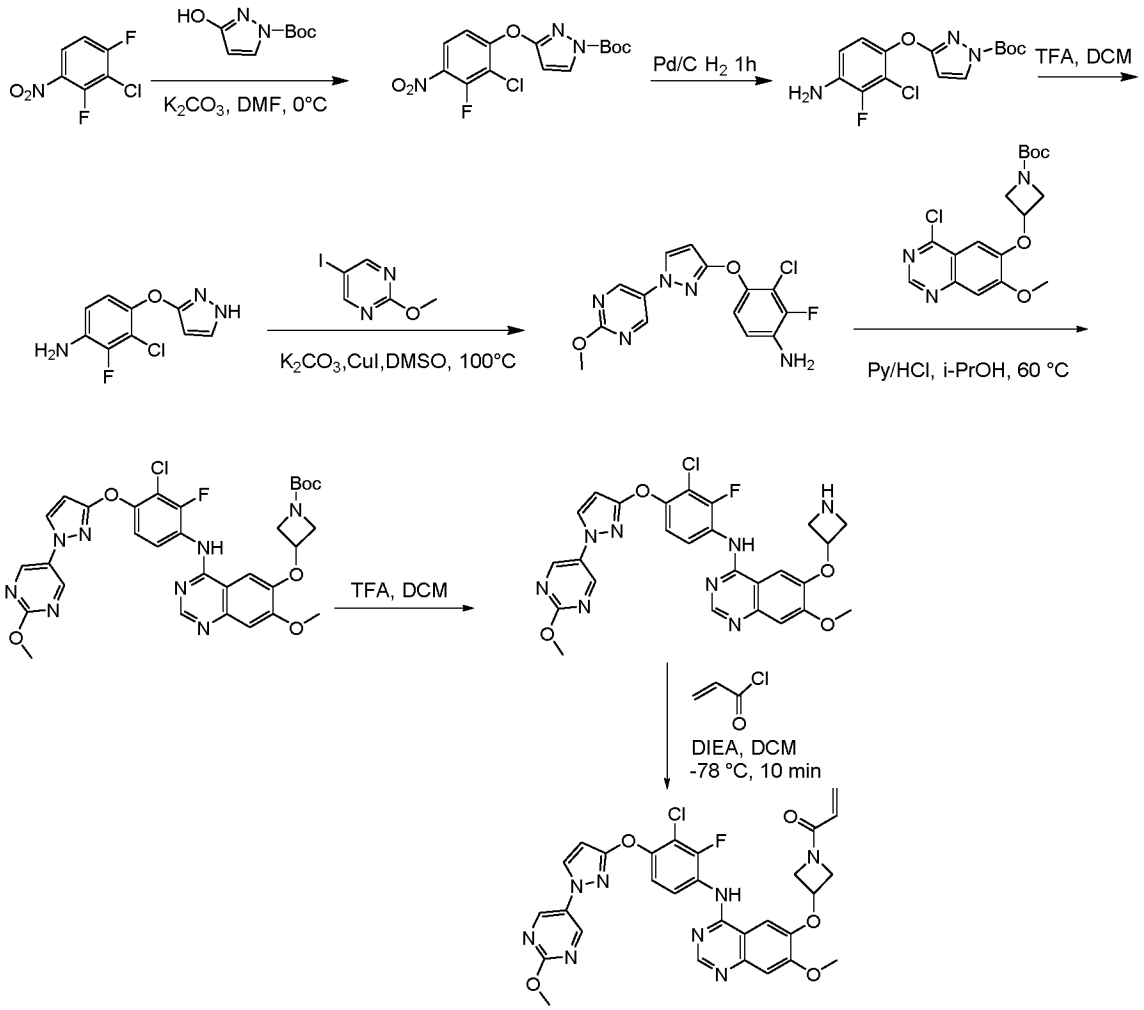
[284] A solution of tert-butyl 3-((4-((2-fluoro-4-((6'-methyl-[3,3'-bipyridin]-5-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (65 mg, 0.12 mmol) in DCM/TFA (6 mL/2 mL) was stirred for 1 hour at room temperature. The solution was poured into water (60 mL) and extracted with CH_2Cl_2 (50 mL × 3). The organic layer was combined, dried over Na_2SO_4 and concentrated in vacuo to afford 6-(azetidin-3-yloxy)-N-(2-fluoro-4-((6'-methyl-[3,3'-bipyridin]-5-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine (50 mg, crude) as a gray white solid. LC/MS: 525 $[M+H]^+$.

Step 5: Preparation of 1-(3-((4-((2-fluoro-4-((6'-methyl-[3,3'-bipyridin]-5-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

[285] To a solution of 6-(azetidin-3-yloxy)-N-(2-fluoro-4-((6'-methyl-[3,3'-bipyridin]-5-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine (45 mg, 0.09 mmol) in CH_2Cl_2 (6 mL) was added DIEA (22 mg, 0.18 mmol) and acryloyl chloride (8 mg, 0.09 mmol) at -78 °C. The solution was stirred at -78 °C for 3 min. The reaction solution was concentrated and purified by prep-HPLC (CH_3CN/H_2O=60:40) to afford AB-BD-12-29 (11.5 mg, 23 %) as a white solid. LC/MS: 579 $[M+H]^+$.

^1H NMR (400 MHz, CD_3OD) δ 9.04 (d, J = 2.0 Hz, 1H), 8.81 (d, J = 2.0 Hz, 1H), 8.69 (s, 1H), 8.66 – 8.61 (m, 1H), 8.52 (d, J = 2.4 Hz, 1H), 8.09 – 8.02 (m, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.68 (s, 1H), 7.64 – 7.59 (m, 1H), 7.31 (s, 1H), 7.18-7.16 (m, 1H), 7.10-7.08 (m, 1H), 6.39-6.37 (m, 1H), 6.29-6.27 (m, 1H), 5.79-5.78 (m, 1H), 5.32 – 5.26 (m, 1H), 4.87 – 4.85 (m, 1H), 4.63-4.61 (m, 1H), 4.46-4.43 (m, 1H), 4.19 – 4.07 (m, 4H), 2.79 (s, 3H).

Example 32: Preparation of 1-(3-((4-((3-chloro-2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (Compound 111)



Step 1: Preparation of tert-butyl 3-(2-chloro-3-fluoro-4-nitrophenoxy)-1H-pyrazole-1-carboxylate

[286] To a solution of 2-chloro-1,3-difluoro-4-nitrobenzene (2 g, 10.4 mmol) in DMF (10 mL) was added tert-butyl 3-hydroxy-1H-pyrazole-1-carboxylate (1.9 g, 10.3 mmol) and K_2CO_3 (4.3 g, 31 mmol). The reaction was stirred at 0 °C for 4 h. The mixture was diluted with water and extracted with EA. The organic layer was concentrated and purified by column chromatography (PE/EA = 10/1) to afford the product (2.1 g, 57%) as a white solid. LC/MS: 302.0 $[M-55]^+$.

Step 2: Preparation of tert-butyl 3-(4-amino-2-chloro-3-fluorophenoxy)-1H-pyrazole-1-carboxylate

[287] To a solution of tert-butyl 3-(2-chloro-3-fluoro-4-nitrophenoxy)-1H-pyrazole-1-carboxylate (2.1 g, 5.9 mmol) in MeOH (15 mL) was added Pd/C (600 mg). The mixture was stirred at 20 °C for 1 h. The reaction mixture was filtered and the filtrate was concentrated in vacuo to afford the product (1.2 g, 63%) as a yellow oil. LC/MS: 271.8 $[M-55]^+$.

Step 3: Preparation of 4-((1H-pyrazol-3-yl)oxy)-3-chloro-2-fluoroaniline

[288] To a solution of tert-butyl 3-(4-amino-2-chloro-3-fluorophenoxy)-1H-pyrazole-1-carboxylate (1.1 g, 3.4 mmol) in DCM (10 mL) was added TFA (2 mL). The mixture was stirred at 20 °C for 1 h. The mixture was quenched with sat. $NaHCO_3$ solution and extracted with DCM (30 mL*2). The combined organic layers were washed with brine and dried over Na_2SO_4, filtered and the filtrate was concentrated to afford 3-chloro-2-fluoro-4-(1H-pyrazol-3-yloxy)aniline (700 mg, 92%) as a colorless oil. LC/MS: 227.9 $[M+H]^+$.

Step 4: Preparation of 3-chloro-2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)aniline

[289] To a solution of 4-((1H-pyrazol-3-yl)oxy)-3-chloro-2-fluoroaniline (300 mg, 1.32 mmol) in DMSO (5 mL) was added Trans-N,N'-Dimethyl-cyclohexane-1,2-diamine (210 mg, 1.32 mmol), 5-iodo-2-methoxypyrimidine (342 mg, 1.45 mmol), K_2CO_3 (546 mg, 3.95 mmol) and CuI (252 mg, 1.32 mmol). The mixture was stirred at 100 °C for 16 h. The reaction mixture was dissolved in EA and washed with brine, dried over Na2SO4 and filtered. The filtrate was concentrated and purified by Combi-Flash (eluted by EA/PE = 0-60%) to afford 3-chloro-2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)aniline (320 mg, 72%) as a brown solid. LC/MS: 335.8 $[M+H]^+$.

Step 5: Preparation of tert-butyl 3-((4-((3-chloro-2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate

[290] To a solution of tert-butyl 3-((4-chloro-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (153 mg, 0.5 mmol) in i-PrOH (5 mL) was added 3-chloro-2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)aniline (140 mg, 0.5 mmol) and pyridine hydrochloride (72 mg, 0.6 mmol). The reaction mixture was stirred at 80 °C for 2 h. The mixture was concentrated and purified by column chromatorgraphy (PE/EA = 3/1) to afford the product (150 mg, 50%) as a yellow solid. LC/MS: 665.0 [M+H]+.

Step 6: Preparation of 6-(azetidin-3-yloxy)-N-(3-chloro-2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine

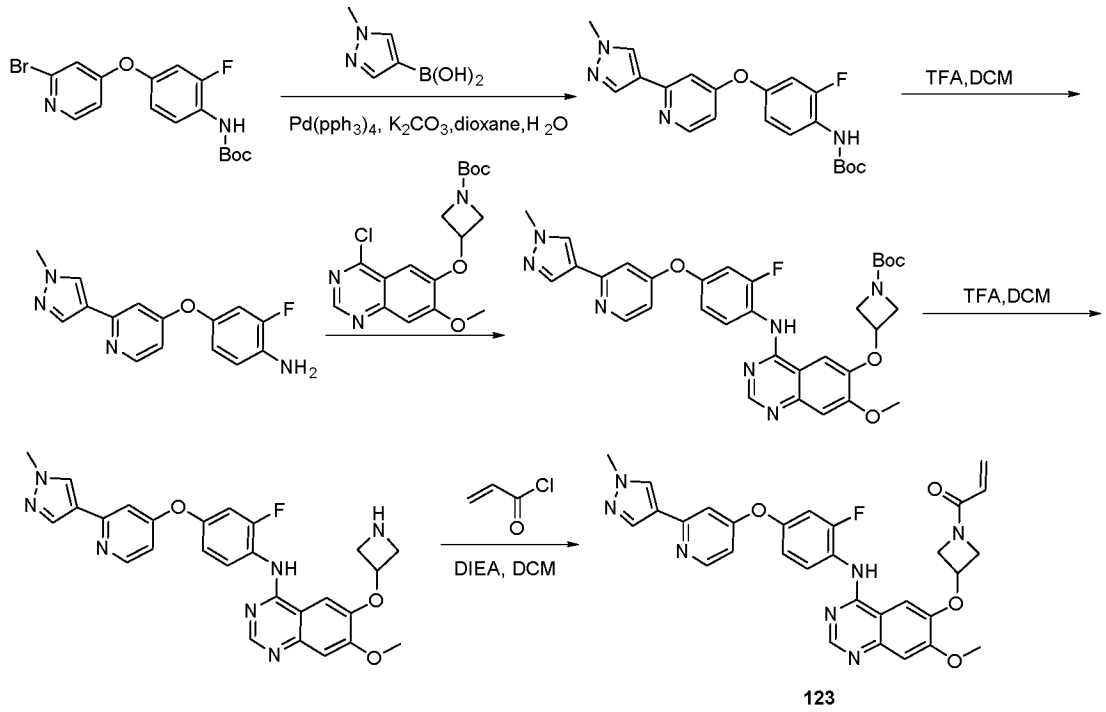
[291] To a solution of tert-butyl 3-((4-((3-chloro-2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (148 mg, 0.22 mmol) in DCM (3 mL) was added TFA (1 mL). The mixture was stirred at 25 °C for 30 min. The mixture was adjusted pH = 8 with sat. $NaHCO_3$ solution and extracted with DCM (10 mL×2). The organic layer was concentrated in vacuo to afford the crude product (150 mg). LC/MS: 565.0 $[M+H]^+$.

Step 7: Preparation of 1-(3-((4-((3-chloro-2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

[292] To a solution of 6-(azetidin-3-yloxy)-N-(3-chloro-2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine (100 mg, 0.18 mmol) in DCM (2 mL) was added DIEA (137 mg, 1.062 mmol) and prop-2-enoyl chloride (11 mg, 0.124 mmol) in DCM (1 mL) at -78 °C. The mixture was stirred at -78 °C for 5 min. The mixture was diluted with ACN/H_2O = 3/1 (5 mL). Then the mixture was concentrated in vacuo and purified by prep-HPLC (ACN/0.1%TFA in H_2O = 15/85 to 40/60) to afford the desired product (16.6 mg, 15%) as a white solid. LC/MS: 619.0 $[M+H]^+$.

^{1}H NMR (400 MHz, MeOD) δ 8.94 (s, 2H), 8.75 (s, 1H), 8.29 (d, J = 2.7 Hz, 1H), 7.68 (s, 1H), 7.58-7.52 (m, 1H), 7.37-7.30 (m, 2H), 6.46-6.38 (m, 1H), 6.35-6.27 (m, 2H), 5.81-5.80 (m, 1H), 5.35-5.28 (m, 1H), 4.90-4.86 (m, 1H), 4.69-4.61 (m, 1H), 4.52-4.45 (m, 1H), 4.23-4.11 (m, 4H), 4.07 (s, 3H).

Example 33: 1-(3-((4-((2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (Compound 123)



123

Step 1: Preparation of tert-butyl (2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl) pyridin-4-yl) oxy) phenyl) carbamate

[293] To a solution of tert-butyl (4-((2-bromopyridin-4-yl)oxy)-2-fluorophenyl)carbamate (300 mg, 0.79 mmol) in dioxane/H_2O (10 mL/2 mL) was added (1-methyl-1H-pyrazol-4-yl)boronic acid (117.9 mg, 0.94 mmol), $Pd(pph_3)_4$ (90 mg, 0.078 mmol) and K_2CO_3 (322 mg, 2.34 mmol). The reaction mixture was stirred at 80 °C for 2 h. The mixture was concentrated and purified by Combi-Flash (EA/PE = 0-30%) to afford tert-butyl (2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl) pyridin-4-yl) oxy) phenyl) carbamate (300 mg, 99 %) as a yellow solid. LC/MS: 385.4$[M+H]^+$.

Step 2: Preparation of 2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl) pyridin-4-yl) oxy) aniline

[294] To a solution of tert-butyl (2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl) pyridin-4-yl) oxy) phenyl) carbamate (280 mg, 0.73 mmol) in DCM (12 mL) was added TFA (2.4 mL). The solution was stirred at rt for 30 min. The reaction mixture was poured into ice $NaHCO_3$ (10 mL) and extracted with EA. The organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated to afford the crude product (180 mg). LC/MS: 285.2 $[M+H]^+$.

Step 3: Preparation of tert-butyl 3-((4-((2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate

[295] To a solution of 2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl) pyridin-4-yl) oxy) aniline (180 mg, 0.63 mmol) in ACN (10 mL) was added tert-butyl 3-((4-chloro-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (230 mg, 0.63 mmol) and TsOH (108 mg, 0.63 mmol). The mixture was stirred for 2 hours at 80 °C. The mixture was concentrated and purified by Combi-Flash (DCM/MeOH = 0-10%) to afford tert-butyl 3-((4-((2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (300 mg, 77 %) as a yellow solid. LC/MS: 614.6$[M+H]^+$.

Step 4: Preparation of 6-(azetidin-3-yloxy)-N-(2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine

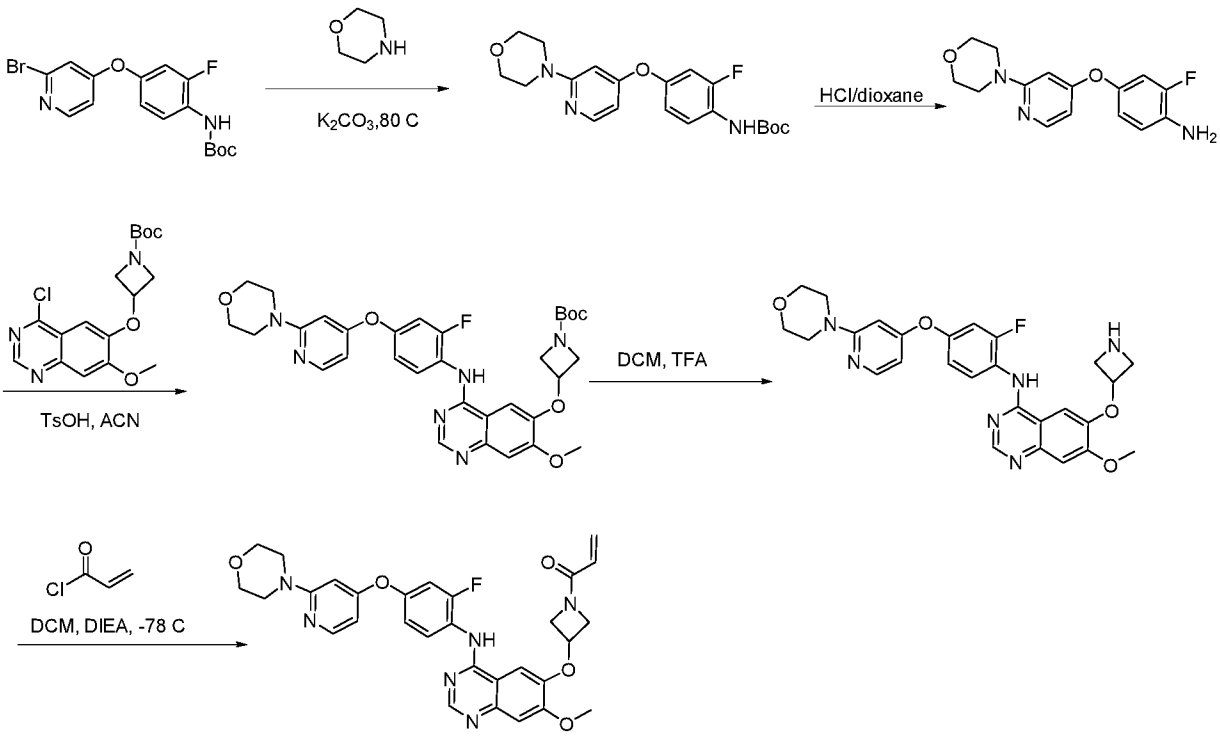
[296] To a solution of tert-butyl 3-((4-((2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (280 mg, 0.46 mmol) in DCM (12 mL) was added TFA (2.4 mL). The solution was stirred at rt for 30 min. The mixture was poured into ice $NaHCO_3$ (10 mL) and extracted with EA. The organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated to afford the crude product (180 mg). LC/MS: 514.5 $[M+H]^+$.

