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(54) Title: QUINAZOLINE DERIVATIVES, COMPOSITIONS AND METHODS THEREOF

(57) Abstract: The invention provides novel quinazoline derivatives, substituted at the C4 position with an unsubstituted or substituted, 3- to 10-membered monocyclic, bicyclic or bridged nitrogen heterocyclic ring moiety, that are shown to be potent and selective inhibitors of KRas, in particular KRas (G12D) and pharmaceutical compositions thereof and methods for treating diseases and disorders associated with or related to KRas activities, such as various types of cancer.

QUINAZOLINE DERIVATIVES, COMPOSITIONS AND METHODS THEREOF

Priority Claims and Related Applications

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 63/352,853, filed June 16, 2022, the entire content of which is incorporated herein by reference for all purposes.

Technical Fields of the Invention

[0002] The invention generally relates to novel compounds and therapeutic uses thereof. More particularly, the invention provides novel quinazoline derivatives that are shown to be potent and selective inhibitors of KRas, in particular KRas (G12D). The invention also provides pharmaceutical compositions comprising compounds of the invention and methods for treating diseases and disorders associated with or related to KRas activities, such as various types of cancer.

Background of the Invention

[0003] KRAS (Kirsten rat sarcoma virus) is a gene that provides instructions for making a protein called KRas, a part of the RAS/MAPK pathway. The protein relays signal from outside the cell to the cell's nucleus instructing the cell to grow and divide (proliferate) or to mature and take on specialized functions (differentiate). KRas serves as a molecular switch cycling between inactive (GDP-bound) and active (GTP-bound) states to transduce upstream cellular signals received from multiple tyrosine kinases to downstream effectors to regulate a wide variety of processes, such as cellular proliferation. The role of activated KRas in malignancy was first observed over thirty years ago. (Santos et al. **1984** *Science* 223:661-664; Alamgeer et al. **2013** *Current Opin Pharmacol.* 13:394-401.)

[0004] KRas mutation occurs in nearly 30% of human cancers. For example, mutations of KRas are observed in pancreatic ductal adenocarcinomas, colon and rectal carcinomas, and non-small cell lung carcinomas. Mutations often occur in the glycine residue of KRas at position 12

with KRas(G12D) being the most prevalent and oncogenic variant. KRas(G12D) mutation has been shown to be present in about 25% of all pancreatic ductal adenocarcinoma patients, about 13% of all colorectal carcinoma patients, about 10% of all rectal carcinoma patients, about 4% of all non-small cell lung carcinoma patients and about 1.7% of all small cell lung carcinoma patients (The AACR Project GENIE Consortium, **2017** *Cancer Discovery* 7(8):818-831, Dataset Version 4).

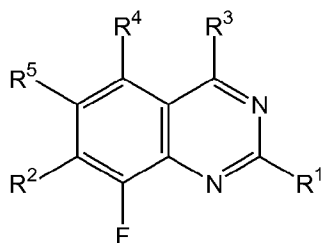
[0005] Despite extensive efforts over the past thirty years to develop inhibitors of KRas to treat cancer, no KRas(G12D) inhibitor has been clinically demonstrated with sufficient safety and/or efficacy to warrant regulatory approval. (McCormick **2015** *Clin Cancer Res.* 21 (8):1797-1801; Sun et al. **2012** *Agnew Chem Int Ed Engl.* 51(25):6140-6143; Ostrem et al. **2013** *Nature* 503:548-551; Fell et al. **2018** *ACS Med. Chem. Lett.* 9:1230-1234; Cox, et al. **2014** *Nature Rev Drug Discov.* 13 (11), 828-51; Patricelli et al. **2016** *Cancer Discov.* 6(3), 316-29; Hunter et al. **2015** *Mol Cancer Res.* 13(9), 1325-35.)

[0006] There remains an urgent need for potent and selective KRas inhibitors, in particular, inhibitors of KRas mutants, especially KRas(G12D), that are safe and effective in treating diseases and conditions associated with aberrant expression of KRAS, such as various types of cancer (*e.g.*, ductal cancer, colorectal cancer, rectal cancer, cell lung cancer).

Summary of the Invention

[0007] The invention provides novel quinazoline derivatives as KRas inhibitors, in particular KRas (G12D) inhibitors, which have been shown to exhibit favorable potency and selectivity profiles over known KRas inhibitors. These novel compounds selectively target, bind to, inhibit and/or modulates the activity of KRas. The compound is also orally available with pharmacokinetic profiles suitable for development into an orally administered therapeutic agent for treating various diseases and disorders associated with or related to KRas activities, such as various types of cancer.

[0008] In one aspect, the invention generally relates to a compound having the structural Formula (I):

**I**

or a pharmaceutically acceptable form or an isotope derivative thereof,

wherein

R^1 is XR^{11} or $NR^{12}R^{13}$, wherein X is O, S or absent, R^{11} is $(CH_2)_iR^{14}$, and i is an integer selected from 0-6 (*e.g.*, 0, 1, 2, 3, 4, 5 or 6), wherein $(CH_2)_i$ is optionally substituted;

R^2 is an unsubstituted or substituted 6- to 10-membered (*e.g.*, 6-, 7-, 8-, 9- or 10-membered) unsaturated monocyclic or bicyclic ring, comprising 0-5 (*e.g.*, 0, 1, 2, 3, 4 or 5) heteroatoms selected from N, O and S;

R^3 is $L-R^{3'}$, wherein

L is a single bond or $NR(CH_2)_k$, wherein k is an integer selected from 0-3 (*e.g.*, 0, 1, 2 or 3); and

$R^{3'}$ is an unsubstituted or substituted, 3- to 10-membered (*e.g.*, 3-, 4-, 5-, 6-, 7-, 8-, 9- or 10-membered) saturated or unsaturated monocyclic, bicyclic or bridged ring moiety that comprises 0-5 (*e.g.*, 0, 1, 2, 3, 4 or 5) heteroatoms selected from N, O and S;

each of R^4 and R^5 is independently selected from the group consisting of H, halogen, CN, OH, unsubstituted or substituted C_{1-4} alkyl, unsubstituted or substituted C_{1-4} alkoxy, NO_2 , NRR' , $C(O)NRR'$, $NRC(O)R''$, $C(O)R''$, $OC(O)R''$, $C(O)OR$, unsubstituted or substituted 3- to 8-membered (*e.g.*, 3-, 4-, 5-, 6-, 7- or 8-membered) carbocycle, and unsubstituted or substituted 3- to 8-membered (*e.g.*, 3-, 4-, 5-, 6-, 7- or 8-membered) heterocycle, *provided that* (a) R^4 and R^5 are not H at the same time, and (b) where R^4 is H R^5 is an unsubstituted or substituted 3- to 8-membered (*e.g.*, 3-, 4-, 5-, 6-, 7- or 8-membered) carbocycle, or unsubstituted or substituted 3- to 8-membered (*e.g.*, 3-, 4-, 5-, 6-, 7- or 8-membered) heterocycle;

each of R^{12} and R^{13} is independently selected from the group consisting of H, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted carbocyclic ring, and unsubstituted or substituted heterocyclic ring; or R^{12} and R^{13} , together with the N atom they are bound to, are joined to form an unsubstituted or substituted heterocyclic or heteroaryl ring;

R¹⁴ is selected from the group consisting of H, halogen, CN, OH, NO₂, unsubstituted or substituted C₁₋₆ alkyl, NRR', C(O)NRR', NRC(O)R'', SO₂NRR', NR-SO₂R', NRC(O)NRR', C(O)CH₂-aryl, C(O)OCH₂-aryl, NRC(O)OCH₂-phenyl, C(O)R'', OC(O)R'', C(O)OR, unsubstituted or substituted 3- to 6-membered (*e.g.*, 3-, 4-, 5-, 6-membered) carbocyclic ring, unsubstituted or substituted 4- to 6-membered (*e.g.*, 4-, 5-, 6-membered) heterocyclic ring; unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl; and

each of R and R' is independently selected from H, unsubstituted or substituted C₁₋₄ alkyl, or unsubstituted or substituted 4- to 6-membered (*e.g.*, 4-, 5- or 6-membered) carbocyclic ring, or where R and R' are attached to the same N atom, together form an unsubstituted or substituted 4- to 6-membered (*e.g.*, 4-, 5- or 6-membered) heterocyclic ring; and

R'' is H, unsubstituted or substituted C₁₋₄ alkoxy, unsubstituted or substituted C₁₋₄ alkyl, or unsubstituted or substituted 4- to 6-membered (*e.g.*, 4-, 5- or 6-membered) carbocyclic ring.

[0009] In another aspect, the invention generally relates to a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable excipient, carrier, or diluent.

[0010] In yet another aspect, the invention generally relates to a unit dosage form comprising a pharmaceutical composition disclosed herein.

[0011] In yet another aspect, the invention generally relates to a method for inhibiting cell proliferation *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound disclosed herein.

[0012] In yet another aspect, the invention generally relates to a method for inhibiting KRas(G12D) activity in a cell, comprising contacting the cell with a compound disclosed herein.

[0013] In yet another aspect, the invention generally relates to a method for treating a disease or disorder mediated by a Ras mutant protein, comprising administering to a subject in need thereof a therapeutically effective amount of the compound disclosed herein.

[0014] In yet another aspect, the invention generally relates to a method for treating or reducing cancer, or a related disease or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of the compound disclosed herein.

[0015] In yet another aspect, the invention generally relates to a method for treating or reducing cancer, or a related disease or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of the compound disclosed herein.

[0016] In yet another aspect, the invention generally relates to use of a compound disclosed herein, and a pharmaceutically acceptable excipient, carrier, or diluent, in preparation of a medicament for treating a disease or disorder.

Definitions

[0017] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. General principles of organic chemistry, as well as specific functional moieties and reactivity, are described in “Organic Chemistry”, Thomas Sorrell, University Science Books, Sausalito: 2006.

[0018] As used herein, “at least” a specific value is understood to be that value and all values greater than that value.

[0019] The term “comprising”, when used to define compositions and methods, is intended to mean that the compositions and methods include the recited elements, but do not exclude other elements. The term “consisting essentially of”, when used to define compositions and methods, shall mean that the compositions and methods include the recited elements and exclude other elements of any essential significance to the compositions and methods. For example, “consisting essentially of” refers to administration of the pharmacologically active agents expressly recited and excludes pharmacologically active agents not expressly recited. The term consisting essentially of does not exclude pharmacologically inactive or inert agents, e.g., pharmaceutically acceptable excipients, carriers or diluents. The term “consisting of”, when used to define compositions and methods, shall mean excluding trace elements of other ingredients and substantial method steps. Embodiments defined by each of these transition terms are within the scope of this invention.

[0020] Unless specifically stated or obvious from context, as used herein, the term “about” is understood as within a range of normal tolerance in the art, for example within 2 standard deviations of the mean. About can be understood as within 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, 0.05%, or 0.01% of the stated value. Unless otherwise clear from context, all numerical values provided herein can be modified by the term about.

[0021] As used herein, the terms “administration” of or “administering” a disclosed compound encompasses the delivery to a subject of a compound as described herein, or a

prodrug or other pharmaceutically acceptable form thereof, using any suitable formulation or route of administration, as discussed herein.

[0022] As used herein, the term “co-administer” refers to the presence of two pharmacological agents in a subject’s body (*e.g.*, in the blood) at the same time. The two pharmacological agents can be administered concurrently or sequentially.

[0023] The terms “disease”, “disorder” and “condition” are used interchangeably unless indicated otherwise.

[0024] As used herein, the terms "effective amount" or "therapeutically effective amount" refer to that amount of a compound or pharmaceutical composition described herein that is sufficient to achieve the intended application including, but not limited to, disease treatment, as illustrated below.

[0025] In some embodiments, the amount is that is sufficient to negatively modulate or inhibit the activity of KRas (G12D). In some embodiments, the amount is that effective for reduction or amelioration of a symptom to stop or reversion of progression of a disease or disorder such as cancer. In some embodiments, the amount is that effective for detectable killing or inhibition of the growth or spread of cancer cells; the size or number of tumors; or other measure of the level, stage, progression or severity of the cancer.

[0026] The therapeutically effective amount can vary depending upon the intended application, or the subject and disease condition being treated, *e.g.*, the desired biological endpoint, the pharmacokinetics of the compound, the disease being treated, the mode of administration, and the weight and age of the patient, which can readily be determined by one of ordinary skill in the art. Such amount may be administered as a single dosage or according to a regimen. The term also applies to a dose that will induce a particular response in target cells, *e.g.*, reduction of cell migration. The specific dose will vary depending on, for example, the particular compounds chosen, the species of subject and their age/existing health conditions or risk for health conditions, the dosing regimen to be followed, the severity of the disease, whether it is administered in combination with other agents, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried.

[0027] As used herein, the terms “KRas(G12D)” or “KRas G12D” are used interchangeably and refers to a mutant form of a mammalian KRas protein that contains an amino acid substitution of an aspartic acid for a glycine at amino acid position 12. The assignment of amino

acid codon and residue positions for human KRas is based on the amino acid sequence identified by UniProtKB/Swiss-Prot P01116: Variantp.Gly12Asp.

[0028] As used herein, an “inhibitor” of “KRas(G12D)” or “KRas G12D” refers to a compound of the invention capable of negatively modulating or inhibiting all or a portion of the enzymatic activity of KRas G12D.

[0029] As used herein, a “KRas G12D-associated” disease or disorder refers to diseases or disorders associated with or mediated by or having a KRas G12D mutation. Examples of KRas G12D-associated diseases or disorders include various KRas G12D-associated cancer types.

[0030] As used herein, the term “contacting” refers to the bringing together of indicated moieties *in vitro* or *in vivo*. For example, “contacting” a KRas G12D with a compound disclosed herein includes the administration of the compound to a subject having KRas G12D, as well as, for example, introducing the compound into a sample containing a cellular or purified preparation containing the KRas G12D. In some embodiments, a cell in which inhibition of KRas G12D activity is desired is contacted with an effective amount of a compound disclosed herein or pharmaceutically acceptable form thereof to negatively modulate the activity of KRas G12D. By negatively modulating the activity of KRas G12D, the methods disclosed herein are designed to inhibit undesired cellular proliferation resulting from enhanced KRas G12D activity within the cell. The cells may be contacted in a single dose or multiple doses in accordance with a particular treatment regimen to achieve the desired negative modulation of KRas G12D. The ability of compounds to bind KRas G12D may be monitored *in vitro* using methods known in the art. The inhibitory activity of exemplary compounds in cells may be monitored, for example, by measuring the inhibition of KRas G12D activity using methods known in the art.

[0031] As used herein, the terms “unsubstituted or substituted” and “optionally substituted” are used interchangeably and refer to where a given chemical moiety (*e.g.*, an alkyl group) can (but is not required to) be bonded other substituents (*e.g.*, heteroatoms). For instance, an alkyl group that is optionally substituted can be a fully saturated alkyl chain (*e.g.*, a pure hydrocarbon). Alternatively, the same optionally substituted alkyl group can have substituents different from hydrogen. For instance, it can, at any point along the chain be bounded to a halogen atom, a hydroxyl group, or any other substituent described herein. Thus, the term “optionally substituted” means that a given chemical moiety has the potential to contain other functional groups, but does not necessarily have any further functional groups. Suitable substituents used in

the optional substitution of the described groups include, without limitation, halogen, oxo, CN, -COOH, -CH₂CN, -O-C₁-C₆ alkyl, C₁-C₆ alkyl, -OC₁-C₆ alkenyl, -OC₁-C₆ alkynyl, -C₁-C₆ alkenyl, -C₁-C₆ alkynyl, -OH, -OP(O)(OH)₂, -OC(O)C₁-C₆ alkyl, -C(O)C₁-C₆ alkyl, -OC(O)OC₁-C₆ alkyl, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -NHC(O)C₁-C₆ alkyl, -C(O)NHC₁-C₆ alkyl, -S(O)₂-C₁-C₆ alkyl, -S(O)NHC₁-C₆ alkyl, and S(O)N(C₁-C₆ alkyl)₂.

[0032] As used herein, a "pharmaceutically acceptable form" of a disclosed compound includes, but is not limited to, pharmaceutically acceptable salts, esters, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives of disclosed compounds. In one embodiment, a "pharmaceutically acceptable form" includes, but is not limited to, pharmaceutically acceptable salts, esters, isomers, prodrugs and isotopically labeled derivatives of disclosed compounds. In some embodiments, a "pharmaceutically acceptable form" includes, but is not limited to, pharmaceutically acceptable salts, esters, stereoisomers, prodrugs and isotopically labeled derivatives of disclosed compounds.

[0033] In certain embodiments, the pharmaceutically acceptable form is a pharmaceutically acceptable salt. As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of subjects without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge et al. describes pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* (1977) 66:1-19. Pharmaceutically acceptable salts of the compounds provided herein include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, besylate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-

naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. In some embodiments, organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, lactic acid, trifluoroacetic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like.

[0034] The salts can be prepared in situ during the isolation and purification of the disclosed compounds, or separately, such as by reacting the free base or free acid of a parent compound with a suitable base or acid, respectively. Pharmaceutically acceptable salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines, including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt can be chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

[0035] In certain embodiments, the pharmaceutically acceptable form is a pharmaceutically acceptable ester. As used herein, the term "pharmaceutically acceptable ester" refers to esters that hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Such esters can act as a prodrug as defined herein. Pharmaceutically acceptable esters include, but are not limited to, alkyl, alkenyl, alkynyl, aryl, aralkyl, and cycloalkyl esters of acidic groups, including, but not limited to, carboxylic acids, phosphoric acids, phosphinic acids, sulfinic acids, sulfonic acids and boronic acids. Examples of esters include formates, acetates, propionates, butyrates, acrylates and ethylsuccinates. The esters can be formed with a hydroxy or carboxylic acid group of the parent compound.

[0036] In certain embodiments, the pharmaceutically acceptable form is a “solvate” (*e.g.*, a hydrate). As used herein, the term “solvate” refers to compounds that further include a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. The solvate can be of a disclosed compound or a pharmaceutically acceptable salt thereof. Where the solvent is water, the solvate is a “hydrate”. Pharmaceutically acceptable solvates and hydrates are complexes that, for example, can include 1 to about 100, or 1 to about 10, or 1 to about 2, about 3 or about 4, solvent or water molecules. It will be understood that the term “compound” as used herein encompasses the compound and solvates of the compound, as well as mixtures thereof.

[0037] In certain embodiments, the pharmaceutically acceptable form is a prodrug. As used herein, the term “prodrug” (or “pro-drug”) refers to compounds that are transformed *in vivo* to yield a disclosed compound or a pharmaceutically acceptable form of the compound. A prodrug can be inactive when administered to a subject, but is converted *in vivo* to an active compound, for example, by hydrolysis (*e.g.*, hydrolysis in blood). In certain cases, a prodrug has improved physical and/or delivery properties over the parent compound. Prodrugs can increase the bioavailability of the compound when administered to a subject (*e.g.*, by permitting enhanced absorption into the blood following oral administration) or which enhance delivery to a biological compartment of interest (*e.g.*, the brain or lymphatic system) relative to the parent compound. Exemplary prodrugs include derivatives of a disclosed compound with enhanced aqueous solubility or active transport through the gut membrane, relative to the parent compound.

[0038] The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, *e.g.*, Bundgard, H., *Design of Prodrugs* (1985), pp. 7- 9, 21-24 (Elsevier, Amsterdam). A discussion of prodrugs is provided in Higuchi, T., et al., “Pro-drugs as Novel Delivery Systems,” *A.C.S. Symposium Series*, Vol. 14, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein. Exemplary advantages of a prodrug can include, but are not limited to, its physical properties, such as enhanced water solubility for parenteral administration at physiological pH compared to the parent compound, or it can enhance absorption from the digestive tract, or it can enhance drug stability for long-term storage.

[0039] As used herein, the term “pharmaceutically acceptable excipient, carrier, or diluent” refers to a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject pharmaceutical agent from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations. Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate, magnesium stearate, and polyethylene oxide-polypropylene oxide copolymer as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

[0040] As used herein, the term “subject” refers to any animal (*e.g.*, a mammal), including, but not limited to humans, non-human primates, rodents, and the like, which is to be the recipient of a particular treatment. Typically, the terms “subject” and “patient” are used interchangeably herein in reference to a human subject.

[0041] In some embodiments, the subject has experienced and/or exhibited at least one symptom of the disease or disorder to be treated with a compound disclosed herein and/or according to a herein disclosed method. In some embodiments, the subject has been identified or diagnosed as having a cancer having a KRas G12D mutation. In some embodiments, the subject has a cancer that is positive for a KRas G12D mutation. In some embodiments, the subject is suspected of having a KRas G12D gene-associated cancer.

[0042] In some embodiments of any of the methods or uses described herein, an assay is used to determine whether the subject has KRas G12D mutation using a sample (*e.g.*, a

biological sample or a biopsy sample (e.g., a paraffin-embedded biopsy sample) from a subject. Various techniques may be employed, for example, next generation sequencing, immunohistochemistry, fluorescence microscopy, break apart FISH analysis, Southern blotting, Western blotting, FACS analysis, Northern blotting, and PCR-based amplification (e.g., RT-PCR and quantitative real-time RT-PCR).

[0043] As used herein, the terms “treatment” or “treating” a disease or disorder refers to a method of reducing, delaying or ameliorating such a condition before or after it has occurred. Treatment may be directed at one or more effects or symptoms of a disease and/or the underlying pathology. Treatment is aimed to obtain beneficial or desired results including, but not limited to, therapeutic benefit and/or a prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient can still be afflicted with the underlying disorder. For prophylactic benefit, the pharmaceutical compounds and/or compositions can be administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made. The treatment can be any reduction and can be, but is not limited to, the complete ablation of the disease or the symptoms of the disease. As compared with an equivalent untreated control, such reduction or degree of prevention is at least 5%, 10%, 20%, 40%, 50%, 60%, 80%, 90%, 95%, or 100% as measured by any standard technique.

[0044] As used herein, the term "therapeutic effect" refers to a therapeutic benefit and/or a prophylactic benefit as described herein. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof.

[0045] Compounds of the present invention are, subsequent to their preparation, preferably isolated and purified to obtain a composition containing an amount by weight equal to or greater than 95% (“substantially pure”), which is then used or formulated as described herein. In certain embodiments, the compounds of the present invention are more than 99% pure.

[0046] Solvates and polymorphs of the compounds of the invention are also contemplated herein. Solvates of the compounds of the present invention include, for example, hydrates.

[0047] As used herein, the term an “isolated” or “substantially isolated” molecule (such as a polypeptide or polynucleotide) is one that has been manipulated to exist in a higher concentration than in nature or has been removed from its native environment. For example, a subject antibody is isolated, purified, substantially isolated, or substantially purified when at least 10%, or 20%, or 40%, or 50%, or 70%, or 90% of non-subject-antibody materials with which it is associated in nature have been removed. For example, a polynucleotide or a polypeptide naturally present in a living animal is not “isolated,” but the same polynucleotide or polypeptide separated from the coexisting materials of its natural state is “isolated.” Further, recombinant DNA molecules contained in a vector are considered isolated for the purposes of the present invention. Isolated RNA molecules include in vivo or in vitro RNA replication products of DNA and RNA molecules. Isolated nucleic acid molecules further include synthetically produced molecules. Additionally, vector molecules contained in recombinant host cells are also isolated. Thus, not all “isolated” molecules need be “purified.”

[0048] As used herein, the term “purified” when used in reference to a molecule, it means that the concentration of the molecule being purified has been increased relative to molecules associated with it in its natural environment, or environment in which it was produced, found or synthesized. Naturally associated molecules include proteins, nucleic acids, lipids and sugars but generally do not include water, buffers, and reagents added to maintain the integrity or facilitate the purification of the molecule being purified. According to this definition, a substance may be 5% or more, 10% or more, 20% or more, 30% or more, 40% or more, 50% or more, 60% or more, 70% or more, 80% or more, 90% or more, 95% or more, 98% or more, 99% or more, or 100% pure when considered relative to its contaminants.

[0049] Definitions of specific functional groups and chemical terms are described in more detail below. When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example, “C₁₋₄ alkyl” is intended to encompass, C₁, C₂, C₃, C₄, C₁₋₃, C₁₋₂, C₂₋₄, C₃₋₄ and C₂₋₃ alkyl groups.

[0050] As used herein, the term “alkyl” refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to ten carbon atoms (*e.g.*, C₁₋₁₀ alkyl). Whenever it appears herein, a numerical range such as

“1 to 10” refers to each integer in the given range; *e.g.*, “1 to 10 carbon atoms” means that the alkyl group can consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc., up to and including 10 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated. In some embodiments, “alkyl” can be a C₁₋₆ alkyl group. In some embodiments, alkyl groups have 1 to 10, 1 to 8, 1 to 6, or 1 to 3 carbon atoms. Representative saturated straight chain alkyls include, but are not limited to, -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, and -n-hexyl; while saturated branched alkyls include, but are not limited to, -isopropyl, -sec-butyl, -isobutyl, -tert-butyl, -isopentyl, 2-methylbutyl, 3-methylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylbutyl, and the like. The alkyl is attached to the parent molecule by a single bond. Unless stated otherwise in the specification, an alkyl group is optionally substituted by one or more of substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, -Si(R^x)₃, -OR^x, -SR^x, -OC(O)-R^x, -N(R^x)₂, -C(O)R^x, -C(O)OR^x, -OC(O)N(R^x)₂, -C(O)N(R^x)₂, -N(R^x)C(O)OR^x, -N(R^x)C(O)R^x, -N(R^x)C(O)N(R^x)₂, -N(R^x)C(NR^x)N(R^x)₂, -N(R^x)S(O)_tN(R^x)₂ (where t is 1 or 2), -P(=O)(R^x)(R^x), or -O-P(=O)(OR^x)₂ wherein each R^x is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein. In a non-limiting embodiment, a substituted alkyl can be selected from fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 3-fluoropropyl, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, benzyl, and phenethyl.

[0051] Unless otherwise specifically defined, the term “aromatic” or “aryl” refers to cyclic, aromatic hydrocarbon groups that have 1 to 2 aromatic rings, including monocyclic or bicyclic groups such as phenyl, biphenyl or naphthyl. Where containing two aromatic rings (bicyclic, etc.), the aromatic rings of the aryl group may be joined at a single point (*e.g.*, biphenyl), or fused (*e.g.*, naphthyl). The aryl group may be optionally substituted by one or more substituents, *e.g.*, 1 to 5 substituents, at any point of attachment. Exemplary substituents include, but are not

limited to, H, halogen, -O-C₁-C₆ alkyl, C₁-C₆ alkyl, -C₁-C₆ alkenyl, -OC₁-C₆ alkynyl, -C₁-C₆ alkenyl, -C₁-C₆ alkynyl, -OH, -OP(O)(OH)₂, -OC(O)C₁-C₆ alkyl, -C(O)C₁-C₆ alkyl, -OC(O)OC₁-C₆alkyl, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(O)₂-C₁-C₆ alkyl, -S(O)NHC₁-C₆alkyl, and S(O)N(C₁-C₆ alkyl)₂. The substituents can themselves be optionally substituted. Furthermore, when containing two fused rings the aryl groups herein defined may have an unsaturated or partially saturated ring fused with a fully unsaturated ring. Exemplary ring systems of these aryl groups include indanyl, indenyl, tetrahydronaphthalenyl, and tetrahydrobenzoannulenyl.

[0052] The term “halogen” or “halo” refers to fluorine (F), chlorine (Cl), bromine (Br) and iodine (I).

[0053] As used herein, the terms “heteroaryl” or “hetero-aromatic” refer to groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 p electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to three heteroatoms per ring selected from the group consisting of N, O, and S. Examples of heteroaryl groups include acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, 6,7-dihydro-5H-pyrrolo[1,2-a]imidazole, furanyl, furazanyl, imidazolyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indoliziny, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridoaxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinoliziny, quinoxalinyl, quinuclidinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3- triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

“Heteroaryl” also refers to bicyclic ring systems having, in addition to carbon atoms, from one to

three heteroatoms per ring selected from the group consisting of N, O, and S in which one ring system may be saturated or partially saturated.

[0054] Heteroaryl groups may be substituted with 0, 1, 2, 3, or 4 substituents independently selected from alkenyl, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonyloxy, alkylthio, alkylthioalkyl, alkynyl, carboxy, carboxyalkyl, cyano, cyanoalkyl, formyl, haloalkoxy, haloalkyl, halogen, hydroxy, hydroxyalkyl, mercapto, nitro, $-NZ_1Z_2$, and (NZ_1Z_2) carbonyl. The term " NZ_1Z_2 " as used herein, means two groups, Z_1 and Z_2 , which are appended to the parent molecular moiety through a nitrogen atom. Z_1 and Z_2 are each independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, and formyl. Representative examples of NZ_1Z_2 include, but are not limited to, amino, methylamino, acetylamino, and acetylmethylamino.

[0055] As used herein, the term "alkoxy" refers to an -O-alkyl radical.

[0056] As used herein, the terms "cycloalkyl" and "carbocyclyl" each refers to a monocyclic or polycyclic radical that contains only carbon and hydrogen, and can be saturated or partially unsaturated. Unless stated otherwise in the specification, the term is intended to include both substituted and unsubstituted cycloalkyl groups. Partially unsaturated cycloalkyl groups can be termed "cycloalkenyl" if the carbocycle contains at least one double bond, or "cycloalkynyl" if the carbocycle contains at least one triple bond. Cycloalkyl groups include groups having from 3 to 13 ring atoms (i.e., C_{3-13} cycloalkyl). Whenever it appears herein, a numerical range such as "3 to 10" refers to each integer in the given range; e.g., "3 to 13 carbon atoms" means that the cycloalkyl group can consist of 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, *etc.*, up to and including 13 carbon atoms. The term "cycloalkyl" also includes bridged and spiro-fused cyclic structures containing no heteroatoms. The term also includes monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of ring atoms) groups. Polycyclic aryl groups include bicycles, tricycles, tetracycles, and the like. In some embodiments, "cycloalkyl" can be a C_{3-8} cycloalkyl radical. In some embodiments, "cycloalkyl" can be a C_{3-5} cycloalkyl radical. Illustrative examples of cycloalkyl groups include, but are not limited to the following moieties: C_{3-6} carbocyclyl groups include, without limitation, cyclopropyl (C_3), cyclobutyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6) and the like. Examples of C_{3-7} carbocyclyl groups include norbornyl (C_7). Examples of C_{3-8} carbocyclyl groups include the aforementioned C_{3-7} carbocyclyl groups as well as cycloheptyl

(C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, and the like. Examples of C₃₋₁₃ carbocyclyl groups include the aforementioned C₃₋₈ carbocyclyl groups as well as octahydro-1H indenyl, decahydronaphthalenyl, spiro[4.5]decanyl and the like. Unless stated otherwise in the specification, a cycloalkyl group can be optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, -Si(R^a)₃, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -OC(O)N(R^a)₂, -C(O)N(R^a)₂, -N(R^a)C(O)OR^a, -N(R^a)C(O)R^a, -N(R^a)C(O)N(R^a)₂, -N(R^a)C(NR^a)N(R^a)₂, -N(R^a)S(O)_tN(R^a)₂ (where t is 1 or 2), -P(=O)(R^a)(R^a), or -O-P(=O)(OR^a)₂ where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein. The terms "cycloalkenyl" and "cycloalkynyl" mirror the above description of "cycloalkyl" wherein the prefix "alk" is replaced with "alken" or "alkyn" respectively, and the parent "alkenyl" or "alkynyl" terms are as described herein. For example, a cycloalkenyl group can have 3 to 13 ring atoms, such as 5 to 8 ring atoms. In some embodiments, a cycloalkynyl group can have 5 to 13 ring atoms.

[0057] As used herein, the term "heterocycloalkyl" refers to a cycloalkyl radical, which have one or more skeletal chain atoms selected from an atom other than carbon, *e.g.*, O, N, S, P or combinations thereof. Unless stated otherwise in the specification, the term is intended to include both substituted and unsubstituted heterocycloalkyl groups. Illustrative examples of heterocycloalkyl include 2-hydroxy-aziridin-1-yl, 3-oxo-1-oxacyclobutan-2-yl, 2,2-dimethyl-tetrahydrofuran-3-yl, 3-carboxy-morpholin-4-yl, 1-cyclopropyl-4-methyl-piperazin-2-yl, 2-pyrrolinyl, 3-pyrrolinyl, dihydro-2H-pyran-2-yl, 1,2,3,4-tetrahydropyridine, 3,4-dihydro-2H-[1,4]oxazine, *etc.*

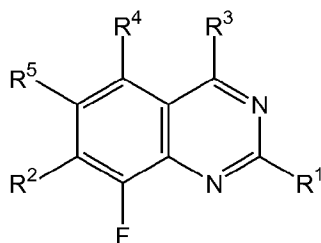
[0058] As used herein, the terms "heterocycle", "heterocyclic" or "heterocyclo" refer to fully saturated or partially unsaturated cyclic groups, for example, 3 to 7 membered monocyclic, 7 to 12 membered bicyclic, or 10 to 15 membered spirocyclic or tricyclic ring systems, which have at

least one heteroatom (selected from the group consisting of N, O, and S) in at least one ring, wherein 0, 1, 2 or 3 atoms of each ring may be substituted by a substituent. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom of the ring or ring system. A heterocyclic group is optionally substituted. Examples of heterocyclic groups include, but not limited to, epoxy, azetidiny, aziridinyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, pyrrolidinonyl, piperidinyl, piperazinyl, imidazolidinyl, imidazopyridinyl, thiazolidinyl, dithianyl, trithianyl, dioxolanyl, oxazolidinyl, oxazolidinonyl, decahydroquinolinyl, piperidonyl, 4-piperidinonyl, quinuclidinyl, thiomorpholinyl, thiomorpholinyl 1,1 dioxide, morpholinyl, azepanyl, oxazepanyl, azabicyclobexanyls, azabicycloheptanyl, azabicyclooctanyls, azabicyclononanyls (e.g., octahydroindoliziny), azaspiroheptanyls, dihydro-1H,3H,5H-oxazolo[3,4-c]oxazolyl, tetrahydro-1'H,3'H- spiro[cyclopropane-1,2'-pyrrolizine], hexahydro-1H-pyrroliziny, hexahydro-1H-pyrrolo[2,1- c][1,4]oxazinyl, octahydroindoliziny, oxaazaspiroononanyls, oxaazaspirooctanyls, diazaspiroononanyls, oxaazabicycloheptanyls, hexahydropyrroliziny 4(1H)-oxide, and tetrahydro- 2H-thiopyranyl 1-oxide and tetrahydro-2H-thiopyranyl 1,1-dioxide.

Detailed Description of the Invention

[0059] The invention is based in part on the discovery of KRas inhibitors, in particular KRas (G12D) inhibitors, that selectively target, bind to, inhibit or modulate the activity of KRas. The novel compounds exhibit favorable potency and selectivity as well as pharmacokinetics profiles suitable for development into an orally administered therapeutic agent for treating diseases and disorders associated with or related to KRas activities, such as various types of cancer.

[0060] In one aspect, the invention generally relates to a compound having the structural Formula (I):

**I**

or a pharmaceutically acceptable form or an isotope derivative thereof,

wherein

R^1 is XR^{11} or $NR^{12}R^{13}$, wherein X is O, S or absent, R^{11} is $(CH_2)_iR^{14}$, and i is an integer selected from 0-6 (*e.g.*, 0, 1, 2, 3, 4, 5 or 6), wherein $(CH_2)_i$ is optionally substituted;

R^2 is an unsubstituted or substituted 6- to 10-membered (*e.g.*, 6-, 7-, 8-, 9- or 10-membered) unsaturated monocyclic or bicyclic ring, comprising 0-5 (*e.g.*, 0, 1, 2, 3, 4 or 5) heteroatoms selected from N, O and S;

R^3 is $L-R^{3'}$, wherein

L is a single bond or $NR(CH_2)_k$, wherein k is an integer selected from 0-3 (*e.g.*, 0, 1, 2 or 3); and

$R^{3'}$ is an unsubstituted or substituted, 3- to 10-membered (*e.g.*, 3-, 4-, 5-, 6-, 7-, 8-, 9- or 10-membered) saturated or unsaturated monocyclic, bicyclic or bridged ring moiety that comprises 0-5 (*e.g.*, 0, 1, 2, 3, 4 or 5) heteroatoms selected from N, O and S;

each of R^4 and R^5 is independently selected from the group consisting of H, halogen, CN, OH, unsubstituted or substituted C_{1-4} alkyl, unsubstituted or substituted C_{1-4} alkoxy, NO_2 , NRR' , $C(O)NRR'$, $NRC(O)R''$, $C(O)R''$, $OC(O)R''$, $C(O)OR$, unsubstituted or substituted 3- to 8-membered (*e.g.*, 6-, 7- or 8-membered) carbocycle, and unsubstituted or substituted 3- to 8-membered (*e.g.*, 6-, 7- or 8-membered) heterocycle, *provided that* (a) R^4 and R^5 are not H at the same time, and (b) where R^4 is H R^5 is an unsubstituted or substituted 3- to 8-membered (*e.g.*, 6-, 7- or 8-membered) carbocycle, or unsubstituted or substituted 3- to 8-membered (*e.g.*, 6-, 7- or 8-membered) heterocycle;

each of R^{12} and R^{13} is independently selected from the group consisting of H, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted carbocyclic ring, and unsubstituted or substituted heterocyclic ring; or R^{12} and R^{13} , together with the N atom they are bound to, are joined to form an unsubstituted or substituted heterocyclic or heteroaryl ring;

R^{14} is selected from the group consisting of H, halogen, CN, OH, NO_2 , unsubstituted or substituted C_{1-6} alkyl, NRR' , $C(O)NRR'$, $NRC(O)R''$, SO_2NRR' , $NR-SO_2R'$, $NRC(O)NRR'$, $C(O)CH_2$ -aryl, $C(O)OCH_2$ -aryl, $NRC(O)OCH_2$ -phenyl, $C(O)R''$, $OC(O)R''$, $C(O)OR$, unsubstituted or substituted 3- to 6-membered (*e.g.*, 3-, 4-, 5-, 6-membered) carbocyclic ring, unsubstituted or substituted 4- to 6-membered (*e.g.*, 4-, 5-, 6-membered) heterocyclic ring; unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl; and

each of R and R' is independently selected from H, unsubstituted or substituted C_{1-4} alkyl, or unsubstituted or substituted 4- to 6-membered (*e.g.*, 4-, 5- or 6-membered) carbocyclic ring, or where R and R' are attached to the same N atom, together form an unsubstituted or substituted 4- to 6-membered (*e.g.*, 4-, 5- or 6-membered) heterocyclic ring; and

R'' is H, unsubstituted or substituted C_{1-4} alkoxy, unsubstituted or substituted C_{1-4} alkyl, or unsubstituted or substituted 4- to 6-membered (*e.g.*, 4-, 5- or 6-membered) carbocyclic ring.

[0061] In certain embodiments, at least one of R^4 and R^5 is not H.

[0062] In certain embodiments, one of R^4 and R^5 is H and the other is not H.

[0063] In certain embodiments, neither R^4 nor R^5 is H.

[0064] In certain embodiments, at least one of R^4 and R^5 is not H.

[0065] In certain embodiments, R^4 is halogen, CN, OH, unsubstituted or substituted C_{1-4} alkyl, unsubstituted or substituted C_{1-4} alkoxy, NO_2 , NRR' , $C(O)NRR'$, $NRC(O)R''$, $C(O)R''$, $OC(O)R''$ or $C(O)OR$.

[0066] In certain embodiments, R^5 is halogen, CN, OH, unsubstituted or substituted C_{1-4} alkyl, unsubstituted or substituted C_{1-4} alkoxy, NO_2 , NRR' , $C(O)NRR'$, $NRC(O)R''$, $C(O)R''$, $OC(O)R''$ or $C(O)OR$.

[0067] In certain embodiments, R^5 is an unsubstituted or substituted 3- to 8-membered (*e.g.*, 3-, 4-, 5-, 6-, 7- or 8-membered) carbocycle.

[0068] In certain embodiments, R^5 is an unsubstituted or substituted 3- to 8-membered (*e.g.*, 3-, 4-, 5-, 6-, 7- or 8-membered) heterocycle.

[0069] In certain embodiments, R^4 is H and R^5 is an unsubstituted or substituted 3- to 6-membered (*e.g.*, 3-, 4-, 5- or 6-membered) carbocycle.

[0070] In certain embodiments, R^4 is H and R^5 is an unsubstituted or substituted 4- to 7-membered (*e.g.*, 4-, 5-, 6- or 7-membered) heterocycle.

[0071] In certain embodiments, one of R^4 and R^5 is a halogen and the other is selected from halogen, CN, methyl and ethyl.

[0072] In certain embodiments, one of R^4 and R^5 is a halogen and the other is selected from OH, OCH_3 , $C(O)NH_2$ and $C(O)NHCH_3$.

[0073] In certain embodiments, one of R^4 and R^5 is halogen, CN, methyl and ethyl and the other is an unsubstituted or substituted 3- to 8-membered (*e.g.*, 3-, 4-, 5-, 6-, 7- or 8-membered) carbocycle.

[0074] In certain embodiments, one of R^4 and R^5 is halogen, CN, methyl and ethyl and the other is an unsubstituted or substituted 3- to 8-membered (*e.g.*, 3-, 4-, 5-, 6-, 7- or 8-membered) heterocycle.

[0075] In certain embodiments, one of R^4 and R^5 is unsubstituted or substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

[0076] In certain embodiments, one of R^4 and R^5 is unsubstituted or substituted tetrahydrofuran, tetrahydropyran, cyclic sulfone, cyclic sulfonamide, cyclic amide, cyclic carbamate, azetidine, pyrrolidine, piperidine, pyrazole, imidazole, 1,3-oxazole, 1,2-oxazole, 1,3-thiazole, 1,2,4-triazole, 1,2,3-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, furan, pyridine, pyrimidine, pyridazine, pyrazine, or triazine.

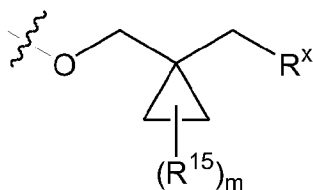
[0077] In certain embodiments, R^1 is $X(CH_2)_iR^{14}$, wherein X is O.

[0078] In certain embodiments, R^{14} is a C_{3-6} carbocyclic ring substituted with 0-5 (*e.g.*, 0, 1, 2, 3, 4 or 5) R^{15} , wherein each R^{15} is independently selected from D, halo, C_{1-3} alkyl optionally substituted with one or more of halo, OH, NRR' , CN, $CONRR'$ or SO_2NRR' .

[0079] In certain embodiments, i is 1.

[0080] In certain embodiments, R^{14} is C_{3-4} cycloalkyl ring substituted with 0-5 (*e.g.*, 0, 1, 2, 3, 4 or 5) R^{15} .

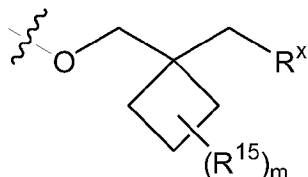
[0081] In certain embodiments, R^1 has the structure:



wherein R^x is OH, halo, NRR' , CN, $CONRR'$ or SO_2NRR' .

[0082] In certain embodiments, R^{15} is F, m is 0, 1 or 2, and R^x is CH_2OH .

[0083] In certain embodiments, R^1 has the structure:



wherein R^x is OH, halo, NRR' , CN, $CONRR'$ or SO_2NRR' .

[0084] In certain embodiments, R^{15} is F, m is 0, 1 or 2, and CH_2OH .

[0085] In certain embodiments, R^1 is $NR^{12}R^{13}$.

[0086] In certain embodiments, X is absent and R^1 is $(CH_2)_iR^{14}$.

[0087] In certain embodiments, R^{14} is NRR' .

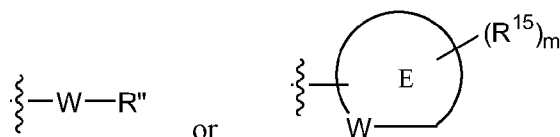
[0088] In certain embodiments, R^{14} comprises one or more of amino, amide, sulfonamide, and carboxylic ester groups.

[0089] In certain embodiments, R^{14} is a mono- or bicyclic, unsubstituted or substituted C_{4-10} heterocyclic ring.

[0090] In certain embodiments, R^{14} is a monocyclic, unsubstituted or substituted C_{4-7} heterocyclic ring.

[0091] In certain embodiments, R^{14} is a bicyclic, unsubstituted or substituted C_{6-10} heterocyclic ring.

[0092] In certain embodiments, R^{14} has the structure of:



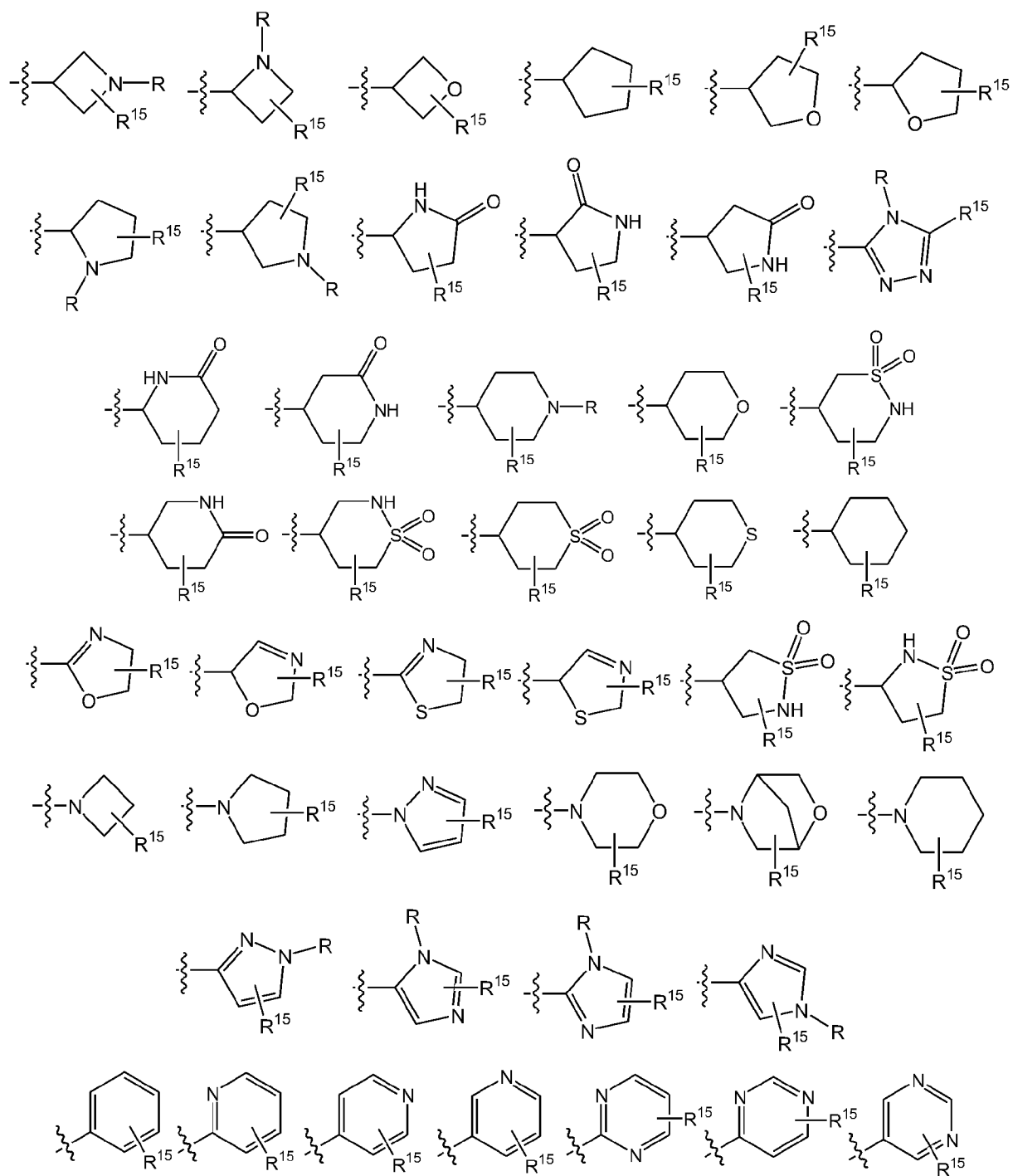
wherein

Ring E is a 4- to 7-membered (*e.g.*, 4-, 5-, 6- or 7-membered) unsubstituted or substituted monocyclic or bicyclic carbocyclic or heterocyclic ring;

W is O, S, N, NR , $C(O)$, $S(O)_2$, $NHC(O)$, $C(O)NH$, $OC(O)$, $C(O)O$, $S(O)_2NH$, or $NHS(O)_2$; and

R^{15} is selected from the group consisting of halogen, OH, CN, C_{1-6} alkyl, C_{1-6} alkoxy, $=CRR'$, NRR' , $C(O)NRR'$, $NRC(O)R''$, $NRC(O)NRR'$, $C(O)R$, $C(O)OR$, $S(O)_2NRR'$, or $NRS(O)_2R$, $S(O)_2NRR'$ and $NRS(O)_2NRR'$.

[0093] Additional non-limiting examples of R^{14} include:

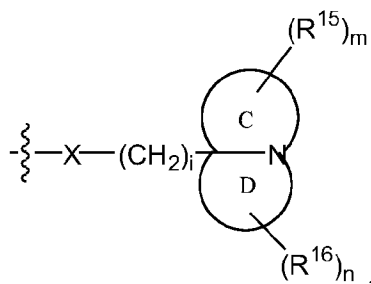


wherein R^{15} is as defined herein.

[0094] In certain embodiments, R^1 is $X(CH_2)_iR^{14}$, wherein X is S.

[0095] In certain embodiments, R^1 is $NR^{12}R^{13}$.

[0096] In certain embodiments, R^1 has the structure of:



wherein

each of Ring C and Ring D is a 4- to 7-membered heterocyclic ring;

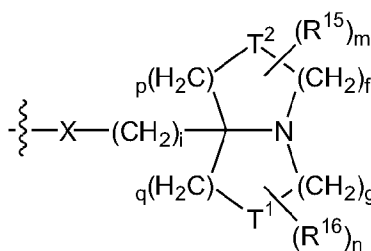
X is O or S;

each of R^{15} and R^{16} is independently selected from the group consisting of halogen, OH, CN, NRR' , $=CRR'$, C_{1-6} alkyl and C_{1-6} alkoxy;

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

each of m and n is independently 0, 1, 2 or 3.

[0097] In certain embodiments, R^1 has the structure of:



wherein

each of T^1 and T^2 is independently $CR^{17}R^{18}$, $C=CR^{17}R^{18}$, NR^{19} , O, S or $S(O)_2$;

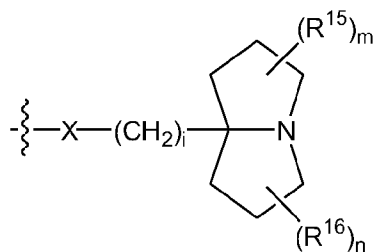
each of R^{17} and R^{18} is independently selected from the group consisting of: H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^{19} is selected from the group consisting of: H, C_{1-6} alkyl, and C_{1-6} alkoxy;

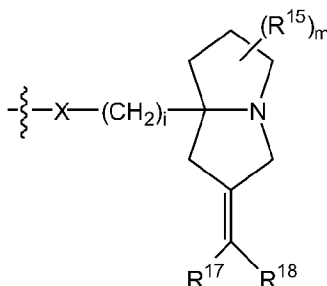
each of f , g , p and q is independently 0, 1, 2 or 3, provided that if one of f and p is 0, the other is not 0 and if one of g and q is 0, the other is not 0; and

each of m and n is independently 0, 1, 2 or 3.

[0098] In certain embodiments, each of T^1 and T^2 is $CR^{17}R^{18}$, each of f , g , p and q is 1, with R^1 having the structure of:

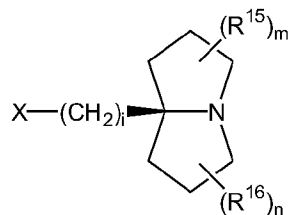


[0099] In certain embodiments, T^1 is $C=CR^{17}R^{18}$ and T^2 is $CR^{17}R^{18}$, each of f , g , p and q is 1, with R^1 having the structure of:



wherein each of R^{17} and R^{18} is independently H or halo.

[00100] In certain embodiments, the following group has the indicated chirality:



[00101] In certain embodiments, m is 0, n is 1, and R^{16} is F. In certain embodiments, X is O. In certain embodiments, i is 1.

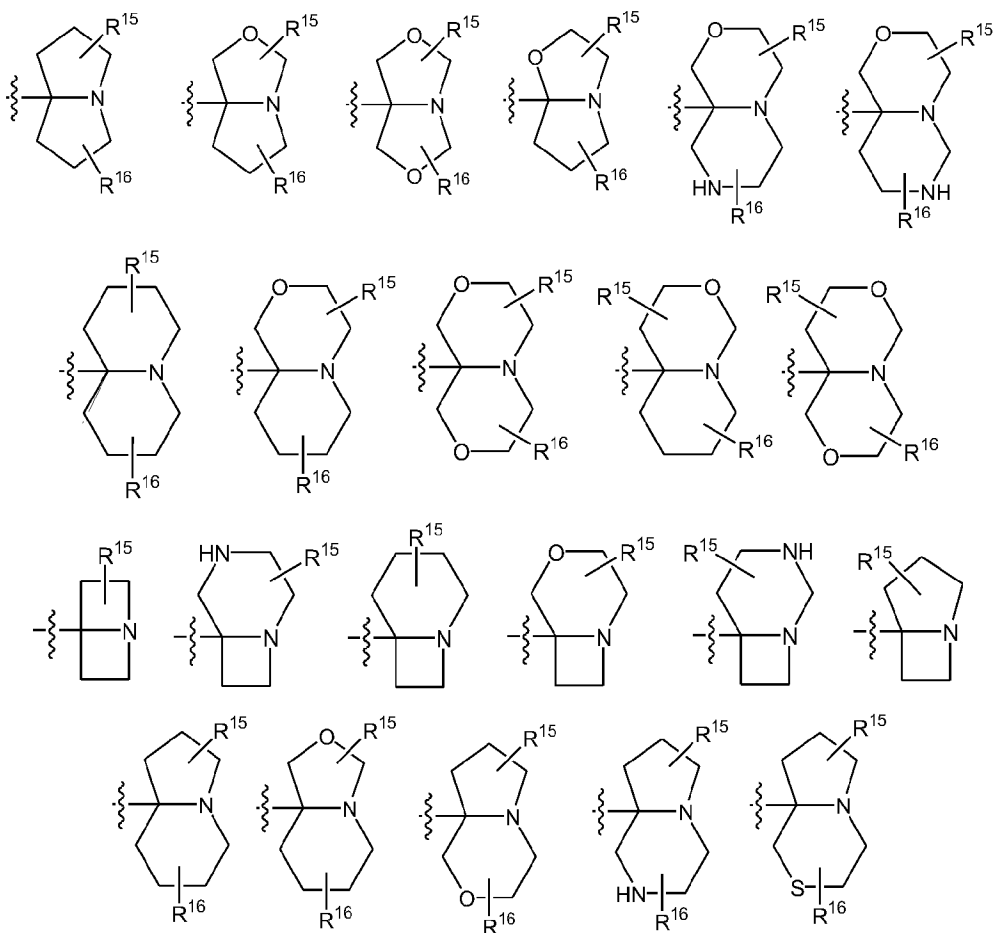
[00102] In certain embodiments, X is absent and R^1 is $(CH_2)_iR^{14}$.

[00103] In certain embodiments, R^{14} is NRR' .

[00104] In certain embodiments, R^{14} comprises one or more of amino, amide, sulfonamide, and carboxylic ester groups.

[00105] In certain embodiments, R^{14} is a mono- or bicyclic, unsubstituted or substituted C_{4-10} heterocyclic ring. In certain embodiments, R^{14} is a monocyclic, unsubstituted or substituted C_{4-7} heterocyclic ring. In certain embodiments, R^{14} is a bicyclic, unsubstituted or substituted C_{6-10} heterocyclic ring.

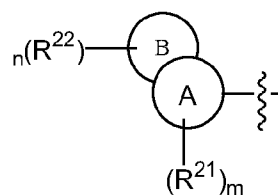
[00106] Non-limiting examples of R^{14} include:



wherein R^{15} and R^{16} are as defined herein.

[00107] In certain embodiments, R^2 is an unsubstituted or substituted 6- to 10-membered (*e.g.*, 5-, 6-, 7-, 8-, 9- or 10-membered) unsaturated bicyclic ring, comprising 0-5 (*e.g.*, 0, 1, 2, 3, 4 or 5) heteroatoms selected from N, O and S.

[00108] In certain embodiments, R^2 has the structure of:



wherein

Ring A is a 6-membered aryl or heteroaryl ring with 0-2 N atoms;

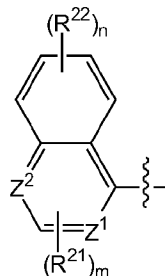
Ring B is a 5- or 6-membered aryl or heteroaryl with 0-3 (*e.g.*, 0, 1, 2 or 3) heteroatoms selected from N, O and S;

each of R^{21} and R^{22} is independently selected from the group consisting of halogen, OH, CN, NRR' , unsubstituted or substituted C_{1-6} alkyl, and unsubstituted or substituted C_{1-6} alkoxy, $(CH_2)_xNRR'$, $(CH_2)_xC(=O)NRR'$, $(CH_2)_xOC(=O)R$, $(CH_2)_xOC(=O)OR$;

each of m and n is independently 0, 1, 2 or 3; and

each x is independently 0, 1 or 2.

[00109] In certain embodiments, R^2 is:



wherein each of Z^1 and Z^2 is independently selected from CH and N.

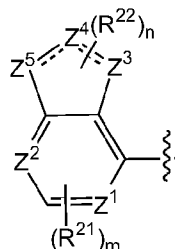
[00110] In certain embodiments, each of Z^1 and Z^2 is CH.

[00111] In certain embodiments, Z^1 is CH and Z^2 is N.

[00112] In certain embodiments, Z^1 is Z and Z^2 is CH.

[00113] In certain embodiments, each of Z^1 and Z^2 is N.

[00114] In certain embodiments, R^2 is:



wherein

each of Z^1 and Z^2 is independently selected from CH and N; and

each of Z^3 , Z^4 and Z^5 is independently selected from CR'' , N, NR, O or S, provided that

Ring B remains an aromatic ring, wherein R is H or a C_{1-4} alkyl.

[00115] In certain embodiments, each of Z^1 and Z^2 is CH.

[00116] In certain embodiments, Z^1 is CH and Z^2 is N.

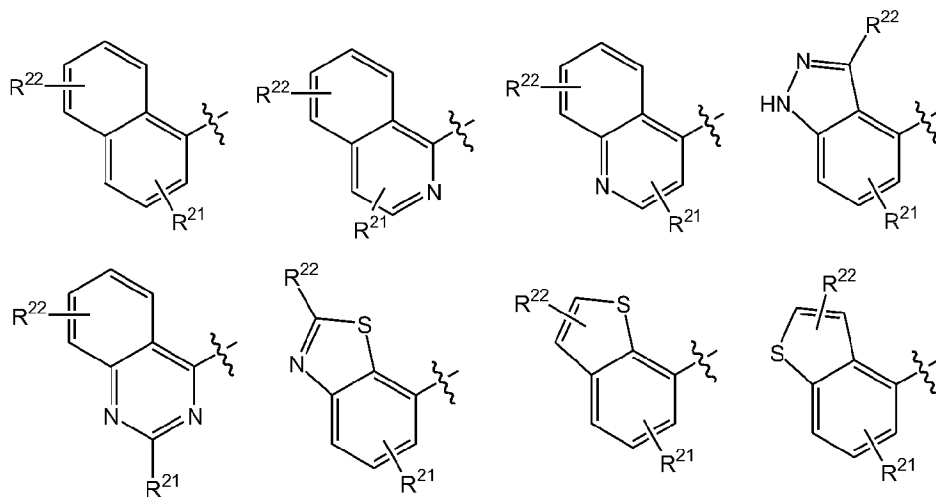
[00117] In certain embodiments, Z^1 is Z and Z^2 is CH.

[00118] In certain embodiments, each of Z^1 and Z^2 is N.

[00119] In certain embodiments, each of Z^3 , Z^4 and Z^5 is not a heteroatom.

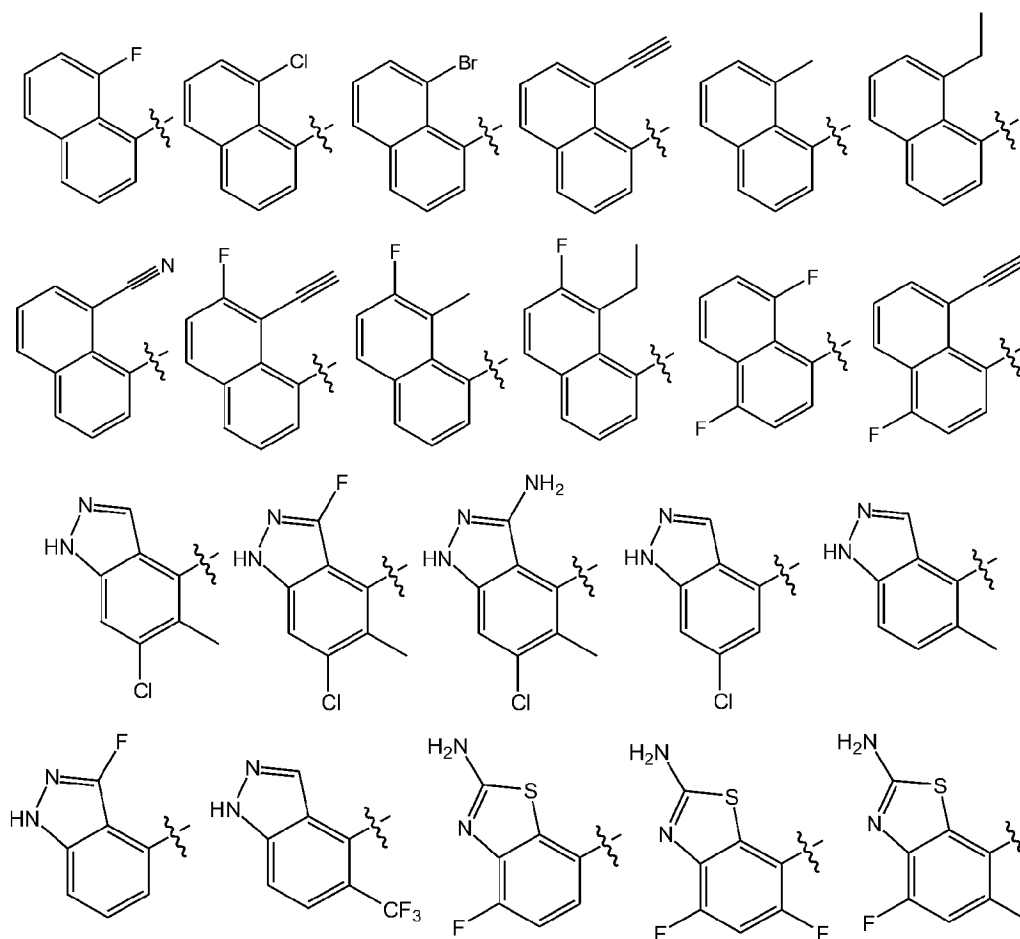
[00120] In certain embodiments, at least one of Z^3 , Z^4 and Z^5 is a heteroatom.

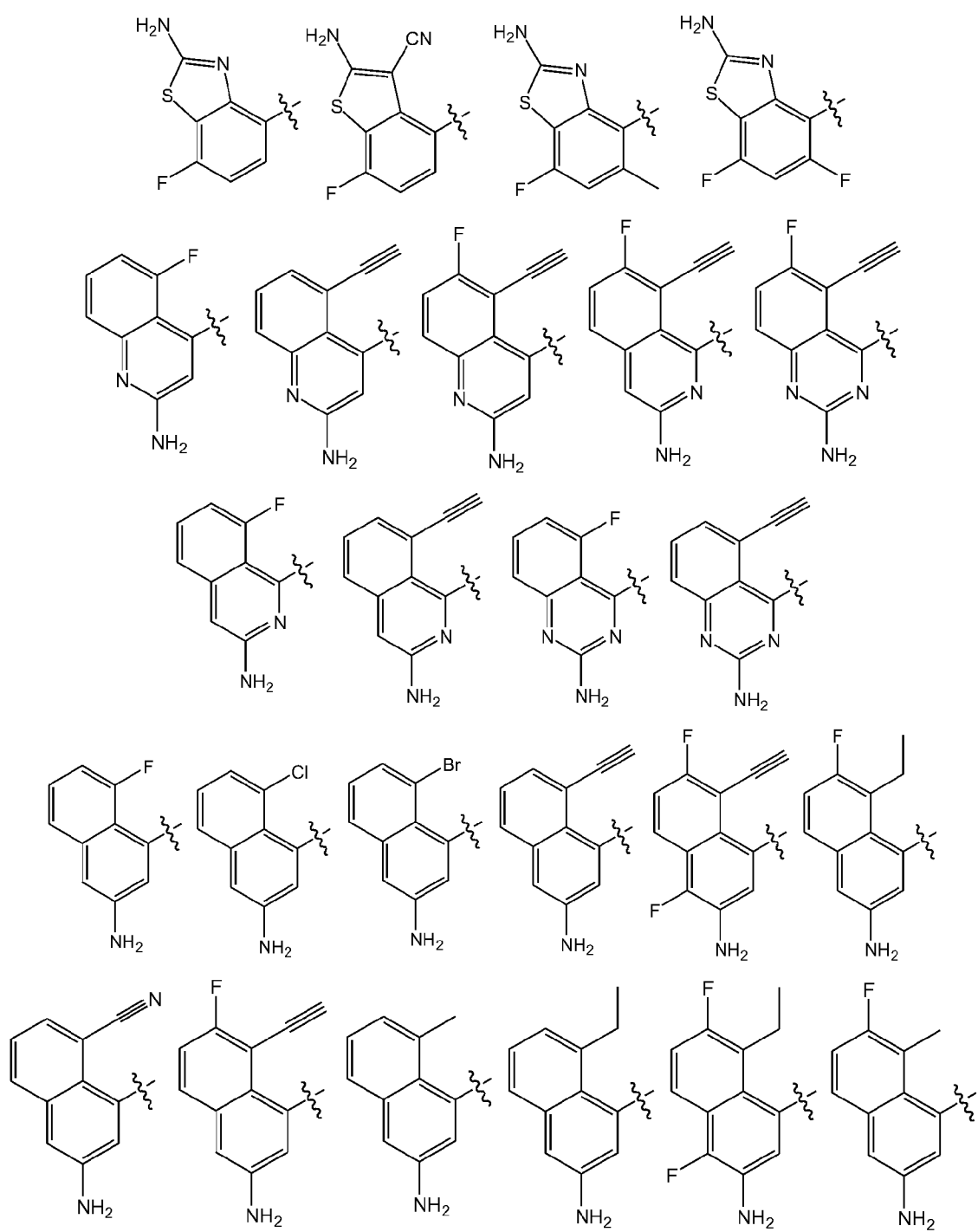
[00121] Exemplary R^2 groups include:

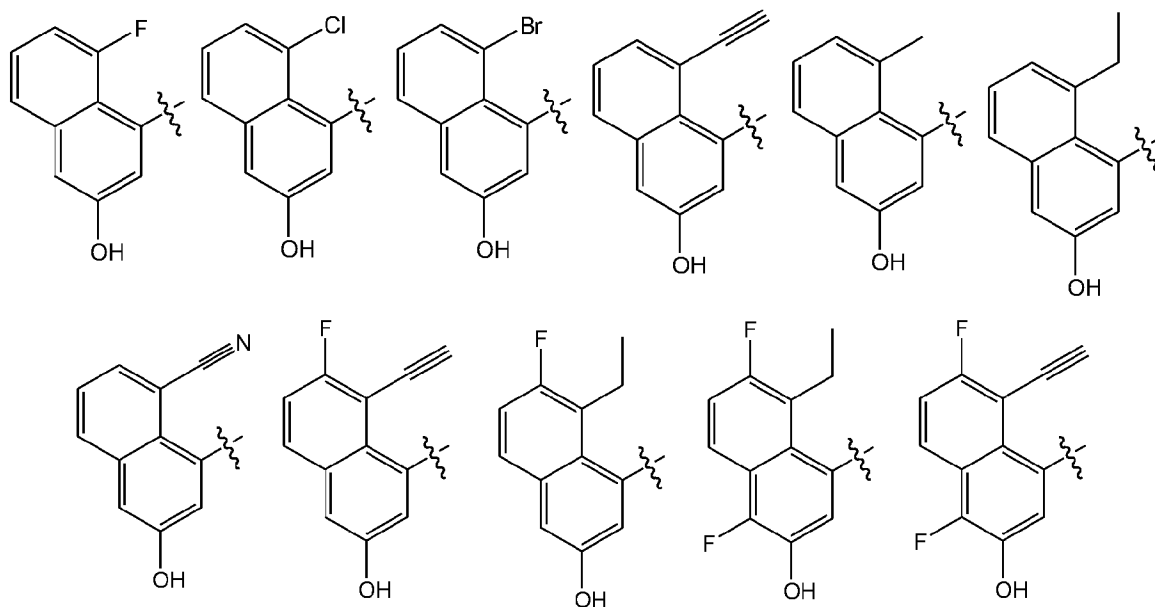


wherein R^{21} and R^{22} are as defined herein.

[00122] Non-limiting examples of R^2 include:



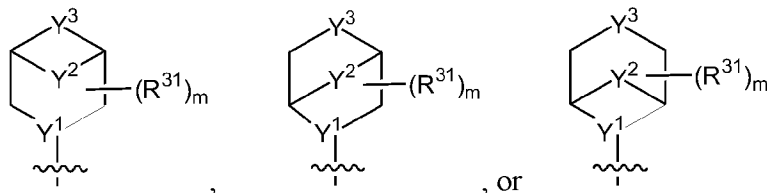




[00123] In certain embodiments, R^3 is an unsubstituted or substituted, saturated or unsaturated bicyclic or bridged ring moiety that comprises at least one N atom.

[00124] In certain embodiments, L is a single bond.

[00125] In certain embodiments, R^3 is:



wherein

Y^1 is N or CR'' ;

Y^2 is $(CH_2)_j$, NR or CH_2OCH_2 ;

Y^3 is NR, CR'' , O or S;

each R^{31} is independently selected from the group consisting of halogen, OH, NRR' , $C(O)NRR'$, unsubstituted or substituted C_{1-6} alkyl, and unsubstituted or substituted C_{1-6} alkoxy, $NRC(O)R''$, $NRC(O)NRR'$, $C(O)R''$, and $C(O)OR$, $S(O)_2NRR'$, $NRS(O)_2R$ and $NRS(O)_2NRR'$;

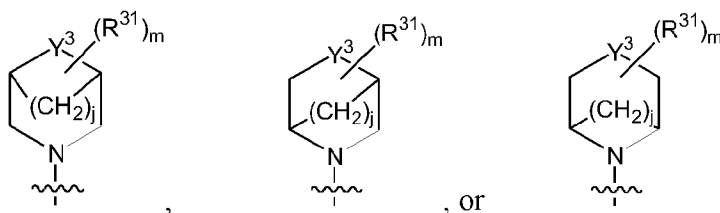
each j is independently 0, 1, 2 or 3; and

m is 0, 1, 2 or 3.

[00126] In certain embodiments, j is 2. In certain embodiments, j is 1. In certain embodiments, j is 0.

[00127] In certain embodiments, m is 2. In certain embodiments, m is 1. In certain embodiments, m is 0.

[00128] In certain embodiments, R^3 is:



[00129] In certain embodiments, Y^3 is NR.

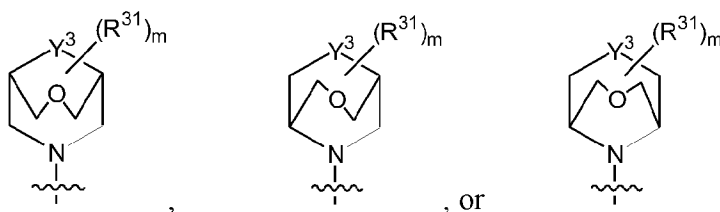
[00130] In certain embodiments, Y^3 is CR''.

[00131] In certain embodiments, Y^3 is O.

[00132] In certain embodiments, Y^3 is S.

[00133] In certain embodiments, j is 2.

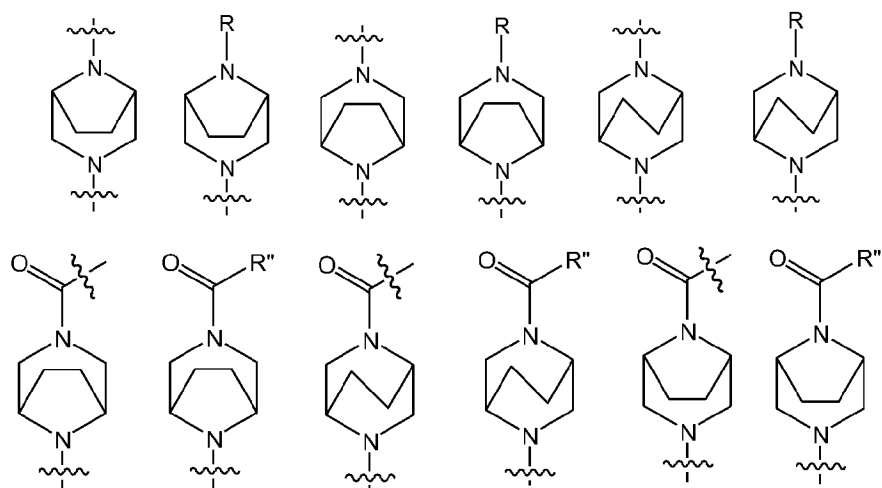
[00134] In certain embodiments, R^3 is:

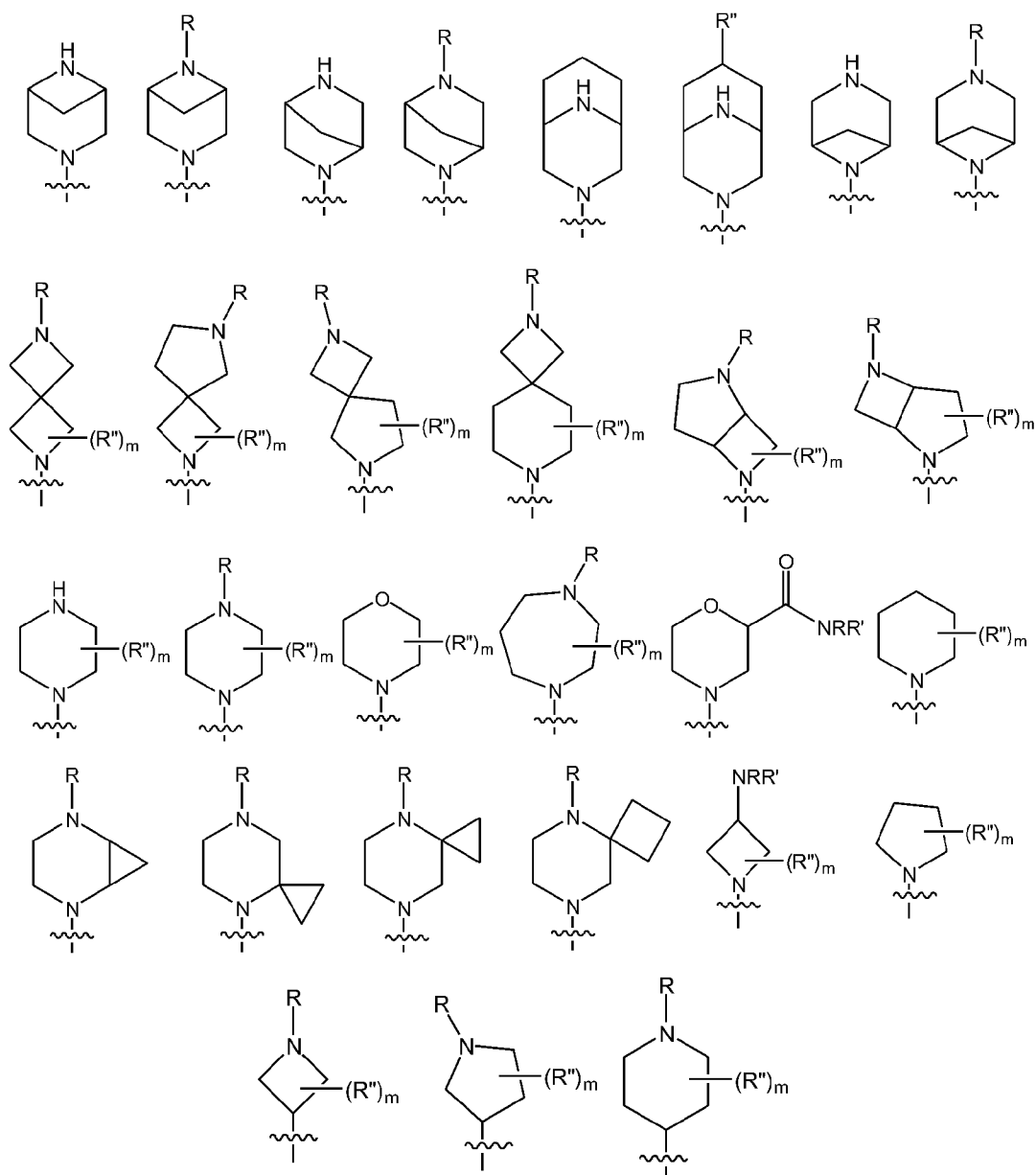


[00135] In certain embodiments, Y^3 is NR.

[00136] In certain embodiments, Y^3 is CR''.

[00137] Non-limiting examples of R^3 include:





wherein R, R' and m are as defined herein.

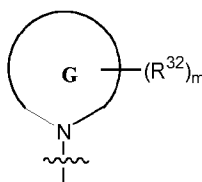
[00138] In certain embodiments, m is 0.

[00139] In certain embodiments, m is 1.

[00140] In certain embodiments of formula (I), L is a single bond and R^{3'} is an unsubstituted or substituted, 3- to 10-membered (*e.g.*, 3-, 4-, 5-, 6-, 7-, 8-, 9- or 10-membered) saturated or unsaturated monocyclic that comprises 0-3 (*e.g.*, 0, 1, 2 or 3) heteroatoms selected from N, O and S.

[00141] In certain embodiments, $R^{3'}$ is an unsubstituted or substituted, 6-membered saturated or unsaturated monocyclic that comprises 1-3 heteroatoms selected from N, O and S.

[00142] In certain embodiments, $R^{3'}$ has the structure:



wherein

Ring G is a 5- to 7-membered (*e.g.*, 5-, 6- or 7-membered) heterocyclic ring with 1-3 heteroatoms selected from N, O and S;

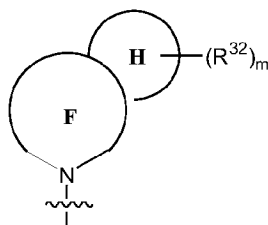
each R^{32} is independently selected from the group consisting of halogen, OH, NRR' , $C(O)NRR'$, unsubstituted or substituted C_{1-6} alkyl, and unsubstituted or substituted C_{1-6} alkoxy, $NRC(O)R''$, $NRC(O)NRR'$, $C(O)R''$, and $C(O)OR$, $S(O)_2NRR'$, $NRS(O)_2R$ and $NRS(O)_2NRR'$; and

m is 0, 1, 2 or 3.

[00143] In certain embodiments, Ring G is 6-membered.

[00144] In certain embodiments, $R^{3'}$ is an unsubstituted or substituted, 10- to 12-membered (*e.g.*, 10-, 11- or 12-membered) saturated or unsaturated bicyclic that comprises 1-5 (*e.g.*, 1, 2, 3, 4 or 5) heteroatoms selected from N, O and S.

[00145] In certain embodiments, $R^{3'}$ has the structure:



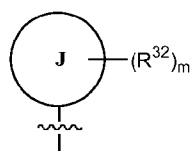
wherein

Rings F and H together form a hetero-bicyclic ring;

each R^{32} is independently selected from the group consisting of halogen, OH, NRR' , $C(O)NRR'$, unsubstituted or substituted C_{1-6} alkyl, and unsubstituted or substituted C_{1-6} alkoxy, $NRC(O)R''$, $NRC(O)NRR'$, $C(O)R''$, and $C(O)OR$, $S(O)_2NRR'$, $NRS(O)_2R$ and $NRS(O)_2NRR'$; and

m is 0, 1, 2 or 3.

- [00146] In certain embodiments, Ring F is 7-membered and Ring H is 5-membered.
- [00147] In certain embodiments of formula (I), L is $\text{NR}(\text{CH}_2)_k$ and R^3 is $\text{NR}(\text{CH}_2)_k\text{R}^{3'}$.
- [00148] In certain embodiments, k is 0.
- [00149] In certain embodiments, k is 1.
- [00150] In certain embodiments, $\text{R}^{3'}$ is an unsubstituted or substituted, 3- to 6-membered (*e.g.*, 3-, 4-, 5-, 6-membered) monocyclic ring moiety that comprises 0-3 (*e.g.*, 0, 1, 2 or 3) heteroatoms selected from N, O and S.
- [00151] In certain embodiments, $\text{R}^{3'}$ has the structure:



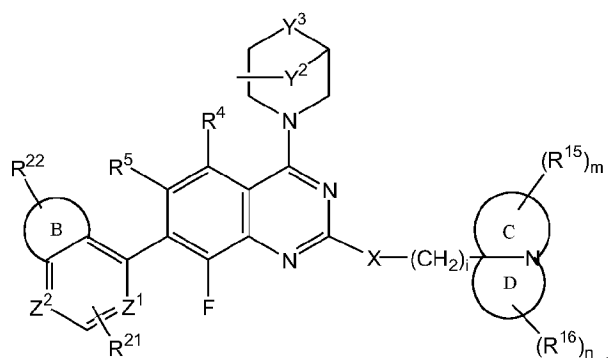
wherein

Ring J is a 5- to 7-membered (*e.g.*, 5-, 6- or 7-membered) carbocyclic or heterocyclic ring with 0-3 (*e.g.*, 0, 1, 2 or 3) heteroatoms selected from N, O and S;

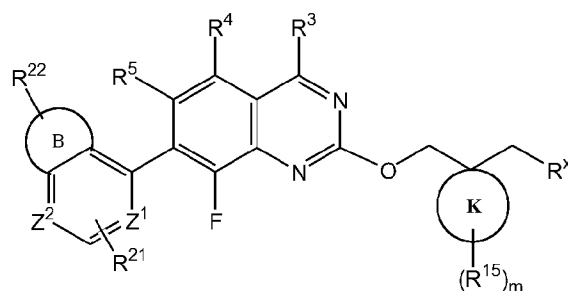
each R^{32} is independently selected from the group consisting of halogen, OH, NRR' , $\text{C}(\text{O})\text{NRR}'$, unsubstituted or substituted C_{1-6} alkyl, and unsubstituted or substituted C_{1-6} alkoxy, $\text{NRC}(\text{O})\text{R}''$, $\text{NRC}(\text{O})\text{NRR}'$, $\text{C}(\text{O})\text{R}''$, and $\text{C}(\text{O})\text{OR}$, $\text{S}(\text{O})_2\text{NRR}'$, $\text{NRS}(\text{O})_2\text{R}$ and $\text{NRS}(\text{O})_2\text{NRR}'$; and

m is 0, 1, 2 or 3.