Step 5: Preparation of 1-(3-((4-((2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

[297] To a solution of 6-(azetidin-3-yloxy)-N-(2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine (100 mg, 0.19 mmol) in DCM (10 mL) was added acryloyl chloride (13.75 mg, 0.15 mmol) and DIEA (74 mg, 0.57 mmol). The reaction was stirred at -78 °C for 15 min. The reaction was quenched with MeCN and water, concentrated and purified by Prep-HPLC (0.1% TFA in water /MeCN from 70% to 15%) to afford 1-(3-((4-((2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (27 mg, 25 %) as a white solid. LC/MS: 568.5$[M+H]^+$.

1H NMR (400 MHz, DMSO) δ 9.53 (s, 1H), 8.44 (d, J = 4.0 Hz, 1H), 8.42-8.40 (m, 1H), 8.30 (s, 1H), 8.03-7.96 (m, 1 H), 7.64-7.59 (m, 1H), 7.52 (s, 1H), 7.36-7.26 (m, 3H), 7.12-7.10 (m, 1H), 6.76-6.74 (m, 1H), 6.42-6.35 (m, 1H), 6.17-6.10 (m, 1H), 5.72-5.69 (m, 1H), 5.23-5.12 (m, 1H), 4.83-4.79 (m, 1H), 4.60-4.55 (m, 1H), 4.31-4.28 (m, 1H), 3.98-3.94 (m, 4H), 3.88 (s, 3H).

Example 34: Preparation of 1-(3-((4-((2-fluoro-4-((2-morpholinopyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (Compound 124)



124

Step 1: Preparation of tert-butyl (2-fluoro-4-((2-morpholinopyridin-4-yl)oxy)phenyl)carbamate

[298] To a solution of tert-butyl (4-((2-bromopyridin-4-yl)oxy)-2-fluorophenyl)carbamate (250 mg, 0.65 mmol) in CH_3CN (10 mL) was added morpholine (112 mg, 1.29 mmol) and K_2CO_3 (328 mg, 2.58 mmol). The reaction mixture was stirred at 90 °C for 5 h. The reaction solution was diluted with water (100 mL) and extracted by EA (50 mL x 3). The combined organic layers were wash with brine, dried over Na_2SO_4, filtered and the filtrate was concentrated. The crude product was purified by Combi-flash (PE/EA = 2:1) to afford tert-butyl (2-fluoro-4-((2-morpholinopyridin-4-yl)oxy)phenyl)carbamate (230 mg, 91%). LC/MS: 388$[M+H]^+$.

Step 2: Preparation of 2-fluoro-4-((2-morpholinopyridin-4-yl)oxy)aniline

[299] A solution of tert-butyl (2-fluoro-4-((2-(thiazol-5-yl)pyridin-4-yl)oxy)phenyl)carbamate (230 mg, 0.6 mmol) in HCl/dioxane (10 mL) was stirred at 25 °C for 2 h. The reaction solution was concentrated in vacuo to afford 2-fluoro-4-((2-morpholinopyridin-4-yl)oxy)aniline (188 mg, crude). LC/MS: 287 $[M+H]^+$.

Step 3: Preparation of tert-butyl 3-((4-((2-fluoro-4-((2-morpholinopyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate

[300] To a solution of 2-fluoro-4-((2-morpholinopyridin-4-yl)oxy)aniline (188 mg, 0.66 mmol) in ACN (5 mL) was added tert-butyl 3-((4-chloro-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (205 mg, 0.66 mmol) and TsOH (57 mg, 0.33 mmol). The reaction was stirred at 80 °C for 4 h. The mixture was concentrated and purified by Combi-Flash (DCM/MeOH = 10:1) to afford tert-butyl 3-((4-((2-fluoro-4-((2-morpholinopyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (178 mg, 44 %) as a yellow solid. LC/MS: 617 $[M+H]^+$.

Step 4: Preparation of 6-(azetidin-3-yloxy)-N-(2-fluoro-4-((2-morpholinopyridin-4-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine

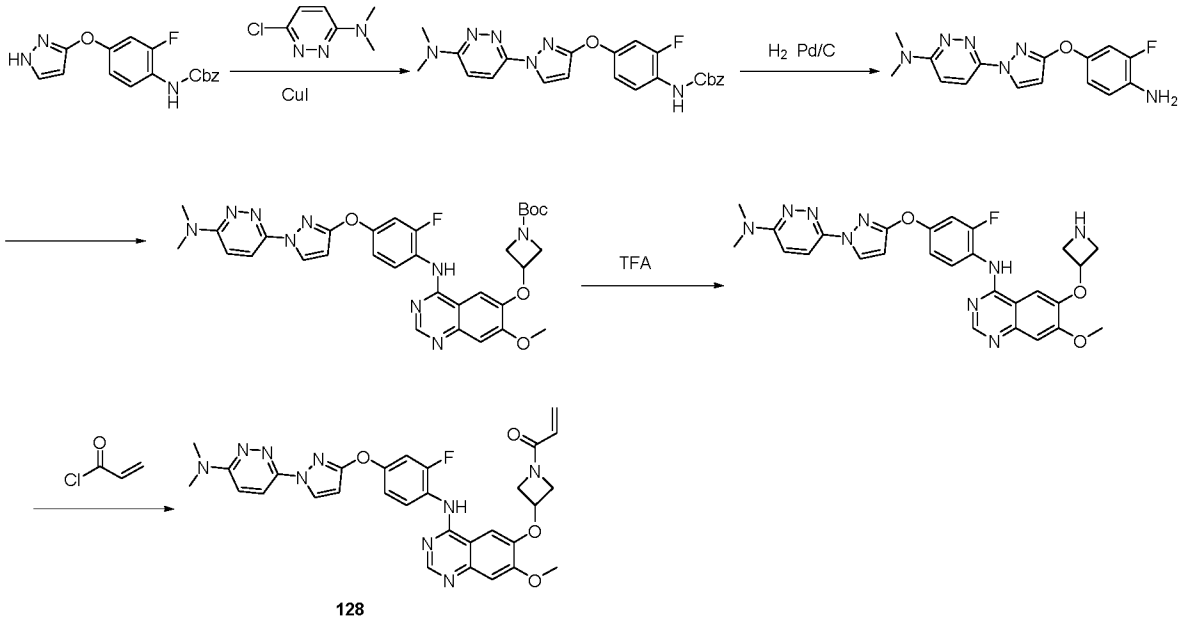
[301] To a solution of tert-butyl 3-((4-((2-fluoro-4-((2-morpholinopyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (178 mg, 0.29 mmol) in DCM (20 mL) was added TFA (5 mL). The reaction solution was stirred at 25 °C for 2 h. The mixture was concentrated under reduced vacuum. The residue was dissolved with EA. The organic layer was washed with saturated sodium bicarbonate, dried over Na_2SO_4, filtered and the filtrate was concentrated in vacuo to afford 6-(azetidin-3-yloxy)-N-(2-fluoro-4-((2-morpholinopyridin-4-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine (103 mg, crude) as a yellow solid. LC/MS: 519 $[M+H]^+$.

Step 5: Preparation of 1-(3-((4-((2-fluoro-4-((2-morpholinopyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

[302] To a solution of 6-(azetidin-3-yloxy)-N-(2-fluoro-4-((2-morpholinopyridin-4-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine (103 mg, 0.2 mmol) in DCM (5 mL) was added DIEA (28 mg, 0.2 mmol) and acryloyl chloride (20 mg, 0.2 mmol). The reaction solution was stirred at -78 °C for 10 min. The reaction was quenched with H_2O, concentrated and purified by prep-HPLC (ACN-H_2O (0.1% TFA), 30%-55%) to afford 1-(3-((4-((2-fluoro-4-((2-morpholinopyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (14 mg, 12%) as a yellow solid.

1H NMR (400 MHz, DMSO) δ 9.93 (s, 1H), 8.51 (s, 1H), 8.10 (d, J = 5.7 Hz, 1H), 7.64 – 7.54 (m, 2H), 7.23-7.31 (m, 2H), 7.07 (dd, J = 8.7, 1.9 Hz, 1H), 6.50 – 6.29 (m, 3H), 6.14 (dd, J = 17.0, 2.1 Hz, 1H), 5.71 (dd, J = 10.3, 2.1 Hz, 1H), 5.25-5.16 (m, 1H), 4.86 – 4.76 (m, 1H), 4.62-4.54 (m, 1H), 4.35-4.26 (m, 1H), 4.04-4.39 (m, 4H), 3.74 – 3.64 (m, 4H), 3.49-3.42 (m, 4H).

Example 35: Preparation of 1-(3-((4-((4-((1-(6-(dimethylamino)pyridazin-3-yl)-1H-pyrazol-3-yl)oxy)-2-fluorophenyl) amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (Compound 128)



Step 1: Preparation of benzyl (4-((1-(6-(dimethylamino)pyridazin-3-yl)-1H-pyrazol-3-yl)oxy)-2-fluorophenyl)carbamate

[303] To a solution of benzyl (4-((1H-pyrazol-3-yl)oxy)-2-fluorophenyl)carbamate (300 mg, 0.92 mmol) and 6-chloro-N,N-dimethylpyridazin-3-amine (145 mg, 0.92 mmol) in dioxane (10 mL) was added t-BuXPhOS (156 mg, 0.36 mmol), tris(dibenzylideneacetone)dipalladium (84 mg, 0.09 mmol) and Cs_2CO_3 (450 mg, 1.38 mmol) at room temperature under N_2 atmosphere. The resulting mixture was stirred at 80 °C for 5 hours. The solid was filtered off and washed with EA (10 mL×2). The solution was concentrated in vacuum to give a crude product. The crude product was purified by flash chromatography with PE: EA = 1:0 ~ 2:1 to afford the desired compound (110 mg, 26.6 %) as a red solid. LC/MS: 448.9$[M+H]^+$.

Step 2: Preparation of 6-(3-(4-amino-3-fluorophenoxy)-1H-pyrazol-1-yl)-N,N-dimethylpyridazin-3-amine

[304] To a solution of benzyl (4-((1-(6-(dimethylamino)pyridazin-3-yl)-1H-pyrazol-3-yl)oxy)-2-fluoro phenyl)carbamate (110 mg, 0.25 mmol) in THF (5 mL) was added Pd/C (5.3 mg, 0.05 mmol). The mixture was stirred at 45 °C for 3 hours under H_2 atmosphere. The catalyst was filtered off and washed with THF (5 mL*2). The solution was concentrated in vacuum to give the product (80 mg, 100 %) as a brown solid. LC/MS: 315.0$[M+H]^+$.

Step 3: Preparation of tert-butyl 3-((4-((4-((1-(6-(dimethylamino)pyridazin-3-yl)-1H-pyrazol-3-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate

[305] To a solution of 6-[3-(4-amino-3-fluorophenoxy)pyrazol-1-yl]-N,N-dimethylpyridazin-3-amine (110 mg, 0.35 mmol) and tert-butyl {3-[(4-chloro-7-methoxyquinazolin-6-yl)oxy]azetidin-1-yl} formate (128 mg, 0.35 mmol) in i-PrOH (6 mL) was added HCl (0.5 mL). The mixture was stirred at room temperature overnight. The solvent was removed in vacuum then the residue was dissolved with DCM (10 mL) and adjust pH to 9 with Et_3N. The mixture was concentrated in vacuum and the residue was purified by Prep-TLC with MeOH: DCM = 1: 20 to give the desired product (70 mg, 31.0 %) as a yellow solid. LC/MS: 643.8 $[M+H]^+$.

Step 4: Preparation of 6-(azetidin-3-yloxy)-N-(4-((1-(6-(dimethylamino)pyridazin-3-yl)-1H-pyrazol-3-yl)oxy)-2-fluorophenyl)-7-methoxyquinazolin-4-amine

[306] A solution of tert-butyl 3-((4-((4-((1-(6-(dimethylamino)pyridazin-3-yl)-1H-pyrazol-3-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (70 mg, 0.11 mmol) in DCM (7.5 mL) and TFA (2.5 mL) was stirred at room temperature for 3 hours. The solvent was removed in vacuum to give the title compound (70 mg, TFA salt, 100 % yield) as a brown solid. LC/MS: 544.1 $[M+H]^+$.

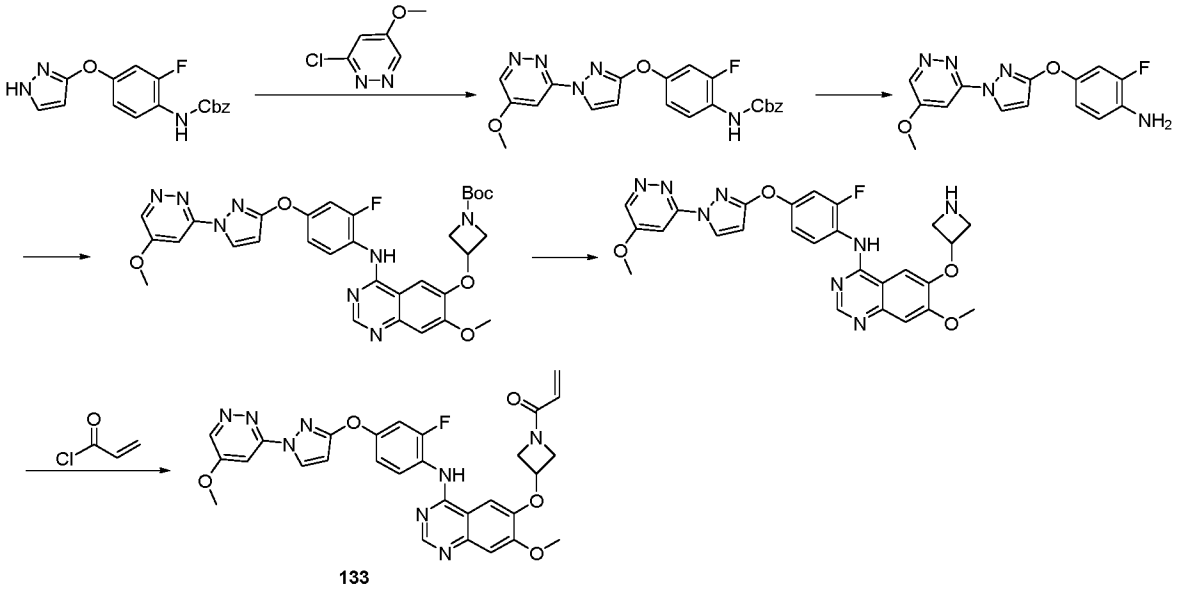
Step 5: Preparation of 1-(3-((4-((4-((1-(6-(dimethylamino)pyridazin-3-yl)-1H-pyrazol-3-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

[307] To a solution of 6-(azetidin-3-yloxy)-N-[4-({1-[6-(dimethylamino)pyridazin-3-yl]pyrazol-3-yl}oxy)-2-fluorophenyl]-7-methoxyquinazolin-4-amine (70 mg, TFA salt, 0.11 mmol) and TEA (33 mg, 0.33 mmol) in DCM (10 mL) was added prop-2-enoyl chloride (9.9 mg, 0.11 mmol) at -78 °C. The

reaction mixture was stirred at -78 °C for 2 hours. The reaction was quenched by adding water (1 mL) and concentrated in vacuum. The residue was purified by Prep-TLC with MeOH: DCM = 1: 10 to give the title compound (30 mg, 45.6 %) as a white solid. LC/MS: 597.9 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 9.55 (s, 1H), 8.60 (d, J = 2.7 Hz, 1H), 8.39 (s, 1H), 7.78 (d, J = 9.7 Hz, 1H), 7.59 - 7.44 (m, 2H), 7.33 (d, J = 9.8 Hz, 1H), 7.28 (dd, J = 11.2, 2.7 Hz, 1H), 7.25 (s, 1H), 7.15 - 7.09 (m, 1H), 6.44 - 6.32 (m, 2H), 6.14 (dd, J = 17.0, 2.1 Hz, 1H), 5.70 (dd, J = 10.3, 2.1 Hz, 1H), 5.24 - 5.16 (m, 1H), 4.85 - 4.77 (m, 1H), 4.63 - 4.53 (m, 1H), 4.33 - 4.25 (m, 1H), 4.02 - 3.89 (m, 4H), 3.14 (s, 6H).

Example 36: Preparation of 1-(3-((4-((2-fluoro-4-((1-(5-methoxypyridazin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one (Compound 133)



Step 1: Preparation of benzyl (2-fluoro-4-((1-(5-methoxypyridazin-3-yl)-1H-pyrazol-3-yl)oxy) phenyl)carbamate

[308] To a solution of benzyl (4-((1H-pyrazol-3-yl)oxy)-2-fluorophenyl)carbamate (250 mg, 0.76 mmol) and 3-chloro-5-methoxypyridazine (110 mg, 0.76 mmol) in toluene (10 mL) was added tris(dibenzylideneacetone)dipalladium (70 mg, 0.08 mmol), t-BuONa (110 mg, 1.14 mmol) and t-BuXPhos (32 mg, 0.08 mmol). The resulting mixture was stirred at 80 °C for 5 hours. The solid was filtered off and washed with EA (5 mL×2). The combined solution was concentrated in vacuum and the residue was purified by Prep-TLC with PE: EA = 2:1 to afford the desired compound (150 mg, 45.3 %) as a red solid. LC/MS: 436.1$[M+H]^+$.

Step 2: Preparation of 2-fluoro-4-((1-(5-methoxypyridazin-3-yl)-1H-pyrazol-3-yl)oxy)aniline

[309] To a solution of benzyl (2-fluoro-4-((1-(5-methoxypyridazin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl) carbamate (150 mg, 0.32 mmol) in THF (5 mL) was added Pd/C (7.2 mg, 0.07 mmol). The mixture was stirred at 45 °C for 3 hours. The catalyst was filtered off and washed with THF (5 ml*2). The combined

solution was concentrated in vacuum to give the product (102 mg, 99.5 %) a yellow solid. LC/MS: 301.9$[M+H]^+$.

Step 3: Preparation of tert-butyl-3-((4-((2-fluoro-4-((1-(5-methoxypyridazin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate

[310] To a solution of tert-butyl-3-((4-chloro-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (147 mg, 0.4 mmol) and 2-fluoro-4-((1-(5-methoxypyridazin-3-yl)-1H-pyrazol-3-yl)oxy)aniline (120 mg, 0.4 mmol) in i-PrOH (6 mL) was added HCl (0.5 mL). The mixture was stirred at room temperature overnight. The solvent was removed in vacuum then the residue was dissolved with DCM (10 mL) and adjust pH to 8 with Et_3N. The mixture was concentrated in vacuum and the residue was purified by Prep-TLC with MeOH: DCM = 1: 20 to give the desired product (120 mg, 47.5 %) as a yellow solid. LC/MS: 630.8 $[M+H]^+$.