- [00152] In certain embodiments, Ring J is 6-membered.
- [00153] In certain embodiments of formula (I), the compound has the structural formula:



- [00154] In certain embodiments of formula (I), the compound has the structural formula:



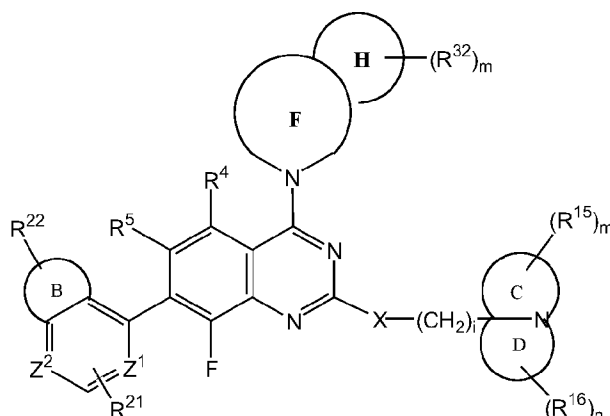
wherein

Ring K is a C₃₋₄ cycloalkyl;

R^x is OH, halo, NRR', CN, CONRR' or SO₂NRR'; and

m is 0, 1, 2 or 3.

[00155] In certain embodiments of formula (I), the compound has the structural formula:



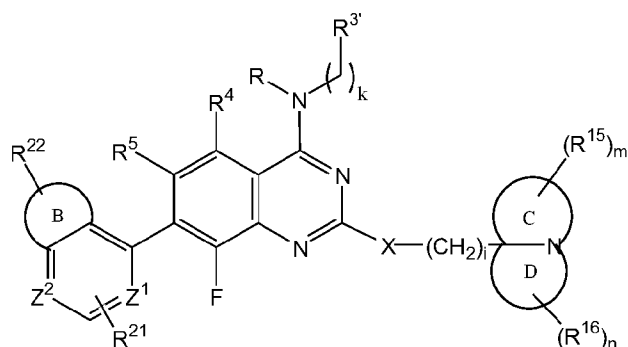
wherein

Rings F and H together form a hetero-bicyclic ring;

each R³² is independently selected from the group consisting of halogen, OH, NRR', C(O)NRR', unsubstituted or substituted C₁₋₆ alkyl, and unsubstituted or substituted C₁₋₆ alkoxy, NRC(O)R'', NRC(O)NRR', C(O)R'', and C(O)OR, S(O)₂NRR', NRS(O)₂R and NRS(O)₂NRR'; and

m is 0, 1, 2 or 3.

[00156] In certain embodiments of formula (I), the compound has the structural formula:

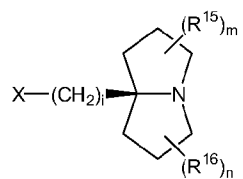


wherein

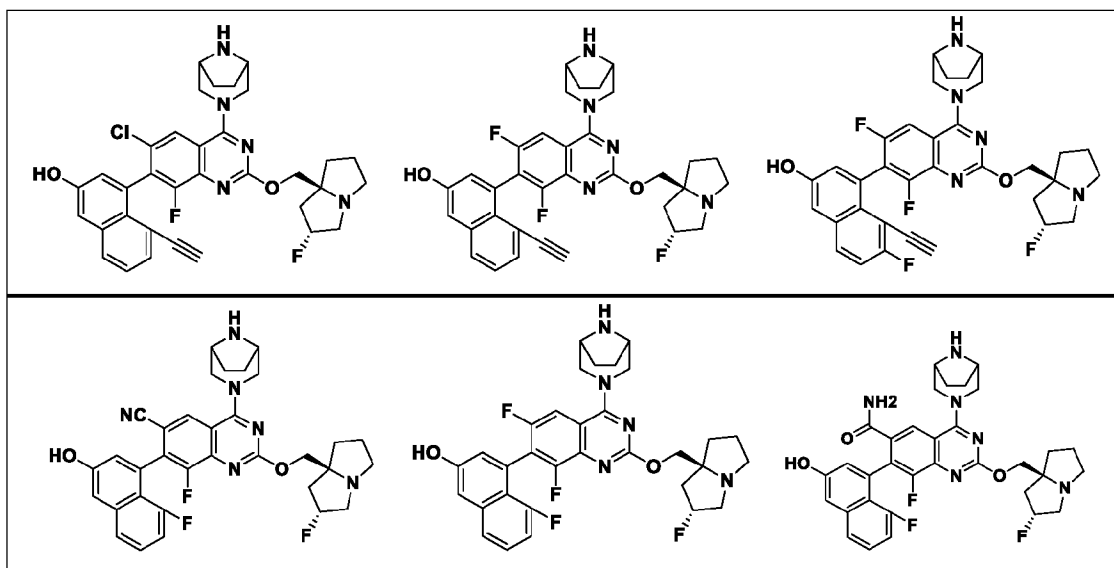
$R^{3'}$ is an unsubstituted or substituted, 3- to 6-membered (*e.g.*, 3-, 4-, 5-, 6-membered) monocyclic ring moiety that comprises 0-3 (*e.g.*, 0, 1, 2 or 3) heteroatoms selected from N, O and S; and

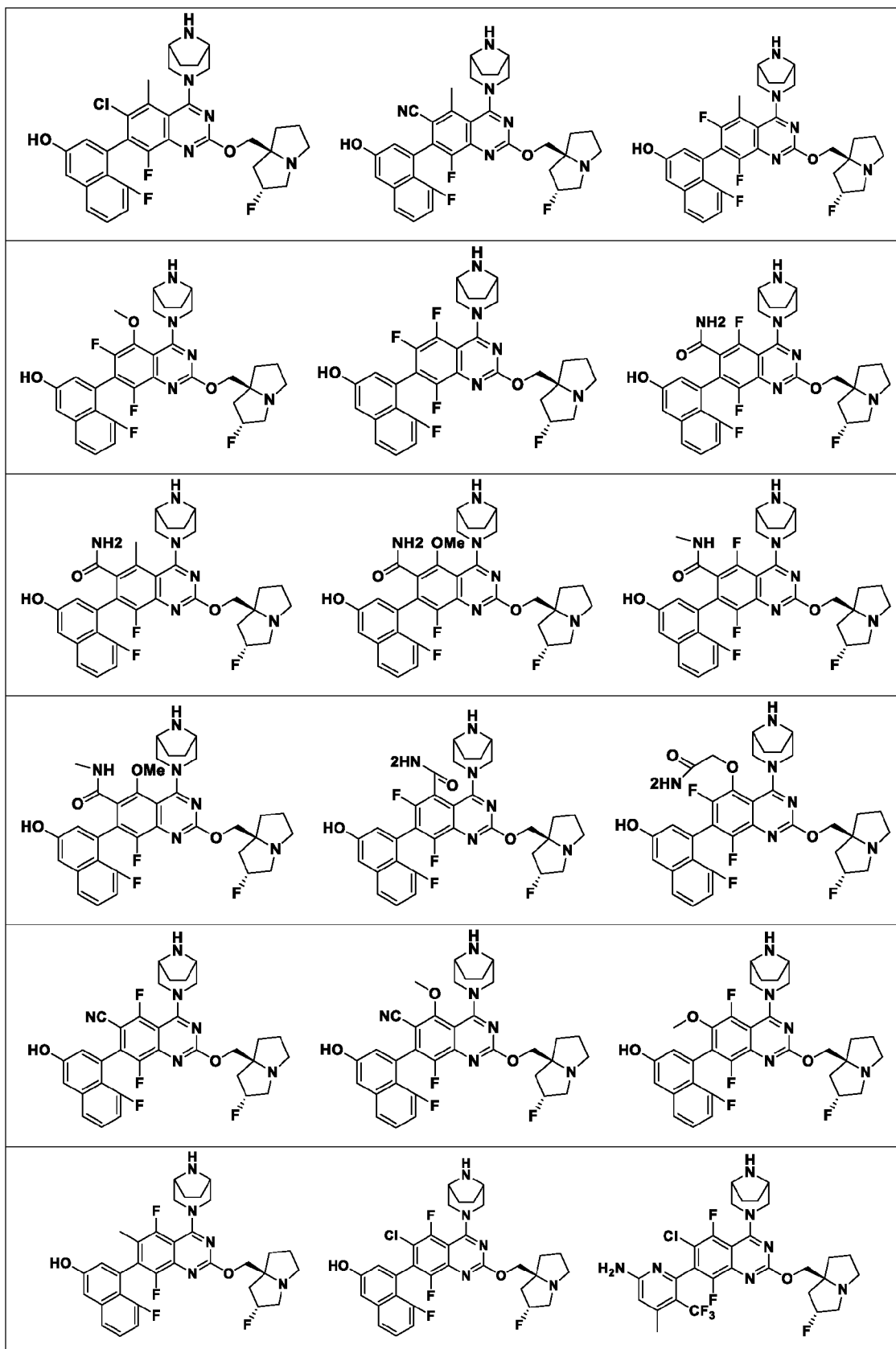
k is 0, 1 or 2.

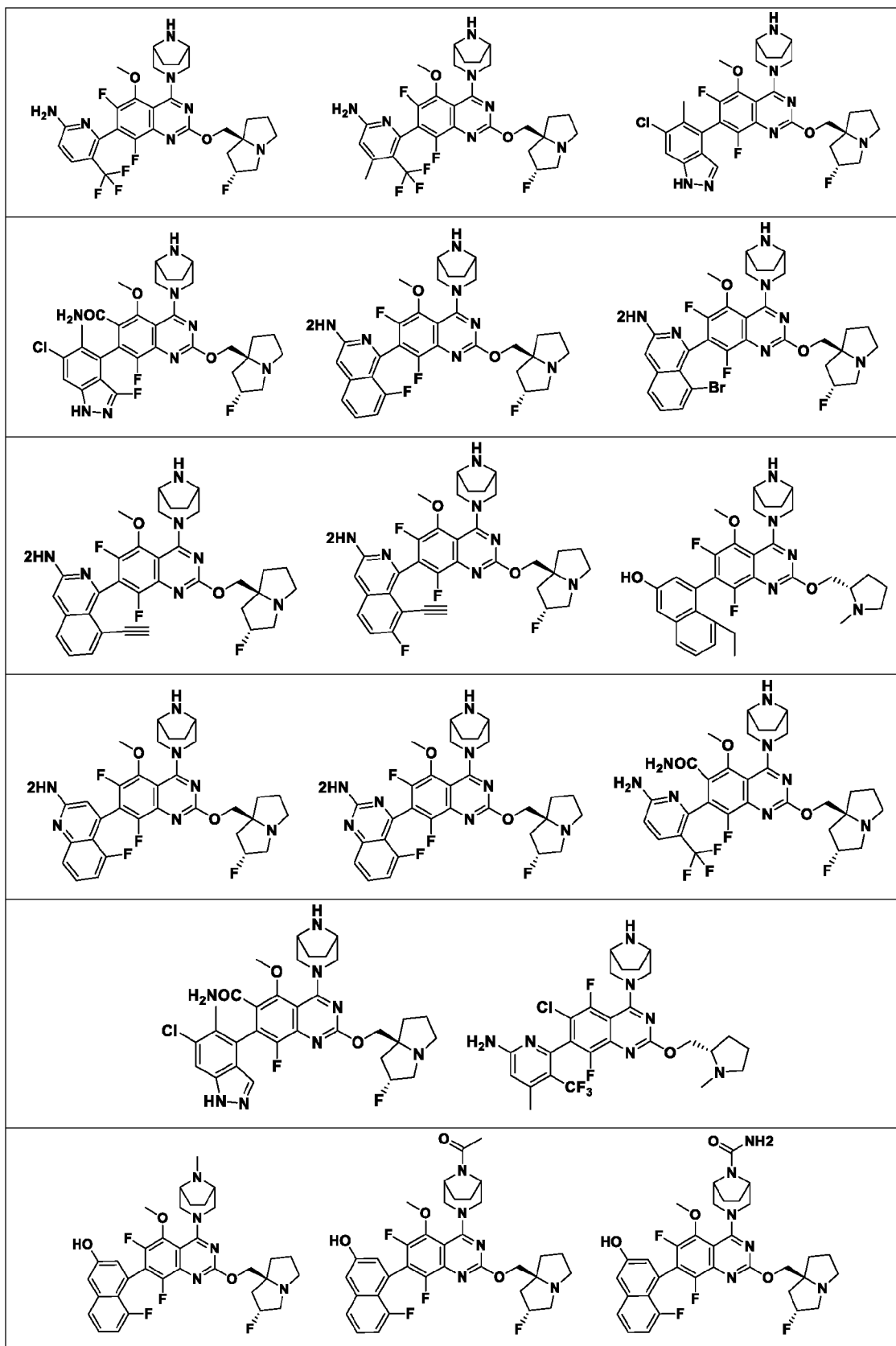
[00157] In certain embodiments, a disclosed compound has the chirality shown below:

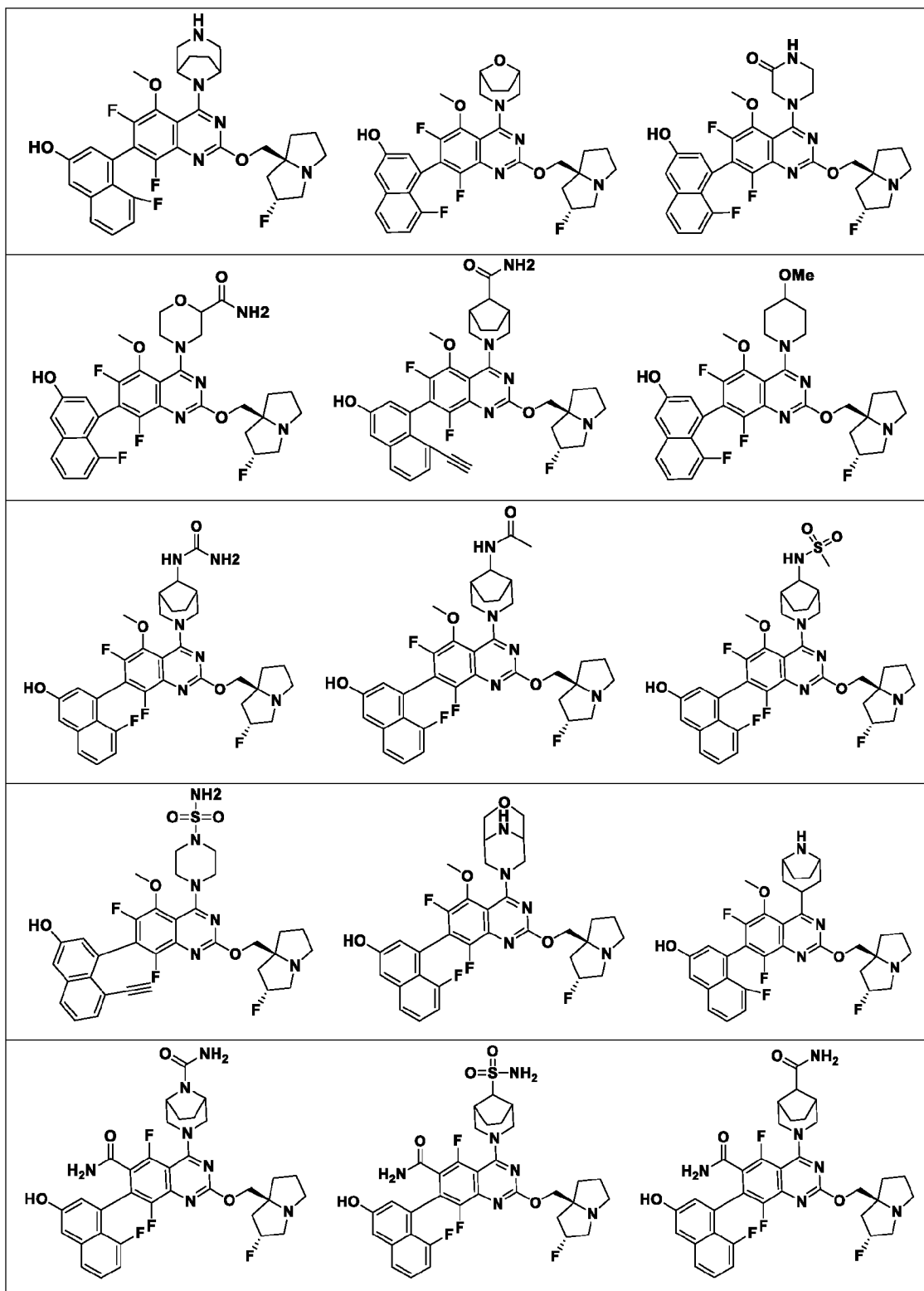


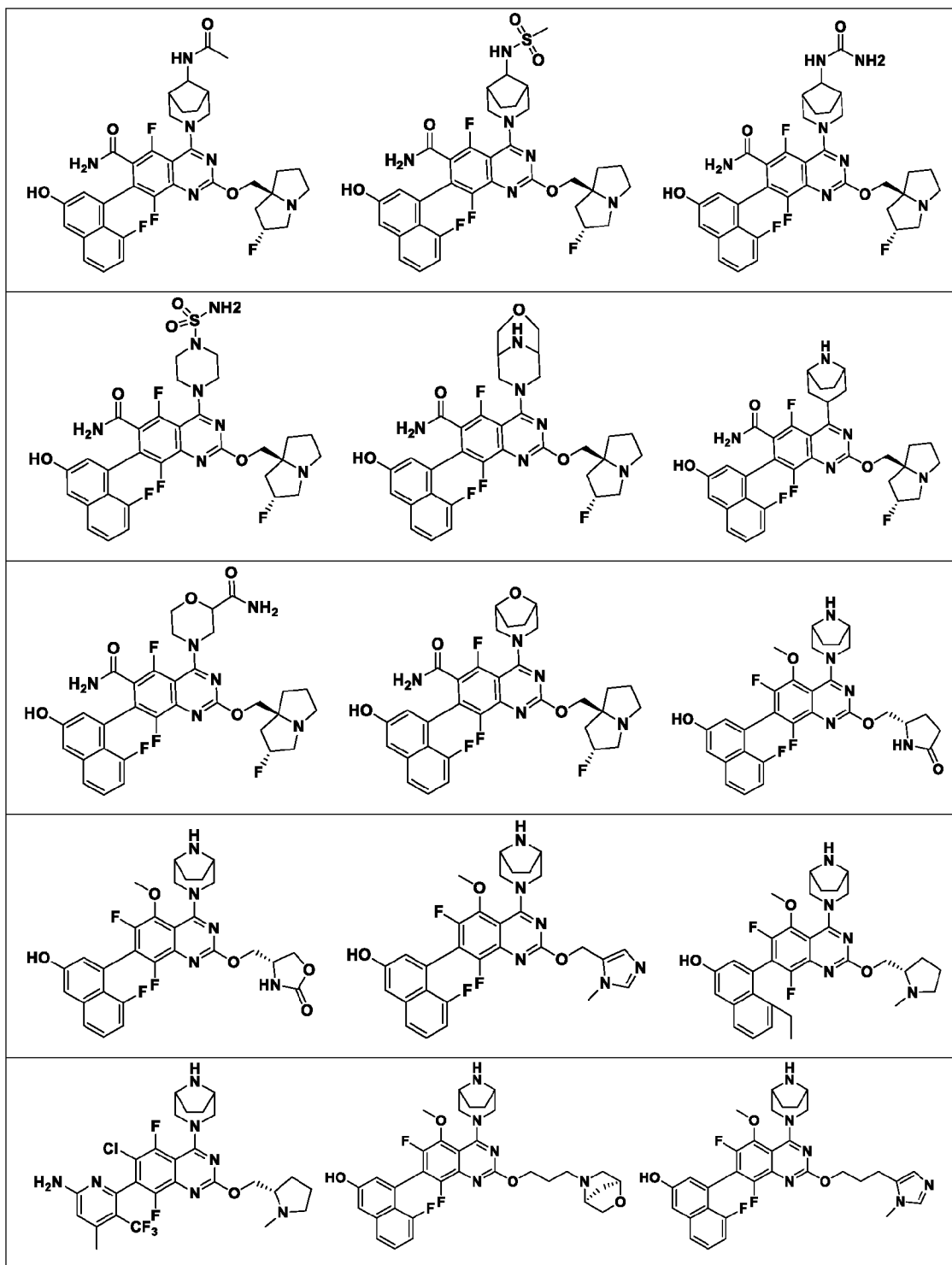
[00158] Non-limiting examples of compounds of the present invention include:

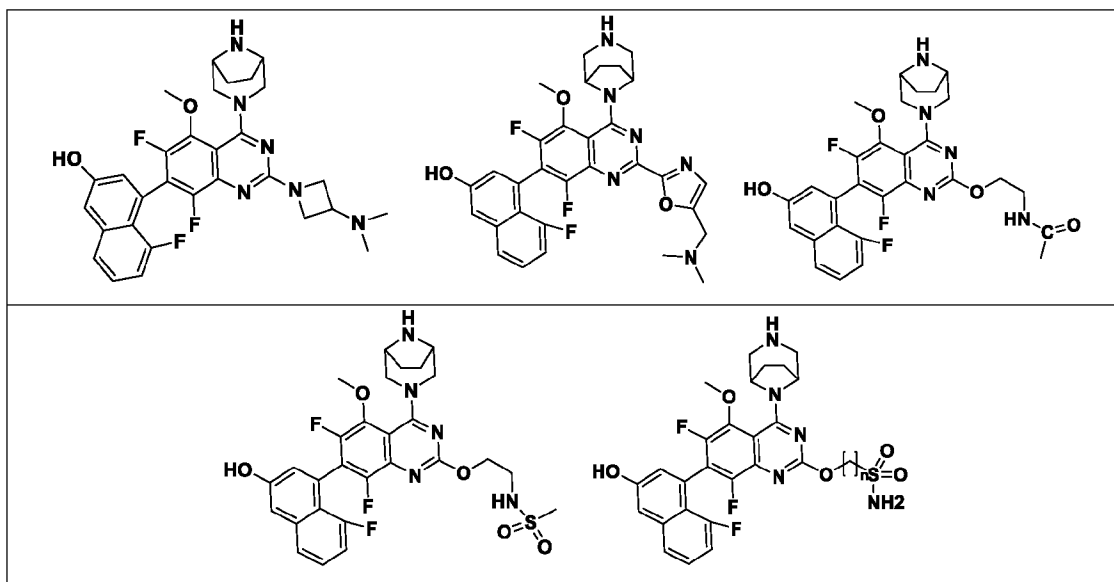










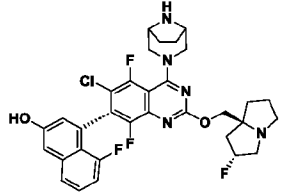
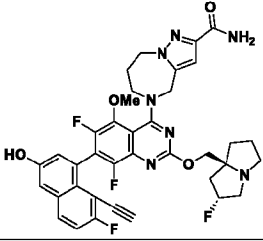
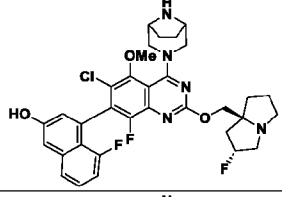
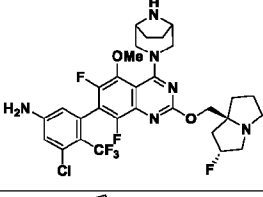
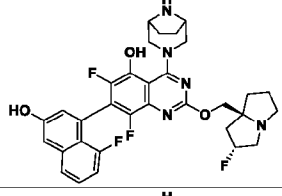
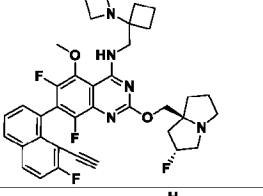
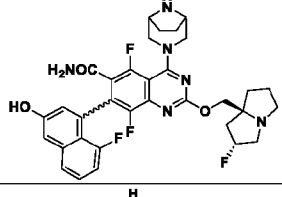
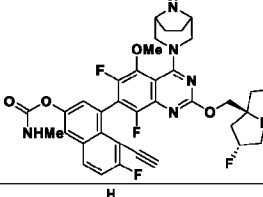
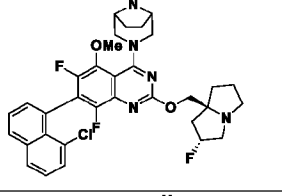
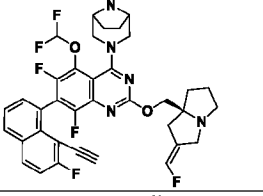
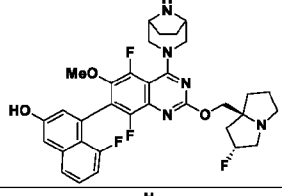
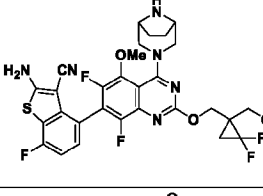
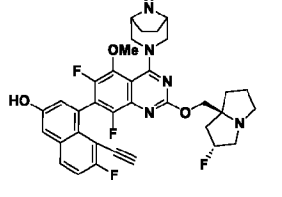


[00159] In certain embodiments, a compound of the invention is selected from **Table 1**.

Table 1. List of Exemplary Compounds

Example #	Structure	Example #	Structure
1		45	
2		46	
3		47	
4		48	

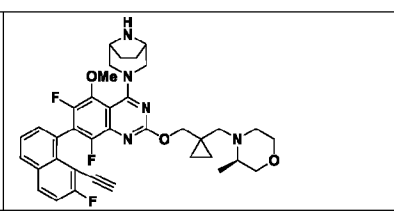
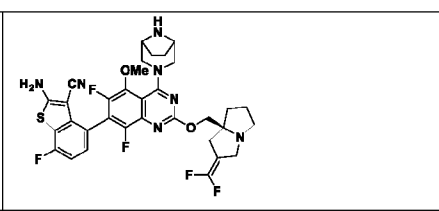
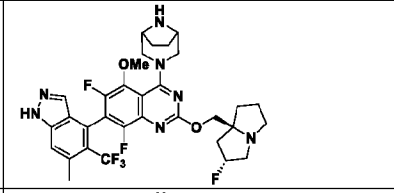
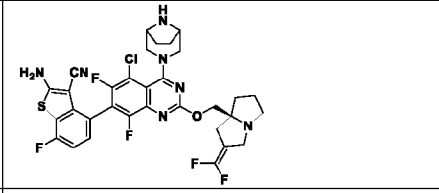
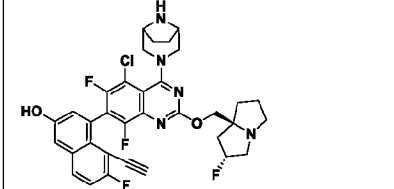
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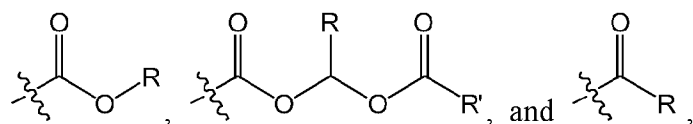
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[00160] In certain embodiments, the invention provides one or more pro-drug versions of a compound disclosed herein.

[00161] In certain embodiments, a pro-drug comprises an ester, a carbonate and/or a carbamate moiety.

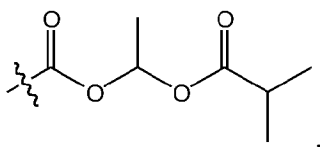
[00162] In certain embodiments, one or both of R^2 and R^3 in formula (I) comprises an ester, a carbonate and/or a carbamate moiety.

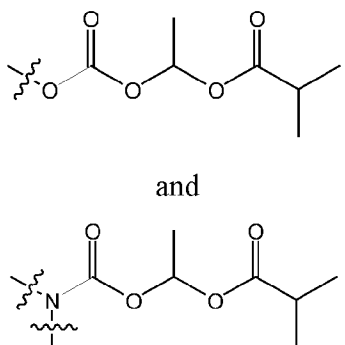
[00163] In certain embodiments, the ester, carbonate and carbamate moieties are selected from:



R or R' = H or substituted or unsubstituted C_{1-6} alkyl or substituted or unsubstituted 3- to 6-membered (*e.g.*, 3-, 4-, 5-, or 6-membered) carbocycle.

[00164] In certain embodiments, the ester, carbonate and carbamate moieties are selected from:





[00165] In certain embodiments, a compound of invention has one or more deuterium atoms in place of hydrogen. In certain embodiments, a compound of invention has one deuterium atom in place of a hydrogen atom.

[00166] In another aspect, the invention generally relates to a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable excipient, carrier, or diluent.

[00167] In certain embodiments, the pharmaceutical composition is suitable for oral administration.

[00168] In yet another aspect, the invention generally relates to a unit dosage form comprising a pharmaceutical composition disclosed herein.

[00169] In certain embodiments, the unit dosage form is in the form of a tablet or capsule.

[00170] Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[00171] The pharmaceutical compositions of the invention include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. In certain embodiments, the compound of the formulae herein is administered transdermally (e.g., using a

transdermal patch). Other formulations may conveniently be presented in unit dosage form, e.g., tablets and sustained release capsules, and in liposomes, and may be prepared by any methods well known in the art of pharmacy. See, for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, PA (17th ed. 1985).

[00172] Such preparative methods include the step of bringing into association with the molecule to be administered ingredients such as the carrier that constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers, liposomes or finely divided solid carriers or both, and then if necessary, shaping the product.

[00173] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds described herein or derivatives thereof are admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (i) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (ii) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (iii) humectants, as for example, glycerol, (iv) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate, (v) solution retarders, as for example, paraffin, (vi) absorption accelerators, as for example, quaternary ammonium compounds, (vii) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, (viii) adsorbents, as for example, kaolin and bentonite, and (ix) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard- filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethyleneglycols, and the like. Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others known in the art.

[00174] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers, such as for example, ethyl alcohol, isopropyl

alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, and fatty acid esters of sorbitan, or mixtures of these substances, and the like. Besides such inert diluents, the composition can also include additional agents, such as wetting, emulsifying, suspending, sweetening, flavoring, or perfuming agents.

[00175] In yet another aspect, the invention generally relates to a method for inhibiting cell proliferation *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound disclosed herein.

[00176] In yet another aspect, the invention generally relates to a method for inhibiting KRas(G12D) activity in a cell, comprising contacting the cell with a compound disclosed herein.

[00177] In yet another aspect, the invention generally relates to a method for treating a disease or disorder mediated by a Ras mutant protein, comprising administering to a subject in need thereof a therapeutically effective amount of the compound disclosed herein.

[00178] In yet another aspect, the invention generally relates to a method for treating or reducing cancer, or a related disease or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of the compound disclosed herein.

[00179] In yet another aspect, the invention generally relates to a method for treating or reducing cancer, or a related disease or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of the compound disclosed herein.

[00180] In yet another aspect, the invention generally relates to use of a compound disclosed herein, and a pharmaceutically acceptable excipient, carrier, or diluent, in preparation of a medicament for treating a disease or disorder.

[00181] Examples of diseases or disorders that may be treated or reduced by compositions or methods of the invention include, but are not limited to, tumors, cancers, autoimmune diseases, macroglobulinemia, and the like.

[00182] In certain embodiments, the cancer is selected from the group consisting of carcinoma, squamous carcinoma, adenocarcinoma, sarcoma, leukemia, neuroma, melanoma, and lymphoma.

[00183] Examples of cancers targeted in the present invention include, but are not particularly limited to, head and neck cancer, digestive organ cancer (esophageal cancer, stomach cancer,

duodenal cancer, liver cancer, biliary cancer (e.g., gallbladder and bile duct cancer), pancreatic cancer, colorectal cancer (e.g., colon cancer, and rectal cancer), etc.), lung cancer (e.g., non-small-cell lung cancer, small-cell lung cancer, and mesothelioma), breast cancer, genital cancer (ovarian cancer, uterine cancer (e.g., cervical cancer and endometrial cancer), etc.), urological cancer (e.g., kidney cancer, bladder cancer, prostate cancer, and testicular tumor), hematopoietic tumor (e.g., leukemia, lymphoma, malignant lymphoma, and multiple myeloma), sarcoma (e.g., osteosarcoma, and soft-tissue sarcoma), skin cancer, brain tumor, a carcinoma, squamous carcinoma, adenocarcinoma, neuroma, melanoma and the like. Examples include lung cancer, pancreatic cancer, rectal cancer, colon cancer colorectal cancer and uterine cancer. In certain embodiments, squamous carcinoma is a cancer of uterine cervix, tarsus, conjunctiva, vagina, lung, oral cavity, skin, bladder, tongue, larynx or esophagus. In one embodiment, adenocarcinoma is a cancer of prostate, small intestine, endometrium, uterine cervix, large intestine, lung, pancreas, esophagus, rectum, uterus, stomach, breast or ovary. In certain embodiments, tumor is rectal cancer, colon cancer, colorectal cancer, pancreatic cancer, lung cancer, breast cancer leukemia or uterine cancer.

[00184] In certain embodiments, the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, lung cancer, endometrial cancer, appendix cancer, cholangiocarcinoma, bladder urothelial cancer, ovarian cancer, gastric cancer, breast cancer, bile duct cancer, and a hematologic malignancy.

[00185] In certain embodiments, a subject suffering from any of the disease selected from the above does not have to have KRAS G12D mutant protein. In certain embodiments, a subject suffering from any of the disease selected from the above has KRAS G12D mutant protein.

[00186] In certain embodiments, the subject has a mutation of KRAS, HRAS and/or NRAS.

[00187] The amount of the active compound administered will be dependent on the subject being treated, the severity of the disorder or condition, the route of administration, the disposition of the compound and the discretion of the prescribing physician. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be used without causing any harmful side effect, with such larger doses typically divided into several smaller doses for administration throughout the day.

[00188] Any appropriate route of administration can be employed, for example, oral, intramuscular, intravenous, transdermal, subcutaneous, sublingual, parenteral, nasal, pulmonary,

inhalational, buccal, intraperitoneal, rectal, intrapleural, and intrathecal administration. Most suitable means of administration for a particular patient will depend on the nature and severity of the disease or condition being treated or the nature of the therapy being used and on the nature of the active compound.

[00189] In certain preferred embodiments, the compound is administered orally.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, sachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion, or packed in liposomes and as a bolus, etc. Soft gelatin capsules can be useful for containing such suspensions, which may beneficially increase the rate of compound absorption.

[00190] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets optionally may be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. Methods of formulating such slow or controlled release compositions of pharmaceutically active ingredients, such as those herein and other compounds known in the art, are known in the art and described in several issued US Patents, some of which include, but are not limited to, US Patent Nos. 4,369,172; and 4,842,866, and references cited therein. Coatings can be used for delivery of compounds to the intestine (see, *e.g.*, U.S. Patent Nos. 6,638,534, 5,217,720, and 6,569,457, 6,461,631, 6,528,080, 6,800,663, and references cited therein). A useful formulation for the compounds of this invention is the form of enteric pellets of which the enteric layer comprises hydroxypropylmethylcellulose acetate succinate.

[00191] In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying

and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

[00192] Compositions suitable for topical administration include lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; and pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia.

[00193] Compositions suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

[00194] Such injection solutions may be in the form, for example, of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant.

[00195] Compounds of the present invention may also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and

metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott, Ed., *Methods in Cell Biology*, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

[00196] The pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

[00197] The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

[00198] Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches and iontophoretic administration are also included in this invention.

[00199] Methods of treatment disclosed herein may be employed in combination with or in addition to other therapies. In certain embodiments, the subject being treated is further administered one or more of chemotherapy, radiotherapy, targeted therapy, immunotherapy, and hormonal therapy.

[00200] Exemplary additional therapeutically active agents include, but are not limited to, small organic molecules such as drug compounds, *e.g.*, compounds approved by the U.S. Food and Drug Administration (FDA) as provided in the Code of Federal Regulations (CFR), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins and cells.

[00201] In certain embodiments, a compound of the invention may be administered in combination with endocrine therapy, *e.g.*, agents such as letrozole, fulvestrant, tamoxifen, exemestane, or anastrozole.

[00202] In some embodiments, a compound of the invention may be administered in combination with a chemotherapeutic agent, *e.g.*, docetaxel, paclitaxel, cisplatin, carboplatin, capecitabine, gemcitabine or vinorelbine. In other embodiments, a compound of the invention may be administered in combination with an anti-HER2 agent, *e.g.*, trastuzumab or pertuzumab.

[00203] In certain embodiments, the method disclosed herein is in combination with one or more of immune check point blockade, co-signaling of T cells, and tumor targeting antibody therapies.

[00204] In certain embodiments, the method further comprises administering a chemotherapeutic agent to the subject.

[00205] In certain embodiments, the method further comprises administering a radiotherapy to the subject. In certain embodiments, the method further comprises administering a targeted therapy to the subject. In certain embodiments, the method further comprises administering an immunotherapy to the subject. In certain embodiments, the method further comprises administering hormonal therapy to the subject.

[00206] As used herein, the term "chemotherapeutic agent" refers to a chemical compound useful in the treatment of cancer. Examples of chemotherapeutic agents include Erlotinib (TARCEVA®, Genentech/OSI Pharm.), Bortezomib (VELCADE®, Millennium Pharm.),

Fulvestrant (FASLODEX®, AstraZeneca), Sutent (SU11248, Pfizer), Letrozole (FEMARA®, Novartis), Imatinib mesylate (GLEEVEC®, Novartis), PTK787/ZK 222584 (Novartis), Oxaliplatin (Eloxatin®, Sanofi), 5-FU (5-fluorouracil), Leucovorin, Rapamycin (Sirolimus, RAPAMUNE®, Wyeth), Lapatinib (TYKERB®, GSK572016, Glaxo Smith Kline), Lonafermin (SCH 66336), Sorafenib (BAY43-9006, Bayer Labs), and Gefitinib (IRESSA®, AstraZeneca), AG1478, AG1571 (SU 5271; Sugen), alkylating agents such as thiotepa and CYTOXAN® cyclophosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylmelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analog topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogs); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogs, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (*e.g.*, calicheamicin, especially calicheamicin gammall and calicheamicin omegall (Angew Chem. Intl. Ed. Engl. (1994) 33: 183-186); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabacin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6- diazo-5-oxo-L-norleucine, ADRIAMYCIN® (doxorubicin), morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esonibicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogs such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6- mercaptopurine, thiamnipyne, thioguanine;

pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiothane, testolactone; anti-adrenals such as aminogluthethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK[®] polysaccharide complex (JHS Natural Products, Eugene, Oreg.); razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepe; taxoids, *e.g.*, TAXOL[®] (paclitaxel; Bristol-Myers Squibb Oncology, Princeton, N.J.), ABRAXANE[®] (Cremophor-free), albumin-engineered nanoparticle formulations of paclitaxel (American Pharmaceutical Partners, Schaumburg, 111.), and TAXOTERE[®] (doxetaxel; Rhone-Poulenc Rorer, Antony, France); chloranmbucil; GEMZAR[®] (gemcitabine); 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; etoposide (VP- 16); ifosfamide; mitoxantrone; vincristine; NAVELBINE[®] (vinorelbine); novantrone; teniposide; edatrexate; daunomycin; aminopterin; capecitabine (XELODA[®]); ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylomithine (DMFO); retinoids such as retinoic acid; and pharmaceutically acceptable salts, acids and derivatives of any of the above.

[00207] Examples of the second (or further) agent or therapy may include, but are not limited to, immunotherapies (*e.g.* PD-1 inhibitors (pembrolizumab, nivolumab, cemiplimab), PD-L1 inhibitors (atezolizumab, avelumab, durvalumab), CTLA4 antagonist, cell signal transduction inhibitors (*e.g.*, imatinib, gefitinib, bortezomib, erlotinib, sorafenib, sunitinib, dasatinib, vorinostat, lapatinib, temsirolimus, nilotinib, everolimus, pazopanib, trastuzumab, bevacizumab, cetuximab, ranibizumab, pegaptanib, panitumumab and the like), mitosis inhibitors (*e.g.*, paclitaxel, vincristine, vinblastine and the like), alkylating agents (*e.g.*, cisplatin, cyclophosphamide, chromabucil, carmustine and the like), anti-metabolites (*e.g.*, methotrexate,

5-FU and the like), intercalating anticancer agents, (*e.g.*, actinomycin, anthracycline, bleomycin, mitomycin-C and the like), topoisomerase inhibitors (*e.g.*, irinotecan, topotecan, teniposide and the like), immunotherapeutic agents (*e.g.*, interleukin, interferon and the like) and antihormonal agents (*e.g.*, tamoxifen, raloxifene and the like).

[00208] Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

[00209] Isomeric mixtures containing any of a variety of isomer ratios may be utilized in accordance with the present invention. For example, where only two isomers are combined, mixtures containing 50:50, 60:40, 70:30, 80:20, 90:10, 95:5, 96:4, 97:3, 98:2, 99:1, or 100:0 isomer ratios are contemplated by the present invention. Those of ordinary skill in the art will readily appreciate that analogous ratios are contemplated for more complex isomer mixtures.

[00210] If, for instance, a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic methods well known in the art, and subsequent recovery of the pure enantiomers.

[00211] Isotopically-labeled compounds are also within the scope of the present disclosure. As used herein, an "isotopically-labeled compound" refers to a presently disclosed compound including pharmaceutical salts and prodrugs thereof, each as described herein, in which one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds presently disclosed include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively.

[00212] By isotopically-labeling the presently disclosed compounds, the compounds may be useful in drug and/or substrate tissue distribution assays. Tritiated (^3H) and carbon-14 (^{14}C) labeled compounds are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (^2H) can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds presently disclosed, including pharmaceutical salts, esters, and prodrugs thereof, can be prepared by any means known in the art.

[00213] Further, substitution of normally abundant hydrogen (^1H) with heavier isotopes such as deuterium can afford certain therapeutic advantages, *e.g.*, resulting from improved absorption, distribution, metabolism and/or excretion (ADME) properties, creating drugs with improved efficacy, safety, and/or tolerability. Benefits may also be obtained from replacement of normally abundant ^{12}C with ^{13}C . (See, WO 2007/005643, WO 2007/005644, WO 2007/016361, and WO 2007/016431.)

[00214] Stereoisomers (*e.g.*, cis and trans isomers) and all optical isomers of a presently disclosed compound (*e.g.*, R and S enantiomers), as well as racemic, diastereomeric and other mixtures of such isomers are within the scope of the present disclosure.

[00215] Compounds of the present invention are, subsequent to their preparation, preferably isolated and purified to obtain a composition containing an amount by weight equal to or greater than 95% (“substantially pure”), which is then used or formulated as described herein. In certain embodiments, the compounds of the present invention are more than 99% pure.

[00216] Solvates and polymorphs of the compounds of the invention are also contemplated herein. Solvates of the compounds of the present invention include, for example, hydrates.

[00217] Any appropriate route of administration can be employed, for example, parenteral, intravenous, subcutaneous, intramuscular, intraventricular, intracorporeal, intraperitoneal, rectal, or oral administration. Most suitable means of administration for a particular patient will depend on the nature and severity of the disease or condition being treated or the nature of the therapy being used and on the nature of the active compound.

[00218] Compositions for parenteral injection comprise pharmaceutically-acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use.

Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), carboxymethylcellulose and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity may be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[00219] These compositions can also contain adjuvants such as preservative, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paragen, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption, such as aluminum monostearate and gelatin.

[00220] Compounds of the present invention may also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically-acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott, Ed., *Methods in Cell Biology*, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

[00221] Total daily dose of the compositions of the invention to be administered to a human or other mammal host in single or divided doses may be in amounts, for example, from 0.0001 to 300 mg/kg body weight daily and more usually 1 to 300 mg/kg body weight. The dose, from 0.0001 to 300 mg/kg body, may be given twice a day.

[00222] Materials, compositions, and components disclosed herein can be used for, can be used in conjunction with, can be used in preparation for, or are products of the disclosed methods and compositions. It is understood that when combinations, subsets, interactions, groups, etc. of these materials are disclosed that while specific reference of each various individual and

collective combinations and permutations of these compounds may not be explicitly disclosed, each is specifically contemplated and described herein. For example, if a method is disclosed and discussed and a number of modifications that can be made to a number of molecules including in the method are discussed, each and every combination and permutation of the method, and the modifications that are possible are specifically contemplated unless specifically indicated to the contrary. Likewise, any subset or combination of these is also specifically contemplated and disclosed. This concept applies to all aspects of this disclosure including, but not limited to, steps in methods using the disclosed compositions. Thus, if there are a variety of additional steps that can be performed, it is understood that each of these additional steps can be performed with any specific method steps or combination of method steps of the disclosed methods, and that each such combination or subset of combinations is specifically contemplated and should be considered disclosed.

Examples

[00223] The following examples are given for the purpose of illustrating the invention, but not for limiting the scope or spirit of the invention.

[00224] Compounds of the invention, including those specifically disclosed herein above and herein below, may be prepared as described in the following schemes. Although the present invention has been described in detail with preferred embodiments, those of ordinary skill in the art should understand that modifications, variations, and equivalent replacements made to the present invention within the scope of the present invention belong to the protection of the present invention.

List of Abbreviations and acryonyms:

Ac = Acetyl

AcO = Acetate

Ac₂O = Acetic anhydride

AIBN = a,a'-Azobisisobutyronitrile

All = Allyl

Alloc = Allyloxycarbonyl

Am = Amyl (Pentyl)

Ar = Aryl

B₂Pin₂ = bis(pinacolato)diboron

9-BBN = 9-Borabicyclononane

BINAP = 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl

Bn = Benzyl

Boc = tert-Butoxycarbonyl

BOP = Bis(2-oxo-3-oxazolidinyl)phosphine

Bu or n-Bu = n-Butyl

s-Bu or sBu = sec-Butyl

t-Bu or tBu = tert-Butyl

BuOH = Butanol

Bz = Benzoyl

Bzl = Benzyl

CAN = Ceric ammonium nitrate

cataCXium A Pd G3 = mesylate [(di(1-adamantyl)-n-butylphosphine)-2-(2'-amino-1,1'-biphenyl)]palladium(II)

CBS = Corey-Bashki-Shibat

Cbz = Benzyloxycarbonyl

CbzCl = Benzyl chloroformate ox

Cod = Cyclooctadiene

Cp = Cyclopentadienyl

CPhos = 2-Dicyclohexylphosphino-2',6'-bis(*N,N*-dimethylamino)biphenyl

CSA = Camphorsulphonic acid

DABCO = 1,4-Diazabicyclo[2.2.2]octane

DAST = Diethylaminosulphur trifluoride

dba = Dibenzylideneacetone

DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCC = 1,3-Dicyclohexylcarbodiimide

DCM = Dichloromethane

DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DEAD = Diethyl azodicarboxylate

DHP = Dihydropiran
DHQD = Dihydroquinidine
DIBAL = Diisobutylaluminium hydride
DIC = Diisopropylcarbodiimide
DIPEA = Diisopropylethylamine
DMA = N,N-Dimethylacetamide
DMAC = N,N-Dimethylacetamide
DMAP = 4-Dimethylaminopyridine
DME = 1,2-Dimethoxyethane
DMF = N,N-Dimethylformamide
DMP = Dess-Martin periodinane
DMPU = 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone
DMS = Dimethylsulphide
DMSO = Dimethylsulphoxide
DPA = Diisopropylamine
DPPA = Diphenylphosphoryl azide
Ddppb = 1,4-bis(diphenylphosphino)butane
Dppe = 1,2-bis(diphenylphosphino)ethane
Dppf = 1,2-bis(diphenylphosphino)ferrocene
dppp = 1,3-bis(diphenylphosphino)propane
Dtbbpy = 4, 4'-di-tert-butyl-2,2'-dipyridyl
EDC = 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDCI = 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
Eq = equivalent
ESI or ES = Electrospray ionization
Et = ethyl
Et₂O = Diethyl ether
EtOAc = Ethyl acetate
Fmoc = 9-Fluorenylmethoxycarbonyl
h = hour

HATU = 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate

HMDS = Hexamethyldisilazane

HMPA = Hexamethylphosphoramide

HOAt = 7-Aza-1-hydroxybenzotriazole

HOBt = 1-Hydroxybenzotriazole

HPLC = high pressure liquid chromatography

IPA = Isopropyl alcohol

Im = Imidazole

KHMDS = Potassium bis(trimethylsilyl)amide

KOAc = Potassium acetate

LAH = Lithium aluminium hydride

LDA = Lithium diisopropylamide

LHMDS = Lithium bis(trimethylsilyl)amide

MCPBA = meta-chloroperoxybenzoic acid

Me = Methyl

MeCN = Acetonitrile

MeOH = Methanol

MOM = Methoxymethyl

Mg = magnesium

MS = Molecular sieves

Ms = Methanesulphonyl

MTBE = Methyl tert-butyl ether

m/z = mass divided by charge

NaHMDS = Sodium bis(trimethylsilyl)amide

NBS = N-Bromosuccinimide

NCS = N-Chlorosuccinimide

NIS = N-Iodosuccinimide

NMM = N-Methylmorpholine

NMO = N-Methylmorpholine-N-oxide

NMP = N-Methylpyrrolidone

NMR = Nuclear magnetic resonance

Ns = p-Nitrophenylsulphonyl

Pd(dppf)Cl₂ = [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium

Pd(PPh₃)₄ = tetrakis(triphenylphosphine)palladium

PDC = Pyridinium dichlorochromate

PCC = Pyridinium chlorochromate

Ph = Phenyl

PhMe = toluene

Piv = Pivaloyl, 2,2-dimethylacetyl

PMB = p-Methoxybenzyl

PPA = Polyphosphoric acid

PPTS = Pyridinium p-toluensulphonate

n-Pr = n-Propyl

Pr = Propyl

i-Pr or iPr = iso-propyl

PTC = Phase transfer catalyst

PTSA = p-Toluenesulphonic acid

Pv = Pivaloyl, 2,2-dimethylacetyl

Py = Pyridine

rac. = racemic

Red-Al® = Sodium bis(2-methoxyethoxy)aluminium hydride

RT = room temperature

RuPhos = 2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl

Sat. = saturated

SFC = supercritical fluid chromatography

SEM = 2-(Trimethylsilyl)ethoxymethyl

SPhos = 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl

TBAF = Tetrabutylammonium fluoride

TBDMS = tert-Butyldimethylsilyl

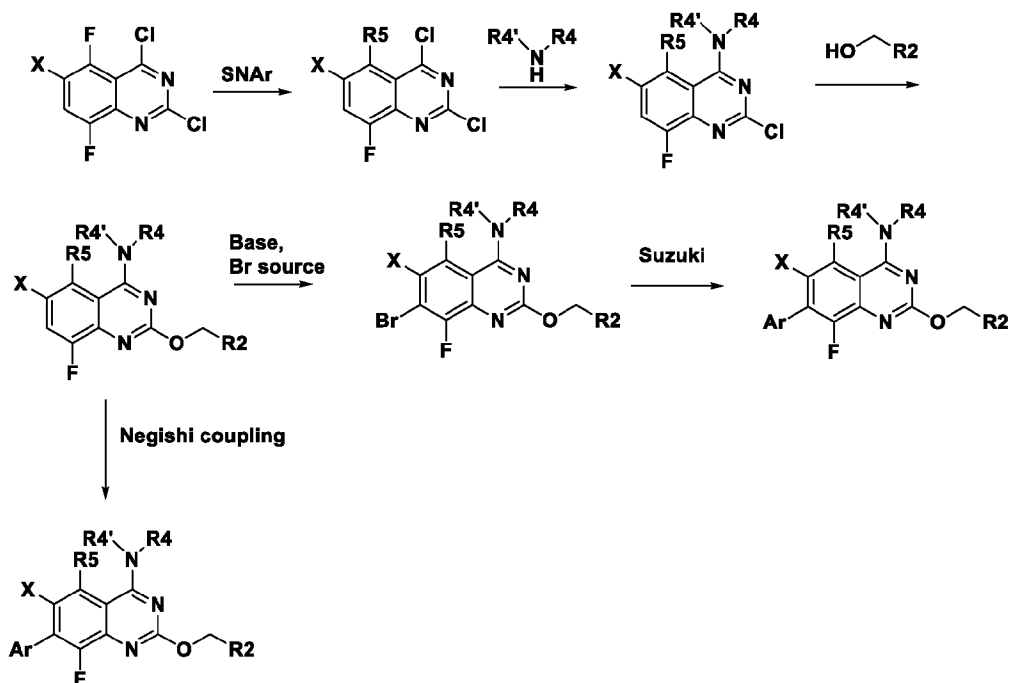
TBDPS = tert-Butyldiphenylsilyl

TBHP = tert-Butylhydroperoxide

TBS = tert-Butyldimethylsilyl
TEA = Triethylamine
TES = Triethylsilyl
Tf = Trifluoromethanesulfonyl
TfO = Trifluoromethanesulfonate
Tf₂O = Trifluoromethanesulfonyl anhydride
TfOH = Trifluoromethanesulfonic acid
TFA = Trifluoroacetic acid
TFAA = Trifluoroacetic anhydride
Thexyl = 2,3-dimethyl-2-butyl
THF = Tetrahydrofuran
THP = Tetrahydropyranyl
TIPS = Triisopropylsilyl
TLC = Thin layer chromatography
TMEDA = N,N,N',N'-Tetramethylethylenediamine
TMG = Tetramethylguanidine
TMS = Trimethylsilyl
Tol = p-Tolyl
TPAP = Tetra-n-propylammonium perruthenate
TPS = Tripropylsilyl
Tr = Trityl, triphenylmethyl
Troc = 2,2,2-Trichloroethoxycarbonyl
Trt = Trityl, triphenylmethyl
Ts = p-Toluenesulphonyl
p-TsOH = p-Toluenesulphonic acid
UV = ultraviolet
XantPhos = 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos = 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
Z = Benzyloxycarbonyl

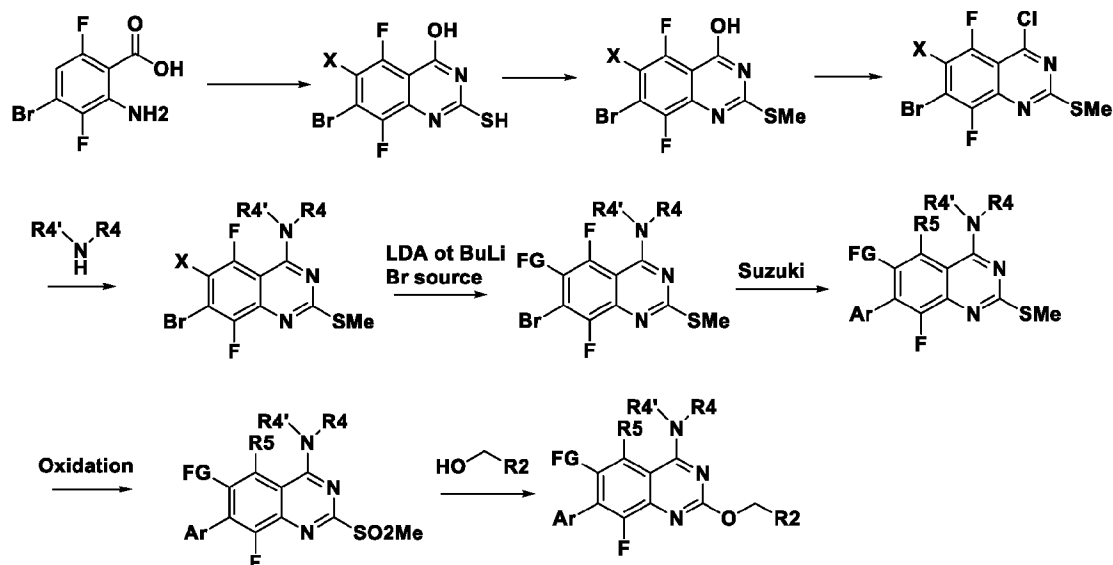
General Synthetic Schemes

Scheme 1:



[00225] Scheme 1 illustrates one procedure for preparing the compounds of disclosure using metal-catalyzed reaction to prepare the substituted quinazoline. Displacement of 4-chloro group of 1,3-disubstituted quinazoline with a protected piperazine or amine provides 2-chloro-4-amine-substituted quinazoline intermediate. Then the second chloro group was displaced with an appropriate alcohol to fetch an ether substituted quinazoline intermediate. This intermediate could be utilized in two different ways to prepare the final target compounds. The first method is to install bromine atom at C7 position after deprotonation with strong base such as BuLi or LDA. Pd-catalyzed Suzuki reaction will be applied to couple a suitable aryl boronic acid or ester followed by the deprotection of all the protecting group to yield the final product. The second method is to apply a zincate to deprotonate C7 to form an aromatic zinc reagent, then couple with an appropriate aryl halide to form C7-aryl substituted quinazolines. Final deprotection yields the desired target compounds.

Scheme 2:

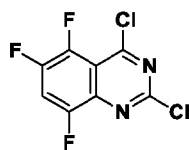


[00226] Scheme 2 illustrates the other procedure for preparing the compounds of disclosure by using C7 brominated amino benzoic acid as starting material. 2-Amino benzoic acid reacts with chlorosulfonyl isocyanate and provides 2-thiol-3-hydroxyl quinazoline. After methylation of thiol, 4-hydroxyl group was transformed to 4-chloride. Displacement of 4-chloro group with a protected piperazine or amine provides 4-amine-2-thiol quinazoline intermediate. Then some functional group transformation can be carried out at C6 and more reactive C5-fluoro was displaced with an appropriate alcohol or other nucleophile. This intermediate was coupled to aryl boronic acid or ester by Pd-catalyzed Suzuki reaction followed by the deprotection of all the protecting group to yield the final target compounds.

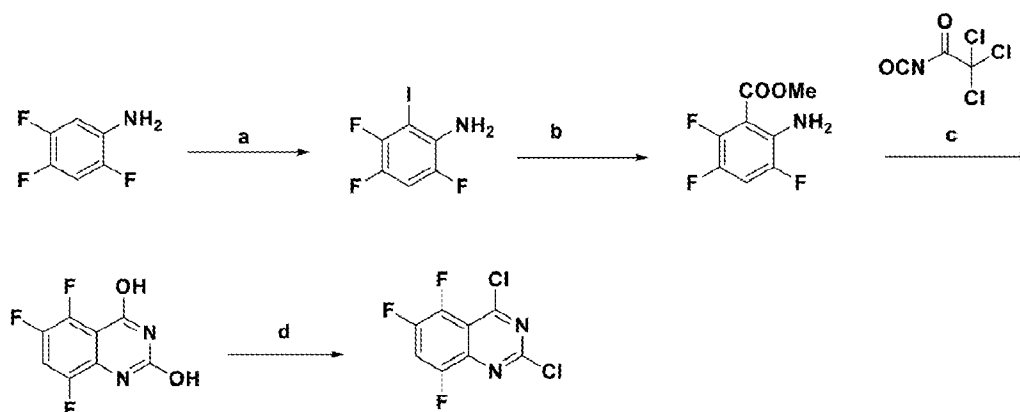
Intermediate Syntheses:

Intermediate 1:

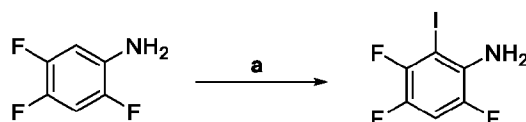
2,4-dichloro-5,6,8-trifluoroquinazoline



Synthetic scheme:

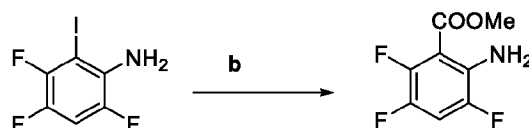


Step 1: Synthesis of 3,4,6-trifluoro-2-iodoaniline



[00227] To a solution of 2,4,5- trifluoroaniline (5.0 g, 34.0 mmol, 1.0 eq) in dioxane (50 mL) was added solution of iodine (4.32 g, 17.00 mmol, 0.5 eq) in dioxane (10 mL), followed by a solution of NaIO₃ (5.98 g, 34.0 mmol, 1.0 eq) in water (10 mL). The mixture was heated at 70 °C for 15 h. The mixture was diluted with water (40 mL) and extracted with DCM (50 mL x 3). The organic layers were washed with saturated Na₂SO₃ solution (50 mL), brine (50 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (petroleum ether: EtOAc = 10: 1) to afford 3,4,6-trifluoro-2-iodoaniline (8.0 g, 86.2%) as a white solid. ¹H NMR (300 MHz, CDCl₃): δ 6.98 (ddd, *J* = 10.5, 9.6, 7.2 Hz, 1H), 4.10 (s, 2H).

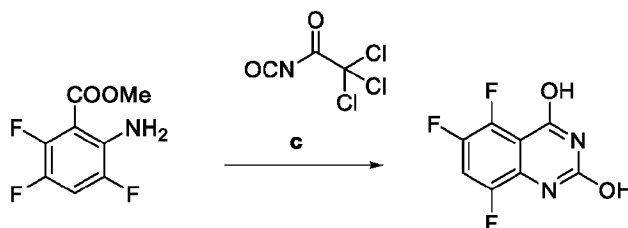
Step 2: Synthesis of methyl 2-amino-3,5,6-trifluorobenzoate



[00228] To a solution of 3,4,6-trifluoro-2-iodoaniline (1.0 g, 3.66 mmol, 1.0 eq) in MeOH (10 mL) was added TEA (1.10 g, 10.99 mmol, 3.0 eq) and Pd(dppf)Cl₂ (268 mg, 0.37 mmol, 0.1 eq). The mixture was stirred at 80 °C for 15 h under 1.5 MPa CO. The mixture was filtered, and the filtrate was concentrated to give a crude product, which was purified by silica gel column chromatography (petroleum ether: EtOAc = 5: 1) to afford methyl 2-amino-3,5,6-trifluorobenzoate (700 mg, 93.2%) as a white solid.

[00229] ^1H NMR (300 MHz, CDCl_3): δ 7.04 (m, 1H), 5.56 (s, 2H), 3.94 (s, 3H). LCMS: m/z 206.1 ($\text{M}+\text{H}^+$).

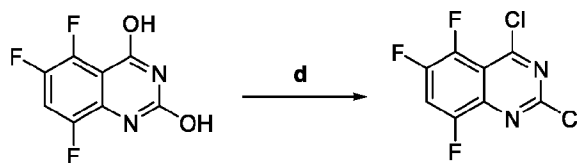
Step 3: Synthesis of 5,6,8-trifluoroquinazoline-2,4-diol



[00230] To a solution of methyl 2-amino-3,5,6-trifluorobenzoate (630 mg, 3.09 mmol, 1.0 eq) in THF (8 mL) was added 2,2,2-trichloroacetyl isocyanate (875 mg, 4.65 mmol, 1.5 eq). The mixture was stirred at room temperature for 10 min. The reaction mixture was concentrated under reduced pressure to give an intermediate.

[00231] To a solution of above intermediate in MeOH (30 mL) was added NH_3 in MeOH (7 M, 1.15 mL, 8.03 mmol, 2.6 eq). The mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to give the crude product, 5,6,8-trifluoroquinazoline-2,4-diol (830 mg) as a white solid. LCMS: m/z 217.1 ($\text{M}+\text{H}^+$).

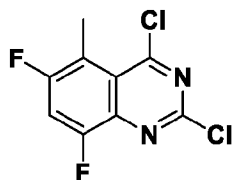
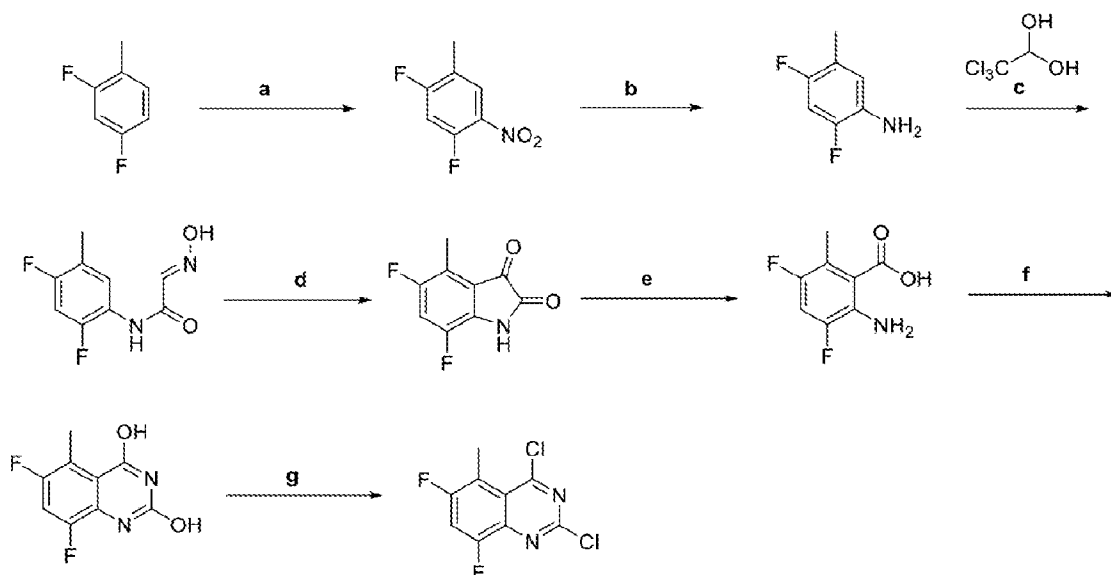
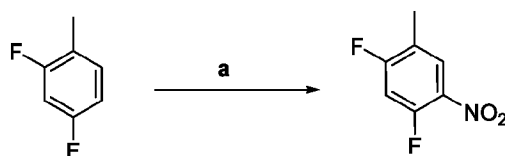
Step 4: Synthesis of 2,4-dichloro-5,6,8-trifluoroquinazoline



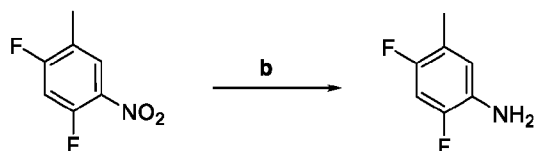
[00232] To a solution of 5,6,8-trifluoroquinazoline-2,4-diol (450 mg, 1.84 mmol, 1.0 eq) in POCl_3 (6.5 g, 42.77 mmol, 23.2 eq) was added DIEA (1.19 g, 9.22 mmol, 5.0 eq). The mixture was stirred at 90°C for 15 h under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (petroleum ether: EtOAc = 20: 1) to afford 2,4-dichloro-5,6,8-trifluoroquinazoline (300 mg, 64.6% for 2 steps) as a white solid. ^1H NMR (300 MHz, CDCl_3): δ 7.69 – 7.61 (m, 1H).

Intermediate 2:

2,4-dichloro-6,8-difluoro-5-methylquinazoline

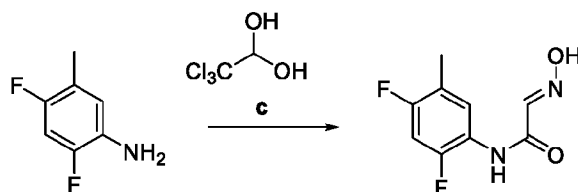
**Synthetic scheme:****Step 1: Synthesis of 1,5-difluoro-2-methyl-4-nitrobenzene**

[00233] 2,4-difluoro-1-methylbenzene (20.0 g, 156.1 mmol, 1.0 eq) was added slowly in portion to H_2SO_4 (120 mL) at room temperature, then cooled down to $-10\text{ }^\circ\text{C}$, HNO_3 (9.84 g, 171.7 mmol, 1.1 eq) was added dropwise. The mixture was stirred at the same temperature for 2 h and poured into ice. The precipitate solid was filtered and dried to give crude 1,5-difluoro-2-methyl-4-nitrobenzene (21.0 g, 77.8%) as a yellow solid, which was used for the next step without further purification. ^1H NMR (400 MHz, CDCl_3): δ 7.99 (t, $J = 8.0$ Hz, 1H), 6.98 (t, $J = 9.2$ Hz, 1H), 2.32 (s, 3H).

Step 2: Synthesis of 2,4-difluoro-5-methylaniline

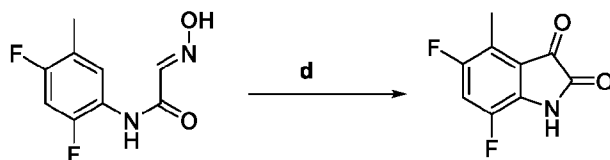
[00234] A mixture of 1,5-difluoro-2-methyl-4-nitrobenzene (5.0 g, 28.9 mmol) and Pd/C (10%, 1.7 g) in MeOH (50 mL) was hydrogenated with a balloon of hydrogen at room temperature for 3 h. HPLC showed the reaction was completed. The mixture was filtered and concentrated to give crude product, 2,4-difluoro-5-methylaniline (3.1 g, 75.6%) as a gray solid, which was used for next step without further purification. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 6.92 (t, $J = 10.0$ Hz, 1H), 6.17 (t, $J = 8.8$ Hz, 1H), 4.87 (brs, 1H), 2.08 (s, 3H). LCMS: m/z 144.1 ($\text{M}+\text{H}^+$).

Step 3: Synthesis of (E)-N-(2,4-difluoro-5-methylphenyl)-2-(hydroxyimino)acetamide

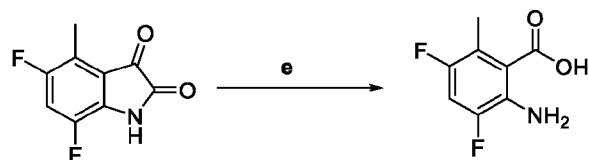


[00235] To a solution of Na_2SO_4 (22.2 g, 156.5 mmol, 8.0 eq) and hydroxylamine hydrochloride (4.8 g, 68.5 mmol, 3.5 eq) in H_2O (84 mL) was added 2,2,2-trichloroethane-1,1-diol (4.9 g, 29.3 mmol, 1.5 eq). The mixture was stirred at room temperature for a few minutes, then added at room temperature a solution prepared by the addition of con. HCl (2.2 mL) to 2,4-difluoro-5-methylaniline (2.8 g, 19.6 mmol, 1.0 eq) in EtOH (8.4 mL) and H_2O (5.6 mL). The reaction was heated to 60 $^\circ\text{C}$ and stirred for overnight. HPLC showed the reaction went to completion. The mixture was cooled to room temperature, filtered and concentrated to give crude product (E)-N-(2,4-difluoro-5-methylphenyl)-2-(hydroxyimino)acetamide (4.0 g, 95.5%) as a gray solid, which was used for next step without any further purification. LCMS: m/z 213.1 ($\text{M}-\text{H}^-$).

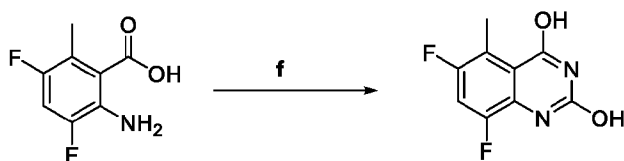
Step 4: Synthesis of 5,7-difluoro-4-methylindoline-2,3-dione



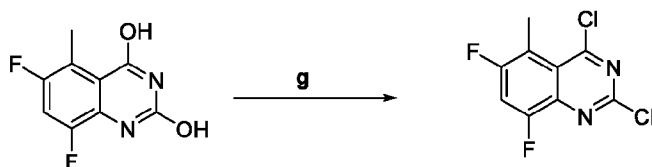
[00236] (E)-N-(2,4-difluoro-5-methylphenyl)-2-(hydroxyimino)acetamide (3.0 g, 15.2 mmol, 1.0 eq) was added to concentrated H_2SO_4 (98%, 30 mL) at 60 $^\circ\text{C}$. The mixture was heated to 90 $^\circ\text{C}$ and stirred for 1 h. After cooled to room temperature, the reaction mixture was added water (300 mL), then the solid was collected by filtration and washed with water to provide 5,7-difluoro-4-methylindoline-2,3-dione (4.2 g, 38.0%) as a red solid. LCMS: m/z 196.1 ($\text{M}-\text{H}^-$).

Step 5: Synthesis of 2-amino-3,5-difluoro-6-methylbenzoic acid

[00237] To a solution of 5,7-difluoro-4-methylindoline-2,3-dione (1.0 g, 5.3 mmol, 1.0 eq) in aqueous NaOH (24.0 mL, 47.9 mmol, 9.0 eq, 2M) was added H₂O₂ (3.2 g, 26.6 mmol, 5.0 eq, 30%). The mixture was stirred at room temperature for 30 min, then quenched by saturated Na₂SO₃ solution. The aqueous layer was extracted with EtOAc (30 mL x 3) to remove neutral impurities. The aqueous phase was acidified with 1M HCl to pH 4 and extracted with EtOAc (30 mL x 3). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated to give crude product 2-amino-3,5-difluoro-6-methylbenzoic acid (600.0 mg, 63.2%) as a brow solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.15 (brs, 1H), 7.26-7.19 (m, 1H), 2.21 (s, 3H). LCMS: *m/z* 188.1 (M+H⁺).

Step 6: Synthesis of 6,8-difluoro-5-methylquinazoline-2,4-diol

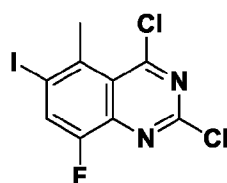
[00238] To a solution of 2-amino-3,5-difluoro-6-methylbenzoic acid (800.0 mg, 4.5 mmol, 1.0 eq) in DCM (16 mL) was added chlorosulfonyl isocyanate (1.4 g, 10.0 mmol, 2.3 eq). The mixture was stirred at room temperature for 4 h. HPLC show the reaction went to completion. The solution was concentrated, then was added 6 N HCl (24 mL). The mixture was stirred at 100 °C overnight, then cooled to room temperature, filtered, and concentrated to give crude product, 6,8-difluoro-5-methylquinazoline-2,4-diol (700.0 mg, 73.5%) as a gray solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.35 (brs, 1H), 11.13 (brs, 1H), 7.68 (t, *J* = 10.2 Hz, 1H), 2.53 (s, 3H). LCMS: *m/z* 213.1 (M+H⁺).

Step 7: Synthesis of 2,4-dichloro-6,8-difluoro-5-methylquinazoline

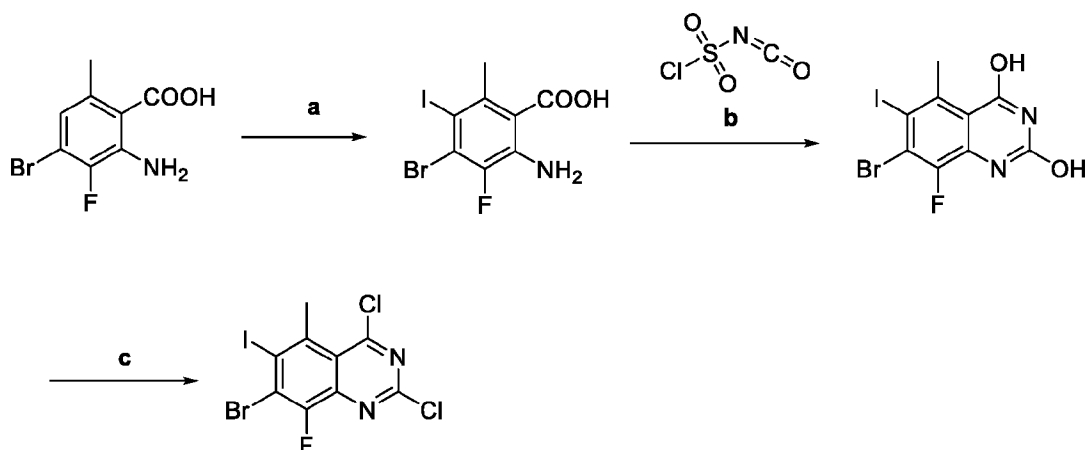
[00239] A solution of 6,8-difluoro-5-methylquinazoline-2,4-diol (456 mg, 2.2 mmol, 1.0 eq) in POCl_3 (4.5 mL) was added DIEA (1.1 g, 8.6 mmol, 4.0 eq) and stirred at 90 °C for 3 h under nitrogen atmosphere. The mixture was concentrated to give the crude product, which was purified by silica gel column chromatography (petroleum ether/EtOAc = 60: 1~10: 1) to provide the desired product, 2,4-dichloro-6,8-difluoro-5-methylquinazoline (190 mg, 35.5%) as a white solid. ^1H NMR (300 MHz, CDCl_3): δ 7.49 (t, J = 9.0 Hz, 1H), 2.90-2.82 (m, 3H).

Intermediate 3:

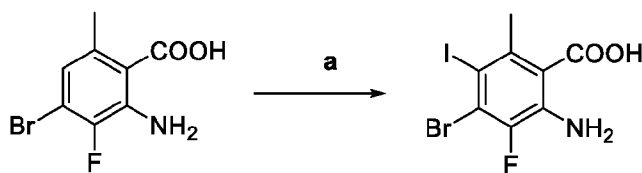
2,4-dichloro-8-fluoro-5-methylquinazoline-6-carbonitrile



Synthetic scheme:



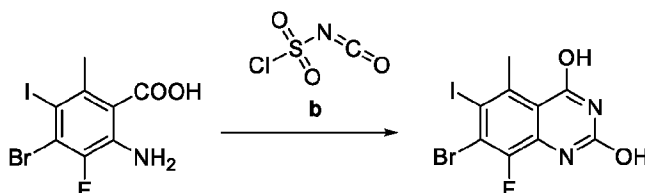
Step 1: Synthesis of 2-amino-4-bromo-3-fluoro-5-iodo-6-methylbenzoic acid



[00240] To a solution of 2-amino-4-bromo-3-fluoro-6-methylbenzoic acid (1.5 g, 6.07 mmol, 1.0 eq) in DCM (15.00 mL) was added NIS (2.04 g, 9.10 mmol, 1.5 eq). The reaction was stirred at room temperature for 15 h, then diluted with DCM (30 mL) and water (10 mL). The aqueous layer was separated and extracted with DCM (20 mL x 3). The combined organic layers were

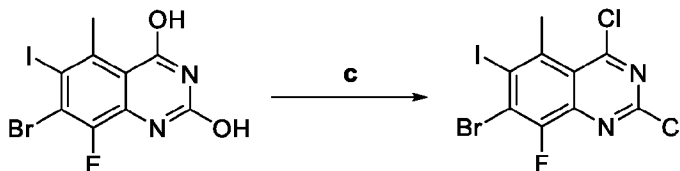
washed with brine (20 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (petroleum ether: EtOAc = 1: 1) to afford the desired product, 2-amino-4-bromo-3-fluoro-5-iodo-6-methylbenzoic acid (1.3 g, 57.5%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 2.74 (s, 3H). LCMS: m/z 373.9, 375.9 (M+H⁺).

Step 2 Synthesis of 7-bromo-8-fluoro-6-iodo-5-methylquinazoline-2,4-diol



[00241] To a solution of 2-amino-4-bromo-3-fluoro-5-iodo-6-methylbenzoic acid (1.3 g, 3.48 mmol, 1.0 eq) in DCM (13 mL) was added chlorosulfonyl isocyanate (1.15 g, 8.16 mmol, 2.3 eq) at 0 °C. The reaction mixture was stirred at room temperature for 15 h, then concentrated. The crude material was dissolved in 6 N HCl (13 mL) and heated at 100 °C for 6 h. The reaction mixture was poured into ice-water and filtered. The filtrate was concentrated to give crude compound 7-bromo-8-fluoro-6-iodo-5-methylquinazoline-2,4-diol (1.0 g) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 1.50 (s, 3H). LCMS: 398.9, 400.8 (M+H⁺).

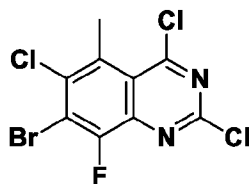
Step 3: Synthesis of 7-bromo-2,4-dichloro-8-fluoro-6-iodo-5-methylquinazoline



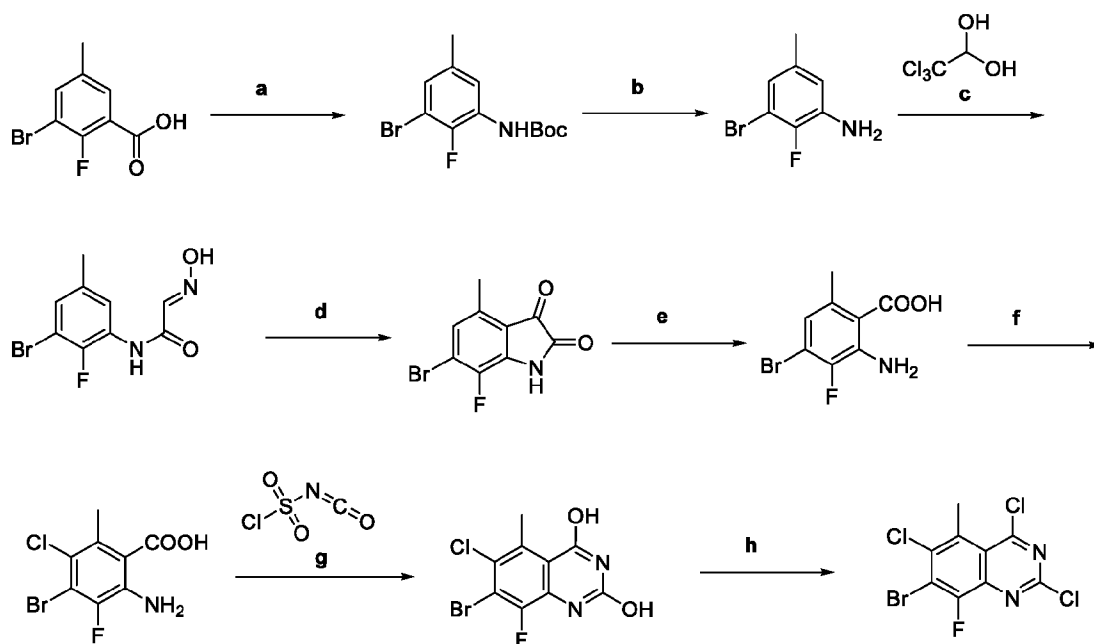
[00242] To a solution of 7-bromo-8-fluoro-6-iodo-5-methylquinazoline-2,4-diol (1.0 g, 2.51 mmol, 1.0 eq) in POCl₃ (5 mL) was added TEA (1.01 g, 10.0 mmol, 4.0 eq). The reaction mixture was stirred at 90 °C for 12 h, then concentrated to give the crude product, which was purified by silica gel column chromatography (petroleum ether: EtOAc = 50: 1~20: 1) to provide the desired product, 7-bromo-2,4-dichloro-8-fluoro-6-iodo-5-methylquinazoline (1.1 g, crude) as a yellow solid.

Intermediate 4:

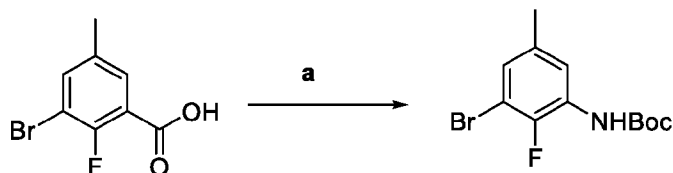
2,4,6-trichloro-8-fluoro-5-methylquinazoline



Synthetic scheme:



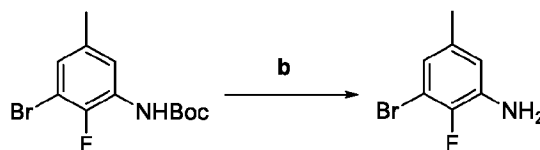
Step 1: Synthesis of tert-butyl (3-bromo-2-fluoro-5-methylphenyl) carbamate



[00243] To a solution of 3-bromo-2-fluoro-5-methylbenzoic acid (4.5 g, 19.3 mmol, 1.0 eq) in toluene and *t*-BuOH (67.5 mL and 34.2 mL) were added DPPA (6.6 g, 24.1 mmol, 1.25 eq) and DIEA (3.0 g, 23.1 mmol, 1.2 eq). The reaction was stirred at 120 °C for 15 h. The mixture was cooled down and diluted EtOAc (40 mL) and water (10 mL). The aqueous layer was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (petroleum ether: EtOAc = 20: 1) to give the desired product, tert-butyl (3-bromo-2-fluoro-5-methylphenyl)carbamate (5.5 g, 94.8%) as a yellow solid. ¹H NMR (400 MHz,

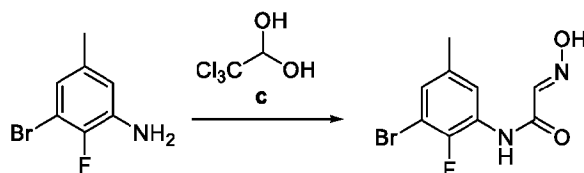
CDCl₃): δ 7.88 (d, J = 7.2 Hz, 1H), 6.98 (dd, J = 6.4, 2.0 Hz, 1H), 6.66 (brs, 1H), 2.29 (s, 3H), 1.52 (s, 9H).

Step 2: Synthesis of 3-bromo-2-fluoro-5-methylaniline



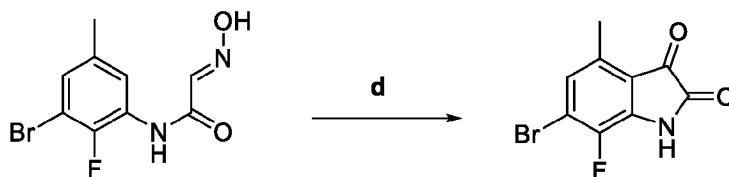
[00244] To a solution of tert-butyl (3-bromo-2-fluoro-5-methylphenyl)carbamate (3.2 g, 10.52 mmol, 1.0 eq) in *i*PrOH (32.00 mL) was added conc. HCl (37%, 8.7 mL). The reaction was stirred at 60 °C for 2 h. The reaction system was concentrated and added H₂O and 1M NaOH to adjust the pH to 7-8. The mixture was added with EtOAc (30 mL) and water (10 mL). The aqueous layer was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (Petroleum ether: EtOAc = 5: 1) to give the desired product, 3-bromo-2-fluoro-5-methylaniline (1.76 g, 83.7%) as a white solid. ¹H NMR (300 MHz, CDCl₃): δ 6.69 (dd, J = 5.7, 0.9 Hz, 1H), 6.49 (dd, J = 7.5, 0.9 Hz, 1H), 3.64 (brs, 2H), 2.20 (s, 3H). LCMS: 204.0, 206.0 (M+H⁺).

Step 3: Synthesis of (E)-N-(3-bromo-2-fluoro-5-methylphenyl)-2-(hydroxyimino)acetamide



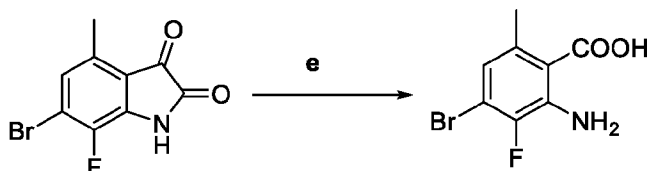
[00245] To a solution of 3-bromo-2-fluoro-5-methylaniline (6.08 g, 36.9 mmol, 1.5 eq) in H₂O (124.0 mL) was added NH₂OH·HCl (6.0 g, 86.1 mmol, 3.5 eq) and Na₂SO₄ (27.9 g, 196.8 mmol, 8.0 eq), followed by the addition of a solution of compound 2,2,2-trichloroethane-1,1-diol (5.0 g, 24.6 mmol, 1.0 eq) in EtOH (17.45 mL) and conc. HCl (4.1 mL). The reaction was stirred at 60 °C for 15 h and concentrated to give the crude product, (E)-N-(3-bromo-2-fluoro-5-methylphenyl)-2-(hydroxyimino)acetamide (6.4 g, crude) as a yellow solid, which was used without further purification.

Step 4: Synthesis of 6-bromo-7-fluoro-4-methylindoline-2,3-dione



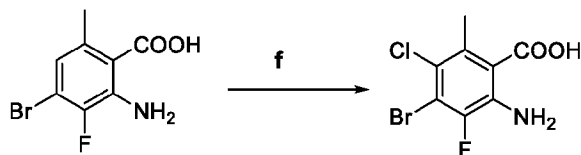
[00246] (E)-N-(3-bromo-2-fluoro-5-methylphenyl)-2-(hydroxyimino)acetamide (6.4 g, 23.2 mmol, 1.0 eq) was added to concentrated H₂SO₄ (98%, 12.0 mL) in portion and stirred 90 °C for 1 h. The reaction mixture was poured into the ice water (20 mL). The precipitate formed was collected by filtration, washed with water (40 mL), dried in vacuo to give crude product, 6-bromo-7-fluoro-4-methylindoline-2,3-dione (5.4 g, crude) as a yellow solid, which was used without further purification. ¹H NMR (400 MHz, CDCl₃): δ 7.97 (brs, 1H), 7.12 (d, *J* = 5.6 Hz, 1H), 2.53 (s, 3H). LCMS: *m/z* 256.0, 258.0 (M-H⁺).

Step 5: Synthesis of 2-amino-4-bromo-3-fluoro-6-methylbenzoic acid



[00247] To a solution of 6-bromo-7-fluoro-4-methylindoline-2,3-dione (5.4 g, 21.0 mmol, 1.0 eq) in aq. NaOH (86 mL) was added H₂O₂ (5 mL), the reaction mixture was stirred at 30°C for 3 h. The mixture was added with EtOAc (50 mL) and water (20 mL). The aqueous layer was separated and adjusted the pH to 3 by 1N HCl. The precipitate formed was collected by filtration, washed with water (30 mL), dried in vacuo to give crude product, 2-amino-4-bromo-3-fluoro-6-methylbenzoic acid (3.1 g, crude) as a yellow solid. LCMS: *m/z* 248.0, 250.0 (M+H⁺).

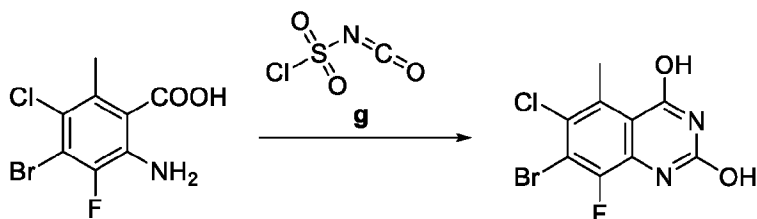
Step 6: Synthesis of 2-amino-4-bromo-5-chloro-3-fluoro-6-methylbenzoic acid



[00248] To a solution of 2-amino-4-bromo-3-fluoro-6-methylbenzoic acid (1.0 g, 4.04 mmol, 1.0 eq) in con. H₂SO₄ (10.00 mL) was added NCS (1.8 g, 14.1 mmol, 3.5 eq). The reaction mixture was stirred at 80 °C for 15 h and poured into the ice water (10 mL). The precipitate

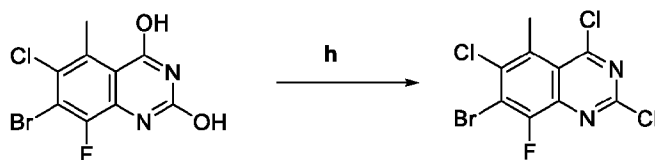
formed was collected by filtration, washed with water (10 mL), dried in vacuo to give crude product, 2-amino-4-bromo-5-chloro-3-fluoro-6-methylbenzoic acid (1.2 g, crude) as a yellow solid, which was used directly. LCMS: m/z 562.9, 566.9 ($2M+H^+$).

Step 7: Synthesis of 7-bromo-6-chloro-8-fluoro-5-methylquinazoline-2,4-diol



[00249] To a solution of 2-amino-4-bromo-5-chloro-3-fluoro-6-methylbenzoic acid (550 mg, 1.95 mmol, 1.0 eq) in DCM (6 mL) was added chlorosulfonyl isocyanate (670 mg, 4.70 mmol, 2.43 eq) at 0 °C. The reaction was stirred at room temperature for 15 h. The mixture was concentrated. The resulting residue was dissolved in 6N HCl (5 mL). The reaction mixture was stirred at 100 °C for 6 h, then poured into the ice water (10 mL). The precipitate formed was collected by filtration, washed with water, dried in vacuo to give crude product, 7-bromo-6-chloro-8-fluoro-5-methylquinazoline-2,4-diol (220 mg, crude) as a yellow solid. LCMS: m/z 306.9, 308.9 ($M+H^+$).

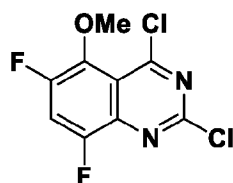
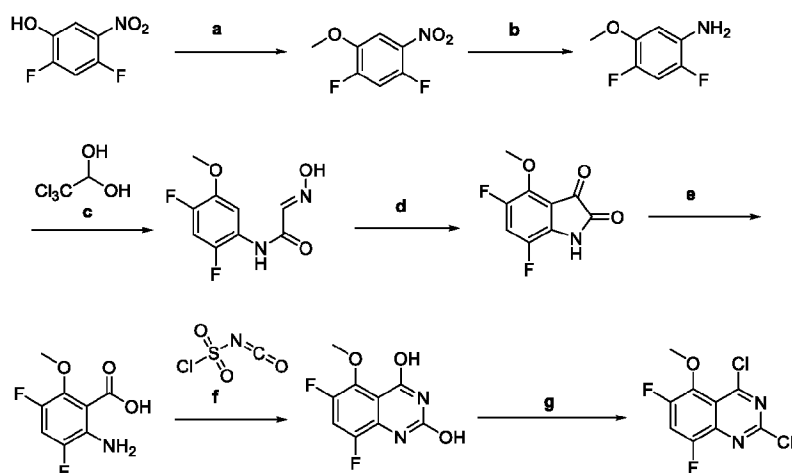
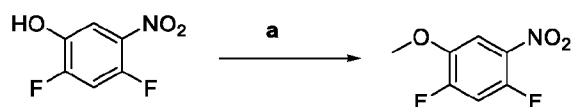
Step 8: Synthesis of 7-bromo-2,4,6-trichloro-8-fluoro-5-methylquinazoline



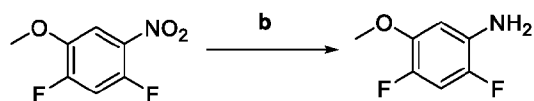
[00250] To a solution of 7-bromo-6-chloro-8-fluoro-5-methylquinazoline-2,4-diol (800 mg, 2.61 mmol, 1.0 eq) in $POCl_3$ (5 mL) was added DIEA (1.34 g, 10.45 mmol, 4.0 eq). The reaction was stirred at 90 °C for 12 h. The mixture was concentrated to give the crude product. The crude product was purified by silica gel column chromatography (Petroleum ether: EtOAc = 20: 1~5: 1) to give the crude product, 7-bromo-2,4,6-trichloro-8-fluoro-5-methylquinazoline (400 mg, 44.7%, six step yield) as a yellow solid, which was used without further purification.

Intermediate 5:

2,4-dichloro-6,8-difluoro-5-methoxyquinazoline

**Synthetic scheme:****Step 1: Synthesis of 1,5-difluoro-2-methoxy-4-nitrobenzene**

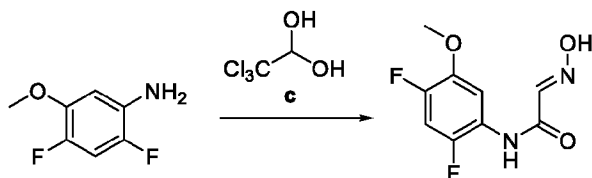
[00251] To a solution of 2,4-difluoro-5-nitrophenol (10.0g, 57.1 mmol, 1.0 eq) in DMF (150 mL) cooled at 0 °C was added NaH (4.6 g, 115.0 mmol, 2.0 eq) and stirred at 0 °C for 30 min. To the reaction was added MeI (12.2 g, 86.0 mmol, 1.5 eq) dropwise. The mixture was stirred at room temperature for 3.5 h and poured into ice water (450 mL). The aqueous layer was extracted with EtOAc (150 mL x 3). The combined organic layers were washed with H₂O (150 mL), brine (150 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (petroleum ether / EtOAc = 7 / 3) to give the desired product, 1,5-difluoro-2-methoxy-4-nitrobenzene (10.5 g, 97.2 %) as a yellow solid. ¹H NMR (300 MHz, CDCl₃) δ 7.70 (t, *J* = 5.4 Hz, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 3.96 (s, 3H).

Step 2: Synthesis of 2,4-difluoro-5-methoxyaniline

[00252] To a solution of 1,5-difluoro-2-methoxy-4-nitrobenzene (5.0 g, 5.3 mmol, 1.0 eq) in EtOH (50 mL) was added Pd/C (1.0 g, 20% w/w) at room temperature. The reaction was stirred

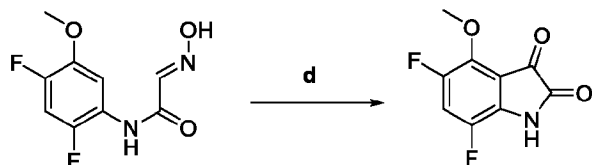
at 50 °C for 5 h under H₂ atmosphere. The mixture was filtered, and the filtrate was concentrated to give crude product, which was purified by silica gel column chromatography (petroleum ether / EtOAc = 10 / 1) to afford the desired product, 2,4-difluoro-5-methoxyaniline (3.0 g, 71.4 %) as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 6.81 (t, *J* = 10.5 Hz, 1H), 6.41 (t, *J* = 8.4 Hz, 1H), 3.82 (s, 3H), 3.56 (brs, 2H). LCMS: *m/z* 160.1 (M+H⁺).

Step 3: Synthesis of (E)-N-(2,4-difluoro-5-methoxyphenyl)-2-(hydroxyimino)acetamide



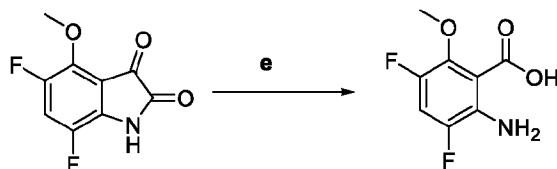
[00253] To a mixture of Na₂SO₄ (19.2 g, 135.7 mmol, 8.0 eq), NH₂OH-HCl (4.1 g, 59.4 mmol, 3.5 eq), and 2,2,2-trichloroethane-1,1-diol (4.2 g, 25.4 mmol, 1.5 eq) in H₂O (81.0 mL) was added 2,4-difluoro-5-methoxyaniline (2.7 g, 17.0 mmol, 1.0 eq) in EtOH (8.1 mL), H₂O (5.4 mL) and conc. HCl (1.9 mL). The mixture was stirred at 60 °C for 15 h. The precipitate formed was collected by filtration, and washed with H₂O, dried in vacuo to get crude product (E)-N-(2,4-difluoro-5-methoxyphenyl)-2-(hydroxyimino)acetamide (2.0 g, 51.3 %) as a brown solid, which was used directly without further purification. LCMS: *m/z* 231.1 (M+H⁺).

Step 4: Synthesis of 5,7-difluoro-4-methoxyindoline-2,3-dione



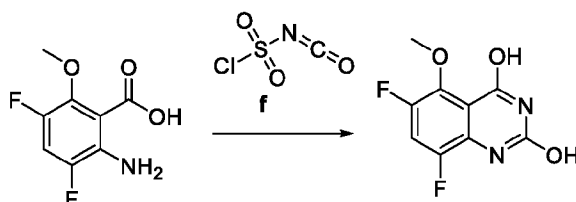
[00254] (E)-N-(2,4-difluoro-5-methoxyphenyl)-2-(hydroxyimino) acetamide (2.0 g, 8.7 mmol, 1.0 eq) was added to con.H₂SO₄ (20 mL) at 60 °C. The mixture was stirred at 90 °C for 2 h and poured into ice water (100 mL). The precipitate formed was collected by filtration and washed with H₂O. The collected solid was dried in vacuo to give the crude product, 5,7-difluoro-4-methoxyindoline-2,3-dione (1.5 g, 81.1 %) as a white solid, which was used without further purification. LCMS: *m/z* 214.1 (M+H⁺).

Step 5: Synthesis of 2-amino-3,5-difluoro-6-methoxybenzoic acid



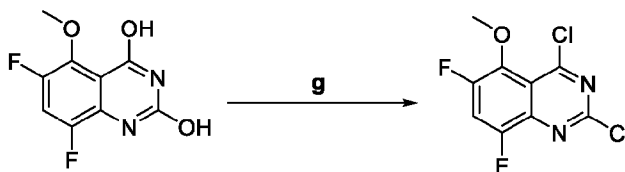
[00255] To a solution of 5,7-difluoro-4-methoxyindoline-2,3-dione (1.7 g, 8.0 mmol, 1.0 eq) in 2N aqueous NaOH (31.9 mL, 63.8 mmol, 8.0 eq) was added 30 % aqueous H₂O₂ (4.5 g, 39.9 mmol, 5.0 eq). The mixture was stirred at room temperature for 15 h. The reaction was quenched with Na₂SO₃, and adjusted pH ~ 2 with con. HCl. The precipitate formed was collected by filtration, and washed with H₂O, dried in vacuo to get crude product, 2-amino-3,5-difluoro-6-methoxybenzoic acid (1.0 g, 61.7 %) as a brown solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.36 (t, *J* = 11.1 Hz, 1H), 3.77 (s, 3H). LCMS: *m/z* 204.1 (M+H⁺).

Step 6: Synthesis of 6,8-difluoro-5-methoxyquinazoline-2,4-diol



[00256] To a solution of 2-amino-3,5-difluoro-6-methoxybenzoic acid (500 mg, 2.5 mmol, 1.0 eq) in DCM (5 mL) was added chlorosulfonyl isocyanate (801 mg, 5.7 mmol, 2.3 eq) at 0 °C under nitrogen atmosphere. The reaction was stirred at room temperature overnight. The mixture was concentrated to give a residue. The residue was resolved in 6N HCl aqueous (15 mL) and stirred at 100 °C overnight. The precipitate formed was collected by filtration, and washed with H₂O, dried in vacuo to get crude product, 6,8-difluoro-5-methoxyquinazoline-2,4-diol (300 mg, 53.4 %) as a brown solid. LCMS: *m/z* 229.1 (M+H⁺).

Step 7: Synthesis of 2,4-dichloro-6,8-difluoro-5-methoxyquinazoline

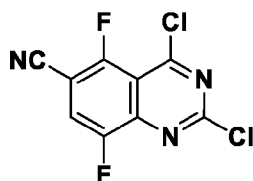


[00257] A solution of 2,4-dichloro-6,8-difluoro-5-methoxyquinazoline (500 mg, 2.2 mmol, 1.0 eq) and DIEA (1.4 g, 11.0 mmol, 5.0 eq) in POCl₃ (5 mL) was stirred at 90 °C for 3 h under nitrogen atmosphere. The mixture was concentrated to give the crude product. The crude product was purified by silica gel column chromatography (DCM/MeOH 60:1~10:1) to give the desired

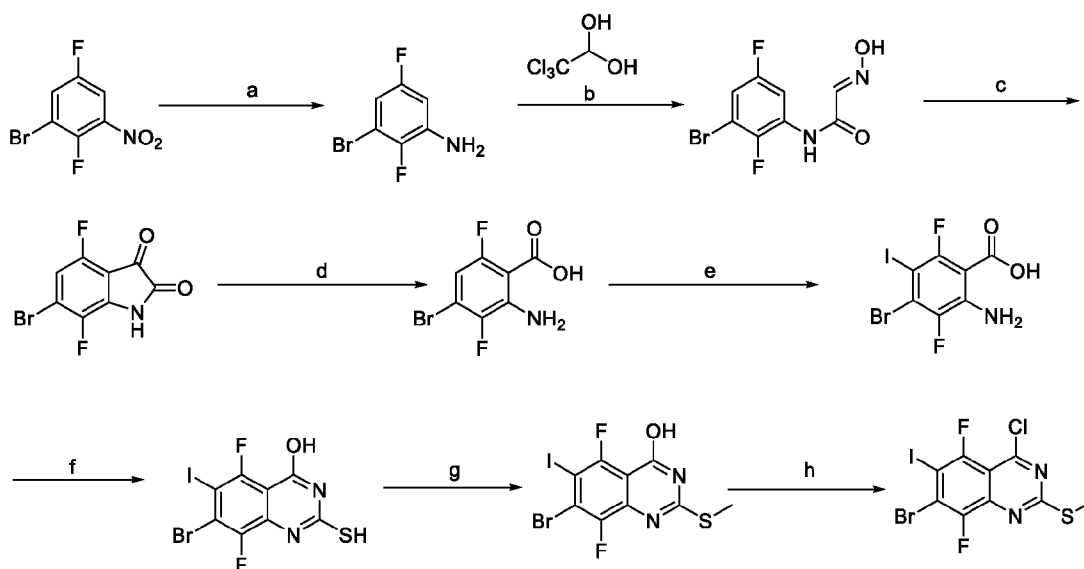
product, 2,4-dichloro-6,8-difluoro-5-methoxyquinazoline (340 mg, 58.5 %) as a white solid. ^1H NMR (300 MHz, CDCl_3) δ 7.61-7.54 (m, 1H), 4.08 (d, $J = 1.5$ Hz, 1H).

Intermediate 6:

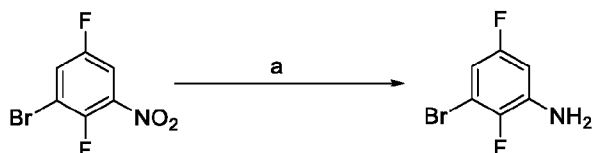
2,4-dichloro-5,8-difluoroquinazoline-6-carbonitrile



Synthetic scheme:



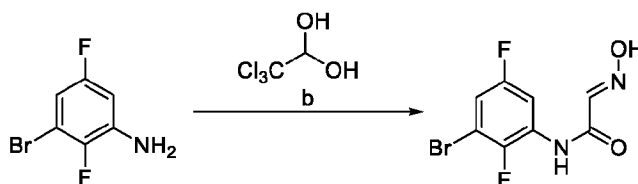
Step 1: Synthesis of 3-bromo-2,5-difluoroaniline



[00258] To a solution of 1-bromo-2,5-difluoro-3-nitrobenzene (100 g, 0.42 mol, 1.0 eq) in EtOH (900 mL) was added Fe powder (70.8 g, 1.26 mol, 3.0 eq) and a solution of NH_4Cl (112.4 g, 2.11 mol, 5.0 eq) in water (180 mL). The resulting mixture was stirred at 80 °C for 2 h. The resulting mixture was filtered. The filter cake was washed with EtOAc (500 mL). The combined filtrate was concentrated under reduced pressure to give a residue. The residue was diluted with water (300 mL) and extracted with EtOAc (400 mL x 3). The organic phase was washed with

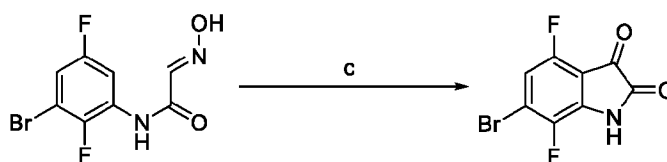
brine (300 mL), dried with Na₂SO₄, filtered and concentrated to give the crude product. The crude product was purified by silica gel column chromatography (petroleum ether: EtOAc = 50:1) to give 3-bromo-2,5-difluoroaniline (68 g, 77.8%) as a yellow oil. ¹H NMR (300 MHz, CDCl₃): δ 6.64 – 6.58 (m, 1H), 6.47 – 6.39 (m, 1H). LCMS: m/z 207.9 (M+H⁺).

Step 2: Synthesis of (E)-N-(3-bromo-2,5-difluorophenyl)-2-(hydroxyimino)acetamide



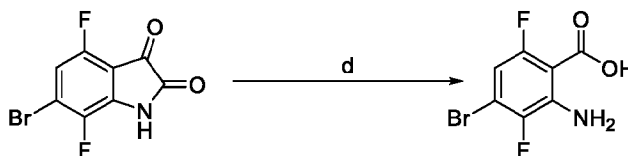
[00259] To a solution of Na₂SO₄ (373.0 g, 2.62 mol, 8.0 eq), Hydroxylamine hydrochloride (79.9 g, 1.15 mol, 3.5 eq) and 2,2,2-trichloroethane-1,1-diol (81.3 g, 0.49 mol, 1.5 eq) in H₂O (1500 mL) was added 3-bromo-2,5-difluoroaniline (68.0 g, 0.32 mol, 1.0 eq) in EtOH (250 mL), H₂O (200 mL) and conc. HCl (50 mL). The reaction mixture was stirred at 60 °C for 15 h. The precipitate formed was collected by filtration, washed with water, dried in vacuo to give (E)-N-(3-bromo-2,5-difluorophenyl)-2-(hydroxyimino) acetamide (95.0 g, crude) as a yellow solid. LCMS: 279.0 (M+H⁺).

Step 3: Synthesis of 6-bromo-4,7-difluoroindoline-2,3-dione



[00260] A solution of (E)-N-(3-bromo-2,5-difluorophenyl)-2-(hydroxyimino) acetamide (95.0 g, crude) in con. H₂SO₄ (500 mL) was stirred at 90 °C for 1 h under nitrogen atmosphere. The reaction mixture was poured into ice water (800 mL). The precipitate formed was collected by filtration, washed with water (200 mL), dried in vacuo to give 6-bromo-4,7-difluoroindoline-2,3-dione (54.9 g, crude) as a black solid. LCMS: m/z 261.9 (M+H⁺).

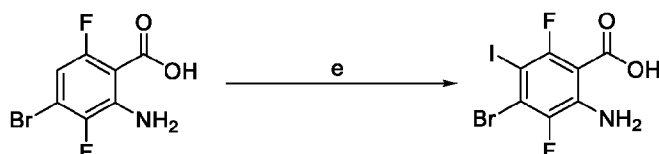
Step 4: Synthesis of 2-amino-4-bromo-3,6-difluorobenzoic acid



[00261] To a solution of 6-bromo-4,7-difluoroindoline-2,3-dione (54.9 g, crude) in 2M NaOH (500 mL) was added 30% H₂O₂ (80 mL). The reaction mixture was stirred at room temperature

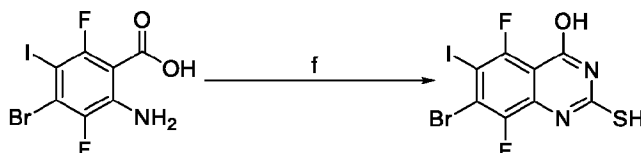
for 15 h. The aqueous layer was extracted with EtOAc (200 mL x 2) to remove neutral impurities. The aqueous phase was acidified with 2 N HCl. The precipitate formed was collected by filtration, washed with water (200 mL), dried in vacuo to give 2-amino-4-bromo-3,6-difluorobenzoic acid (37.6 g, crude) as a yellow solid. LCMS: m/z 251.9 ($M+H^+$).

Step 5: Synthesis of 2-amino-4-bromo-3,6-difluoro-5-iodobenzoic acid



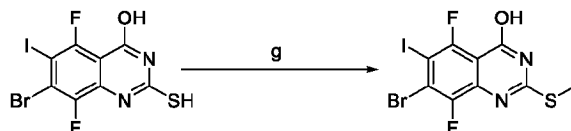
[00262] To a solution of 2-amino-4-bromo-3,6-difluorobenzoic acid (13.4 g, 53.38 mmol, 1.0 eq) in DCM (120 mL) and DMF (40 mL) was added NIS (24.0 g, 106.77 mmol, 2.0 eq). Then the reaction mixture was stirred at room temperature for 4 h under nitrogen atmosphere. The mixture was diluted with water (80 mL) and extracted with EtOAc (100 mL x 3). The organic phase was washed with brine (80 mL), dried with Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by silica gel column chromatography (petroleum ether: EtOAc = 5: 1) to give 2-amino-4-bromo-3,6-difluoro-5-iodobenzoic acid (9.6 g, 47.7%) as a yellow solid. LCMS: m/z 377.9 ($M+H^+$).

Step 6: Synthesis of 7-bromo-5,8-difluoro-6-iodo-2-mercaptoquinazolin-4-ol



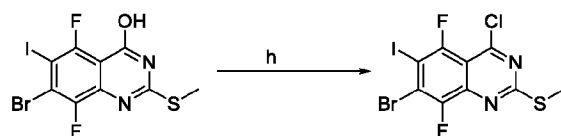
[00263] A solution of 2-amino-4-bromo-3,6-difluoro-5-iodobenzoic acid (6.0 g, 15.9 mmol, 1.0 eq) in $SOCl_2$ (40 mL) was stirred at 50°C for 2 h. The mixture was concentrated and dissolved in Acetone (100 mL), which was added into a solution of Ammonium thiocyanate (1.33 g, 17.5 mmol, 1.1 eq) in Acetone (100 mL) dropwise. The reaction mixture was stirred at room temperature for 1h. The precipitate formed was collected by filtration, dried in vacuo to give 7-bromo-5,8-difluoro-6-iodo-2-mercaptoquinazolin-4-ol (5.5 g, crude) as a yellow solid. LCMS: m/z 418.8 ($M+H^+$).

Step 7: Synthesis of 7-bromo-5,8-difluoro-6-iodo-2-(methylthio)quinazolin-4-ol



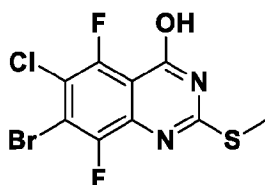
[00264] To a solution of 7-bromo-5,8-difluoro-6-iodo-2-mercaptoquinazolin-4-ol (5.5 g, 13.15 mmol, 1.0 eq) in 1% NaOH (80 mL) was added MeI (1.87 g, 13.15 mmol, 1.0 eq) in MeOH (60 mL). The reaction mixture was stirred at room temperature for 1 h. The aqueous phase was acidified with 2 N HCl. The precipitate formed was collected by filtration, dried in vacuo to give 7-bromo-5,8-difluoro-6-iodo-2-(methylthio)quinazolin-4-ol (5.0 g, crude) as a yellow solid. LCMS: m/z 432.8 ($M+H^+$).

Step 8: Synthesis of 7-bromo-4-chloro-5,8-difluoro-6-iodo-2-(methylthio)quinazoline

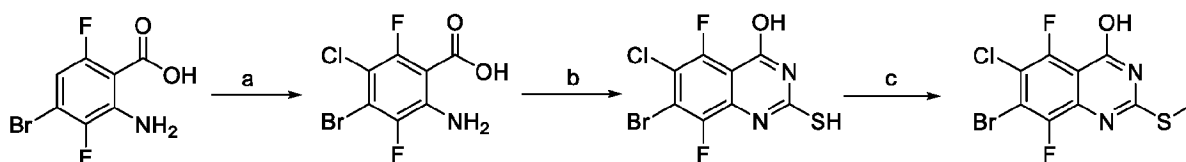


[00265] To a solution of 7-bromo-5,8-difluoro-6-iodo-2-(methylthio)quinazolin-4-ol (2.0 g, 4.62 mmol, 1.0 eq) in $POCl_3$ (15 mL) was added DIEA (1.5 g, 11.54 mmol, 2.5 eq). Then the reaction mixture was stirred at 90 °C for 15 h under nitrogen atmosphere. The mixture was concentrated and purified by silica gel chromatography (eluted with PE: EtOAc = 100:1) to give 7-bromo-4-chloro-5,8-difluoro-6-iodo-2-(methylthio)quinazoline (1.4 g, 67.3%) as a yellow solid. LCMS: m/z no MS signal.

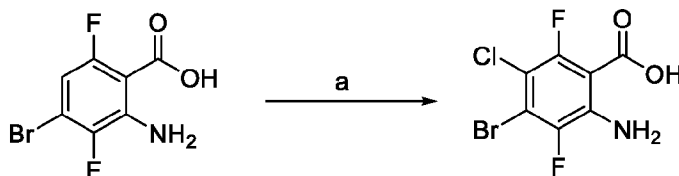
Intermediate 7



Synthetic scheme:

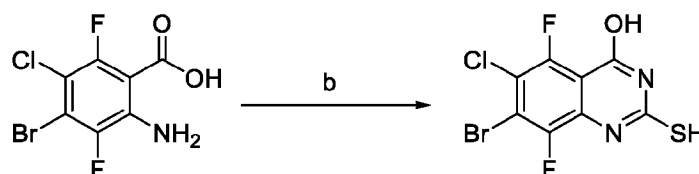


Step 1: Synthesis of 2-amino-4-bromo-5-chloro-3,6-difluorobenzoic acid



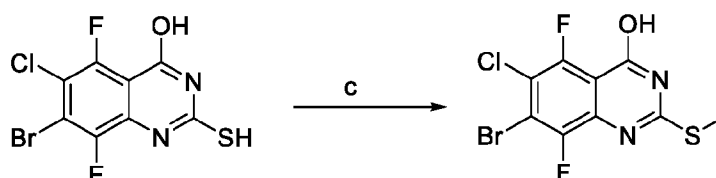
[00266] To a solution of 2-amino-4-bromo-3,6-difluorobenzoic acid (5.0 g, 34.01 mmol, 1.0 eq) in con. H_2SO_4 (30 mL) was added NCS (3.18 g, 23.81 mmol, 1.2 eq) in portion. The mixture was stirred at 80 °C for 15 h. The reaction mixture was poured into ice water (90 mL). The precipitate formed was collected by filtration, washed with ice water (30 mL), dried in vacuo to give 2-amino-4-bromo-5-chloro-3,6-difluorobenzoic acid (4.0 g, crude) as a brown solid. LCMS: m/z 283.9 ($\text{M}-\text{H}^-$).

Step 2: Synthesis of 7-bromo-6-chloro-5,8-difluoro-2-mercaptoquinazolin-4-ol



[00267] A mixture of 2-amino-4-bromo-5-chloro-3,6-difluorobenzoic acid (3.8 g, 13.27 mmol, 1.0 eq) in SOCl_2 (40 mL) was stirred at 50 °C for 3 h. The mixture was concentrated and dissolved in Acetone (50 mL), which was added into a solution of Ammonium thiocyanate (1.11 g, 14.59 mmol, 1.1 eq) in Acetone (50 mL) dropwise. Then the reaction mixture was stirred at room temperature for 1 h. The precipitate formed was collected by filtration, dried in vacuo to give 7-bromo-6-chloro-5,8-difluoro-2-mercaptoquinazolin-4-ol (2.5 g, 38.5% for 2 steps) as a white solid. LCMS: m/z 326.9 ($\text{M}+\text{H}^+$).

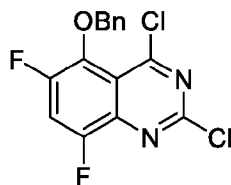
Step 3: Synthesis of 7-bromo-6-chloro-5,8-difluoro-2-(methylthio)quinazolin-4-ol



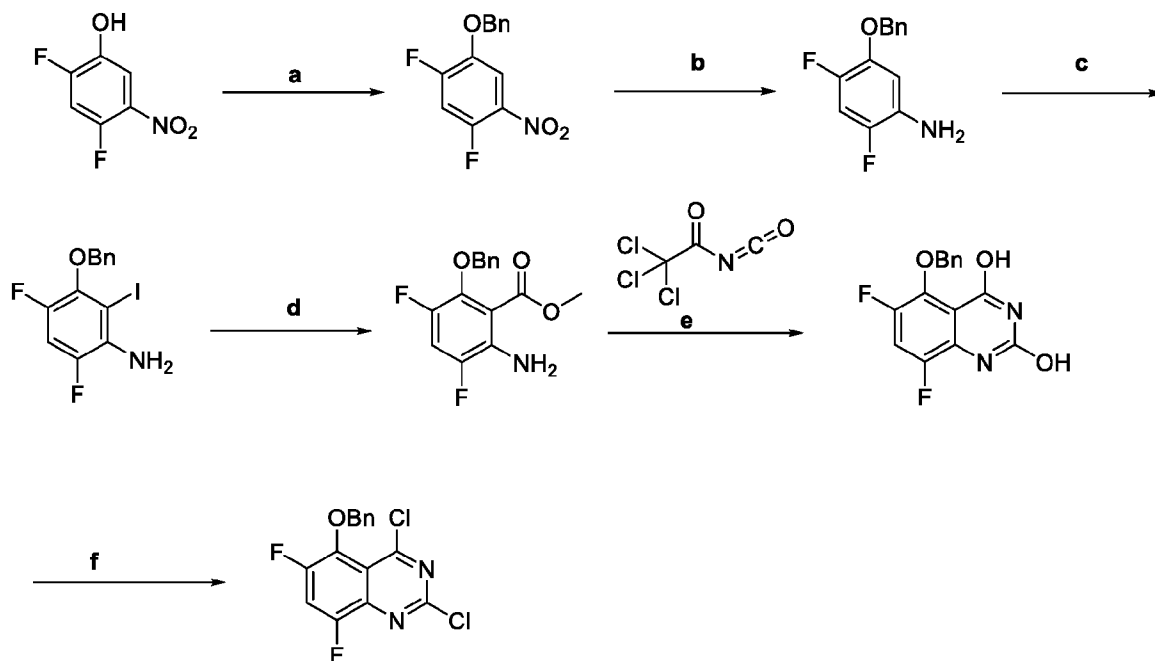
[00268] To a solution of 7-bromo-6-chloro-5,8-difluoro-2-mercaptoquinazolin-4-ol (3.8 g, 11.60 mmol, 1.0 eq) in aq. NaOH (17.4 mL, 17.40 mmol, 1.5 eq, 1M) was added MeI (1.8 g, 12.76 mmol, 1.0 eq) in MeOH (17 mL). Then the reaction mixture was stirred at room temperature for 1 h. The mixture was concentrated to remove MeOH and extracted with EtOAc (50 mL x 2). The organic layers were washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give residue. The residue was purified by silica gel column chromatography (petroleum ether / EtOAc = 2 / 1) to give 7-bromo-6-chloro-5,8-difluoro-2-(methylthio)quinazolin-4-ol (1.7 g, 65.2%) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 3.59 (s, 1H). LCMS: m/z 340.8 ($\text{M}+\text{H}^+$).

Intermediate 8

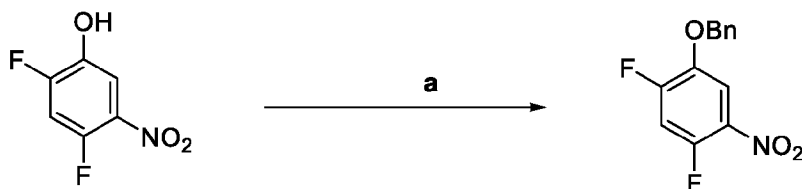
5-(Benzyloxy)-2,4-dichloro-6,8-difluoroquinazoline



Synthetic scheme:



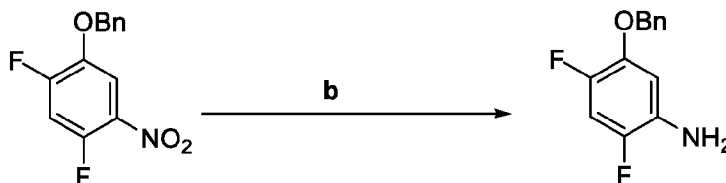
Step 1: Synthesis of 1-(benzyloxy)-2,4-difluoro-5-nitrobenzene



[00269] To a solution of compound 2,4-difluoro-5-nitrophenol (24.3 g, 138.9 mmol, 1.0 eq) and (bromomethyl)benzene (26.1 g, 152.7 mmol, 1.1 eq) in DMF (250 mL) was added K_2CO_3 (57.5 g, 416.4 mmol, 3.0 eq). Then the reaction mixture was stirred at 50 °C for 15 h. The mixture was poured into ice water (1 L). The precipitate formed was collected by filtration, washed with water, dried in vacuo to get compound 1-(benzyloxy)-2,4-difluoro-5-nitrobenzene

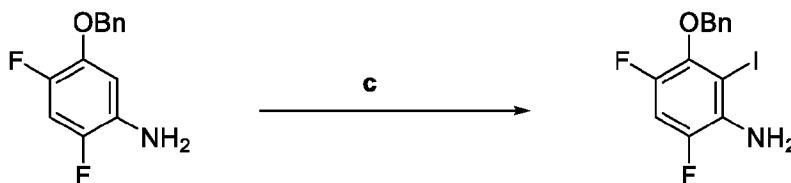
(36.0 g, 97.8%) as a yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 7.76 (t, $J = 7.6$ Hz, 1H), 7.48 – 7.35 (m, 5H), 7.07 (t, $J = 10.0$ Hz, 1H), 5.18 (s, 2H).

Step 2: Synthesis of 5-(benzyloxy)-2,4-difluoroaniline



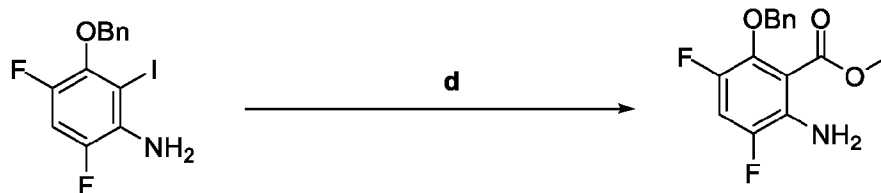
[00270] To a mixture of Fe (6.3 g, 113.1 mmol, 3.0 eq) and NH_4Cl (6.1 g, 113.1 mmol, 3.0 eq) in EtOH (75 mL) and H_2O (25 mL) was added compound 1-(benzyloxy)-2,4-difluoro-5-nitrobenzene (10.0 g, 37.7 mmol, 1.0 eq) in THF (50 mL) at 70 °C. The mixture was stirred at 80 °C for 5 h. The mixture was filtered through a Celite pad, and the filtrate was extracted with EtOAc (150 mL $\times$ 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated to give a crude. The crude was purified by silica gel column chromatography (Petroleum ether/ EtOAc 5/1) to give 5-(benzyloxy)-2,4-difluoroaniline (6.0 g, 64.7%) as a yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 7.44 – 7.30 (m, 5H), 6.82 (t, $J = 10.8$ Hz, 1H), 6.45 (t, $J = 8.4$ Hz, 1H), 5.06 (s, 2H), 3.11 (brs, 2H). LCMS: m/z 236.1 ($\text{M}+\text{H}^+$).

Step 3: Synthesis of 3-(benzyloxy)-4,6-difluoro-2-iodoaniline



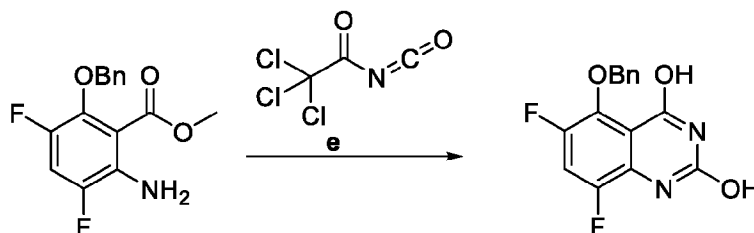
[00271] To a solution of 5-(benzyloxy)-2,4-difluoroaniline (5.0 g, 21.3 mmol, 1.0 eq) in AcOH (50 mL) was added NIS (5.0 g, 22.3 mmol, 1.1 eq). The mixture was stirred at room temperature for 3 h and then quenched with H_2O (20 mL). The resulting mixture was extracted with EtOAc (20 mL $\times$ 3). The combined organic layers were washed with sat. NaHCO_3 aqueous (20 mL $\times$ 3), brine (20 mL), dried over Na_2SO_4 and concentrated to give a crude. The crude was purified by silica gel column chromatography (Petroleum ether/ EtOAc 5/1) to give 3-(benzyloxy)-4,6-difluoro-2-iodoaniline (2.0 g, 30.0%) as a brown solid. LCMS: m/z 362.0 ($\text{M}+\text{H}^+$).

Step 4: Synthesis of methyl 2-amino-6-(benzyloxy)-3,5-difluorobenzoate



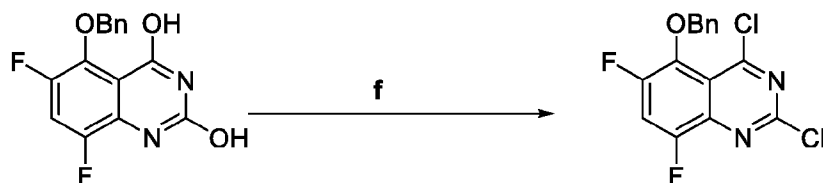
[00272] A mixture of 3-(benzyloxy)-4,6-difluoro-2-iodoaniline (1.8 g, 5.0 mmol, 1.0 eq), TEA (1.3 g, 12.5 mmol, 2.5eq) and Pd(dppf)Cl₂ (723 mg, 1.0 mmol, 0.2 eq) in MeOH (18 mL) was stirred at 65 °C under CO atmosphere. The reaction was concentrated to give a residue. The residue was partitioned between EtOAc (20 mL) and H₂O (15 mL). The layers were separated. The aqueous layer was extracted with EtOAc (100 mL x 3). The crude was purified by silica gel column chromatography (Petroleum ether/ EtOAc 10/1) to give methyl 2-amino-6-(benzyloxy)-3,5-difluorobenzoate (640 mg, 42.7%) as a white solid. ¹H NMR (300 MHz, CDCl₃): δ 7.54 – 7.33 (m, 5H), 6.98 (t, *J* = 10.5 Hz, 1H), 5.04 (s, 2H), 4.70 (brs, 2H), 3.83 (s, 3H). LCMS: *m/z* 294.1 (*M* + H⁺).

Step 5: Synthesis of 5-(benzyloxy)-6,8-difluoroquinazoline-2,4-diol



[00273] To a solution of compound methyl 2-amino-6-(benzyloxy)-3,5-difluorobenzoate (570 mg, 1.9 mmol, 1.0 eq) in THF (6 mL) was added 2,2,2-trichloroacetyl isocyanate (550 mg, 2.9 mmol, 1.5 eq). Then the reaction mixture was stirred at room temperature for 10 min. The mixture was concentrated to give a white solid. The solid was re-dissolved in MeOH (10 mL). Then to the mixture was added NH₃/MeOH(7M) (0.7 mL, 5.1 mmol, 2.6 eq). Then the reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated to give 5-(benzyloxy)-6,8-difluoroquinazoline-2,4-diol (680 mg, crude) as a brown solid. LCMS: *m/z* 303.0 (*M*-H⁻).

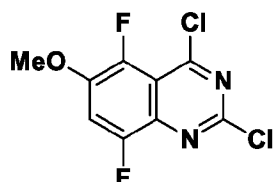
Step 6: Synthesis of 5-(benzyloxy)-2,4-dichloro-6,8-difluoroquinazoline



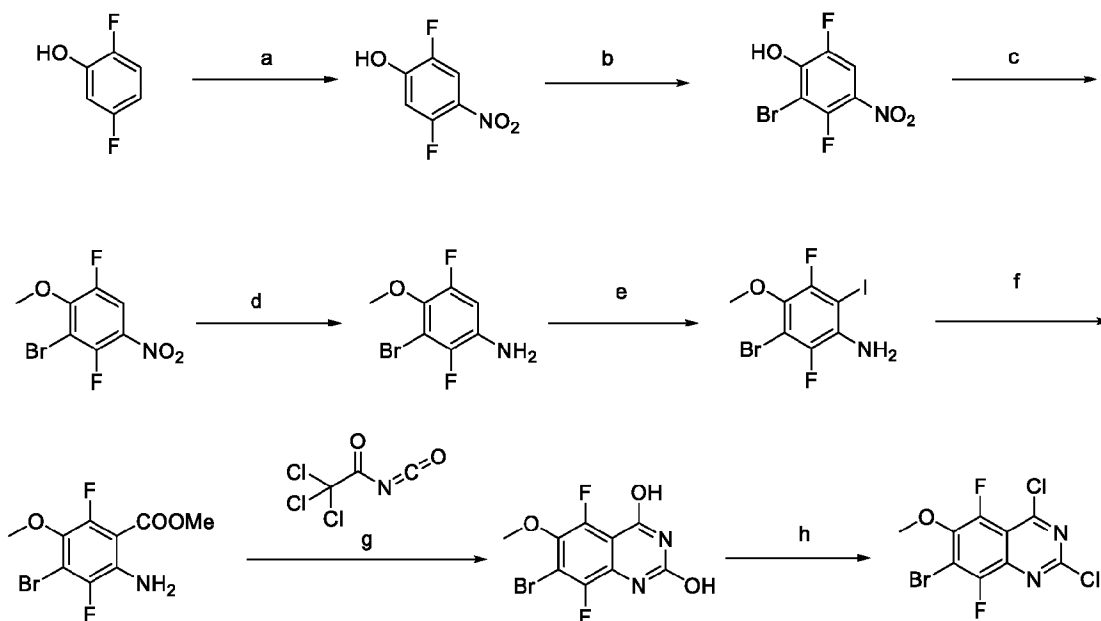
[00274] A solution of compound 5-(benzyloxy)-6,8-difluoroquinazoline-2,4-diol (680 mg, 2.2 mmol, 1.0 eq) and DIEA (865 mg, 6.7 mmol, 5.0 eq) in POCl₃ (3 mL) was stirred at 90 °C for 3 h under nitrogen atmosphere. The mixture was concentrated to give compound 5-(benzyloxy)-2,4-dichloro-6,8-difluoroquinazoline (900 mg, crude) as a black solid.

Intermediate 9:

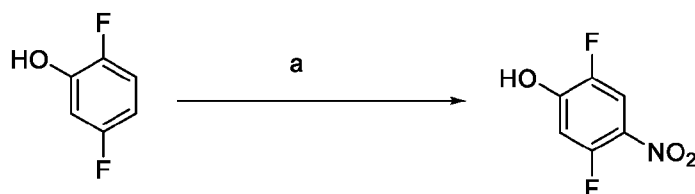
2,4-dichloro-5,8-difluoro-6-methoxyquinazoline



Synthetic scheme:

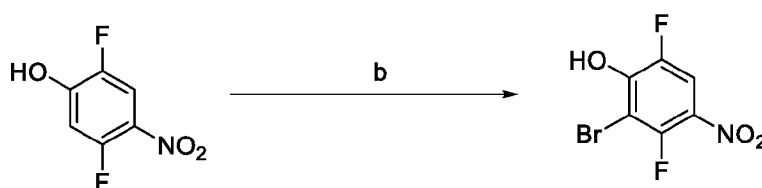


Step 1: Synthesis of 2,5-difluoro-4-nitrophenol



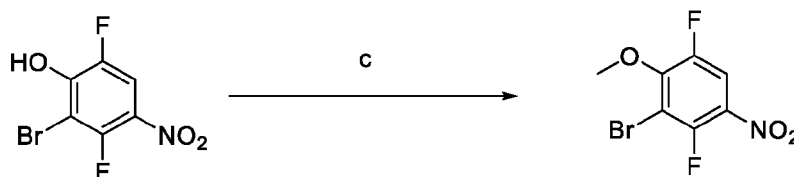
[00275] To a solution of 2,5-difluorophenol (30.0 g, 230.6 mmol, 1.0 eq) in DCM (460 mL) was added con. HNO₃ (14.5 g, 230.6 mmol, 1.0 eq) dropwise at 0°C. Then the reaction mixture was stirred at room temperature for 1 h. The reaction was diluted with water (200 mL) and extracted with DCM (180 mL x 3). The organic phase was washed with brine (200 mL), dried with Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by silica gel column chromatography (Petroleum ether: DCM = 2:1) to give 2,5-difluoro-4-nitrophenol (21.4g, 53.0%) as a yellow solid. ¹H NMR (400 MHz, CD₃OD): δ 7.96 (dd, *J* = 10.8, 7.2 Hz, 1H), 6.88 (dd, *J* = 12.4, 7.2 Hz, 1H). LCMS: *m/z* 174.0 (M-H⁺).

Step 2: Synthesis of 2-bromo-3,6-difluoro-4-nitrophenol



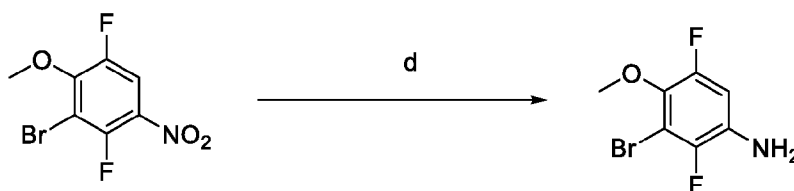
[00276] To a solution of 2,5-difluoro-4-nitrophenol (5.0 g, 28.56 mmol, 1.0 eq) in AcOH (18.0 mL) was added Br₂ (5.0 g, 31.41 mmol, 1.1 eq) dropwise at room temperature. The reaction mixture was stirred at room temperature for 15 h. The reaction was quenched with aqueous Na₂S₂O₃ (30 mL) and extracted with EtOAc (40 mL x 3). The organic phase was washed with brine (50 mL), dried with Na₂SO₄, filtered and concentrated to give residue. The residue was purified by silica gel column chromatography (petroleum ether: EtOAc = 3: 1) to give 2-bromo-3,6-difluoro-4-nitrophenol (6.8 g, 93.0%) as red solid. ¹H NMR (300 MHz, CD₃OD): δ 8.04 (dd, *J* = 10.5, 7.2 Hz, 1H). LCMS: *m/z* 251.9, 253.9 (M-1⁺).

Step 3: Synthesis of 3-bromo-1,4-difluoro-2-methoxy-5-nitrobenzene



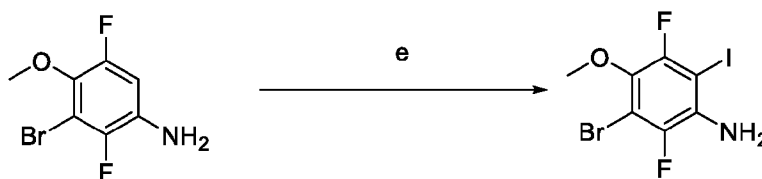
[00277] To a solution of 2-bromo-3,6-difluoro-4-nitrophenol (4.5 g, 17.72 mmol, 1.0 eq) in Acetone (45 mL) was added NaHCO₃ (4.5 g, 53.15 mmol, 3 eq) and Me₂SO₄ (4.5 g, 35.44 mmol, 2 eq). The reaction mixture was stirred at 50 °C for 15 h. The reaction was quenched with H₂O (50 mL) and extracted with EtOAc (50 mL x 3). The organic phase was washed with brine (50 mL), dried with Na₂SO₄, filtered and concentrated to give residue. The residue was purified by silica gel column chromatography (Petroleum ether: EtOAc = 50: 1) to give 3-bromo-1,4-difluoro-2-methoxy-5-nitrobenzene (1.6 g, 33.7%) as a white oily. ¹H NMR (400 MHz, CD₃OD): δ 8.12 (dd, *J* = 11.6, 7.2 Hz, 1H), 4.16 (d, *J* = 3.6 Hz, 3H).

Step 4: Synthesis of 3-bromo-2,5-difluoro-4-methoxyaniline



[00278] To a solution of 3-bromo-1,4-difluoro-2-methoxy-5-nitrobenzene (30.5 g, 113.8 mmol, 1.0 eq) in EtOH (50 mL) was added H₂O (20 mL), Fe (25.4 g, 455.2mmol, 4.0 eq) and NH₄Cl (24.4 g, 455.2mmol, 4.0 eq). The reaction mixture was stirred at 40 °C for 2 h. The mixture was filtered and concentrated to remove EtOH, diluted with water (50 mL) and extracted with EtOAc (60 mL x 3). The organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give residue. The residue was purified by silica gel column chromatography (Petroleum ether: EtOAc = 100: 1) to give 3-bromo-2,5-difluoro-4-methoxyaniline (14.8 g, 54.6%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 6.53 (dd, *J* = 11.6, 8.4 Hz, 1H), 3.85 (d, *J* = 0.8 Hz, 3H). LCMS: *m/z* 237.9, 239.9 (M+H⁺).

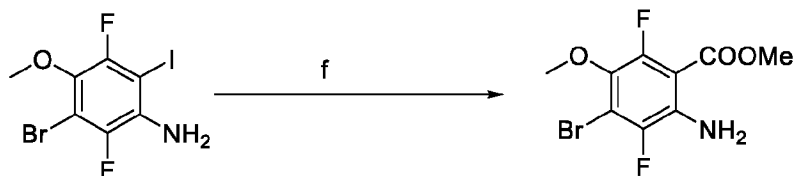
Step 5: Synthesis of 3-bromo-2,5-difluoro-6-iodo-4-methoxyaniline



[00279] To a solution of 3-bromo-2,5-difluoro-4-methoxyaniline (3.0 g, 12.60 mmol, 1.0 eq) in DMSO (30 mL) was added I₂ (9.60 g, 37.81 mmol, 3.0 eq). Then the reaction mixture was stirred at room temperature for 15 h. The reaction was quenched with aqueous Na₂S₂O₃ (20 mL)

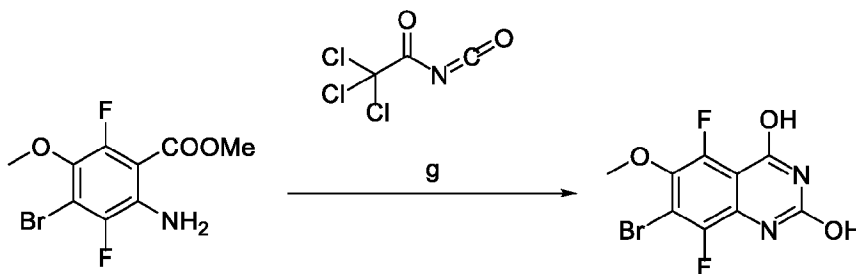
and extracted with EtOAc (30 mL x 3). The organic phase was washed with water (20 mL x 3) and brine (20 mL), dried with Na₂SO₄, filtered and concentrated to give residue. The mixture was concentrated and purified by silica gel chromatography (Petroleum ether: EtOAc = 300: 1) to give 3-bromo-2,5-difluoro-6-iodo-4-methoxyaniline (1.6 g, 35%) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 3.86 (d, *J* = 0.6 Hz, 3H). LCMS: *m/z* 363.8, 365.8 (M+H⁺).

Step 6: Synthesis of methyl 2-amino-4-bromo-3,6-difluoro-5-methoxybenzoate



[00280] To a solution of 3-bromo-2,5-difluoro-6-iodo-4-methoxyaniline (2.2 g, 6.05 mmol, 1.0 eq) in MeOH (30 mL) was added TEA (1.8 g, 18.13 mmol, 3.0 eq) and Pd(dppf)Cl₂ (907 mg, 1.25 mmol, 0.2 eq) in the sealed tube. Then the reaction mixture was stirred at 70 °C for 8 h under CO (1 MPa). The mixture was concentrated and diluted with H₂O (20 mL), extracted with EtOAc (15 mL x 3). The organic phase was washed with brine (15 mL), dried with Na₂SO₄, filtered and concentrated to give residue. The residue was purified by silica gel chromatography (Petroleum ether: EtOAc = 300: 1) to give methyl 2-amino-4-bromo-3,6-difluoro-5-methoxybenzoate (1.4 g, 78%) as yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 3.93 (s, 3H), 3.85 (s, 3H). LCMS: *m/z* 296.0, 297.9 (M+H⁺).

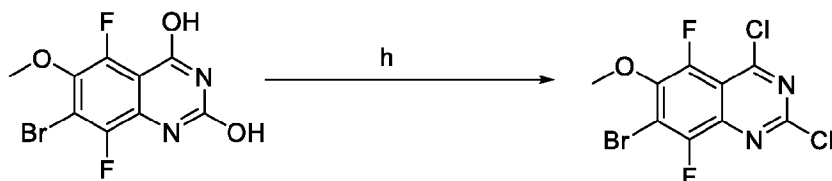
Step 7: Synthesis of 7-bromo-5,8-difluoro-6-methoxyquinazoline-2,4-diol



[00281] To a solution of methyl 2-amino-4-bromo-3,6-difluoro-5-methoxybenzoate (1.4 g, 4.73 mmol, 1.0 eq) in THF (14 mL) was added 2,2,2-trichloroacetyl isocyanate (1.4 g, 7.09 mmol, 1.5 eq). The reaction mixture was stirred at room temperature for 10 min. The mixture was concentrated and dissolved in MeOH (14 mL). To the solution was added NH₃/MeOH (7M, 1.76 ml, 12.30 mmol, 1.0 eq) dropwise. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to give 7-bromo-5,8-difluoro-

6-methoxyquinazoline-2,4-diol (2.8 g, crude) as a yellow solid. LCMS: m/z 306.9, 308.9 ($M+H^+$).

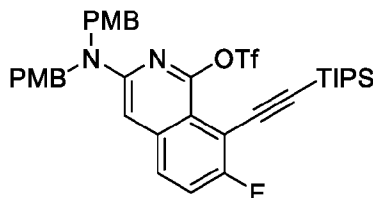
Step 8: Synthesis of 7-bromo-2,4-dichloro-5,8-difluoro-6-methoxyquinazoline



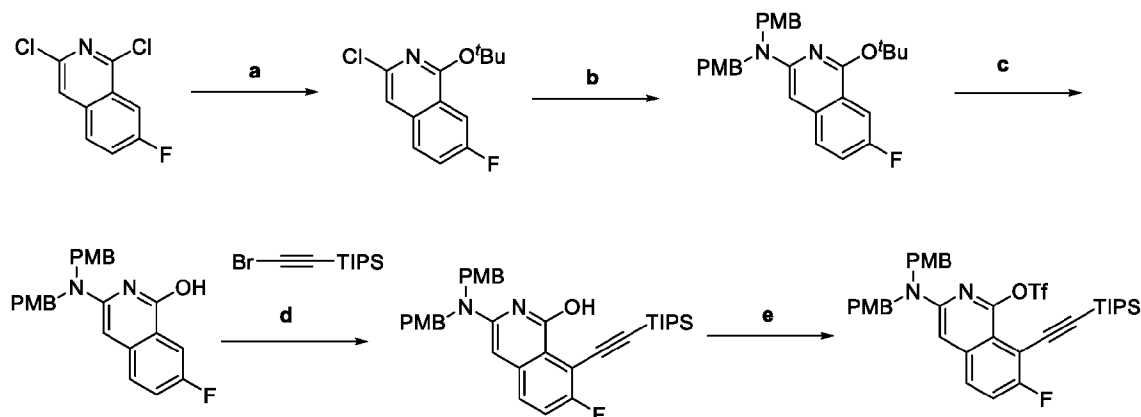
[00282] To a solution of 7-bromo-5,8-difluoro-6-methoxyquinazoline-2,4-diol (730 mg, 2.49 mmol, 1.0 eq) in $POCl_3$ (10 mL) was added DIEA (1.61 g, 12.46 mmol, 5.0 eq). Then the reaction mixture was stirred at 90 °C for 1 h. The mixture was concentrated to give residue. The residue was purified by silica gel column chromatography (Petroleum ether: EtOAc = 10:1) to give 7-bromo-2,4-dichloro-5,8-difluoro-6-methoxyquinazoline (620 mg, 76.9% for two steps) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 4.11 (d, J = 2.8 Hz, 3H).

Intermediate 10:

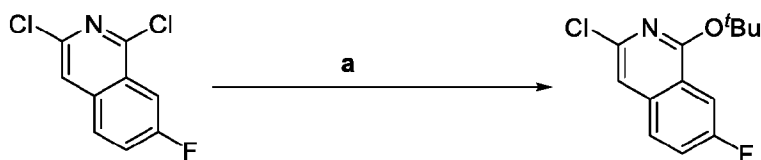
3-(Bis(4-methoxybenzyl)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)isoquinolin-1-yl trifluoromethanesulfonate



Synthetic scheme:

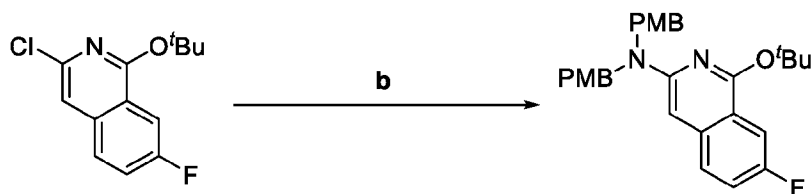


Step 1: Synthesis of 1-(tert-butoxy)-3-chloro-7-fluoroisoquinoline



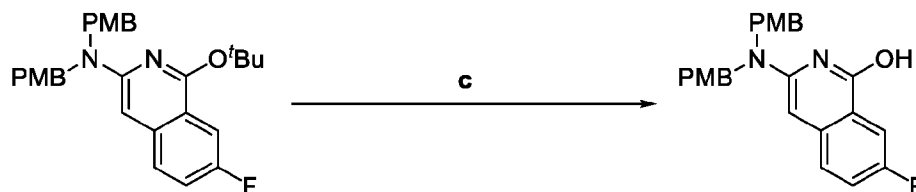
[00283] To a solution of compound 1,3-dichloro-7-fluoroisoquinoline (5.0 g, 23.3 mmol, 1.0 eq) in toluene (100 mL) was added *t*-BuOK in THF (30.2 mL, 30.2 mmol, 1.3 eq, 1.0 M in THF) at room temperature. The reaction was stirred at 80 °C for 4 h under nitrogen atmosphere. The reaction mixture was concentrated to give a crude. The crude was added water (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic phases were washed with brine (100 mL), dried and concentrated to give a residue. The crude product was purified by silica gel column chromatography (Petroleum ether: EtOAc = 50: 1) to give compound 1-(tert-butoxy)-3-chloro-7-fluoroisoquinoline (5.6 g, 95.2%) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 7.75 (dd, *J* = 9.6, 2.4 Hz, 1H), 7.63-7.58 (m, 1H), 7.39 (td, *J* = 8.4, 2.4 Hz, 1H), 7.18 (s, 1H), 1.72 (s, 9H).

Step 2: Synthesis of 1-(tert-butoxy)-7-fluoro-N, N-bis(4-methoxybenzyl)isoquinolin-3-amine



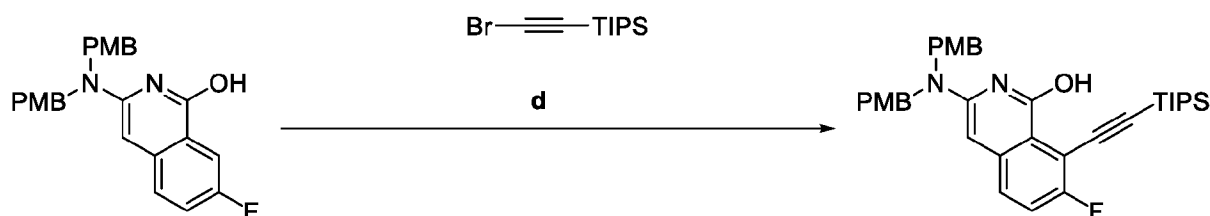
[00284] To a solution of compound 1-(tert-butoxy)-3-chloro-7-fluoroisoquinoline (5.6 g, 22.1 mmol, 1.0 eq) in THF (110 mL) was added HN(PMB)₂ (8.5 g, 33.2 mmol, 1.5 eq), *t*-BuONa (4.3 g, 44.3 mmol, 2.0 eq) and S-Phos Pd G3 (1.0 g, 1.3 mmol, 0.058 eq) at room temperature. The reaction was stirred at 80 °C for 15 h under nitrogen atmosphere. The crude was added water (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic phases were washed with brine (100 mL), dried and concentrated to give a residue. The crude product was purified by silica gel column chromatography (Petroleum ether: EtOAc = 30: 1) to give compound 1-(tert-butoxy)-7-fluoro-N, N-bis(4-methoxybenzyl)isoquinolin-3-amine (5.2 g, 49.6%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 7.67 – 7.58 (m, 1H), 7.38 – 7.33 (m, 1H), 7.26 – 7.16 (m, 6H), 6.85 – 6.78 (m, 4H), 4.69 (s, 4H), 3.77 (s, 6H), 1.63 (s, 9H). LCMS: *m/z* 475.2 (M+H⁺).

Step 3: Synthesis of 3-(bis(4-methoxybenzyl)amino)-7-fluoroisoquinolin-1-ol



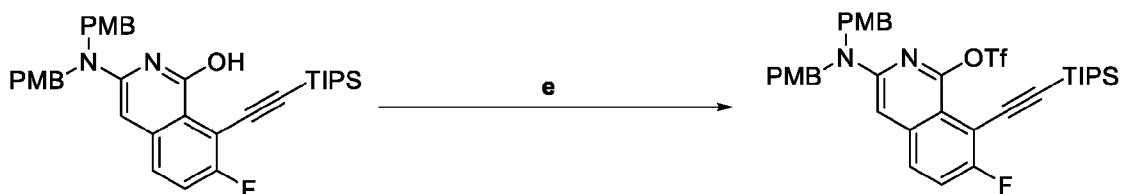
[00285] To a solution of compound 1-(tert-butoxy)-7-fluoro-N, N-bis(4-methoxybenzyl)isoquinolin-3-amine (2.0 g, 4.2 mmol, 1.0 eq) in *i*PrOH (12 mL) was added HCl in dioxane (12 mL, 4.0 M in dioxane) at room temperature. The reaction was stirred at room temperature for 1 h. The reaction mixture was concentrated to give a crude. The crude was added aqueous sodium bicarbonate solution (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic phases were washed with brine (50 mL), dried and concentrated to give a residue. The crude product was purified by silica gel column chromatography (Petroleum ether: EtOAc = 5: 1) to give compound 3-(bis(4-methoxybenzyl)amino)-7-fluoroisoquinolin-1-ol (1.6 g, 90.9%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 10.05 (brs, 1H), 7.79 – 7.71 (m, 1H), 7.25 – 7.14 (m, 6H), 6.86 (d, *J* = 8.8 Hz, 4H), 5.67 (brs, 1H), 4.44 (s, 4H), 3.79 (s, 6H). LCMS: *m/z* 419.2 (M+H⁺).

Step 4: Synthesis of 3-(bis(4-methoxybenzyl)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)isoquinolin-1-ol



[00286] To a solution of compound 3-(bis(4-methoxybenzyl)amino)-7-fluoroisoquinolin-1-ol (1.8 g, 4.3 mmol, 1.0 eq) in dioxane (30 mL) was added (bromoethynyl)triisopropylsilane (1.8 g, 6.9 mmol, 1.6 eq), KOAc (844 mg, 8.6 mmol, 2.0 eq) and [Ru(cumene)Cl]₂ (263 mg, 0.43 mmol, 0.1 eq) at room temperature. The reaction was stirred at 110 °C for 15 h under nitrogen atmosphere. The reaction was concentrated to give a crude product. The crude product was purified by silica gel column chromatography (Petroleum ether: EtOAc = 50: 1) to give compound 3-(bis(4-methoxybenzyl)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)isoquinolin-1-ol (1.8 g, 70.0%) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 7.22 – 7.09 (m, 6H), 6.85 (d, *J* = 8.4 Hz, 4H), 5.55 (s, 1H), 4.39 (s, 4H), 3.79 (s, 6H), 1.18 (s, 21H). LCMS: *m/z* 599.3 (M+H⁺).

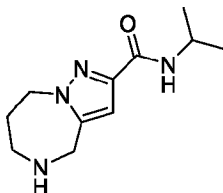
Step 5: Synthesis of 3-(bis(4-methoxybenzyl)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)isoquinolin-1-yl trifluoromethanesulfonate



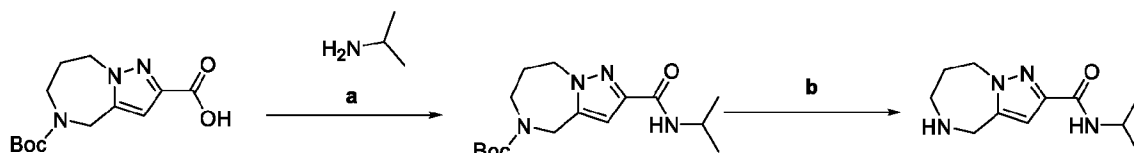
[00287] To a solution of compound 3-(bis(4-methoxybenzyl)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)isoquinolin-1-ol (1.9 g, 3.2 mmol, 1.0 eq) in DCM (38 mL) was added Ti_2O (2.7 g, 9.6 mmol, 3.0 eq) and TEA (1.9 g, 19.2 mmol, 6.0 eq). The reaction was stirred at -40 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a crude. The crude was purified by silica gel column chromatography (Petroleum ether: EtOAc = 10: 1) to give 3-(bis(4-methoxybenzyl)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)isoquinolin-1-yl trifluoromethanesulfonate (2.0 g, 86.2%) as a yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 7.42 – 7.27 (m, 2H), 7.14 (d, J = 8.4 Hz, 4H), 6.84 (d, J = 8.4 Hz, 4H), 6.55 (s, 1H), 4.68 (s, 4H), 3.79 (s, 6H), 1.20-1.15 (m, 21H).

Intermediate 11:

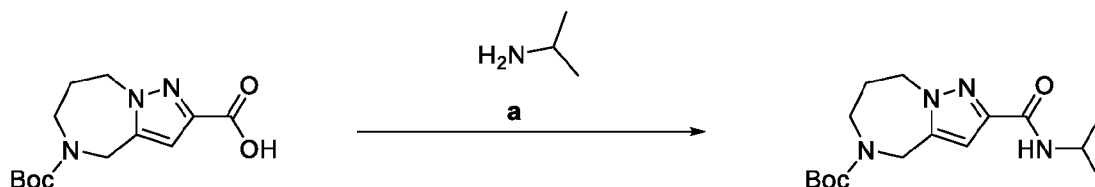
N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



Synthetic scheme:

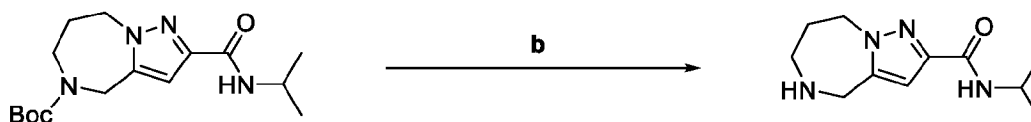


Step 1: Synthesis of tert-butyl 2-(isopropylcarbamoyl)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate



[00288] To a solution of 5-(tert-butoxycarbonyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxylic acid (400 mg, 1.42 mmol, 1.0 eq) in DMF (8.0 mL) was added propan-2-amine (168 mg, 2.84 mmol, 2.0 eq), DIEA (551 mg, 4.27 mmol, 3.0 eq) and HATU (811 mg, 2.13 mmol, 1.5 eq). Then the mixture was stirred at room temperature for 2 h. The mixture was concentrated, diluted with water (15 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with water (10 mL x 3) and brine (10 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by flash silica gel column chromatography (0-5% MeOH in DCM) to give tert-butyl 2-(isopropylcarbamoyl)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate (340 mg 74.2%) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 6.63 (s, 1H), 4.55 – 4.34 (m, 4H), 4.31 – 4.18 (m, 1H), 3.72 (s, 2H), 1.93 (s, 2H), 1.40 (s, 9H), 1.24 (d, *J* = 6.4 Hz, 6H). LCMS: *m/z* 323.2 (M+H⁺).

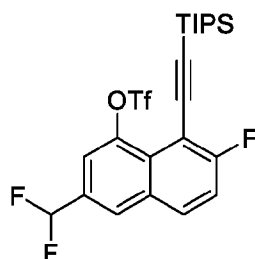
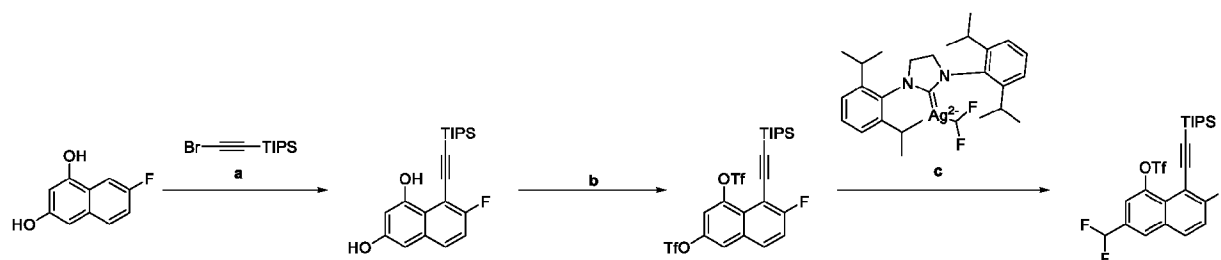
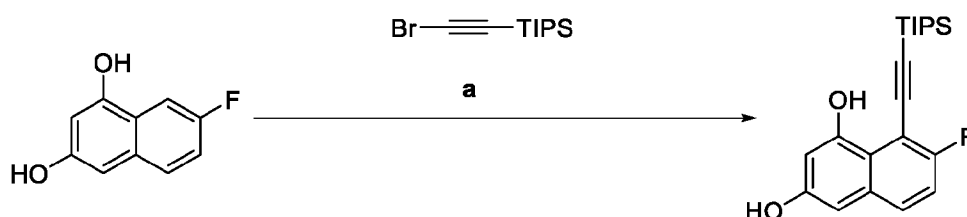
Step 2: Synthesis of N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



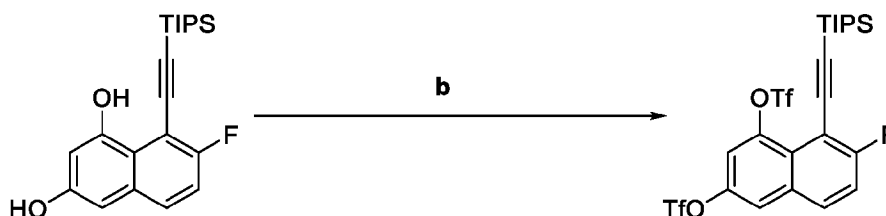
[00289] To a solution of tert-butyl 2-(isopropylcarbamoyl)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate (330 mg, 1.02 mmol, 1.0 eq) in DCM (3.0 mL) was added TFA (0.6 mL). The mixture was stirred at room temperature for 2 h. The pH was adjusted to around 9 by a solution of NaHCO₃ and extracted with DCM/MeOH = 3/1 (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (190 mg crude) as a white solid. LCMS: *m/z* 223.1 (M+H⁺).

Intermediate 12:

3-(difluoromethyl)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate

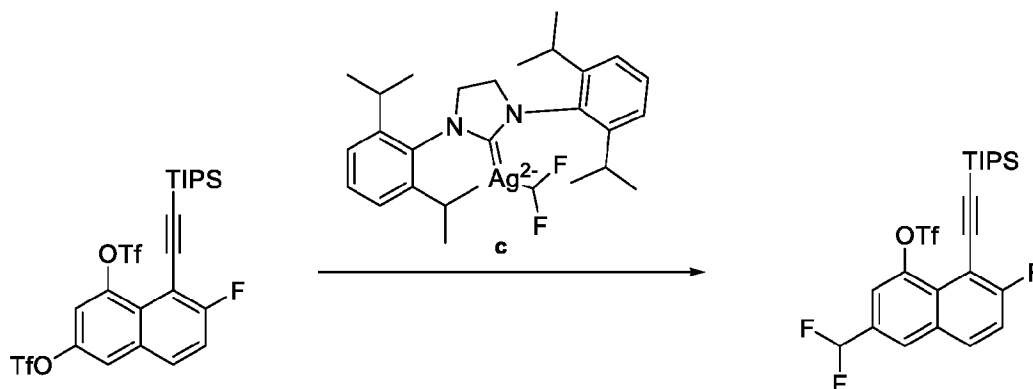
**Synthesis scheme:****Step 1: Synthesis of 7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalene-1,3-diol**

[00290] To a solution of 7-fluoronaphthalene-1,3-diol (1.0 g, 5.6 mmol, 1.0 eq) in Dioxane (10 mL) was added (bromoethynyl)triisopropylsilane (1.5 g, 5.9 mmol, 1.05 eq), AcOK (1.1 g, 11.2 mmol, 2.0 eq) and Dichloro(p-cymene) ruthenium (II) dimer (343 mg, 0.50 mmol, 0.1 eq). The mixture was stirred at 110 °C for 3 h under N₂. The mixture was filtered and the filtrate was concentrated to give a crude. The crude was purified by column chromatography (Petroleum ether/EtOAc = 5: 1) to give 7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalene-1,3-diol (1.3 g, 64.6%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 7.86 – 7.80 (m, 2H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.47 – 7.43 (m, 1H), 7.37 (t, *J* = 8.8 Hz, 1H), 1.18 – 1.17 (m, 21H).