Step 4: Preparation of 6-(azetidin-3-yloxy)-N-(2-fluoro-4-((1-(5-methoxypyridazin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine

[311] A solution of tert-butyl-3-((4-((2-fluoro-4-((1-(5-methoxypyridazin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carboxylate (120 mg, 0.19 mmol) in DCM (7.5 mL) and TFA (2.5 mL) was stirred at room temperature for 3 hours. The solvent was removed in vacuum to give the title compound (120 mg, TFA salt, 100 % yield) as a yellow solid. LC/MS: 531.1 $[M+H]^+$.

Step 5: Preparation of 1-(3-((4-((4-((1-(6-(dimethylamino)pyridazin-3-yl)-1H-pyrazol-3-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one

[312] To a solution of 6-(azetidin-3-yloxy)-N-(2-fluoro-4-((1-(5-methoxypyridazin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)-7-methoxyquinazolin-4-amine (120 mg, TFA salt, 0.19 mmol) and TEA (64 mg, 0.63 mmol) in DCM (10 mL) was added prop-2-enoyl chloride (19 mg, 0.21 mmol) at -78 °C. The reaction mixture was stirred at -78 °C for 2 hours. The reaction was quenched by adding water (1 mL) and concentrated in vacuum. The residue was purified by Prep-TLC with MeOH: DCM = 1: 10 to give the title compound (100 mg, 90.0 %) as a white solid. LC/MS: 585.1 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 9.61 (s, 1H), 8.95 (d, J = 2.7 Hz, 1H), 8.84 (d, J = 2.8 Hz, 1H), 8.39 (s, 1H), 7.58 - 7.51 (m, 2H), 7.50 (d, J = 2.6 Hz, 1H), 7.30 (dd, J = 11.2, 2.7 Hz, 1H), 7.26 (s, 1H), 7.17 - 7.12 (m, 1H), 6.45 (d, J = 2.8 Hz, 1H), 6.38 (dd, J = 17.0, 10.3 Hz, 1H), 6.14 (dd, J = 17.0, 2.1 Hz, 1H), 5.71 (dd, J = 10.3, 2.1 Hz, 1H), 5.24 - 5.16 (m, 1H), 4.81 (dd, J = 9.4, 6.9 Hz, 1H), 4.57 (dd, J = 11.0, 6.5 Hz, 1H), 4.30 (dd, J = 9.7, 3.4 Hz, 1H), 4.02 (s, 3H), 4.00 - 3.93 (d, J = 7.1 Hz, 4H).

The compounds listed in Table 3 below were prepared analogously with procedures described in Examples 1 to 36.

Compound #	HNMR DATA
21	^{1}H NMR (400 MHz, DMSO) δ 9.33 (s, 1H), 8.60 (d, J = 2.6 Hz, 1H), 8.47 (d, J = 2.6 Hz, 1H), 8.27 (s, 1H), 8.11 (dd, J = 8.9, 2.9 Hz, 1H), 7.51 (t, J = 8.8 Hz, 1H), 7.24 (dd, J = 11.3, 2.7 Hz, 1H), 7.12 – 7.07 (m, 2H), 7.05 (s, 1H), 6.98 (d, J = 8.9 Hz, 1H), 6.41 – 6.31 (m, 3H), 6.12 (dd, J = 17.0, 2.2 Hz, 1H), 5.68 (dd, J = 10.3, 2.2 Hz, 1H), 4.71 (t, J = 8.0 Hz, 1H), 4.45 – 4.41 (m, 2H), 4.18 – 4.12 (m, 1H), 4.00 – 3.94 (m, 4H), 3.89 (s, 3H).
24	^{1}H NMR (400 MHz, DMSO) δ 10.70 (s, 1H), 8.71 (s, 1H), 8.65 (d, J = 1.9 Hz, 1H), 8.12 (dd, J = 8.7, 2.5 Hz, 1H), 7.74 – 7.67 (m, 3H), 7.47 (dd, J = 8.7, 1.8 Hz, 1H), 7.20 (d, J = 7.1 Hz, 2H), 6.90 (d, J = 9.2 Hz, 2H), 6.37 (dd, J = 17.0, 10.3 Hz, 1H), 6.13 (dd, J = 17.0, 2.2 Hz, 1H), 5.69 (dd, J = 10.3, 2.2 Hz, 1H), 4.72 (t, J = 7.7 Hz, 1H), 4.45 (d, J = 7.1 Hz, 2H), 4.20 (dd, J = 8.8, 4.2 Hz, 1H), 4.07 (s, 3H), 3.98 (d, J = 5.1 Hz, 1H), 3.89 (s, 3H).
25	^{1}H NMR (400 MHz, DMSO) δ 10.21 (s, 1H), 9.03 (s, 2H), 8.76 (s, 1H), 8.53 (d, J = 2.7 Hz, 1H), 7.62 (t, J = 9.0 Hz, 1H), 7.40 (dd, J = 11.3, 2.6 Hz, 1H), 7.29 (s, 1H), 7.25 – 7.19 (m, 2H), 6.74 (d, J = 5.1 Hz, 1H), 6.37 (dd, J = 17.0, 10.3 Hz, 1H), 6.29 (d, J = 2.6 Hz, 1H), 6.12 (dd, J = 17.0, 2.2 Hz, 1H), 5.68 (dd, J = 10.3, 2.2 Hz, 1H), 4.70 (t, J = 8.1 Hz, 1H), 4.55 – 4.40 (m, 2H), 4.30 (q, J = 7.0 Hz, 2H), 4.19 (dd, J = 8.6, 5.2 Hz, 1H), 4.02 – 3.98 (m, 1H), 3.97 (s, 3H), 1.50 (t, J = 6.9 Hz, 3H).
26	^{1}H NMR (400 MHz, DMSO) δ 9.20 (s, 1H), 8.86 (s, 2H), 8.34 (s, 1H), 7.84 (s, 1H), 7.62 (dd, J = 11.2, 2.6 Hz, 1H), 7.54 (t, J = 9.0 Hz, 1H), 7.35 (dd, J = 8.8, 1.9 Hz, 1H), 7.24 (s, 1H), 7.01 (s, 1H), 6.42 – 6.32 (m, 2H), 6.12 (dd, J = 17.0, 2.2 Hz, 1H), 5.67 (dd, J = 10.3, 2.2 Hz, 1H), 4.65 (t, J = 7.7 Hz, 1H), 4.50 – 4.37 (m, 2H), 4.27 (q, J = 7.0 Hz, 2H), 4.14 (dd, J = 8.6, 4.9 Hz, 1H), 4.02 – 3.93 (m, 4H), 1.47 (t, J = 6.9 Hz, 3H).
39	^{1}H NMR (400 MHz, DMSO) δ 9.47 (s, 1H), 9.02 (s, 2H), 8.52 (d, J = 2.8 Hz, 1H), 8.36 (s, 1H), 7.58 – 7.41 (m, 2H), 7.35 – 7.20 (m, 2H), 7.15 – 7.10 (m, 1H), 6.48 – 6.32 (m, 2H), 6.20-6.05 (m,1H), 5.70 (dd, J = 10.4, 2.1 Hz, 1H), 5.25-5.10 (m, 1H), 4.86 – 4.76 (m, 1H), 4.65-4.50 (m, 1H), 4.43 – 4.36 (m, 2H), 4.34 – 4.23 (m, 1H), 4.05-3.85 (m, 4H), 1.36 (t, J = 7.2 Hz, 3H).

Compound #	HNMR DATA
40	^{1}H NMR (400 MHz, DMSO) δ 9.49 (s, 1H), 9.00 (s, 2H), 8.51 (d, J = 2.6 Hz, 1H), 8.37 (s, 1H), 7.56 – 7.49 (m, 2H), 7.29 – 7.23 (m, 2H), 7.12 (dd, J = 8.6, 2.5 Hz, 1H), 6.43 – 6.34 (m, 2H), 6.14 (dd, J = 17.0, 2.1 Hz, 1H), 5.70 (dd, J = 10.3, 2.2 Hz, 1H), 5.26 – 5.16 (m, 2H), 4.81 (dd, J = 9.0, 6.6 Hz, 1H), 4.57 (dd, J = 11.1, 6.2 Hz, 1H), 4.29 (dd, J = 9.7, 3.8 Hz, 1H), 3.96 (s, 4H), 1.35 (d, J = 6.2 Hz, 7H).
41	^{1}H NMR (400 MHz, DMSO) δ 9.49 (s, 1H), 8.62 (d, J = 1.2 Hz, 1H), 8.51 (d, J = 2.6 Hz, 1H), 8.37 (s, 1H), 8.28 – 8.23 (m, 1H), 7.57 – 7.49 (m, 2H), 7.32 – 7.24 (m, 2H), 7.13 (dd, J = 8.7, 1.9 Hz, 1H), 6.42 – 6.34 (m, 2H), 6.14 (dd, J = 17.0, 2.1 Hz, 1H), 5.70 (dd, J = 10.3, 2.1 Hz, 1H), 5.22 – 5.17 (m, 1H), 4.81 (dd, J = 9.3, 6.8 Hz, 1H), 4.57 (dd, J = 10.9, 6.4 Hz, 1H), 4.29 (d, J = 6.4 Hz, 1H), 3.96 (s, 7H).
42	^{1}H NMR (400 MHz, DMSO) δ 9.61 (s, 1H), 8.70 (d, J = 2.7 Hz, 1H), 8.39 (s, 1H), 8.01 (d, J = 9.4 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.44 (d, J = 9.4 Hz, 1H), 7.32 (dd, J = 11.2, 2.7 Hz, 1H), 7.26 (s, 1H), 7.15 (dd, J = 8.7, 1.9 Hz, 1H), 6.42 (d, J = 2.7 Hz, 1H), 6.40 – 6.34 (m, 1H), 6.14 (dd, J = 17.0, 2.1 Hz, 1H), 5.70 (dd, J = 10.3, 2.1 Hz, 1H), 5.24 – 5.17 (m, 1H), 4.81 (dd, J = 9.2, 6.7 Hz, 1H), 4.57 (dd, J = 10.8, 6.4 Hz, 1H), 4.30 (dd, J = 9.8, 3.2 Hz, 1H), 4.07 (s, 3H), 3.97 (s, 4H).
44	^{1}H NMR (400 MHz, DMSO) δ 9.54 (s, 1H), 9.27 (s, 2H), 8.63 (d, J = 5.7 Hz, 1H), 8.41 (s, 1H), 7.83 (d, J = 2.3 Hz, 1H), 7.65 (t, J = 8.8 Hz, 1H), 7.53 (s, 1H), 7.37 (dd, J = 10.9, 2.6 Hz, 1H), 7.26 (s, 1H), 7.15 (dd, J = 8.7, 1.9 Hz, 1H), 6.95 (dd, J = 5.7, 2.4 Hz, 1H), 6.39 (dd, J = 17.0, 10.3 Hz, 1H), 6.15 (dd, J = 17.0, 2.1 Hz, 1H), 5.71 (dd, J = 10.3, 2.1 Hz, 1H), 5.25 – 5.17 (m, 1H), 4.81 (dd, J = 9.2, 6.5 Hz, 1H), 4.58 (dd, J = 10.9, 6.6 Hz, 1H), 4.31 (dd, J = 9.8, 3.4 Hz, 1H), 3.98 (d, J = 11.9 Hz, 7H).
45	^{1}H NMR (400 MHz, DMSO) δ 9.52 (s, 1H), 9.13 (d, J = 2.0 Hz, 1H), 8.63 (d, J = 5.7 Hz, 1H), 8.40 (s, 1H), 8.32 (dd, J = 8.1, 2.4 Hz, 1H), 7.73 (d, J = 2.3 Hz, 1H), 7.64 (t, J = 8.8 Hz, 1H), 7.52 (s, 1H), 7.41 – 7.34 (m, 2H), 7.26 (s, 1H), 7.16 (dd, J = 8.7, 1.8 Hz, 1H), 6.95 (dd, J = 5.6, 2.4 Hz, 1H), 6.39 (dd, J = 17.0, 10.3 Hz, 1H), 6.15 (dd, J = 17.0, 2.2 Hz, 1H), 5.71 (dd, J = 10.3, 2.1 Hz, 1H), 5.24 – 5.17 (m, 1H), 4.81 (dd, J = 9.4, 6.5 Hz, 1H), 4.58 (dd, J = 11.0, 6.3 Hz, 1H), 4.31 (dd, J = 9.9, 3.3 Hz, 1H), 3.97 (s, 4H), 2.53 (s, 3H).

Compound #	HNMR DATA
46	^{1}H NMR (400 MHz, DMSO) δ 9.64 (s, 1H), 9.34 (s, 2H), 8.66 (d, J = 5.7 Hz, 1H), 8.43 (s, 1H), 7.89 (d, J = 2.3 Hz, 1H), 7.65 (t, J = 8.7 Hz, 1H), 7.54 (s, 1H), 7.38 (dd, J = 10.9, 2.6 Hz, 1H), 7.27 (s, 1H), 7.16 (dd, J = 8.5, 2.0 Hz, 1H), 6.99 (dd, J = 5.7, 2.4 Hz, 1H), 6.39 (dd, J = 17.0, 10.3 Hz, 1H), 6.15 (dd, J = 17.0, 2.1 Hz, 1H), 5.71 (dd, J = 10.3, 2.1 Hz, 1H), 5.24 – 5.18 (m, 1H), 4.81 (dd, J = 9.6, 6.8 Hz, 1H), 4.58 (dd, J = 10.5, 6.6 Hz, 1H), 4.31 (dd, J = 10.4, 3.8 Hz, 1H), 3.97 (s, 4H), 2.70 (s, 3H).
47	^{1}H NMR (400 MHz, DMSO) δ 9.34 (s, 2H), 8.67 (d, J = 5.7 Hz, 1H), 8.49 (s, 1H), 7.90 (d, J = 2.3 Hz, 1H), 7.65 (t, J = 8.8 Hz, 1H), 7.40 (dd, J = 10.9, 2.6 Hz, 1H), 7.30 – 7.17 (m, 4H), 7.00 (dd, J = 5.7, 2.4 Hz, 1H), 6.65 (s, 1H), 6.37 (dd, J = 17.0, 10.3 Hz, 1H), 6.12 (dd, J = 17.0, 2.2 Hz, 1H), 5.69 (dd, J = 10.3, 2.2 Hz, 1H), 4.74 (t, J = 8.0 Hz, 1H), 4.49 – 4.42 (m, 2H), 4.18 (dd, J = 8.7, 4.0 Hz, 1H), 4.03 (s, 3H), 3.97 (d, J = 4.8 Hz, 1H), 2.70 (s, 3H).
49	1H NMR (400 MHz, DMSO) δ 9.82 (s, 1H), 9.03 (s, 2H), 8.63 – 8.39 (m, 2H), 7.64 – 7.48 (m, 2H), 7.39 – 7.22 (m, 2H), 7.18 – 7.10 (m, 1H), 6.39 (d, J = 2.5 Hz, 1H), 5.19 (s, 1H), 4.77 (dd, J = 9.6, 6.6 Hz, 1H), 4.54 (dd, J = 10.7, 6.5 Hz, 1H), 4.17 (dd, J = 10.2, 3.3 Hz, 1H), 4.05-3.89 (m, 7H), 2.01 (s, 3H).
52	1H NMR (400 MHz, DMSO) δ 11.16 (s, 1H), 8.86 (s, 1H), 8.84 (d, J = 2.5 Hz, 1H), 8.65 (d, J = 2.7 Hz, 1H), 8.26-8.23 (m, 1H), 7.73 (s, 1H), 7.60 (t, J = 8.8 Hz, 1H), 7.42 – 7.35 (m, 2H), 7.23 – 7.18 (m, 1H), 6.45 (d, J = 2.7 Hz, 1H), 6.41-6.34 (m, 1H), 6.15-6.13 (m, 1H), 5.72-5.71 (m, 1H), 5.27-5.21 (m, 1H), 4.85 – 4.79 (m, 1H), 4.62-4.55 (m, 1H), 4.36-4.29 (m, 1H), 4.04 (s, 3H), 3.95-3.94 (m, 1H), 2.53 (s, 3H), 2.39 (s, 3H).
53	1H NMR (400 MHz, MeOD) δ 8.80 (d, J = 2.3 Hz, 1H), 8.69 (s, 1H), 8.36 (d, J = 2.7 Hz, 1H), 8.22 (d, J = 2.3 Hz, 1H), 7.72-7.65 (m, 1H), 7.60-7.52 (m, 1H), 7.30 – 7.16 (m, 3H), 6.43-6.35 (m, 1H), 6.33 – 6.26 (m, 2H), 5.79-5.78 (m, 1H), 5.32-5.25 (m, 1H), 4.87-4.84 (m, 1H), 4.63-4.62 (m, 1H), 4.46 (d, J = 10.1 Hz, 1H), 4.19-4.17 (m, 1H), 4.17-4.12 (m, 1H), 4.11 (s, 2H), 2.63 (s, 3H).

Compound #	HNMR DATA
54	1H NMR (400 MHz, MeOD) δ 8.46 (s, 1H), 8.40 (s, 1H), 7.90 (d, J = 2.5 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.35 (s, 1H), 7.24 (s, 1H), 7.18 – 7.08 (m, 2H), 6.39-6.37 (m, 1H), 6.31 – 6.22 (m, 2H), 5.77-5.76 (m, 1H), 5.29 – 5.22 (m, 1H), 4.86 – 4.81 (m, 1H), 4.61-4.60 (m, 1H), 4.43-4.42 (m, 1H), 4.15-4.14 (m, 1H), 4.05 (s, 3H), 2.56 (s, 3H), 2.34 (s, 3H).
56	1H NMR (400 MHz, MeOD) δ 8.49 (s, 1H), 8.37 (d, J = 2.0 Hz, 1H), 8.34 (d, J = 2.7 Hz, 1H), 7.68 (d, J = 2.1 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.23 (s, 1H), 7.20 – 7.10 (m, 2H), 6.42 – 6.34 (m, 1H), 6.32 – 6.23 (m, 2H), 5.77-5.76 (m, 1H), 5.29 – 5.23 (m, 1H), 4.87 – 4.82 (m, 1H), 4.62-4.61 (m, 1H), 4.43-4.42 (m, 1H), 4.14-4.13 (m, 1H), 4.06 (s, 3H), 3.96 (s, 3H), 2.43 (s, 3H).
58	1H NMR (400 MHz, MeOD) δ 9.19 (s, 1H), 8.73 (s, 1H), 8.70 – 8.62 (m, 1H), 7.78 (t, J = 8.6 Hz, 1H), 7.69 (d, J = 1.7 Hz, 1H), 7.64-7.63 (m, 2H), 7.51-7.50 (m, 1H), 7.37 – 7.29 (m, 1H), 6.40-6.39 (m, 1H), 6.29-6.28 (m, 1H), 5.79-5.78 (m, 1H), 5.35 – 5.26 (m, 1H), 4.88-4.42 (m, 1H), 4.64-4.63 (m, 1H), 4.47 (d, J = 7.4 Hz, 1H), 4.21 – 4.13 (m, 1H), 4.12 (s, 3H), 2.69 (d, J = 5.5 Hz, 3H).
59	1H NMR (400 MHz, MeOD) δ 8.71 (s, 1H), 8.61 (d, J = 0.9 Hz, 1H), 8.41 (s, 1H), 7.69 (d, J = 1.4 Hz, 2H), 7.65 (d, J = 8.6 Hz, 1H), 7.42 (d, J = 0.9 Hz, 1H), 7.33 (dd, J = 10.7, 2.5 Hz, 1H), 7.29 (s, 1H), 7.25 – 7.21 (m, 1H), 6.45-6.36 (m, 1H), 6.33-6.26 (m, 1H), 5.79 (dd, J = 10.1, 2.1 Hz, 1H), 5.33-5.26 (m, 1H), 4.86 – 4.83 (m, 1H), 4.64 (dd, J = 10.9, 5.9 Hz, 1H), 4.49 – 4.43 (m, 1H), 4.17 (dd, J = 10.3, 7.9 Hz, 1H), 4.11 (s, 3H), 2.17 (s, 3H).
61	1H NMR (400 MHz, MeOD) δ 8.70 (s, 1H), 8.41 (d, J = 5.2 Hz, 1H), 7.81 (d, J = 5.2 Hz, 1H), 7.72 (s, 1H), 7.69 (s, 1H), 7.63 (t, J = 8.6 Hz, 1H), 7.31 – 7.29 (m, 1H), 7.28 – 7.22 (m, 1H), 7.20 – 7.13 (m, 1H), 6.45 – 6.25 (m, 2H), 5.79-5.78 (m, 1H), 5.36 – 5.23 (m, 1H), 4.87-4.84 (m, 1H), 4.64-4.63 (m, 1H), 4.46-4.45 (m, 1H), 4.22 – 4.05 (m, 4H), 2.49 (s, 3H).