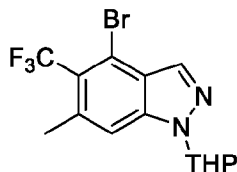
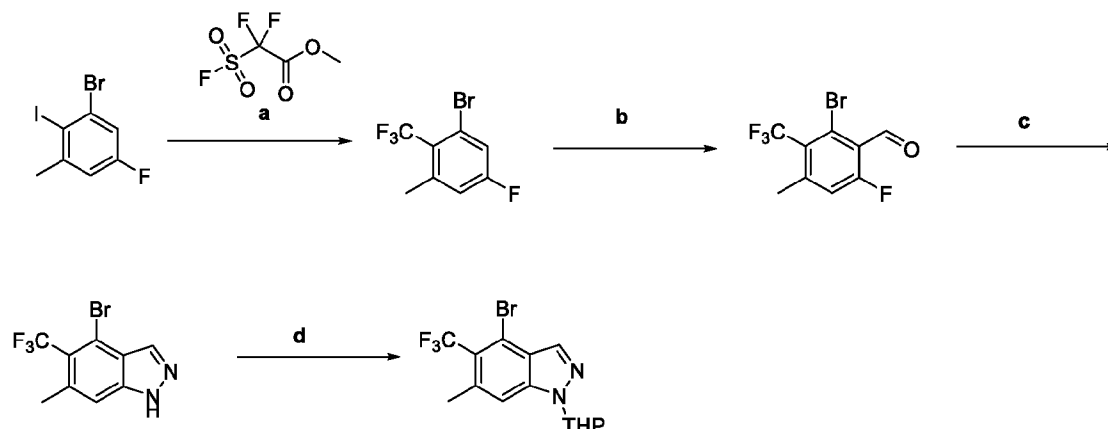
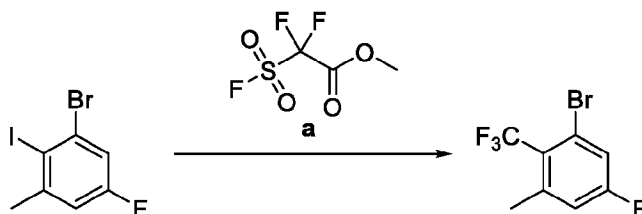
Step 2: Synthesis of 7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalene-1,3-diyl bis(trifluoromethanesulfonate)

[00291] To a solution of 7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalene-1,3-diol (1.2 g, 3.3 mmol, 1.0 eq) in DCM (20 mL) was added TiF_2O (3.77 g, 13.3 mmol, 4.0 eq) and DIEA (2.6 g, 20.0 mmol, 6.0 eq) at 0 °C. The reaction mixture was stirred at room temperature for 3 h under N_2 . The mixture was diluted with water (15 mL) and extracted with DCM (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried over Na_2SO_4 , filtered off and concentrated to give a residue. The residue was purified by column chromatography (Petroleum ether : EtOAc = 10: 1) to give 7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalene-1,3-diyl bis(trifluoromethanesulfonate) (1.3 g, 62.4%) as a yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 7.87 (dd, $J = 9.2, 5.2$ Hz, 1H), 7.80 (d, $J = 2.4$ Hz, 1H), 7.51 – 7.47 (m, 2H), 1.17 – 1.16 (m, 21H).

Step 3: Synthesis of 3-(difluoromethyl)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate

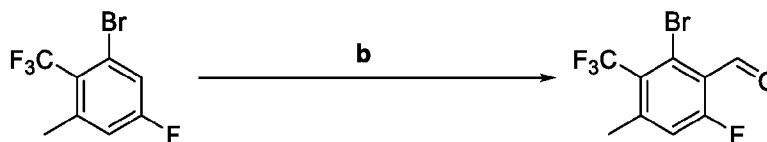


[00292] To a solution of 7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalene-1,3-diyl bis(trifluoromethanesulfonate) (500.0 mg, 0.8 mmol, 1.0 eq) in Dioxane (5 mL) was added (1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene)(difluoromethyl)argentate(I) (573.6 mg, 1.04 mmol, 1.3 eq) and t-BuXPhos-Pd-G3 (63.5 mg, 0.08 mmol, 0.1 eq) at room temperature. The reaction mixture was stirred at 100 °C for 12 h under N_2 . The mixture was quenched by the addition of saturated aqueous NH_4Cl solution (10 mL) and then extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 , filtered off and concentrated to give residue. The residue was purified by silica gel column chromatography (Petroleum ether : EtOAc = 50: 1) to give 3-(difluoromethyl)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate (220 mg, 52.2%) as a yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 7.98 (s, 1H), 7.90 (dd, $J = 9.2, 5.6$ Hz, 1H), 7.65 (s, 1H), 7.45 (t, $J = 8.8$ Hz, 1H), 6.76 (t, $J = 55.6$ Hz, 1H), 1.18 – 1.16 (m, 21H).

Intermediate 13:**4-bromo-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazole****Synthetic scheme:****Step 1: Synthesis of 1-bromo-5-fluoro-3-methyl-2-(trifluoromethyl)benzene**

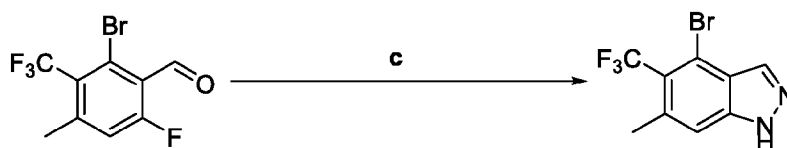
[00293] To a solution of 1-bromo-5-fluoro-2-iodo-3-methylbenzene (20.0 g, 63.7 mmol, 1.0 eq) in DMF (400 mL) was added methyl 2,2-difluoro-2-(fluor sulfonyl) acetate (85.6 g, 446.0 mmol, 7.0 eq) and CuI (85.0 mg, 446.0 mmol, 7.0 eq). The reaction mixture was stirred at 70 °C for 15 h under nitrogen atmosphere. The reaction was filtered and diluted with water (400 mL). The mixture was extracted with EtOAc (400 mL x 3). The organic phases were washed with brine (300 mL x 3), dried with Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by silica gel column chromatography (petroleum ether) to give 1-bromo-5-fluoro-3-methyl-2-(trifluoromethyl)benzene (8.0 g, 49.0%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 7.32 (dd, *J* = 7.5, 2.1 Hz, 1H), 6.94 (dd, *J* = 8.7, 2.1 Hz, 1H), 2.53 (q, *J* = 3.6 Hz, 3H).

Step 2: Synthesis of 2-bromo-6-fluoro-4-methyl-3-(trifluoromethyl)benzaldehyde



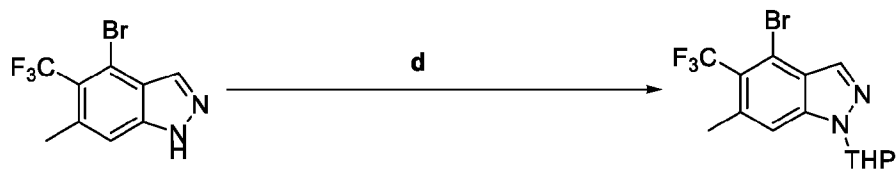
[00294] To a solution of 1-bromo-5-fluoro-3-methyl-2-(trifluoromethyl)benzene (12.4 g, 48.4 mmol, 1.0 eq) in THF (250 mL) was added LDA (48.4 mL, 97.0 mmol, 2.0 eq, 2.0 M in THF/hexane) dropwise at -78 °C under nitrogen atmosphere. Then the reaction mixture was stirred at -78 °C for 30 min. To the reaction mixture was added DMF (10.6 g, 145.3 mmol, 3.0 eq) dropwise at -78 °C under nitrogen atmosphere. The reaction mixture was stirred at -78 °C for 30 min. The mixture was quenched with aqueous ammonium chloride solution (250 mL) and extracted with EtOAc (250 mL x 3). The combined organic phases were washed with brine (250 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 50: 1) to give 2-bromo-6-fluoro-4-methyl-3-(trifluoromethyl)benzaldehyde (11.0 g, 79.9%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 10.32 (s, 1H), 7.06 (d, *J* = 10.5 Hz, 1H), 2.59 (q, *J* = 3.9 Hz, 3H).

Step 3: Synthesis of 4-bromo-6-methyl-5-(trifluoromethyl)-1H-indazole



[00295] To a solution of 2-bromo-6-fluoro-4-methyl-3-(trifluoromethyl)benzaldehyde (11.0 g, 38.7 mmol, 1.0 eq) in DMSO (165 mL) was added hydrazine (24.8 g, 774.8 mmol, 20.0 eq) dropwise at room temperature. Then the reaction mixture was stirred at 60 °C for 2 h. The mixture was quenched with water (200 mL) and extracted with EtOAc (200 mL x 3). The combined organic phases were washed with brine (200 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 5: 1) to give 4-bromo-6-methyl-5-(trifluoromethyl)-1H-indazole (6.0 g, 55.6%) as a white solid. ¹H NMR (300 MHz, CDCl₃): δ 10.24 (brs, 1H), 8.19 (s, 1H), 7.33 (s, 1H), 2.65 (q, *J* = 3.3 Hz, 3H). LCMS: 279.0, 280.9 (M+H⁺).

Step 4: Synthesis of 4-bromo-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazole

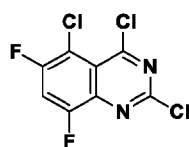


[00296] To a solution of 4-bromo-6-methyl-5-(trifluoromethyl)-1H-indazole (1.0 g, 3.6 mmol, 1.0 eq) and p-TsOH (61.9 mg, 0.36 mmol, 0.1 eq) in DCM (20 mL) was added DHP (1.2 g, 14.4 mmol, 4.0 eq) in MeCN (5 mL) dropwise at room temperature. Then the reaction mixture was stirred at room temperature for 2 h. The mixture was quenched with water (40 mL) and extracted with EtOAc (40 mL x 3). The combined organic phases were washed with brine (40 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 10: 1) to give 4-bromo-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazole (1.2 g, 92.3%) as a colorless oil.

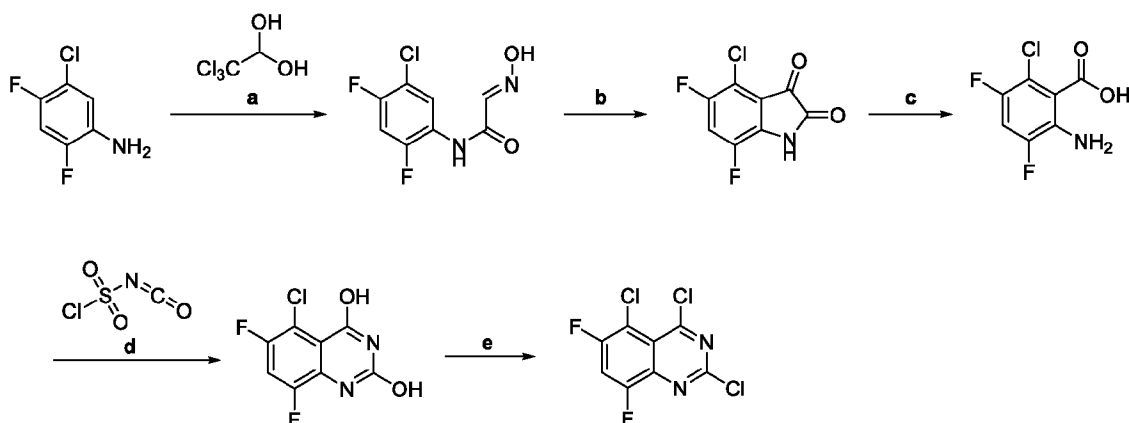
¹H NMR (300 MHz, CDCl₃): δ 8.11 (s, 1H), 7.42 (s, 1H), 5.68 (dd, J = 9.0, 2.7 Hz, 1H), 4.06 – 3.95 (m, 1H), 3.82 – 3.68 (m, 1H), 2.66 (q, J = 3.0 Hz, 3H), 2.58 – 2.44 (m, 1H), 2.22 – 2.05 (m, 2H), 1.80 – 1.67 (m, 3H). LCMS: 363.0, 365.1 (M+H⁺).

Intermediate 14:

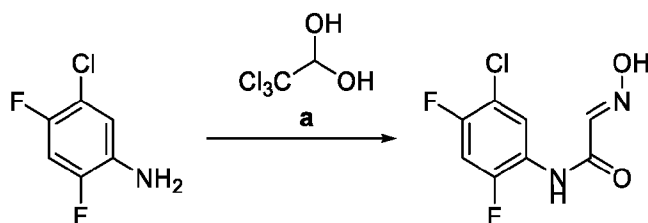
2,4,5-trichloro-6,8-difluoroquinazoline



Synthetic scheme:

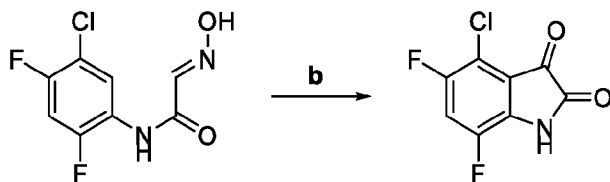


Step 1: Synthesis of (E)-N-(5-chloro-2,4-difluorophenyl)-2-(hydroxyimino)acetamide



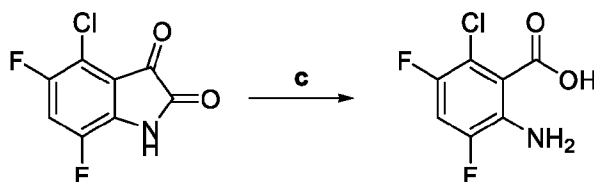
[00297] To a solution of 5-chloro-2,4-difluoroaniline (10.0 g, 61.14 mmol, 1.0 eq), $\text{NH}_2\text{OH}\cdot\text{HCl}$ (12.7 g, 184.43 mmol, 3.0 eq), Na_2SO_4 (69.5 g, 489.14 mmol, 8.0 eq), chloral hydrate (15.2 g, 91.72 mmol, 1.5 eq) in water (250 mL) and EtOH (35 mL) was added HCl (12 M, 9.2 mL, 110.40 mmol, 1.8 eq). The reaction mixture was stirred at 60 °C for 16 h. The resulting mixture was cooled to room temperature and filtered, the filter cake was dried to afford the crude, which was extracted with EtOAc (50 mL) and filtered, the filtrate was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and organic phase was concentrated to dryness to give the residue. The residue was purified by silica gel chromatography (petroleum ether / EtOAc = 5:1) to afford (E)-N-(5-chloro-2,4-difluorophenyl)-2-(hydroxyimino)acetamide (11.0 g, 76.7%) as a yellowish solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 12.37 (s, 1H), 10.01 (s, 1H), 8.05 (t, J = 8.0 Hz, 1H), 7.74 (s, 1H), 7.65 (t, J = 10.0 Hz, 1H).

Step 2: Synthesis of 4-chloro-5,7-difluoroindoline-2,3-dione



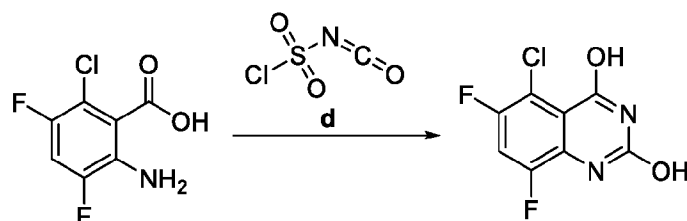
[00298] (E)-N-(5-chloro-2,4-difluorophenyl)-2-(hydroxyimino)acetamide (7.0 g, 29.84 mmol, 1.0 eq) was added portion-wise to H_2SO_4 (98%, 70 mL) at 60 °C. The reaction was stirred at 90 °C for 4 h. The resulting mixture was cooled to room temperature and poured slowly into ice water (150 mL). The resulting precipitate was collected by filtration, washed with water (10 mL x 3) and dried under reduced pressure to afford 4-chloro-5,7-difluoroindoline-2,3-dione (5.0 g, 77.0%) as a grey solid. LCMS: 215.9 ($\text{M}-\text{H}^-$).

Step 3: Synthesis of 2-amino-6-chloro-3,5-difluorobenzoic acid



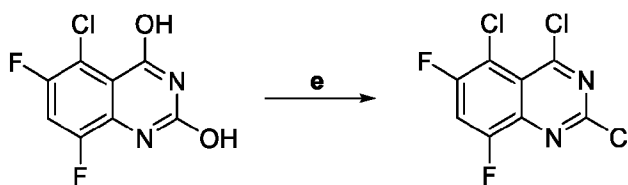
[00299] To a solution of 4-chloro-5,7-difluoroindoline-2,3-dione (10.0 g, 45.97 mmol, 1.0 eq) in NaOH (2 mol/L aqueous solution, 400 mL) was added dropwise H_2O_2 (30 mL, 37% aqueous solution) at 0 °C. The reaction mixture was stirred at room temperature for 15 h. After completion, the excess H_2O_2 was quenched with the addition of Na_2SO_3 (36.9 g) and the mixture was stirred for 20 min, then filtered, the filtrate was extracted by EtOAc, the product was in the aqueous phase, which was adjusted to pH = 1-2 with conc. HCl. The mixture was extracted by EtOAc, dried and concentrated under reduced pressure to afford 2-amino-6-chloro-3,5-difluorobenzoic acid (3.0 g, 31.5%) as a yellow solid. LCMS: 205.9 (M-H⁻).

Step 4: Synthesis of 5-chloro-6,8-difluoroquinazoline-2,4-diol



[00300] To a solution of 2-amino-6-chloro-3,5-difluorobenzoic acid (1.0 g, 4.92 mmol, 1.0 eq) in DCM (10 mL) was added dropwise ClSO_2NCO (1.6 g, 11.08 mmol, 2.3 eq) at 0 °C. The reaction mixture was stirred at room temperature for 12 h and concentrated under reduced pressure. To the mixture was added concentrated HCl (6 N, 20 mL) and stirred at 100 °C for 16 h. The resulting mixture was cooled to room temperature and filtered, the filter cake was washed by water (2 mL x 3) and dried under reduced pressure to afford 5-chloro-6,8-difluoroquinazoline-2,4-diol (0.35 g, crude) as a grey solid, which was used directly for the next step without further purification. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.51 (s, 1H), 11.36 (s, 1H), 7.95 (t, J = 9.2 Hz, 1H). LCMS: 233.0 (M+H⁺).

Step 5: Synthesis of 2,4,5-trichloro-6,8-difluoroquinazoline

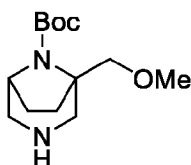


[00301] To a solution of 5-chloro-6,8-difluoroquinazoline-2,4-diol (0.8 g, 3.44 mmol, 1.0 eq) in POCl_3 (8 mL, 86.09 mmol, 25.0 eq) was added DIEA (0.6 g, 4.59 mmol, 1.3 eq). The reaction mixture was stirred at 110 °C for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with DCM (20 mL) washed with ice water (20 mL x 2),

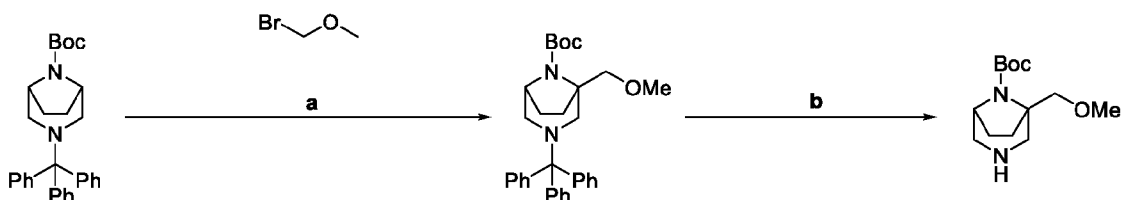
dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the residue, which was purified by silica gel column chromatography (petroleum ether / EtOAc = 10:1) to give 2,4,5-trichloro-6,8-difluoroquinazoline (0.9 g, 30.3% yield for 2 steps) as an off-white solid. ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 7.50 (t, J = 9.3 Hz, 1H).

Intermediate 15:

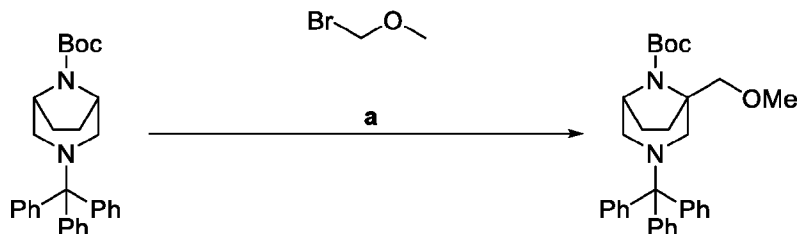
tert-butyl 1-(methoxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



Synthetic scheme:



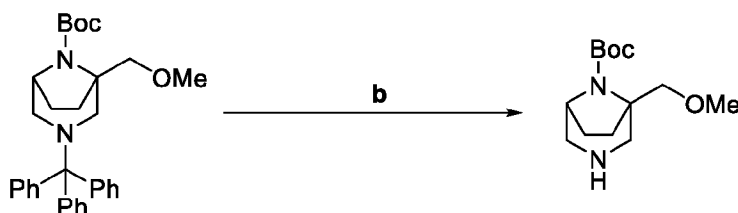
Step 1: Synthesis of tert-butyl 1-(methoxymethyl)-3-trityl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00302] To a solution of tert-butyl (1R,5S)-3-trityl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.0 g, 2.20 mmol, 1.0 eq) and TMDEA (N, N, N', N'-tetramethylethylenediamine) (435 mg, 3.74 mmol, 1.7 eq) in THF (14.3 mL) at 0 °C was added s-BuLi (2.9 mL, 1.3 mol/L in hexane, 3.77 mmol, 1.7 eq). The mixture was stirred at 0 °C for 0.8 h. Then the mixture was added MOMBr (825 mg, 6.60 mmol, 3.0 eq) and stirred at 25 °C for 12 h. The reaction mixture was quenched with saturated NH_4Cl (10 mL). The mixture was diluted with EtOAc (20 mL x 2) and washed with water (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 , filtered, and concentrated to afford the crude product. The residue was purified by silica gel

column chromatography (petroleum ether / EtOAc = 20:1) to give *tert*-butyl 1-(methoxymethyl)-3-trityl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (600 mg, 54.7%) as a white solid. ¹H NMR (300 MHz, methanol-*d*₄): δ 8.33 – 7.90 (m, 15H), 4.87 – 4.73 (m, 1H), 4.50 – 4.40 (m, 1H), 4.18 (d, *J* = 9.2 Hz, 1H) 3.99 (s, 3H), 3.76 (d, *J* = 10.4 Hz, 1H), 3.63 (d, *J* = 10.4 Hz, 1H), 3.30 – 3.20 (m, 1H), 3.03 – 2.91 (m, 1H), 2.80 – 2.62 (m, 2H), 2.56 – 2.37 (m, 2H), 1.90 (s, 9H).

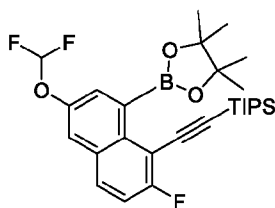
Step 2: Synthesis of *tert*-butyl 1-(methoxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



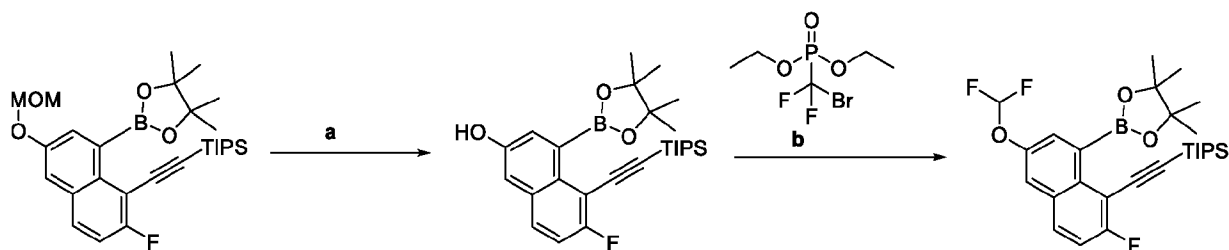
[00303] A solution of *tert*-butyl 1-(methoxymethyl)-3-trityl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (600 mg, 1.20 mmol, 1.0 eq) in 1,4-dioxane (13.2 mL) was added 1N HCl (3.9 mL) at room temperature and stirred for 1 h. The reaction mixture was quenched with H₂O (20 mL) and adjusted the pH to 8 with saturated NaHCO₃ (5 mL). The mixture was extracted with EtOAc (20 mL x 2). The organic layer was washed with water (50 mL) and brine (50 mL), dried over Na₂SO₄, filtered and concentrated to afford the *tert*-butyl 1-(methoxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (600 mg, crude) as a yellow oil. LCMS: *m/z* 201.2 (M-56+H⁺).

Intermediate 16:

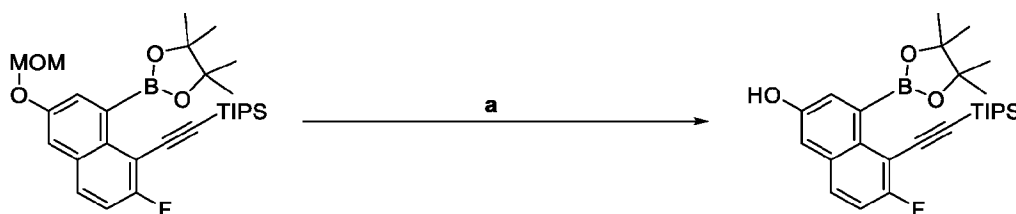
((6-(difluoromethoxy)-2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane



Synthetic scheme:

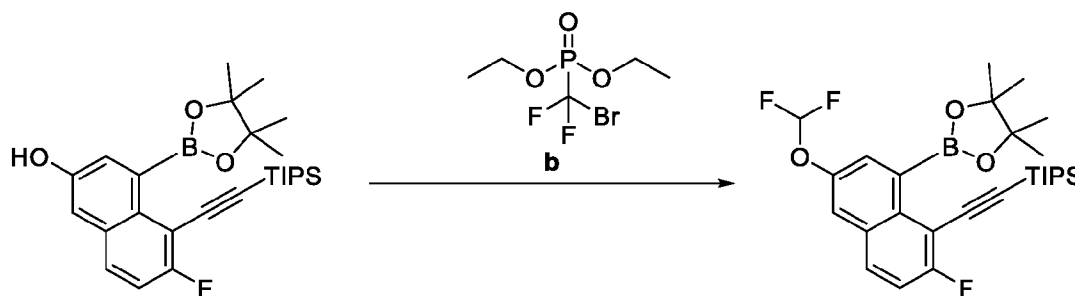


Step 1: Synthesis of 6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol



[00304] To a solution of ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (4.0 g, 7.8 mmol, 1.0 eq) in DCM (40 mL) was added HCl/Dioxane (8.0 mL). The reaction mixture was stirred at 30 °C for 3 h. The mixture was diluted with water (20 mL) and extracted with DCM (20 mL x 3). The combined organic phase was dried over Na₂SO₄ and concentrated to give a residue. The crude product was purified by column chromatography (Petroleum ether: EtOAc = 10: 1) to give 6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (3.2 g, 87.6%) as a yellow solid. LCMS: *m/z* 469.2 (M+H⁺).

Step 2: Synthesis of ((6-(difluoromethoxy)-2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane

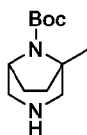


[00305] To a solution of 6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (1.0 g, 2.13 mmol, 1.0 eq) in ACN (12.5 mL) and H₂O (12.5 mL) was added KOH (2.39 g, 42.6 mmol, 20.0 eq), diethyl (bromodifluoromethyl)phosphonate (1.14 g, 4.26 mmol, 2.0 eq) at room temperature. The

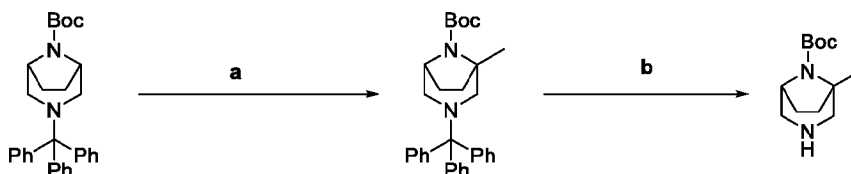
reaction mixture was stirred at room temperature for 30 min. The mixture was diluted with water (10 mL) and extracted with DCM (10 mL x 3). The combined organic phase was dried over Na₂SO₄ and concentrated to give a residue. The crude product was purified by column chromatography (Petroleum ether: EtOAc = 70: 1) to give ((6-(difluoromethoxy)-2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (700 mg, 63.4%) as a colorless liquid. LCMS: *m/z* 519.3 (M+H⁺).

Intermediate 17:

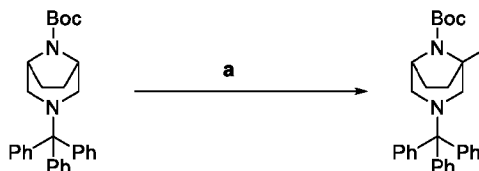
tert-butyl 1-methyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



Synthetic scheme:



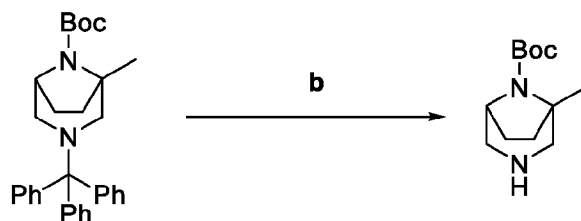
Step 1: Synthesis of tert-butyl 1-methyl-3-trityl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00306] To a solution of tert-butyl 3-trityl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (3.0 g, 6.6 mmol, 1.0 eq) and TMDEA (1.3 g, 11.2 mmol, 1.7 eq) in THF (40 mL) at 0 °C was added *s*-BuLi (8.7 mL, 1.3 mol/L in hexane, 11.2 mmol, 1.7 eq). The mixture was stirred at 0 °C for 1 h. Then CH₃I (5.6 g, 39.6 mmol, 6.0 eq) was added and the mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched with sat. NH₄Cl (50 mL). The mixture was diluted with EtOAc (50 mL) and washed with water (50 mL x 2). The organic layer was dried over Na₂SO₄, filtered, and concentrated to give a residue. The residue was purified by silica gel column chromatography (petroleum ether / EtOAc = 20:1) to give the tert-butyl 1-methyl-3-trityl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2.0 g, 64.7%) as a white solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.67 – 7.00 (m, 15H), 4.02 (d, *J* = 6.3 Hz, 1H), 2.80 (d, *J* = 10.5 Hz, 1H), 2.68 (d,

$J = 11.1$ Hz, 1H), 2.49 – 2.40 (m, 1H), 2.25 – 2.08 (m, 1H), 2.03 – 1.83 (m, 1H), 1.82 – 1.60 (m, 3H), 1.27 (s, 3H), 1.09 (s, 9H).

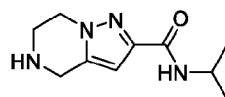
Step 2: Synthesis of tert-butyl 1-methyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



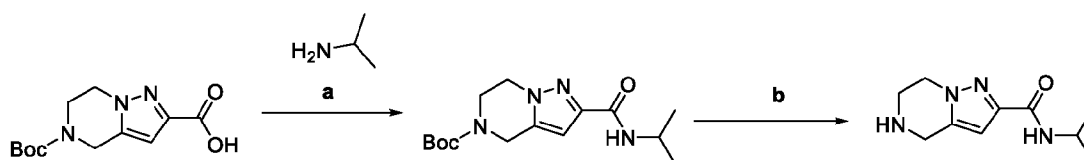
[00307] To a solution of tert-butyl 1-methyl-3-trityl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.4 g, 3.0 mmol, 1.0 eq) in 1,4-dioxane (30 mL) was added 1N HCl (9 mL, 9.0 mmol, 3.0 eq). The reaction was stirred at room temperature for 1 h. The reaction mixture was quenched with NaHCO_3 until pH ~ 8. The mixture was extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4 and concentrated to give tert-butyl 1-methyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.5 g, crude) as yellow oil. LCMS: 171.2 ($\text{M}-56+\text{H}^+$).

Intermediate 18:

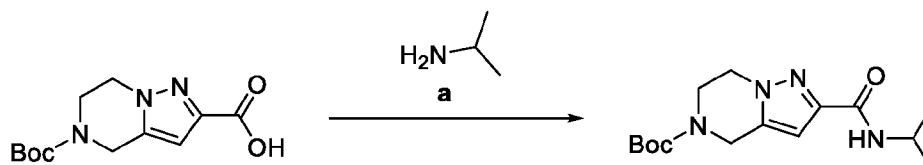
N-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide



Synthetic scheme:

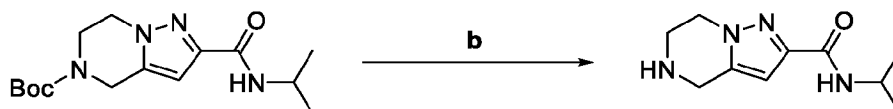


Step 1: Synthesis of tert-butyl 2-(isopropylcarbamoyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate



[00308] To a solution of 5-(tert-butoxycarbonyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (500 mg, 1.9 mmol, 1.0 eq) in DMF (8.0 mL) was added propan-2-amine (221 mg, 3.7 mmol, 2.0 eq), DIEA (725 mg, 5.6 mmol, 3.0 eq) and HATU (1.1 g, 2.8 mmol, 1.5 eq). The reaction mixture was stirred at room temperature for 2 h under nitrogen atmosphere. The mixture was diluted with water (15 mL) and extracted with EtOAc (20 mL x 3). The organic phases were washed with brine (20 mL x 3), dried with Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by silica gel column chromatography (DCM: MeOH = 40: 1) to give tert-butyl 2-(isopropylcarbamoyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (520 mg, 90.1%) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 6.70 – 6.63 (m, 1H), 6.59 (s, 1H), 4.65 (s, 2H), 4.30 – 4.20 (m, 1H), 4.16 (t, *J* = 5.2 Hz, 1H), 3.89 (t, *J* = 5.2 Hz, 2H), 1.49 (s, 9H), 1.24 (d, *J* = 6.4 Hz, 6H). LCMS: 309.2 (M+H⁺).

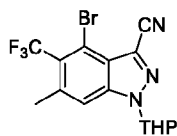
Step 2: Synthesis of N-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide



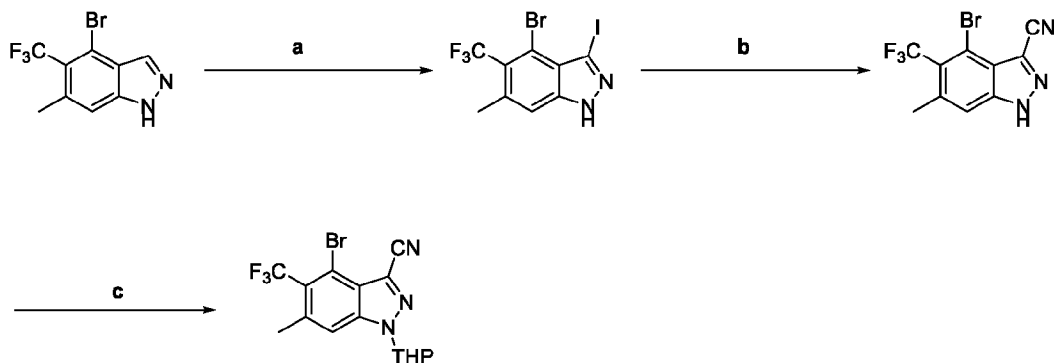
[00309] To a solution of tert-butyl 2-(isopropylcarbamoyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (520 mg, 1.7 mmol, 1.0 eq) in DCM (4 mL) was added TFA (2 mL). The reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give N-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide (350 mg, crude) as a yellow solid. LCMS: 209.2 (M+H⁺).

Intermediate 19:

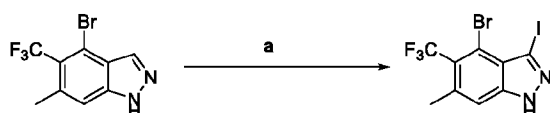
4-bromo-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazole-3-carbonitrile



Synthetic scheme:

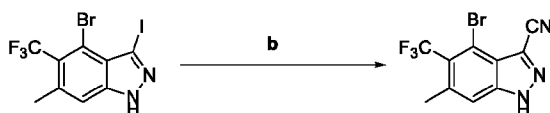


Step 1: Synthesis of 4-bromo-3-iodo-6-methyl-5-(trifluoromethyl)-1H-indazole



[00310] To a solution of 4-bromo-6-methyl-5-(trifluoromethyl)-1H-indazole (2.6 g, 9.4 mmol, 1.0 eq) in DMF (50 mL) was added KOH (2.1 g, 37.4 mmol, 4.0 eq) and I₂ (7.1 g, 28.1 mmol, 3.0 eq). The reaction mixture was stirred at room temperature for 12 h. The mixture was diluted with aqueous sodium thiosulfate solution (60 mL) and extracted with EtOAc (60 mL x 3). The organic phase was washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by silica gel column chromatography (petroleum ether / EtOAc = 5:1) to give 4-bromo-3-iodo-6-methyl-5-(trifluoromethyl)-1H-indazole (2.0 g, 52.9%) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 10.83 (brs, 1H), 7.37 (s, 1H), 2.67 – 2.60 (m, 3H). LCMS: 404.8, 406.9 (M+H⁺).

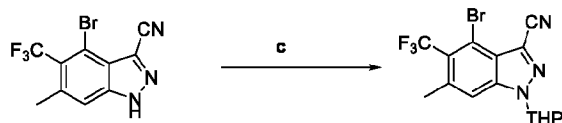
Step 2: Synthesis of 4-bromo-6-methyl-5-(trifluoromethyl)-1H-indazole-3-carbonitrile



[00311] To a solution of 4-bromo-3-iodo-6-methyl-5-(trifluoromethyl)-1H-indazole (2.0 g, 5.0 mmol, 1.0 eq) in DMF (40 mL) was added Zn(CN)₂ (1.2 g, 9.9 mmol, 2.0 eq), Zn (194 mg, 3.0 mmol, 0.6 eq), CuI (943 mg, 5.0 mmol, 1.0 eq) and Pd(dppf)Cl₂ (362 mg, 0.50 mmol, 0.1 eq). The reaction mixture was stirred at 100 °C for 15 h under nitrogen atmosphere. The mixture was diluted with aqueous sodium thiosulfate solution (50 mL) and extracted with EtOAc (50 mL x 3). The organic phase was washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by silica gel column chromatography (petroleum ether: EtOAc = 3: 1) to give 4-bromo-6-methyl-5-(trifluoromethyl)-1H-indazole-3-carbonitrile

(200 mg, 13.3%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 14.85 (brs, 1H), 7.79 (s, 1H), 2.75 – 2.57 (m, 3H). LCMS: 301.9, 304.0 (M-H $^+$).

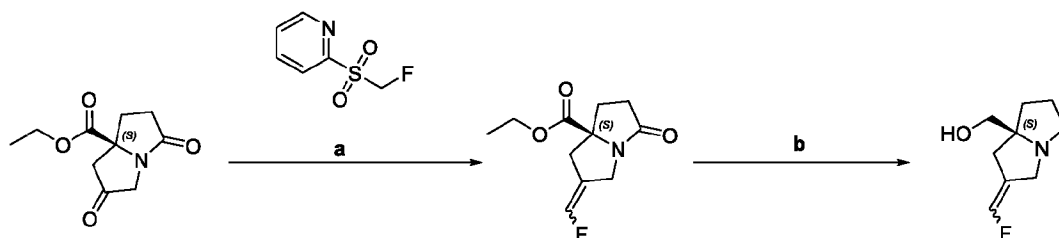
Step 3: Synthesis of 4-bromo-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazole-3-carbonitrile



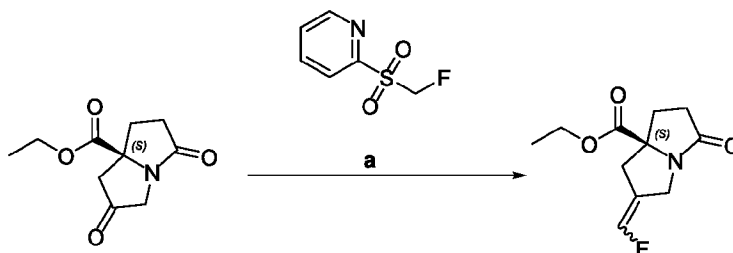
[00312] To a solution of 4-bromo-6-methyl-5-(trifluoromethyl)-1H-indazole-3-carbonitrile (320 mg, 1.1 mmol, 1.0 eq) and PTSA (18 mg, 0.11 mmol, 0.1 eq) in DCM (6 mL) was added DHP (133 mg, 1.6 mmol, 1.5 eq) in MeCN (1.5 mL). The reaction mixture was stirred at room temperature for 12 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 3). The organic phase was washed with brine (20 mL), dried over Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by prep-TLC (petroleum ether : EtOAc = 5: 1) to give 4-bromo-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazole-3-carbonitrile (250 mg, 61.2%) as a white solid. ^1H NMR (300 MHz, CDCl_3): δ 7.57 (s, 1H), 5.79 (dd, J = 7.8, 3.0 Hz, 1H), 3.94 – 3.82 (m, 1H), 3.81 – 3.68 (m, 1H), 2.71-2.64 (m, 3H), 2.56 – 2.40 (m, 1H), 2.26 – 2.06 (m, 2H), 1.90 – 1.65 (m, 3H).

Intermediate 20:

Synthesis scheme:

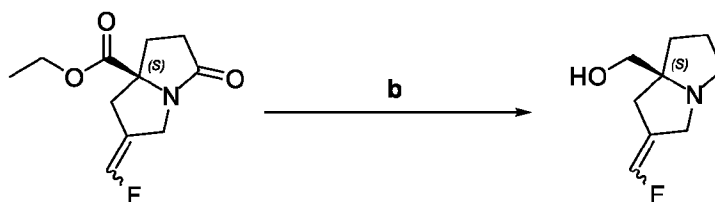


Step 1: Synthesis of ethyl (S)-2-(fluoromethylene)-5-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate



[00313] To a solution of 2-((fluoromethyl)sulfonyl) pyridine (4.6 g, 26.3 mmol, 1.1 eq) in THF (260 mL) under nitrogen was added KHMDS (31 mL, 30.77 mmol, 1.3 eq) at -78 °C. After 30 min, ethyl (S)-2,5-dioxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (5.0 g, 23.67 mmol, 1.0 eq) in THF (130 mL) was added slowly at -78 °C. After 3 h, the reaction system was warmed to room temperature and stirred overnight. Upon completion, the reaction was added saturated aqueous ammonium chloride solution (40 mL), followed by 3M HCl (80 mL). The mixture was stirred for 1 h at room temperature, diluted with water (50 mL), extracted with EtOAc (100 mL x 3), the combined organic layer was washed with saturated brine (50 mL) and dried over Na₂SO₄, filtered and concentrated to give a residue, which was purified by silica gel column chromatography (Petroleum ether: EtOAc = 5: 1) to give ethyl (S)-2-(fluoromethylene)-5-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (2.4 g, 44.6%) as a yellow oil. LCMS: m/z 228.1 (M+H⁺).

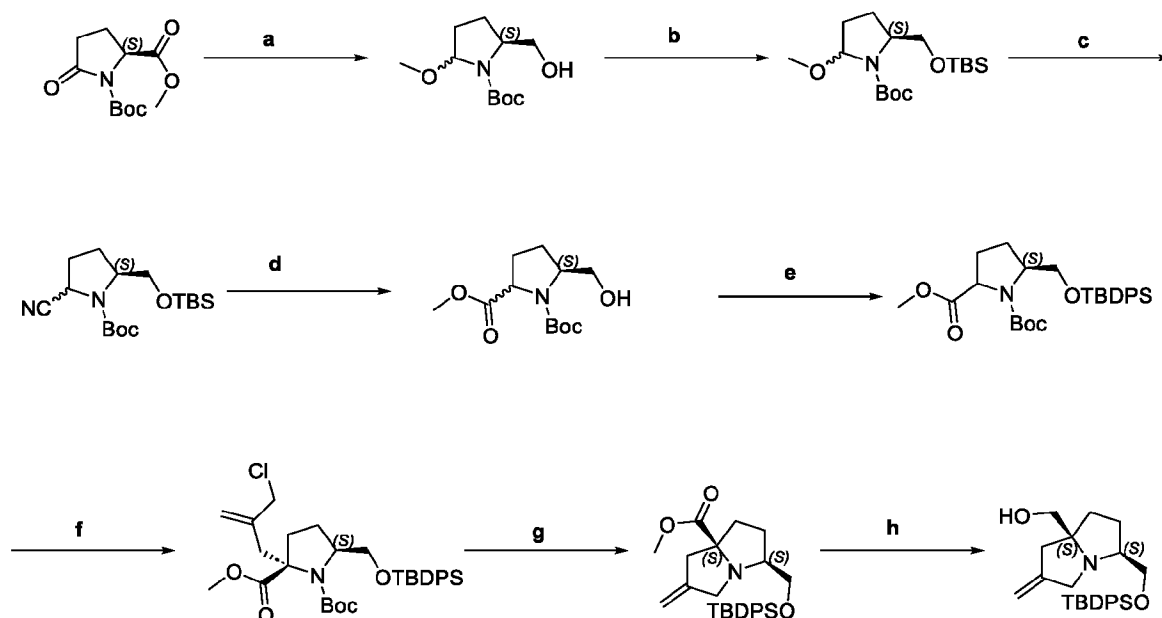
Step 2: Synthesis of (S)-(2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol



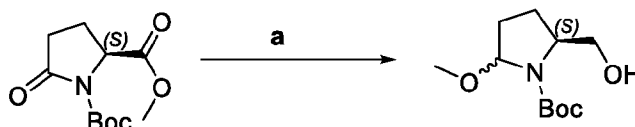
[00314] To a solution of ethyl (S)-2-(fluoromethylene)-5-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (2.8 g, 12.32 mmol, 1.0 eq) in THF (233 mL) was added DIBAL-H (1.5 M, 83.8 mL, 125.68 mmol, 10.2 eq) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. Upon completion, the reaction system was added Na₂SO₄·10H₂O (5 g). The solid was filtered and concentrated to give a residue, which was purified by silica gel column chromatography (DCM: MeOH = 8: 1) to give (S)-(2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (800 mg, 37.9%) as a yellow oil. LCMS: m/z 172.2 (M+H⁺).

Intermediate 21:

Synthetic scheme:

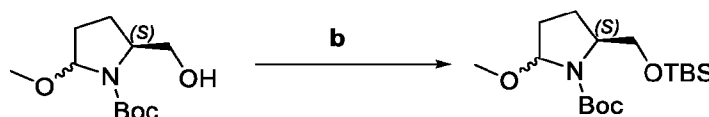


Step 1: Synthesis of tert-butyl (2S)-2-((hydroxymethyl)-5-methoxypyrrolidine-1-carboxylate



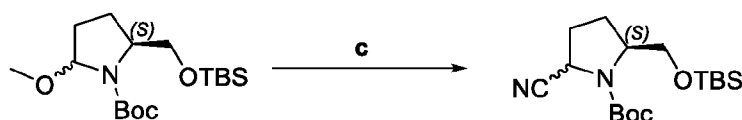
[00315] To a solution of 1-(tert-butyl) 2-methyl (S)-5-oxopyrrolidine-1,2-dicarboxylate (100.0 g, 411.1 mmol, 1.0 eq) in DCM (1.0 L) was added DIBAL-H (1.5M, 1.1 L, 1.6 mol, 4.0 eq) dropwise at -78 °C. The reaction mixture was stirred at room temperature for 2 h. The mixture was quenched by addition of MeOH (1.0 L) at 0 °C. The resulting white emulsion was poured into ice HCl (2 M, 1.0 L) solution at 0 °C. The mixture was stirred for 15 h at room temperature. The layers were separated. The aqueous layer was extracted with DCM (1.0 L x 2). The combined organic layers were washed with brine (1.0 L), dried over Na₂SO₄, filtered off and concentrated to give a residue. The residue was purified by silica gel chromatography (petroleum ether: EtOAc = 4: 1) to give tert-butyl (2S)-2-((hydroxymethyl)-5-methoxypyrrolidine-1-carboxylate (35.0 g, 36.8%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 4.29 (brs, 1H), 4.07 – 3.46 (m, 4H), 3.43 – 3.20 (m, 3H), 2.14 – 1.67 (m, 4H), 1.49 (s, 9H).

Step 2: Synthesis of tert-butyl (2S)-2-(((tert-butyldimethylsilyl)oxy)methyl)-5-methoxypyrrolidine-1-carboxylate



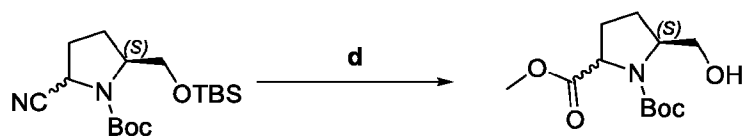
[00316] To a solution of tert-butyl (2S)-2-(hydroxymethyl)-5-methoxypyrrolidine-1-carboxylate (35.0 g, 151.3 mmol, 1.0 eq) in DCM (350 mL) was added Imidazole (15.5 g, 227.0 mmol, 1.5 eq) and TBSCl (27.4 g, 181.6 mmol, 1.2 eq) in portions at 0 °C. The reaction was stirred at room temperature for 15 h under N₂. The reaction was quenched with water (300 mL) and separated. The aqueous layer was extracted with DCM (300 mL x 2). The combined organic layers were washed with brine (300 mL), dried over Na₂SO₄, filtered off and concentrated to give a crude. The crude was purified by silica gel chromatography (petroleum ether: EtOAc = 5: 1) to give tert-butyl (2S)-2-(((tert-butyldimethylsilyl)oxy)methyl)-5-methoxypyrrolidine-1-carboxylate (40.0 g, 76.5%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 5.53 – 4.86 (m, 1H), 4.04 – 3.20 (m, 6H), 2.25 – 1.68 (m, 4H), 1.48 (s, 9H), 0.88 (s, 9H), 0.05 (s, 6H).

Step 3: Synthesis of tert-butyl (2S)-2-(((tert-butyldimethylsilyl)oxy)methyl)-5-cyanopyrrolidine-1-carboxylate



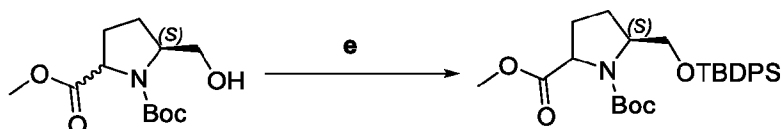
[00317] To a solution of tert-butyl (2S)-2-(((tert-butyldimethylsilyl)oxy)methyl)-5-methoxypyrrolidine-1-carboxylate (40.0 g, 115.8 mmol, 1.0 eq) in DCM (400 mL) was added TMSOTf (3.9 g, 17.4 mmol, 0.15 eq) and TMSCN (17.2 g, 173.6 mmol, 1.5 eq) dropwise at -78 °C. The reaction was stirred at -78 °C for 1 h under N₂. The reaction was quenched with sat. NaHCO₃ aqueous solution (200 mL) at -78 °C, and separated. The aqueous layer was extracted with DCM (200 mL x 2). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄, filtered off and concentrated to give a crude. The crude was purified by silica gel chromatography (petroleum ether: EtOAc = 10: 1) to give tert-butyl (2S)-2-(((tert-butyldimethylsilyl)oxy)methyl)-5-cyanopyrrolidine-1-carboxylate (20.0 g, 50.8%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 4.55 – 4.40 (m, 1H), 4.05 – 3.52 (m, 3H), 2.52 – 2.00 (m, 4H), 1.52 (s, 9H), 0.87 (s, 9H), 0.03 (s, 6H).

Step 4: Synthesis of 1-(tert-butyl) 2-methyl (5S)-5-(hydroxymethyl)pyrrolidine-1,2-dicarboxylate



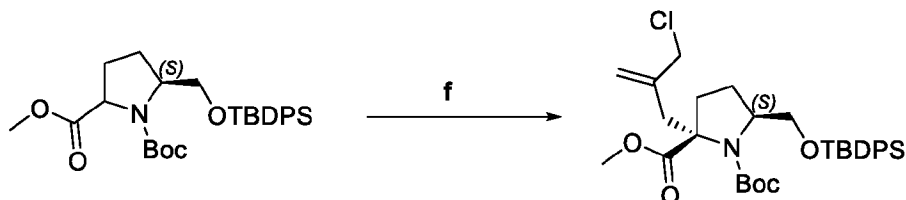
[00318] To a solution of tert-butyl (2S)-2-(((tert-butyldimethylsilyl)oxy)methyl)-5-cyanopyrrolidine-1-carboxylate (20.0 g, 58.7 mmol, 1.0 eq) in MeOH (200 mL) was added K_2CO_3 (20.3 g, 146.8 mmol, 2.5 eq). The reaction was stirred at room temperature for 3 h under N_2 . The reaction mixture was adjusted pH ~ 2 with 10% HCl aqueous solution. The resulting mixture was stirred at room temperature for 15 h. The mixture was extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4 , filtered off and concentrated to give a crude. The crude was purified by silica gel chromatography (petroleum ether: EtOAc = 5: 1) to give 1-(tert-butyl) 2-methyl (5S)-5-(hydroxymethyl)pyrrolidine-1,2-dicarboxylate (10.0 g, 65.6%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 4.40 – 4.00 (m, 2H), 3.72 (s, 3H), 3.69 – 3.57 (m, 2H), 2.34 – 2.03 (m, 2H), 1.98 – 1.84 (m, 1H), 1.72 – 1.58 (m, 1H), 1.41 (s, 9H). LCMS: 282.2 ($M+Na^+$).

Step 5: Synthesis of 1-(tert-butyl) 2-methyl (5S)-5-(((tert-butyldiphenylsilyl)oxy)methyl)pyrrolidine -1,2-dicarboxylate



[00319] To a solution of 1-(tert-butyl) 2-methyl (5S)-5-(hydroxymethyl)pyrrolidine-1,2-dicarboxylate (10.0 g, 38.6 mmol, 1.0 eq) in DCM (100 mL) was added Imidazole (3.9 g, 57.8 mmol, 1.5 eq) and TBDPSCl (12.7 g, 46.3 mmol, 1.2 eq) dropwise at 0 °C. The reaction was stirred at room temperature for 15 h under N_2 . The reaction was quenched with water (300 mL) and separated. The aqueous layer was extracted with DCM (300 mL x 2). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4 , filtered off and concentrated to give a crude. The crude was purified by silica gel chromatography (petroleum ether: EtOAc = 5: 1) to give 1-(tert-butyl) 2-methyl (5S)-5-(((tert-butyldiphenylsilyl)oxy)methyl)pyrrolidine-1,2-dicarboxylate (10.0 g, 52.1%) as a colorless oil. LCMS: 398.2 ($M-100+H^+$).

Step 6: Synthesis of 1-(tert-butyl) 2-methyl (2S,5S)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-2-(2-(chloromethyl)allyl)pyrrolidine-1,2-dicarboxylate



[00320] To a solution of 1-(tert-butyl) 2-methyl (5S)-5-(((tert-butyl)diphenylsilyl)oxy)methyl)pyrrolidine-1,2-dicarboxylate (10.0 g, 20.1 mmol, 1.0 eq) in THF (100 mL) was added HMPA (18.0 g, 100.5 mmol, 5.0 eq) and LDA (2M) (20.1 mL, 40.2 mmol, 2.0 eq) dropwise at -78 °C. Then the reaction mixture was stirred at -78 °C for 30 min. The mixture was added 3-chloro-2-(chloromethyl)prop-1-ene (5.0 g, 40.2 mmol, 2.0 eq) dropwise at -78 °C and stirred at room temperature for 15 h. The reaction was quenched with sat. NH₄Cl solution (100 mL) at 0 °C and separated. The aqueous layer was extracted with EtOAc (100 mL x 2). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered off and concentrated to give a crude. The crude was purified by silica gel chromatography (petroleum ether: EtOAc = 5: 1) to give 1-(tert-butyl) 2-methyl (2S,5S)-5-(((tert-butyl)diphenylsilyl)oxy)methyl)-2-(2-(chloromethyl)allyl)pyrrolidine-1,2-dicarboxylate (4.0 g, 34.0%) as a colorless oil. LCMS: 486.2 (M-100+H⁺).

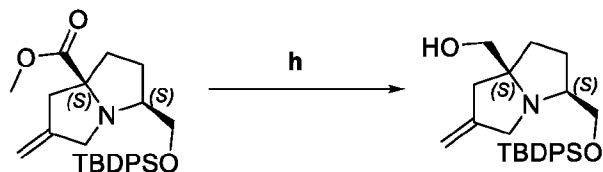
Step 7: Synthesis of methyl (5S,7aS)-5-(((tert-butyl)diphenylsilyl)oxy)methyl)-2-methylene tetrahydro-1H-pyrrolizine-7a(5H)-carboxylate



[00321] To a solution of 1-(tert-butyl) 2-methyl (2S,5S)-5-(((tert-butyl)diphenylsilyl)oxy)methyl)-2-(2-(chloromethyl)allyl)pyrrolidine-1,2-dicarboxylate (4.0 g, 6.8 mmol, 1.0 eq) in DCM (40 mL) was added TFA (7.8 g, 68.2 mmol, 10.0 eq). Then the reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated to give a residue. The residue was dissolved in MeOH (40 mL). The mixture was added K₂CO₃ until pH > 7. The reaction was stirred at room temperature for 40 min. The reaction was quenched with water (40 mL). The resulting mixture was extracted with DCM (40 mL x 3). The combined organic layers were washed with brine (40 mL), dried over Na₂SO₄, filtered off and concentrated to give a crude. The crude was purified by silica gel chromatography (petroleum ether: EtOAc = 5: 1) to give methyl (5S,7aS)-5-(((tert-butyl)diphenylsilyl)oxy)methyl)-2-methylenetetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (2.0 g, 65.1%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 7.68 (t, J = 6.8 Hz, 4H), 7.50 – 7.32 (m, 6H), 4.97 – 4.82 (m, 2H), 3.79 – 3.60 (m, 5H), 3.55 (t,

$J = 6.8$ Hz, 1H), 3.24 (d, $J = 14.8$ Hz, 1H), 2.99 – 2.78 (m, 2H), 2.47 – 2.30 (m, 2H), 2.10 – 1.96 (m, 1H), 1.80 – 1.63 (m, 2H), 1.05 (s, 9H). LCMS: 450.2 ($M+H^+$).

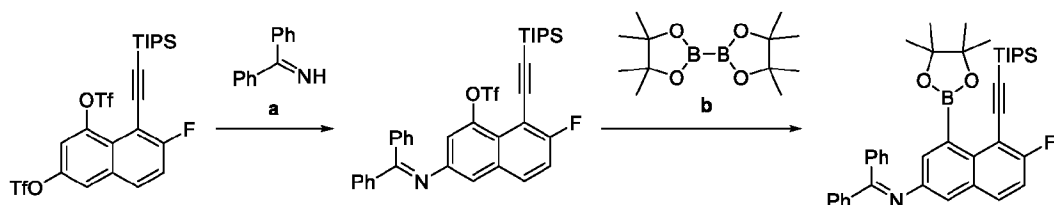
Step 8: Synthesis of ((5S,7aS)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-2-methylene tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol



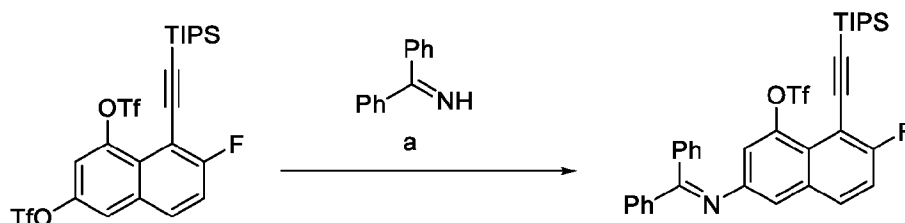
[00322] To a solution of methyl ((5S,7aS)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-2-methylenetetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (2.0 g, 4.4 mmol, 1.0 eq) in THF (20 mL) was added LAH (4.4 mL, 1 M in THF, 4.4 mmol, 1.0 eq) at 0 °C. Then the reaction mixture was stirred at room temperature for 2 h. The mixture was quenched with water (0.17 mL), 15% NaOH aqueous solution (0.17 mL) and water (0.51 mL) in turns at 0 °C. The resulting mixture was dried over Na_2SO_4 , filtered off and concentrated to give a crude. The crude was purified by silica gel chromatography (petroleum ether: EtOAc = 2: 1) to give ((5S,7aS)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (1.0 g, 53.2%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.75 – 7.62 (m, 4H), 7.48 – 7.34 (m, 6H), 4.96 – 4.83 (m, 2H), 3.67 3.47 (m, 3H), 3.42 – 3.28 (m, 1H), 3.21 (s, 2H), 3.06 – 2.80 (m, 2H), 2.42 – 2.24 (m, 2H), 2.07 – 1.88 (m, 2H), 1.76 – 1.63 (m, 2H), 1.06 (s, 9H). LCMS: 422.2 ($M+H^+$).

Intermediate 22:

Synthetic scheme:

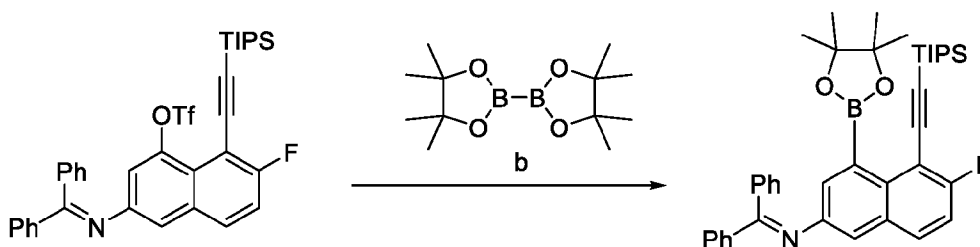


Step 1 Synthesis of 3-((diphenylmethylene)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate



[00323] To a solution of 7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalene-1,3-diyl bis(trifluoromethanesulfonate) (4.0 g, 6.4 mmol, 1.0 eq) in toluene (40 mL) was added diphenylmethanimine (2.3 g, 12.8 mmol, 2.0 eq), Cs_2CO_3 (6.3 g, 19.2 mmol, 3.0 eq), $\text{Pd}_2(\text{dba})_3$ (588 mg, 0.64 mmol, 0.10 eq) and Xantphos (744 mg, 1.3 mmol, 0.20 eq). The reaction mixture was stirred at 100 °C for 2 h under N_2 . The reaction mixture was partitioned between EtOAc (40 mL) and H_2O (40 mL). The layers were separated. The aqueous layer was extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to a crude. The crude was purified by silica gel column chromatography (Petroleum ether: EtOAc = 100: 1) to give 3-((diphenylmethylene)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate (2.0 g, 47.6%) as a yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 7.84 – 7.79 (m, 4H), 7.58 – 7.48 (m, 6H), 7.29 – 7.27 (m, 1H), 7.19 – 7.17 (m, 2H), 7.09 – 7.02 (m, 1H), 1.31 – 1.12 (m, 21H).

Step 2: Synthesis of N-(6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)-1,1-diphenylmethanimine

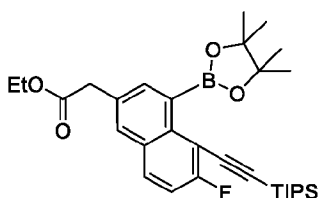


[00324] To a solution of 3-((diphenylmethylene)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate (1.0 g, 1.5 mmol, 1.0 eq) in toluene (10 mL) was added KOAc (450 mg, 4.5 mmol, 3.0 eq) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (222 mg, 0.31 mmol, 0.2 eq) at room temperature. The reaction mixture was stirred at 110 °C for 18 h under nitrogen atmosphere. The mixture was filtered, and the filtrate was concentrated to give a residue. The residue was partitioned between EtOAc (10 mL) and H_2O (10 mL). The layers were separated. The aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated to a crude. The

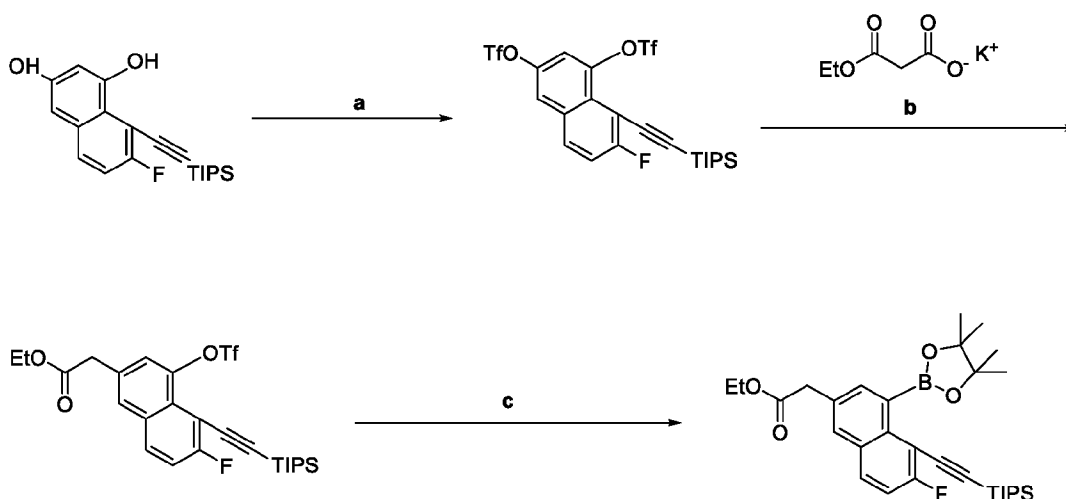
crude was purified by silica gel column chromatography (Petroleum ether : EtOAc = 100 : 1) to give N-(6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)-1,1-diphenylmethanimine (600 mg, 62.1%) as a yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 7.49 (d, J = 2.8 Hz, 2H), 7.58 – 7.41 (m, 4H), 7.29 (s, 1H), 7.25 – 7.06 (m, 7H), 1.26 (s, 21H), 1.15 (s, 12H).

Intermediate 23:

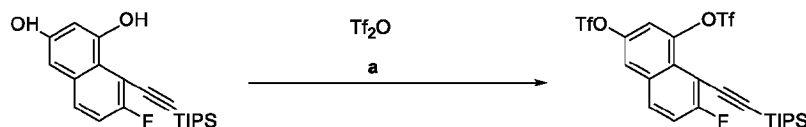
ethyl 2-(6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)acetate



Synthetic scheme:



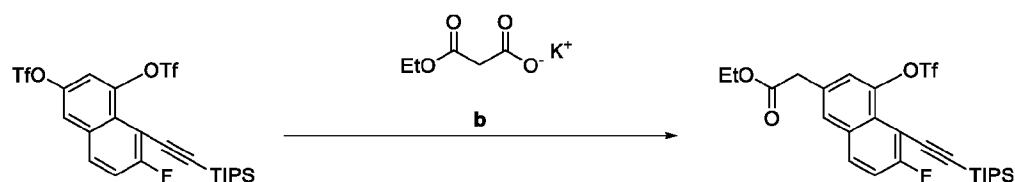
Step 1: Synthesis of 7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalene-1,3-diyl bis(trifluoromethanesulfonate)



[00325] To a solution of 7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalene-1,3-diol (3.0 g, 8.4 mmol, 1.0 eq) in DCM (60 mL) was added DIEA (6.5 g, 50.4 mmol, 6.0 eq) and Tf_2O (9.5 g, 33.6 mmol, 4.0 eq) at 0 °C under N_2 atmosphere. The reaction mixture was stirred at 0 °C for 2 h.

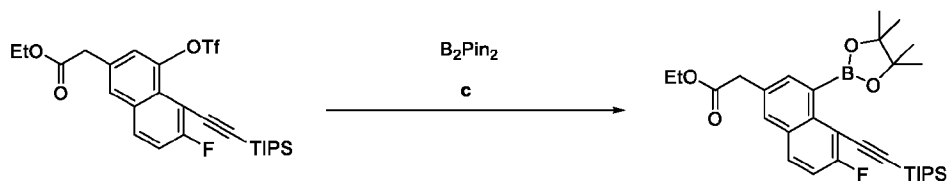
The mixture was diluted with water (20 mL) and extracted with DCM (20 mL x 3). The combined organic phase was dried over Na₂SO₄ and concentrated to give a residue. The crude product was purified by column chromatography (Petroleum ether: EtOAc = 20: 1) to give 7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalene-1,3-diyl bis(trifluoromethanesulfonate) (4.7 g, 89.9%) as a yellow solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.55 (d, *J* = 2.4 Hz, 1H), 8.50-8.30 (m, 1H), 8.12 (d, *J* = 2.1 Hz, 1H), 7.86 (t, *J* = 9.0 Hz, 1H), 3.34 (s, 3H), 1.12 (s, 18H).

Step 2: Synthesis of ethyl 2-(6-fluoro-4-(((trifluoromethyl)sulfonyl)oxy)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)acetate



[00326] To a solution of 7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalene-1,3-diyl bis(trifluoromethanesulfonate) (2.0 g, 3.2 mmol, 1.0 eq) and potassium 3-ethoxy-3-oxopropanoate (817 mg, 4.8 mmol, 1.5 eq) in Xylene (34.3 mL) was added DMAP (39 mg, 0.32 mmol, 0.1 eq) at room temperature under N₂ atmosphere. The reaction mixture was stirred at room temperature for 5 min. Allylpalladium(II) Chloride Dimer (23 mg, 0.064 mmol, 0.02 eq) and BINAP (118 mg, 0.19 mmol, 0.06 eq) were added, then the reaction mixture was stirred at 140 °C for 5 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic phase was dried over Na₂SO₄ and concentrated to give a residue. The crude product was purified by column chromatography (Petroleum ether: EtOAc = 30: 1) to give ethyl 2-(6-fluoro-4-(((trifluoromethyl)sulfonyl)oxy)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)acetate (1.0 g, 55.7%) as a yellow liquid. LCMS: *m/z* 561.2 (M+H⁺).

Step 3: Synthesis of ethyl 2-(6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)acetate



[00327] To a solution of ethyl 2-(6-fluoro-4-(((trifluoromethyl)sulfonyl)oxy)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)acetate (500 mg, 0.89 mmol, 1.0 eq), B₂Pin₂ (452 mg, 1.78 mmol, 2.0 eq) and KOAc (262 mg, 2.67 mmol, 3.0 eq) in PhMe (5.0 mL) was added

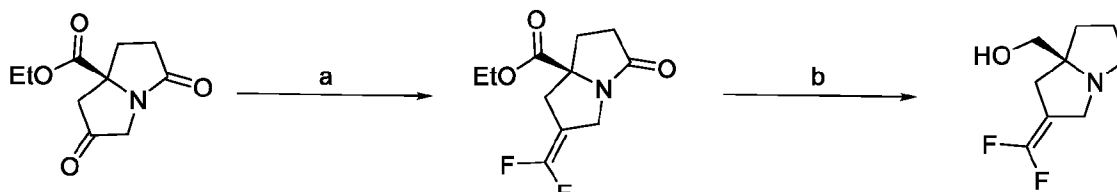
Pd(dppf)Cl₂ (65 mg, 0.089 mmol, 0.1 eq) at room temperature under N₂ atmosphere. The reaction mixture was stirred at 130 °C for 2 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give a residue. The crude product was purified by column chromatography (Petroleum ether: EtOAc = 50: 1) to give ethyl 2-(6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)acetate (450 mg, 93.9%) as a yellow liquid. ¹H NMR (400 MHz, CDCl₃): δ 7.80-7.60 (m, 3H), 7.23 (d, *J* = 8.8 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.73 (s, 2H), 1.30-1.20 (m, 18H), 1.15 (s, 18H).

Intermediate 24:

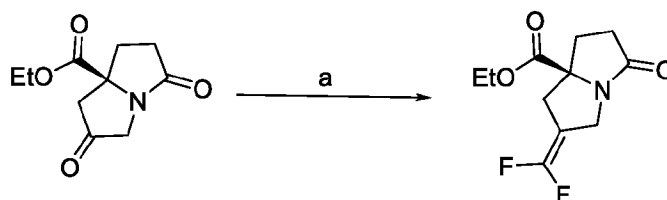
(S)-(2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol



Synthetic scheme



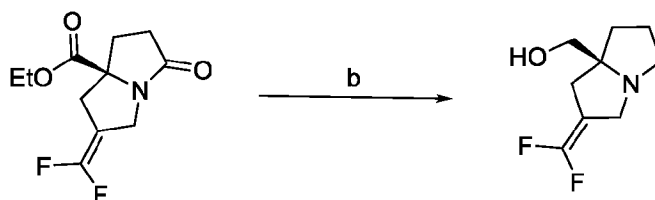
Step 1: Synthesis of ethyl (S)-2-(difluoromethylene)-5-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate



[00328] To a solution of ethyl (S)-2,5-dioxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (500 mg, 2.4 mmol, 1.0 eq) and HMPT (1.2 g, 7.1 mmol, 3.0 eq) in THF (8 mL) was added CF₂Br₂ (1.8 g, 7.1 mmol, 3.0 eq) at 0 °C under nitrogen atmosphere. The reaction mixture was warmed to room temperature and Zn (465 mg, 7.1 mmol, 3.0 eq) was added. The reaction was

stirred at 80 °C for 3 h under nitrogen atmosphere. The mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 3). The organic phase was washed with brine (20 mL), dried with Na₂SO₄, filtered and concentrated to give a crude. The crude was purified by silica gel column chromatography (dichloromethane : ethyl acetate = 8 : 1) to give ethyl (S)-2-(difluoromethylene)-5-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (160 mg, 27.6%) as yellow oil. ¹H NMR (300 MHz, CDCl₃): δ 4.41 – 4.39 (m, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.81 – 3.65 (m, 1H), 3.19 – 3.05 (m, 1H), 2.85 – 2.73 (m, 1H), 2.68 – 2.65 (m, 1H), 2.53 – 2.35 (m, 2H), 2.22 – 2.07 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 3H). LCMS: 246.1 (M+H⁺).

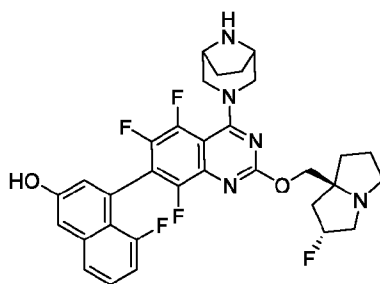
Step 2: Synthesis of (S)-(2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol



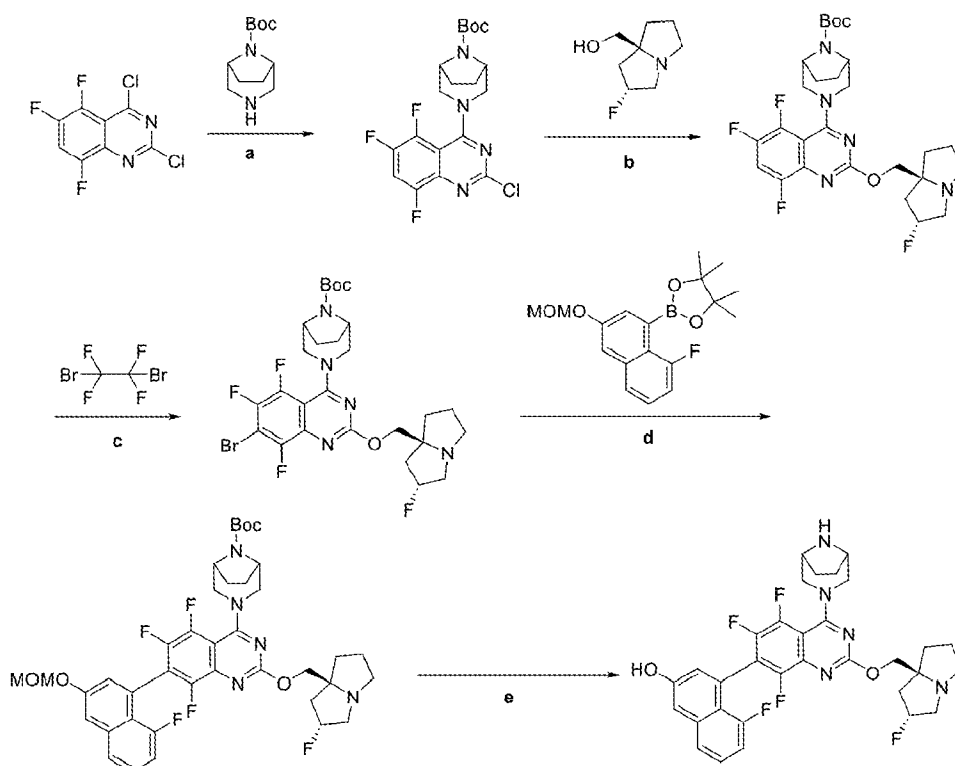
[00329] To a solution of ethyl (S)-2-(difluoromethylene)-5-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (160 mg, 0.65 mmol, 1.0 eq) in THF (3 mL) was added DIBAL-H (4.4 mL, 6.5 mmol, 10.0 eq, 1.5 M in toluene) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1 h. The mixture was quenched with Na₂SO₄·10H₂O, filtered and concentrated to give (S)-(2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (80 mg, 65.0%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 3.65 – 3.56 (m, 1H), 3.39 – 3.19 (m, 3H), 3.12 – 3.02 (m, 1H), 2.69 – 2.58 (m, 1H), 2.47 – 2.37 (m, 1H), 2.36 – 2.28 (m, 1H), 1.99 – 1.92 (m, 1H), 1.91 – 1.84 (m, 1H), 1.83 – 1.76 (m, 1H), 1.75 – 1.69 (m, 1H). LCMS: 190.1 (M+H⁺).

Example 1

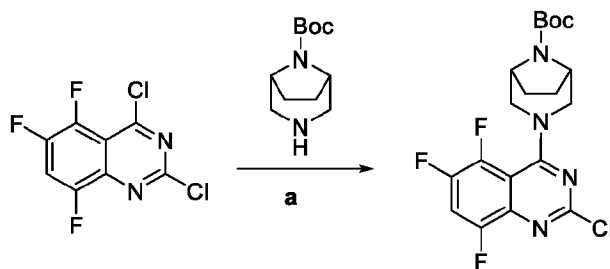
4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5,6,8-trifluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-5-fluoronaphthalen-2-ol



Synthetic scheme:



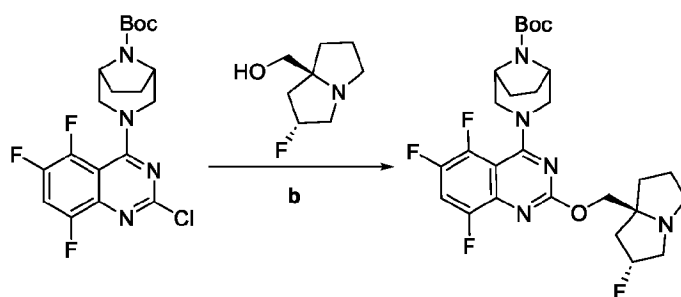
Step 1: Synthesis of tert-butyl 3-(2-chloro-5,6,8-trifluoroquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00330] To a solution of 2,4-dichloro-5,6,8-trifluoroquinazoline (300 mg, 1.19 mmol, 1.0 eq) in DCM (5 mL) was added DIEA (461 mg, 3.57 mmol, 3.0 eq) and dropwise a solution of tert-

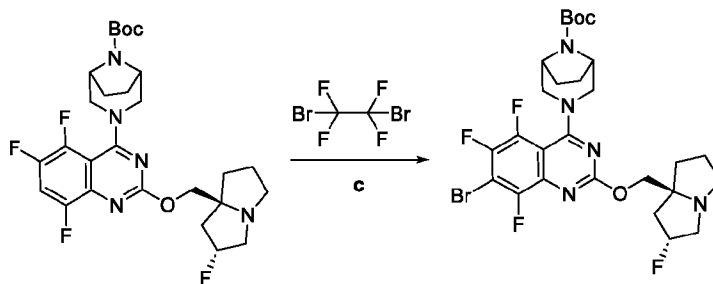
butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (232 mg, 1.19 mmol, 1.0 eq) in DCM (2 mL) stirring at -60 °C under nitrogen atmosphere. The mixture was stirred at -60 °C for 2 h under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (petroleum ether: EtOAc = 10: 1) to afford tert-butyl 3-(2-chloro-5,6,8-trifluoroquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (300 mg, 58.9%) as a white solid. ¹H NMR (300 MHz, CDCl₃): δ 7.40 – 7.28 (m, 1H), 4.43 – 4.13 (m, 2H), 4.12 – 3.97 (m, 2H), 3.59 – 3.44 (m, 2H), 1.89 – 1.78 (m, 2H), 1.70 – 1.55 (m, 2H), 1.44 (s, 9H). LCMS: m/z 429.1 (M+H⁺).

Step 2: Synthesis of tert-butyl 3-(5,6,8-trifluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



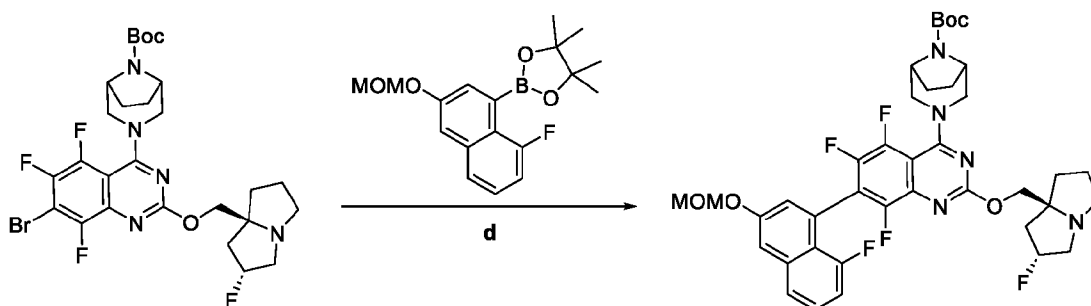
[00331] To a solution of 2,4-dichloro-5,6,8-trifluoroquinazoline (280 mg, 0.65 mmol, 1.0 eq) in DMSO (3 mL) was added (2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (156 mg, 0.98 mmol, 1.5 eq) and KF (304 mg, 5.23 mmol, 8.0 eq). The mixture was stirred at 120 °C for 2 h. The reaction mixture was diluted with H₂O (5 mL) and extracted with EtOAc (5 mL x 3). The organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (DCM: MeOH = 40: 1) to afford tert-butyl 3-(5,6,8-trifluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (150 mg, 41.6%) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 7.35 – 7.28 (m, 1H), 5.30 (d, *J* = 54 Hz, 1H), 4.43 – 4.19 (m, 4H), 4.17 – 3.98 (m, 3H), 3.55 – 3.15 (m, 5H), 3.06 – 2.95 (m, 1H), 2.37 – 2.29 (m, 1H), 2.24 – 2.16 (m, 1H), 2.06 – 1.95 (m, 4H), 1.93 – 1.87 (m, 2H), 1.80 – 1.71 (m, 2H), 1.50 (s, 9H). LCMS: m/z 552.3 (M+H⁺).

Step 3: Synthesis of tert-butyl 3-(7-bromo-5,6,8-trifluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo [3.2.1] octane-8-carboxylate



[00332] To a solution of tert-butyl 3-(5,6,8-trifluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (150 mg, 0.27 mmol, 1.0 eq) in THF (3 mL) was added LDA (2 M in THF, 0.27 mL, 0.54 mmol, 2.0 eq) at -65 °C under nitrogen atmosphere. The mixture was stirred at -65 °C for 30 min. Then 1,2-dibromo-1,1,2,2-tetrafluoroethane (105 mg, 0.41 mmol, 1.5 eq) was added. The mixture was stirred at room temperature for another 1 h, then quenched with H₂O (5 mL) and extracted with EtOAc (5 mL x 3). The organic layers were combined and washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give crude product, which was purified by silica gel column chromatography (DCM: MeOH = 40: 1) to provide tert-butyl 3-(7-bromo-5,6,8-trifluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (70 mg, 40.9%) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 5.28 (d, *J* = 53.6 Hz, 1H), 4.39 – 3.99 (m, 6H), 3.53 – 3.41 (m, 3H), 3.31 – 3.15 (m, 2H), 3.03 – 2.91 (m, 1H), 2.31 – 1.69 (m, 10H), 1.50 (s, 9H). LCMS: *m/z* 630.2, 632.2 (M+H⁺).

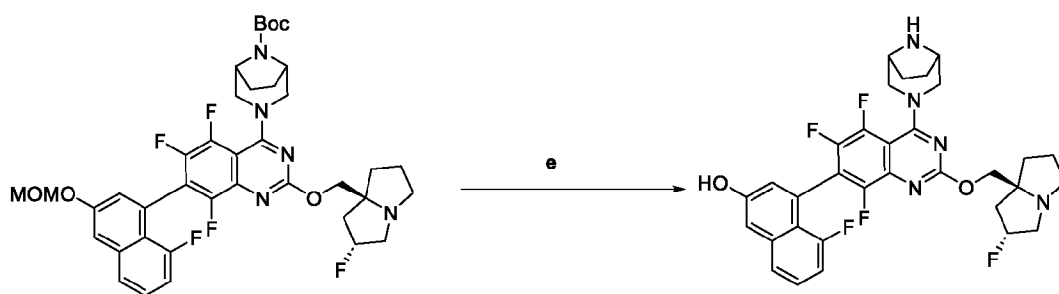
Step 4: Synthesis of tert-butyl 3-(5,6,8-trifluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00333] To a solution of tert-butyl 3-(7-bromo-5,6,8-trifluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-

diazabicyclo[3.2.1]octane-8-carboxylate (70 mg, 0.11 mmol, 1.0 eq) in dioxane (2 mL) and H₂O (0.5 mL) was added 2-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (55 mg, 0.17 mmol, 1.5 eq), K₂CO₃ (46 mg, 0.33 mmol, 3.0 eq) and Pd(PPh₃)₄ (13 mg, 0.01 mmol, 0.1 eq) under N₂. The mixture was stirred at 100 °C for 5 h. The reaction mixture was diluted with H₂O (5 mL) and extracted with EtOAc (5 mL x 3). The organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (DCM: MeOH = 20: 1) to afford tert-butyl 3-(5,6,8-trifluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (54 mg, 64.3%) as a white solid. LCMS: m/z 756.0 (M+H⁺).

Step 5: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5,6,8-trifluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-5-fluoronaphthalen-2-ol

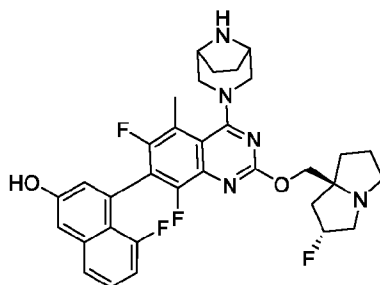


[00334] To a solution of tert-butyl 3-(5,6,8-trifluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (54 mg, 0.07 mmol) in DCM (2 mL) was added HCl in dioxane (4 M, 1 mL). The reaction was stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure, then diluted with MeOH (2 mL). The solution pH was adjusted to around 9 by adding aq. NaHCO₃ (2 mL). Then the mixture was concentrated under reduced pressure and diluted with solvent mixture of DCM and MeOH (15: 1, 5 mL), filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (0.1% FA in H₂O) to afford 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5,6,8-trifluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-5-fluoronaphthalen-2-ol (14.8 mg, 31.5%) formic salt as a

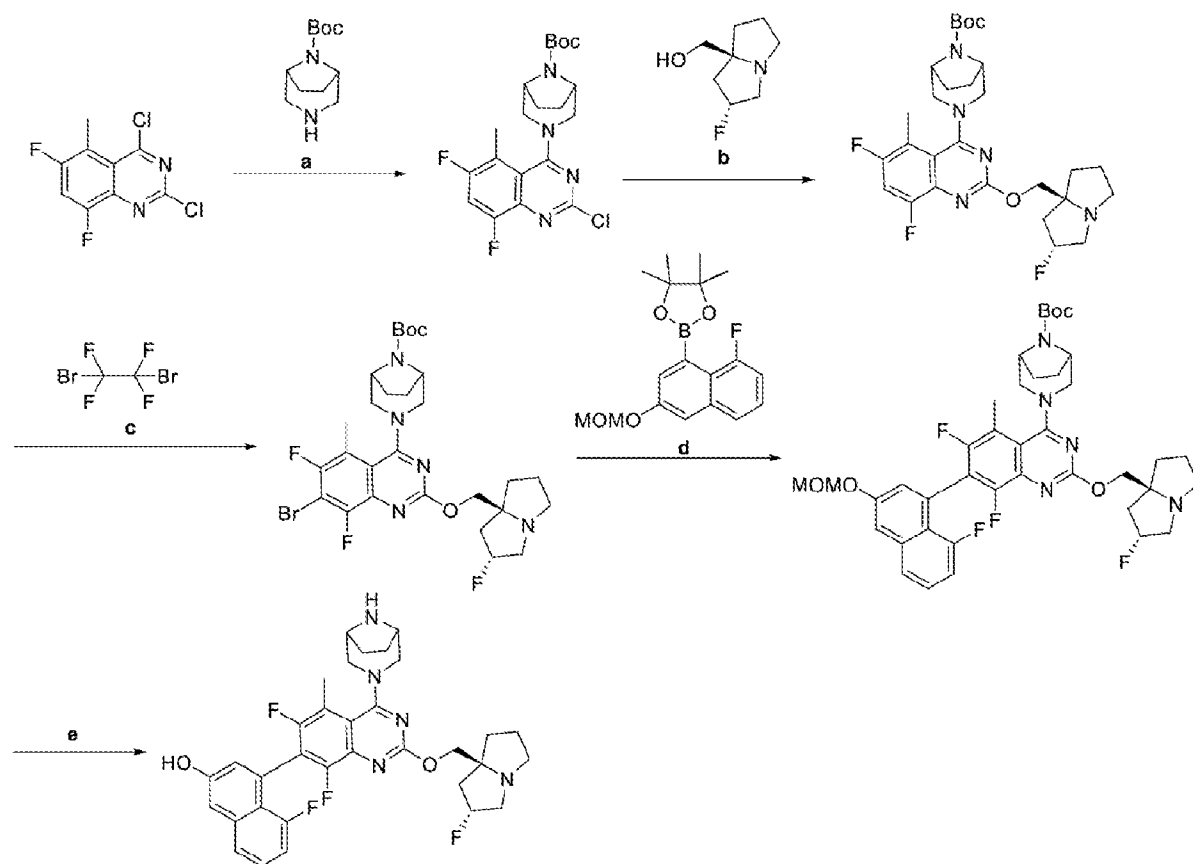
white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.22 (bs, 1H), 7.69 (d, $J = 8.4$ Hz, 1H), 7.49 – 7.37 (m, 2H), 7.18 (d, $J = 2.4$ Hz, 1H), 7.05 (m, 1H), 5.28 (d, $J = 53.6$ Hz, 1H), 4.13 – 4.05 (m, 2H), 4.03 – 3.95 (m, 2H), 3.75 – 3.61 (m, 2H), 3.44 (m, 2H), 3.14 – 3.04 (m, 2H), 3.01 (s, 1H), 2.83 (m, 1H), 2.19 – 1.95 (m, 3H), 1.89 – 1.63 (m, 7H). LCMS: m/z 612.0 ($\text{M}+\text{H}^+$).

Example 2

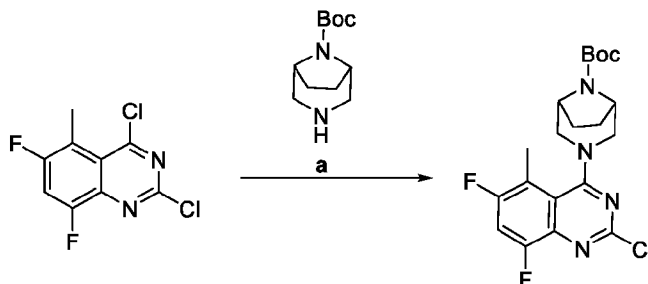
4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-7-yl)-5-fluoronaphthalen-2-ol



Synthetic scheme:

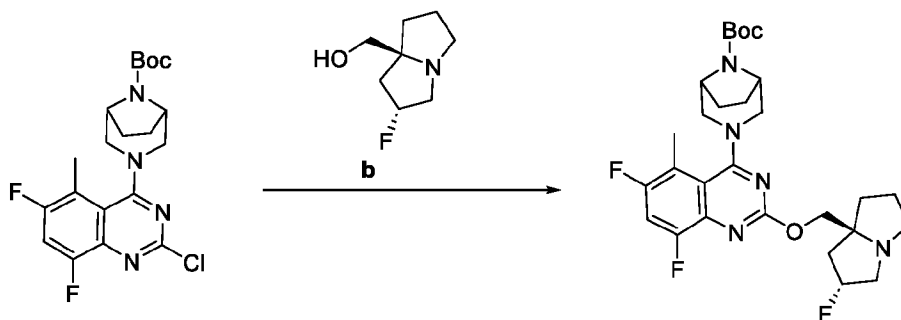


Step 1: Synthesis of tert-butyl 3-(2-chloro-6,8-difluoro-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00335] To a solution of 2,4-dichloro-6,8-difluoro-5-methylquinazoline (100 mg, 0.4 mmol, 1.0 eq) and DIEA (155 mg, 1.2 mmol, 3.0 eq) in DCM (2 mL) was added tert-butyl (1R,5S)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (85 mg, 0.4 mmol, 1.0 eq) at -40 °C under nitrogen atmosphere. The reaction was stirred at the same temperature for 2 h, then concentrated to give a residue. The residue was partitioned between DCM (10 mL) and water (5 mL). The layers were separated. The aqueous layer was extracted with DCM (5 mL x 3). The combined organic layers were washed with H₂O (5 mL), brine (5 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by preparation TLC (petroleum ether/EtOAc = 1: 1) to afford the desired product, tert-butyl 3-(2-chloro-6,8-difluoro-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (130 mg, 76.2%) as a yellow solid. LCMS: m/z 425.2 (M+H⁺).

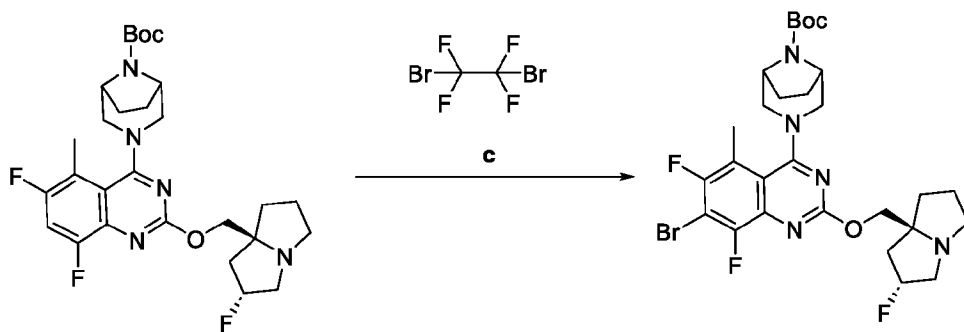
Step 2: Synthesis of tert-butyl 3-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-4-yl)-3,8-diazabicyclo [3.2.1]octane-8-carboxylate



[00336] To a mixture of tert-butyl 3-(2-chloro-6,8-difluoro-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (152 mg, 0.36 mmol, 1.0 eq) and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (68 mg, 0.43 mmol, 1.2 eq) in THF (0.8 mL)

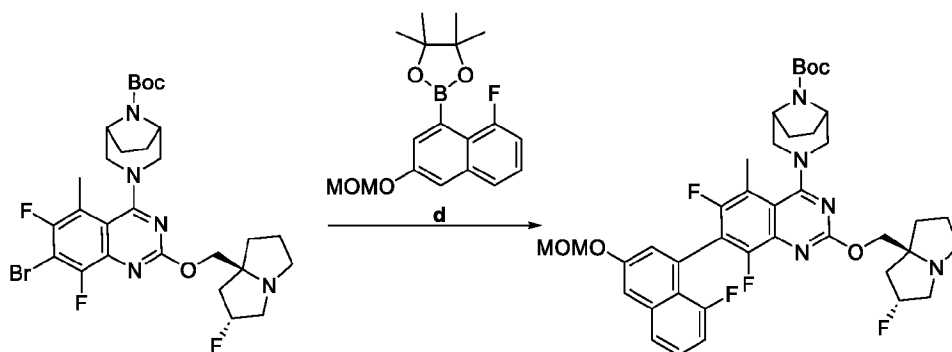
in DMF (0.8 mL) were added DABCO (40 mg, 0.36 mmol, 1.0 eq) and Cs_2CO_3 (350 mg, 1.07 mmol, 3.0 eq) under nitrogen atmosphere. The solution was stirred at room temperature for 15 h. H_2O (3 mL), was added and the mixture was extracted with EtOAc (3 mL x 3). The combined organic layers were washed with H_2O (3 mL), brine (3 mL), dried over Na_2SO_4 and evaporated to dryness. The crude residue was purified by silica gel column chromatography (DCM/MeOH = 15: 1) to give the desired product, tert-butyl (1R,5S)-3-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (147 mg, 74.6%) as a white solid. LCMS: m/z 548.3 ($\text{M}+\text{H}^+$).

Step 3: Synthesis of tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-4-yl)-3,8-diazabicyclo [3.2.1]octane-8-carboxylate



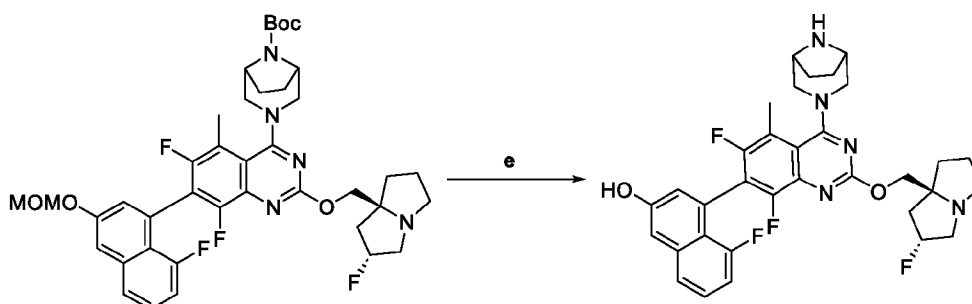
[00337] To a solution of tert-butyl 3-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (120 mg, 0.22 mmol, 1.0 eq) in THF (3 mL) was added LDA (0.2 mL, 0.44 mmol, 2.0 eq) at -65 °C under N_2 atmosphere and stirred for 30 min, then added 1,2-dibromo-1,1,2,2-tetrafluoroethane (107 mg, 0.33 mmol, 1.5 eq). The reaction was stirred at the same temperature for 2.5 h, then quenched with water. The mixture was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with H_2O (5 mL), brine (5 mL), dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by prep-TLC (DCM/MeOH = 12: 1) to afford the desired product, tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (118 mg, 86.1%) as a brown solid.

Step 4: Synthesis of tert-butyl 3-(6,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00338] A solution of tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (118 mg, 0.19 mmol, 1.0 eq), 2-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (94 mg, 0.28 mmol, 1.5 eq), K₂CO₃ (130 mg, 0.94 mmol, 5.0 eq) and Pd(PPh₃)₄ (33 mg, 0.03 mmol, 0.15 eq) in dioxane (2 mL) and H₂O (0.5 mL) was stirred at 100 °C for 15 h under nitrogen atmosphere. The mixture was concentrated to give the crude product. The crude product was purified by Prep-TLC (DCM/MeOH = 12: 1) to afford the desired product, tert-butyl 3-(6,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (130 mg, 91.5%) as a white solid. LCMS: m/z 752.3 (M+H⁺).

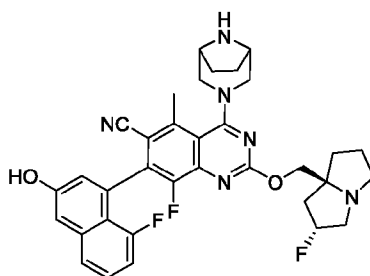
Step 5: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-7-yl)-5-fluoronaphthalen-2-ol



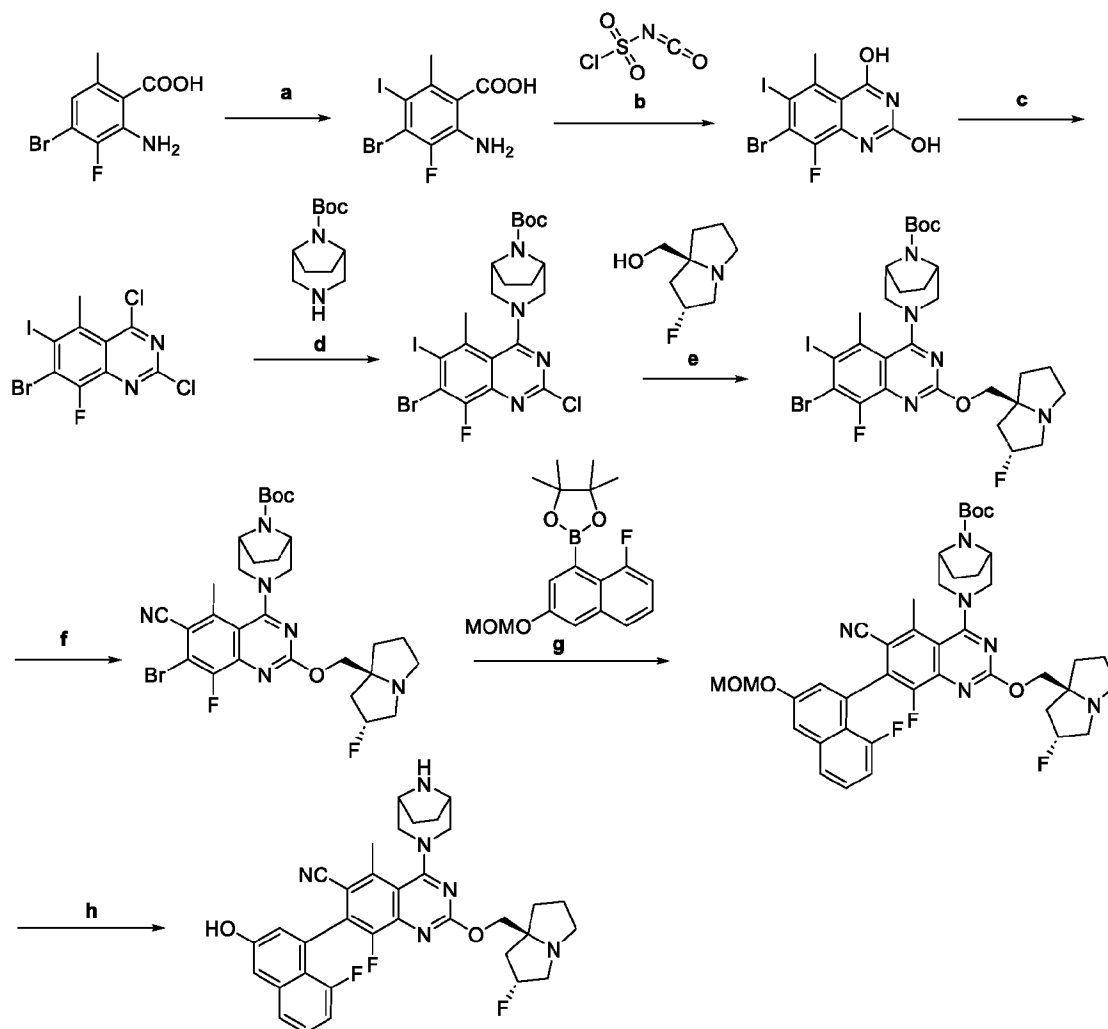
[00339] A solution of tert-butyl 3-(6,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (130 mg, 0.17 mmol, 1.0 eq) in DCM (2 mL) was added HCl in dioxane (4M, 2 mL) and stirred for 3 h. The precipitate formed was collected by filtration, washed with DCM (3 mL). The solid was partitioned between EtOAc (10 mL) and aqueous NaHCO₃ (5 mL). The layers were separated. The aqueous layer was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with H₂O (5 mL), brine (5 mL), dried over Na₂SO₄ and concentrated to give compound 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-7-yl)-5-fluoronaphthalen-2-ol (39 mg, 37.1%) as a white solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 10.29 (s, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.46-7.39 (m, 1H), 7.36 (s, 1H), 7.11 (d, *J* = 1.8 Hz, 1H), 7.01 (dd, *J* = 13.5, 7.5 Hz, 1H), 5.27 (d, *J* = 54.0 Hz, 1H), 4.35-3.85 (m, 4H), 3.59-3.38 (m, 4H), 3.20-2.90 (m, 4H), 2.86-2.76 (m, 1H), 2.75-2.63 (m, 1H), 2.37 (s, 3H), 2.13 (s, 1H), 2.05-1.96 (m, 2H), 1.86-1.74 (m, 3H), 1.52-1.29 (m, 3H). LCMS: *m/z* 608.3 (M+H⁺).

Example 3

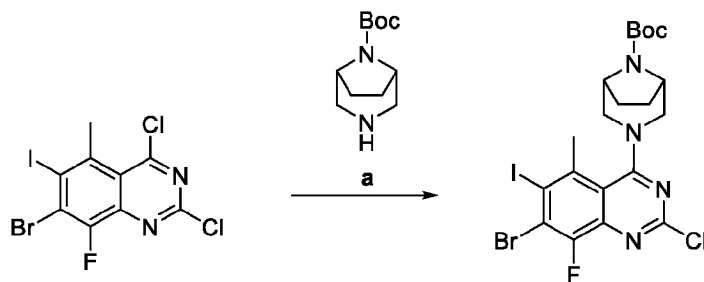
4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazoline-6-carbonitrile



Synthetic scheme:



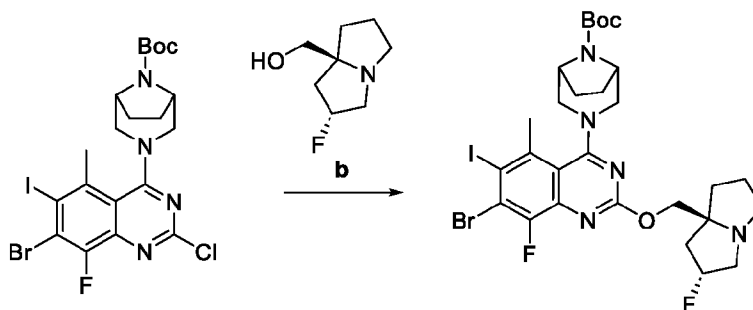
Step 1: Synthesis of tert-butyl 3-(7-bromo-2-chloro-8-fluoro-6-iodo-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00340] To a solution of 7-bromo-2,4-dichloro-8-fluoro-6-iodo-5-methylquinazoline (1.0 g, 2.30 mmol, 1.0 eq) in DCM (10 mL) was added tert-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (488 mg, 2.30 mmol, 1.0 eq) and DIEA (890 mg, 6.90 mmol, 3.0 eq) at -60 °C under nitrogen atmosphere. The reaction was stirred at the same temperature for 2 h. The mixture was

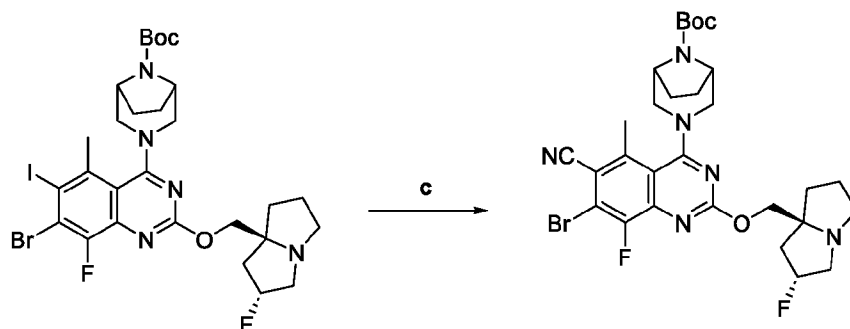
added DCM (30 mL) and water (10 mL) to separated. The aqueous layer was extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (petroleum ether: EtOAc = 1: 1) to give tert-butyl 3-(7-bromo-2-chloro-8-fluoro-6-iodo-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1 g, crude) as a yellow solid. LCMS: m/z 610.9, 612.9 (M+H⁺).

Step 2: Synthesis of tert-butyl 3-(7-bromo-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-iodo-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



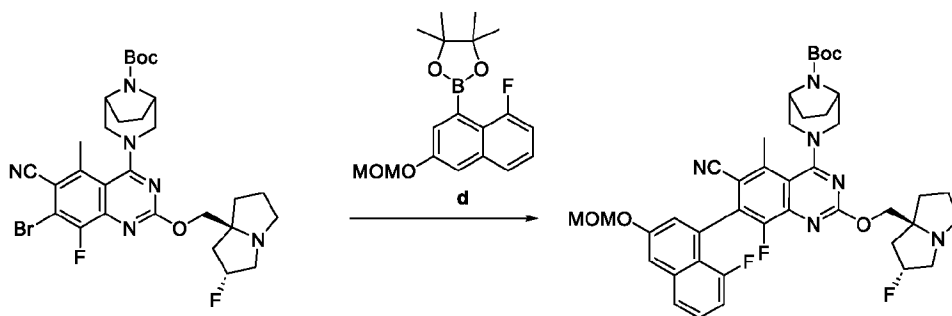
[00341] To a solution of compound tert-butyl 3-(7-bromo-2-chloro-8-fluoro-6-iodo-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (650 mg, 1.06 mmol, 1.0 eq) in THF/DMF (10 mL) was added (((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (505 mg, 3.18 mmol, 3.0 eq), DABCO (119 mg, 1.06 mmol, 1.0 eq) and Cs₂CO₃ (1.03 g, 3.18 mmol, 3.0 eq). The reaction mixture was stirred at room temperature for 3 h. The mixture was partitioned between EtOAc (20 mL) and water (5 mL), the layers were separated. The aqueous layer was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with H₂O (10 mL), brine (10 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (DCM: MeOH = 30: 1~10: 1) to give the desired product, tert-butyl 3-(7-bromo-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-iodo-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (550 mg, 70.5%) as a white solid. ¹H NMR (300 MHz, CDCl₃): δ 5.36 – 5.33 (m, 1H), 4.26 (d, *J* = 24.6 Hz, 2H), 3.78 – 3.66 (m, 2H), 3.20 – 3.08 (m, 3H), 2.59 (s, 3H), 2.24 – 2.00 (m, 3H), 1.83 – 1.71 (m, 6H), 1.44 – 1.38 (m, 2H), 1.25 (s, 9H), 1.10 (s, 1H), 0.88 – 0.68 (m, 3H). LCMS: m/z 734.1, 736.1 (M+H⁺).

Step 3: Synthesis of tert-butyl 3-(7-bromo-6-cyano-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



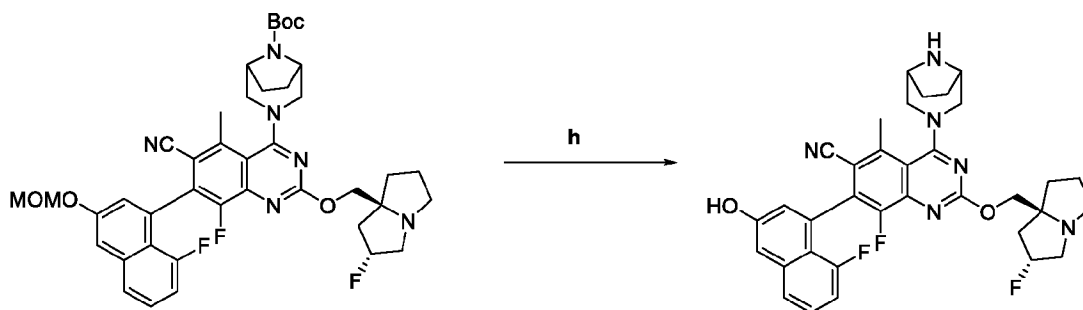
[00342] To a solution of tert-butyl 3-(7-bromo-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-iodo-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (140 mg, 0.19 mmol, 1.0 eq) in DMF (3 mL) was added $\text{Zn}(\text{CN})_2$ (29.1 mg, 0.25 mmol, 1.3 eq), $\text{Pd}(\text{PPh}_3)_4$ (21 mg, 0.019 mmol, 0.1 eq) under nitrogen atmosphere. The reaction mixture was stirred at 100 °C for 12 h. The mixture was partitioned between EtOAc (20 mL) and water (5 mL). The aqueous layer was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with H_2O (10 mL), brine (10 mL), dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by silica gel column chromatography (DCM: MeOH = 30: 1~10: 1) to give the desired product, tert-butyl 3-(7-bromo-6-cyano-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (50 mg, 41.6%) as a yellow solid. LCMS: m/z 633.1, 635.1 ($\text{M}+\text{H}^+$).

Step 4: Synthesis of tert-butyl 3-(6-cyano-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00343] To a solution of tert-butyl 3-(7-bromo-6-cyano-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (40 mg, 0.06 mmol, 1.0 eq) in dioxane (2 mL) and H₂O (0.4 mL) was added 2-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (31.2 mg, 0.09 mmol, 1.5 eq), Cs₂CO₃ (58.6 mg, 0.18 mmol, 3.0 eq) and Pd(PPh₃)₄ (7.3 mg, 0.09 mmol, 1.5 eq) under nitrogen atmosphere. The reaction mixture was stirred at 100 °C for 6 h. EtOAc (20 mL) and water (5 mL) were added. The aqueous layer was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (DCM: MeOH = 30: 1~10: 1) to give the desired product, tert-butyl 3-(6-cyano-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (10 mg, 20.8%) as a yellow solid. LCMS: m/z 759.2, 760.2 (M+H⁺).

Step 5: Synthesis of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazoline-6-carbonitrile

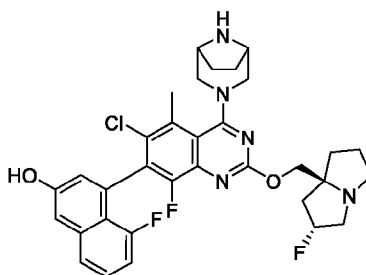


[00344] A solution of tert-butyl 3-(6-cyano-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (10 mg, 0.01 mmol, 1.0 eq) in DCM (0.5 mL) was added HCl in dioxane (4M, 0.5 mL) and stirred at room temperature for 4 h under nitrogen atmosphere. The mixture was concentrated to give the crude product. The residue was partitioned between EtOAc (10 mL) and aqueous NaHCO₃ (5 mL). The layers were separated. The aqueous layer was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with H₂O (5 mL), brine (5 mL), dried over Na₂SO₄ and evaporated

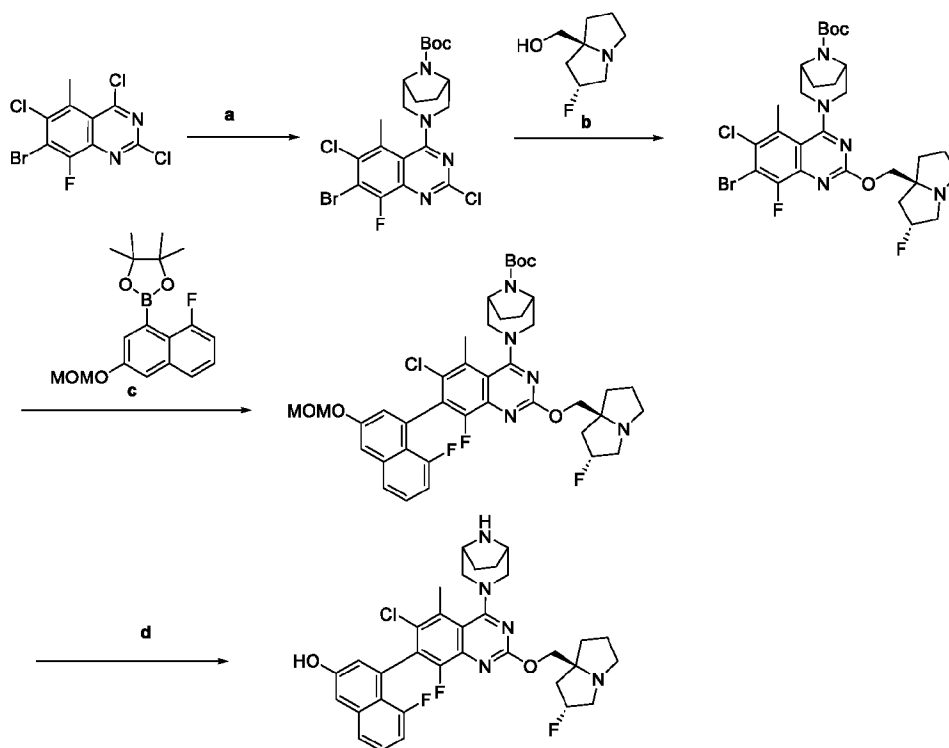
to dryness. The crude product was purified by Prep-HPLC (acetonitrile with 0.1% FA in water, 30% to 40%) to give the desired product, 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazoline-6-carbonitrile (3.8 mg, 46.9%) as a white solid. ¹H NMR (300 MHz, CD₃OD): δ 7.54 (d, J = 8.1 Hz, 1H), 7.41 – 7.40 (m, 1H), 7.38 (s, 1H), 7.08 (d, J = 2.4 Hz, 1H), 6.95 – 6.88 (m, 1H), 5.38 (d, J = 54 Hz, 1H), 4.45 – 4.39 (m, 2H), 3.81 – 3.69 (m, 4H), 3.54 – 3.31 (m, 4H), 3.30 – 2.85 (m, 2H), 2.75 (s, 3H), 2.55 – 2.29 (m, 2H), 2.28 – 2.12 (m, 2H), 2.04 – 1.80 (m, 2H), 1.93 – 1.72 (m, 2H), 1.79 – 1.24 (m, 2H). LCMS: m/z 615.3 (M+H⁺).

Example 4

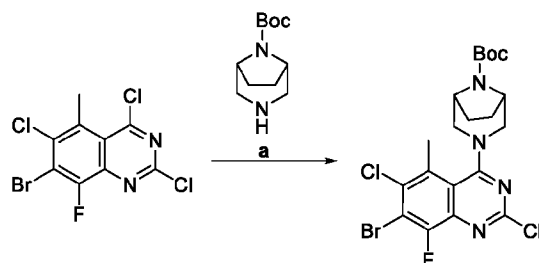
4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-7-yl)-5-fluoronaphthalen-2-ol



Synthetic scheme



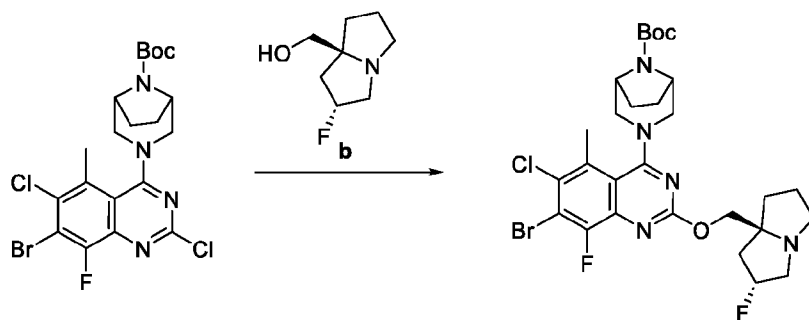
Step 1: Synthesis of tert-butyl 3-(7-bromo-2,6-dichloro-8-fluoro-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00345] To a solution of 7-bromo-2,4,6-trichloro-8-fluoro-5-methylquinazoline (400 mg, 1.16 mmol, 1.0 eq) in DCM (10 mL) was added tert-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (245.9 mg, 1.16 mmol, 1.0 eq) and DIEA (448 mg, 3.48 mmol, 3.0 eq) under nitrogen atmosphere. The reaction was stirred at -60 °C for 2 h, then diluted with DCM (20 mL) and water (10 mL). The organic layer was separated. The aqueous layer was extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (petroleum ether: EtOAc = 10: 1~3: 1) to give the desired product, tert-butyl 3-(7-bromo-2,6-dichloro-8-fluoro-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (380 mg, 62.7%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 4.35 – 4.15 (m, 2H), 3.69 – 3.60

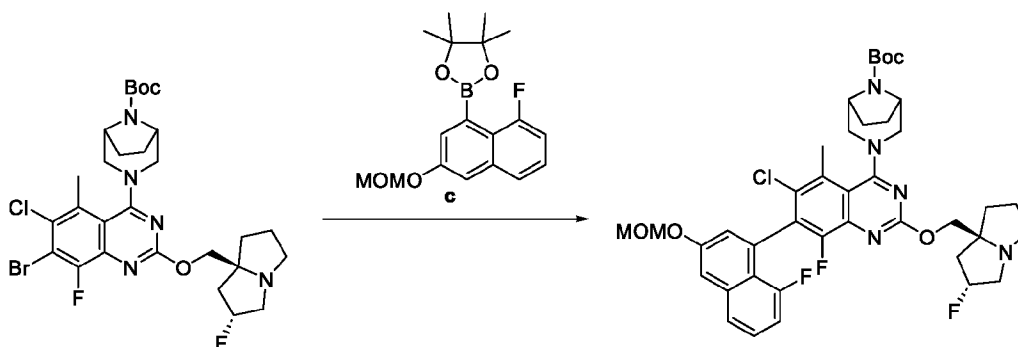
(m, 2H), 2.52 (s, 3H), 1.84 – 1.72 (m, 2H), 1.63 – 1.51 (m, 4H), 1.50 (s, 9H). LCMS: m/z 519.0, 521.0 ($M+H^+$).

Step 2: Synthesis of tert-butyl 3-(7-bromo-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



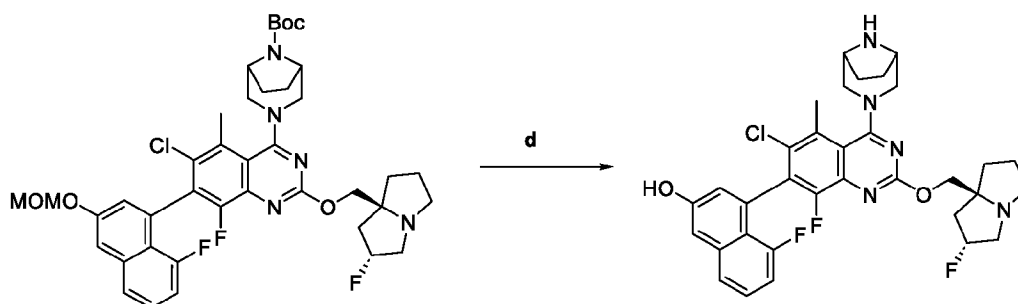
[00346] To a solution of tert-butyl 3-(7-bromo-2,6-dichloro-8-fluoro-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (380 mg, 0.73 mmol, 1.0 eq) in THF/DMF (5 mL/5 mL) was added ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (139.2 mg, 0.87 mmol, 1.2 eq), DABCO (245.2 mg, 2.19 mmol, 3.0 eq) and CS_2CO_3 (713.9 mg, 2.19 mmol, 3.0 eq), the reaction mixture was stirred at room temperature for 3 h. The mixture was concentrated and partitioned between EtOAc (20 mL) and water (10 mL). The layers were separated. The aqueous layer was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with H_2O (10 mL), brine (10 mL), dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by silica gel column chromatography (Petroleum ether: EtOAc = 10: 1~1: 1) to give the desired product, tert-butyl 3-(7-bromo-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (350 mg, 74.5%) as a white solid. LCMS: m/z 642.2, 644.2 ($M+H^+$).

Step 3: Synthesis of tert-butyl 3-(6-chloro-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00347] To a solution of tert-butyl 3-(7-bromo-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (340 mg, 0.53 mmol, 1.0 eq) in dioxane/H₂O (5 mL/1 mL) was added 2-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (211 mg, 0.63 mmol, 1.2 eq), Pd(PPh₃)₄ (61 mg, 0.053 mmol, 0.1 eq) and K₂CO₃ (219 mg, 1.59 mmol, 3.0 eq) under nitrogen atmosphere. The reaction was stirred at 100 °C for 6 h. The mixture was concentrated and partitioned between EtOAc (20 mL) and water (5 mL). The aqueous layer was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (DCM: MeOH = 50: 1~10: 1) to give the desired product, tert-butyl 3-(6-chloro-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (300 mg, 73.8%) as a yellow solid. LCMS: m/z 768.3 (M+H⁺).

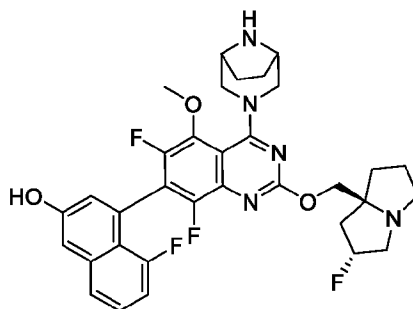
Step 4: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-7-yl)-5-fluoronaphthalen-2-ol



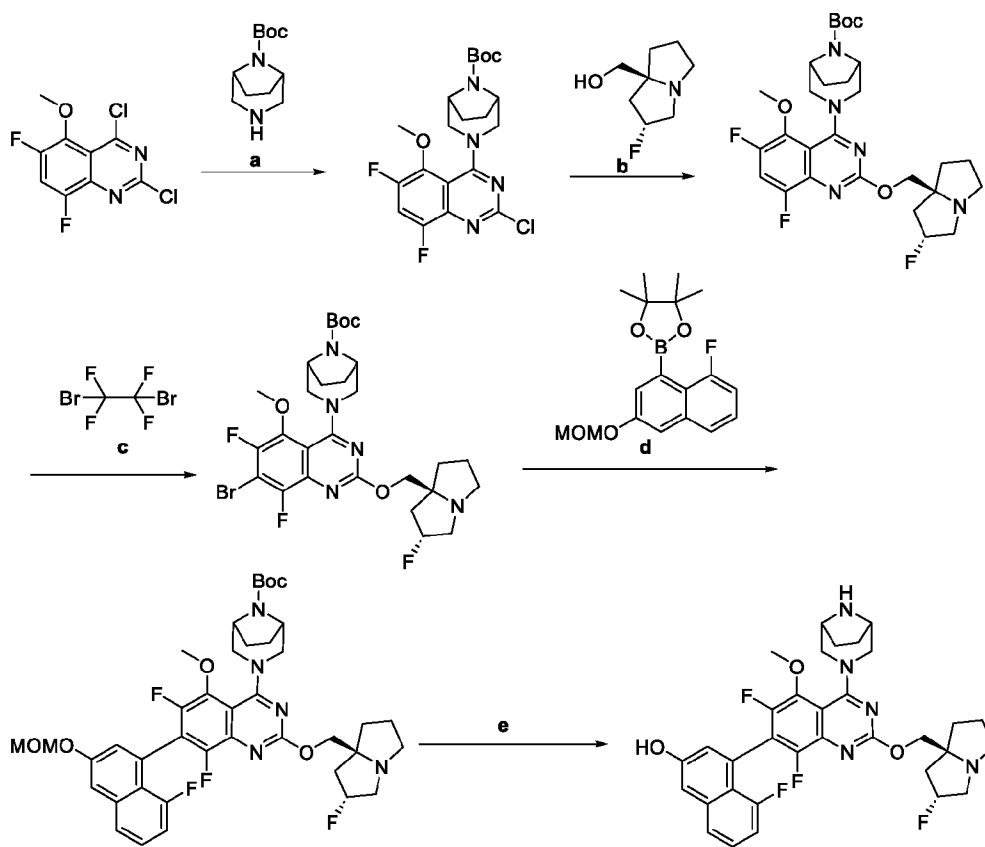
[00348] A solution of tert-butyl 3-(6-chloro-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (300 mg, 0.39 mmol, 1.0 eq) in DCM (1 mL) was added HCl in dioxane (4M, 1 mL) and stirred at room temperature for 4 h. The mixture was concentrated to give the crude residue, which was purified by Prep-HPLC (acetonitrile with 0.1% FA in water, 30% to 40%) to provide the desired product, 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methylquinazolin-7-yl)-5-fluoronaphthalen-2-ol (73 mg, 29.9%) as a white solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.21 (brs, 1H), 7.64 (m, 1H), 7.40 – 7.33 (m, 1H), 7.32 (s, 1H), 7.00 – 6.93 (m, 2H), 5.35 – 5.17 (d, *J* = 54.0 Hz, 1H), 4.11 – 3.97 (m, 3H), 3.56 – 3.51 (m, 4H), 3.11 – 3.08 (m, 3H), 2.83 – 2.80 (m, 2H), 2.50 (s, 3H), 2.14 – 2.13 (m, 1H), 2.03 – 1.99 (m, 2H), 1.88 – 1.79 (m, 3H), 1.77 – 1.55 (m, 3H). LCMS: *m/z* 624.2 (M+H⁺).

Example 5

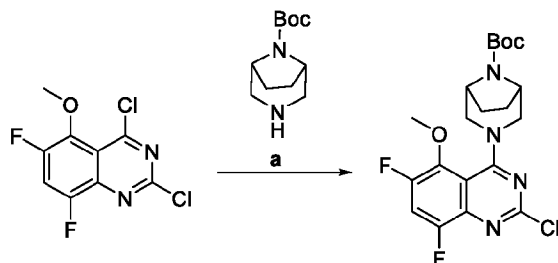
4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-fluoronaphthalen-2-ol



Synthetic scheme



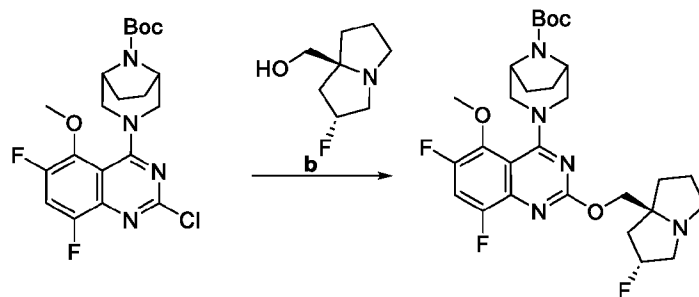
Step 1: Synthesis of tert-butyl 3-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00349] To a solution of 2,4-dichloro-6,8-difluoro-5-methoxyquinazoline (300 mg, 1.1 mmol, 1.0 eq) and DIEA (526 mg, 4.1 mmol, 3.6 eq) in DCM (3 mL) was added tert-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (312 mg, 1.5 mmol, 1.3 eq) at -40 °C under nitrogen atmosphere. The reaction was stirred at the same temperature for 2 h. The mixture was concentrated to give a residue. The residue was partitioned between DCM (10 mL) and water (5 mL). The layers were separated. The aqueous layer was extracted with DCM (5 mL x 3). The combined organic layers were washed with H₂O (5 mL), brine (5 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by prep-TLC (PE/EA 15:1) to give the

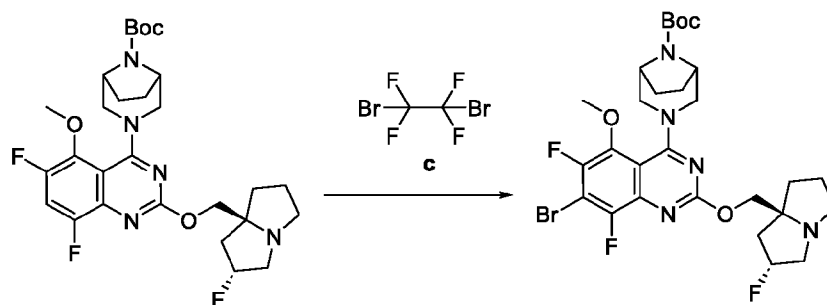
desired product, tert-butyl 3-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (397 mg, 81.9 %) as a yellow solid. LCMS: m/z 441.1 ($M+H^+$).

Step 2: Synthesis of tert-butyl 3-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo [3.2.1]octane-8-carboxylate



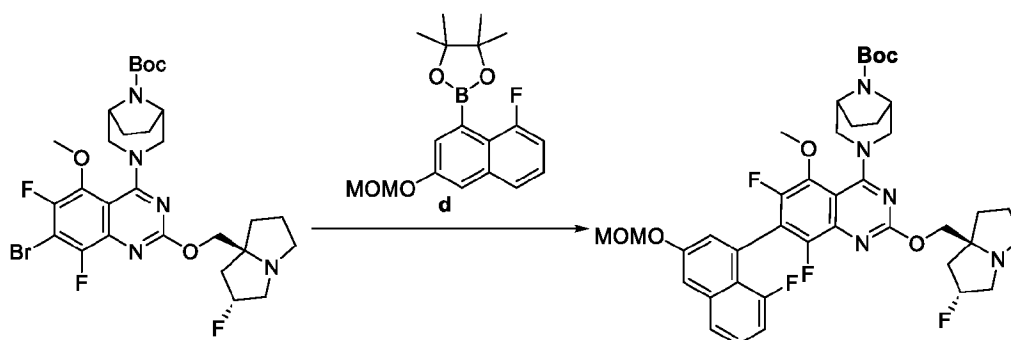
[00350] A solution of tert-butyl 3-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo [3.2.1]octane-8-carboxylate (347 mg, 0.79 mmol, 1.0 eq), ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (150 mg, 0.94 mmol, 1.2 eq), DABCO (88 mg, 0.79 mmol, 1.0 eq) and Cs_2CO_3 (770mg, 2.37 mmol, 3.0 eq) in THF (3.5 mL) and DMF (3.5 mL) was stirred at room temperature for 15 h under nitrogen atmosphere. The mixture was diluted with H_2O (12 mL), extracted with EtOAc (5 mL x 3). The combined organic layers were washed with H_2O (5 mL), brine (5 mL), dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by silica gel column chromatography (DCM / MeOH 15:1) to give the desired product, tert-butyl 3-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (353 mg, 79.3 %) as a yellow solid. LCMS: m/z 564.3 ($M+H^+$).

Step 3: Synthesis of tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00351] To a solution of tert-butyl 3-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (168 mg, 0.30 mmol, 1.0 eq) in THF (2 mL) was added LDA (0.3 mL, 0.60 mmol, 2.0 eq) at -65 °C under N₂ atmosphere. The mixture was stirred at -65 °C for 30 min. The mixture 1,2-dibromo-1,1,2,2-tetrafluoroethane (147 mg, 0.45 mmol, 1.5 eq) was added and stirred for 2 h. The reaction was quenched with water. The mixture was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with H₂O (5 mL), brine (5 mL), dried over Na₂SO₄ and evaporated to dryness. The reaction was repeated two times. The crude product was purified by prep-TLC (DCM/ MeOH 12:1) to give the desired product, tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (237 mg, 61.5 %) as a brown solid.

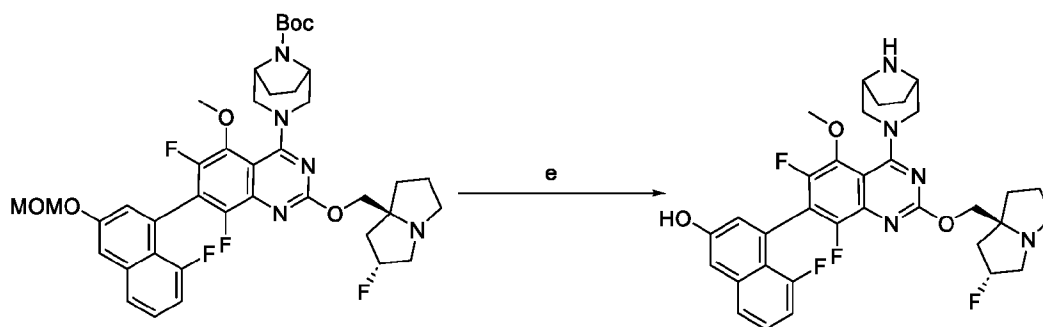
Step 4: Synthesis of tert-butyl 3-(6,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00352] A solution of tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.16 mmol, 1.0 eq), 2-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-

4,4,5,5-tetramethyl-1,3,2-dioxaborolane (78 mg, 0.23 mmol, 1.5 eq), K_2CO_3 (107 mg, 0.78 mmol, 5.0 eq) and $Pd(PPh_3)_4$ (27 mg, 0.02 mmol, 0.15 eq) in dioxane (2 mL) and H_2O (0.5 mL) was stirred at 100 °C for 15 h under nitrogen atmosphere. The mixture was concentrated to give the crude product. The crude product was purified by Prep-TLC (DCM/MeOH = 12/1) to give the desired product, tert-butyl 3-(6,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (120 mg, 99 %) as a white solid. LCMS: m/z 768.3 ($M+H^+$).

Step 5: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-fluoronaphthalen-2-ol



[00353] A solution of tert-butyl 3-(6,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (120 mg, 0.16 mmol, 1.0 eq) in DCM (2 mL) was added HCl in dioxane (4M, 2 mL) and stirred at room temperature for 3 h. The precipitate formed was collected by filtration and washed with DCM. The solid was partitioned between EtOAc (10 mL) and aqueous $NaHCO_3$ (5 mL). The layers were separated. The aqueous layer was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with H_2O (5 mL), brine (5 mL), dried over Na_2SO_4 and evaporated to give the desired product, 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-fluoronaphthalen-2-ol (34 mg, 33.1%) as a white solid. ^1H NMR (300 MHz, $DMSO-d_6$) δ 10.32 (bs, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.50-7.42 (m, 1H), 7.37 (m, 1H), 7.15 (d, J = 1.8 Hz, 1H), 7.08-6.90 (m, 1H), 5.27 (d, J = 54.0 Hz, 1H), 4.10-3.89 (m, 4H), 3.76 (s, 3H), 3.50-3.35 (m, 4H), 3.13-3.04 (m, 2H), 3.02-2.97 (m, 1H), 2.85-

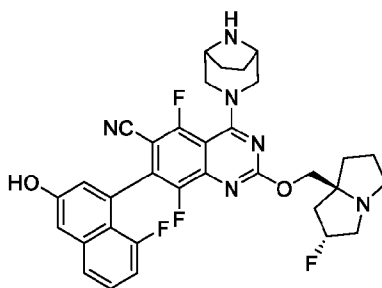
2.77 (m, 1H), 2.16-2.10 (m, 1H), 2.05-1.95 (m, 2H), 1.90-1.75 (m, 3H), 1.65-1.55 (m, 4H), 1.23 (brs, 1H). LCMS: m/z 624.3 (M+H⁺).

Example 6 (included in Example 11 and 12)

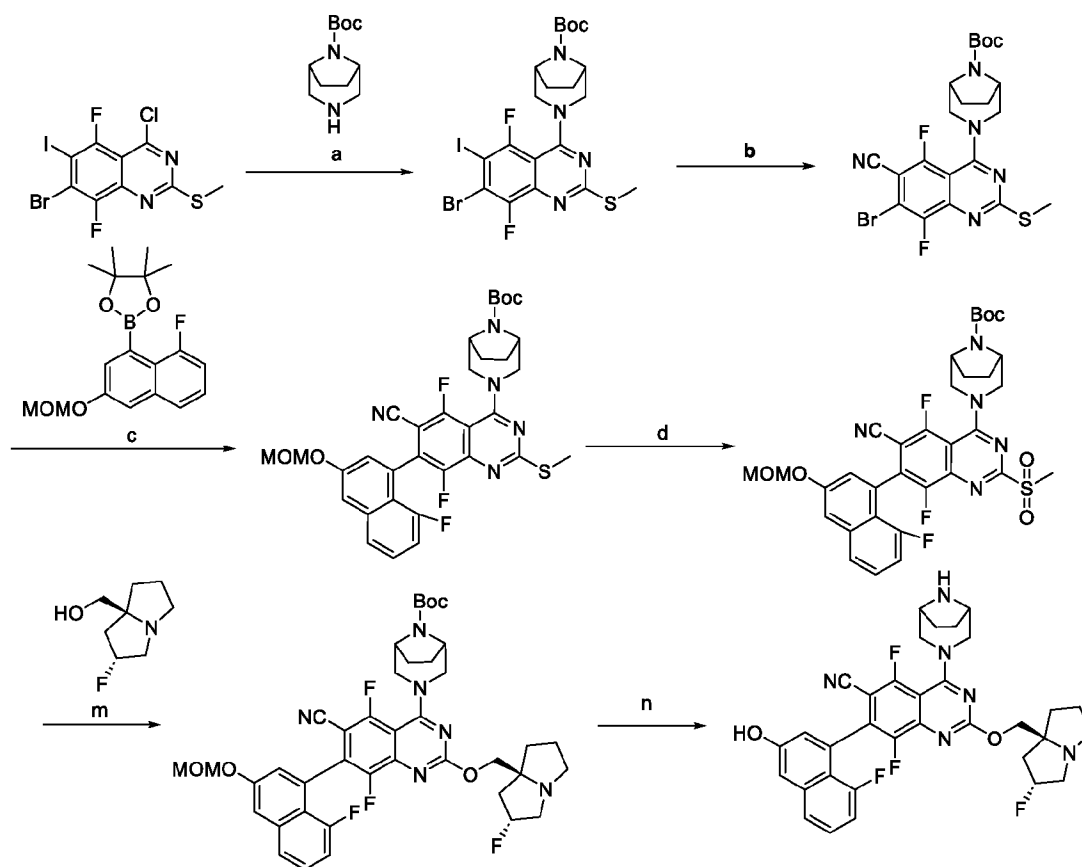
4-(4-((3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-fluoronaphthalen-2-ol

Example 7

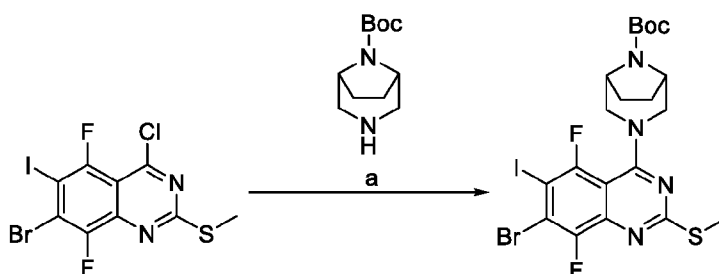
4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5,8-difluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazoline-6-carbonitrile



Synthetic scheme:



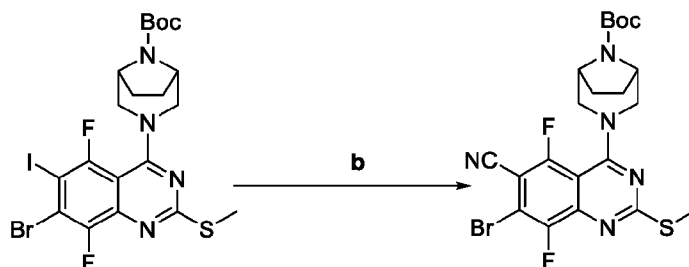
Step 1: Synthesis of tert-butyl 3-(7-bromo-5,8-difluoro-6-iodo-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00354] To a solution of 7-bromo-4-chloro-5,8-difluoro-6-iodo-2-(methylthio)quinazoline (1.4 g, 3.11 mmol, 1.2 eq) and DIEA (1.0 g, 7.77 mmol, 3.0 eq) in DCM (15 mL) stirring at -65 °C under nitrogen atmosphere was added dropwise tert-butyl (1R,5S)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (550 mg, 2.59 mmol, 1.0 eq) in DCM (5 mL). The mixture was stirring at -65 °C for 2h under nitrogen atmosphere. The residue was quenched with 1N HCl (15 mL) and extracted with DCM (30 mL x 3). The organic phase was washed with brine (30 mL), dried with Na₂SO₄, filtered and concentrated to give a residue. The residue was

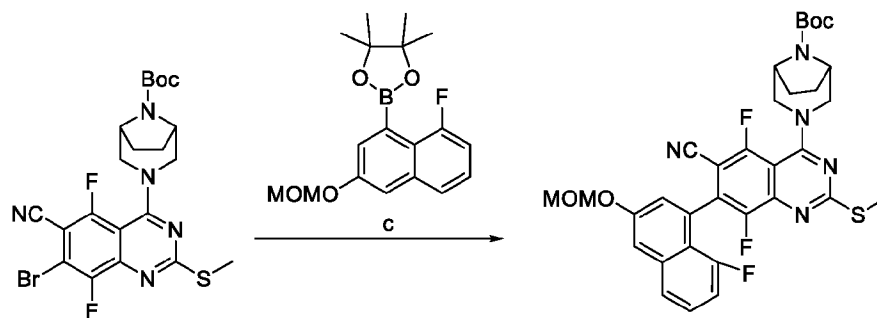
purified by silica gel column chromatography (petroleum ether: EtOAc = 30: 1) to give tert-butyl 3-(7-bromo-5,8-difluoro-6-iodo-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.0 g, 61.5%) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 4.30 (s, 2H), 4.08 (d, *J* = 13.8 Hz, 2H), 3.51 (s, 2H), 2.60 (s, 3H), 1.95 – 1.80 (m, 2H), 1.70 – 1.62 (m, 2H), 1.50 (s, 9H). LCMS: *m/z* 627.0 (M + H⁺).

Step 2: Synthesis of tert-butyl 3-(7-bromo-6-cyano-5,8-difluoro-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



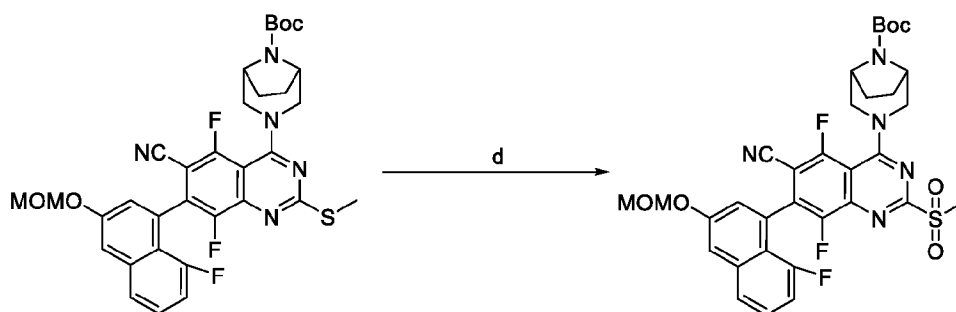
[00355] To a solution of tert-butyl 3-(7-bromo-5,8-difluoro-6-iodo-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.0 g, 1.59 mmol, 1.0 eq) in DMF (10 mL) was added CuCN (214 mg, 2.39 mmol, 1.5 eq). Then the reaction mixture was stirred at 95°C for 48 h under nitrogen atmosphere. The mixture was diluted with water (15 mL) and extracted with EtOAc (20 mL x 3). The organic phase was washed with water (20 mL x 2) and brine (20 mL), dried with Na₂SO₄, filtered and concentrated to give residue. The residue was purified by silica gel column chromatography (petroleum ether: EtOAc = 20: 1) to give tert-butyl 3-(7-bromo-6-cyano-5,8-difluoro-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (500 mg, 59.6%) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 4.32 (s, 2H), 4.22 – 3.98 (m, 2H), 3.56 (d, *J* = 12.6 Hz, 2H), 2.61 (s, 3H), 1.95 – 1.82 (m, 2H), 1.64 – 1.59 (m, 2H), 1.51 (s, 9H). LCMS: *m/z* 526.1 (M + H⁺).

Step 3: Synthesis of tert-butyl 3-(6-cyano-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



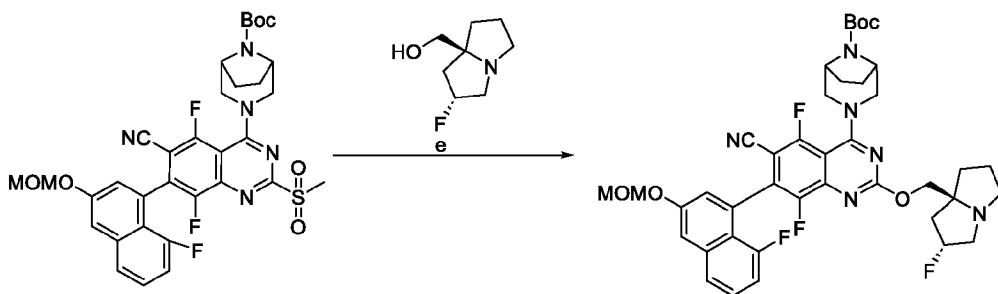
[00356] To a solution of tert-butyl 3-(7-bromo-6-cyano-5,8-difluoro-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (500 mg, 0.95 mmol, 1.0 eq) in Dioxane (8 mL) and H₂O (2 mL) was added 2-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (474 mg, 1.42 mmol, 1.5 eq), K₂CO₃ (657 mg, 4.76 mmol, 5.0 eq) and Pd (PPh₃)₄ (165 mg, 0.14 mmol, 0.15 eq). The reaction mixture was stirred at 100 °C for 2 h under nitrogen atmosphere. The mixture was diluted with water (15 mL) and extracted with EtOAc (20 mL x 3). The organic phase was washed with brine (20 mL), dried with Na₂SO₄, filtered and concentrated to give residue. The residue was purified by silica gel column chromatography (petroleum ether: EtOAc = 5: 1) to give tert-butyl 3-(6-cyano-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy) naphthalen-1-yl)-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (350 mg, 56.4%) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 7.64 (d, *J* = 7.8 Hz, 1H), 7.58 (t, *J* = 2.4 Hz, 1H), 7.46 – 7.38 (m, 1H), 7.22 (d, *J* = 2.4 Hz, 1H), 7.04 – 6.95 (m, 1H), 5.33 (s, 2H), 4.36 (s, 2H), 4.23 – 4.05 (m, 2H), 3.65– 3.56 (m, 2H), 3.54 (s, 3H), 2.62 (s, 3H), 1.98– 1.88 (m, 2H), 1.76– 1.68 (m, 2H), 1.52 (s, 9H). LCMS: *m/z* 652.2 (M+H⁺).

Step 4: Synthesis of tert-butyl 3-(6-cyano-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy) naphthalen-1-yl)-2-(methylsulfonyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00357] To a solution of tert-butyl 3-(6-cyano-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (350 mg, 0.53 mmol, 1.0 eq) in DCM (6.00 mL) was added m-CPBA (309 mg, 1.34 mmol, 2.5 eq, 75%) at 0 °C under nitrogen atmosphere. Then the reaction mixture was stirred at room temperature for 3 h. The mixture was diluted with Na₂SO₃ solution (15 mL) and extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (15 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by silica gel column chromatography (petroleum ether: EtOAc = 2: 1) to give tert-butyl 3-(6-cyano-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy) naphthalen-1-yl)-2-(methylsulfonyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1] octane-8-carboxylate (270 mg, 73.5%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 7.66 (d, *J* = 8.4 Hz, 1H), 7.62 (t, *J* = 2.4 Hz, 1H), 7.47 – 7.41 (m, 1H), 7.22 (d, *J* = 2.4 Hz, 1H), 7.04 – 6.95 (m, 1H), 5.34 (d, *J* = 1.2 Hz, 2H), 4.51 – 4.23 (m, 4H), 3.73 (s, 2H), 3.55 (s, 3H), 3.40 (s, 3H), 1.99 – 1.91 (m, 2H), 1.69 – 1.60 (m, 2H), 1.53 (s, 9H). LCMS: *m/z* 684.2 (M+H⁺).

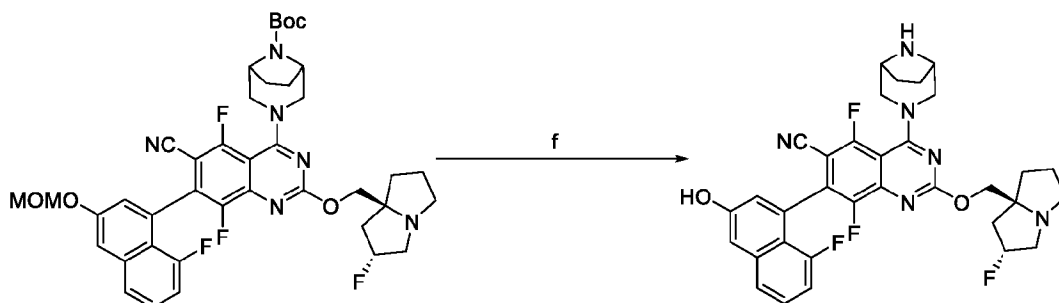
Step 5: Synthesis of tert-butyl 3-(6-cyano-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy) naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy) quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00358] To a solution of tert-butyl 3-(6-cyano-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(methylsulfonyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (170 mg, 0.24 mmol, 1.0 eq) and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (119 mg, 0.74 mmol, 3.0 eq) in THF (5.00 mL) was added LiHMDS (1M in THF) (0.74 mL, 0.74 mmol, 3.0 eq) dropwise at 0 °C under nitrogen atmosphere. Then the reaction mixture was stirred at 0 °C for 1 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (15 mL), dried over Na₂SO₄ and concentrated to give the crude product.

The crude product was purified by prep-TLC (DCM: MeOH = 20: 1) to give tert-butyl 3-(6-cyano-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (130 mg, 68.7%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 7.63 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 1.6 Hz, 1H), 7.48 – 7.37 (m, 1H), 7.21 (d, *J* = 2.4 Hz, 1H), 6.98 (dd, *J* = 12.8, 7.6 Hz, 1H), 5.32 (s, 2H), 5.31 – 5.19 (m, 1H), 4.44 – 4.23 (m, 4H), 4.23 – 4.14 (m, 2H), 3.58 (d, *J* = 13.2 Hz, 2H), 3.54 (s, 3H), 3.35 – 3.15 (m, 3H), 3.03 – 2.95 (m, 1H), 2.34 – 2.08 (m, 4H), 2.00 – 1.80 (m, 6H), 1.52 (s, 9H). LCMS: *m/z* 763.3 (M+H⁺).

Step 6: Synthesis of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5,8-difluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazoline-6-carbonitrile

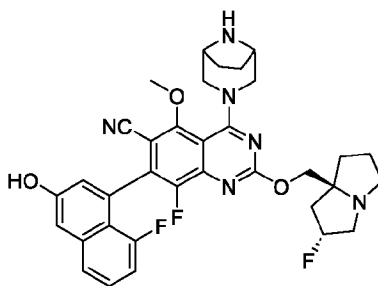


[00359] To a solution of tert-butyl 3-(6-cyano-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (30 mg, 0.039 mmol, 1.0 eq) in DCM (2.0 mL) was added HCl/dioxane (4N) (0.5 mL) dropwise at 0 °C. Then the reaction mixture was stirred at room temperature for 3 h. The mixture was basified with saturated aqueous NaHCO₃ (3 mL) and extracted with EtOAc (10 mL × 5). The combined organic phase was washed with brine (8 mL), dried over Na₂SO₄ and concentrated to give the crude product. The crude product was purified by prep-TLC (DCM: MeOH = 6: 1) to give 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5,8-difluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazoline-6-carbonitrile (14.2 mg, 58.4%) as a white solid. ¹H NMR (300 MHz, CD₃OD): δ 7.62 (d, *J* = 8.1 Hz, 1H), 7.49 – 7.35 (m, 1H), 7.36 (t, *J* = 2.4 Hz, 1H), 7.12 (d, *J* = 2.4 Hz, 1H), 7.00 – 6.91 (m, 1H), 5.34 (d, *J* = 53.7 Hz, 1H), 4.46 – 4.28 (m, 3H), 4.27 – 34.15 (m, 1H), 3.81 – 3.73 (m, 2H), 3.71 – 3.58 (m, 2H), 3.47 – 3.34 (m, 2H), 3.29 – 3.26 (m, 1H), 3.17 – 3.04 (m, 1H), 2.47 – 2.32 (m, 1H), 2.30 – 2.23

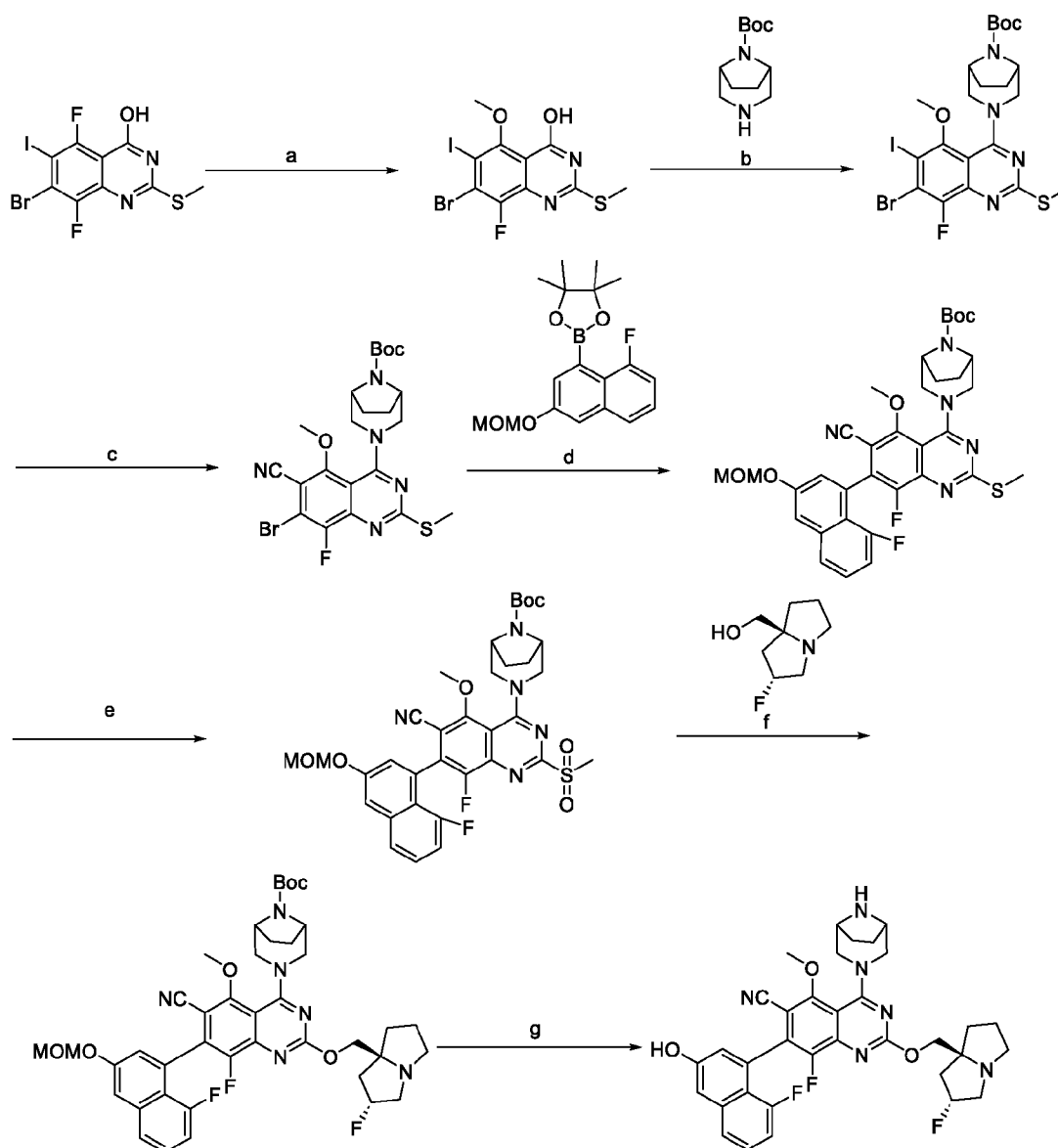
(m, 1H), 2.21 – 2.13 (m, 1H), 2.11 – 1.93 (m, 3H), 1.94 – 1.82 (m, 4H). ^{19}F NMR (300 MHz, CD_3OD): δ -101.895, -117.116, -131.465, -173.756. LCMS: m/z 619.2 ($\text{M}+\text{H}^+$).

Example 8

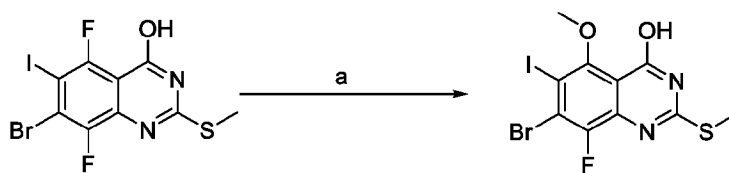
4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline-6-carbonitrile formate



Synthesis scheme



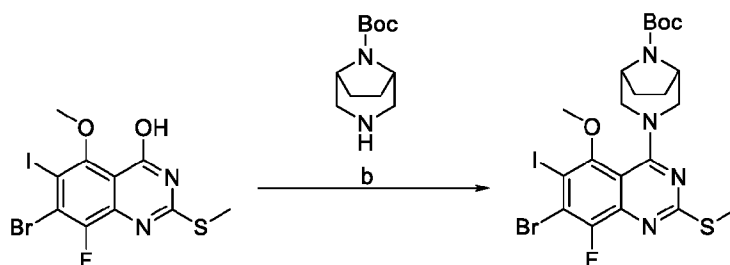
Step 1: Synthesis of 7-bromo-8-fluoro-6-iodo-5-methoxy-2-(methylthio)quinazolin-4-ol



[00360] To a solution of MeOH (666.2 mg, 20.82 mmol, 3.0 eq) in DMF (30.0 mL) was added NaH (593.6 mg, 24.31 mmol, 3.5 eq) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 1 h. Then 7-bromo-5,8-difluoro-6-iodo-2-(methylthio)quinazolin-4-ol (3.0 g, 6.94 mmol, 1.0 eq) was added. The reaction mixture was stirred at room temperature

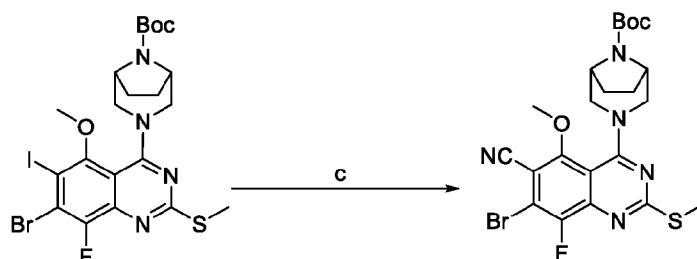
for 15 h. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution (10 mL) and extracted with EtOAc (30 mL x 3). The organic phase was washed with brine (20 mL), dried with Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by silica gel column chromatography (Petroleum ether: EtOAc = 3:1) to give 7-bromo-8-fluoro-6-iodo-5-methoxy-2-(methylthio)quinazolin-4-ol (2.2 g, 71.4%) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 12.81 (brs, 1H), 3.74 (s, 3H), 2.56 (s, 3H). LCMS: m/z 444.8, 446.8 ($\text{M}+\text{H}^+$).