Compound #	HNMR DATA
62	1H NMR (400 MHz, MeOD) δ 8.71 (s, 1H), 8.60-8.62 (m, 1H), 8.40-8.41 (m, 1H), 7.69 (d, J = 1.4 Hz, 2H), 7.64-7.66 (m, 1H), 7.41-7.43 (m, 1H), 7.32-7.34 (m, 1H), 7.29 (s, 1H), 7.22-7.24 (m, 1H), 6.36-6.39 (m, 1H), 6.28-6.30(m, 1H), 5.78-5.80 (m, 1H), 5.28-5.31 (m, 1H), 4.83-4.86 (m, 1H), 4.63-4.64 (m, 1H), 4.45-4.47 (m, 1H), 4.17-4.19(m, 1H), 4.11 (s, 3H), 2.17 (s, 3H).
63	1H NMR (400 MHz, CD3OD) δ 8.91 (d, J = 1.2 Hz, 1H), 8.72 (s, 1H), 7.83 (d, J = 1.2 Hz, 1H), 7.70 – 7.66 (m, 2H), 7.37-7.35 (m, 1H), 7.32 (s, 1H), 7.29 – 7.24 (m, 1H), 6.39-6.37 (m, 1H), 6.29 (dd, J = 16.8, 2.0 Hz, 1H), 5.79-5.78 (m, 1H), 5.33 – 5.28 (m, 1H), 4.89-4.87 (m, 1H), 4.64-4.62 (m, 1H), 4.47-4.43 (m, 1H), 4.19 – 4.09 (m, 4H), 2.70 (s, 3H).
65	1H NMR (400 MHz, MeOD) δ 8.70 (s, 1H), 8.59 (d, J = 5.6 Hz, 1H), 8.18 (s, 1H), 7.72-7.64 (m, 4H), 7.34 (dd, J = 10.8, 2.5 Hz, 1H), 7.30 (s, 1H), 7.26 – 7.23 (m, 1H), 6.44-6.36 (m, 1H), 6.33-6.26 (m, 1H), 5.79 (dd, J = 10.1, 2.1 Hz, 1H), 5.33 – 5.26 (m, 1H), 4.92-4.90 (m, 1H), 4.64 (dd, J = 11.3, 6.1 Hz, 1H), 4.50-4.43 (m, 1H), 4.18-4.13 (m, 1H), 4.10 (s, 3H), 2.14 (s, 3H).
67	1H NMR (400 MHz, DMSO) δ 9.63 (s, 1H), 9.01 (s, 2H), 8.43 (s, 1H), 7.78 (s, 1H), 7.68 (d, J = 8.7 Hz, 2H), 7.63 (dd, J = 10.8, 2.7 Hz, 1H), 7.52 (s, 1H), 7.41 (dd, J = 8.7, 1.8 Hz, 1H), 7.27 (s, 1H), 6.39 (dd, J = 17.0, 10.3 Hz, 1H), 6.14 (dd, J = 17.0, 2.1 Hz, 1H), 5.71 (dd, J = 10.3, 2.1 Hz, 1H), 5.31 – 5.03 (m, 2H), 4.91 – 4.71 (m, 1H), 4.58 (dd, J = 10.9, 6.6 Hz, 1H), 4.31 (dd, J = 9.8, 3.2 Hz, 1H), 4.01-3.94 (m, 4H), 1.34 (d, J = 6.2 Hz, 6H).
68	1H NMR (400 MHz, DMSO) δ 9.56 (s, 1H), 8.73 (s, 2H), 8.40 (s, 1H), 7.66 (t, J = 8.7 Hz, 1H), 7.60 (dd, J = 10.8, 2.7 Hz, 1H), 7.52 (d, J = 2.4 Hz, 2H), 7.43 – 7.36 (m, 2H), 7.27 (s, 1H), 6.45-6.33 (m, 1H), 6.16 (d, J = 2.1 Hz, 1H), 5.75 – 5.62 (m, 1H), 5.25-5.16 (m , 1H), 4.91 – 4.77 (m, 1H), 4.57 (dd, J = 11.2, 6.4 Hz, 1H), 4.30 (d, J = 6.8 Hz, 1H), 4.01-3.94 (m, 4H), 2.84 (d, J = 4.8 Hz, 3H).

Compound #	HNMR DATA
69	1H NMR (400 MHz, DMSO) δ 9.62 (s, 1H), 8.79 (s, 2H), 8.42 (s, 1H), 7.66 (t, J = 8.8 Hz, 1H), 7.61 (dd, J = 10.8, 2.7 Hz, 1H), 7.53 (d, J = 6.1 Hz, 2H), 7.39 (dd, J = 8.7, 1.8 Hz, 1H), 7.27 (s, 1H), 6.39 (dd, J = 17.0, 10.3 Hz, 1H), 6.14 (dd, J = 17.0, 2.1 Hz, 1H), 5.71 (dd, J = 10.3, 2.1 Hz, 1H), 5.24 – 5.17 (m, 1H), 4.88 – 4.77 (m, 1H), 4.58 (dd, J = 10.9, 6.6 Hz, 1H), 4.30 (dd, J = 9.9, 3.3 Hz, 1H), 3.97 (s, 4H), 3.16 (s, 6H).
70	1H NMR (400 MHz, DMSO) δ = 9.57 (s, 1H), 8.40 (s, 1H), 8.02 (s, 1H), 7.78 (s, 1H), 7.64 (t, J= 8.8 Hz, 1H), 7.56 (dd, J= 10.8, 2.8 Hz, 1H), 7.52 (s, 1H), 7.34 (dd, J= 8.8, 1.6 Hz, 1H), 7.27 (s, 1H), 7.24 (s, 1H), 6.39 (dd, J= 16.8, 10.4 Hz, 1H), 6.14 (dd, J= 16.8, 2.0, 1H), 5.71 (dd, J= 10.4, 2.0 Hz, 1H), 5.26-5.14 (m, 1H), 4.87 – 4.76 (m, 1H), 4.64-4.56 (m, 1H), 4.30 (dd, J= 10.0, 2.8 Hz, 1H), 4.0-3.94 (m, 4H), 3.85 (s, 3H).
72	1H NMR (400 MHz, DMSO) δ 9.67 (s, 1H), 8.97 (d, J = 7.5 Hz, 1H), 8.58 (s, 1H), 8.42 (s, 1H), 8.24 (d, J = 2.5 Hz, 1H), 7.92 (dd, J = 8.9, 2.5 Hz, 1H), 7.65 (s, 1H), 7.48 (d, J = 8.9 Hz, 1H), 7.35 (s, 1H), 7.08 (dd, J = 7.5, 2.6 Hz, 1H), 6.93 (d, J = 2.5 Hz, 1H), 5.57 - 5.42 (m, 1H), 5.35 (dd, J = 16.6, 3.6 Hz, 1H), 5.28 – 5.22 (m, 1H), 4.99 - 4.93 (m, 1H), 4.66 - 4.58 (m, 1H), 4.46 - 4.36 (m, 3H), 4.03 (d, J = 9.4 Hz, 1H), 3.75 - 3.65 (m, 4H), 3.49 - 3.40 (m, 1 H), 3.18 - 3.12 (m, 2H), 2.95 - 2.80 (m, 3H).
73	1H NMR (400 MHz, DMSO) δ 9.75 (s, 1H), 8.97 (d, J = 7.5 Hz, 1H), 8.57 (s, 1H), 8.42 (s, 1H), 8.27 (d, J = 2.4 Hz, 1H), 7.96 (dd, J = 8.9, 2.4 Hz, 1H), 7.66 (s, 1H), 7.48 (d, J = 8.9 Hz, 1H), 7.29 (s, 1H), 7.08 (dd, J = 7.5, 2.6 Hz, 1H), 6.94 (d, J = 2.5 Hz, 1H), 5.53 (dd, J = 48.4, 3.6 Hz, 1H), 5.41 – 5.23 (m, 2H), 5.04 - 4.93 (m, 1H), 4.71 - 4.58 (m, 1H), 4.43 (d, J = 10.2 Hz, 1H), 4.03 (d, J = 9.0 Hz, 1H), 3.98 (s, 3H).
74	1H NMR (400 MHz, DMSO) δ 9.47 (s, 1H), 9.03 (s, 2H), 8.53 (d, J = 2.7 Hz, 1H), 8.36 (s, 1H), 7.56 - 7.45 (m, 2H), 7.29 – 7.23 (m, 2H), 7.12 (dd, J = 8.7, 1.9 Hz, 1H), 6.38 (d, J = 2.6 Hz, 1H), 5.52 (dd, J = 48.4, 3.6 Hz, 1H), 5.34 (dd, J = 16.6, 3.6 Hz, 1H), 5.22 – 5.16 (m, 1H), 5.01 - 4.91 (m, 1H), 4.66 – 4.59 (m, 1H), 4.43 (d, J = 10.5 Hz, 1H), 4.06 - 3.93 (m, 7H).

Compound #	HNMR DATA
75	1H NMR (400 MHz, DMSO) δ 9.69 (s, 1H), 8.98 (d, J = 7.5 Hz, 1H), 8.57 (s, 1H), 8.42 (s, 1H), 8.24 (d, J = 2.1 Hz, 2H), 7.94 (dd, J = 8.8, 2.0 Hz, 1H), 7.62 (s, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.29 (s, 1H), 7.08 (dd, J = 7.4, 2.5 Hz, 1H), 6.94 (d, J = 2.3 Hz, 1H), 6.69 - 6.56 (m, 1H), 6.18 (d, J = 15.4 Hz, 1H), 5.29 - 5.21 (m, 1H), 4.85 – 4.76 (m, 1H), 4.55 (dd, J = 10.7, 6.6 Hz, 1H), 4.27 (d, J = 7.2 Hz, 1H), 4.02 - 3.92 (m, 4H), 3.03 (d, J = 5.7 Hz, 2H), 2.15 (s, 6H).
76	1H NMR (400 MHz, DMSO) δ = 9.48 (s, 1H), 8.91 (d, J= 2.8 Hz, 1H), 8.58 (d, J= 2.8 Hz, 1H), 8.36 (s, 1H), 8.06 (dd, J= 8.4, 2.8 Hz, 1H), 7.53 (t, J= 8.8 Hz, 1H), 7.47 (s, 1H), 7.39 (d, J= 8.4 Hz, 1H), 7.29 – 7.24 (m, 2H), 7.14 – 7.08 (m, 1H), 6.36 (d, J= 2.4 Hz, 1H), 5.65 - 5.45 (m, 1H), 5.34 (dd, J= 16.8, 3.6 Hz, 1H), 5.23-5.16 (m, 1H), 5.01-4.91 (m, 1H), 4.68-4.60 (m, 1H), 4.43 (d, J=10.0 Hz, 1H), 4.03 (d, J= 8.4 Hz, 1H), 3.96 (s, 3H), 2.50 (s, 3H).
77	1H NMR (400 MHz, DMSO) δ 9.64 (s, 1H), 8.98 (d, J = 7.5 Hz, 1H), 8.58 (s, 1H), 8.42 (s, 1H), 8.23 (d, J = 2.5 Hz, 1H), 8.14 (s, 1H), 7.96 – 7.90 (m, 1H), 7.58 (s, 1H), 7.49 (d, J = 8.9 Hz, 1H), 7.30 (s, 1H), 7.25 (s, 1H), 7.08 (dd, J = 7.5, 2.6 Hz, 1H), 6.94 (d, J = 2.4 Hz, 1H), 5.30 - 5.21 (m, 1H), 5.02 - 4.92 (m, 1H), 4.70 - 4.63 (m, 1H), 4.60 – 4.29 (m, 6H), 4.05 (d, J = 10.5 Hz, 1H), 3.98 (s, 3H), 2.60 - 2.51 (m, 6H), 2.35 - 2.25 (m, 2H), 1.26 (s, 6H).
78	1H NMR (400 MHz, DMSO) δ 9.67 (s, 1H), 8.98 (d, J = 7.5 Hz, 1H), 8.57 (s, 1H), 8.42 (s, 1H), 8.23 (d, J = 2.5 Hz, 1H), 8.20 (s, 1H), 7.92 (dd, J = 8.9, 2.5 Hz, 1H), 7.59 (s, 1H), 7.49 (d, J = 8.9 Hz, 1H), 7.30 (s, 1H), 7.23 (s, 1H), 7.10 - 7.06 (m, 1H), 6.94 (d, J = 2.4 Hz, 1H), 5.29 - 5.20 (m, 1H), 5.03 - 4.90 (m, 1H), 4.70 - 4.59 (m, 1H), 4.51 -4.41 (m, 1H), 4.13 - 4.02 (s, 1H), 3.98 (s, 3H), 2.51 - 2.50 (m, 6H), 2.41 - 2.35 (m, 2H), 2.14 (s, 3H), 1.25 (s, 6H).
79	1H NMR (400 MHz,) δ 9.24 – 9.13 (m, 1H), 9.00 (s, 2H), 8.49 (d, J = 2.6 Hz, 1H), 8.20 (s, 1H), 8.16 (s, 1H), 7.51-7.45 (m, 1H), 7.21 (dd, J = 11.2, 2.8 Hz, 1H), 7.12 – 7.05 (m, 2H), 7.00 (s, 1H), 6.42 – 6.25 (m, 3H), 6.09 (dd, J = 17.0, 2.2 Hz, 1H), 5.65 (dd, J = 10.3, 2.2 Hz, 1H), 4.74 – 4.66 (m, 1H), 4.46 - 4.34 (m, 2H), 4.28 (t, J = 5.8 Hz, 2H), 4.15 – 4.07 (m, 1H), 3.96 – 3.87 (m, 4H), 2.92 (t, J = 5.7 Hz, 2H), 2.36 (s, 6H).

Compound #	HNMR DATA
82	1H NMR (400 MHz, DMSO) δ 9.59 (s, 1H), 8.52 (s, 1H), 7.93 (d, J = 13.4 Hz, 1H), 7.67 (s, 1H), 7.59 (s, 1H), 7.51 (d, J = 9.1 Hz, 1H), 7.32 – 7.22 (m, 2H), 6.38 (dd, J = 17.0, 10.1 Hz, 1H), 6.15 (d, J = 16.6 Hz, 1H), 5.82 – 5.66 (m, 2H), 5.24 (s, 1H), 4.87- 4.76 (m, 1H), 4.73 - 4.51 (m, 2H), 4.28 (d, J = 7.6 Hz, 1H), 3.97 (s, 4H), 3.54 - 3.39 (m, 2H), 2.05 – 1.80 (m, 4H), 1.78 - 1.64 (m, 2H), 1.40 – 1.26 (m, 2H).
83	1H NMR (400 MHz, DMSO) δ 10.16 (s, 1H), 9.04 (s, 2H), 8.62 – 8.46 (m, 2H), 7.54 (t, J = 8.7 Hz, 1H), 7.32 (d, J = 11.2 Hz, 1H), 7.23 – 7.01 (m, 3H), 6.60 (s, 1H), 6.45-6.30 (m, 2H), 6.12 (d, J = 17.0 Hz, 1H), 5.68 (d, J = 10.6 Hz, 1H), 4.80-4.65 (m, 1H), 4.50-4.34 (m, 2H), 4.24-4.13 (m, 1H), 3.97 (s, 4H), 3.20-3.02 (m, 1H).
84	1H NMR (400 MHz, DMSO) δ 10.79 (s, 1H), 8.82 (s, 1H), 8.72 (s, 1H), 8.65 (d, J = 2.7 Hz, 1H), 8.11 (dd, J = 10.7, 1.9 Hz, 1H), 7.58 (t, J = 8.8 Hz, 1H), 7.39 (dd, J = 11.2, 2.6 Hz, 1H), 7.21 (d, J = 8.3 Hz, 3H), 6.97 (s, 1H), 6.44 (d, J = 2.7 Hz, 1H), 6.37 (dd, J = 16.9, 10.3 Hz, 1H), 6.13 (dd, J = 17.0, 2.2 Hz, 1H), 5.69 (dd, J = 10.3, 2.2 Hz, 1H), 4.74 – 4.69 (m, 1H), 4.48 - 4.40 (m, 2H), 4.20 (dd, J = 9.0, 3.6 Hz, 1H), 4.07 (s, 3H), 3.98 (d, J = 5.5 Hz, 1H), 2.48 - 2.47 (m, 1H).
85	1H NMR (400 MHz, DMSO) δ 9.39 (s, 1H), 8.97 (d, J = 7.5 Hz, 1H), 8.43 (d, J = 11.2 Hz, 2H), 8.25 (d, J = 2.5 Hz, 1H), 8.15 (s, 1H), 7.95 (dd, J = 8.9, 2.5 Hz, 1H), 7.47 (d, J = 8.9 Hz, 1H), 7.19 (s, 1H), 7.12 - 7.06 (m, 2H), 6.92 (d, J = 2.5 Hz, 1H), 6.39 (dd, J = 17.0, 10.3 Hz, 1H), 6.21 (d, J = 7.1 Hz, 1H), 6.13 (dd, J = 17.0, 2.2 Hz, 2H), 5.69 (dd, J = 10.3, 2.2 Hz, 1H), 4.74 (t, J = 7.8 Hz, 1H), 4.58 – 4.41 (m, 2H), 4.32 (t, J = 8.0 Hz, 2H), 4.15 (dd, J = 8.6, 5.2 Hz, 1H), 3.98 (dd, J = 9.9, 5.1 Hz, 1H), 3.60 (t, J = 8.0 Hz, 4H), 2.86 (t, J = 8.0 Hz, 2H), 2.56 - 2.53 (m, 4H).
86	1HNMR (400 MHz, MeOD) δ 8.88 (d, J = 2.5 Hz, 1H), 8.69 (s, 1H), 8.27 (s, 1H), 7.90 (d, J = 2.4 Hz, 1H), 7.73 – 7.63 (m, 2H), 7.53-7.52 (m, 1H), 7.40 (d, J = 9.1 Hz, 1H), 7.31 (s, 1H), 6.37-6.36 (m, 1H), 6.27-6.26 (m, 1H), 5.77-5.76 (m, 1H), 5.32 – 5.24 (m, 1H), 4.86 – 4.81 (m, 1H), 4.61-4.60 (m, 1H), 4.44-4.43 (m, 1H), 4.16 – 4.11 (m, 1H), 4.10 (s, 3H), 4.09 (s, 3H).