Step 2: Synthesis of tert-butyl-3-(7-bromo-8-fluoro-6-iodo-5-methoxy-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



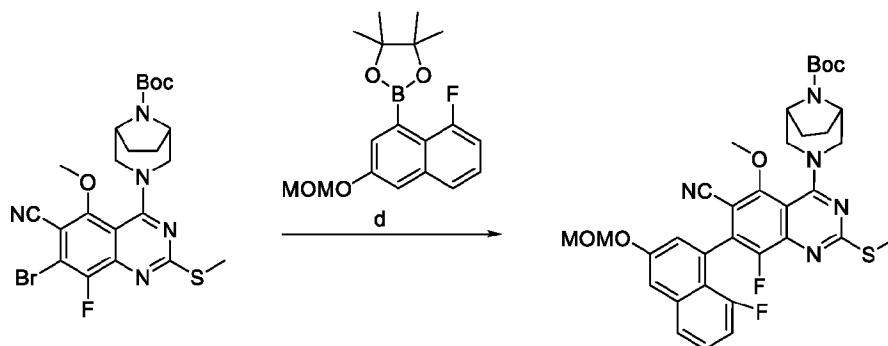
[00361] To a solution of 7-bromo-8-fluoro-6-iodo-5-methoxy-2-(methylthio)quinazolin-4-ol (2.20 g, 4.95 mmol, 1.0 eq) in DMF (25.0 mL) was added tert-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2.10 g, 9.91 mmol, 2.0 eq), DBU (2.26 g, 14.87 mmol, 3.0 eq) and BOP (3.29g, 7.43mmol, 1.5 eq). The reaction mixture was stirred at 90 °C for 5 h under nitrogen atmosphere. The mixture was diluted with water (15 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with H_2O (20 mL x 2), brine (20 mL x 3), dried over Na_2SO_4 , filtered and concentrated to give the crude product. The crude product was purified by silica gel column chromatography (Petroleum ether: EtOAc = 5: 1) to give tert-butyl 3-(7-bromo-8-fluoro-6-iodo-5-methoxy-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.5 g, 47.4%) as a yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 4.39 – 4.25 (m, 3H), 3.58 (s, 3H), 3.48 – 3.46 (m, 2H), 2.61 (s, 3H), 1.86 – 1.78 (m, 2H), 1.58 (s, 3H), 1.5 (s, 9H). LCMS: m/z 638.9, 641.0 ($\text{M}+\text{H}^+$).

Step 3: Synthesis of tert-butyl-3-(7-bromo-6-cyano-8-fluoro-5-methoxy-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00362] To a solution of tert-butyl 3-(7-bromo-8-fluoro-6-iodo-5-methoxy-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.0 g, 1.56 mmol, 1.0 eq) in DMF (10 mL) was added CuCN (211 mg, 2.35 mmol, 1.5 eq). The reaction mixture was stirred at 90°C for 36 h under nitrogen atmosphere. The mixture was diluted with water (15 mL) and extracted with EtOAc (20 mL x 3). The organic phase was washed with water (20 mL x 2) and brine (20 mL), dried with Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by silica gel column chromatography (petroleum ether: EtOAc = 20: 1) to give tert-butyl 3-(7-bromo-6-cyano-8-fluoro-5-methoxy-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (720 mg, 85.5%) as a yellow solid. LCMS: m/z 538.1, 540.1 (M + H⁺).

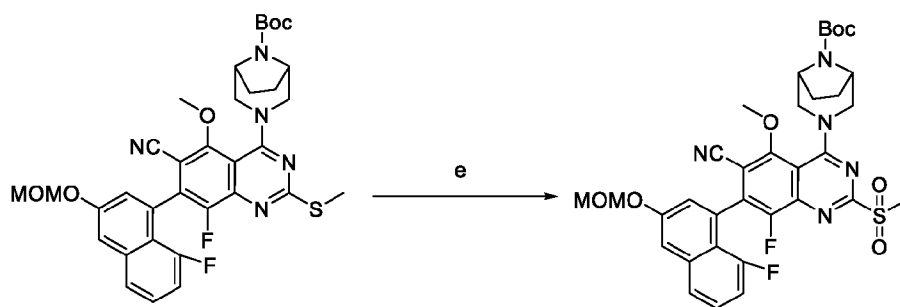
Step 4: Synthesis of tert-butyl 3-(6-cyano-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-5-methoxy-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00363] To a solution of tert-butyl 3-(7-bromo-6-cyano-8-fluoro-5-methoxy-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (720 mg, 1.33 mmol, 1.0 eq) in Dioxane (10 mL) and H₂O (2.5 mL) was added 2-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (666 mg, 2.0 mmol, 1.5 eq), K₂CO₃ (554 mg, 4.0 mmol, 3.0 eq) and Pd(PPh₃)₄ (232 mg, 0.20 mmol, 0.15 eq). The reaction mixture was stirred at 100 °C for 2 h under nitrogen atmosphere. The mixture was

diluted with water (15 mL) and extracted with EtOAc (20 mL x 3). The organic phase was washed with brine (20 mL), dried with Na₂SO₄, filtered and concentrated to give residue. The residue was purified by silica gel column chromatography (petroleum ether: EtOAc = 7: 1) to give tert-butyl 3-(6-cyano-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-5-methoxy-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (290 mg, 32.6%) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 7.62 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 2.4 Hz, 1H), 7.45 – 7.35 (m, 1H), 7.23 (d, *J* = 2.4 Hz, 1H), 7.01 – 6.92 (m, 1H), 5.33 (s, 2H), 4.51 – 4.17 (m, 3H), 3.88 (s, 3H), 3.64 – 3.53 (m, 2H), 3.54 (s, 3H), 2.62 (s, 3H), 2.03 – 1.74 (m, 3H), 1.73 – 1.59 (m, 2H), 1.52 (s, 9H). LCMS: *m/z* 664.2 (M+H⁺).

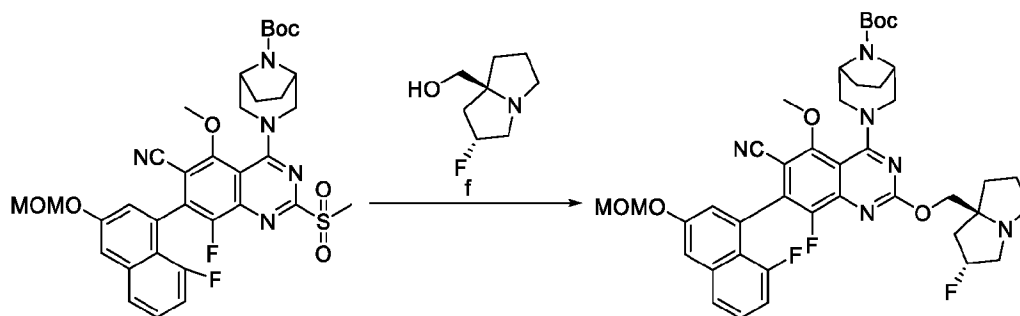
Step 5: Synthesis of tert-butyl 3-(6-cyano-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-5-methoxy-2-(methylsulfonyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00364] To a solution of tert-butyl 3-(6-cyano-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-5-methoxy-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (290 mg, 0.43 mmol, 1.0 eq) in DCM (5.00mL) was added *m*-CPBA (251 mg, 1.09 mmol, 2.5 eq, 75%) at 0 °C under nitrogen atmosphere. Then the reaction mixture was stirred at room temperature for 3 h. The mixture was diluted with Na₂SO₃ solution (15 mL) and extracted with EtOAc (15 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by silica gel column chromatography (petroleum ether: EtOAc = 2: 1) to give tert-butyl 3-(6-cyano-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-5-methoxy-2-(methylsulfonyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (150 mg, 49.3%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 7.65 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 2.4 Hz, 1H), 7.48 – 7.38 (m, 1H), 7.23 (d, *J* = 2.4 Hz, 1H), 7.03 – 6.92 (m, 1H), 5.34 (s, 2H), 4.48 – 4.28

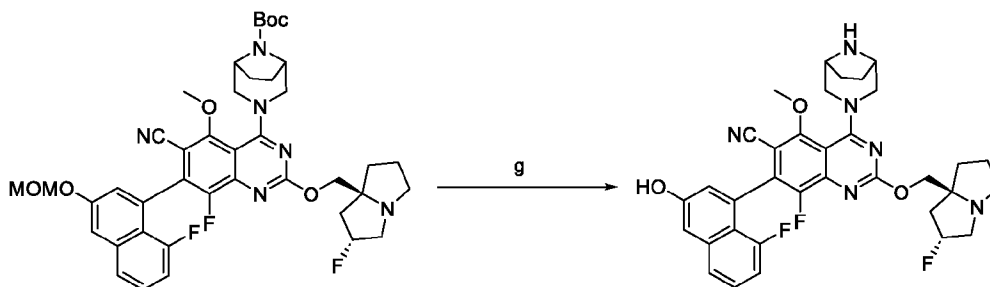
(m, 2H), 3.94 (s, 3H), 3.55 (s, 3H), 3.53 – 3.44 (m, 1H), 3.41 (s, 3H), 3.39 – 3.28 (m, 1H), 2.00 (s, 1H), 1.93 – 1.86 (m, 2H), 1.53 (s, 3H), 1.52 (s, 9H). LCMS: m/z 696.2 ($M+H^+$).

Step 6: Synthesis of tert-butyl 3-(6-cyano-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00365] To a solution of tert-butyl 3-(6-cyano-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-5-methoxy-2-(methylsulfonyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (120 mg, 0.17 mmol, 1.0 eq) and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (82 mg, 0.51 mmol, 3.0 eq) in THF (5.00 mL) was added LiHMDS (1M in THF) (0.51 mL, 0.51 mmol, 3.0 eq) dropwise at 0 °C under nitrogen atmosphere. Then the reaction mixture was stirred at 0 °C for 1 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (15 mL), dried over Na_2SO_4 and concentrated to give the crude product. The crude product was purified by prep-TLC (DCM: MeOH = 20: 1) to give tert-butyl 3-(6-cyano-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (110 mg, 82.7%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 8.4 Hz, 1H), 7.55 (t, J = 2.4 Hz, 1H), 7.45 – 7.34 (m, 1H), 7.23 (d, J = 2.4 Hz, 1H), 6.96 (dd, J = 12.8, 7.2 Hz, 1H), 5.47 – 5.23 (s, 3H), 4.45 – 4.26 (m, 4H), 3.88 (s, 3H), 3.54 (s, 3H), 3.53 – 3.45 (m, 2H), 3.38 – 3.23 (m, 2H), 3.21 – 2.89 (m, 2H), 2.42 – 2.21 (m, 3H), 2.10 – 1.97 (m, 3H), 1.92 – 1.82 (m, 3H), 1.71 – 1.63 (m, 3H), 1.51 (s, 9H). LCMS: m/z 775.3 ($M+H^+$).

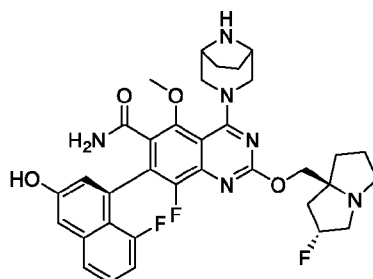
Step 7: Synthesis of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline-6-carbonitrile formate (1: 1)



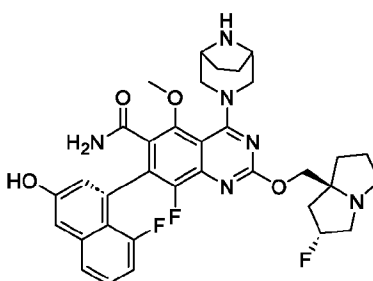
[00366] To a solution of tert-butyl 3-(6-cyano-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (25 mg, 0.03 mmol, 1.0 eq) in ACN (2.0 mL) was added TFA (0.5 mL) dropwise at 0 °C. Then the reaction mixture was stirred at room temperature for 3 h. The mixture was basified with saturated aqueous NaHCO₃ (5 mL) and extracted with EtOAc (10 mL × 5). The combined organic phase was washed with brine (8 mL), dried over Na₂SO₄ and concentrated to give the crude product. The crude product was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 30% to 40%) to give 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline-6-carbonitrile formate (1: 1) (2.6 mg, 12.8%) as a white solid. ¹H NMR (300 MHz, CD₃OD): δ 8.51 (brs, 1H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.45 – 7.37 (m, 1H), 7.34 (t, *J* = 2.4 Hz, 1H), 7.09 (d, *J* = 2.4 Hz, 1H), 6.98 – 6.89 (m, 1H), 5.33 (d, *J* = 53.7 Hz, 1H), 4.49 – 4.28 (m, 3H), 4.27 – 4.05 (m, 1H), 3.91 (s, 3H), 3.82 – 3.59 (m, 4H), 3.57 – 3.33 (m, 3H), 3.17 – 3.04 (m, 1H), 2.47 – 2.32 (m, 1H), 2.31 – 2.24 (m, 1H), 2.21 – 2.14 (m, 1H), 2.13 – 1.95 (m, 3H), 1.94 – 1.77 (m, 4H). ¹⁹F NMR (300 MHz, CD₃OD): δ -117.136, -132.669, -173.759. LCMS: *m/z* 631.2 (M + H⁺).

Example 9 and 10

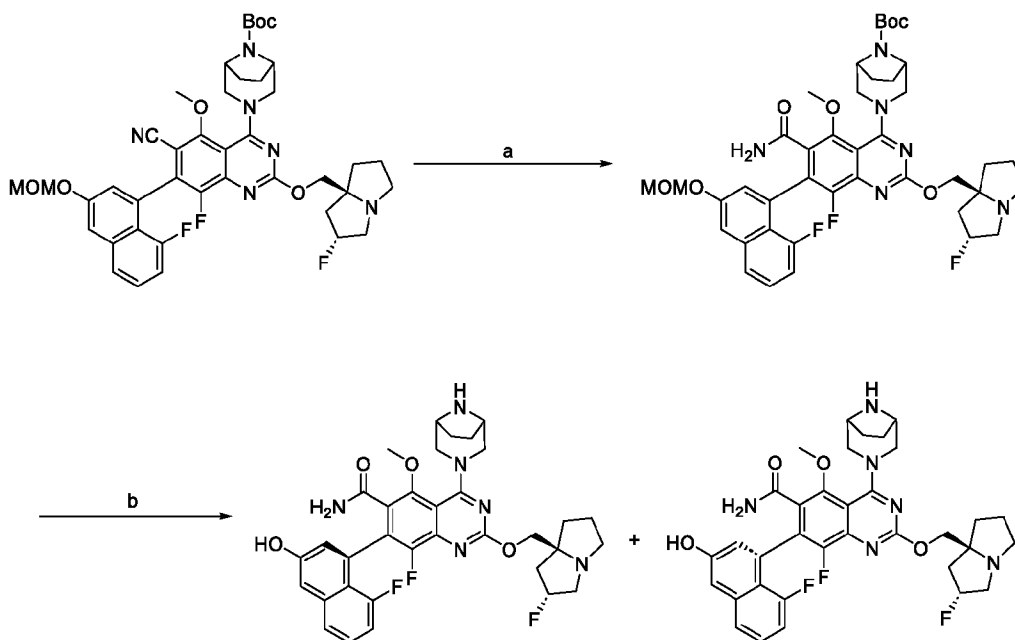
(R)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline-6-carboxamide formate (1: 1)



(S)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline-6-carboxamide formate (1: 1)

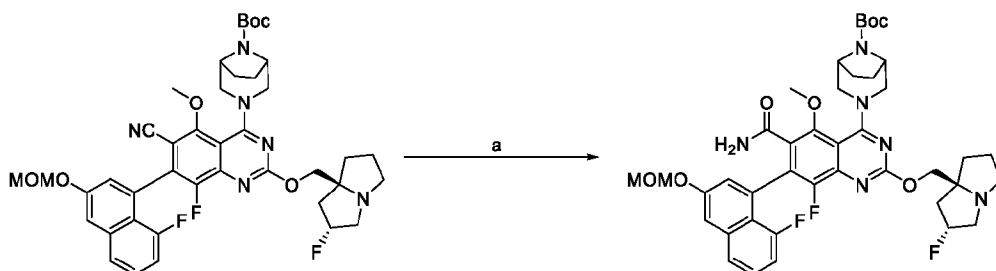


Synthesis scheme



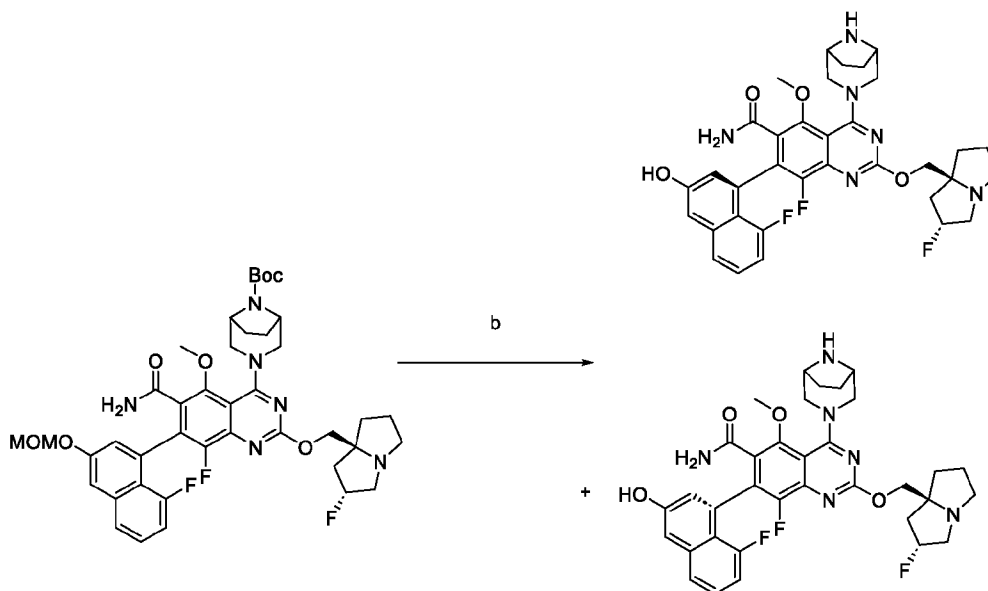
the two isomers (R or S) cannot be confirmed

Step 1: Synthesis of tert-butyl 3-(6-carbamoyl-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00367] To a solution of tert-butyl 3-(6-cyano-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (80 mg, 0.10 mmol, 1.0 eq) in DMSO (2 mL) was added K_2CO_3 (21 mg, 0.15 mmol, 1.5 eq) and 30% H_2O_2 (2 d). The mixture was stirred at room temperature for 2 h. The mixture was diluted with water (8 mL) and extracted with EtOAc (8 mL x 3). The combined organic phase was washed with water (8 mL x 3) and brine (8 mL), dried over Na_2SO_4 and concentrated to give the crude product. The crude product was purified by prep-TLC (DCM: MeOH = 15: 1) to give tert-butyl 3-(6-carbamoyl-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (50 mg, 61.0%) as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, J = 7.2 Hz, 1H), 7.50 – 7.47 (m, 1H), 7.39 – 7.33 (m, 1H), 7.20 (d, J = 2.1 Hz, 1H), 6.98 – 6.89 (m, 1H), 5.64 – 5.21 (m, 5H), 5.28 – 5.16 (m, 1H), 4.40 – 4.23 (m, 4H), 4.09 – 3.94 (m, 1H), 3.74 (s, 3H), 3.53 (s, 3H), 3.42 – 3.17 (m, 3H), 3.08 – 2.99 (m, 1H), 2.37 – 2.18 (m, 4H), 2.02 – 1.86 (m, 6H), 1.51 (s, 9H). LCMS: m/z 793.3 ($M+H^+$).

Step 2: Synthesis of (R)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline-6-carboxamide formate (1: 1) and (S)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline-6-carboxamide formate (1: 1)



R or S was randomly assigned

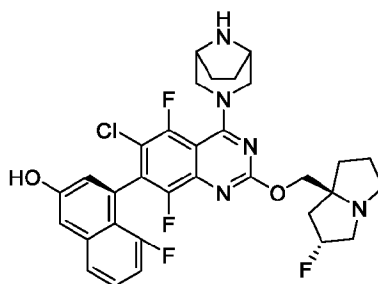
[00368] To a solution of tert-butyl 3-(6-carbamoyl-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (50 mg) in ACN (3 mL) was added TFA (1 mL). The mixture was stirred at room temperature for 2 h. The mixture was basified with saturated aqueous NaHCO_3 (10 mL) and extracted with EtOAc (15 mL $\times$ 5). The combined organic layers were dried over Na_2SO_4 and concentrated to give crude product. The crude product was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 30% to 40%) to give compound (R)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline-6-carboxamide formate (1: 1) (2.7 mg, 6.9%) and (S)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline-6-carboxamide formate (1: 1) (3.3 mg, 8.5%) as a white solid, the two isomers (*R* or *S*) cannot be confirmed. (R)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline-6-carboxamide formate (1: 1) as **Peak 1**: ^1H NMR (300 MHz, CD_3OD): δ 7.53 (d, J = 8.1 Hz, 1H), 7.34 (td, J = 8.1, 5.1 Hz, 1H), 7.24 (t, J = 2.4 Hz, 1H), 7.07 (d, J = 2.4 Hz, 1H), 6.92 – 6.82 (m,

1H), 5.41 (d, $J = 53.7$ Hz, 1H), 4.49 – 4.35 (m, 3H), 3.88 (s, 2H), 3.77 (s, 3H), 3.75 – 3.55 (m, 3H), 3.54 – 3.39 (m, 3H), 3.24 – 3.16 (m, 1H), 2.52 – 2.39 (m, 1H), 2.38 – 2.32 (m, 1H), 2.29 – 2.21 (m, 1H), 2.20 – 2.03 (m, 3H), 2.02 – 1.92 (m, 4H). ^{19}F NMR (300 MHz, CD_3OD): δ -116.065, -133.757, -173.881.

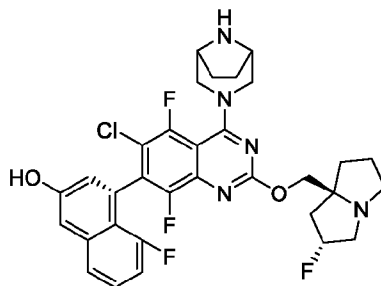
[00369] (S)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline-6-carboxamide formate (1: 1) as **Peak 2**: ^1H NMR (300 MHz, CD_3OD): δ 7.53 (d, $J = 8.1$ Hz, 1H), 7.34 (td, $J = 8.1, 5.1$ Hz, 1H), 7.24 (t, $J = 2.4$ Hz, 1H), 7.07 (d, $J = 2.4$ Hz, 1H), 6.92 – 6.82 (m, 1H), 5.36 (d, $J = 53.7$ Hz, 1H) 4.40 – 4.25 (m, 3H), 3.76 (s, 3H), 3.71 (s, 2H), 3.66 – 3.53 (m, 2H), 3.52 – 3.41 (m, 1H), 3.40 – 3.33 (m, 3H), 3.14 – 3.06 (m, 1H), 2.49 – 2.39 (m, 1H), 2.31 – 2.24 (m, 1H), 2.23 – 2.15 (m, 1H), 2.21 – 1.98 (m, 3H), 1.95 – 1.81 (m, 4H). ^{19}F NMR (300 MHz, CD_3OD): δ -115.945, -133.865, -173.716. LCMS: 649.3/649.2 ($\text{M}+\text{H}^+$).

Example 11 and 12

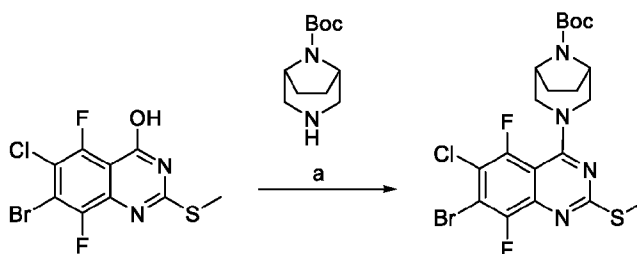
4-((S)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-5,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-5-fluoronaphthalen-2-ol



4-((R)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-5,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-5-fluoronaphthalen-2-ol

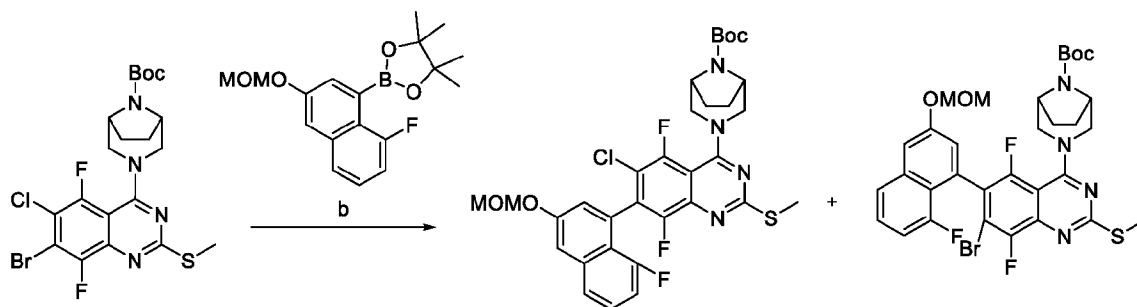


Step 1: Synthesis of tert-butyl 3-(7-bromo-6-chloro-5,8-difluoro-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



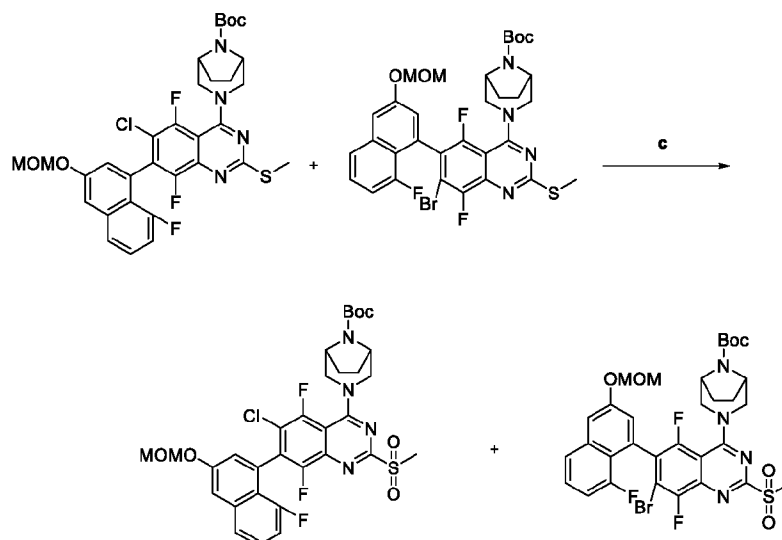
[00370] To a solution of 7-bromo-6-chloro-5,8-difluoro-2-(methylthio)quinazolin-4-ol (1.7 g, crude, 4.98 mmol, 1.0 eq) in DMF (34 mL) was added tert-butyl (1R,5S)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2.1 g, crude, 9.95 mmol, 2.0 eq), DBU (1.5 g, 9.95 mmol, 2.0 eq) and BOP (3.3 g, 7.47 mmol, 1.5 eq). The mixture was stirred at 100 °C for 1 h under nitrogen atmosphere. The reaction mixture was diluted with H₂O (70 mL) and extracted with DCM (70 mL x 2). The organic layers were washed with water (70 mL x 3) and brine (70 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give residue. The residue was purified by silica gel column chromatography (petroleum ether / EtOAc = 30 / 1) to give tert-butyl (1R,5S)-3-(7-bromo-6-chloro-5,8-difluoro-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (530 mg, 19.8 %) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 4.30 (s, 2H), 4.12 – 4.00 (m, 2H), 3.60 – 3.38 (m, 2H), 1.93 – 1.81 (m, 2H), 1.73 – 1.64 (m, 2H), 1.55 (s, 3H), 1.50 (s, 9H). LCMS: m/z 535.0, 537.0 (M+H⁺).

Step 2: Synthesis of tert-butyl 3-(6-chloro-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and tert-butyl (1R,5S)-3-(7-bromo-5,8-difluoro-6-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (mixture)



[00371] To a solution of tert-butyl (1R,5S)-3-(7-bromo-6-chloro-5,8-difluoro-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (500 mg, 0.93 mmol, 1.0 eq) in Dioxane (20 mL) and H₂O (5 mL) was added 2-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (620 mg, 1.87 mmol, 2.0 eq), K₂CO₃ (387 mg, 2.80 mmol, 3.0 eq) and Pd(PPh₃)₄ (107 mg, 0.09 mmol, 0.1 eq). The mixture was stirred at 80 °C for 7 h under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether / EtOAc = 20 / 1) to give tert-butyl (1R,5S)-3-(6-chloro-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and tert-butyl (1R,5S)-3-(7-bromo-5,8-difluoro-6-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (380 mg, mixture) as a white solid. LCMS: m/z 661.2 (M+H⁺); 705.1 (M+H⁺).

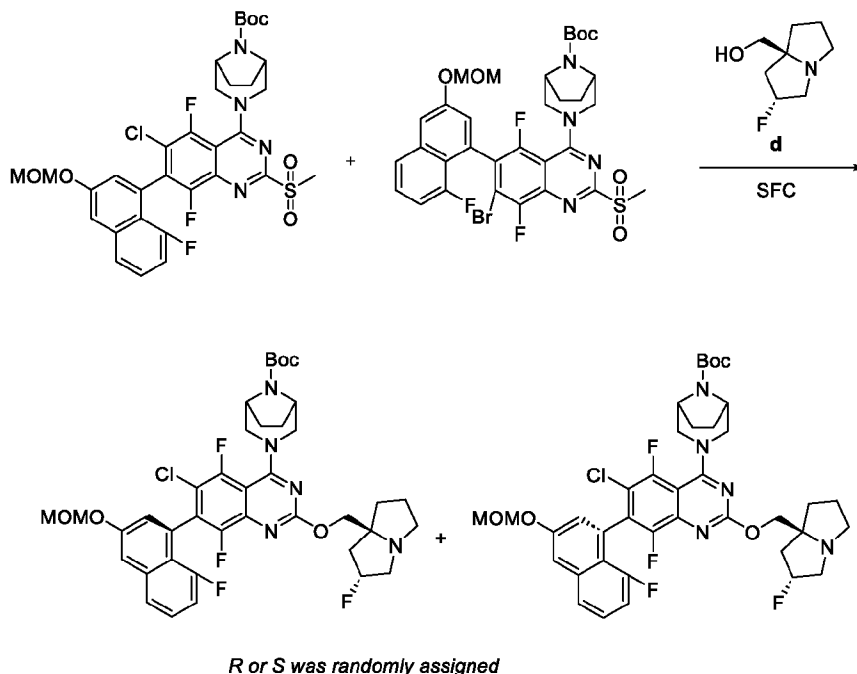
Step 3: Synthesis of tert-butyl 3-(6-chloro-5,8-difluoro-7-(8-fluoro-3-(methoxy methoxy)naphthalen-1-yl)-2-(methylsulfonyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and tert-butyl 3-(7-bromo-5,8-difluoro-6-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(methylsulfonyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (mixture)



[00372] To a solution of tert-butyl 3-(6-chloro-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and tert-butyl 3-(7-bromo-5,8-difluoro-6-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (300 mg, mixture, ~0.45 mmol, ~1.0 eq) in DCM (10 mL) was added *m*-CPBA (188 mg, 1.09 mmol, 2.4 eq). The mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with saturated aqueous Na₂SO₃ (10 mL) and extracted with DCM (10 mL x 2). The organic layers were washed with saturated aqueous NaHCO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give residue. The residue was purified by silica gel column chromatography (petroleum ether / EtOAc = 3 / 1) to give tert-butyl 3-(6-chloro-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(methylsulfonyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and tert-butyl 3-(7-bromo-5,8-difluoro-6-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(methylsulfonyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (250 mg, mixture) as a white solid. LCMS: *m/z* 693.2 (M+H⁺); 737.1 (M+H⁺).

Step 4: Synthesis of tert-butyl 3-((S)-6-chloro-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and tert-butyl (1R,5S)-3-((R)-6-chloro-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-

(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



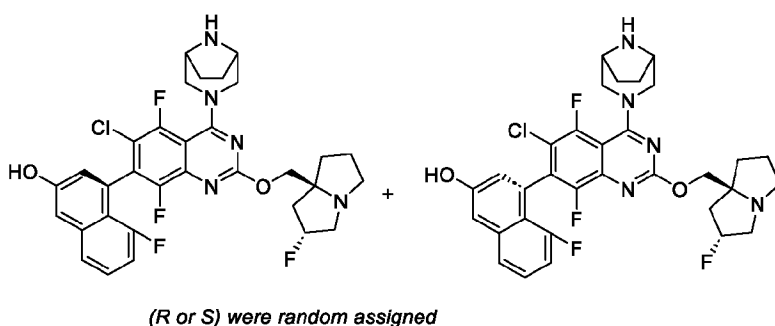
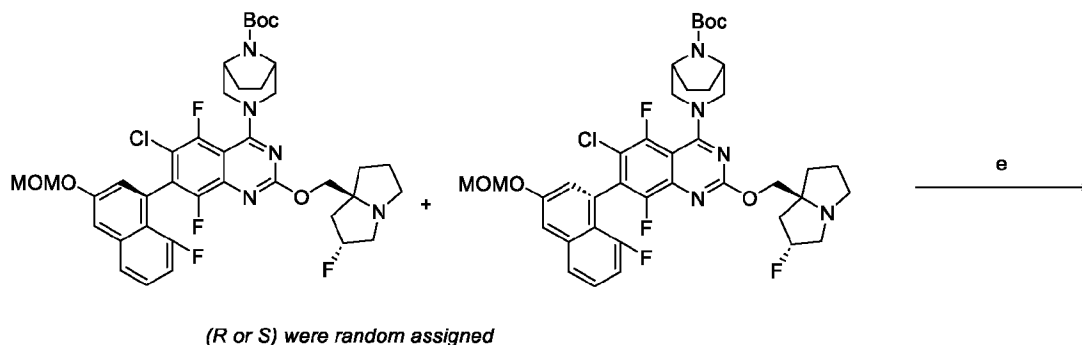
[00373] To a solution of tert-butyl 3-(6-chloro-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(methylsulfonyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and tert-butyl 3-(7-bromo-5,8-difluoro-6-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(methylsulfonyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (250 mg, mixture, ~0.36 mmol, ~1.0 eq) in THF (10 mL) was added B41163-10 (172 mg, 1.08 mmol, 3.0 eq) and LiHMDS (1 M in THF, 1.08 mL, 1.08 mmol, 3.0 eq) dropwise at 0 °C under nitrogen atmosphere. The mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with H₂O (10 mL) and extracted with EtOAc (10 mL x 3). The organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give residue. The residue was purified by SFC to give tert-butyl (1R,5S)-3-((S)-6-chloro-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (44 mg), and tert-butyl (1R,5S)-3-((R)-6-chloro-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-

diazabicyclo[3.2.1]octane-8-carboxylate (55 mg), as a white solid, the two isomers (*R* or *S*) was randomly assigned.

[00374] tert-butyl 3-((*S*)-6-chloro-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate: ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.81 (d, *J* = 7.8 Hz, 1H), 7.72 (t, *J* = 2.1 Hz, 1H), 7.57 – 7.45 (m, 1H), 7.29 (d, *J* = 2.4 Hz, 1H), 7.20 – 7.10 (m, 1H), 5.39 (s, 2H), 5.27 (d, *J* = 54.3 Hz, 1H), 4.31 – 3.96 (m, 6H), 3.45 (s, 3H), 3.43 – 3.33 (m, 2H), 3.12 – 3.04 (m, 2H), 2.99 (s, 1H), 2.87 – 2.76 (m, 1H), 2.15 – 1.73 (m, 10H), 1.45 (s, 9H).
LCMS: *m/z* 772.3 (M+H⁺).

[00375] tert-butyl 3-((*R*)-6-chloro-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate: ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.81 (d, *J* = 7.8 Hz, 1H), 7.72 (t, *J* = 2.1 Hz, 1H), 7.57 – 7.45 (m, 1H), 7.29 (d, *J* = 2.4 Hz, 1H), 7.20 – 7.10 (m, 1H), 5.39 (s, 2H), 5.27 (d, *J* = 54.3 Hz, 1H), 4.35 – 3.97 (m, 6H), 3.45 (s, 3H), 3.43 – 3.33 (m, 2H), 3.12 – 3.04 (m, 2H), 2.99 (s, 1H), 2.87 – 2.76 (m, 1H), 2.18 – 1.65 (m, 10H), 1.45 (s, 9H).
LCMS: *m/z* 772.3 (M+H⁺).

Step 5: 4-((*S*)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-5,8-difluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)quinazolin-7-yl)-5-fluoronaphthalen-2-ol and 4-((*R*)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-5,8-difluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)quinazolin-7-yl)-5-fluoronaphthalen-2-ol



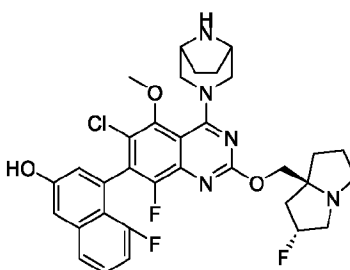
[00376] To a solution of tert-butyl 3-((S)-6-chloro-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy) naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (44 mg) in DCM (2 mL) was added HCl/Dioxane (4M, 1 mL). The mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and diluted with MeOH (2 mL). The pH was adjusted to around 9 by adding aq NaHCO₃ (2 mL). Then the mixture was concentrated under reduced pressure and diluted with DCM / MeOH = 15/1, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (ACN/ H₂O) to give 4-((S)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-5,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-5-fluoronaphthalen-2-ol (16.1 mg, 45.0%) as a white solid. ¹H NMR (400 MHz, CD₃OD): δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.38 (td, *J* = 8.0, 5.2 Hz, 1H), 7.32 (t, *J* = 2.4 Hz, 1H), 7.00 (d, *J* = 2.4 Hz, 1H), 6.94 – 6.86 (m, 1H), 5.37 (d, *J* = 53.4 Hz, 1H), 4.45 – 4.32 (m, 3H), 4.29 (d, *J* = 5.6 Hz, 1H), 4.25 – 4.20 (m, 1H), 3.92 – 3.85 (m, 2H), 3.71 – 3.57 (m, 2H), 3.51 – 3.36 (m, 3H), 2.45 – 1.92 (m, 10H). ¹⁹F NMR (400 MHz, CD₃OD): δ -111.218, -118.194, -130.437, -173.840. LCMS: 628.20 (M+H⁺).

[00377] To a solution of tert-butyl 3-((R)-6-chloro-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (55 mg) in DCM (2 mL) was added HCl/Dioxane (4M, 1 mL). The mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and diluted with MeOH (2 mL). The pH was adjusted to around 9 by adding aq NaHCO₃ (2 mL). Then the mixture was concentrated under reduced pressure and diluted with DCM / MeOH = 15/1, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (ACN/ H₂O) to give 4-((R)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-5,8-difluoro-2-(((2R,7aS)-2-fluoro tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-5-fluoronaphthalen-2-ol (12.2 mg, 27.7%) as a white solid.

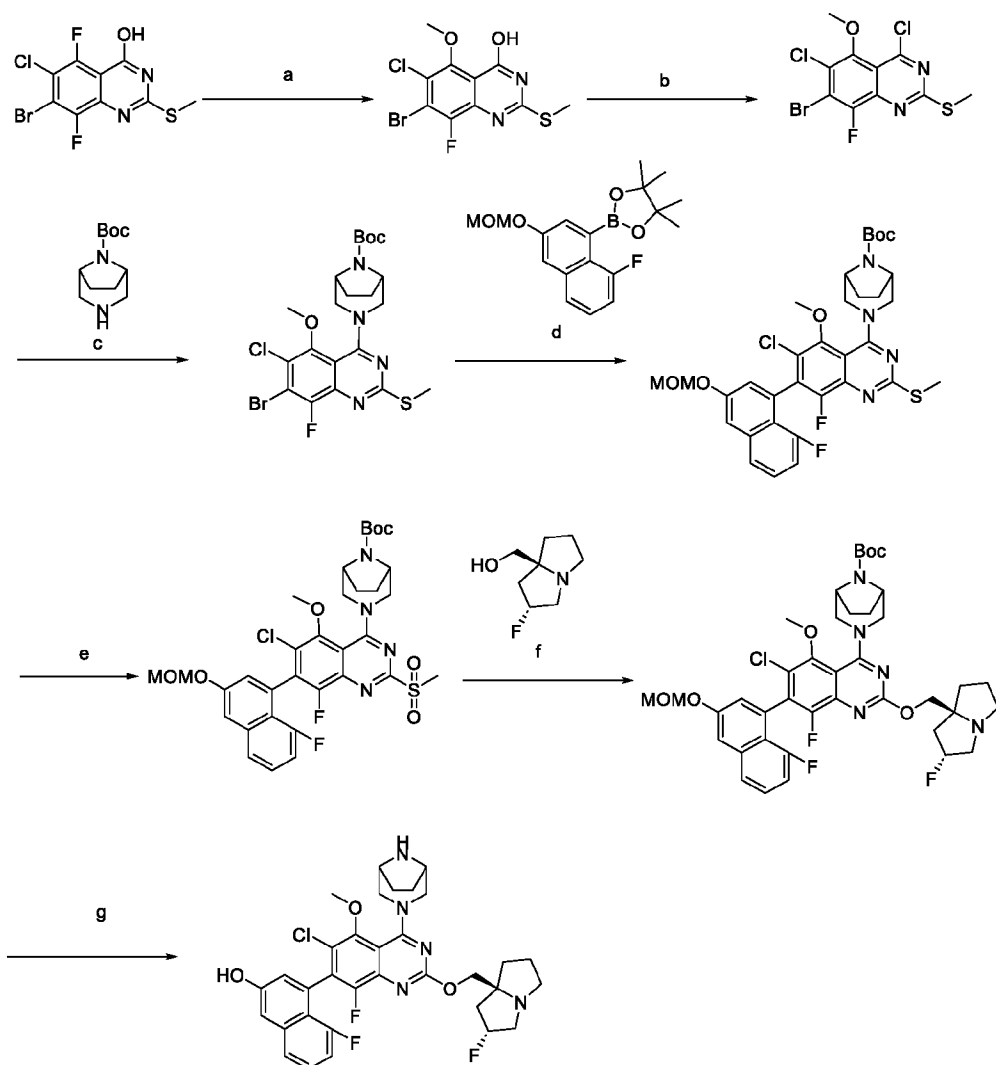
¹H NMR (400 MHz, CD₃OD): δ 7.60 (d, *J* = 8.4 Hz, 1H), 7.39 (td, *J* = 8.0, 5.2 Hz, 1H), 7.34 (t, *J* = 2.4 Hz, 1H), 7.00 (d, *J* = 2.4 Hz, 1H), 6.95 – 6.87 (m, 1H), 5.38 (d, *J* = 53.4 Hz, 1H), 4.65 – 4.55 (m, 2H), 4.53 – 4.45 (m, 1H), 4.34 – 4.28 (m, 1H), 4.19 – 4.12 (m, 2H), 3.92 – 3.55 (m, 6H), 2.69 – 2.04 (m, 10H). ¹⁹F NMR (400 MHz, CD₃OD): δ -111.205, -118.318, -130.257, -174.103. LCMS: 628.20 (M+H⁺).

Example 13

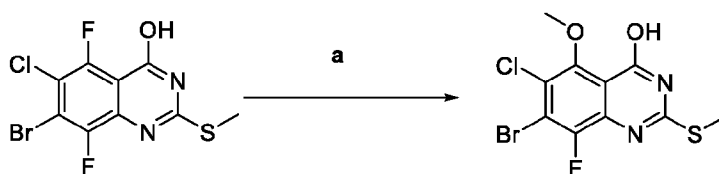
4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-fluoronaphthalen-2-ol hydrochloride



Synthetic scheme:



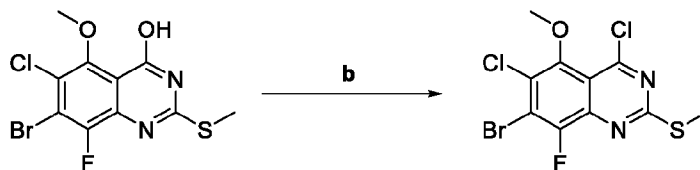
Step 1: Synthesis of 7-bromo-6-chloro-8-fluoro-5-methoxy-2-(methylthio)quinazolin-4-ol



[00378] To a solution of MeOH (563 mg, 17.57 mmol, 3.0 eq) in DMF (8 mL) was added NaH (750 mg, 18.74 mmol, 3.2 eq, 60% in oil) slowly and the mixture stirred at 0°C for 30 min. Then a solution of 7-bromo-6-chloro-5,8-difluoro-2-(methylthio)quinazolin-4-ol (2.0 g, 5.88 mmol, 1.0 eq) in DMF (30 mL) was added dropwise at 0°C. The reaction mixture was stirred at room temperature for 15 h under nitrogen atmosphere. The mixture was poured into aqueous NH₄Cl, the precipitate formed was collected by filtration, washed with water (10 mL), dried in

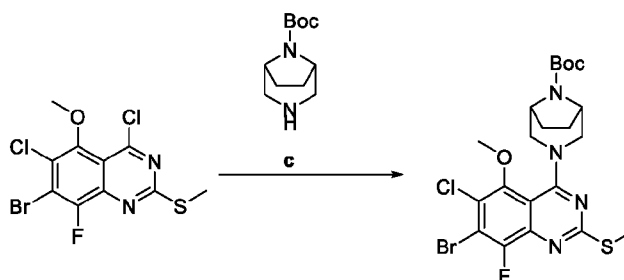
vacuo to give crude compound 7-bromo-6-chloro-8-fluoro-5-methoxy-2-(methylthio)quinazolin-4-ol (1.93 g, crude) as a yellow solid. ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 3.81 (s, 3H), 2.57 (s, 3H). LCMS: m/z 352.9, 354.9 ($\text{M} + \text{H}^+$).

Step 2: Synthesis of 7-bromo-4,6-dichloro-8-fluoro-5-methoxy-2-(methylthio)quinazoline



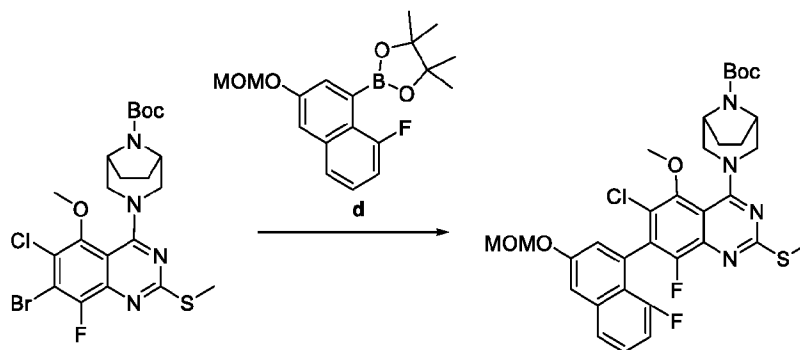
[00379] To a solution of 7-bromo-6-chloro-8-fluoro-5-methoxy-2-(methylthio)quinazolin-4-ol (1.93 g, 5.46 mmol, 1.0 eq) in POCl_3 (15 mL) was added DIEA (3.53 g, 27.29 mmol, 5.0 eq). Then the reaction mixture was stirred at $90\text{ }^\circ\text{C}$ for 2 h. The mixture was concentrated and purified by silica gel chromatography (eluted with PE: EtOAc = 1:1) to give 7-bromo-4,6-dichloro-8-fluoro-5-methoxy-2-(methylthio)quinazoline (680 mg, 31.1% for 2 steps) as yellow solid.

Step 3: Synthesis of tert-butyl 3-(7-bromo-6-chloro-8-fluoro-5-methoxy-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



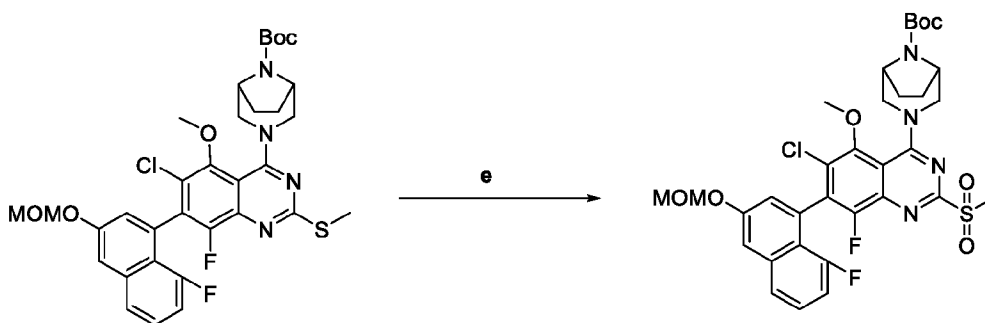
[00380] To a solution of 7-bromo-4,6-dichloro-8-fluoro-5-methoxy-2-(methylthio)quinazoline (680 mg, 1.85 mmol, 1.2 eq) and DIEA (597 mg, 4.62 mmol, 3.0 eq) in DCM (15 mL) stirring at $-40\text{ }^\circ\text{C}$ under nitrogen atmosphere was added dropwise tert-butyl (1R,5S)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (327 mg, 1.54 mmol, 1.0 eq) in DCM (5 mL). The mixture was stirring at $-40\text{ }^\circ\text{C}$ for 2 h. The residue was quenched with 1N HCl (15 mL) and extracted with DCM (30 mL x 3). The organic phase was washed with brine (30 mL), dried with Na_2SO_4 , filtered and concentrated to give residue. The residue was purified by silica gel column chromatography (petroleum ether: EtOAc = 5: 1) to give tert-butyl 3-(7-bromo-6-chloro-8-fluoro-5-methoxy-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (850 mg, 83.9%) as white solid. LCMS: m/z 547.0, 549.0 ($\text{M} + \text{H}^+$).

Step 4: Synthesis of tert-butyl 3-(6-chloro-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-5-methoxy-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



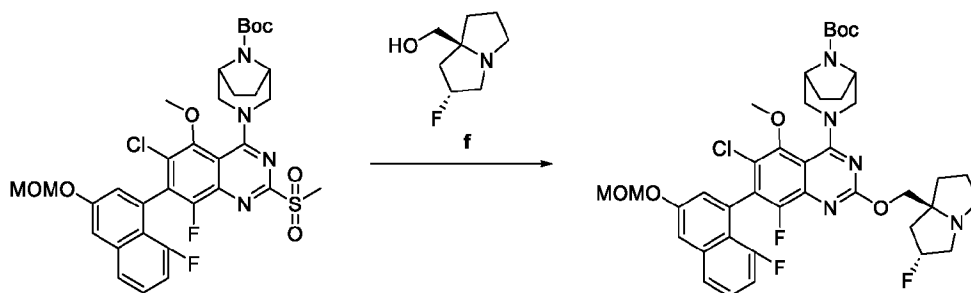
[00381] To a solution of tert-butyl 3-(7-bromo-6-chloro-8-fluoro-5-methoxy-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (200 mg, 0.37 mmol, 1.0 eq) in dioxane (8 mL) and H₂O (2 mL) was added 7-bromo-6-chloro-5,8-difluoro-2-(methoxymethoxy)quinazolin-4-ol (145 mg, 0.44 mmol, 1.5 eq), K₂CO₃ (151 mg, 1.10 mmol, 3.0 eq) and Pd (PPh₃)₄ (43 mg, 0.04 mmol, 0.15 eq). The reaction mixture was stirred at 90 °C for 15 h. The mixture was diluted with water (15 mL) and extracted with EtOAc (20 mL x 3). The organic phase was washed with brine (20 mL), dried with Na₂SO₄, filtered and concentrated to give residue. The residue was purified by silica gel column chromatography (petroleum ether: EtOAc = 20: 1) to give tert-butyl 3-(6-chloro-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-5-methoxy-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (140 mg, 56.9%) as yellow solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.80 (d, *J* = 8.1 Hz, 1H), 7.70 (t, *J* = 2.1 Hz, 1H), 7.57 – 7.41 (m, 1H), 7.28 (d, *J* = 2.4 Hz, 1H), 7.13 (dd, *J* = 13.2, 7.5 Hz, 1H), 5.39 (s, 2H), 4.32 – 4.03 (m, 4H), 3.66 (s, 3H), 3.45 (s, 3H), 3.17 (d, *J* = 5.1 Hz, 2H), 2.56 (s, 3H), 1.86 – 1.52 (m, 4H), 1.45 (s, 9H). LCMS: *m/z* 673.2 (M + H⁺).

Step 5: Synthesis of tert-butyl 3-(6-chloro-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-5-methoxy-2-(methylsulfonyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00382] To a solution of tert-butyl 3-(6-chloro-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-5-methoxy-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (140 mg, 0.21 mmol, 1.0 eq) in DCM (6.00 mL) was added m-CPBA (110 mg, 0.62 mmol, 3.0 eq, 98%) at 0°C. Then the reaction mixture was stirred at room temperature for 2 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with saturated aqueous Na₂SO₃ (10 mL), saturated aqueous NaHCO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by silica gel column chromatography (Petroleum ether/ EtOAc 3:1) to give tert-butyl 3-(6-chloro-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-5-methoxy-2-(methylsulfonyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 68.0%) as a yellow solid. LCMS: 705.2 m/z (M + H⁺).

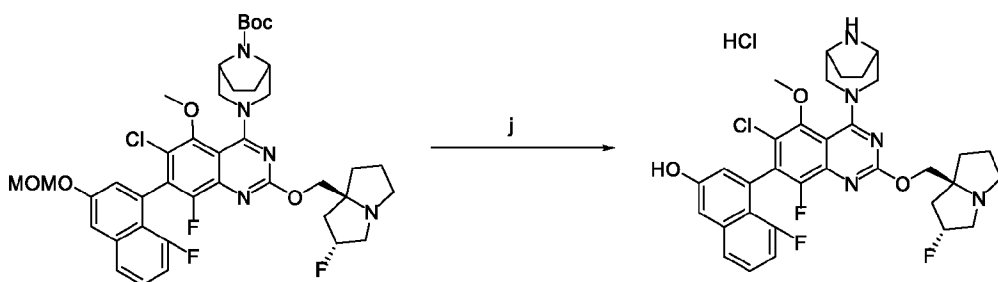
Step 6: Synthesis of tert-butyl 3-(6-chloro-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00383] To a solution of tert-butyl 3-(6-chloro-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-5-methoxy-2-(methylsulfonyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.14 mmol, 1.0 eq) and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (68 mg, 0.43 mmol, 3.0 eq) in THF (5.00

mL) was added LiHMDS (1M in THF) (0.42 mL, 0.42 mmol, 3.0 eq) dropwise at 0 °C. Then the reaction mixture was stirred at 0 °C for 1 h. The mixture was quenched with H₂O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give the crude product. The crude product was purified by prep-TLC (DCM/MeOH 20:1) to give tert-butyl 3-(6-chloro-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (50 mg, 45.5%) as a white solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.79 (d, *J* = 8.1 Hz, 1H), 7.69 (t, *J* = 2.1 Hz, 1H), 7.50 (td, *J* = 7.8, 5.1 Hz, 1H), 7.26 (d, *J* = 2.1 Hz, 1H), 7.12 (dd, *J* = 13.2, 7.6 Hz, 1H), 5.41 – 5.17 (m, 3H), 4.35 – 3.92 (m, 6H), 3.66 (s, 3H), 3.45 (s, 3H), 3.42 – 3.34 (m, 1H), 3.18 – 2.80 (m, 5H), 2.20 – 1.68 (m, 10H), 1.45 (s, 9H). LCMS: 784.3(M + H⁺).

Step 7: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-fluoronaphthalen-2-ol hydrochloride

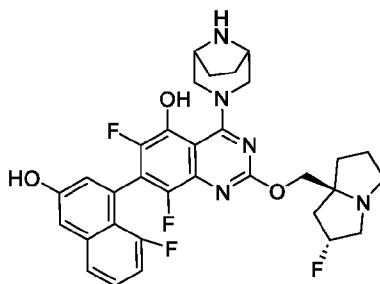


[00384] To a solution of tert-butyl 3-(6-chloro-8-fluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (50 mg, 0.064 mmol, 1.0 eq) in DCM (2.00mL) was added HCl/dioxane (4N) (0.5 mL) dropwise at 0 °C. Then the reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC (0.1 % FA in H₂O/ ACN) to give 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-fluoronaphthalen-2-ol hydrochloride (3.6 mg, 8.3%) as a white solid. ¹H NMR (300 MHz, CD₃OD): δ 7.59 (d, *J* = 8.1 Hz, 1H), 7.46 – 7.27 (m, 2H), 7.01 – 6.81 (m, 2H), 5.50 (d, *J* = 52.2 Hz, 1H), 4.65 – 4.65 (m, 3H), 4.40 – 4.22 (m, 1H), 4.13 (d, *J* = 9.6 Hz, 2H), 3.84 – 3.64 (m, 8H), 3.41 – 3.30 (s, 1H), 2.58

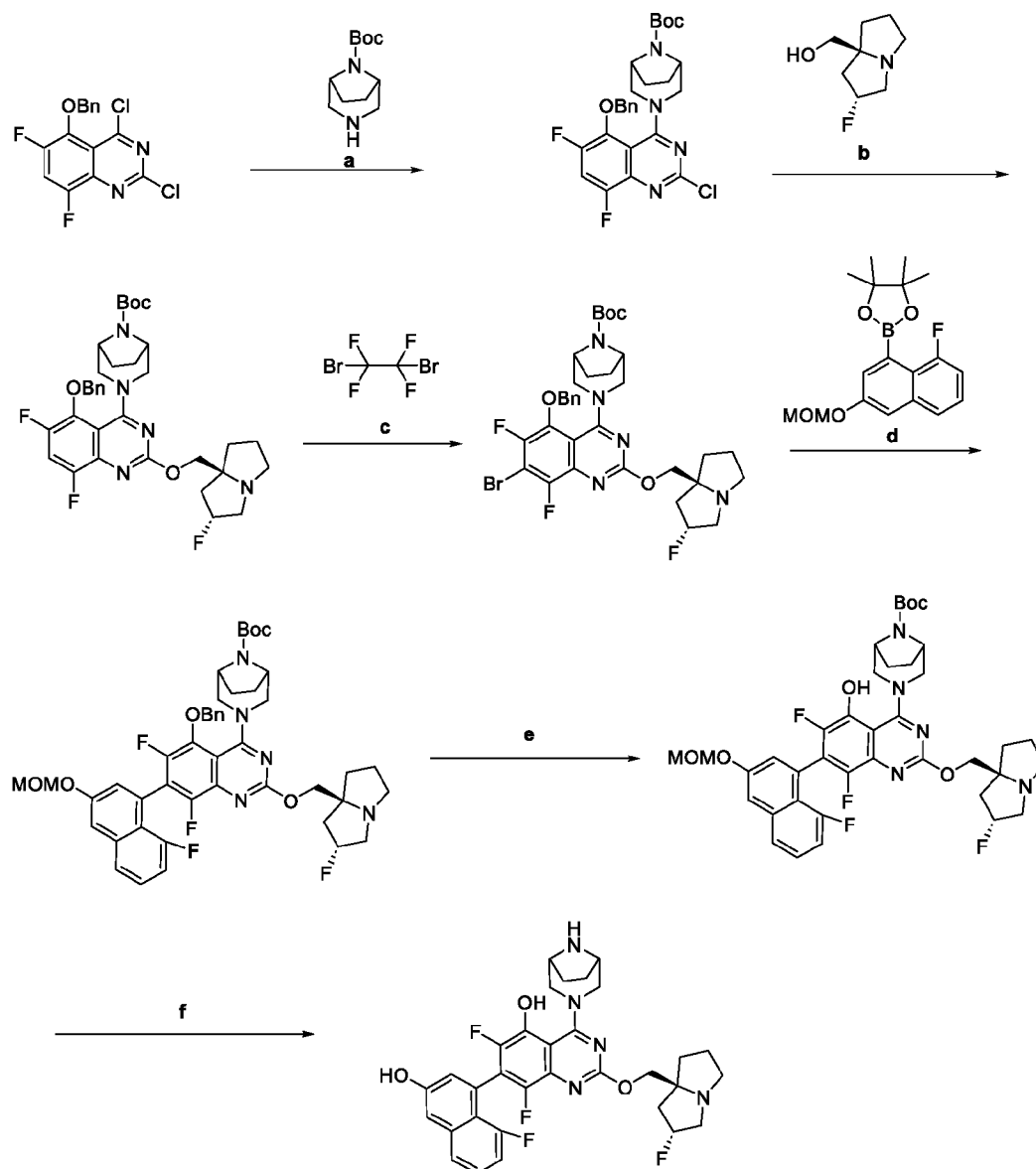
– 2.03 (m, 10H). ^{19}F NMR (300 MHz, CD_3OD): δ -118.277, -130.645, -174.096. LCMS: m/z 640.2 ($\text{M}+\text{H}^+$).

Example 14

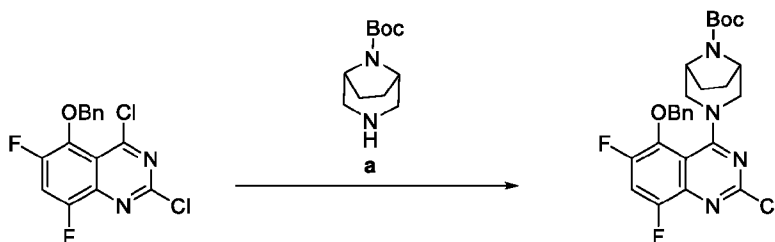
4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-5-ol formate



Synthetic scheme:



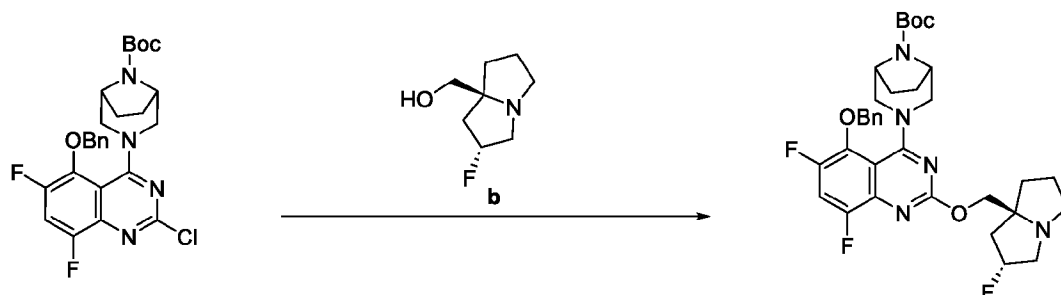
Step 1: Synthesis of tert-butyl 3-(5-(benzyloxy)-2-chloro-6,8-difluoroquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00385] To a solution of compound 5-(benzyloxy)-2,4-dichloro-6,8-difluoroquinazoline (900 mg, 2.6 mmol, 1.0 eq) and DIEA (1.2 g, 9.5 mmol, 3.6 eq) in DCM (10 mL) was added tert-butyl

(1R,5S)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (840 mg, 4.0 mmol, 1.5 eq) at -40 °C. The reaction mixture was stirred at -40 °C for 2 h under nitrogen atmosphere. The mixture was concentrated to give a residue. The residue was partitioned between DCM (20 mL) and water (10 mL). The layers were separated. The aqueous layer was extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by prep-TLC (PE/EA 5:1) to give compound tert-butyl 3-(5-(benzyloxy)-2-chloro-6,8-difluoroquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (500 mg, 50.9% for three steps) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 7.36 – 7.28 (m, 4H), 7.23 – 7.15 (m, 2H), 4.87 (s, 2H), 4.54 – 3.83 (m, 4H), 3.46 – 3.21 (m, 2H), 1.85 – 1.58 (m, 4H), 1.45 (s, 9H). LCMS: m/z 517.2 (M + H⁺).

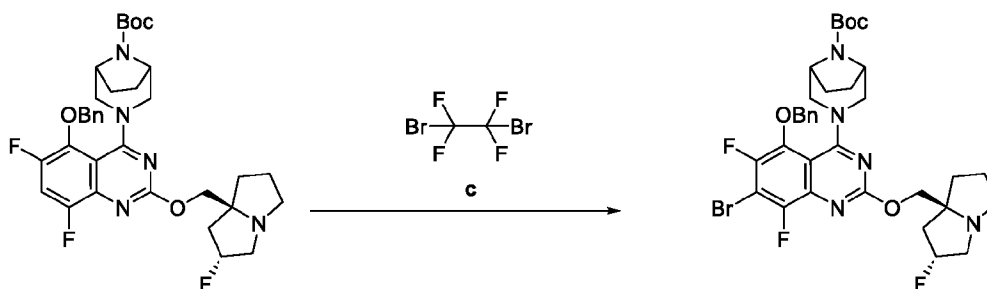
Step 2: Synthesis of tert-butyl 3-(5-(benzyloxy)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00386] A solution of compound tert-butyl 3-(5-(benzyloxy)-2-chloro-6,8-difluoroquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (500 mg, 0.97 mmol, 1.0 eq), compound ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (185 mg, 1.2 mmol, 1.2 eq), DABCO (108 mg, 0.97 mmol, 1.0 eq), and Cs₂CO₃ (962 mg, 3.0 mmol, 3.0 eq) in THF (5 mL) and DMF (5 mL) was stirred at room temperature for 15 h under nitrogen atmosphere. The mixture was added H₂O (20 mL), extracted with EtOAc (10 mL x 3). The combined organic layers were washed with H₂O (5 mL), brine (5 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (DCM / MeOH 20:1) to give compound tert-butyl 3-(5-(benzyloxy)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (353 mg, 48.5%) as a yellow solid. ¹H NMR (300 MHz, CD₃OD-*d*₄): δ 7.52 (t, *J* = 10.5 Hz, 1H), 7.35 – 7.29 (m, 3H), 7.28 – 7.22 (m, 2H), 5.32 (d, *J* =

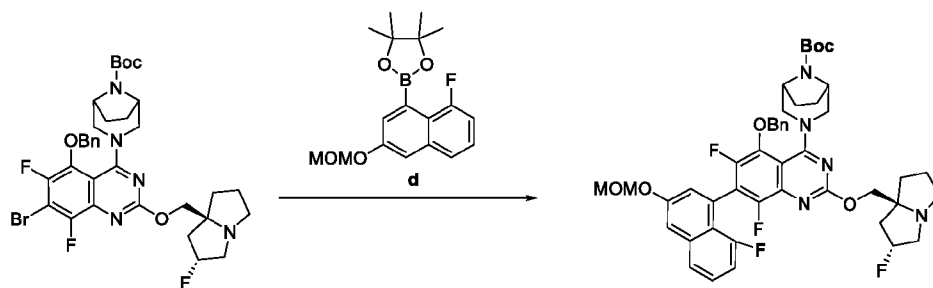
54.9 Hz, 1H), 4.97 – 4.90 (m, 4H), 4.61 – 4.58 (m, 1H), 4.27 – 4.14 (m, 4H), 3.39 – 3.36 (m, 1H), 3.30 – 2.97 (m, 4H), 2.40 – 1.72 (m, 10H), 1.48 (s, 9H). LCMS: m/z 640.3 ($M + H^+$).

Step 3: Synthesis of tert-butyl 3-(5-(benzyloxy)-7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



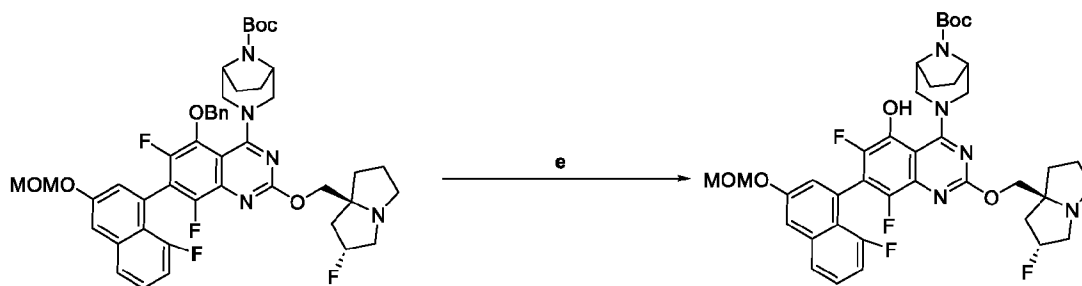
[00387] To a solution of compound tert-butyl 3-(5-(benzyloxy)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (270 mg, 0.42 mmol, 1.0 eq) in THF (5 mL) was added *n*-BuLi (0.5 mL, 1.3 mmol, 3.0 eq) at -65 °C under N₂ atmosphere. The mixture was stirred at -65 °C for 30 min. The mixture was added 1,2-dibromo-1,1,2,2-tetrafluoroethane (208 mg, 0.80 mmol, 1.9 eq) at the same temperature, and stirred for 2.5 h. The reaction was quenched with water. The mixture was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with H₂O (5 mL), brine (5 mL), dried over Na₂SO₄ and evaporated to dryness. The reaction was repeated for two times. The crude product was purified by prep-TLC (DCM/ MeOH 30:1) to give compound tert-butyl 3-(5-(benzyloxy)-7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (200 mg, 66.2%) as a yellow solid. LCMS: m/z 718.2/720.2 ($M + H^+$).

Step 4: Synthesis of tert-butyl 3-(5-(benzyloxy)-6,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00388] A solution of compound tert-butyl 3-(5-(benzyloxy)-7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.14 mmol, 1.0 eq), 2-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (69 mg, 0.21 mmol, 1.5 eq), K_2CO_3 (96 mg, 0.70 mmol, 5.0 eq) and $Pd(PPh_3)_4$ (24 mg, 0.02 mmol, 0.15 eq) in dioxane (2 mL) and H_2O (0.4 mL) was stirred at 100 °C for 15 h under nitrogen atmosphere. The mixture was concentrated to give the crude product. The crude product was purified by Prep-TLC (DCM/MeOH 15/1) to give compound tert-butyl 3-(5-(benzyloxy)-6,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (60 mg, 51.3%) as a white solid. LCMS: m/z 844.3 ($M + H^+$).

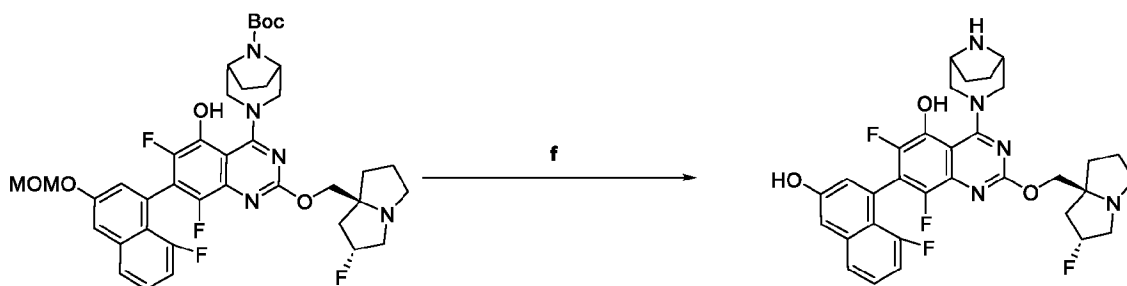
Step 5: Synthesis of tert-butyl 3-(6,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-hydroxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00389] A mixture of compound tert-butyl 3-(5-(benzyloxy)-6,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (55 mg, 0.07 mmol, 1.0 eq) and Pd/C (11 mg, 20 % w/w) in MeOH (2 mL) was stirred at room temperature for 2 h under H_2 atmosphere. The mixture was filtered, and the filtrate was concentrated to give crude product. The crude product was purified by Prep-TLC (DCM/MeOH 10/1) to give compound

tert-butyl 3-(6,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-hydroxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (26 mg, 53.1%) as a white solid. LCMS: m/z 754.3 ($M + H^+$).

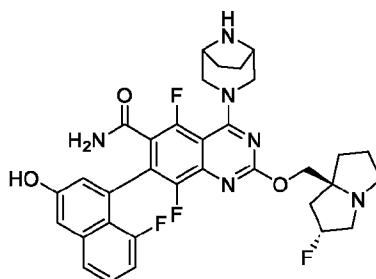
Step 6: Synthesis of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-5-ol formate (1: 1)



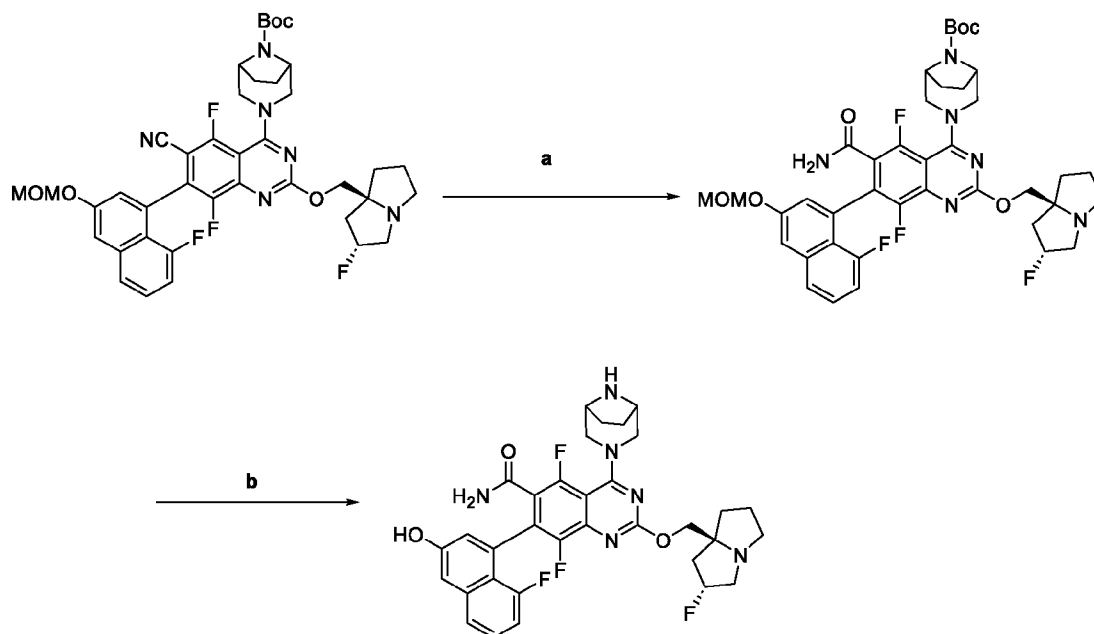
[00390] A solution of compound tert-butyl 3-(6,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-hydroxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (21 mg, 0.03 mmol, 1.0 eq) and HCl/Dioxane (0.21 mL, 0.84 mmol, 30.0 eq) in DCM (1 mL) was stirred at room temperature for 3 h under nitrogen atmosphere. The reaction was adjusted pH~8 with sat. NaHCO_3 aqueous. The mixture was extracted with DCM (5 mL x 3). The combined organic layers were washed with brine (2 mL), dried over Na_2SO_4 , filtered and concentrated to give a crude. The crude was purified by prep-HPLC (HCOOH system) to give 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-5-ol formate (1: 1) (8.6 mg, 47.0%) as a white solid. ^1H NMR (300 MHz, CD_3OD): δ 8.50 (brs, 1H), 7.57 (d, $J = 8.1$ Hz, 1H), 7.43 – 7.31 (m, 1H), 7.29 (s, 1H), 7.04 (s, 1H), 6.89 (dd, $J = 12.9, 7.5$ Hz, 1H), 5.41 (d, $J = 51.6$ Hz, 1H), 4.55 – 4.30 (m, 5H), 4.09 – 3.97 (m, 2H), 3.62 – 3.45 (m, 5H), 2.52 – 2.40 (m, 1H), 2.39 – 2.13 (m, 6H), 2.06 – 1.90 (m, 3H). ^{19}F NMR (300 MHz, CD_3OD): δ -117.824, -146.324, -174.200. LCMS: m/z 610.2 ($M + H^+$).

Example 15

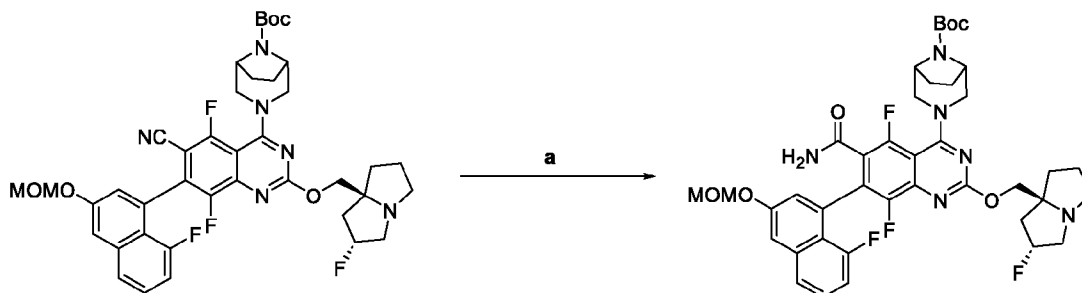
4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5,8-difluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazoline-6-carboxamide formate



Synthetic scheme:

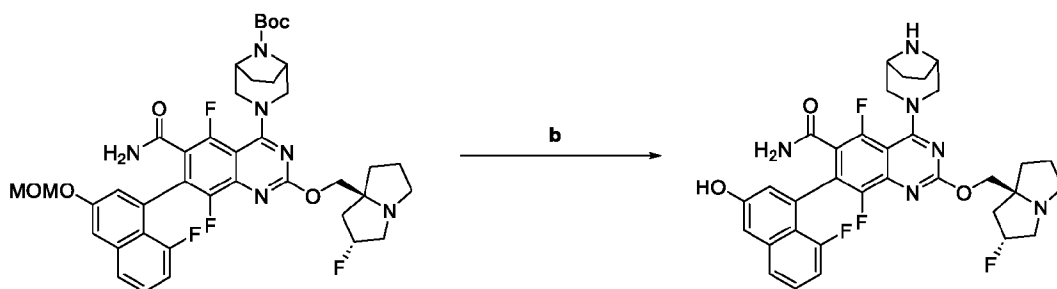


Step 1: Synthesis of tert-butyl 3-(6-carbamoyl-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00391] To a solution of tert-butyl 3-(6-cyano-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (200 mg, 0.26 mmol, 1.0 eq) in DMSO (2 mL) was added K₂CO₃ (54 mg, 0.39 mmol, 1.5 eq) and 30% H₂O₂ (5 drops). The mixture was stirred at room temperature for 2 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with water (5 mL x 3) and brine (5 mL), dried over Na₂SO₄ and concentrated to give the crude product. The crude product was purified by prep-TLC (DCM: MeOH = 20: 1) to give tert-butyl 3-(6-carbamoyl-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (30 mg, 60% purity) as a yellow solid. LCMS: m/z 781.3 (M+H⁺).

Step 2: Synthesis of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5,8-difluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazoline-6-carboxamide formate (1: 1)

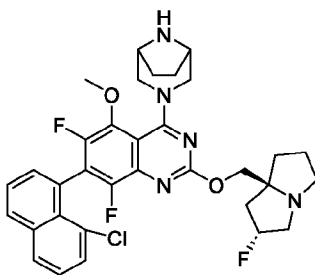


[00392] To a solution of tert-butyl 3-(6-carbamoyl-5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy) naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (30 mg) in ACN (3 mL) was added TFA (1 mL). The mixture was stirred at room temperature for 2 h. The mixture was lyophilization directly to remove the TFA, basified with saturated aqueous NaHCO₃ (8 mL) and extracted with EtOAc (10 mL x 5). The combined organic layers were dried over Na₂SO₄ and concentrated to give crude product. The crude product was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 30% to 40%) to give compound 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5,8-difluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazoline-6-carboxamide formate (1: 1)

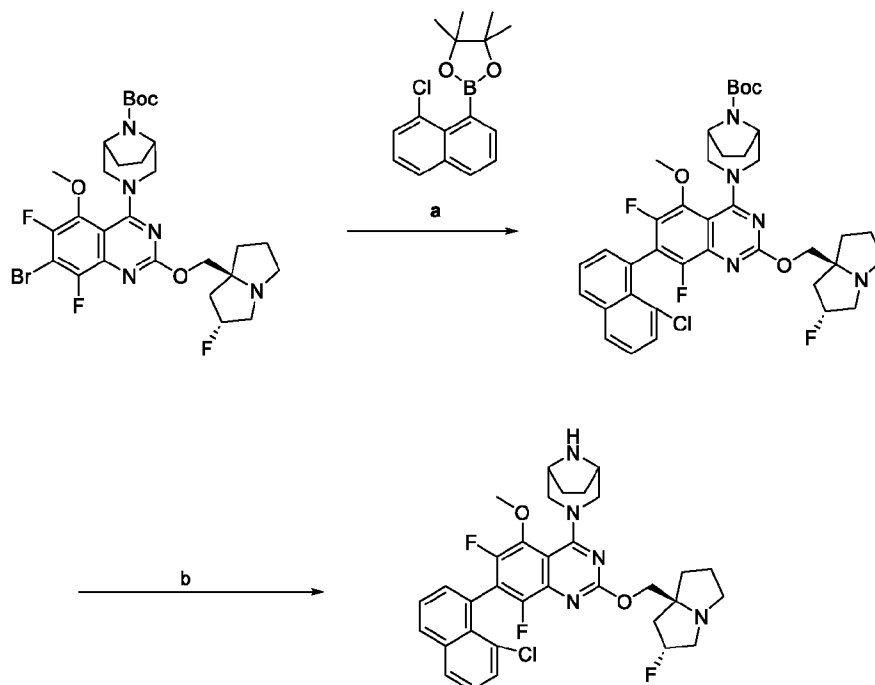
(3.3 mg, 1.9% for two steps) as a white solid. ^1H NMR (400 MHz, CD_3OD): δ 7.55 (d, $J = 8.4$ Hz, 1H), 7.40 – 7.32 (m, 1H), 7.26 (s, 1H), 7.06 (d, $J = 2.4$ Hz, 1H), 6.88 (dd, $J = 12.8, 7.6$ Hz, 1H), 5.48 (d, $J = 52.4$ Hz, 1H), 4.63 – 4.35 (m, 4H), 4.10 (s, 2H), 3.96 – 3.38 (m, 6H), 2.67 – 2.40 (m, 2H), 2.40 – 2.19 (m, 3H), 2.13 – 2.01 (m, 5H). ^{19}F NMR (300 MHz, CD_3OD): δ -113.243, -116.195, -132.670, -174.039. LCMS: m/z 637.2 ($\text{M} + \text{H}^+$).