Compound #	HNMR DATA
87	1H NMR (400 MHz, MeOD) δ 8.72 (s, 1H), 8.54-8.56 (m, 1H), 7.90-7.91 (m, 1H), 7.89-7.90 (m, 1H), 7.83 (s, 1H), 7.68-7.69 (m, 2H), 7.51-7.53 (m, 1H), 7.40-7.42 (m, 1H), 7.29 (s, 1H), 6.35-6.37 (m, 3H), 5.79-5.81 (m, 1H), 5.30-5.32 (m, 1H), 4.64-4.65 (m, 1H), 4.47-4.49 (m, 1H), 4.15 -4.17(m, 1H), 4.12 (s, 3H).
88	1H NMR (400 MHz, DMSO) δ 11.1 (s, 1H), 8.84 (s, 1H), 8.02-7.96 (m, 2H), 7.77-7.68 (m, 3H), 7.52-7.48 (m, 1H), 7.33 (t, J = 8.0 Hz, 2H), 6.42-6.35 (m, 1H), 6.17-6.13 (m, 1H), 5.74 – 5.71 (m, 1H), 5.27-5.21 (m, 1H), 4.85-4.81 (m, 1H), 4.62-4.58 (m, 1H), 4.35-4.33 (m, 1H), 4.08 (s, 3H), 4.04 (s, 3H), 3.99-9.97 (m, 1H).
89	1H NMR (400 MHz, MeOD) δ 8.70 (s, 1H), 7.78 – 7.72 (m, 2H), 7.67-7.65 (m, 2H), 7.48-7.47 (m, 1H), 7.39 – 7.35 (m, 1H), 7.29 (s, 1H), 7.26 (s, 1H), 6.97 – 6.91 (m, 2H), 6.36 (m, 1H), 6.29-6.28 (m, 1H), 5.79-5.78 (m, 1H), 5.32 – 5.27 (m, 1H), 4.86-4.82 (m, 1H), 4.63-4.62 (m, 1H), 4.48-4.44 (m, 1H), 4.17-4.13 (m, 1H), 4.11 (s, 3H), 3.82 (s, 3H).
90	1H NMR (400 MHz, MeOD) δ 9.14 (d, J= 2.0 Hz, 1H), 8.69 (s, 1H), 8.42-8.41 (m, 1H), 7.84 (d, J= 8.2 Hz, 1H), 7.81 (s, 1H), 7.69 (d, J= 8.6 Hz, 1H), 7.65 (d, J= 1.3 Hz, 1H), 7.52 (d, J= 2.7 Hz, 0.5H), 7.49 (d, J= 2.6 Hz, 0.5H), 7.40-7.38 (m, 1H), 7.27 (s, 1H), 6.32-6.30 (m, 2H), 5.77-5.76 (m, 1H), 5.31 – 5.23 (m, 1H), 4.86 – 4.82 (m, 1H), 4.65 – 4.58 (m, 1H), 4.47 – 4.41 (m, 1H), 4.13-4.12 (m, 1H), 4.09 (s, 3H).
91	1H NMR (400 MHz, MeOD) δ 8.65 (d, J = 2.9 Hz, 1H), 8.54 (d, J = 5.5 Hz, 1H), 8.36 (s, 1H), 7.59 (t, J = 8.7 Hz, 1H), 7.49 (s, 1H), 7.40 (d, J = 5.5 Hz, 1H), 7.25-7.24 (m, 2H), 7.21 – 7.15 (m, 1H), 6.40-6.39 (m, 1H), 6.35 – 6.24 (m, 2H), 5.77-5.76 (m, 1H), 5.28 – 5.22 (m, 1H), 4.87 – 4.81 (m, 1H), 4.61-4.60 (m, 1H), 4.43-4.42 (m, 1H), 4.16-4.15 (m, 1H), 4.07 (s, 3H), 4.04 (s, 3H).

Compound #	HNMR DATA
92	1H NMR (400 MHz, MeOD) δ 8.59 (d, J = 2.0 Hz, 1H), 8.54 (s, 1H), 8.09-8.08 (m, 1H), 7.69 (t, J = 8.7 Hz, 1H), 7.57 (s, 1H), 7.45-7.44 (m, 1H), 7.38 (s, 1H), 7.37 – 7.32 (m, 1H), 7.26 (s, 1H), 6.84-6.83 (m, 1H), 6.40-6.39 (m, 1H), 6.29-6.28 (m, 1H), 5.78-5.77 (m, 1H), 5.31 – 5.22 (m, 1H), 4.87 – 4.80 (m, 1H), 4.62-4.61 (m, 1H), 4.45-4.44 (m, 1H), 4.16-4.15 (m, 1H), 4.07 (s, 3H), 3.93 (s, 3H).
94	1H NMR (400 MHz, DMSO) δ 11.01 (s, 1H), 8.84 (s, 1H), 8.60-8.59 (m, 3H), 7.71 (s, 1H), 7.60 (t, J = 8.0 Hz,1H), 7.44-7.40 (m, 1H), 7.34 (s, 1H), 7.23–7.21 (m, 1H), 6.42-6.34 (m, 2H), 6.17-6.12 (m, 1H), 5.73-5.70 (m, 1H), 5.27-5.20 (m, 1H), 4.85-4.81 (m, 1H), 4.62-4.57 (m, 1H), 4.35-4.30 (m, 1H), 4.04 (s, 3H), 4.0-3.98 (m, 1H), 3.95 (s, 3H).
95	1H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 8.77-8.74 (m, 2H), 8.69 (d, J = 4.0 Hz, 1H), 7.68 (s, 1H), 7.61 (t, J = 8.0 Hz ,1H), 7.46-7.43 (m, 1H), 7.32 (s, 1H), 7.27–7.24 (m, 1H), 7.02-7.00 (m, 1H), 6.45 (d, J = 3.2 Hz, 1H), 6.42-6.35 (m, 1H), 6.17-6.12 (m, 1H), 5.73-5.70 (m, 1H), 5.26-5.20 (m, 1H), 4.84-4.80 (m, 1H), 4.61-4.57 (m, 1H), 4.34-4.31 (m, 1H), 4.03 (s, 3H), 3.99 (s, 3H), 3.97-3.94 (m, 1H).
97	1H NMR (400 MHz, DMSO) δ 9.41 (s, 1H), 9.03 (s, 2H), 8.53 (d, J = 2.7 Hz, 1H), 8.29 (s, 1H), 7.56 – 7.49 (m, 1H), 7.26 (dd, J = 11.3, 2.7 Hz, 1H), 7.14-7.09 (m, 2H), 7.04 (s, 1H), 6.45 (d, J = 5.6 Hz, 1H), 6.38 (d, J = 2.6 Hz, 1H), 4.70 – 4.59 (m, 1H), 4.40 (d, J = 6.0 Hz, 2H), 4.07 (dd, J = 8.9, 3.8 Hz, 1H), 3.99 (s, 2H), 3.97 (s, 3H), 3.92 (d, J = 4.5 Hz, 1H), 2.00 (s, 3H).
98	1H NMR (400 MHz, CD3OD) δ 8.68 (s, 1H), 8.45 (d, J = 2.8 Hz, 1H), 8.09 (d, J = 3.2 Hz, 1H), 7.71 (d, J = 9.2 Hz, 1H), 7.65 (s, 1H), 7.55 (t, J = 8.8 Hz, 1H), 7.50-7.49 (m, 1H), 7.30 (s, 1H), 7.21-7.19 (m, 1H), 7.18 – 7.13 (m, 1H), 6.39-6.37 (m, 1H), 6.28-6.26 (m, 1H), 6.19 (d, J = 2.8 Hz, 1H), 5.78-5.76 (m, 1H), 5.30 – 5.25 (m, 1H), 4.85-4.82 (m, 1H), 4.63-4.62 (m, 1H), 4.45-4.43 (m, 1H), 4.45-4.42 (m, 1H), 4.10 (s, 3H), 3.90 (s, 3H).

Compound #	HNMR DATA
99	1H NMR (400 MHz, CD3OD) δ 8.68 (s, 1H), 8.57 (d, J = 2.4 Hz, 1H), 7.76 (t, J = 8.0 Hz, 1H), 7.66 (s, 1H), 7.57 (t, J = 8.4 Hz, 1H), 7.31 – 7.29 (m, 2H), 7.24-7.23 (m, 1H), 7.19 – 7.16 (m, 1H), 6.67-6.65 (m, 1H), 6.39-6.37 (m, 1H), 6.29-6.27 (m, 1H), 6.22 (d, J = 2.8 Hz, 1H), 5.78-5.76 (m, 1H), 5.31 – 5.26 (m, 1H), 4.85-4.82 (m, 1H), 4.63-4.62 (m, 1H), 4.45-4.43 (m, 1H), 4.15-4.13 (m, 1H), 4.10 (s, 3H), 3.99 (s, 3H).
100	1H NMR (400 MHz, DMSO) δ 9.62 (s, 1H), 9.03 (s, 2H), 8.53 (d, J = 2.7 Hz, 1H), 8.35 (s, 1H), 7.53 (t, J = 8.8 Hz, 1H), 7.29 (d, J = 2.7 Hz, 1H), 7.15 – 7.10 (m, 2H), 7.07 (s, 1H), 6.51 (d, J = 6.4 Hz, 1H), 6.38 (d, J = 2.6 Hz, 1H), 5.49 (dd, J = 48.4, 3.5 Hz, 1H), 5.31 (dd, J = 16.6, 3.5 Hz, 1H), 4.90-4.80 (s, 1H), 4.60 – 4.20 (m, 4H), 4.01 (s, 3H), 3.97 (s, 3H).
101	1H NMR (400 MHz, MeOD) δ 8.94 (s, 2H), 8.69 (s, 1H), 8.26 (d, J = 2.7 Hz, 1H), 7.70 (s, 1H), 7.56 (t, J = 8.6 Hz, 1H), 7.32 (s, 1H), 7.19-7.18 (m, 2H), 6.45 (d, J = 11.5 Hz, 1H), 6.36-6.29 (m, 1H), 6.27 (d, J = 2.7 Hz, 1H), 5.34 – 5.25 (m, 1H), 4.89-4.85 (m, 1H), 4.64-4.63 (m, 1H), 4.46-4.45 (m, 1H), 4.28 – 4.22 (m, 2H), 4.17-4.16 (m, 1H), 4.10 (s, 3H), 4.05 (s, 3H), 2.92 (s, 6H).
102	1H NMR (400 MHz, MeOD) δ = 9.07 (s, 1H), 8.70 (s, 1H), 8.51 – 8.43 (m, 2H), 7.69-7.67 (m, 2H), 7.62 (d, J=2.2 Hz, 1H), 7.32 (s, 1H), 7.27-7.25 (m, 1H), 7.18 (d, J=8.7 Hz, 1H), 6.98-6.96 (m, 1H), 6.43 – 6.36 (m, 1H), 6.29-6.27 (m, 1H), 5.79-5.79 (m, 1H), 5.33 – 5.26 (m, 1H), 4.86-4.85 (m, 1H), 4.64-4.63 (m, 1H), 4.48-4.43 (m, 1H), 4.16-4.11 (m, 1H), 4.11 (s, 3H).
103	1H NMR (400 MHz, MeOD) δ = 8.73 (s, 1H), 8.53 (d, J=5.7 Hz, 1H), 7.92 (d, J=3.2 Hz, 1H), 7.78 (d, J=2.3 Hz, 1H), 7.71-7.70 (m, 3H), 7.31-7.28 (m, 2H), 7.23 – 7.19 (m, 1H), 7.13-7.12 (m, 1H), 6.40-6.39 (m, 1H), 6.30-6.28 (m, 1H), 5.79-5.78 (m, 1H), 5.34 – 5.27 (m, 1H), 4.87-4.86 (m, 1H), 4.64-4.63 (m, 1H), 4.50 – 4.44 (m, 1H), 4.16-4.15 (m, 1H), 4.12 (s, 3H).

Compound #	HNMR DATA
104	1H NMR (400 MHz, MeOD) δ 9.19 (s, 1H), 8.73 (s, 1H), 8.62 (s, 2H), 8.04 (s, 1H), 7.77 (t, J = 8.5 Hz, 1H), 7.73 (s, 1H), 7.40-7.39 (m, 1H), 7.36 – 7.24 (m, 3H), 6.46 – 6.24 (m, 2H), 5.79-5.78 (m, 1H), 5.40 – 5.25 (m, 1H), 4.88 – 4.86 (m, 1H), 4.65-4.63 (m, 1H), 4.47-4.45 (m, 1H), 4.20 – 4.07 (m, 4H).
105	1H NMR (400 MHz, MeOD) δ 8.99 – 8.91 (m, 2H), 8.70 – 8.67 (m, 1H), 8.28 – 8.24 (m, 1H), 7.66-7.65 (m, 1H), 7.569-7.52 (m, 1H), 7.28 (d, J = 4.8 Hz, 1H), 7.26 – 7.14 (m, 2H), 6.33 – 6.25 (m, 1H), 5.59-5.58 (m, 1H), 5.33 – 5.22 (m, 2H), 5.04-5.00 (m, 1H), 4.71 – 4.54 (m, 2H), 4.19 (d, J = 9.9 Hz, 1H), 4.11 (s, 3H), 4.06 (s, 3H).
108	^{1}H NMR (400 MHz, MeOD) δ 8.72 (s, 1H), 8.63 (d, *J* = 5.8 Hz, 1H), 7.74 – 7.64 (m, 2H), 7.53 (d, *J* = 2.0 Hz, 1H), 7.42 (d, *J* = 2.3 Hz, 1H), 7.33 (s, 1H), 7.29-7.28 (m, 1H), 7.22 – 7.18 (m, 1H), 7.09-7.06 (m, 1H), 6.69 (d, *J* = 2.0 Hz, 1H), 6.40-6.39 (m, 1H), 6.29 (dd, *J* = 17.0, 2.1 Hz, 1H), 5.79-5.78 (m, 1H), 5.34 – 5.25 (m, 1H), 4.87 (d, *J* = 6.5 Hz, 1H), 4.64-4.63 (m, 1H), 4.46-4.44 (m, 1H), 4.21 – 4.16 (m, 1H), 4.13 (s, 3H), 4.11 (s, 3H).
109	^{1}H NMR (400 MHz, MeOD) δ 8.73 (s, 1H), 8.57 (d, *J* = 6.8 Hz, 1H), 8.41 (s, 2H), 7.85 – 7.76 (m, 2H), 7.73 (s, 1H), 7.42-7.40 (m, 1H), 7.36 (s, 1H), 7.34 – 7.29 (m, 1H), 7.27-7.26 (m, 1H), 6.40-6.38 (m, 1H), 6.29-6.27 (m, 1H), 5.79-5.78 (m, 1H), 5.31-5.30 (m, 1H), 4.88-4.75 (m, 1H), 4.68-4.59 (m, 1H), 4.49-4.41 (m, 1H), 4.22 – 4.08 (m, 1H), 4.12 (s, 3H).
110	^{1}H NMR (400 MHz, MeOD) δ 8.72 (s, 1H), 8.58 (d, *J* = 6.5 Hz, 1H), 7.89 (s, 2H), 7.79 (t, *J* = 8.5 Hz, 1H), 7.70 (s, 1H), 7.43 (d, *J* = 10.2 Hz, 1H), 7.32 (d, *J* = 11.8 Hz, 3H), 7.10 (s, 1H), 6.40-6.39 (m, 1H), 6.29-6.27 (m, 1H), 5.79-5.77 (m, 1H), 5.35 – 5.26 (m, 1H), 4.89-4.82 (m, 1H), 4.64-4.63 (m, 1H), 4.47-4.46 (m, 1H), 4.19 – 4.14 (m, 1H), 4.12 (s, 3H).

Compound #	HNMR DATA
112	^{1}H NMR (400 MHz, DMSO) δ 11.10 (s, 1H), 8.85 (s, 1H), 8.60 – 8.53 (m, 1H), 8.26 – 8.20 (m, 1H), 7.75 – 7.66 (m, 2H), 7.54 – 7.46 (m, 1H), 7.39 – 7.33 (m, 1H), 7.31 – 7.22 (m, 2H), 7.00 – 6.91 (m, 1H), 6.38-6.36 (m, 1H), 6.15-6.13 (m, 1H), 5.72-5.70 (m, 1H), 5.28 – 5.21 (m, 1H), 4.86 – 4.79 (m, 1H), 4.60-4.58 (m, 1H), 4.33-4.30 (m, 1H), 4.04 (s, 3H), 3.97-3.95 (m, 1H), 3.82 (s, 3H), 2.39 (s, 3H).
113	^{1}H NMR (400 MHz, DMSO) δ 11.23 (s, 1H), 8.87 (s, 1H), 8.64 (d, J = 6.4 Hz, 1H), 8.14 (s, 1H), 7.76 – 7.71 (m, 2H), 7.56-7.53 (m, 1H), 7.43 – 7.41 (m, 2H), 7.31-7.29 (m, 1H), 7.06-7.03 (m, 1H), 6.39-6.37 (m, 1H), 6.16-6.13 (m, 1H), 5.73-5.72 (m, 1H), 5.28 – 5.23 (m, 1H), 4.83-4.82 (m, 1H), 4.60-4.59 (m, 1H), 4.34-4.32 (m, 1H), 4.05 (s, 3H), 3.98-3.96 (m, 1H), 2.48 (s, 3H).
114	1H NMR (400 MHz, DMSO) δ = 9.50 (s, 1H), 8.71 (d, J= 2.8 Hz, 1H), 8.65 (d, J= 5.6 Hz, 1H), 8.38 (s, 1H), 7.56 (t, J= 8.8 Hz, 1H), 7.51 (s, 1H), 7.38 – 7.34 (m, 2H), 7.26 (s, 1H), 7.18 (dd, J= 8.8, 2.0 Hz, 1H), 6.46 (d, J= 2.8 Hz, 1H), 6.39 (dd, J= 16.8, 10.4 Hz, 1H), 6.14 (dd, J= 16.8, 2.0 Hz, 1H), 5.71 (dd, J= 10.4, 2.0 Hz, 1H), 5.23-.17 (m, 1H), 4.84 – 4.77 (m, 1H), 4.61 – 4.54 (m, 1H), 4.33 – 4.27 (m, 1H), 4.0-3.94 (m, 7H).
115	^{1}H NMR (400 MHz, DMSO) δ 9.81 (s, 1H), 9.14 (dd, J = 14.8, 1.4 Hz, 2H), 8.75 (d, J = 2.8 Hz, 1H), 8.38 (s, 1H), 7.67 (s, 1H), 7.57 (t, J = 8.8 Hz, 1H), 7.38 (dd, J = 11.2, 2.8 Hz, 1H), 7.26 (s, 1H), 7.24 – 7.19 (m, 1H), 6.56 (d, J = 2.8 Hz, 1H), 6.42-6.34 (m, 1H), 6.17-6.11 (m, 1H), 5.70 (dd, J = 10.4, 2.1 Hz, 1H), 5.27-5.22 (m, 1H), 4.88 – 4.83 (m, 1H), 4.63-4.55 (m, 1H), 4.32-4.26 (m, 1H), 4.01-3.92 (m, 4H).
116	1H NMR (400 MHz, DMSO) δ = 10.91 (s, 1H), 8.78 (s, 1H), 8.40 - 8.32 (m, 2H), 7.76 (d, J= 1.2 Hz, 1H), 7.70 (s, 1H), 7.57 (t, J= 8.8 Hz, 1H), 7.37-7.32 (m, 2H), 7.22 – 7.14 (m, 1H), 6.61 (b, 2H), 6.38 (dd, J= 16.8, 10.4 Hz, 1H), 6.31 (d, J= 2.8 Hz, 1H), 6.15 (dd, J= 16.8, 2.0 Hz, 1H), 5.72 (dd, J= 10.4, 2.0 Hz, 1H), 5.26-5.20 (m, 1H), 4.88 – 4.78 (m, 1H), 4.59 (dd, J= 10.4, 6.4 Hz, 1H), 4.32 (dd, J= 10.0, 2.8 Hz, 1H), 4.03 (s, 3H), 4.00 – 3.95 (m, 1H).

Compound #	HNMR DATA
117	1H NMR (301 MHz, DMSO) δ = 9.50 (s, 1H), 9.43 (s, 2H), 8.82 (d, J= 2.8 Hz, 1H), 8.37 (s, 1H), 7.56 (t, J= 8.8 Hz, 1H), 7.50 (s, 1H), 7.35 (dd, J= 11.2, 2.8 Hz, 1H), 7.25 (s, 1H), 7.19 (dd, J= 8.0, 2.0 Hz, 1H), 6.56 (d, J= 2.8 Hz, 1H), 6.39 (dd, J= 16.8, 10.4 Hz, 1H), 6.14 (dd, J= 16.8, 2.0 Hz, 1H), 5.70 (dd, J= 10.4, 2.0 Hz, 1H), 5.23-5.14 (m, 1H), 4.85-4.76 (m, 1H), 4.62-4.52 (m, 1H), 4.34-4.25 (m, 1H), 4.01-3.92 (m, 4H).
118	1H NMR (400 MHz, DMSO) δ = 9.52 (s, 1H), 8.48 (d, J= 2.8 Hz, 1H), 8.38 (s, 1H), 8.31 (d, J= 5.6 Hz, 1H), 7.55 (t, J= 8.8 Hz, 1H), 7.50 (s, 1H), 7.32 (dd, J= 11.2, 2.8 Hz, 1H), 7.25 (s, 1H), 7.15 (dd, J= 8.8, 1.6 Hz, 1H), 6.92 (s, 2H), 6.84 (d, J= 5.6 Hz, 1H), 6.42 – 6.33 (m, 2H), 6.14 (dd, J= 16.8, 2.0 Hz, 1H), 5.70 (dd, J= 10.4, 2.0 Hz, 1H), 5.22-5.16 (m, 1H), 4.84-4.76 (m, 1H), 4.57 (dd, J=11.2, 6.8 Hz, 1H), 4.30 (dd, J= 10.0, 3.2 Hz, 1H), 4.0-3.93 (m, 4H).
119	^{1}H NMR (400 MHz, DMSO) δ 9.73 (s, 1H), 8.95 (d, J = 2.8 Hz, 1H), 8.44 (s, 1H), 8.37 (d, J = 9.2 Hz, 1H), 8.14 (d, J = 9.2 Hz, 1H), 7.63 – 7.51 (m, 2H), 7.40 (dd, J = 11.2, 2.7 Hz, 1H), 7.26 (s, 1H), 7.22 (dd, J = 8.8, 1.8 Hz, 1H), 6.54 (d, J = 2.8 Hz, 1H), 6.45-6.35 (m, 1H), 6.20-6.10 (m, 1H), 5.71 (dd, J = 10.4, 2.1 Hz, 1H), 5.25-5.10 (m, 1H), 4.86 – 4.76 (m, 1H), 4.65-4.50 (m, 1H), 4.34 – 4.23 (m, 1H), 4.05-3.85 (m, 7H).
120	^{1}H NMR (400 MHz, DMSO) δ 9.50 (s, 1H), 8.73 (d, J = 0.8 Hz, 1H), 8.67 (d, J = 2.8 Hz, 1H), 8.38 (s, 1H), 7.57 (t, J = 8.8 Hz, 1H), 7.51 (s, 1H), 7.34 (dd, J = 11.2, 2.7 Hz, 1H), 7.25 (s, 1H), 7.20 – 7.15 (m, 1H), 7.01 (d, J = 0.8 Hz, 1H), 6.43 – 6.35 (m, 2H), 6.17 – 6.11 (m, 1H), 5.72 – 5.68 (m, 1H), 5.22 – 5.17 (m, 1H), 4.83 – 4.78 (m, 1H), 4.60 – 4.54 (m, 1H), 4.32 – 4.27 (m, 1H), 4.01 – 3.94 (m, 7H).
121	1H NMR (400 MHz, DMSO) δ = 11.14 (s, 1H), 8.93 (s, 1H), 8.86 (s, 1H), 8.74 (d, J= 2.8 Hz, 1H), 7.72 (s, 1H), 7.64 (s, 1H), 7.62 (t, J= 8.8 Hz, 1H), 7.45 (dd, J=11.2, 2.4 Hz, 1H), 7.38 (s, 1H), 7.25 (dd, J= 8.8, 2.0 Hz, 1H), 6.49 (d, J= 2.8 Hz, 1H), 6.38 (dd, J= 16.8, 10.4 Hz, 1H), 6.14 (dd, J= 16.8, 2.0 Hz, 1H), 5.72 (dd, J= 10.4, 2.0 Hz, 1H), 5.27-5.20 (m, 1H), 4.87 – 4.78 (m, 1H), 4.65-4.55 (m, 1H), 4.35-4.30 (m, 1H), 4.04 (s, 3H), 4.00 – 3.94 (m, 1H), 2.54 (s, 3H).

Compound #	HNMR DATA
122	^{1}H NMR (400 MHz, DMSO) δ 11.00 (s, 1H), 8.93 (d, J = 1.2 Hz, 1H), 8.81 (s, 1H), 8.64 (d, J = 2.8 Hz, 1H), 8.45 (s, 1H), 7.71 (s, 1H), 7.59 (t, J = 8.8 Hz, 1H), 7.43 (dd, J = 11.2, 2.7 Hz, 1H), 7.36 (s, 1H), 7.25 (dd, J = 2.0 Hz, 1H), 6.45 (d, J = 2.8 Hz, 1H), 6.43 – 6.33 (m, 1H), 6.20-6.10 (m, 1H), 5.72 (dd, J = 10.4, 2.0 Hz, 1H), 5.30 – 5.19 (m, 1H), 4.88 – 4.78 (m, 1H), 4.64-4.53 (m, 1H), 4.37 – 4.27 (m, 1H), 4.03 (s, 3H), 4.01 – 3.95 (m, 1H), 2.55 (s, 3H).
125	1H NMR (400 MHz, DMSO) δ 9.59 (s, 1H), 8.72 (d, J = 3.0 Hz, 1H), 8.40 (s, 1H), 7.61-7.50 (m, 2H), 7.36 (dd, J = 11.1, 2.7 Hz, 1H), 7.26 (s, 1H), 7.19 – 7.14 (m, 1H), 6.48 (d, J = 3.0 Hz, 1H), 6.44 – 6.34 (m, 1H), 6.14 (dd, J = 17.0, 2.1 Hz, 1H), 5.71 (dd, J = 10.3, 2.1 Hz, 1H), 5.24-5.16 (m, 1H), 4.86-4.77 (m, 1H), 4.62-4.53 (m, 1H), 4.31 (d, J = 3.7 Hz, 1H), 4.03 (s, 6H), 4.05-3.91 (m, 4H).
126	1H NMR (400 MHz, DMSO) δ = 11.00 (s, 1H), 8.83 (s, 1H), 8.76 (d, J= 5.6 Hz, 1H), 8.73 (d, J= 2.8 Hz, 1H), 7.70 (s, 1H), 7.62 (t, J= 8.8 Hz, 1H), 7.54 (d, J= 5.6 Hz, 1H), 7.47 (dd, J= 10.8, 2.4 Hz, 1H), 7.34 (s, 1H), 7.26 (dd, J= 8.8, 2.0 Hz, 1H), 6.47 (d, J= 2.8 Hz, 1H), 6.38 (dd, J= 16.8, 10.4 Hz, 1H), 6.15 (dd, J= 16.8, 2.0 Hz, 1H), 5.72 (dd, J= 10.4, 2.0 Hz, 1H), 5.27 – 5.20 (m, 1H), 4.86 – 4.79 (m, 1H), 4.63 – 4.56 (m, 1H), 4.37 – 4.29 (m, 1H), 4.04 (s, 3H), 3.99 – 3.95 (m, 1H), 2.66 (s, 3H).
127	^{1}HNMR (400 MHz, DMSO) δ 9.48 (s, 1H), 8.81 (d, J = 2.8 Hz, 1H), 8.37 (s, 1H), 7.96 (d, J = 9.2 Hz, 1H), 7.77 (d, J = 9.2 Hz, 1H), 7.60-7.45 (m, 2H), 7.33 (dd, J = 11.2, 2.7 Hz, 1H), 7.25 (s, 1H), 7.16 (dd, J = 8.8, 1.8 Hz, 1H), 6.48 – 6.32 (m, 2H), 6.20-6.05 (m,1H), 5.70 (dd, J = 10.4, 2.1 Hz, 1H), 5.25-5.10 (m, 1H), 4.86 – 4.76 (m, 1H), 4.65-4.50 (m, 1H), 4.34 – 4.23 (m, 1H), 4.05-3.85 (m, 4H), 2.65 (s, 3H).
129	1H NMR (400 MHz, DMSO) δ = 9.51 (s, 1H), 9.40 (s, 2H), 8.82 (d, J= 2.8 Hz, 1H), 8.37 (s, 1H), 7.56 (t, J= 8.8 Hz, 1H), 7.51 (s, 1H), 7.33 (dd, J= 11.2, 2.8 Hz, 1H), 7.25 (s, 1H), 7.17 (dd, J=8.8, 2.0 Hz, 1H), 6.52 (d, J= 2.8 Hz, 1H), 6.39 (dd, J= 16.8, 10.2 Hz, 1H), 6.14 (dd, J= 16.8, 2.0 Hz, 1H), 5.71 (dd, J= 10.2, 2.0 Hz, 1H), 5.23-5.16 (m, 1H), 4.84 – 4.78 (m, 1H), 4.61-4.54 (m, 1H), 4.3-4.26 (m, 1H), 4.00 – 3.94 (m, 4H), 3.93 (s, 3H).

Compound #	HNMR DATA
130	1H NMR (400 MHz, DMSO) δ = 9.55 (s, 1H), 8.49 (s, 2H), 8.40 (s, 1H), 7.63 (t, J= 8.8 Hz, 1H), 7.62 (s, 1H), 7.54 (dd, J= 10.8, 2.8 Hz, 1H), 7.51 (s, 1H), 7.32 (dd, J= 8.8, 2.0 Hz, 1H), 7.26 (s, 1H), 6.98 (s, 2H), 6.38 (dd, J= 16.8, 10.4 Hz, 1H), 6.14 (dd, J= 16.8, 2.0, 1H), 5.70 (dd, J= 10.4, 2.0 Hz, 1H), 5.23 – 5.16 (m, 1H), 4.84 – 4.77 (m, 1H), 4.61 – 4.54 (m, 1H), 4.33 – 4.27 (m, 1H), 4.00 – 3.93 (m, 4H).
131	1H NMR (400 MHz, DMSO) δ 9.86 (s, 1H), 9.06 (s, 2H), 8.45 (s, 1H), 7.89 (s, 1H), 7.72 – 7.58 (m, 3H), 7.42 – 7.35 (m, 1H), 7.28 (s, 1H), 6.39 (dd, J = 17.0, 10.3 Hz, 1H), 6.14 (dd, J = 17.0, 2.1 Hz, 1H), 5.71 (dd, J = 10.3, 2.1 Hz, 1H), 5.25-5.16 (m, 1H), 4.88 – 4.77 (m, 1H), 4.59 (dd, J = 10.9, 6.5 Hz, 1H), 4.30 (dd, J = 9.7, 3.3 Hz, 1H), 3.98 (s, 3H), 3.96 – 3.93 (m, 1H), 2.24 (td, J = 8.0, 4.0 Hz, 1H), 1.14 – 0.96 (m, 4H).
132	1H NMR (400 MHz, DMSO) δ 9.56 (s, 1H), 8.94 (s, 2H), 8.60 – 8.30 (m, 3H), 7.67 – 7.52 (m, 3H), 7.35 – 7.25 (m, 2H), 7.12 (d, J = 8.6 Hz, 1H), 6.86 (dd, J = 5.6, 2.2 Hz, 1H), 6.39 (dd, J = 17.0, 10.3 Hz, 1H), 6.14 (dd, J = 17.0, 2.0 Hz, 1H), 5.71 (dd, J = 10.3, 2.0 Hz, 1H), 5.25-5.16 (m, 1H), 4.85 – 4.78 (m, 1H), 4.61 – 4.54 (m, 1H), 4.30 (d, J = 6.6 Hz, 1H), 4.01-3.94 (m, 4H).
134	^{1}H NMR (400 MHz, DMSO) δ 9.98 (s, 1H), 8.46 (s, 1H), 7.68 – 7.51 (m, 4H), 7.37 – 7.25 (m, 3H), 6.42-6.34 (m, 1H), 6.18-6.10 (m, 1H), 5.70 (dd, J = 10.4, 2.1 Hz, 1H), 5.27-5.21 (m, 1H), 4.87 – 4.80 (m, 1H), 4.62-4.56 (m, 1H), 4.32 – 4.27 (m, 1H), 4.02-3.92 (m, 4H), 3.78 (s, 3H), 2.36 (s, 3H).
135	1H NMR (400 MHz, DMSO) δ 10.01 (s, 1H), 8.46 (s, 1H), 8.16-8.08 (m, 1H), 7.78-7.74 (m, 1H), 7.70-7.60 (m, 2H), 7.53 (dd, J = 10.8, 2.7 Hz, 1H), 7.43 (s, 1H), 7.35-7.25 (m, 2H), 6.42-6.34 (m 1H), 6.18-6.10 (m, 1H), 5.70 (dd, J = 10.4, 2.1 Hz, 1H), 5.27-5.21 (m, 1H), 4.87 – 4.81 (m, 1H), 4.62-4.56 (m, 1H), 4.53-4.45 (m, 1H), 4.32-4.26 (m, 1H), 4.01-3.93 (m, 4H), 1.42 (d, J = 6.8 Hz, 6H).

Compound #	HNMR DATA
136	1H NMR (400 MHz, DMSO) δ = 9.63 (s, 1H), 9.32 (s, 1H), 9.10 (s, 1H), 8.44 (b, 1H), 8.39 (s, 1H), 7.66 (t, J= 8.8 Hz, 1H), 7.59 (dd, J= 10.8, 2.8 Hz, 1H), 7.57 (s, 1H), 7.53 (s, 1H), 7.38 – 7.34 (m, 1H), 7.27 (s, 1H), 6.39 (dd, J= 16.8, 10.4 Hz, 1H), 6.14 (dd, J= 16.8, 2.0 Hz, 1H), 5.71 (dd, J= 10.4, 2.0 Hz, 1H), 5.23-5.18 (m, 1H), 4.84 – 4.79 (m, 1H), 4.60-4.54 (m, 1H), 4.32-4.27 (m, 1H), 4.08 - 4.02 (m, 1H)3.97 (s, 3H).
137	1H NMR (400 MHz, DMSO) δ 9.71 (s, 1H), 9.43 (s, 2H), 8.43 (s, 1H), 8.26 (s, 1H), 7.75 – 7.62 (m, 2H), 7.55 (s, 1H), 7.43 (dd, J = 8.8, 1.8 Hz, 1H), 7.27 (s, 1H), 6.39 (dd, J = 17.0, 10.3 Hz, 1H), 6.14 (dd, J = 17.0, 2.1 Hz, 1H), 5.71 (dd, J = 10.3, 2.1 Hz, 1H), 5.24-5.20 (m, 1H), 4.88 – 4.75 (m, 1H), 4.58 (dd, J = 10.8, 6.7 Hz, 1H), 4.30 (d, J = 6.6 Hz, 1H), 3.97 (s, 4H).
138	1H NMR (400 MHz, DMSO) δ 10.17 – 10.03 (m, 1H), 9.13 (s, 2H), 8.47 (s, 1H), 7.96 (s, 1H), 7.74 – 7.61 (m, 3H), 7.42 (d, J = 8.8 Hz, 1H), 7.29 (s, 1H), 6.41 – 6.34 (m, 1H), 6.14 (dd, J = 17.2, 2.2 Hz, 1H), 5.71 (dd, J = 10.4, 2.1 Hz, 1H), 5.27-5.21 (m, 1H), 4.87 – 4.81 (m, 1H), 4.62-4.56 (m, 1H), 4.32-4.27 (m, 1H), 4.01-3.92 (m, 4H), 2.66 (s, 3H).
139	1H NMR (400 MHz, DMSO) δ 10.16 (s, 1H), 8.48 (s, 1H), 7.70 – 7.59 (m, 4H), 7.44 (d, J = 2.0 Hz, 1H), 7.42-7.37 (m, 1H), 7.29 (s, 1H), 6.61 (d, J = 2.0 Hz, 1H), 6.41 – 6.34 (m, 1H), 6.14 (dd, J = 17.2, 2.2 Hz, 1H), 5.71 (dd, J = 10.4, 2.1 Hz, 1H), 5.27-5.21 (m, 1H), 4.87 – 4.81 (m, 1H), 4.62-4.56 (m, 1H), 4.32-4.27 (m, 1H), 4.02 – 3.93 (m, 7H).
140	1H NMR (400 MHz, DMSO) δ 9.55 (s, 1H), 9.03 (s, 2H), 8.40 (s, 1H), 7.79 (s, 1H), 7.74 – 7.59 (m, 2H), 7.51 (s, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.27 (s, 1H), 6.43 – 6.31 (m, 1H), 6.14 (d, J = 17.1 Hz, 1H), 5.70 (d, J = 10.0 Hz, 1H), 5.28-5.14 (m, 1H), 4.87-4.75 (m, 1H), 4.63-4.53 (m, 1H), 4.44 – 4.25 (m, 3H), 4.05-3.91 (m, 4H), 1.40-1.30 (m, 3H).

Assays

1. Preparation of HCC827-SVD, HCC827-ASV and HCC827-YVMA cell lines

[313] HCC827-SVD cell line were generated by first transducing HCC827 cells (ATCC) with lentiviral particles expressing codon-optimized human EGFR exon 20 insertion mutant D770_N771insSVD, and then selecting under 5 μg/mL purimycin treatment for a week. The resulting cells were further transduced with lentiviral particles carrying EGFR sgRNA and CAS9 to knockout the endogenous alleles of EGFR, and then selected under 500 μg/mL hygromycin B treatment for two weeks. Single clone was subsequently generated by limiting dilution approach. Endogenous EGFR knockout was confirmed by Sanger sequencing of cell genomic DNA and expression of exogenous mutant EGFR was verified by Western blot analysis.