Example 16

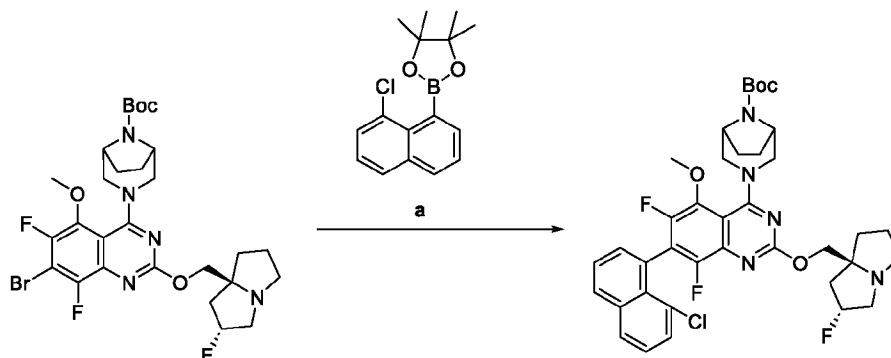
4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-chloronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline hydrochloride formate (1:1:1)



Synthetic scheme:

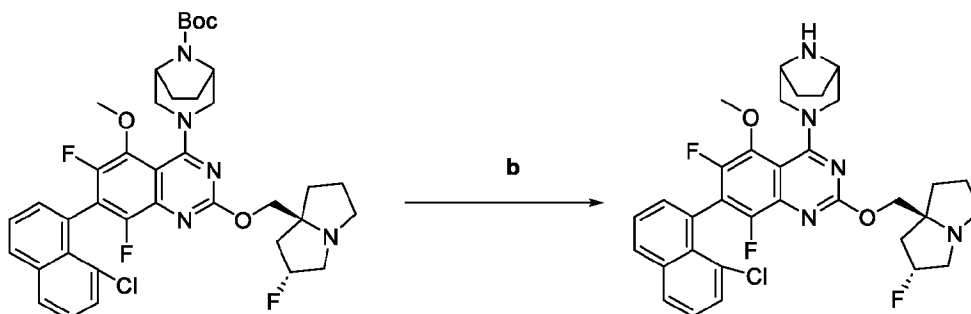


Step 1: Synthesis of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-chloronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline



[00393] To a solution of tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (20 mg, 0.03 mmol, 1.0 eq) in Dioxane (1 mL) and H₂O (0.2 mL) was added 2-(8-chloronaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (14 mg, 0.05 mmol, 1.5 eq), K₂CO₃ (21 mg, 0.16 mmol, 5.0 eq) and Pd(PPh₃)₄ (6 mg, 0.01 mmol, 0.15 eq). Then the reaction mixture was stirred at 100 °C for 15 h under N₂. The filtrate collected by filtration was concentrated to give a crude. The crude was purified by silica gel column chromatography (DCM : MeOH = 15 : 1) to give 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-chloronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline (20 mg, 88.9%) as a white solid. LCMS: m/z 724.3 (M+H⁺).

Step 2: Synthesis of tert-butyl 3-(7-(8-chloronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate hydrochloride formate (1:1:1)

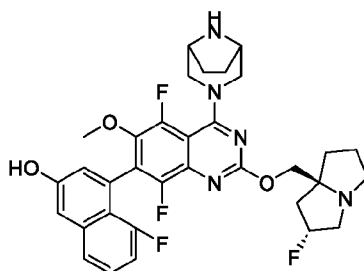


[00394] To a solution of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-chloronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-

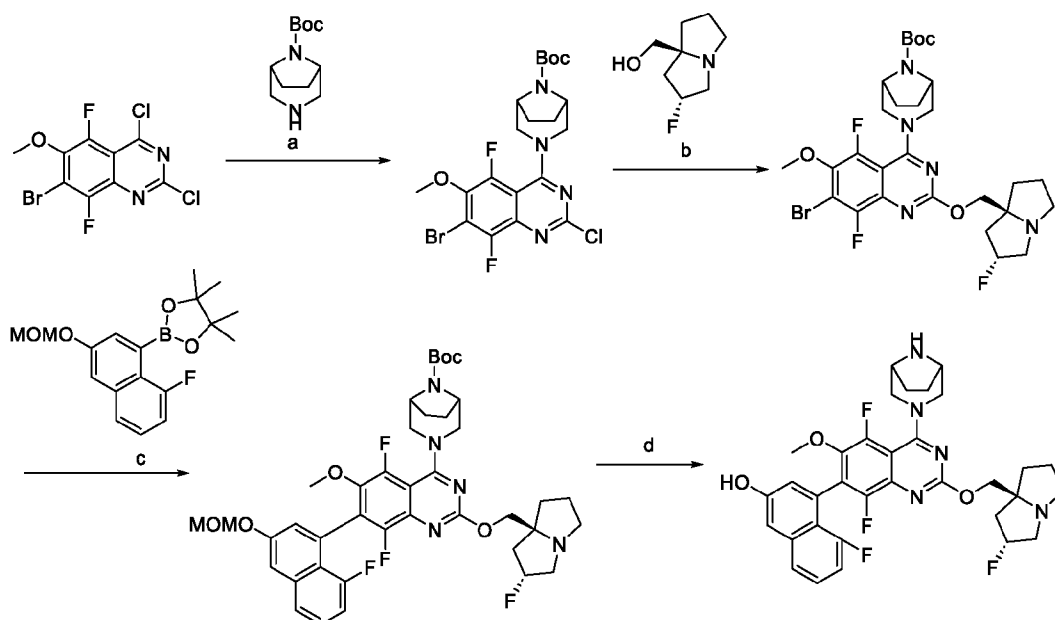
methoxyquinazoline (20 mg, 0.03 mmol, 1.0 eq) in DCM (1 mL) was added HCl in dioxane (0.3 mL, 1.2 mmol, 44.4 eq). The mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated to give a crude. The crude was purified by Prep-HPLC (HCOOH system) to give tert-butyl 3-(7-(8-chloronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate hydrochloride formate (1:1:1) (4 mg, 20.5%) as a white solid. ^1H NMR (400 MHz, $\text{MeOD-}d_4$): δ 8.51 (brs, 1H), 8.13 (d, $J = 8.4$ Hz, 1H), 8.01 (d, $J = 8.4$ Hz, 1H), 7.74 – 7.68 (m, 1H), 7.61 (dd, $J = 7.2, 1.2$ Hz, 1H), 7.59 – 7.49 (m, 2H), 5.40 (d, $J = 53.2$ Hz, 1H), 4.53 – 4.34 (m, 3H), 4.23 – 4.10 (m, 1H), 4.08 – 3.92 (m, 2H), 3.89 (s, 3H), 3.73 – 3.42 (m, 5H), 3.25 – 3.09 (m, 1H), 2.52 – 1.93 (m, 10H). ^{19}F NMR (400 MHz, $\text{MeOD-}d_4$): δ -132.682, -136.903, -173.848. LCMS: m/z 624.2 ($\text{M} + \text{H}^+$).

Example 17

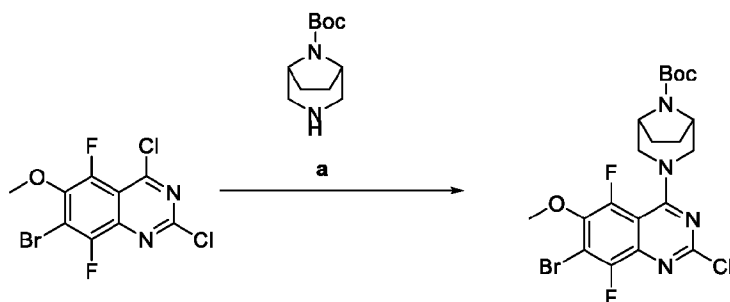
4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-methoxyquinazolin-7-yl)-5-fluoronaphthalen-2-ol hydrochloride



Synthetic scheme:

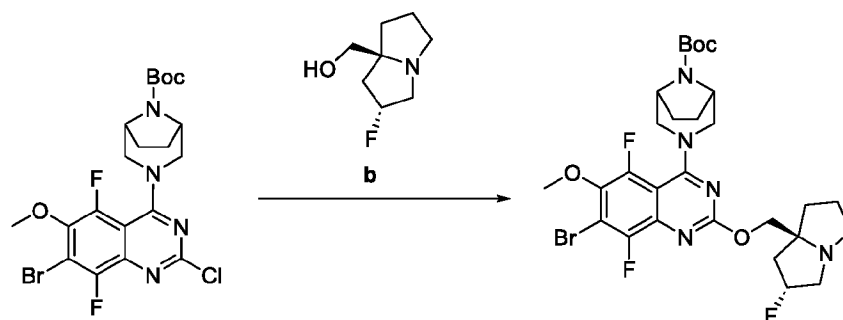


Step 1: Synthesis of tert-butyl 3-(7-bromo-2-chloro-5,8-difluoro-6-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



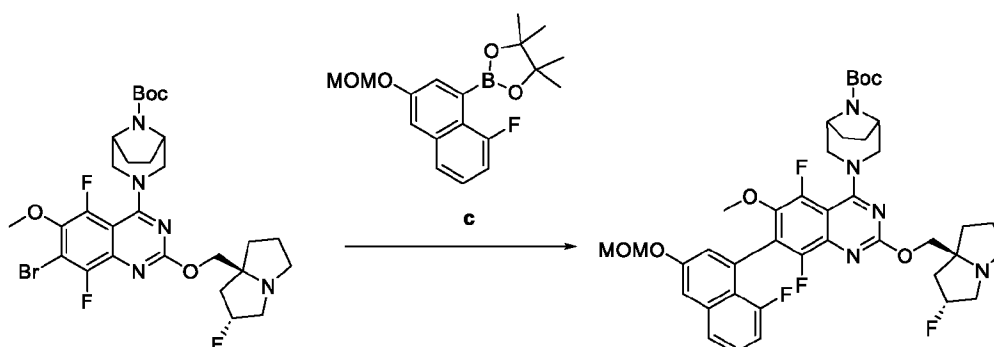
[00395] To a solution of 7-bromo-2,4-dichloro-5,8-difluoro-6-methoxyquinazoline (500 mg, 1.45 mmol, 1.2 eq) in DCM (6.00 mL) was added DIEA (470 mg, 3.63 mmol, 3.0 eq) and a solution of tert-butyl (1R,5S)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (257 mg, 1.21 mmol, 1.0 eq) in DCM (3 mL) dropwise at -40 °C. Then the reaction mixture was stirred at -40 °C for 2 h. The mixture was quenched with H₂O (10 mL) and extracted with DCM (8 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give the residue. The residue was purified by prep-TLC to give tert-butyl 3-(7-bromo-2-chloro-5,8-difluoro-6-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (600 mg, 79.8 %) as a yellow solid. ¹H NMR (300 MHz, CDCl₃) δ 4.31 (s, 2H), 4.19 – 4.05 (m, 2H), 4.01 (d, *J* = 1.2 Hz, 3H), 3.56 (s, 2H), 1.96 – 1.82 (m, 2H), 1.72 – 1.66 (m, 2H), 1.51 (s, 9H). LCMS: *m/z* 519.0, 521.0 (M+H⁺).

Step 2: Synthesis of tert-butyl 3-(7-bromo-5,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



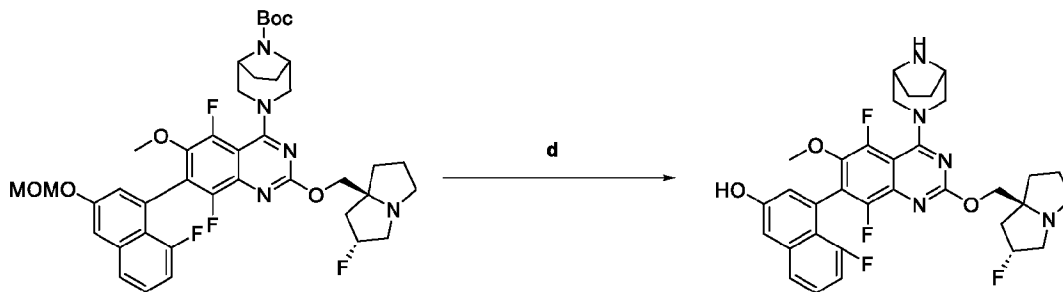
[00396] To a solution of tert-butyl 3-(7-bromo-2-chloro-5,8-difluoro-6-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (300 mg, 0.58 mmol, 1.0 eq) in THF (5 mL) was added (((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (184 mg, 1.15 mmol, 2.0 eq), Cs₂CO₃ (563 mg, 1.73 mmol, 3.0 eq) and SPhos Pd G4 (45 mg, 0.06 mmol, 0.1 eq). Then the reaction mixture was stirred at 80 °C for 20 h. The mixture was quenched with H₂O (8 mL) and extracted with EtOAc (7 mL x 3). The combined organic layers were washed with brine (8 mL), dried over Na₂SO₄ and concentrated to give the crude product. The crude product was purified by prep-TLC to give tert-butyl 3-(7-bromo-5,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (80 mg, 36.5%) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 5.30 (d, *J* = 52.2 Hz, 1H), 4.43 – 3.98 (m, 6H), 3.94 (s, 3H), 3.51 – 2.87 (m, 6H), 2.25 – 1.72 (m, 10H), 1.50 (s, 9H). LCMS: *m/z* 642.2, 644.2 (M+H⁺).

Step 3: Synthesis of tert-butyl 3-(5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00397] To a solution of tert-butyl 3-(7-bromo-5,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (80 mg, 0.13 mmol, 1.0 eq) in 1,4-Dioxane (2.0 mL) and H₂O (0.5 mL) was added 2-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (62 mg, 0.19 mmol, 1.5 eq), K₃PO₄ (79.6 mg, 0.38 mmol, 3.0 eq), X-Phos (11.92 mg, 0.025 mmol, 0.2 eq) and Pd₂(dba)₃ (11.9 mg, 0.013 mmol, 0.1 eq). Then the reaction mixture was stirred at 100 °C for 4 h. The mixture was quenched with H₂O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give the crude product. The crude product was purified by prep-TLC to give tert-butyl 3-(5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (70 mg, 45.5%) as a yellow solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.84 – 7.75 (m, 1H), 7.69 (s, 1H), 7.55 – 7.45 (m, 1H), 7.27 (s, 1H), 7.12 (dd, *J* = 13.5, 7.5 Hz, 1H), 5.50 – 5.28 (m, 3H), 4.34 – 3.91 (m, 8H), 3.63 (s, 3H), 3.45 (s, 3H), 3.01 (s, 1H), 2.24 – 1.66 (m, 10H), 1.45 (s, 9H). LCMS: *m/z* 768.3 (M + H⁺).

Step 4: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-methoxyquinazolin-7-yl)-5-fluoronaphthalen-2-ol hydrochloride (1:1)

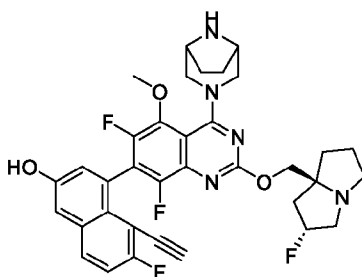


[00398] To a solution of tert-butyl 3-(5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (60 mg, 0.09 mmol, 1.0 eq) in DCM (1.00 mL) was added HCl/dioxane (4 N, 0.5 mL) dropwise at 0 °C. Then the reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC (0.1 % FA in H₂O/ ACN) to give 4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-5,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-

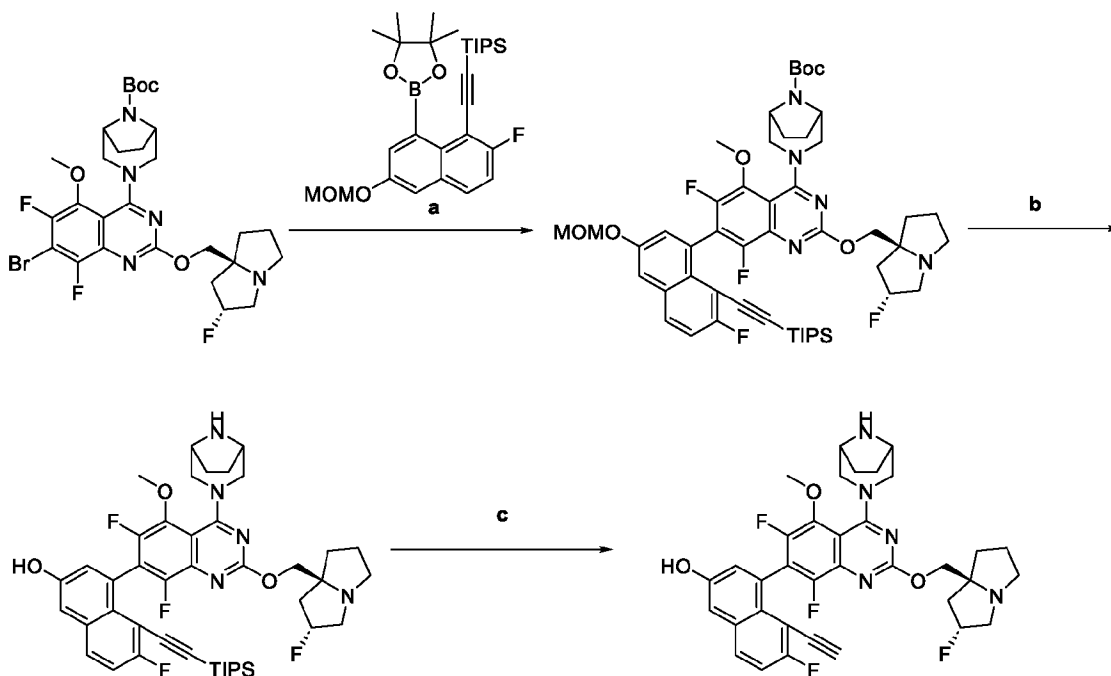
pyrrolizin-7a(5H)-yl)methoxy)-6-methoxyquinazolin-7-yl)-5-fluoronaphthalen-2-ol hydrochloride (1:1) (30.1 mg, 51%) as a white solid. ^1H NMR (400 MHz, CD_3OD): δ 8.50 (brs, 1H), 7.58 (m, $J = 8.4$ Hz, 1H), 7.45 – 7.28 (m, 2H), 7.12 – 7.02 (m, $J = 2.4$ Hz, 1H), 6.90 (dd, $J = 13.2, 7.6$ Hz, 1H), 5.41 (d, $J = 54.0$ Hz, 1H), 4.55 – 4.15 (m, 4H), 3.99 (s, 2H), 3.73 – 3.45 (m, 8H), 3.25 – 3.10 (m, 1H), 2.51 – 1.96 (m, 10H). ^{19}F NMR (400 MHz, CD_3OD): δ -117.235, -131.363, -133.781, -173.916. LCMS: m/z 624.3 ($\text{M} + \text{H}^+$).

Example 18

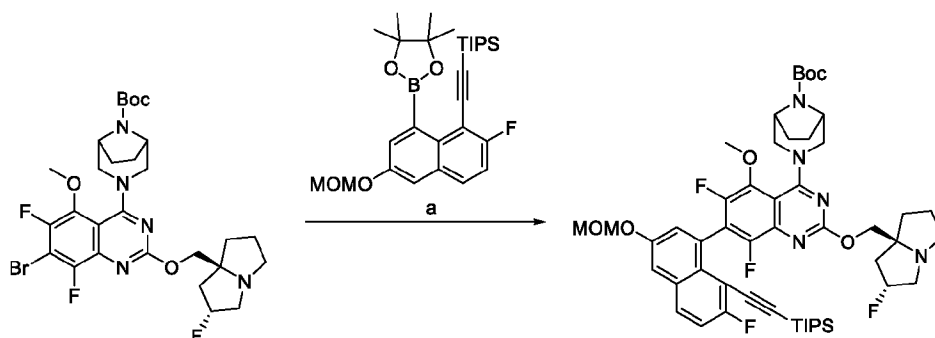
4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate



Synthetic scheme:

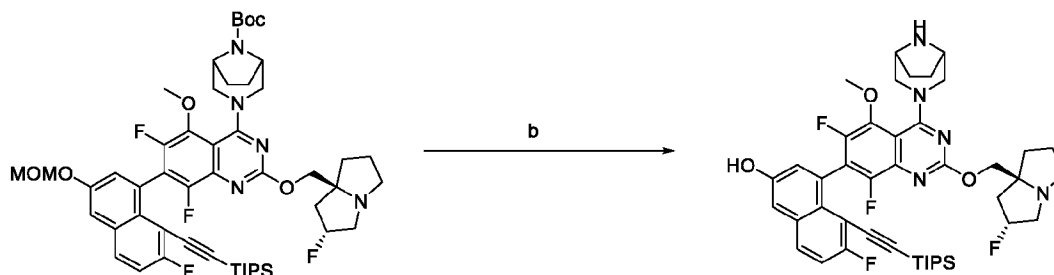


Step 1: Synthesis of tert-butyl 3-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



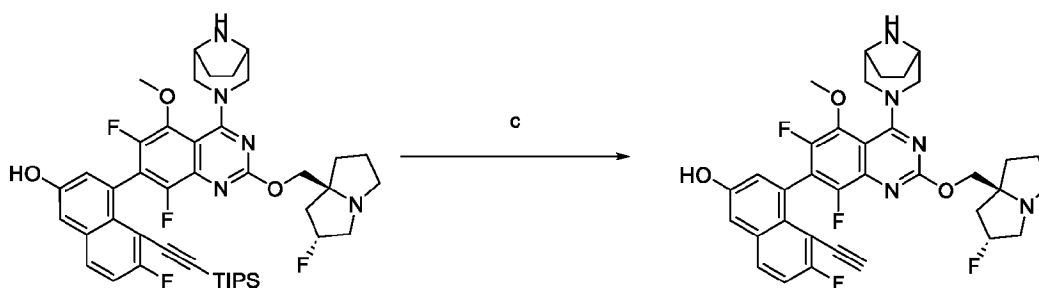
[00399] To a solution of tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (50 mg, 0.08 mmol, 1.0 eq) and ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (60 mg, 0.12 mmol, 1.5 eq) in Toluene (1.5 mL) and H₂O (0.3 mL) was added K₃PO₄ (33 mg, 0.16 mmol, 2.0 eq), rac-BI-DIME (5 mg, 0.02 mmol, 0.2 eq) and Pd₂(dba)₃ (11 mg, 0.01 mmol, 0.15 eq). The mixture was heated under microwave irradiation at 120 °C for 1 h under N₂. The reaction mixture was partitioned between EtOAc (5 mL) and H₂O (3 mL). The layers were separated. The aqueous layer was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with H₂O (3 mL), brine (3 mL), dried over Na₂SO₄ and concentrated to a crude. The crude was purified by Prep-TLC (DCM / MeOH ~ 15 / 1) to give tert-butyl 3-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (50 mg, 67.8%) as a yellow solid. LCMS: m/z 474.8 (M/2+H⁺).

Step 2: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol



[00400] To a solution of tert-butyl 3-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (30 mg, 0.03 mmol, 1.0 eq) in DCM (1 mL) was added HCl in dioxane (0.3 mL, 1.2 mmol, 37.5 eq) at room temperature. The mixture was stirred at room temperature for 1 h. The reaction was adjusted to pH~8 with $\text{NH}_3\cdot\text{H}_2\text{O}$. The mixture was concentrated to give a residue. The residue was re-dissolved in DCM/MeOH (10/1, 5 mL). The filtrate collected by filtration was concentrated to give 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (30 mg, crude) as a yellow solid. LCMS: m/z 804.3 ($\text{M}+\text{H}^+$).

Step 3: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate (1:1)

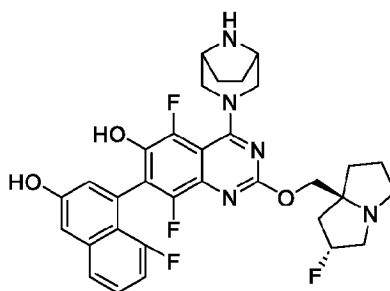


[00401] To a mixture of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (30 mg, 0.04 mmol, 1.0 eq) in DMF (1 mL) was added CsF (85 mg, 0.56 mmol, 15.0 eq). The mixture was stirred at 50 °C for 2 h. The filtrate collected by filtration was concentrated to give a crude. The crude was purified by Prep-HPLC (ACN with 0.1% FA in water, 5% to 35%) to give 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-

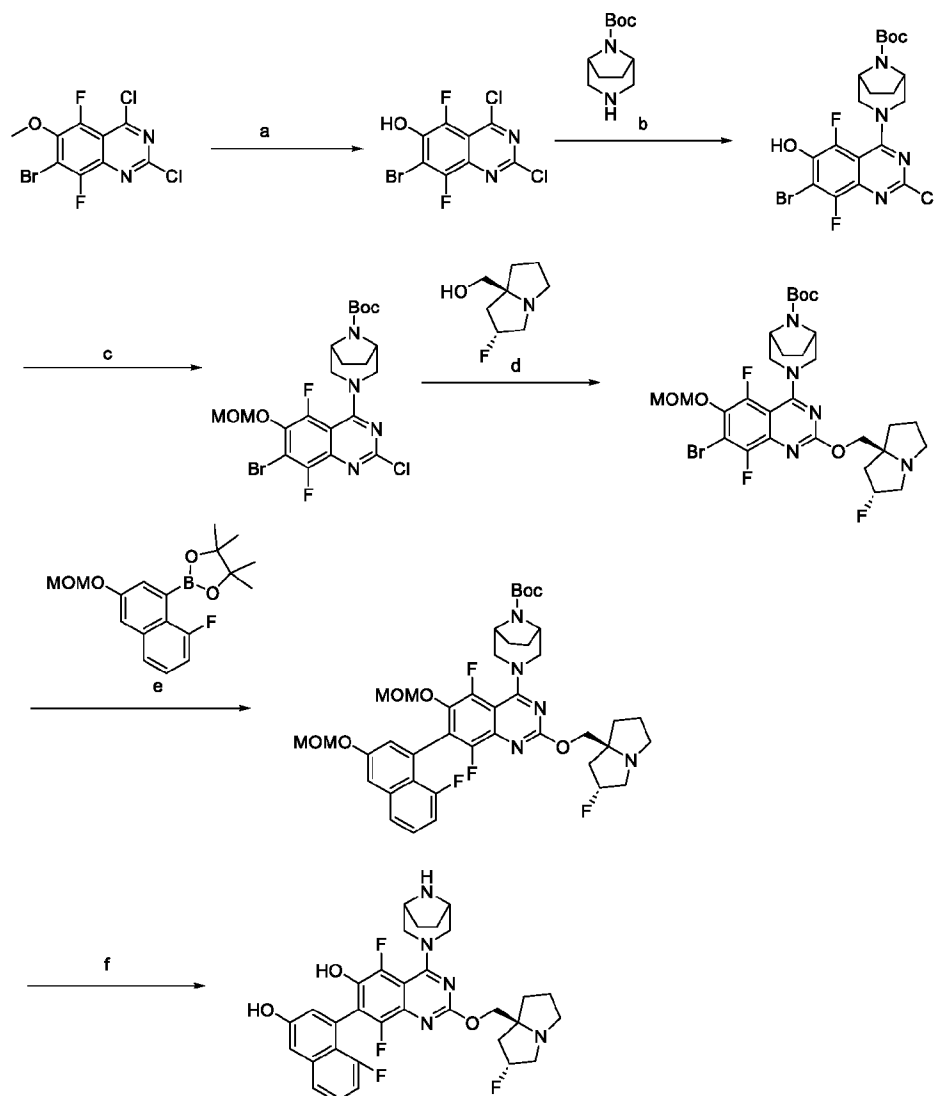
difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate (1:1) (8.4 mg, 32.4% for two steps) as a white solid. ^1H NMR (300 MHz, CD_3OD): δ 7.86 (dd, $J = 9.3, 5.7$ Hz, 1H), 7.39 – 7.27 (m, 2H), 7.12 (d, $J = 2.7$ Hz, 1H), 5.35 (d, $J = 53.4$ Hz, 1H), 4.56 – 4.22 (m, 3H), 4.17 – 3.99 (m, 1H), 3.88 (d, $J = 1.2$ Hz, 3H), 3.86 – 3.74 (m, 2H), 3.68 – 3.34 (m, 6H), 3.12 – 3.08 (m, 1H), 2.43 – 1.87 (m, 10H). ^{19}F NMR (300 MHz, CD_3OD): δ -111.319, -132.635, -137.764, -173.799. LCMS: m/z 648.2 ($\text{M} + \text{H}^+$).

Example 19

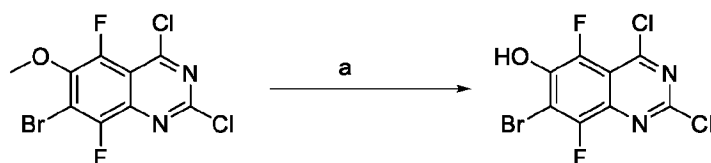
4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5,8-difluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-6-ol hydrochloride formate



Synthetic scheme:



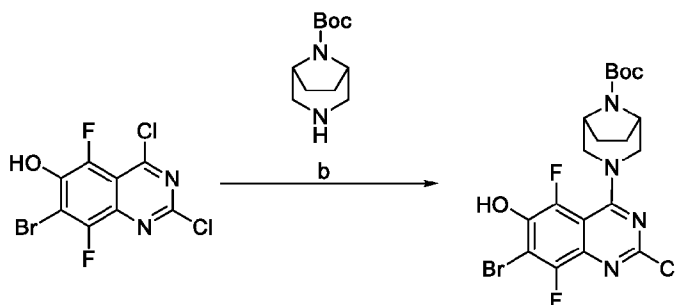
Step 1: Synthesis of 7-bromo-2,4-dichloro-5,8-difluoroquinazolin-6-ol



[00402] To a solution of compound 7-bromo-2,4-dichloro-5,8-difluoro-6-methoxyquinazoline (300 mg, 0.87 mmol, 1.0 eq) in DCM (3.0 mL) was added a solution of BBr_3 (4.4 g, 17.4 mmol, 20.0 eq) in DCM (3.0 mL). The reaction mixture was stirred at room temperature for 15 h. The mixture was quenched with water (10 mL) and extracted with DCM (10 mL x 3). The organic phases were washed with brine (10 mL), dried over Na_2SO_4 , filtered and concentrated to give 7-

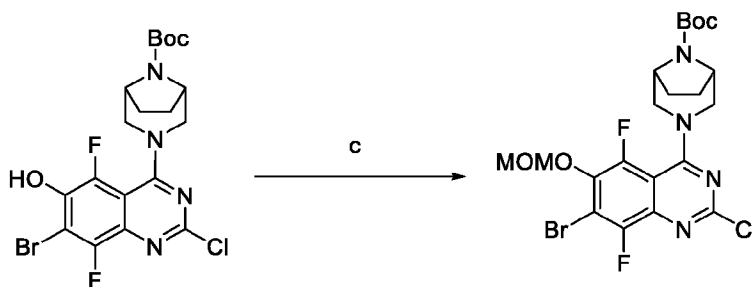
bromo-2,4-dichloro-5,8-difluoroquinazolin-6-ol (300 mg, crude) as brown solid. LCMS: m/z 326.8, 328.8 ($M+H$).

Step 2: Synthesis of tert-butyl 3-(7-bromo-2-chloro-5,8-difluoro-6-hydroxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00403] To a solution of 7-bromo-2,4-dichloro-5,8-difluoroquinazolin-6-ol (300 mg, 0.91 mmol, 1.2 eq) in DCM (10 mL) was added DIEA (294 mg, 2.27 mmol, 3.0 eq) and tert-butyl (1R,5S)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (161 mg, 0.76 mmol, 1.0 eq) dropwise at -40 °C. The reaction mixture was stirred at -40 °C for 2 h. The mixture was diluted with water (10 mL) and extracted with DCM (10 mL x 3). The organic phases were washed with brine (10 mL), dried with Na_2SO_4 , filtered and concentrated to give residue. The residue was purified by silica gel column chromatography (Petroleum ether: EtOAc = 5: 1) to give tert-butyl 3-(7-bromo-2-chloro-5,8-difluoro-6-hydroxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (400 mg, 91 % for 2 steps) as a brown solid. LCMS: m/z 505.0, 507.0 ($M+H^+$)

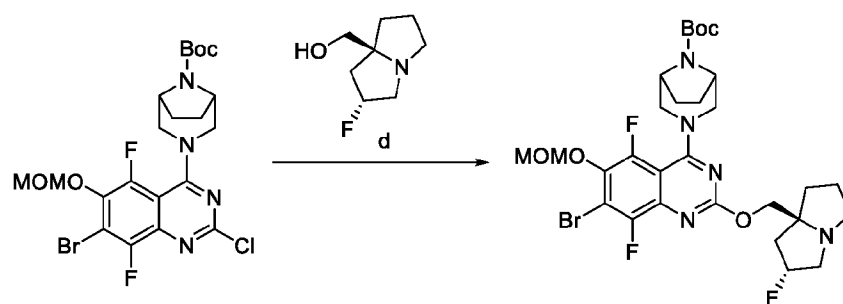
Step 3: Synthesis of tert-butyl 3-(7-bromo-2-chloro-5,8-difluoro-6-(methoxymethoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00404] To a solution of tert-butyl 3-(7-bromo-2-chloro-5,8-difluoro-6-hydroxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (400 mg, 0.79 mmol, 1.0 eq) in DCM (6 mL) was added DIEA (256 mg, 1.98 mmol, 2.5 eq) and Bromomethyl methyl ether (173 mg, 1.38 mmol, 1.75 eq) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 2 h.

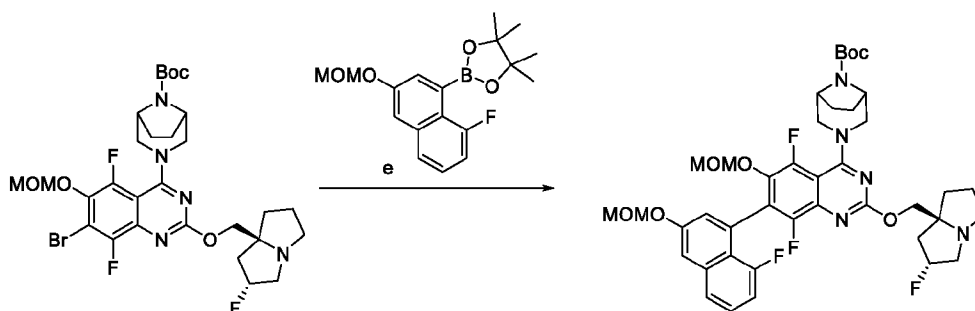
The mixture was quenched with water (10 mL) and extracted with DCM (10 mL x 3). The organic phase was washed with brine (10 mL), dried with Na₂SO₄, filtered and concentrated to give residue. The residue was purified by silica gel column chromatography (Petroleum ether: EtOAc = 8: 1) to give tert-butyl 3-(7-bromo-2-chloro-5,8-difluoro-6-(methoxymethoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (270 mg, 62.3 %) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 5.22 (s, 2H), 4.40 – 4.07 (m, 4H), 3.66 (s, 3H), 3.61 – 3.39 (m, 2H), 2.06 – 1.66 (m, 4H), 1.51 (s, 9H). LCMS: m/z 549.0, 551.0 (M+H⁺)

Step 4: Synthesis of tert-butyl 3-(7-bromo-5,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(methoxymethoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



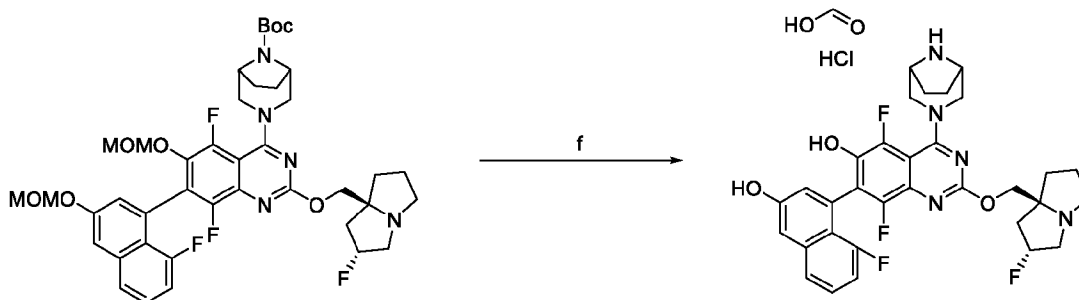
[00405] To a solution of tert-butyl 3-(7-bromo-2-chloro-5,8-difluoro-6-(methoxymethoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (140 mg, 0.26 mmol, 1.0 eq) in 1,4-dioxane (3 mL) was added ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (81 mg, 0.51 mmol, 2.0 eq), Cs₂CO₃ (249 mg, 0.77 mmol, 3.0 eq) and SPhos Pd G4 (21 mg, 0.026 mmol, 0.1 eq). Then the reaction mixture was stirred at 80 °C for 15 h. The mixture was diluted with water (7 mL) and extracted with EtOAc (7 mL x 3). The organic phase was washed with brine (7 mL), dried with Na₂SO₄, filtered and concentrated to give residue. The residue was purified by prep-TLC to give tert-butyl 3-(7-bromo-5,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(methoxymethoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (60 mg, 35.1 %) as a yellow solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 5.49 – 5.24 (s, 1H), 5.21 (s, 2H), 4.383.88 (m, 6H), 3.58 (s, 3H), 3.48 – 3.32 (M, 2H), 3.27 – 2.73 (m, 4H), 2.38 – 1.54 (m, 11H), 1.44 (s, 9H). LCMS: m/z 672.2, 674.2 (M+H⁺)

Step 5: Synthesis of tert-butyl 3-(5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(methoxymethoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00406] To a solution of tert-butyl 3-(7-bromo-5,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(methoxymethoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.15 mmol, 1.0 eq) in 1,4-dioxane (4 mL) was added 2-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (74 mg, 0.22 mmol, 1.5 eq), K_3PO_4 (95 mg, 0.45 mmol, 3.0 eq), H_2O (1 mL), X-Phos (14 mg, 0.03 mmol, 0.2 eq) and $Pd_2(dba)_3$ (14 mg, 0.015 mmol, 0.1 eq). Then the reaction mixture was stirred at 100 °C for 4 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The organic phase was washed with brine (8 mL), dried with Na_2SO_4 , filtered and concentrated to give residue. The residue was purified by prep-TLC to give tert-butyl 3-(5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(methoxymethoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (60 mg, 50.2 %) as a yellow solid. LCMS: m/z 798.2 ($M+H^+$).

Step 6: Synthesis of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5,8-difluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-6-ol hydrochloride formate (1:1:1)

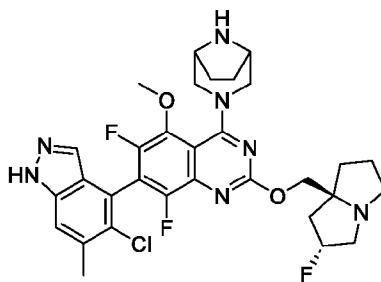


[00407] To a solution of tert-butyl (1R,5S)-3-(5,8-difluoro-7-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(methoxymethoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (60 mg, 0.08 mmol, 1.0 eq) in DCM (1.5 mL) was added HCl/dioxane (4N) (0.5 mL) dropwise at

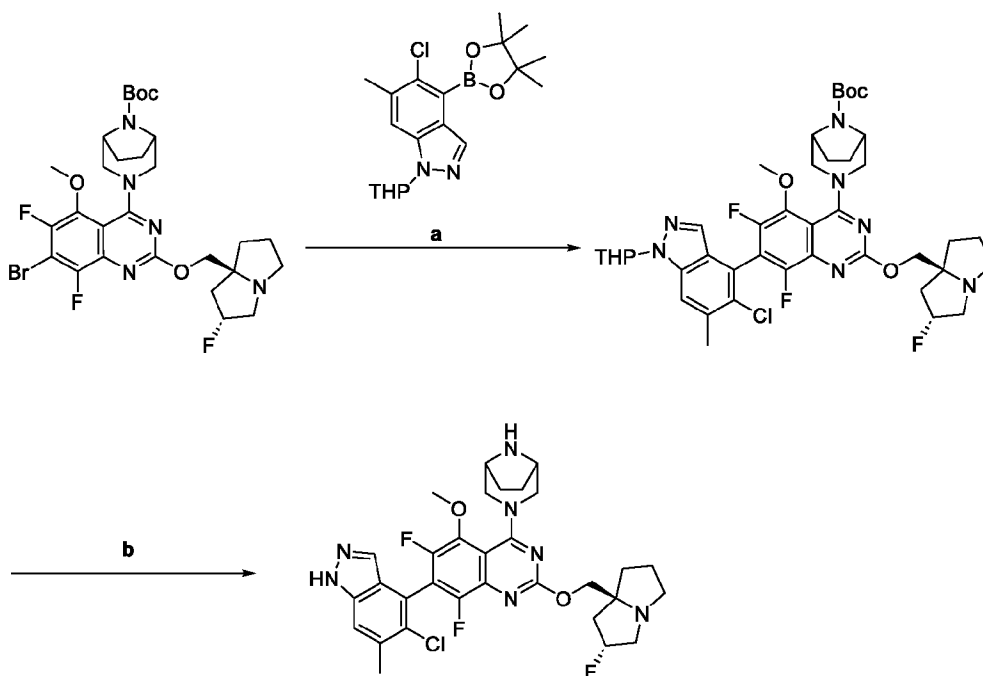
0 °C. Then the reaction mixture was stirred at room temperature for 1 h. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC (0.1 % FA in H₂O/ ACN) to give 4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-5,8-difluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-6-ol hydrochloride formate (1:1:1) (23.1 mg, 42 %) as a white solid. ¹H NMR (400 MHz, CD₃OD): δ 8.48 (brs, 2H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.46 – 7.31 (m, 1H), 7.28 (s, 1H), 7.10 – 7.00 (m, 1H), 6.94 – 6.87 (m, 1H), 5.46 (d, *J* = 52.8 Hz, 1H), 4.55 – 4.43 (m, 2H), 4.32 – 4.18 (m, 2H), 4.08 (s, 2H), 3.80 – 3.54 (m, 5H), 3.30 – 3.24 (m, 1H), 2.62 – 2.02 (m, 10H). ¹⁹F NMR (400 MHz, CD₃OD): δ -117.825, -133.947, -139.261, -174.041. LCMS: *m/z* 610.2 (M+H⁺).

Example 20

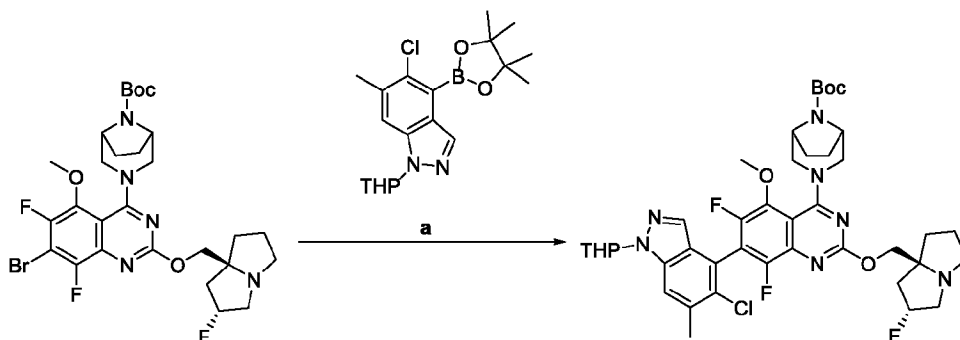
4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(5-chloro-6-methyl-1H-indazol-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline hydrochloride formate (1:1:1)



Synthesis scheme



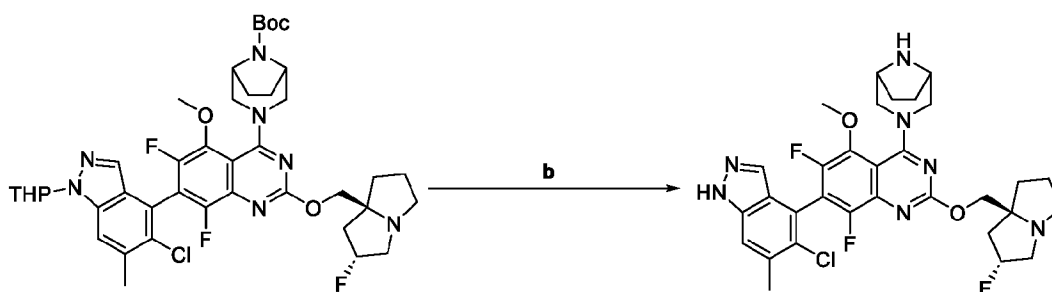
Step 1: Synthesis of tert-butyl 3-(7-(5-chloro-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00408] To a solution of tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (50 mg, 0.08 mmol, 1.0 eq) in Dioxane (1 mL) and H₂O (0.2 mL) was added 5-chloro-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (44 mg, 0.12 mmol, 1.5 eq), K₂CO₃ (54 mg, 0.39 mmol, 5.0 eq) and Pd(PPh₃)₄ (14 mg, 0.01 mmol, 0.15 eq). The reaction mixture was stirred at 100 °C for 15 h under N₂. The reaction mixture was partitioned between EtOAc (5 mL) and water (2 mL). The layers were separated. The aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated to give a

crude. The crude was purified by Prep-TLC (DCM : MeOH = 15 : 1) to give tert-butyl 3-(7-(5-chloro-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (50 mg, 78.9%) as a brown solid. LCMS: m/z 812.2 ($M+H^+$).

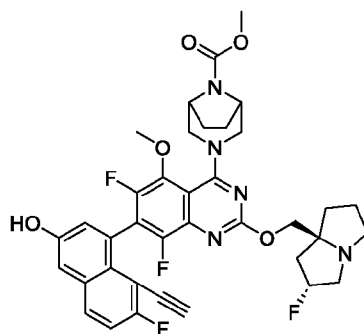
Step 2: Synthesis of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(5-chloro-6-methyl-1H-indazol-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline hydrochloride formate (1:1:1)



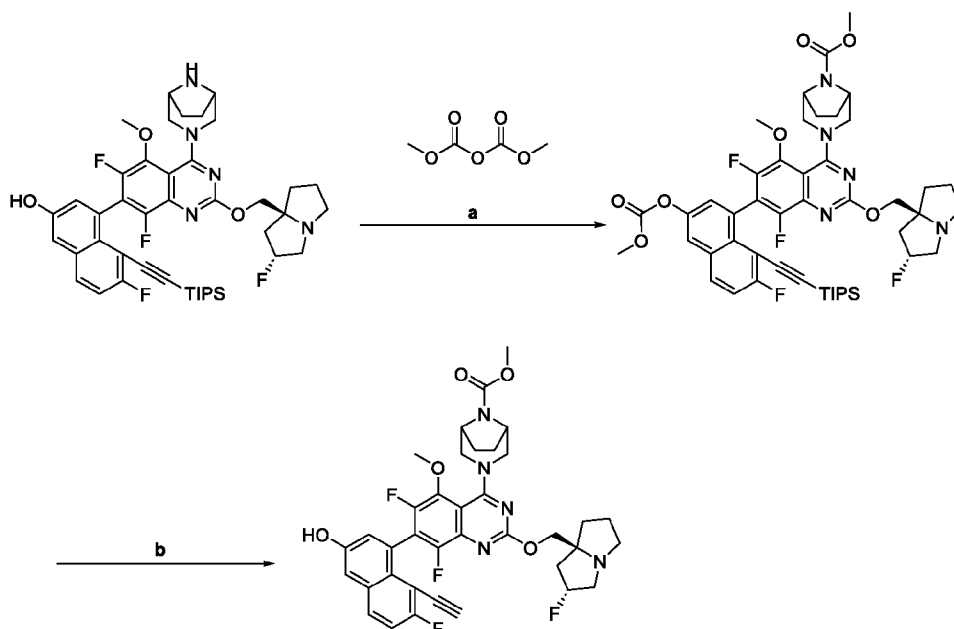
[00409] To a solution of tert-butyl 3-(7-(5-chloro-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (10 mg, 0.012 mmol, 1.0 eq) in DCM (1 mL) was added HCl in dioxane (0.03 mL, 0.12 mmol, 10.0 eq) at room temperature. The mixture was stirred at room temperature for 1 h. The mixture was concentrated to give a crude. The crude was purified by Prep-HPLC (HCOOH system) to give the product 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(5-chloro-6-methyl-1H-indazol-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline hydrochloride formate (1:1:1) (4.4 mg, 58.4%) as a white solid. ^1H NMR (400 MHz, CD_3OD): δ 8.55 (brs, 1H), 7.66 (d, J = 4.8 Hz, 2H), 5.37 (d, J = 53.2 Hz, 1H), 4.45 – 4.25 (m, 4H), 3.91 (s, 3H), 3.82 (s, 2H), 3.58 (d, J = 13.2 Hz, 2H), 3.49 – 3.34 (m, 3H), 3.16 – 3.03 (m, 1H), 2.60 (s, 3H), 2.45 – 1.89 (m, 10H). ^{19}F NMR (400 MHz, CD_3OD): δ -131.101, -137.885, -173.777. LCMS: m/z 628.2 ($M+H^+$).

Example 21

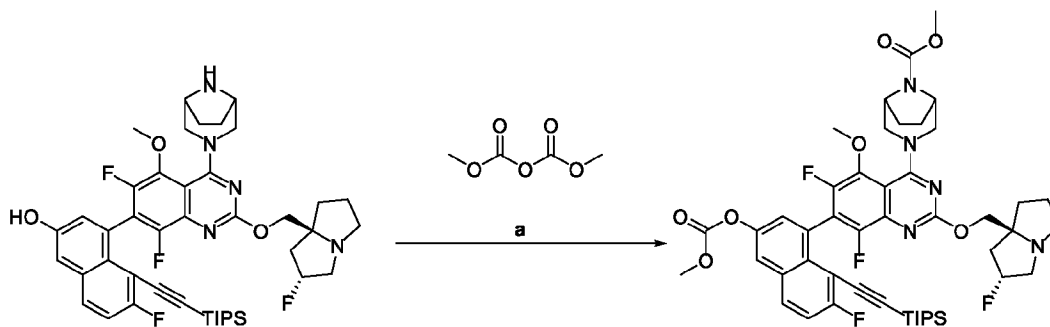
methyl 3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate formate



Synthetic scheme



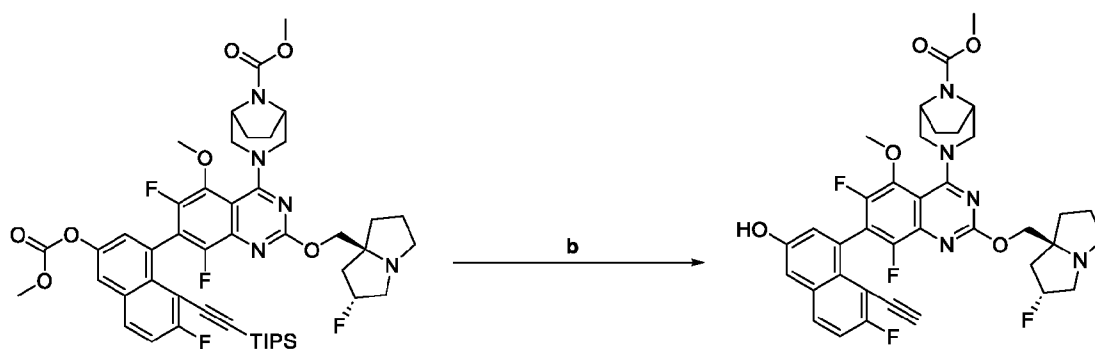
Step 1: Synthesis of methyl 3-(6,8-difluoro-7-(7-fluoro-3-((methoxycarbonyl)oxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00410] To a solution of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-

((triisopropylsilyl)ethynyl)naphthalen-2-ol (60 mg, 0.07 mmol, 1.0 eq) in DCM (1 mL) was added TEA (23 mg, 0.22 mmol, 3.0 eq) and dimethyl dicarbonate (10 mg, 0.07 mmol, 1.0 eq) at 0 °C. The reaction mixture was stirred at room temperature for 1 h under N₂. The mixture was concentrated to give methyl 3-(6,8-difluoro-7-(7-fluoro-3-((methoxycarbonyl)oxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (60 mg, crude) as a yellow solid. LCMS: m/z 460.7 (M/2+H⁺).

Step 2: Synthesis of methyl 3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate formate (1:1)

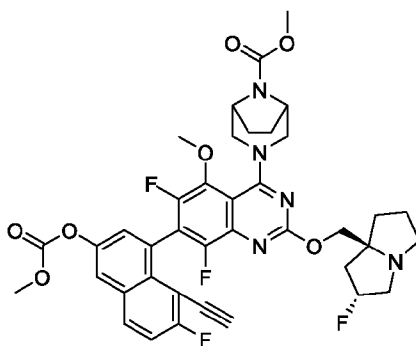


[00411] To a mixture of methyl 3-(6,8-difluoro-7-(7-fluoro-3-((methoxycarbonyl)oxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (60 mg, 0.07 mmol, 1.0 eq) in DMF (1 mL) was added CsF (159 mg, 1.0 mmol, 15.0 eq). The mixture was stirred at 50 °C for 2 h. The filtrate collected by filtration was concentrated to give a crude. The crude was purified by Prep-HPLC (ACN with 0.1% FA in water, 15% to 50%) to give methyl 3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate formate (1:1) (17.4 mg, 31.0% for two steps) as a white solid. ¹H NMR (400 MHz, CD₃OD): δ 7.86 (dd, *J* = 9.2, 5.6 Hz, 1H), 7.38 – 7.27 (m, 2H), 7.13 (d, *J* = 2.4 Hz, 1H), 5.35 (d, *J* = 53.6 Hz, 1H), 4.51 – 4.20 (m, 5H), 4.12 – 3.98 (m, 1H), 3.86 (s, 3H), 3.76 (s, 3H), 3.59 (d, *J* = 13.2 Hz, 1H), 3.49 – 3.34 (m, 4H), 3.15 – 3.05 (m, 1H), 2.46 –

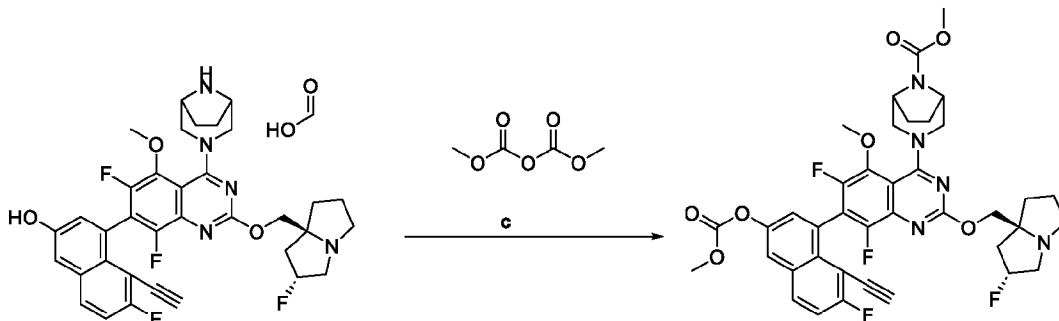
2.14 (m, 3H), 2.11 – 2.02 (m, 2H), 2.00 – 1.81 (m, 4H), 1.79 – 1.63 (m, 1H). ^{19}F NMR (400 MHz, CD_3OD): δ -111.338, -132.816, -138.120, -173.718. LCMS: m/z 706.2 ($\text{M}+\text{H}^+$).

Example 22

Methyl 3-(7-(8-ethynyl-7-fluoro-3-((methoxycarbonyl)oxy)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate formate (1:1)



Step 1: Synthesis of methyl 3-(7-(8-ethynyl-7-fluoro-3-((methoxycarbonyl)oxy)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate formate (1:1)

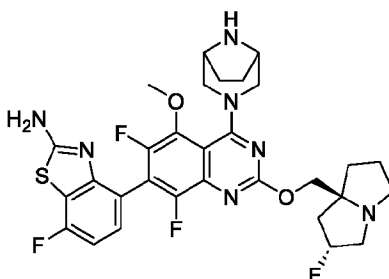


[00412] To a solution of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate (50 mg, 0.07 mmol, 1.0 eq) in DCM (1 mL) was added TEA (23 mg, 0.22 mmol, 3.0 eq) and dimethyl dicarbonate (24 mg, 0.18 mmol, 2.5 eq) at 0 °C. The reaction mixture was stirred at room temperature for 1 h under N_2 . The mixture was concentrated to give a crude. The crude was purified by Prep-HPLC (ACN with 0.1% FA in water, 15% to 50%) to give methyl 3-(7-(8-ethynyl-7-fluoro-3-((methoxycarbonyl)oxy)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-

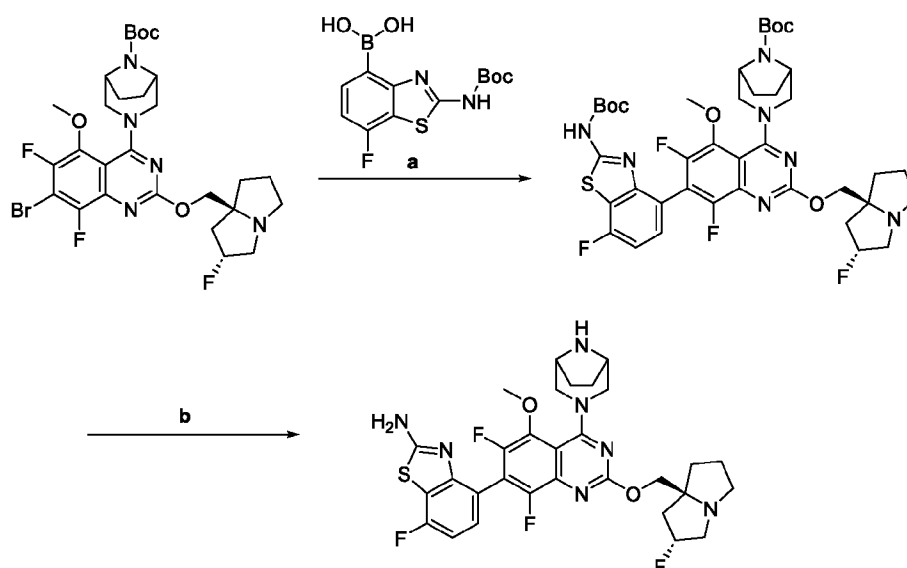
methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate formate (1:1) (17.4 mg, 25.3%) as a white solid.

Example 23

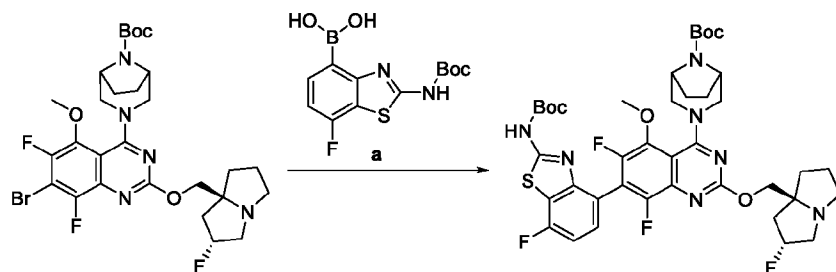
4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-7-fluorobenzo[d]thiazol-2-amine hydrochloride formate (1:1:1)



Synthetic scheme:

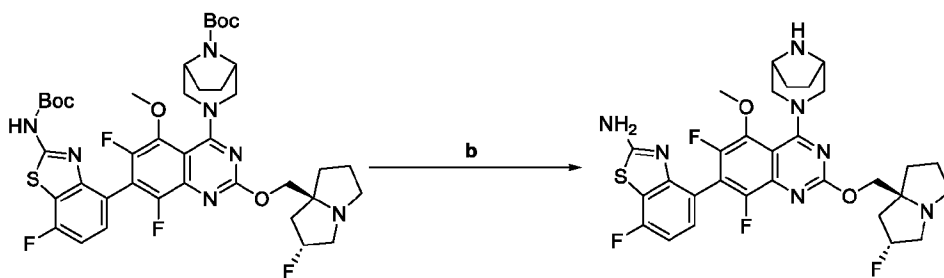


Step 1: Synthesis of compound tert-butyl 3-(7-(2-(((tert-butoxycarbonyl)amino)-7-fluorobenzo[d]thiazol-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00413] To a solution of compound tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (80 mg, 0.12 mmol, 1.0 eq) in 1,4-dioxane (3 mL) and H₂O (1 mL) was added K₃PO₄ (48 mg, 0.22 mmol, 1.8 eq), (2-((tert-butoxycarbonyl)amino)-7-fluorobenzo[d]thiazol-4-yl)boronic acid (58 mg, 0.19 mmol, 1.5 eq) and Pd(dtbpf)Cl₂ (16 mg, 0.02 mmol, 0.2 eq) at room temperature. The reaction mixture was heated to 90 °C and stirred for 2 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give a residue. The crude product was purified by prep-TLC (dichloromethane : Methanol = 10 : 1) to give tert-butyl 3-(7-(2-((tert-butoxycarbonyl)amino)-7-fluorobenzo[d]thiazol-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (60 mg, 58.0%) as a yellow solid. LCMS: m/z 830.2 (M+H⁺).

Step 2: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-7-fluorobenzo[d]thiazol-2-amine hydrochloride formate (1:1:1)

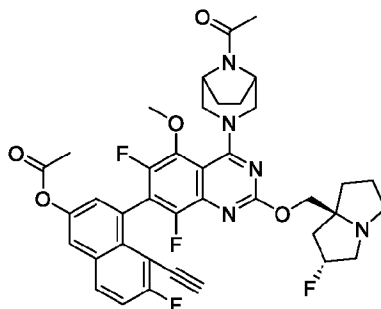


[00414] To a solution of compound tert-butyl 3-(7-(2-((tert-butoxycarbonyl)amino)-7-fluorobenzo[d]thiazol-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (60 mg, 0.07 mmol, 1.0 eq) in DCM (1 mL) was added HCl in dioxane (0.5 mL, 4M in dioxane) at room

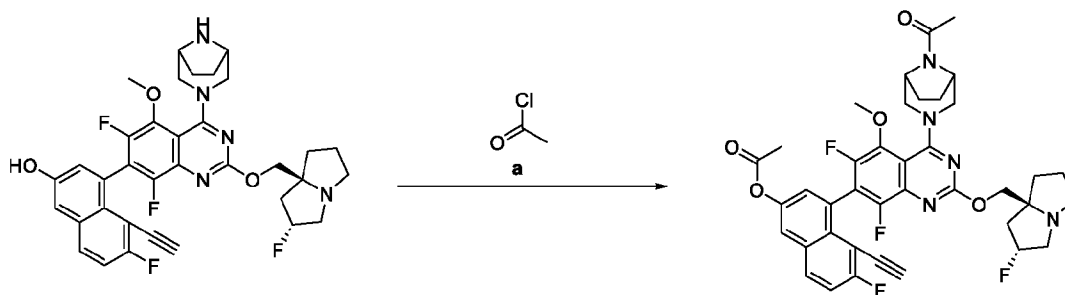
temperature. The reaction was stirred at room temperature for 1 h. The product was concentrated to give a crude. The crude was purified by Prep-HPLC (acetonitrile with 0.1% FA in water, 20% to 60%) to give 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-7-fluorobenzo[d]thiazol-2-amine hydrochloride formate (1:1:1) (16.2 mg, 35.6%) as a white solid. ^1H NMR (400 MHz, CD_3OD): δ 7.61 – 7.43 (m, 1H), 7.29 – 7.13 (m, 1H), 5.60 (d, $J = 51.2$ Hz, 1H), 4.86 – 4.82 (m, 2H), 4.82 – 4.47 (m, 2H), 4.32 – 4.20 (m, 2H), 4.08 (s, 3H), 4.05–3.82 (m, 5H), 3.52–3.43 (m, 1H), 2.85 – 2.56 (m, 2H), 2.56 – 2.43 (m, 1H), 2.43 – 2.30 (m, 2H), 2.30 – 2.20 (m, 1H), 2.20 – 2.00 (m, 4H). ^{19}F NMR (400 MHz, CD_3OD): δ -113.813, -133.894, -134.341, -174.152. LCMS: m/z 630.2 ($\text{M}+\text{H}^+$).

Example 24

4-(4-(8-acetyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-yl acetate formate (1: 1)



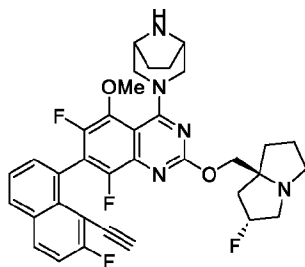
Step 1: Synthesis of 4-(4-(8-acetyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-yl acetate formate (1: 1)



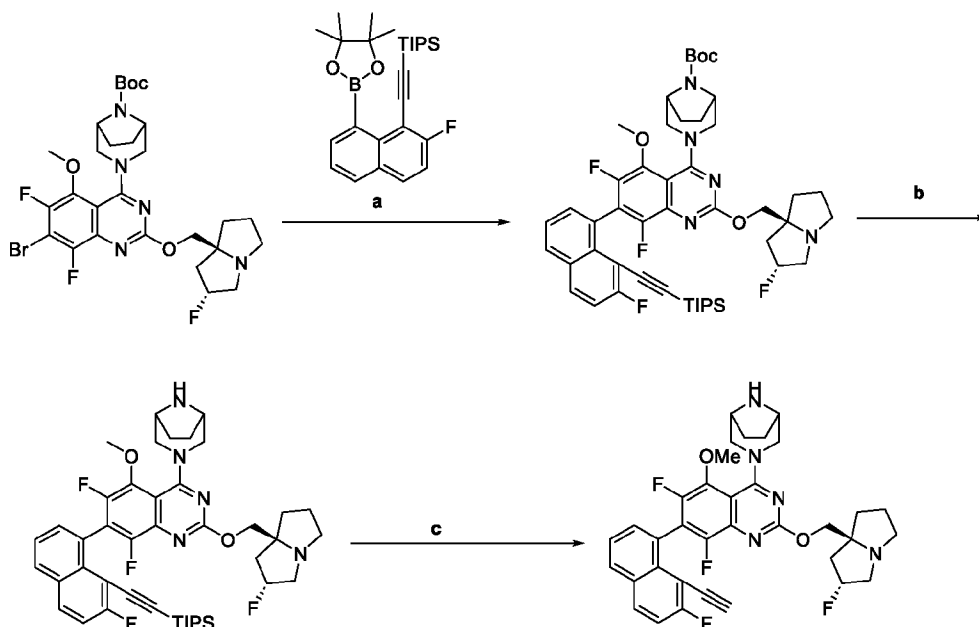
[00415] To a solution of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-yl formate (50 mg, 0.07 mmol, 1.0 eq) in DCM (1 mL) was added TEA (23 mg, 0.22 mmol, 3.0 eq) and acetyl chloride (15 mg, 0.19 mmol, 2.5 eq) at 0 °C. The reaction mixture was stirred at room temperature for 1 h under N₂. The mixture was concentrated to give a crude. The crude was purified by Prep-HPLC (ACN with 0.1% FA in water, 15% to 50%) to give 4-(4-(8-acetyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-yl acetate formate (1: 1) (17.4 mg, 25.3%) as a white solid. ¹H NMR (400 MHz, CD₃OD): δ 8.08 (dd, *J* = 9.2, 5.6 Hz, 1H), 7.88 (d, *J* = 2.4 Hz, 1H), 7.48 (t, *J* = 8.8 Hz, 1H), 7.42 (d, *J* = 2.4 Hz, 1H), 5.32 (d, *J* = 53.4 Hz, 1H), 4.72 (dd, *J* = 19.2, 6.6 Hz, 1H), 4.59 – 4.36 (m, 2H), 4.28 – 4.20 (m, 2H), 4.16 – 4.05 (m, 1H), 3.87 (s, 3H), 3.57 (d, *J* = 15.6 Hz, 1H), 3.51 – 3.46 (m, 1H), 3.44 – 3.36 (m, 2H), 3.26 (s, 2H), 3.21 – 3.11 (m, 1H), 2.34 – 2.22 (m, 5H), 2.17 (s, 4H), 2.16 – 2.04 (m, 4H), 2.03 – 1.89 (m, 3H). ¹⁹F NMR (400 MHz, CD₃OD): δ -106.887, -132.375, -138.313, -173.657. LCMS: *m/z* 732.2 (M+H⁺).

Example 25

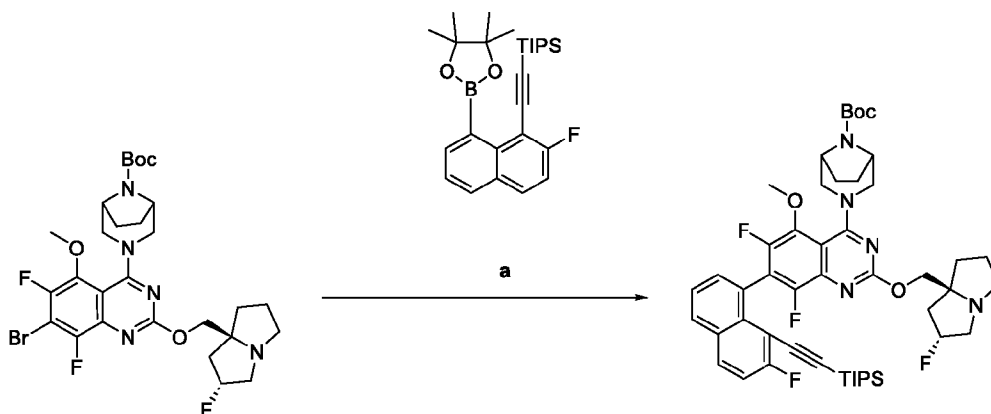
4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline formate



Synthetic scheme



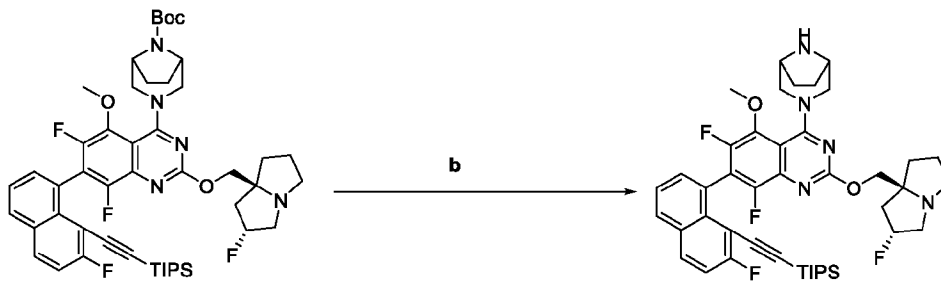
Step 1: Synthesis of tert-butyl 3-(6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00416] To a solution of tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (50 mg, 0.07 mmol, 1.0 eq) in PhMe (1 mL) and H₂O (0.2 mL) was added ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (45.2 mg, 0.10 mmol, 1.5 eq), Pd₂(dba)₃ (9.1 mg, 0.01 mmol, 0.15 eq), rac-BI-DIME (4.6 mg, 0.01 mmol, 0.2 eq) and K₃PO₄ (29.7 mg, 0.14 mmol, 2.0 eq). The mixture was heated at 120 °C for 1 h by microwave. The mixture was filtered, and the filtrate was concentrated to give a crude. The crude was purified by prep-TLC (DCM : MeOH = 15 : 1) to give tert-butyl 3-(6,8-difluoro-

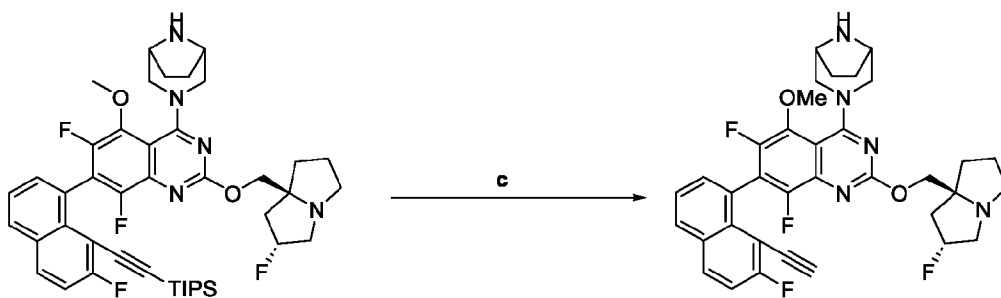
7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (50 mg, 72.3%) as a yellow solid. LCMS: m/z 444.8 ($M/2+H^+$).

Step 2: Synthesis of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline



[00417] To a solution of tert-butyl 3-(6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (50 mg, 0.05 mmol, 1.0 eq) in DCM (1 mL) was added HCl/dioxane (0.2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h under N_2 . The mixture was concentrated to give 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline (60 mg, crude) as a yellow solid. LCMS: m/z 788.2 ($M+H^+$).

Step 3: Synthesis of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline formate (1:1)

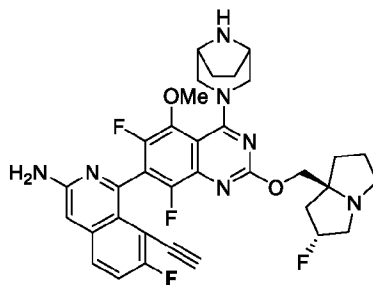


[00418] To a solution of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline (60 mg, 0.07 mmol, 1.0 eq) in DMF (1.5 mL) was

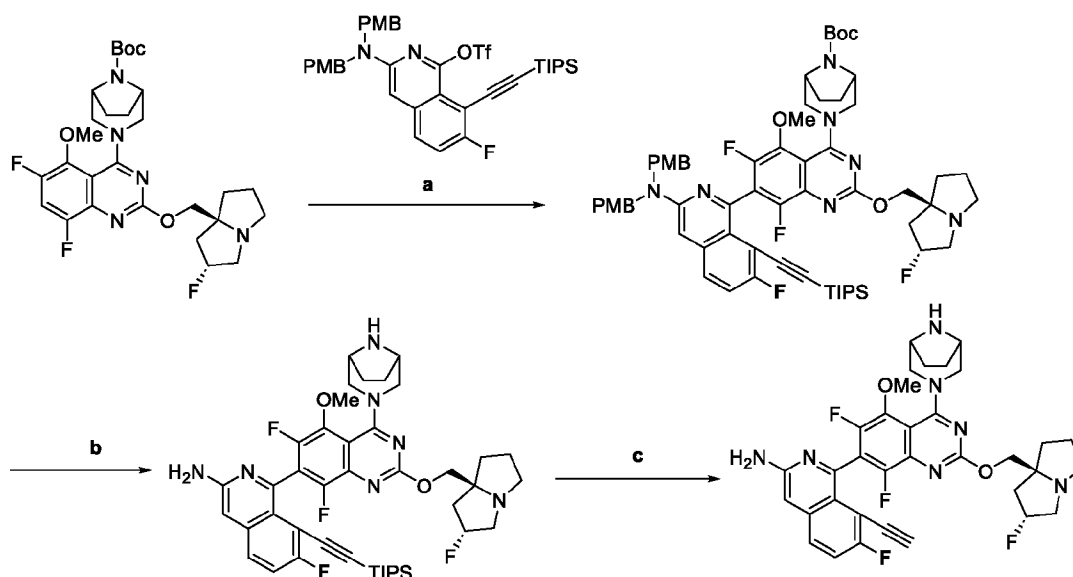
added CsF (159 mg, 1.0 mmol, 20.0 eq). The mixture was stirred at 50 °C for 3 h. The mixture was concentrated to give a crude. The crude was purified by Prep-HPLC (ACN with 0.1% FA in water, 10% to 50%) to give 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline formate (1: 1) (12.5 mg, 35.2%, two steps yield) as a white solid. ¹H NMR (400 MHz, CD₃OD): δ 8.44 (s, 1H), 8.14 – 8.10 (m, 2H), 7.66 (t, J = 7.6 Hz, 1H), 7.56 (d, J = 7.2 Hz, 1H), 7.46 (t, J = 8.8 Hz, 1H), 5.42 (d, J = 51.0 Hz, 1H), 4.52 – 4.46 (m, 3H), 4.21 – 4.01 (m, 3H), 3.90 (s, 3H), 3.80 – 3.50 (m, 5H), 3.45 (s, 1H), 3.25 (s, 1H), 2.44 – 1.89 (m, 10H). ¹⁹F NMR (400 MHz, CD₃OD): δ -106.313, -132.541, -136.720, -173.989. LCMS: m/z 632.3 (M+H⁺).

Example 26

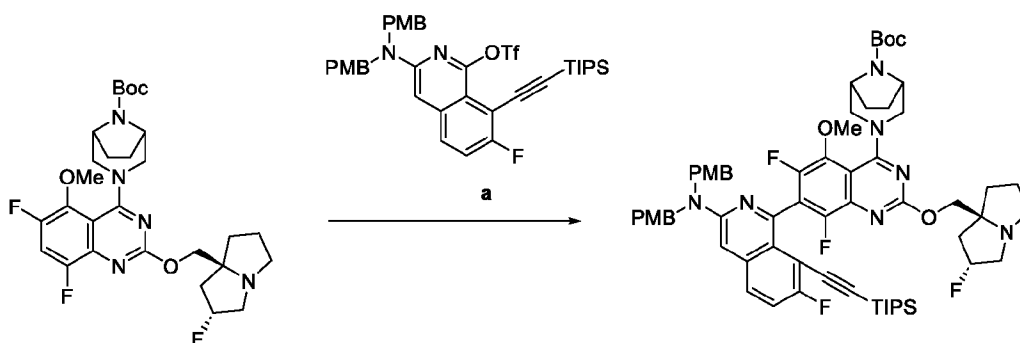
1-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-8-ethynyl-7-fluoroisoquinolin-3-amine



Synthetic scheme:



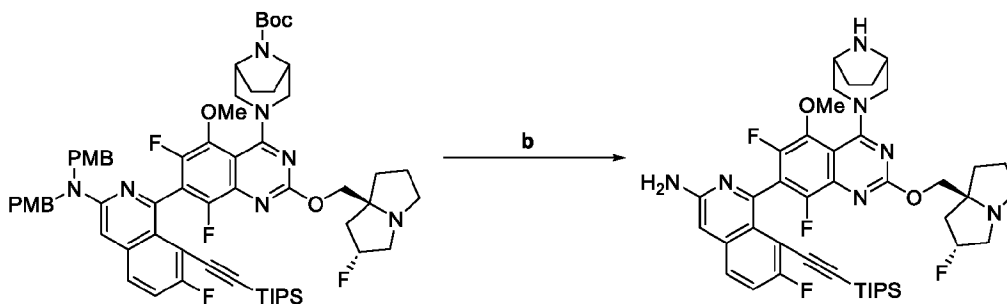
Step 1: Synthesis of tert-butyl 3-(7-(3-(bis(4-methoxybenzyl)amino)-7-fluoro-8-((triisopropylsilyl) ethynyl)isoquinolin-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00419] To a solution of compound tert-butyl 3-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.18 mmol, 1.0 eq) in THF (3 mL) was added (TMP)₂ZnMgCl₂LiCl (1.35 mL, 0.54 mmol, 3.0 eq, 0.4 M in THF) under nitrogen atmosphere. The reaction was stirred at 50 °C for 2 h. To the reaction was added 3-(bis(4-methoxybenzyl)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)isoquinolin-1-yl trifluoromethanesulfonate (153 mg, 0.21 mmol, 1.2 eq) and RuPhos Pd G2 (15 mg, 0.02 mmol, 0.1 eq) in dioxane (1 mL) under nitrogen atmosphere. The reaction was stirred at 50 °C for 15 h. The residue was partitioned between EtOAc (10 mL) and water (10 mL). The layers were separated. The aqueous layer was extracted

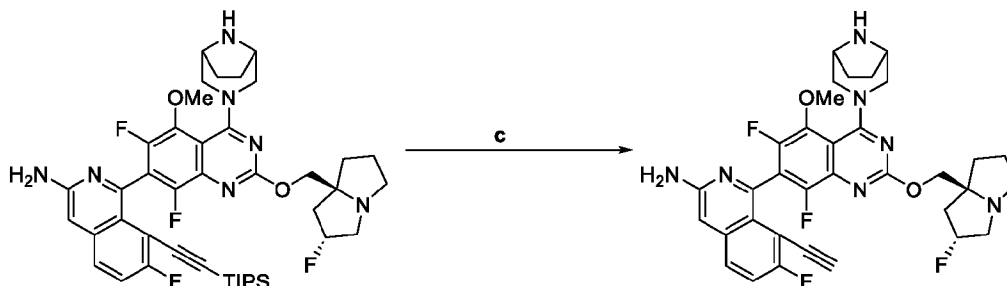
with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over MgSO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (dichloromethane: methanol = 40: 1) to give tert-butyl 3-(7-(3-(bis(4-methoxybenzyl)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)isoquinolin-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (80 mg, 39.4%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 7.51 – 7.43 (m, 1H), 7.25 – 7.20 (m, 1H), 7.18 (d, *J* = 8.4 Hz, 4H), 6.83 (d, *J* = 8.4 Hz, 4H), 6.62 (s, 1H), 5.40 – 5.18 (m, 1H), 4.78 – 4.65 (m, 4H), 4.52 – 4.00 (m, 6H), 3.92 (s, 3H), 3.78 (s, 6H), 3.58 – 3.46 (m, 1H), 3.44 – 3.08 (m, 4H), 3.04 – 2.91 (m, 1H), 1.95 – 1.83 (m, 4H), 1.76 – 1.56 (m, 4H), 1.50 (s, 9H), 0.94 – 0.80 (m, 21H), 0.74 – 0.65 (m, 3H).

Step 2: Synthesis of 1-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-7-fluoro-8-((triisopropylsilyl)ethynyl)isoquinolin-3-amine



[00420] To a solution of compound tert-butyl 3-(7-(3-(bis(4-methoxybenzyl)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)isoquinolin-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (80 mg, 0.07 mmol, 1.0 eq) in DCM (2 mL) was added TFA (2 mL). The reaction was stirred at room temperature for 1 h. The mixture was partitioned between DCM (10 mL) and aqueous sodium bicarbonate solution (10 mL). The layers were separated. The aqueous layer was extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over MgSO₄ and evaporated to dryness. The crude product was purified by prep-TLC (dichloromethane: methanol = 8: 1) to give 1-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-7-fluoro-8-((triisopropylsilyl)ethynyl)isoquinolin-3-amine (30 mg, 53.4%) as a yellow solid. LCMS: *m/z* 804.3 (*M*+*H*⁺).