[314] HCC827-ASV and HCC827-YVMA cell lines were generated in the similar approach as HCC827-SVD except that HCC827 cells (ATCC) were first transduced with lentiviral particles expressing codon-optimized human EGFR exon 20 insertion mutant A769_D770insASV and human ERBB2 exon20 insertion mutant A775_G776ins YVMA, respectively.

2. Cell growth inhibition for HCC827, HCC827-SVD, HCC827-ASV, HCC827-YVMA and A431.

[315] HCC827(ATCC), HCC827-SVD, HCC827-ASV, HCC827-YVMA were seeded in 96-well plates at 5000 cell/well in 90 μL of RPMI growth medium containing 10% FBS and 1% Penicillin Streptomycin. A431 (ATCC) cells were seed in 96-well plates at 5000 cell/well in 90 μL of DMEM growth medium containing 10% FBS and 1% Penicillin Streptomycin. Cells were incubated at 37°C overnight. The following day, the test compound was administered to the cells by using 10x compound stock solution prepared in growth medium at various concentrations. After administration of the compound, cells were then incubated at 37°C for 3 days. Before CellTiter-Glo assay, the plates were equilibrated at room temperature for approximately 10 minutes. 100 ul of CellTiter-Glo® Reagent (Promega) was added to each well. The plates were then incubated at room temperature for 10 minutes and luminescence was recorded by EnSpire plate reader (PerkinElmer).

3. p-EGFR assay of HCC827-SVD, HCC827-ASV and NCI-H2073; p-Her2 assay of HCC827-YVMA using western blot analysis

[316] $3x10^5$/well of NCI-H2073 (ATCC) were plated in 24-well plate and were grown overnight in RPMI growth medium containing 10% FBS and 1% Penicillin Streptomycin. Next day, NCI-H2073 cells were washed and incubated in serum free RPMI medium for 3 hours, followed by 2 hours compound treatment. EGF 100 ng/mL were added to the well and incubated for 15 minutes before harvesting the cells for protein analysis. $1.5x10^5$/well of HCC827-SVD, HCC827-ASV, HCC827-YVMA were plated in 24-well plate and were grown overnight in RPMI growth medium containing 10% FBS and 1% Penicillin Streptomycin. Next day, cells were treated with compounds for 2 hours. To collect protein from cells, cells were washed with PBS and protein were collected in Laemmli sample buffer (1x) (VWR). Protein in cell lysate were separated by SDS-PAGE and transferred to Odyssey nitrocellulose membranes (Licor) with iblot® dry blotting transfer system (ThermoFisher). Nonspecific binding was blocked by incubating membranes with Intercept Blocking Buffer (Licor) for 1 hour at room temperature

with gentle shaking. The membranes were then incubated overnight at 4 °C with primary antibodies mouse anti-EGFR (1:500, Santa Cruz Biotechnology, sc-377073), rabbit anti-p-EGFR (Tyr1068) (1:500, Cell Signaling, 3777), mouse anti-Her2 (1:500, Santa Cruz Biotechnology, sc-33684), rabbit anti-p-Her2 (Tyr1221/1222) (1:500, Cell Signaling, 2249), and mouse anti- GAPDH (1:5,000, Santa Cruz Biotechnology, sc-47724) diluted in Intercept Blocking Buffer containing 0.1% Tween 20. After washing 3 times with TBS-T, the membranes were incubated with IRDye® 800CW goat anti-mouse IgG (1:20,000, Licor), IRDye® 800CW goat anti-rabbit IgG (1:20,000, Licor), IRDye® 680RD Goat anti-Mouse IgG (1:20,000, Licor) for 1 hour. After TBS-T washes, membranes were rinsed in TBS and scanned on Odyssey® CLx Imaging System (Licor). The bands were quantified using Image Studio™ Software (Licor).

4. P-EGFR assay of HCC827-SVD, HCC827-ASV and H2073 using alphaLISA.

[317] NCI-H2073, HCC827-SVD, HCC827-ASV cells were seeded in 96-well plates at $4x10^4$ cell/well in 90 µL of RPMI growth medium containing 10% FBS and 1% Penicillin Streptomycin. The following day, the test compound was administered to HCC827-SVD, HCC827-ASV in 96 wells by using 10x compound stock solution prepared in growth medium at various concentrations. After administration of the compound, cells were then incubated at 37°C for 2 hours. For NCI-H2073 treatment, cells were washed and incubated with serum free RPMI for 3 hours and followed by 2 hours compound treatment. EGF 100 ng/mL was applied to H2073 for 15 minutes before harvesting the cells. The AlphaLISA® SureFire® Ultra™ HV p-EGFR (Tyr1068) assay kit (PerkinElmer) was used to measure p-EGFR level in cell lysate. To prepare lysate, cells were washed with PBS, freshly prepared 1X Lysis Buffer from the kit (50 µL per well) was added to the well and the plate was agitated on a plate shaker (600 rpm) for 20 minutes at room temperature. 8 µL of lysate from wells were transferred to AlphaLisa reading plate (384 well plate) in triplicate. 4 µL of Acceptor beads Mix (from kit) were added to wells. Plate was sealed with Topseal-A adhesive film and covered with foil. After 1-hour incubation at room temperature, 4 µL of Donor beads Mix (from kit) were added to wells under subdued light. Plate was sealed with Topseal-A adhesive film and covered with foil. After 1-hour incubation at room temperature in the dark, Alpha signal was read with EnSpire plate reader (PerkinElmer).

Results

[318] Table 4 illustrates growth inhibition (GI50) by exemplary compounds of the present disclosure in multiple cell lines 3 days after administration.

Table 4. Cell Growth Inhibition of the Compounds of the Present Disclosure

Compound #	Cell growth inhibition, GI50 (nM)				
	HCC827	HCC827-SVD	HCC827-ASV	HCC827-YVMA	A431
1	6.66	31.28	51.33	26.05	539.6
2	2.31	22.45	32.49	6.29	637.2
3	2.56	15.78	34.87	13.05	> 1,000
4	2.8	10.57	24.03	20.35	548.3

Compound #	Cell growth inhibition, GI50 (nM)				
	HCC827	HCC827-SVD	HCC827-ASV	HCC827-YVMA	A431
5	15.45	54.46	54.11	72.4	> 1,000
6	107.5	445.1	674.2	381.7	> 1,000
7	4.99	15.6	35.58	30.31	> 1,000
8	3.63	18.68	33.4	22.99	411.1
9	8.11	22.89	61.15	68.67	> 1,000
10	3.74	14.14	29.41	26.07	502.7
11	9.34	38.96	64.47	53.38	N/A
12	2.13	25.99	67.43	21.74	N/A
13	39.53	228.1	416.9	266	N/A
14	4.69	33.73	49.08	22.58	N/A
15	139.4	37.34	47.1	34.72	>1,000
16	35.97	24.75	18.88	26.71	181.2
17	151.7	25.94	42.91	33.53	>1,000
18	32.29	37.59	26.03	61.71	109.6
19	87.72	40.75	25.15	49.32	144
20	64.52	15.36	24.92	27.91	617.6
21	31.52	23.04	12.86	16.89	275.2
22	46.52	17.14	8.827	22.15	381.7
23	78.16	20.81	35.79	31.62	532.7
24	97.95	56.93	82.78	111.5	356.2
25	654.1	31.46	126.4	325.4	532.8
26	110.9	274.4	180.2	257.6	>1,000
27	80.24	24.92	25.2	25.59	183.1
39	186.4	74.13	32.22	61.7	268.9
40	125.7	89.41	50.8	86.84	175.2
41	118	98.2	45.86	66.57	312.5
42	52.68	59.21	25.81	36.5	560.7
44	752	175	46.04	158.3	>1,000
45	356.7	65.97	58.85	94.04	>1,000
46	>1,000	129.6	90.77	551.4	>1,000
47	774	136.6	46.87	115.4	>1,000
49	>1,000	>1,000	>1,000	>1,000	>1,000
52	92.52	33.5	54.75	71.41	>1,000
53	60.96	50.44	29.36	106.1	>1,000

Compound #	Cell growth inhibition, GI50 (nM)				
	HCC827	HCC827-SVD	HCC827-ASV	HCC827-YVMA	A431
54	100.3	35.86	48.24	58.83	450.8
56	92.31	27.46	33.3	51.19	>1,000
58	189.3	101.5	67.65	125.3	449.7
59	58.38	597.2	178.3	109.4	>1,000
61	>1,000	>1,000	>1,000	>1,000	>1,000
62	427.5	655.3	780.3	279.6	>1,000
63	290.3	>1,000	714.4	>1,000	603.5
65	102.5	34.5	33.58	35.98	>1,000
66	26.03	25.29	20.5	27.06	190.1
67	108.3	28.19	55.31	72.76	178.5
68	428.2	67.76	157.5	120.4	427.2
69	210.9	38.73	113.1	71.79	225.3
70	245.7	50.8	76.6	127.4	255.1
71	104.7	12.79	68.13	101.3	204.6
72	521.8	>1,000	>1,000	183.7	1229
73	88.81	>1,000	>1,000	30.41	114.5
74	>1,000	479.3	262.1	358.1	>1,000
75	555.9	>1,000	>1,000	115.4	1394
76	>1,000	496.8	704	>1,000	>1,000
77	>1,000	>1,000	>1,000	>1,000	>1,000
78	>1,000	>1,000	>1,000	>1,000	>1,000
79	537.6	94.21	167.2	100.6	>1,000
80	29.41	29.48	33.12	48.9	533
81	16.18	13.25	12.69	17.66	222.5
82	965.3	994.9	>1,000	>1,000	>1,000
83	>1,000	>1,000	>1,000	>1,000	>1,000
84	76.37	44.47	80.93	83.33	437.6
85	50.97	637.6	357.4	421.3	>1,000
86	520.5	265.1	103.8	149.7	>1,000
87	62.17	103.3	81.32	67.11	193.4
88	33.69	30.68	25.46	23.12	224.3
89	73.47	97.05	57.62	75.68	402.3
90	13.93	37.37	38.75	49.18	193.1
91	59.88	74.71	62.73	52.98	905.1

Compound #	Cell growth inhibition, GI50 (nM)				
	HCC827	HCC827-SVD	HCC827-ASV	HCC827-YVMA	A431
92	33.04	43.75	21.07	26.49	356
93	27.72	26.41	24.37	36.81	245
94	32.92	40.81	32.95	41.48	348.5
95	44.24	30.73	25.48	38.35	521.1
96	34.02	16.74	18.66	46.61	712.5
97	>1,000	>1,000	>1,000	>1,000	>1,000
98	78.35	56.74	24.32	67.06	507.5
99	101.3	68.17	47.02	67.07	354.4
100	>1,000	251.2	100.3	312.8	>1,000
101	78.03	40.89	32.44	55.03	784.2
102	66.11	68.36	22.53	90.84	>1,000
103	81.11	66.4	24.09	32.43	>1,000
104	59.82	32.45	24.06	45.03	>1,000
105	813.3	213.6	65.2	266.8	>1,000
106	198.2	132.5	66.7	61.01	>1,000
107	272.6	203.7	134.2	78.9	>1,000
108	498.6	186.6	116.6	108.3	>1,000
109	711.3	309.7	145.7	301.6	>1,000
110	189.3	127.2	60.95	92.09	>1,000
111	29.84	62.53	34.62	40.27	421.1
112	>1,000	234.1	117	162	>1,000
113	>1,000	306.6	181.1	297	>1,000
114	64.68	36.52	46.02	28.48	848
115	447.5	433.6	350	397.4	>1,000
116	204.8	631.3	46.02	541.2	>1,000
117	892	326.9	247.2	334.8	>1,000
118	247	114.9	111	144.1	>1,000
119	>1,000	>1,000	781.9	>1,000	>1,000
120	580.9	127.5	116.5	142.9	>1,000
121	580.9	127.5	116.5	142.9	>1,000
122	235.3	99.08	74.39	68	583.6
123	689.6	97	62.1	108.9	>1,000
124	919.9	93.61	63.51	86.8	>1,000
125	57.29	30.34	34.01	30.71	201.9

Compound #	Cell growth inhibition, GI50 (nM)				
	HCC827	HCC827-SVD	HCC827-ASV	HCC827-YVMA	A431
126	321.6	180.5	167.2	105.9	>1,000
127	35.79	32.56	71.51	84.01	425.2
128	19.32	21.79	19.79	15.58	345.5
129	>1,000	>1,000	>1,000	>1,000	>1,000
130	301.9	265.2	612.2	350.8	>1,000
131	46.65	55.94	30.88	41.91	307.1
132	>1,000	>1,000	>1,000	>1,000	>1,000
133	179.1	27.06	33.73	28.81	442.8
134	439.1	110.4	105.3	87.17	1172
135	106.9	61.98	87.67	93.06	728.5
136	76.81	85.96	91.92	78.84	503.2
137	126.2	49.97	91.01	105.9	812.5
138	122.2	31.98	33.59	68.07	>1,000
139	284.2	121.6	58.69	247.1	>1,000
140	155.3	41.31	33.85	113.1	208.5

[319] Table 5 illustrates p-EGFR(Tyr1068) or p-Her2 (Tyr1221/1222) inhibition (EC50) by exemplary compounds of the present disclosure in multiple cell lines carrying wild type (NCI-H2073) or mutant EGFR (HCC827-SVD, HCC827-ASV and HCC827-YVME). P-EGFR and p-Her2 were either measured by Western blot analysis or alphaLISA. Those numbers measured by alphaLISA were shown inside the parenthesis.

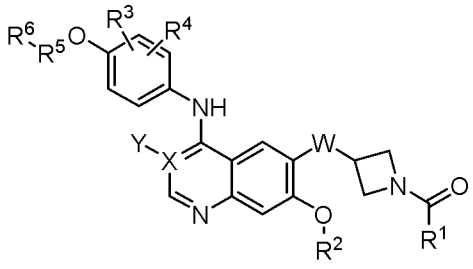
Table 5. p-EGFR(Tyr1068) or p-Her2 (Tyr1221/1222) Inhibition of the Exemplary Compounds of the Present Disclosure

Example #	p-EGFR or pHer2 inhibition, EC50 (nM)			
	p-EGFR	p-EGFR	p-Her2	p-EGFR
	HCC827-SVD	HCC827-ASV	HCC827-YVMA	NCI-H2073
2	(4.6)	(12.9)	2.6	47.6
3	(2.0)	(5.1)	2.5	9.5
8	0.7	1.2	2.5	16.8
14	9.8	6.6	N/A	49.2
15	4.3	7.7	7.7	35.6
16	2.4	5.5	7.5	21.2

Example #	p-EGFR or pHer2 inhibition, EC50 (nM)			
	p-EGFR	p-EGFR	p-Her2	p-EGFR
	HCC827-SVD	HCC827-ASV	HCC827-YVMA	NCI-H2073
17	2.6	5.1	4.4	50.8
19	4.3	6.4	5.5	14.9
20	6	3.6	3.5	21.2
22	2.5	5.2	5.2	10.9

WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a tautomer, stereoisomer or a mixture of stereoisomers, or a pharmaceutically acceptable salt, or hydrate, or deuterated derivative thereof:



(I)

wherein:

R^1 is C_{1-6} alkyl, C_{1-6} alkoxyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkylene-OH, C_{1-6} alkyleneamine, or C_{1-6} alkylene-CN, each of which is substituted with 0,1, 2, or 3 R^a;

R^2 is H, C_1-C_5alkyl, deuterated C_1-C_5alkyl, C_1-C_5alkoxy, C_1-C_5haloalkyl, C_3-C_7cycloalkyl, or heterocycle, each of which is substituted with 0,1, 2, or 3 R^a;

W is O or NH;

X is C or N, wherein when X is C, Y is cyano; when X is N, Y is absent;

R^3 and R^4 are independently hydrogen, halogen, hydroxyl, cyano, C_1-C_5alkyl, C_1-C_5alkoxy, or C_1-C_5haloalkyl;

R^5 is 5- to 6-member cycloalkyl, 5- to 6-member aryl, 5- to 6-member heterocycle, or monocyclic or bicyclic 5- to 12-member heteroaryl, each of which is substituted with 0, 1, 2, or 3 R^a;

R^6 is absent, or C_1-C_5alkyl, C_1-C_5alkoxy, or C_1-C_5haloalkyl, or 5- to 6-member cycloalkyl, 5- to 6-member aryl, 5- to 6-member heterocycle, or monocyclic or bicyclic 5- to 12-member heteroaryl, each of which is substituted with 0, 1, 2, or 3 R^a;

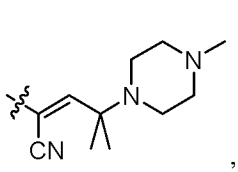
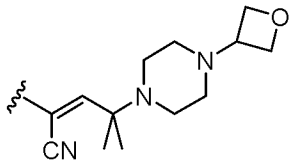
R^a is independently hydrogen, hydroxy, halogen, amino, cyano, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, CO(O)-C_{1-4} alkyl, C_{0-3} alkylene-CN, C_{0-3} alkylene-N-(C_{1-6} alkyl)$_2$, C_{0-3} alkylene-C_{3-8} heterocycloalkyl, heterocycle, heterocycloalkyl, aryl, or heteroaryl, each of which is substituted with 0, 1, 2, or 3 R^b, and may be fully or partially deuterated; and

R^b is independently H, hydroxy, halogen, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, or C_{3-8} heterocycloalkyl.

2. The compound of claim 1, wherein R^1 is C_{1-6} alkyl, C_{1-6} alkoxyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkylene-OH, C_{1-6} alkyleneamine, or C_{1-6} alkylene-CN.

3. The compound of claim 2, wherein R^1 is vinyl substituted with 0,1, 2, or 3 R^a or 1-propynyl.

4. The compound of claim 3, wherein R^1 is -$CFCH_2$, -$CH{=}CHCH_2N(CH_3)_2$,

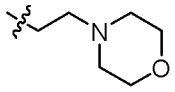

, or

.

5. The compound of claim 1, wherein R^2 is H, C_1-C_5alkyl, C_1-C_5alkoxy, C_1-C_5haloalkyl, or C_3-C_7cycloalkyl, each of which is substituted with 0,1, 2, or 3 R^a.

6. The compound of claim 5, wherein R^2 is C_1-C_5alkyl, each of which is substituted with 0,1, 2, or 3 R^a.

7. The compound of claim 6, wherein R^2 is methyl or ethyl.

8. The compound of claim 6, wherein R^2 is deuterated methyl.

9. The compound of claim 6, wherein R^2 is .

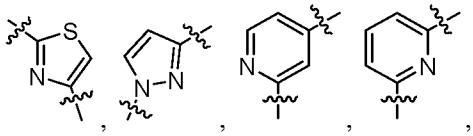
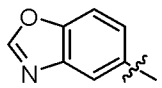
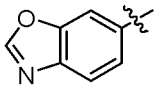
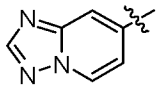
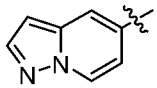
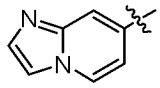
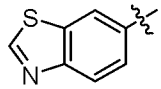
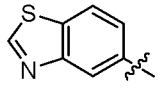
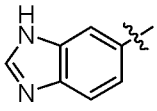
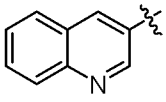
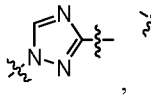
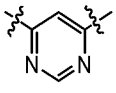
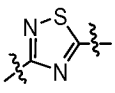
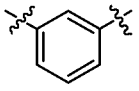
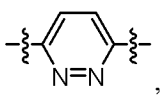
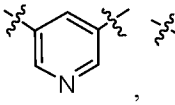
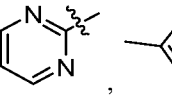
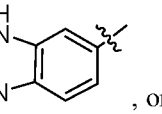
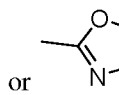
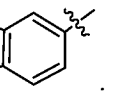
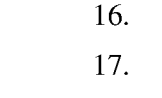
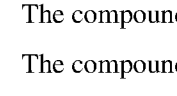
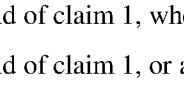
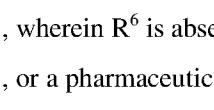
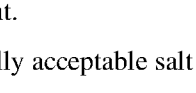
10. The compound of claim 6, wherein R^2 is -$CH_2CH_2N(CH_3)_2$.

11. The compound of claim 1, wherein R^3 and R^4 are independently hydrogen or halogen.

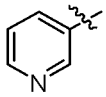
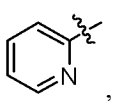
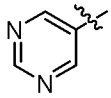
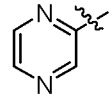
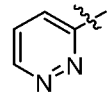
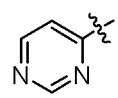
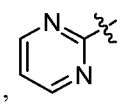
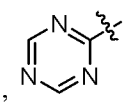
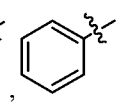
12. The compound of claim 11, wherein R^3 is Cl and R^4 is H.

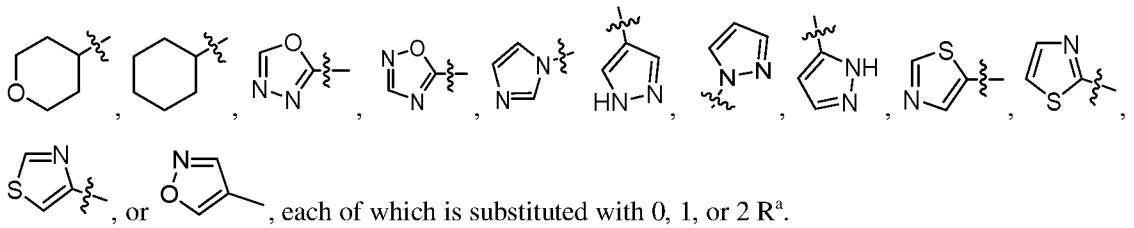
13. The compound of claim 11, wherein R^3 is H and R^4 is F.

14. The compound of claim 1, wherein R^5 is 5- to 6-member cycloalkyl, 5- to 6-member aryl, 5- to 6-member heterocycle, or monocyclic or bicyclic 5- to 12-member heteroaryl.

15. The compound of claim 14, wherein R^5 is ,
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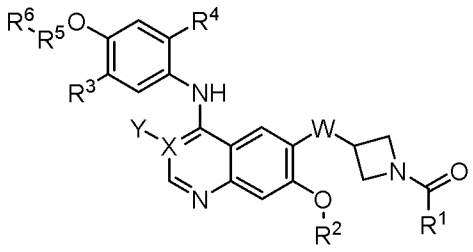
16. The compound of claim 1, wherein R^6 is absent.

17. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^6 is ,
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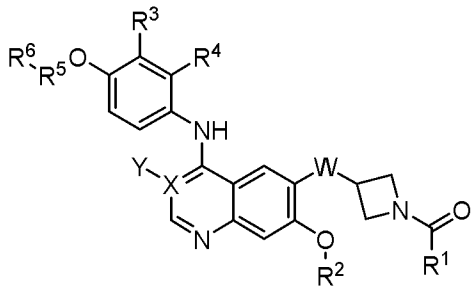
, each of which is substituted with 0, 1, or 2 R^a.

18. The compound of claim 1, wherein the Formula I is Formula (Ia), or a tautomer, stereoisomer or a mixture of stereoisomers, or a pharmaceutically acceptable salt, or hydrate, or deuterated derivative thereof:



(Ia).

19. The compound of claim 1, wherein the Formula (I) is Formula (Ib), or a tautomer, stereoisomer or a mixture of stereoisomers, or a pharmaceutically acceptable salt, or hydrate, or deuterated derivative thereof:



(Ib).

20. The compound according to claim 1, wherein the compound is selected from:

1-(3-((4-((3-chloro-4-(quinolin-3-yloxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-ethoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((3-chloro-4-(pyrazolo[1,5-a]pyridin-5-yloxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((3-chloro-4-((2-methylbenzo[d]oxazol-5-yl)methoxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((3-chloro-4-((2-methyl-1H-benzo[d]imidazol-6-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((4-(benzo[d]thiazol-5-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-ethoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((4-(benzo[d]thiazol-6-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((4-(benzo[d]oxazol-5-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((4-(benzo[d]oxazol-6-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-(methoxy-d3)quinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((3-chloro-4-(imidazo[1,2-a]pyridin-7-yloxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-(methoxy-d3)quinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((1-(5-fluoro-6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((4-(5-isopropyl-1,3,4-oxadiazol-2-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((1-(6-methoxypyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((4-(6-methylpyridin-3-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((4-(6-methoxypyridin-3-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one;

6-((1-acryloylazetidin-3-yl)amino)-7-ethoxy-4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)quinoline-3-carbonitrile;

6-((1-acryloylazetidin-3-yl)amino)-7-ethoxy-4-((2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy)phenyl)amino)quinoline-3-carbonitrile;
6-((1-acryloylazetidin-3-yl)amino)-7-ethoxy-4-((2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)quinoline-3-carbonitrile;
6-((1-acryloylazetidin-3-yl)amino)-7-ethoxy-4-((2-fluoro-4-((4-(6-methoxypyridin-3-yl)thiazol-2-yl)oxy)phenyl)amino)quinoline-3-carbonitrile;
6-((1-acryloylazetidin-3-yl)amino)-7-ethoxy-4-((2-fluoro-4-((4-(6-methylpyridin-3-yl)thiazol-2-yl)oxy)phenyl)amino)quinoline-3-carbonitrile;
1-(3-((4-((2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((1-(2-(methoxy-d3)pyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((7-ethoxy-4-((2-fluoro-4-((1-(2-(methoxy-d3)pyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)quinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((1-(2-(methoxy-d3)pyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one;
1-(3-((7-ethoxy-4-((2-fluoro-4-((1-(2-(methoxy-d3)pyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)quinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((1-(6-(methoxy-d3)pyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((7-ethoxy-4-((2-fluoro-4-((1-(6-(methoxy-d3)pyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)quinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((1-(6-(methoxy-d3)pyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one;
1-(3-((7-ethoxy-4-((2-fluoro-4-((1-(6-(methoxy-d3)pyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)quinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((4-((1-(2-ethoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((1-(2-isopropoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((1-(5-methoxypyrazin-2-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((1-(6-methoxypyridazin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((4-((1-(6-ethoxypyridazin-3-yl)-1H-pyrazol-3-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((2-(2-methoxypyrimidin-5-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((6'-methyl-[2,3'-bipyridin]-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((2-(2-methylpyrimidin-5-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((2-(2-methylpyrimidin-5-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)but-2-yn-1-one;

1-(3-((4-((2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)but-2-yn-1-one;

1-(3-((4-((2-fluoro-4-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((4-((1-(5,6-dimethylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((4-((1-(5-chloro-6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((4-((1-(4,6-dimethylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

5-(3-(4-((6-((1-acryloylazetidin-3-yl)oxy)-7-methoxyquinazolin-4-yl)amino)-3-fluorophenoxy)-1H-pyrazol-1-yl)-2-methylnicotinonitrile;

1-(3-((4-((2-fluoro-4-((1-(5-methoxy-6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-1,2,4-triazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((3-(6-methylpyridin-3-yl)-1,2,4-thiadiazol-5-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((6-(4-methyl-1H-pyrazol-1-yl)pyrimidin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((4-(4-methyl-1H-pyrazol-1-yl)pyrimidin-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((4-(3-methyl-1,2,4-oxadiazol-5-yl)pyridin-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((6-(4-methyl-1H-imidazol-1-yl)pyrimidin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((6-(5-methyl-1,3,4-oxadiazol-2-yl)pyrimidin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((4-(4-methyl-1H-pyrazol-1-yl)pyridin-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((2-(4-methyl-1H-pyrazol-1-yl)pyrimidin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((4-(2-isopropoxypyrimidin-5-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((4-(2-(methylamino)pyrimidin-5-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((4-((4-(2-(dimethylamino)pyrimidin-5-yl)thiazol-2-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((4-(1-methyl-1H-pyrazol-4-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((4-((4-(1-cyclopropyl-1H-pyrazol-4-yl)thiazol-2-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-(2-morpholinoethoxy)quinazolin-6-yl)oxy)azetidin-1-yl)-2-fluoroprop-2-en-1-one;

1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)-2-fluoroprop-2-en-1-one;

2-fluoro-1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

(E)-1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)-4-(dimethylamino)but-2-en-1-one;

2-fluoro-1-(3-((4-((2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

(E)-2-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carbonyl)-4-methyl-4-(4-(oxetan-3-yl)piperazin-1-yl)pent-2-enenitrile;

(E)-2-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidine-1-carbonyl)-4-methyl-4-(4-methylpiperazin-1-yl)pent-2-enenitrile;

1-(3-((7-(2-(dimethylamino)ethoxy)-4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)quinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-(3-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-(3-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((3-fluoro-4-((1-(4-hydroxycyclohexyl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-hydroxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((1-(5-fluoro-6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-(2-morpholinoethoxy)quinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((4-(5-methoxypyridazin-3-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((4-((4-(5-chloropyridin-2-yl)thiazol-2-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((4-(6-methoxypyridazin-3-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((4-(4-methoxyphenyl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((4-(6-(trifluoromethyl)pyridin-3-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-4-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((4-(6-methoxypyridin-3-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((3-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((1-(5-methoxypyrimidin-2-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((1-(6-methoxypyrimidin-4-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((3-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)but-2-yn-1-one;
1-(3-((4-((2-fluoro-4-((1-(5-methoxypyridin-2-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((1-(6-methoxypyridin-2-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
2-fluoro-1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one;
(E)-4-(dimethylamino)-1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)but-2-en-1-one;

1-(3-((4-((2-fluoro-4-((2-(thiazol-5-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((2-(thiazol-2-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((2-(thiazol-4-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
2-fluoro-1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((6-methyl-[3,4'-bipyridin]-2'-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((6'-methyl-[3,3'-bipyridin]-5-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((2-(1-methyl-1H-pyrazol-5-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((4-((2-(1H-pyrazol-4-yl)pyridin-4-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((4-((2-(1H-pyrazol-5-yl)pyridin-4-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((3-chloro-2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((4-((2-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((2-(5-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-4-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
5-(3-(4-((6-((1-acryloylazetidin-3-yl)oxy)-7-methoxyquinazolin-4-yl)amino)-3-fluorophenoxy)-1H-pyrazol-1-yl)pyrazine-2-carbonitrile;
1-(3-((4-((4-((1-(5-aminopyrazin-2-yl)-1H-pyrazol-3-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
5-(3-(4-((6-((1-acryloylazetidin-3-yl)oxy)-7-methoxyquinazolin-4-yl)amino)-3-fluorophenoxy)-1H-pyrazol-1-yl)pyrimidine-2-carbonitrile;
1-(3-((4-((4-((1-(2-aminopyrimidin-4-yl)-1H-pyrazol-3-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
methyl 6-(3-(4-((6-((1-acryloylazetidin-3-yl)oxy)-7-methoxyquinazolin-4-yl)amino)-3-fluorophenoxy)-1H-pyrazol-1-yl)pyridazine-3-carboxylate;
1-(3-((4-((2-fluoro-4-((1-(6-methoxypyrimidin-4-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((1-(6-methylpyrimidin-4-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((1-(5-methylpyrazin-2-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((2-morpholinopyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((4-((1-(4,6-dimethoxy-1,3,5-triazin-2-yl)-1H-pyrazol-3-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((1-(2-methylpyrimidin-4-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((1-(6-methylpyridazin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((4-((1-(6-(dimethylamino)pyridazin-3-yl)-1H-pyrazol-3-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
methyl 5-(3-(4-((6-((1-acryloylazetidin-3-yl)oxy)-7-methoxyquinazolin-4-yl)amino)-3-fluorophenoxy)-1H-pyrazol-1-yl)pyrimidine-2-carboxylate;
1-(3-((4-((4-((4-(2-aminopyrimidin-5-yl)thiazol-2-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((4-((4-(2-cyclopropylpyrimidin-5-yl)thiazol-2-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((2-(2-hydroxypyrimidin-5-yl)pyridin-4-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((1-(5-methoxypyridazin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((4-((4-(1,5-dimethyl-1H-pyrazol-4-yl)thiazol-2-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((4-(1-isopropyl-1H-pyrazol-4-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((4-(isoxazol-4-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
5-(2-(4-((6-((1-acryloylazetidin-3-yl)oxy)-7-methoxyquinazolin-4-yl)amino)-3-fluorophenoxy)thiazol-4-yl)pyrimidine-2-carbonitrile;
1-(3-((4-((2-fluoro-4-((4-(2-methylpyrimidin-5-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((2-fluoro-4-((4-(1-methyl-1H-pyrazol-5-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one; or

1-(3-((4-((4-(2-ethoxypyrimidin-5-yl)thiazol-2-yl)oxy)-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one.

21. The compound of claim 1, wherein the compound is selected from:

1-(3-((4-((3-chloro-4-(quinolin-3-yloxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-ethoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((3-chloro-4-(pyrazolo[1,5-a]pyridin-5-yloxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((3-chloro-4-((2-methylbenzo[d]oxazol-5-yl)methoxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((3-chloro-4-((2-methyl-1H-benzo[d]imidazol-6-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((4-(benzo[d]thiazol-5-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-ethoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((4-(benzo[d]thiazol-6-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((4-(benzo[d]oxazol-5-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((4-(benzo[d]oxazol-6-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-(methoxy-d3)quinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((3-chloro-4-(imidazo[1,2-a]pyridin-7-yloxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-(methoxy-d3)quinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((1-(5-fluoro-6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;

1-(3-((4-((2-fluoro-4-((4-(5-isopropyl-1,3,4-oxadiazol-2-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one; or
1-(3-((4-((2-fluoro-4-((4-(2-methoxypyrimidin-5-yl)thiazol-2-yl)oxy)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one.

22. The compound of claim 1, wherein the compound is selected from:
1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-ethoxyquinazolin-6-yl)oxy)azetidin-1-yl)prop-2-en-1-one;
1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-ethoxyquinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one; or
1-(3-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chlorophenyl)amino)-7-(methoxy-d3)quinazolin-6-yl)amino)azetidin-1-yl)prop-2-en-1-one.

23. A pharmaceutical composition comprising a therapeutically effective amount of the compound according to any one of claims 1 to 22 and at least one additional component selected from pharmaceutically acceptable carriers, pharmaceutically acceptable vehicles, pharmaceutically acceptable excipients, or combinations thereof.

24. A method of treating cancer in a subject comprising administering to the subject a therapeutically effective amount of the compound according to any one of claims 1 to 22 or the pharmaceutical composition of claim 23.

25. The method of claim 24, wherein the cancer is associated with an EGFR or HER2 exon 20 insertion mutation.

26. The method of claim 25, wherein the cancer is breast cancer, lung cancer, pancreatic cancer, colon cancer, head and neck cancer, renal cell carcinoma, squamous cell carcinoma, thyroid cancer, gall bladder cancer, thyroid cancer, bile duct cancer, ovarian cancer, endometrial cancer, prostate cancer, or esophageal cancer.

27. The method of claim 26, wherein the cancer is lung cancer.

28. The method of claim 27, wherein the cancer is non-small cell lung cancer.

29. The method of claim 26, wherein the cancer is pancreatic cancer.

30. The method of claim 26, wherein the cancer is colon cancer.

31. The method of claim 26, wherein the cancer is breast cancer.

32. The method of claim 26, wherein the cancer is head and neck cancer.

33. The method of claim 32, wherein the cancer is sinonasal squamous cell carcinoma.

34. A use of the compound according to any one of claims 1 to 22 or of the pharmaceutical composition of claim 23 in the preparation of a medicament.

35. The method of claim 34, further comprising administering to the subject in combination with an additional anti-cancer agent.

36. The method of claim 35, wherein the compound of claim 1 or the pharmaceutical composition of claim 23 and the additional anti-cancer agent are administered concomitantly.

37. The method of claim 35, wherein the compound of claim 1 or the pharmaceutical composition of claim 23 and the additional anti-cancer agent are administered sequentially.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2021/031742

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/12 C07D413/12 A61K31/517 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/150118 A2 (HANMI PHARM IND CO LTD [KR]; LEE KWANG-OK [KR] ET AL.) 11 December 2008 (2008-12-11) see the compounds of claim 1 wherein R1 is substituted with aryloxy and activity on EGFR and especially example 48 in combination with azetidine derivatives of examples 24 to 33	1-37
X	WO 2005/026151 A1 (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB] ET AL.) 24 March 2005 (2005-03-24) see the compounds according to claim 1 wherein X2 is O, M is CO as EGFR and erbB2 inhibitors and especially example 32	1-37

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 September 2021	16/09/2021

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2021/031742

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2020/262998 A1 (HANMI PHARM IND CO LTD [KR]) 30 December 2020 (2020-12-30) see examples 21 to 30 entitled to the priority of 26.6.2019 -----	1-35

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2021/031742

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008150118 A2	11-12-2008	AR 066876 A1	16-09-2009
		AR 110003 A2	13-02-2019
		AU 2008260772 A1	11-12-2008
		BR PI0811069 A2	09-12-2014
		CA 2687180 A1	11-12-2008
		CN 101679384 A	24-03-2010
		DK 2167492 T3	11-01-2016
		EP 2167492 A2	31-03-2010
		ES 2558623 T3	05-02-2016
		HK 1142591 A1	10-12-2010
		HR P20160007 T1	12-02-2016
		HU E028243 T2	28-12-2016
		IL 202154 A	28-05-2014
		JP 5155391 B2	06-03-2013
		JP 2010529115 A	26-08-2010
		KR 20080107294 A	10-12-2008
		MY 144972 A	30-11-2011
		NZ 582412 A	22-12-2011
		PL 2167492 T3	31-03-2016
		PT 2167492 E	04-02-2016
		RU 2009149307 A	20-07-2011
		TW 200906414 A	16-02-2009
		UA 96045 C2	26-09-2011
		US 2010179120 A1	15-07-2010
		WO 2008150118 A2	11-12-2008
		ZA 201000022 B	28-04-2011
WO 2005026151 A1	24-03-2005	AU 2004272350 A1	24-03-2005
		BR PI0414447 A	14-11-2006
		CA 2539022 A1	24-03-2005
		CN 1882573 A	20-12-2006
		EP 1664028 A1	07-06-2006
		JP 2007505873 A	15-03-2007
		MX PA06002963 A	14-06-2006
		US 2007032508 A1	08-02-2007
		WO 2005026151 A1	24-03-2005
		ZA 200602190 B	26-09-2007
WO 2020262998 A1	30-12-2020	NONE	