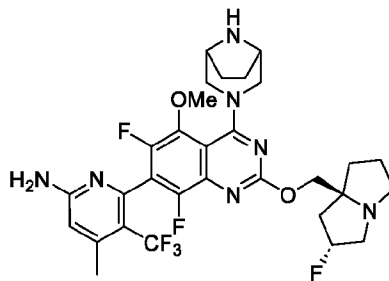
Step 3: Synthesis of 1-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-8-ethynyl-7-fluoroisoquinolin-3-amine



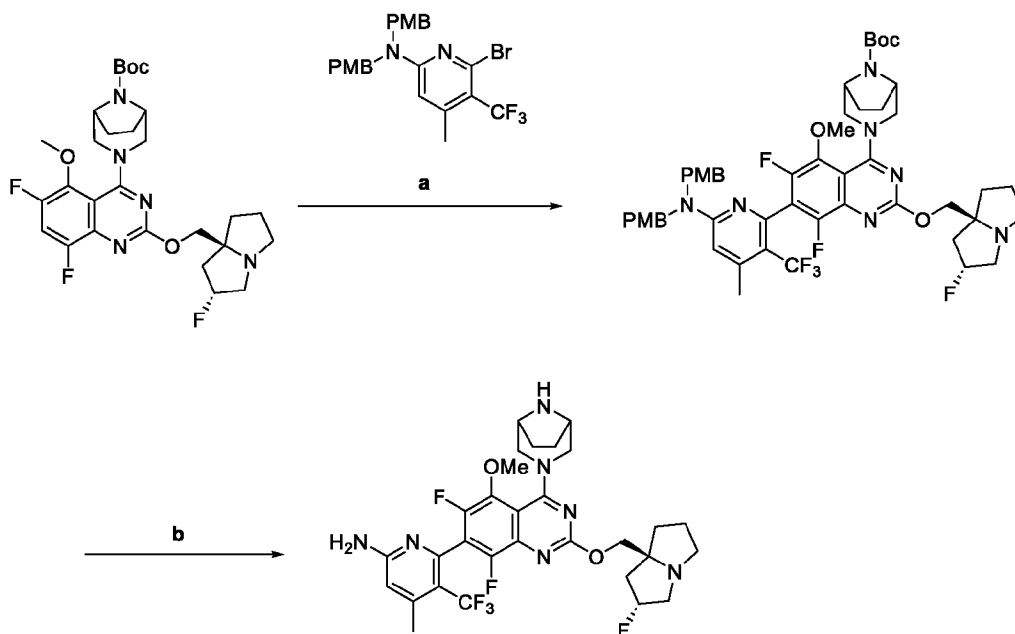
[00421] To a solution of compound 1-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-7-fluoro-8-((triisopropylsilyl)ethynyl)isoquinolin-3-amine (30 mg, 0.04 mmol, 1.0 eq) in DMF (1 mL) was added CsF (60.8 mg, 0.4 mmol, 10.0 eq). The reaction was stirred at 40 °C for 1 h. The mixture was filtered and the filtrate was concentrated to give a crude. The crude product was purified by prep-TLC (dichloromethane: methanol = 3: 1) to give 1-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-8-ethynyl-7-fluoroisoquinolin-3-amine (13 mg, 53.7%) as a yellow solid. ¹H NMR (300 MHz, CD₃OD): δ 7.82 – 7.71 (m, 1H), 7.43 (t, *J* = 9.0 Hz, 1H), 7.01 (s, 1H), 5.34 (d, *J* = 53.7 Hz, 1H), 4.54 – 4.38 (m, 1H), 4.38 – 4.21 (m, 2H), 4.12–3.99 (m, 1H), 3.88 (s, 3H), 3.82–3.70 (m, 2H), 3.69 – 3.57 (m, 1H), 3.52 – 3.49 (m, 1H), 3.48 – 3.35 (m, 2H), 3.30 – 3.24 (m, 2H), 3.12 – 3.02 (m, 1H), 2.44 – 2.12 (m, 4H), 2.11 – 1.95 (m, 4H), 1.93–1.86 (m, 2H). ¹⁹F NMR (300 MHz, CD₃OD): δ -110.415, -133.668, -139.835, -173.726. LCMS: *m/z* 648.2 (M+H⁺).

Example 27

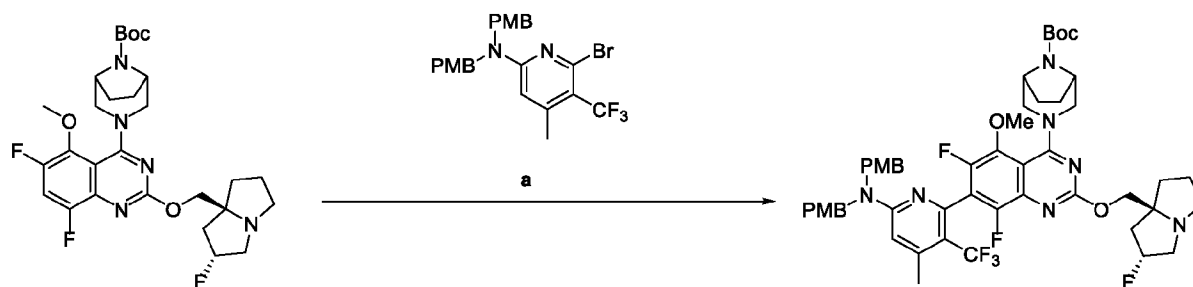
6-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine hydrochloride



Synthesis scheme



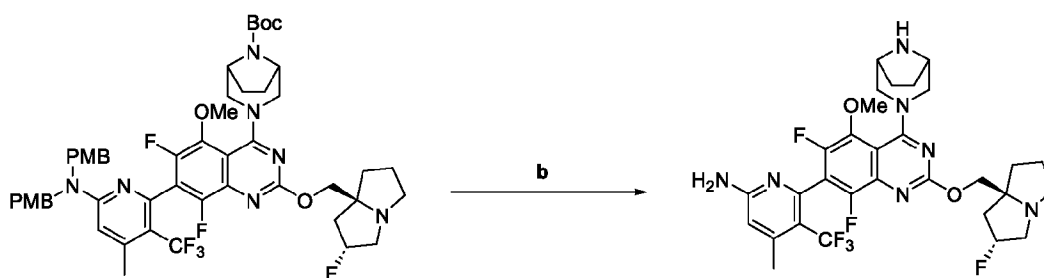
Step 1: Synthesis of tert-butyl 3-(7-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00422] To a solution of tert-butyl 3-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.18 mmol, 1.0 eq) in THF (1 mL) was added (TMP)₂Zn·MgCl₂·LiCl (2.0 mL, 0.78 mmol, 4.4 eq). The reaction mixture was stirred at 50 °C for 2 h under N₂. To the

reaction mixture was added a solution of 6-bromo-N,N-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (114 mg, 0.23 mmol, 1.3 eq) and CPhos Pd G₃ (15 mg, 0.02 mmol, 0.1 eq) in dioxane (1 mL). The reaction mixture was stirred at 80 °C for 12 h. The reaction was quenched with aq. NaHCO₃ solution (5 mL). The mixture was filtered through a Celite pad and washed with EtOAc. The filtrate was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated to give a crude. The crude was purified by Prep-TLC (DCM : MeOH = 15 : 1) to give tert-butyl 3-(7-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (60 mg, 34.5%) as a white solid. LCMS: m/z 978.3 (M+H⁺).

Step 2: Synthesis of 6-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine hydrochloride (1:1)

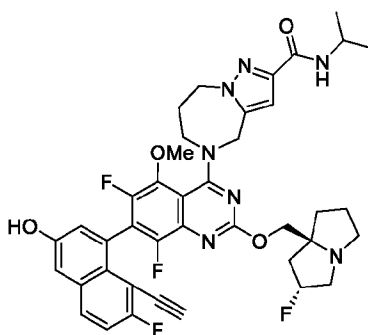


[00423] A solution of tert-butyl 3-(7-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (60 mg, 0.06 mmol, 1.0 eq) in TFA (2 mL) was stirred at 50 °C for 2 h. The reaction mixture was dried by lyophilization to give a crude. The crude was purified by Prep-HPLC (ACN with 0.1% FA in water, 10% to 45%) to give the product. The product was dried by lyophilization with HCl in EtOH to give 6-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluoro tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine hydrochloride (1: 1) (24.5 mg, 59.7%) as a white solid. ¹H NMR (300 MHz, CD₃OD): δ 7.00 (s, 1H), 5.59 (d, *J* = 52.2 Hz, 1H), 4.86 – 4.71 (m, 2H), 4.66 – 4.42 (m, 2H), 4.23 (s, 2H), 4.10 – 3.82 (m, 8H), 3.58 – 3.37 (m, 1H), 2.85 – 2.16 (m, 10H), 2.14

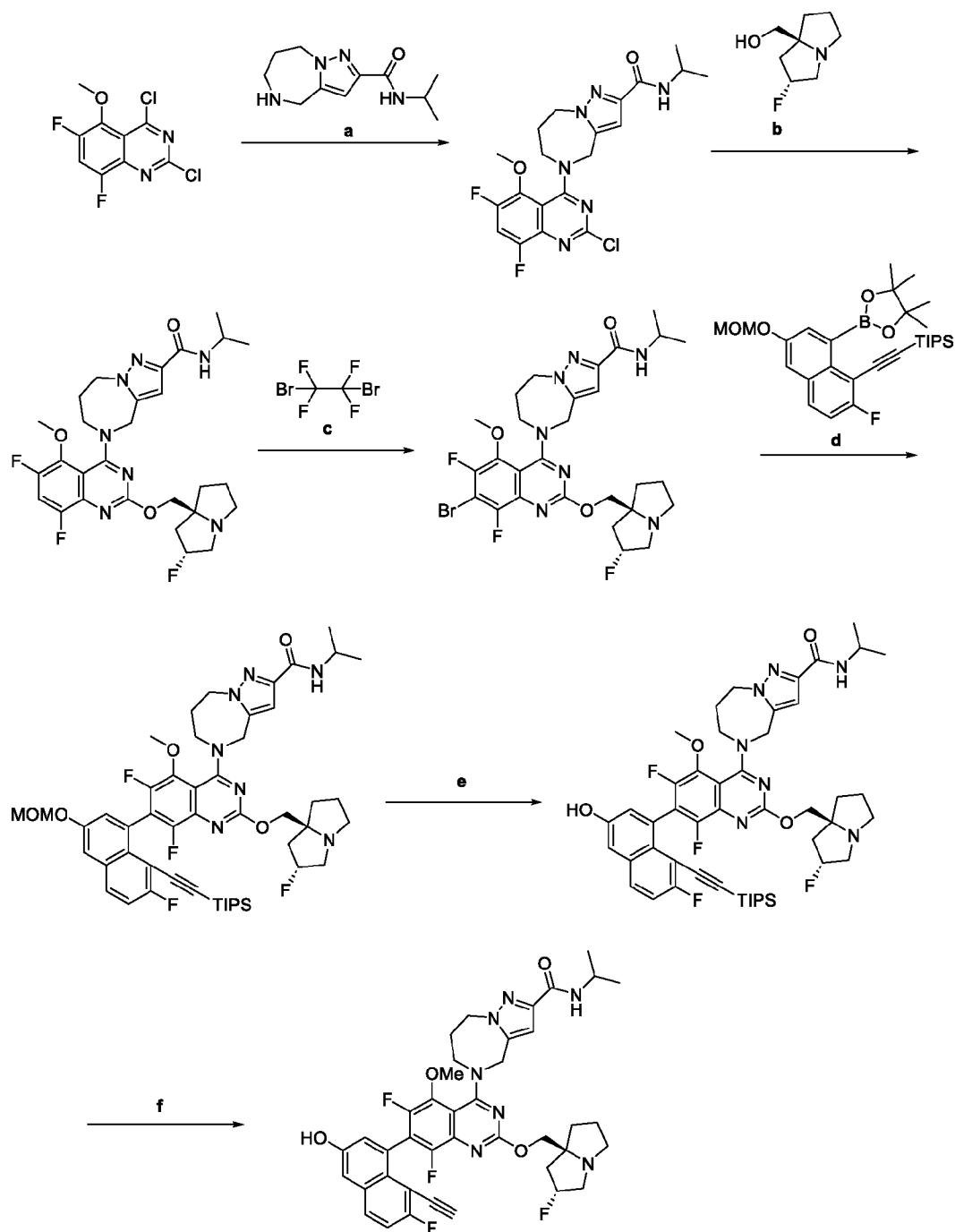
– 1.09 (m, 3H). ^{19}F NMR (300 MHz, CD_3OD): δ -57.678, -133.525, -136.972, -174.107. LCMS: m/z 638.3 ($\text{M}+\text{H}^+$).

Example 28

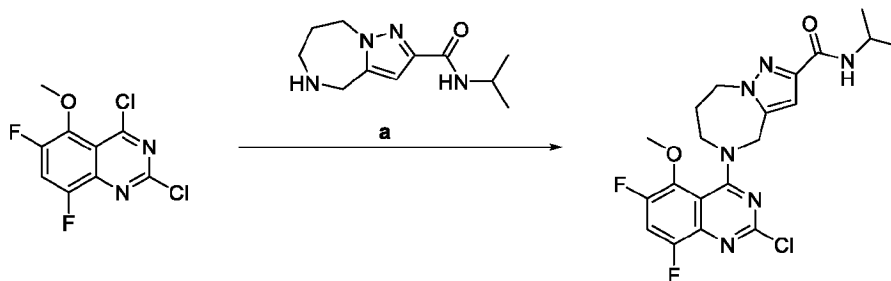
5-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide 2,2,2-trifluoroacetate



Synthetic scheme:

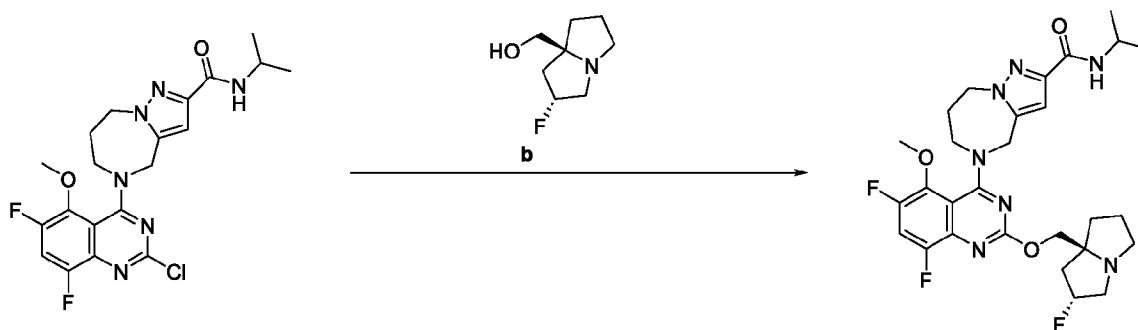


Step 1: Synthesis of 5-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



[00424] To a solution of 2,4-dichloro-6,8-difluoro-5-methoxyquinazoline (227 mg, 0.855 mmol, 1.0 eq) in DCM (5.0 mL) was added DIEA (331 mg, 2.56 mmol, 3.0 eq) and a solution of N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (190 mg, crude) in DCM (3.0 mL) at -20°C under N₂. The mixture was stirred at -20 °C for 2 h. The mixture was diluted with water (20 mL) and extracted with DCM (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by silica gel chromatography (DCM/MeOH = 80/1) to give 5-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (230 mg, 49.8% for two steps) as a white solid. LCMS: m/z 451.10 (M+H⁺).

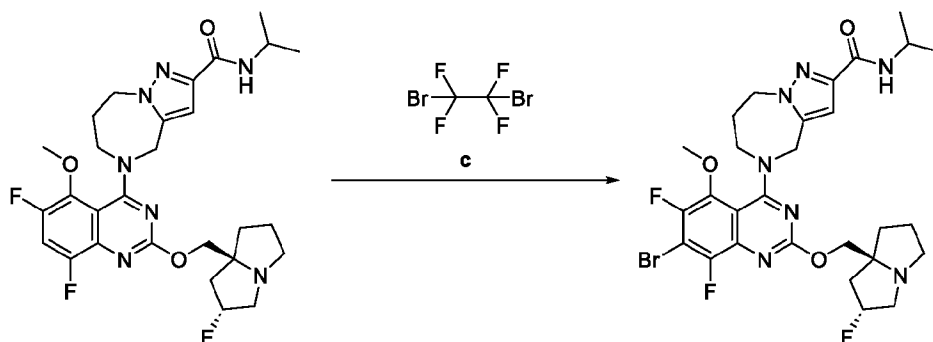
Step 2: Synthesis of 5-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



[00425] To a solution of 5-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (210 mg, 0.47 mmol, 1.0 eq) in 1,4-Dioxane (5.0 mL) was added ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (111 mg, 0.70 mmol, 1.5 eq), Cs₂CO₃ (455 mg, 1.40 mmol, 3.0 eq) and SPhos Pd G4 (37.3 mg, 0.05 mmol, 0.1 eq). Then the reaction mixture was stirred at 100 °C for 12 h. The mixture was diluted with water (15 mL) and extracted with EtOAc (15 mL x 3). The combined

organic phase was washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residual, which was purified by prep-TLC (DCM/MeOH = 10/1) to give 5-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (140 mg, 52.4%) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 7.32 – 7.27 (m, 1H), 6.69 (s, 1H), 6.60 (d, *J* = 8.1 Hz, 1H), 5.33 (d, *J* = 54.0 Hz, 1H), 4.90 – 4.78 (m, 2H), 4.40 – 4.34 (m, 2H), 4.29 – 4.16 (m, 3H), 3.94 – 3.86 (m, 2H), 3.67 (s, 3H), 3.53 – 3.27 (m, 3H), 3.07 – 2.97 (m, 1H), 2.24 – 1.92 (m, 8H), 1.23 (d, *J* = 6.3 Hz, 6H). LCMS: *m/z* 574.2 (M+H⁺).

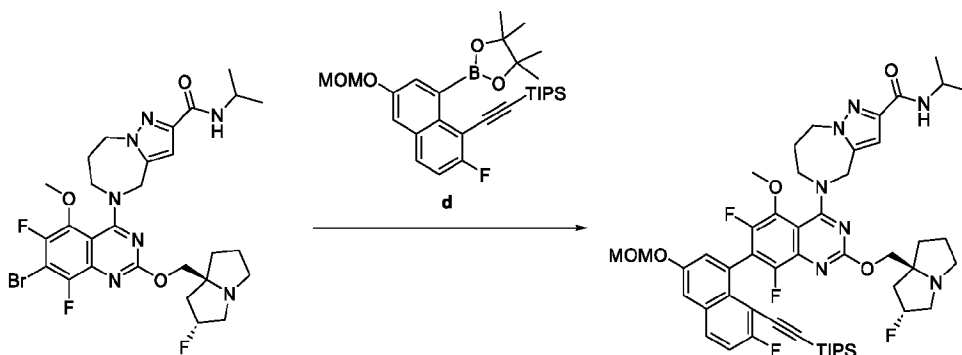
Step 3: Synthesis of 5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



[00426] To a solution of 5-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (140 mg, 0.244 mmol, 1.0 eq) in THF (6.0 mL) was added n-BuLi (2.5M in THF, 0.4 mL, 0.976 mmol, 4.0 eq) dropwise at -65 °C. The reaction mixture was stirred at -65 °C for 1 h. Then 1,2-dibromo-1,1,2,2-tetrafluoroethane (64 mg, 0.244 mmol, 1.0 eq) was added and stirred at -65 °C for 1.5 h. The mixture was diluted with water (15 mL) and extracted with EtOAc (10 mL X 3). The combined organic phase was washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by silica gel chromatography (eluted with DCM/MeOH = 10/1) to give 5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (84 mg, 52.7%) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 6.98 – 6.74 (m, 1H), 6.60 (d, *J* = 8.4

Hz, 1H), 5.41 (d, $J = 54.3$ Hz, 1H), 5.05 – 4.78 (m, 2H), 4.46 – 4.13 (m, 5H), 3.94 (s, 3H), 3.75 (s, 3H), 3.50 – 3.05 (m, 3H), 2.47 – 2.04 (m, 8H), 1.23 (d, $J = 6.6$ Hz, 6H). LCMS: m/z 652.1 ($M+H^+$).

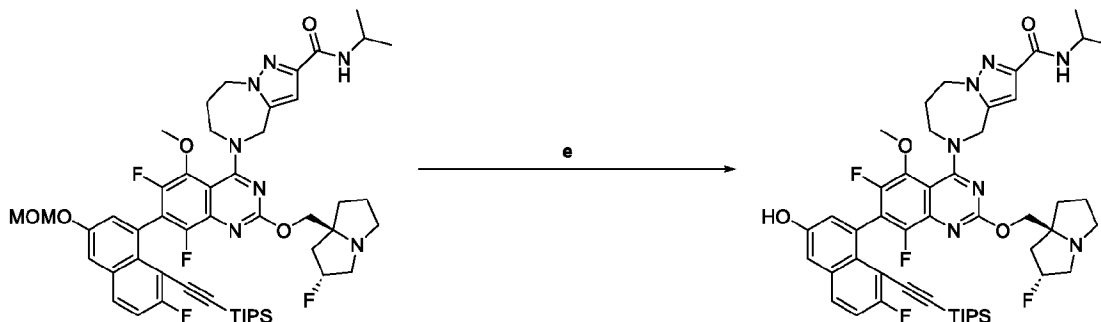
Step 4: Synthesis of 5-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



[00427] To a solution of 5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (60 mg, 0.09 mmol, 1.0 eq) and ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (52 mg, 0.10 mmol, 1.1 eq) in Toluene (5.0 mL) and H₂O (1.0 mL) was added Pd₂(dba)₃ (13 mg, 0.014 mmol, 0.15 eq), rac-BI-DIME (9.3 mg, 0.03 mmol, 0.3 eq) and K₃PO₄ (39 mg, 0.18 mmol, 2.0 eq). The mixture was stirred at 100 °C for 6 h. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (15 mL x 3). The organic phase was washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residual, which was purified by silica gel column chromatography (DCM/MeOH = 80/1) to give 5-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (40 mg, 45.4%) as a yellow solid. LCMS: m/z 958.4 ($M+H^+$).

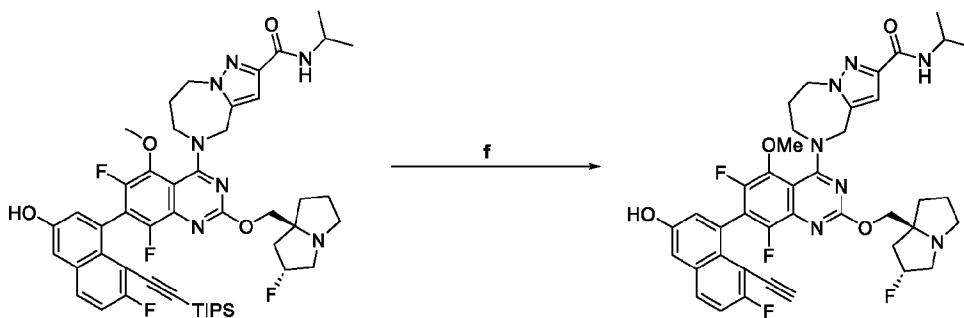
Step 5: Synthesis of 5-(6,8-difluoro-7-(7-fluoro-3-hydroxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-

yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



[00428] To a solution of 5-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl) ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (40 mg, 0.042 mmol, 1.0 eq) in DCM (3 mL) was added HCl (4M in Dioxane) (3.0 mL). The mixture was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure to give 5-(6,8-difluoro-7-(7-fluoro-3-hydroxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (38 mg, crude) as a white solid. LCMS: m/z 914.3 ($M+H^+$).

Step 6: Synthesis of 5-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide 2,2,2-trifluoroacetate (1:0.33)

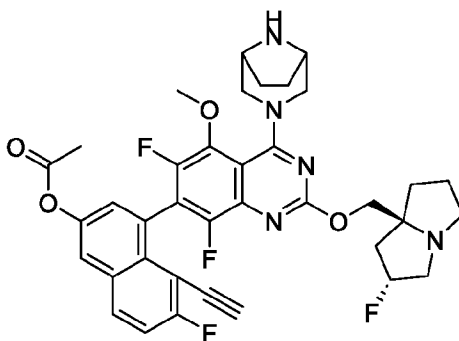


[00429] To a solution of 5-(6,8-difluoro-7-(7-fluoro-3-hydroxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-5,6,7,8-tetrahydro-4H-

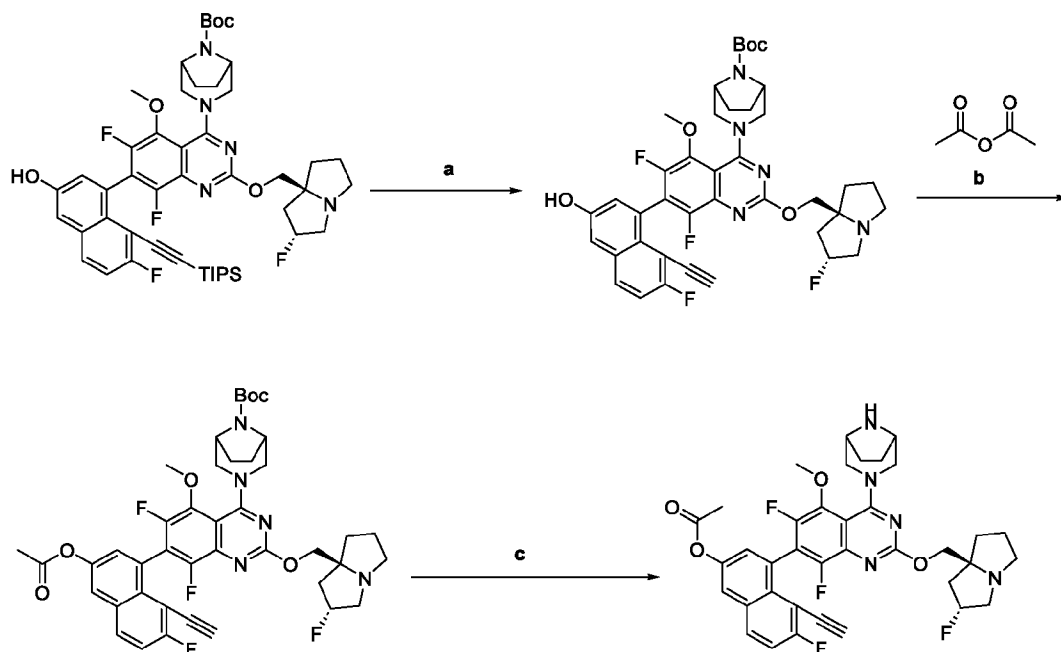
pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (38 mg, 0.042 mmol, 1.0 eq) in DMF (2 mL) was added CsF (31.6 mg, 0.21 mmol, 5.0 eq). The mixture was stirred at room temperature for 3 h. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 30% to 40%) to give 5-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide 2,2,2-trifluoroacetate (1:0.33) (21 mg, 66.1% for two steps) as a white solid. ¹H NMR (300 MHz, CD₃OD): δ 7.87 (dd, J = 9.0, 5.7, Hz, 1H), 7.38 – 7.30 (m, 2H), 7.17 – 7.12 (m, 1H), 6.73 (d, J = 3.3 Hz, 1H), 5.53 (d, J = 52.5 Hz, 1H), 5.14 – 5.02 (m, 2H), 4.60 – 4.35 (m, 4H), 4.22 – 4.08 (m, 3H), 3.97 – 3.77 (m, 6H), 3.46 – 3.35 (m, 2H), 2.59 – 2.04 (m, 8H), 1.23 (d, J = 6.6 Hz, 6H). ¹⁹F NMR (300 MHz, CD₃OD): δ -76.901, -111.176, -133.050, -136.703, -174.109. LCMS: m/z 758.3 (M+H⁺).

Example 29

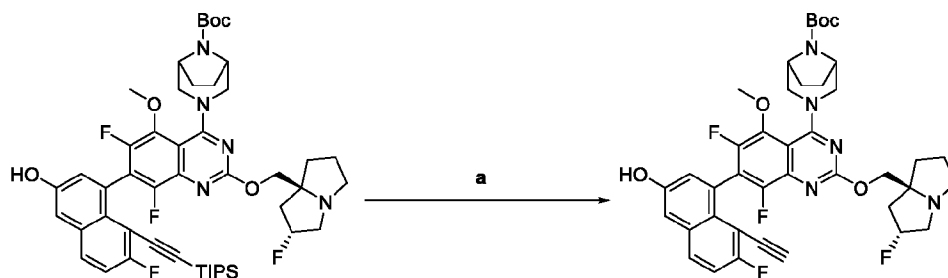
4-(4-((3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-yl acetate formate (1: 1)



Synthetic scheme:

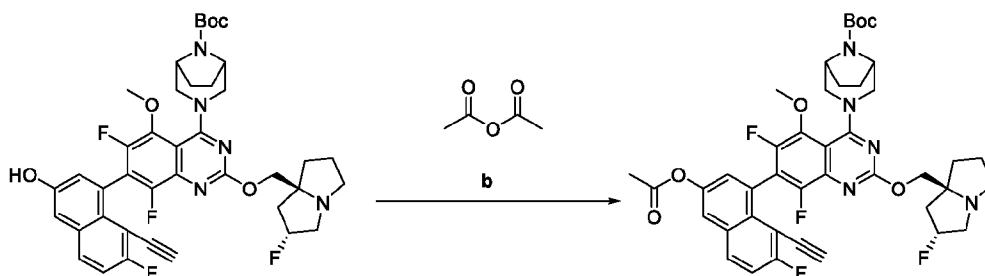


Step 1: Synthesis of tert-butyl 3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



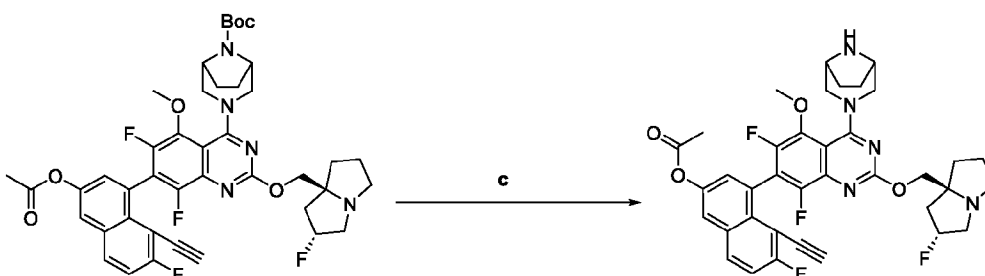
[00430] To a mixture of tert-butyl 3-(6,8-difluoro-7-(7-fluoro-3-hydroxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (50 mg, 0.05 mmol, 1.0 eq) in DMF (1 mL) was added CsF (159 mg, 1.0 mmol, 20.0 eq). The mixture was stirred at 50 °C for 3 h. The filtrate collected by filtration was concentrated to give tert-butyl (1R,5S)-3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (60.0 mg, crude) as a yellow solid. LCMS: m/z 748.2 ($M+H^+$).

Step 2: Synthesis of tert-butyl 3-(7-(3-acetoxy-8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00431] To a solution of tert-butyl 3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (40 mg, 0.05 mmol, 1.0 eq) in DCM (1 mL) was added TEA (16.2 mg, 0.16 mmol, 3.0 eq) and acetic anhydride (6.5 mg, 0.06 mmol, 1.2 eq) at 0 °C. The reaction mixture was stirred at room temperature for 1 h under N₂. The mixture was concentrated to give tert-butyl 3-(7-(3-acetoxy-8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (35 mg, crude) as a yellow solid. LCMS: m/z 790.2 (M+H⁺).

Step 3: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-yl acetate formate

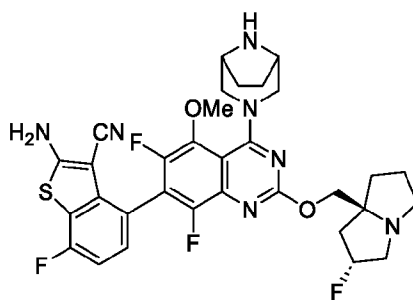


[00432] To a solution of tert-butyl 3-(7-(3-acetoxy-8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (35 mg, 0.04 mmol, 1.0 eq) in DCM (1 mL) was added TFA (0.3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h under N₂. The mixture was concentrated to give a crude. The crude was

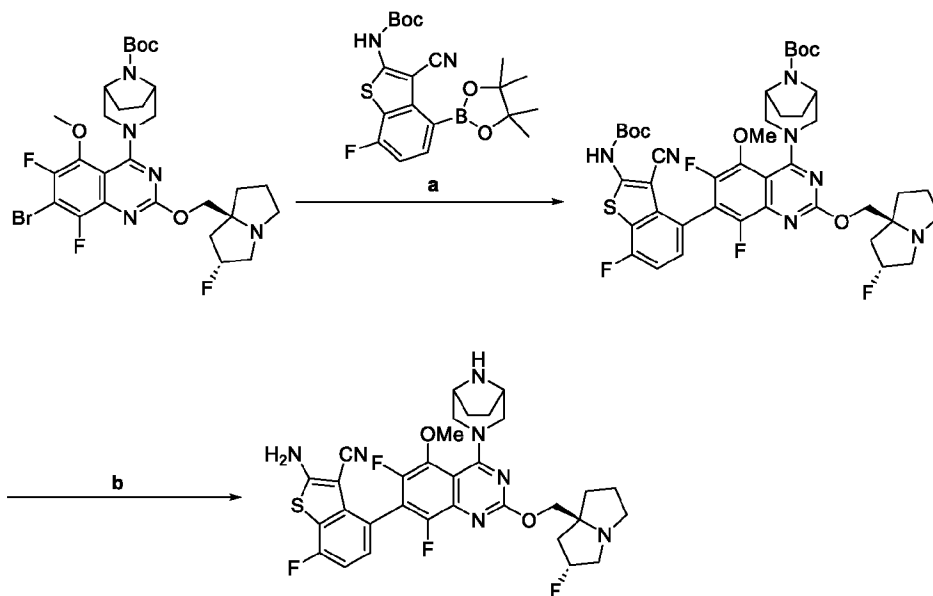
purified by Prep-HPLC (ACN with 0.1% FA in water, 15% to 50%) to give 4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-yl acetate formate (1: 1) (12.1 mg, 39.4%, three steps yield) as a white solid. ^1H NMR (400 MHz, CD_3OD): δ 8.10 (dd, $J = 9.2, 5.6$ Hz, 1H), 7.90 (d, $J = 2.4$ Hz, 1H), 7.49 (t, $J = 8.8$ Hz, 1H), 7.42 (d, $J = 2.4$ Hz, 1H), 5.50 (d, $J = 52.0$ Hz, 1H), 4.60 – 4.56 (m, 3H), 4.14 (d, $J = 19.2$ Hz, 3H), 3.92 (d, $J = 1.2$ Hz, 3H), 3.76 (d, $J = 12.4$ Hz, 4H), 3.63 – 3.54 (m, 2H), 3.36 (s, 1H), 2.72 – 2.55 (m, 2H), 2.51 (s, 3H), 2.49 – 2.08 (m, 8H). ^{19}F NMR (400 MHz, CD_3OD): δ -106.681, -132.374, -136.169, -174.181. LCMS: m/z 690.0 ($\text{M}+\text{H}^+$).

Example 30

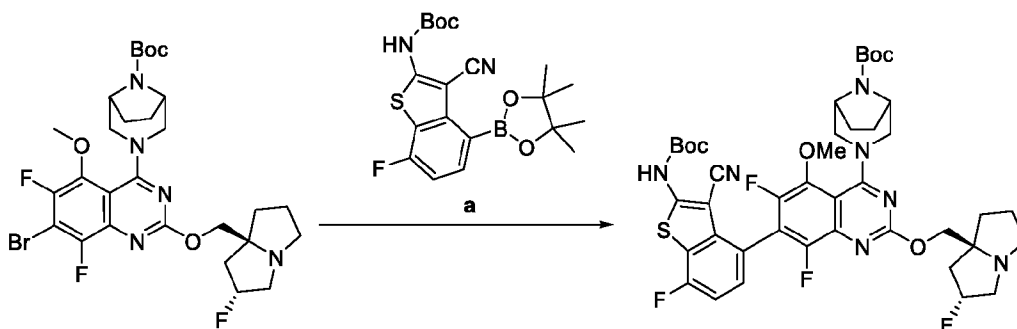
4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy quinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile 2,2,2-trifluoroacetic acid hydrochloride formate



Synthetic scheme:



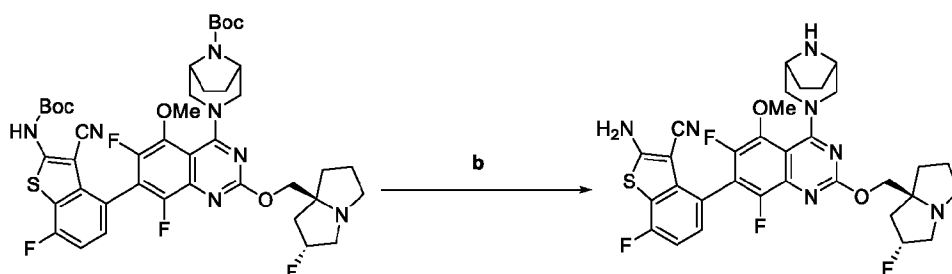
Step 1: Synthesis of compound tert-butyl 3-(7-(2-(((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00433] To a solution of compound tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (80 mg, 0.12 mmol, 1.0 eq) in 1,4-Dioxane (3 mL) and H₂O (1 mL) was added K₃PO₄ (48 mg, 0.22 mmol, 1.8 eq), tert-butyl (3-cyano-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophen-2-yl)carbamate (78 mg, 0.19 mmol, 1.5 eq) and Pd(dtbpf)Cl₂ (16 mg, 0.025 mmol, 0.2 eq) at room temperature. The reaction mixture was stirred at 90 °C for 2 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give a residue. The crude product was purified by prep-TLC (dichloromethane: methanol = 10: 1) to give tert-butyl 3-(7-(2-(((tert-butoxycarbonyl)amino)-3-

cyano-7-fluorobenzo[b]thiophen-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (55 mg, 51.9%) as a yellow solid. LCMS: m/z 854.3 ($M+H^+$).

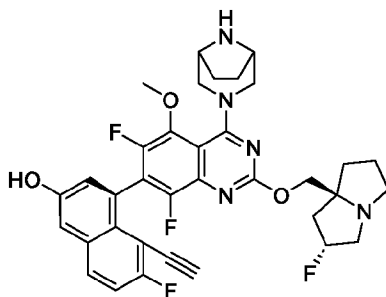
Step 2: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile 2,2,2-trifluoroacetic acid hydrochloride formate (1: 1)



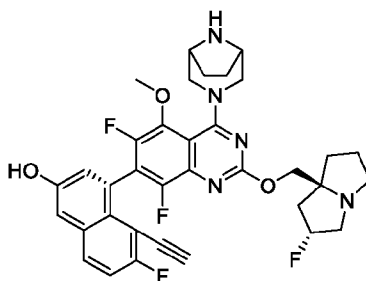
[00434] To a solution of compound tert-butyl 3-(7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (55 mg, 0.06 mmol, 1.0 eq) in DCM (2 mL) was added HCl in dioxane (1 mL, 4 M in dioxane) at room temperature. The reaction was stirred at room temperature for 1 h. The product was concentrated to give a crude. The crude was purified by Prep-HPLC (acetonitrile with 0.1% FA in water, 20% to 60%) to give 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile 2,2,2-trifluoroacetic acid hydrochloride formate (1: 1: 1) (9.7 mg, 23.0%) as a white solid. ^1H NMR (300 MHz, CD_3OD): δ 8.53 (brs, 0.4H), 7.30 (dd, $J = 8.4, 5.1$ Hz, 1H), 7.05 (t, $J = 9.3$ Hz, 1H), 5.37 (d, $J = 52.8$ Hz, 1H), 4.41 – 4.21 (m, 4H), 3.90 (s, 3H), 3.86 – 3.77 (m, 2H), 3.64 – 3.47 (m, 3H), 3.46 – 3.35 (m, 2H), 3.19 – 3.05 (m, 1H), 2.50 – 2.28 (m, 2H), 2.25 – 2.04 (m, 3H), 1.95 – 1.82 (m, 5H). ^{19}F NMR (300 MHz, CD_3OD): δ -76.934, -118.267, -133.032, -138.378, -173.838. LCMS: 654.2 ($M+H^+$).

Example 31 & 32

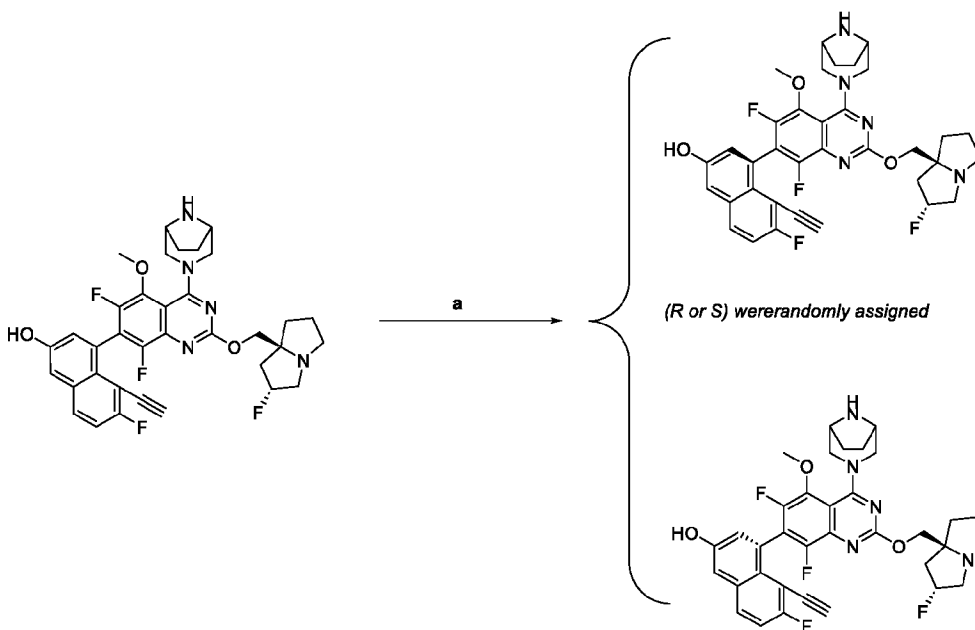
4-((S)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate (1: 1)



4-((R)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



Synthetic scheme:



Step 1: Synthesis of 4-((S)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate (1: 1) and

4-((R)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol

[00435] Compound 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate (60 mg) was purified by SFC (column: ChiralPak AD, 250×30mm I.D., 10 µm, mobile phase: A for CO₂ and B for Isopropanol (0.1% NH₃-H₂O), Gradient: B 40%, Flow rate: 80 mL /min, Column temperature: 38 °C) to afford 4-((S)-4-(((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate (1: 1) (14.5 mg, 24.2%, Re-purified by Prep-HPLC (FA system)) and 4-((R)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol (13.8 mg, 24.6%) respectively, the two isomers (*R* or *S*) was randomly assigned.

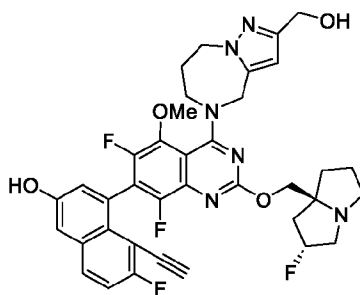
4-((S)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate (1: 1): Chiral purity: 100.0% ee; retention time: 0.463 min; Chiral SFC method: Waters UPC2 analytical SFC (SFC-H), column: ChiralPak AD, 50×4.6mm I.D., 3µm, column temperature: 35 °C, A for CO₂ and B for Isopropanol (0.05% DEA); pressure: 100 bar; flow rate: 3.0 mL/min. ¹H NMR (400 MHz, CD₃OD): δ 8.50 (brs, 1H), 7.86 (dd, *J* = 8.8, 5.6 Hz, 1H), 7.41 – 7.30 (m, 2H), 7.12 (d, *J* = 2.4 Hz, 1H), 5.35 (d, *J* = 53.4 Hz, 1H), 4.56 – 4.35 (m, 3H), 4.17 – 4.08 (m, 1H), 4.05 – 3.96 (m, 2H), 3.89 (s, 3H), 3.78 – 3.69 (m, 1H), 3.62 – 3.46 (m, 4H), 3.41 – 3.38 (m, 1H), 3.25 – 3.15 (m, 1H), 2.48 – 1.90 (m, 10H). ¹⁹F NMR (400 MHz, CD₃OD): δ - 111.253, -132.587, -137.199, -173.949. LCMS: *m/z* 648.2 (M-FA+H⁺).

[00436] 4-((R)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol: Chiral purity: 100.0% ee; retention time: 1.501 min; Chiral SFC method: Waters UPC2 analytical SFC (SFC-H), column: ChiralPak AD, 50×4.6mm I.D., 3µm, column

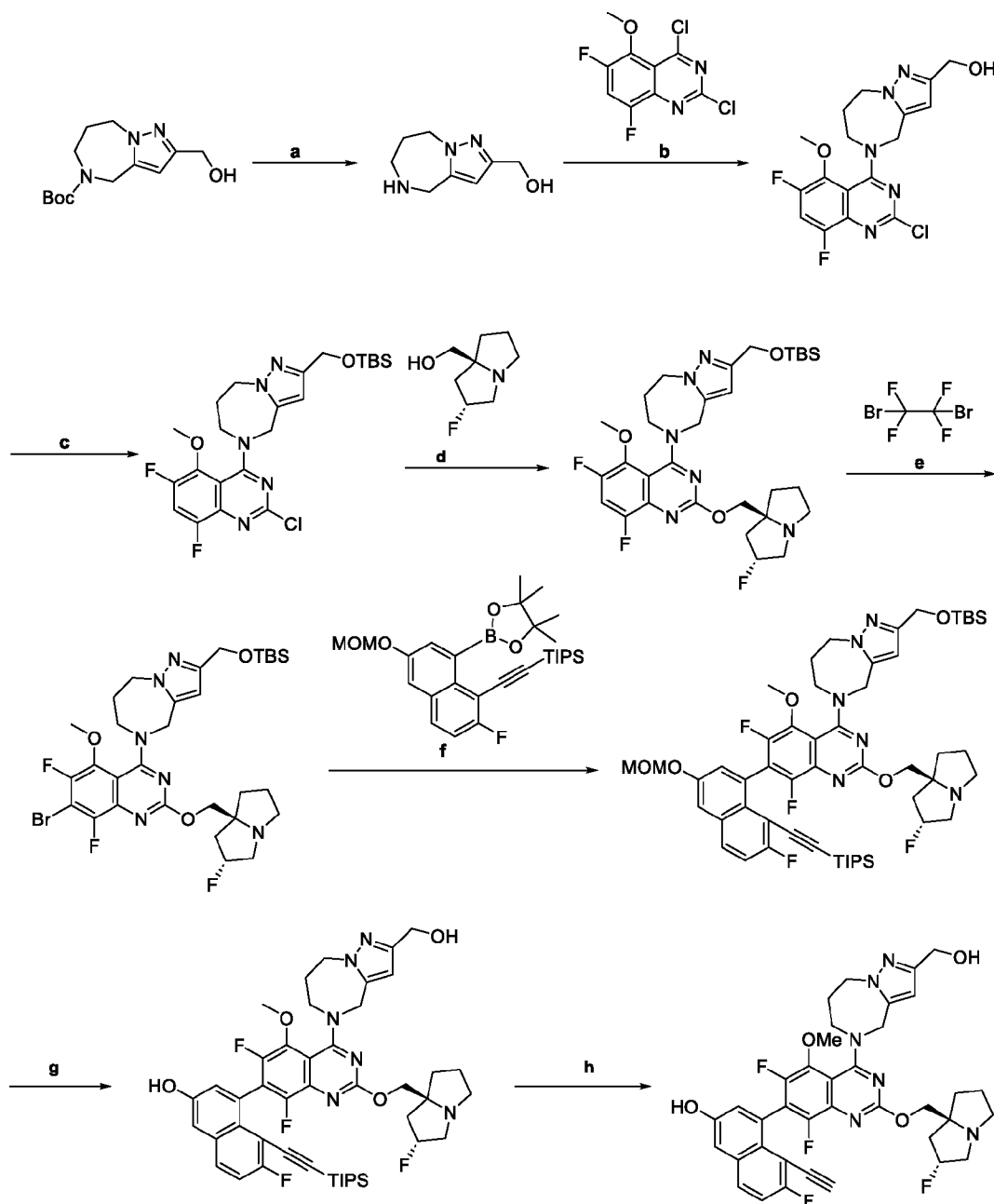
temperature: 35 °C, A for CO₂ and B for Isopropanol (0.05% DEA); pressure: 100 bar; flow rate: 3.0 mL/min. ¹H NMR (300 MHz, CD₃OD): δ 7.85 (dd, J = 9.0, 5.7 Hz, 1H), 7.38 – 7.29 (m, 2H), 7.12 (d, J = 2.4 Hz, 1H), 5.35 (d, J = 53.5 Hz, 1H), 4.54 – 4.38 (m, 1H), 4.37 – 4.22 (m, 2H), 4.11 – 4.00 (m, 1H), 3.85 (s, 3H), 3.69 – 3.55 (m, 3H), 3.49 – 3.35 (m, 2H), 3.31 – 3.19 (m, 3H), 3.09 – 3.00 (m, 1H), 2.39 – 1.79 (m, 10H). ¹⁹F NMR (300 MHz, CD₃OD): δ -111.399, -132.794, -138.848, -173.613. LCMS: m/z 648.2 (M+H⁺).

Example 33

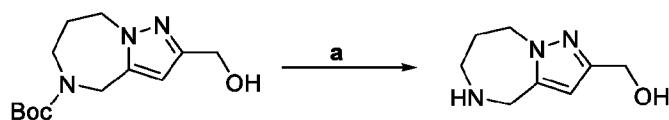
4-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2-(hydroxymethyl)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5(6H)-yl)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate



Synthetic scheme:



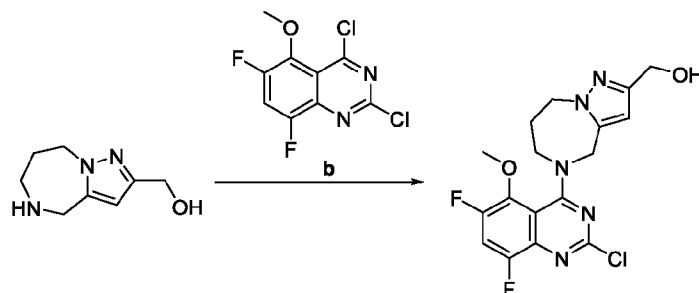
Step 1: Synthesis of (5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methanol



[00437] To a solution of tert-butyl 2-(hydroxymethyl)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate (650 mg, 2.43 mmol, 1.0 eq) in ACN (8.0 mL) was added HCl/Dioxane (0.5 mL). Then the mixture was stirred at room temperature for 1 h. The mixture

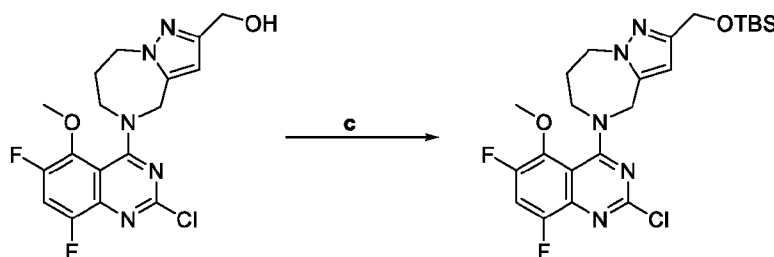
was concentrated to afford (5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methanol (406 mg, crude) as a white solid. LCMS: 168.1 ($M+H^+$).

Step 2: Synthesis of (5-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methanol



[00438] To a solution of 2,4-dichloro-6,8-difluoro-5-methoxyquinazoline (645 mg, 2.43 mmol, 1.0 eq) in DCM (4.0 mL) was added DIEA (1.57 g, 12.2 mmol, 5.0 eq) and a solution of (5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methanol (406 mg, crude) in DCM (2.0 mL) at -20 °C under N_2 . The mixture was stirred at -20 °C for 2 h. The mixture was diluted with water (10 mL) and extracted with DCM (15 mL x 3). The combined organic phase was washed with brine (20 mL), dried over Na_2SO_4 and concentrated to give a residue. The residue was purified by silica gel chromatography (DCM: MeOH = 80: 1) to give (5-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methanol (640 mg, 66.5% for two steps) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (dd, J = 10.4, 9.2 Hz, 1H), 6.14 (s, 1H), 4.89 (s, 2H), 4.62 (s, 2H), 4.45 – 4.38 (m, 2H), 3.99 – 3.93 (m, 2H), 3.75 – 3.73 (m, 3H), 2.20 – 2.14 (m, 2H). LCMS: 395.8 ($M+H^+$).

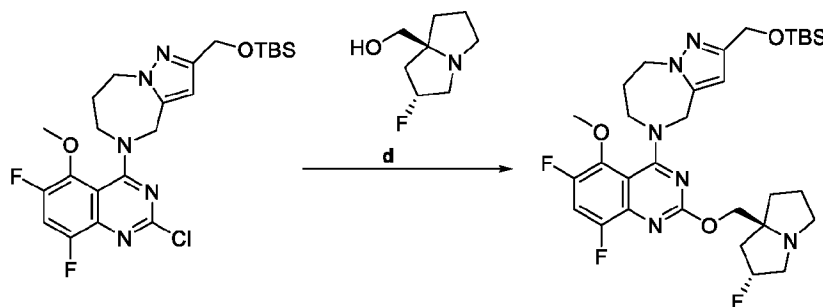
Step 3: Synthesis of 2-(((tert-butyldimethylsilyl)oxy)methyl)-5-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine



[00439] To a solution of (5-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methanol (640 mg, 1.62 mmol, 1.0 eq) in DMF (5.0 mL) was added TBSCl (487 mg, 3.23 mmol, 2.0 eq) and imidine (440 mg, 6.47 mmol, 4.0

eq). The mixture was stirred at room temperature for 15 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic phase was washed with water (10 mL x 2), brine (20 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by prep-TLC (Petroleum ether: EtOAc = 1: 1) to give 2-(((tert-butyl dimethylsilyl)oxy)methyl)-5-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine (690 mg, 83.7%) as a white solid. ¹H NMR (300 MHz, CDCl₃): δ 7.36 (dd, *J* = 10.7, 9.3 Hz, 1H), 6.13 (s, 1H), 4.89 (s, 2H), 4.64 (s, 2H), 4.42 – 4.36 (m, 2H), 3.97 – 3.91 (m, 2H), 3.74 – 3.71 (m, 3H), 2.21 – 2.12 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H). LCMS: 510.1 (M+H⁺).

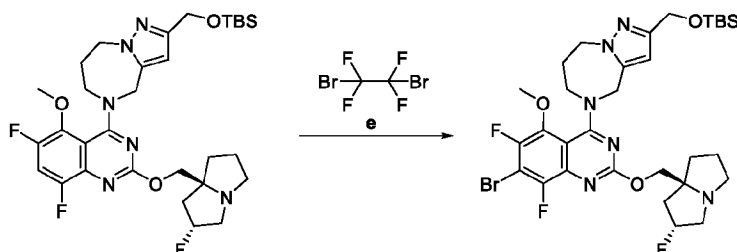
Step 4: Synthesis of 2-(((tert-butyl dimethylsilyl)oxy)methyl)-5-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine



[00440] To a solution of 2-(((tert-butyl dimethylsilyl)oxy)methyl)-5-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine (600 mg, 1.18 mmol, 1.0 eq) in 1,4-Dioxane (5.0 mL) was added ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (281 mg, 1.77 mmol, 1.5 eq), Cs₂CO₃ (1.15 g, 3.54 mmol, 3.0 eq) and S-Phos Pd G4 (93.6 mg, 0.12 mmol, 0.1 eq). Then the reaction mixture was stirred at 100 °C for 12 h. The mixture was diluted with water (15 mL) and extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-TLC (DCM: MeOH = 10: 1) to give 2-(((tert-butyl dimethylsilyl)oxy)methyl)-5-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine (590 mg, 79.3%) as a white solid. ¹H NMR (300 MHz, CDCl₃): δ 7.32 – 7.26 (m, 1H), 6.08 (s, 1H), 5.29 (d, *J* = 53.1, 1H), 4.83 (s, 2H), 4.63 (s,

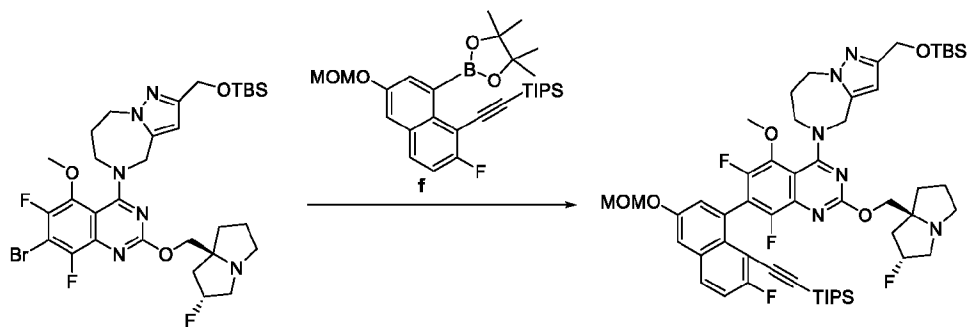
2H), 4.39 – 4.34 (m, 2H), 4.28 – 4.10 (m, 2H), 3.89 – 3.82 (m, 2H), 3.64 (s, 3H), 3.36 – 2.93 (m, 4H), 2.24 – 1.87 (m, 8H), 0.89 (s, 9H), 0.05 (s, 6H). LCMS: 633.3 ($M+H^+$).

Step 5: Synthesis of 5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-2-(((tert-butyl dimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine



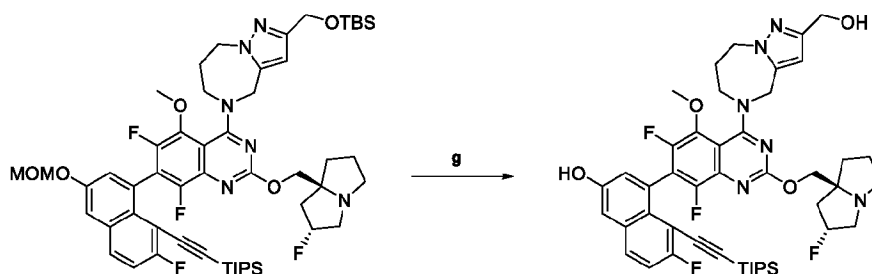
[00441] To a solution of 2-(((tert-butyl dimethylsilyl)oxy)methyl)-5-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine (200 mg, 0.316 mmol, 1.0 eq) in THF (3.0 mL) was added LDA (2.0M in THF 0.6 mL, 1.26 mmol, 4.0 eq) dropwise at -78 °C. The reaction mixture was stirred at -78 °C for 1 h. Then 1,2-dibromo-1,1,2,2-tetrafluoroethane (99 mg, 0.38 mmol, 1.2 eq) was added and stirred at -78 °C for 3 h. The mixture was diluted with water (15 mL) and extracted with EtOAc (15 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated to give a residue. The residue was purified by silica gel chromatography (DCM: MeOH = 10: 1) to give 5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-2-(((tert-butyl dimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine (130 mg, 57.8%) as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$): δ 6.09 (s, 1H), 5.31 (d, J = 54.6, 1H), 4.82 (s, 2H), 4.63 (s, 2H), 4.41 – 4.09 (m, 4H), 3.91 – 3.82 (m, 2H), 3.67 (s, 3H), 3.50 – 2.92 (m, 4H), 2.33 – 1.90 (m, 8H), 0.89 (s, 9H), 0.05 (s, 6H). LCMS: 711.2, 713.2 ($M+H^+$).

Step 6: Synthesis of 2-(((tert-butyl dimethylsilyl)oxy)methyl)-5-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine



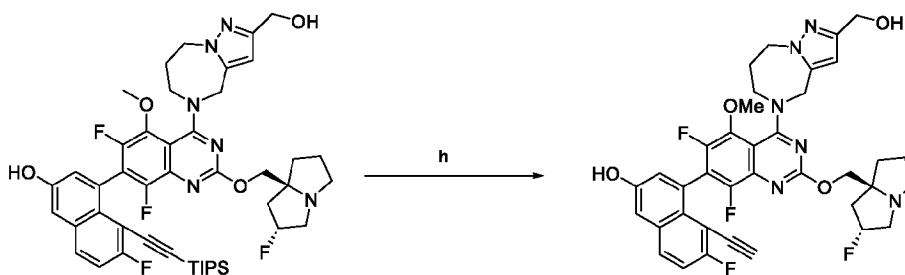
[00442] To a solution of 5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-2-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine (90 mg, 0.126 mmol, 1.0 eq) and ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (84 mg, 0.164 mmol, 1.3 eq) in Dioxane (2.0 mL) and H₂O (0.4 mL) was added K₃PO₄ (80 mg, 0.378 mmol, 3.0 eq) and cataCXium A Pd G₃ (28 mg, 0.04 mmol, 0.3 eq). The mixture was heated under microwave irradiation at 120 °C for 2 h. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (15 mL x 3). The organic phase was washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-TLC (DCM: MeOH = 10: 1) to give 2-(((tert-butyldimethylsilyl)oxy)methyl)-5-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine (50 mg, 38.9%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 7.79 (dd, *J* = 9.0, 5.6 Hz, 1H), 7.52 (d, *J* = 2.5 Hz, 1H), 7.30 (t, *J* = 8.6 Hz, 1H), 7.18 (d, *J* = 2.2 Hz, 1H), 6.19 (s, 1H), 5.36 – 5.22 (m, 3H), 4.91 – 4.66 (m, 4H), 4.46 – 4.35 (m, 2H), 4.33 – 4.00 (m, 2H), 3.96 – 3.76 (m, 2H), 3.72 – 3.67 (m, 3H), 3.52 (s, 3H), 3.39 – 2.87 (m, 4H), 2.30 – 1.90 (m, 8H), 0.90 – 0.83 (m, 27H), 0.70 – 0.62 (m, 3H), 0.09 – 0.06 (m, 6H). LCMS: 509.3 (M/2+H⁺).

Step 7: Synthesis of 4-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2-(hydroxymethyl)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5(6H)-yl)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol



[00443] To a solution of 2-(((tert-butyldimethylsilyl)oxy)methyl)-5-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine (40 mg, 0.039 mmol, 1.0 eq) in DCM (2 mL) was added HCl (4M in Dioxane) (0.6 mL). The mixture was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure to give 4-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2-(hydroxymethyl)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5(6H)-yl)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (34 mg, crude) as a white solid. LCMS: 859.3 ($M+H^+$).

Step 8: Synthesis of 4-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2-(hydroxymethyl)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5(6H)-yl)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate

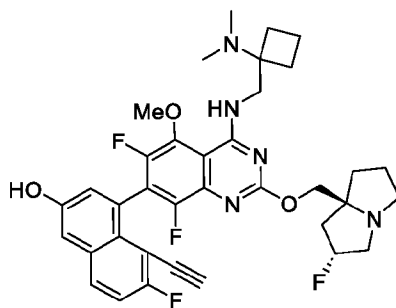


[00444] To a solution of 4-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2-(hydroxymethyl)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5(6H)-yl)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (34 mg, 0.04 mmol, 1.0 eq) in DMF (2 mL) was added CsF (30 mg, 0.20 mmol, 5.0 eq). The mixture was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 30% to 40%) to give 4-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-

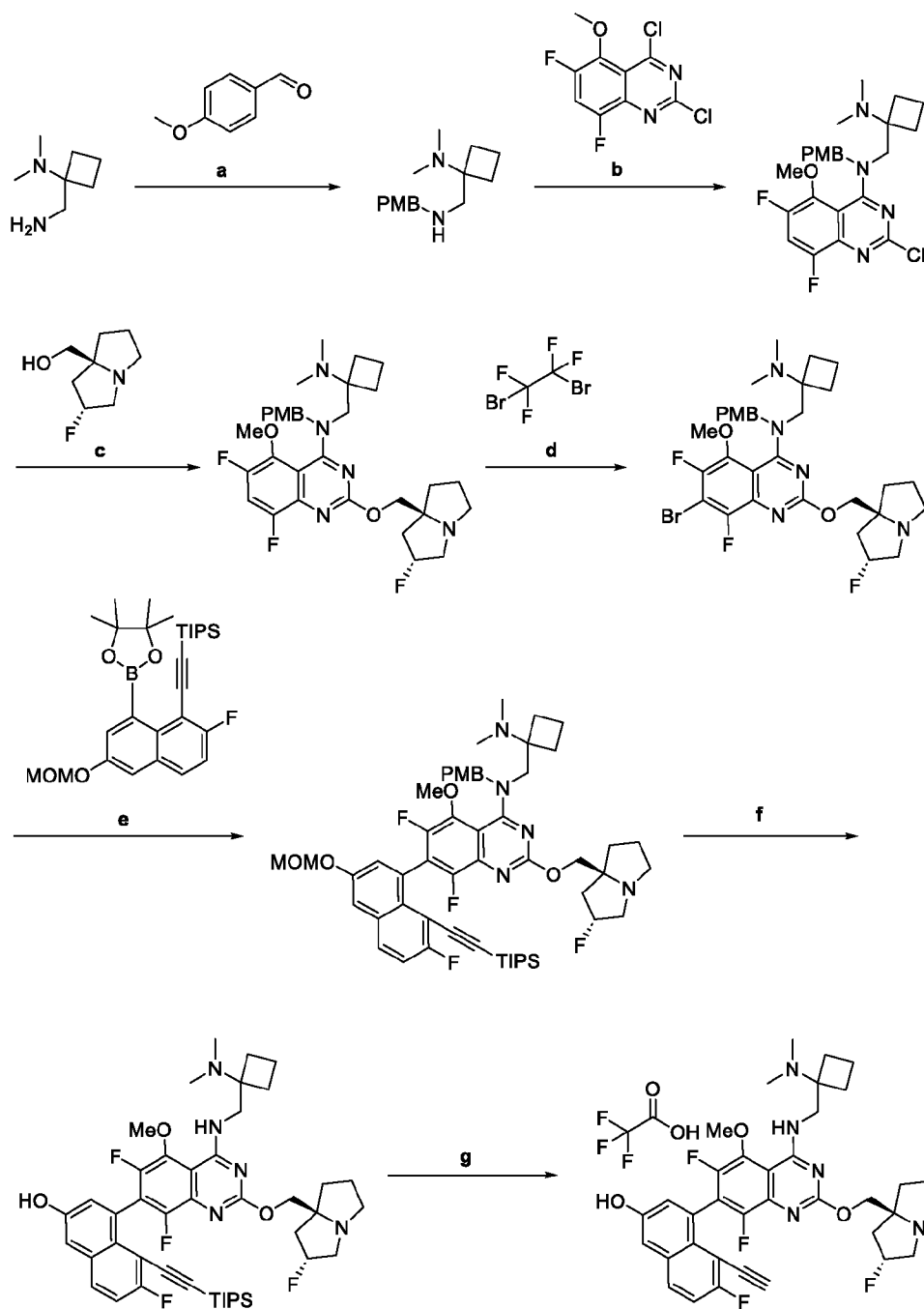
yl)methoxy)-4-(2-(hydroxymethyl)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5(6H)-yl)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate (18 mg, 61.1% for two steps) as a white solid. ^1H NMR (300 MHz, CD_3OD): δ 8.49 (s, 0.5H), 7.87 (dd, $J = 9.3, 6.0$ Hz, 1H), 7.37 – 7.29 (m, 2H), 7.14 (d, $J = 2.4$ Hz, 1H), 6.28 (d, $J = 2.4$ Hz, 1H), 5.43 (d, $J = 52.5$ Hz, 1H), 5.04 (s, 2H), 4.51 (s, 2H), 4.48 – 4.28 (m, 4H), 4.18 – 4.03 (m, 2H), 3.83 (s, 3H), 3.69 – 3.48 (m, 3H), 3.42 – 3.35 (m, 1H), 3.27 – 3.18 (s, 1H), 2.48 – 2.03 (m, 8H). ^{19}F NMR (300 MHz, CD_3OD): δ -111.270, -132.777, -137.413, -173.796. LCMS: 703.2 ($\text{M} + \text{H}^+$).

Example 34

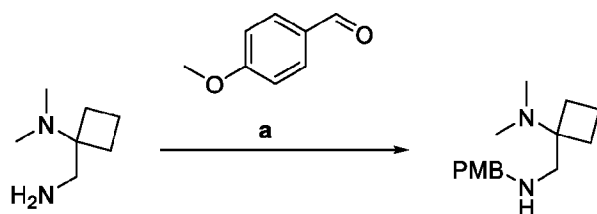
4-(4-(((1-(dimethylamino)cyclobutyl)methyl)amino)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol 2,2,2-trifluoroacetate formate



Synthetic scheme:

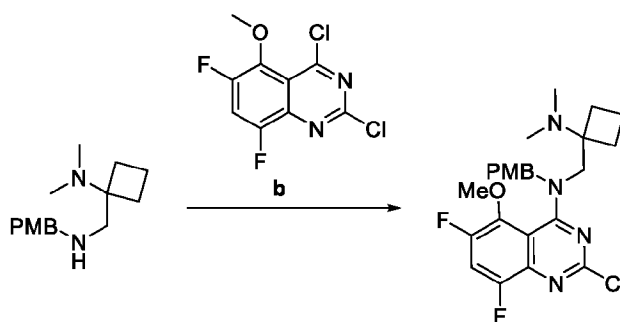


Step 1: Synthesis of 1-(((4-methoxybenzyl)amino)methyl)-N,N-dimethylcyclobutan-1-amine



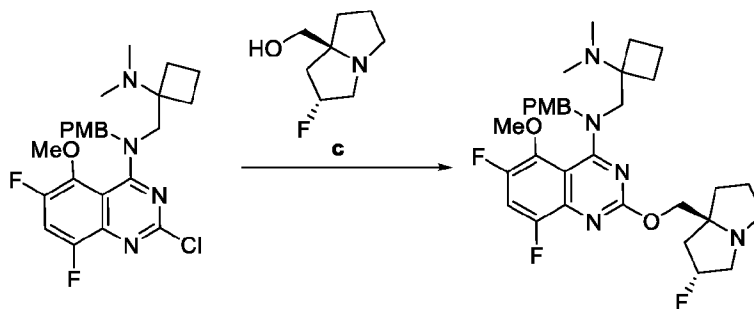
[00445] To a solution of compound 1-(aminomethyl)-N,N-dimethylcyclobutan-1-amine (500 mg, 3.9 mmol, 1.0 eq) in MeOH (10 mL) was added compound 4-methoxybenzaldehyde (530 mg, 3.9 mmol, 1.0 eq). The reaction was stirred at room temperature for 15 h. To the reaction was added NaBH₄ (295 mg, 7.8 mmol, 2.0 eq) at room temperature. The reaction was stirred at room temperature for 3 h. The mixture was quenched with aqueous ammonium chloride solution (0.5 mL) and dried with Na₂SO₄. The mixture was filtered and t-dimethylcyclobutan-1-amine (860 mg, crude) as a white solid. LCMS: 249.2 (M+Na⁺).

Step 2: Synthesis of 2-chloro-N-((1-(dimethylamino)cyclobutyl)methyl)-6,8-difluoro-5-methoxy-N-(4-methoxybenzyl)quinazolin-4-amine



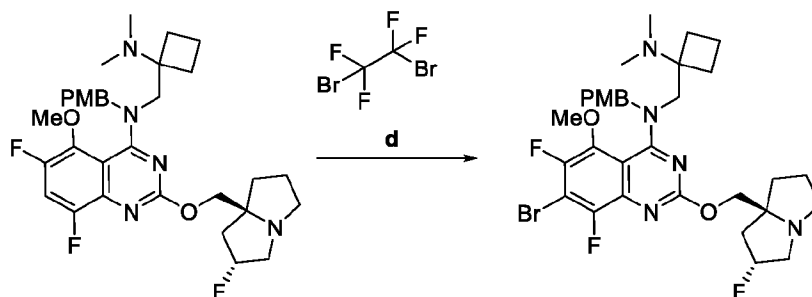
[00446] To a solution of compound 2,4-dichloro-6,8-difluoro-5-methoxyquinazoline (600 mg, 2.27 mmol, 1.0 eq) and DIEA (881 mg, 6.82 mmol, 3.0 eq) in DCM (10 mL) was added compound 1-((4-methoxybenzyl)amino)methyl-N,N-dimethylcyclobutan-1-amine (621 mg, 2.5 mmol, 1.1 eq) at -40 °C. The reaction mixture was stirred at room temperature for 3 h under nitrogen atmosphere. The mixture was quenched with water (30 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with H₂O (20 mL), brine (20 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (DCM: MeOH = 100: 1) to give compound 2-chloro-N-((1-(dimethylamino)cyclobutyl)methyl)-6,8-difluoro-5-methoxy-N-(4-methoxybenzyl)quinazolin-4-amine (520 mg, 48.0%) as a yellow solid. LCMS: 477.2 (M+H⁺).

Step 3: Synthesis of N-((1-(dimethylamino)cyclobutyl)methyl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-N-(4-methoxybenzyl)quinazolin-4-amine



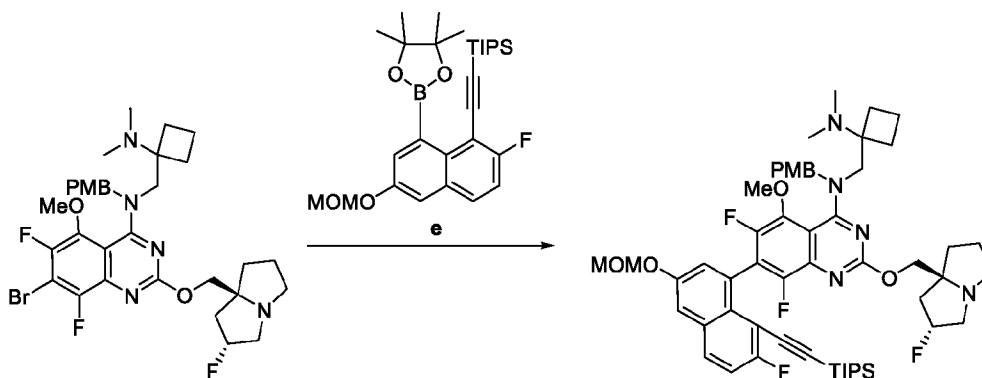
[00447] To a solution of compound 2-chloro-N-((1-(dimethylamino)cyclobutyl)methyl)-6,8-difluoro-5-methoxy-N-(4-methoxybenzyl)quinazolin-4-amine (460 mg, 0.97 mmol, 1.0 eq) in dioxane (10 mL) was added ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (231 mg, 1.45 mmol, 1.5 eq), Cs₂CO₃ (944 mg, 2.9 mmol, 3.0 eq) and SPhos Pd G4 (31 mg, 0.097 mmol, 0.1 eq) at room temperature. The reaction was stirred at 100 °C for 3 h. The mixture was partitioned between EtOAc (20 mL) and water (30 mL). The layers were separated. The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic layers were washed with H₂O (20 mL), brine (20 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (Dichloromethane: Methanol = 60: 1) to give compound N-((1-(dimethylamino)cyclobutyl)methyl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-N-(4-methoxybenzyl)quinazolin-4-amine (390 mg, 67.4%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 7.33 – 7.19 (m, 1H), 7.19 – 7.15 (m, 1H), 6.86 – 6.68 (m, 3H), 5.27 (d, *J* = 53.6 Hz, 1H), 4.88 – 4.65 (m, 2H), 4.35 – 4.18 (m, 2H), 3.97 (s, 3H), 3.76 (s, 3H), 3.41 – 3.15 (m, 3H), 3.05 – 2.94 (m, 1H), 2.68 – 2.36 (m, 6H), 2.28 – 2.11 (m, 3H), 2.07 – 1.78 (m, 7H), 1.31 – 1.42 (m, 2H), 0.93 – 0.78 (m, 2H). LCMS: 600.3 (M+H⁺).

Step 4: Synthesis of 7-bromo-N-((1-(dimethylamino)cyclobutyl)methyl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-N-(4-methoxybenzyl)quinazolin-4-amine



[00448] To a solution of compound N-((1-(dimethylamino)cyclobutyl)methyl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-N-(4-methoxybenzyl)quinazolin-4-amine (390 mg, 0.65 mmol, 1.0 eq) in THF (8 mL) was added *n*BuLi (2.5M, 0.5 mL, 1.3 mmol, 2.0 eq) dropwise at -65 °C. The reaction mixture was stirred at -65 °C for 0.5 h under nitrogen atmosphere. Compound 1,2-dibromo-1,1,2,2-tetrafluoroethane (338 mg, 1.3 mmol, 2.0 eq) was added to the mixture. The reaction mixture was stirred at -65 °C for 0.5 h under nitrogen atmosphere. The reaction mixture was quenched with aqueous ammonium chloride solution (20 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with H₂O (10 mL), brine (10 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (Dichloromethane: Methanol = 80: 1) to give compound 7-bromo-N-((1-(dimethylamino)cyclobutyl)methyl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-N-(4-methoxybenzyl)quinazolin-4-amine (210 mg, 47.7%) as a yellow solid. LCMS: 678.2, 680.2 (M+H⁺).

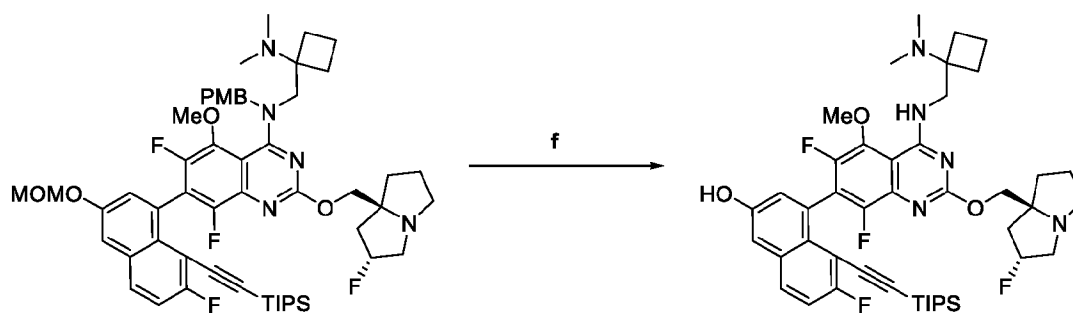
Step 5: Synthesis of N-((1-(dimethylamino)cyclobutyl)methyl)-6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-N-(4-methoxybenzyl)quinazolin-4-amine



[00449] To a solution of compound 7-bromo-N-((1-(dimethylamino)cyclobutyl)methyl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-N-(4-methoxybenzyl)quinazolin-4-amine (210 mg, 0.31 mmol, 1.0 eq) in toluene (4 mL) and H₂O (0.8 mL) was added compound ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (318 mg, 0.62 mmol, 2.0 eq), K₃PO₄ (197 mg, 0.93 mmol, 3.0 eq), rac-BI-DIME (15 mg, 0.047 mmol, 0.15 eq) and Pd₂(dba)₃

(85 mg, 0.093 mmol, 0.3 eq). The mixture was heated under microwave irradiation at 120 °C for 1 h. The reaction mixture was poured into water (10 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with H₂O (10 mL), brine (10 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (Dichloromethane: Methanol = 60: 1) to give compound N-((1-(dimethylamino)cyclobutyl)methyl)-6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-(((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-N-(4-methoxybenzyl)quinazolin-4-amine (132 mg, 43.3%) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 7.86 – 7.72 (m, 1H), 7.50 (d, *J* = 2.7 Hz, 1H), 7.38 – 7.28 (m, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 6.94 – 6.74 (m, 4H), 5.40 – 5.15 (m, 1H), 5.27 (s, 2H), 5.07 – 4.91 (m, 1H), 4.74 – 4.52 (m, 1H), 4.32 – 4.16 (m, 2H), 4.11 – 4.06 (m, 2H), 3.78 (s, 3H), 3.49 (s, 3H), 3.34 – 3.22 (m, 2H), 3.19 – 3.12 (m, 1H), 3.06 – 2.92 (m, 1H), 2.58–2.42 (m, 3H), 2.31 – 2.04 (m, 6H), 1.37 – 1.05 (m, 6H), 1.41 – 1.16 (m, 6H), 0.93 – 0.76 (m, 18H), 0.75 – 0.58 (m, 3H). LCMS: 984.4 (M+H⁺).

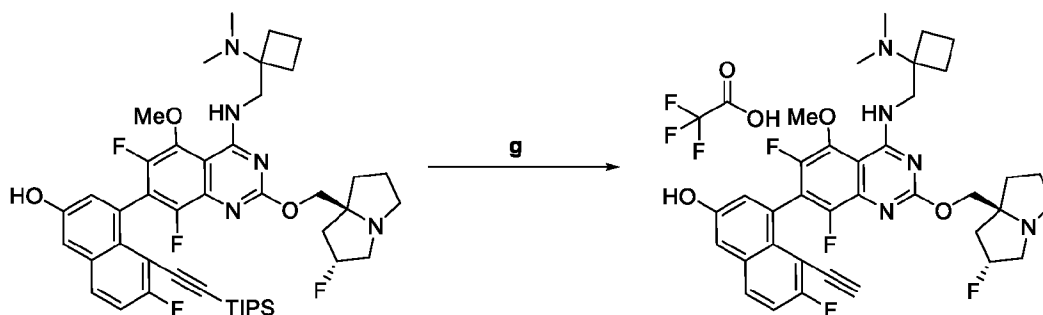
Step 6: Synthesis of 4-(4-(((1-(dimethylamino)cyclobutyl)methyl)amino)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-(((triisopropylsilyl)ethynyl)naphthalen-2-ol



[00450] To a solution of compound N-((1-(dimethylamino)cyclobutyl)methyl)-6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-(((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-N-(4-methoxybenzyl)quinazolin-4-amine (90 mg, 0.09 mmol, 1.0 eq) in DCM (5 mL) was added HCl in dioxane (5 mL). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure to give compound 4-(4-(((1-(dimethylamino)cyclobutyl)methyl)amino)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-

((triisopropylsilyl)ethynyl)naphthalen-2-ol (80 mg, crude) as a white solid. LCMS: 820.4 ($M+H^+$).

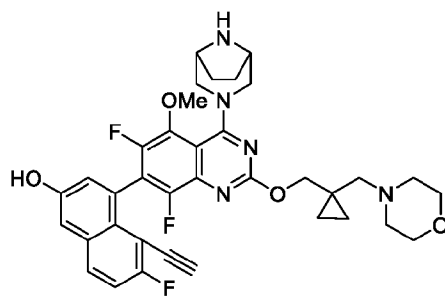
Step 7: Synthesis of 4-(4-(((1-(dimethylamino)cyclobutyl)methyl)amino)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol 2,2,2-trifluoroacetate (1:1)



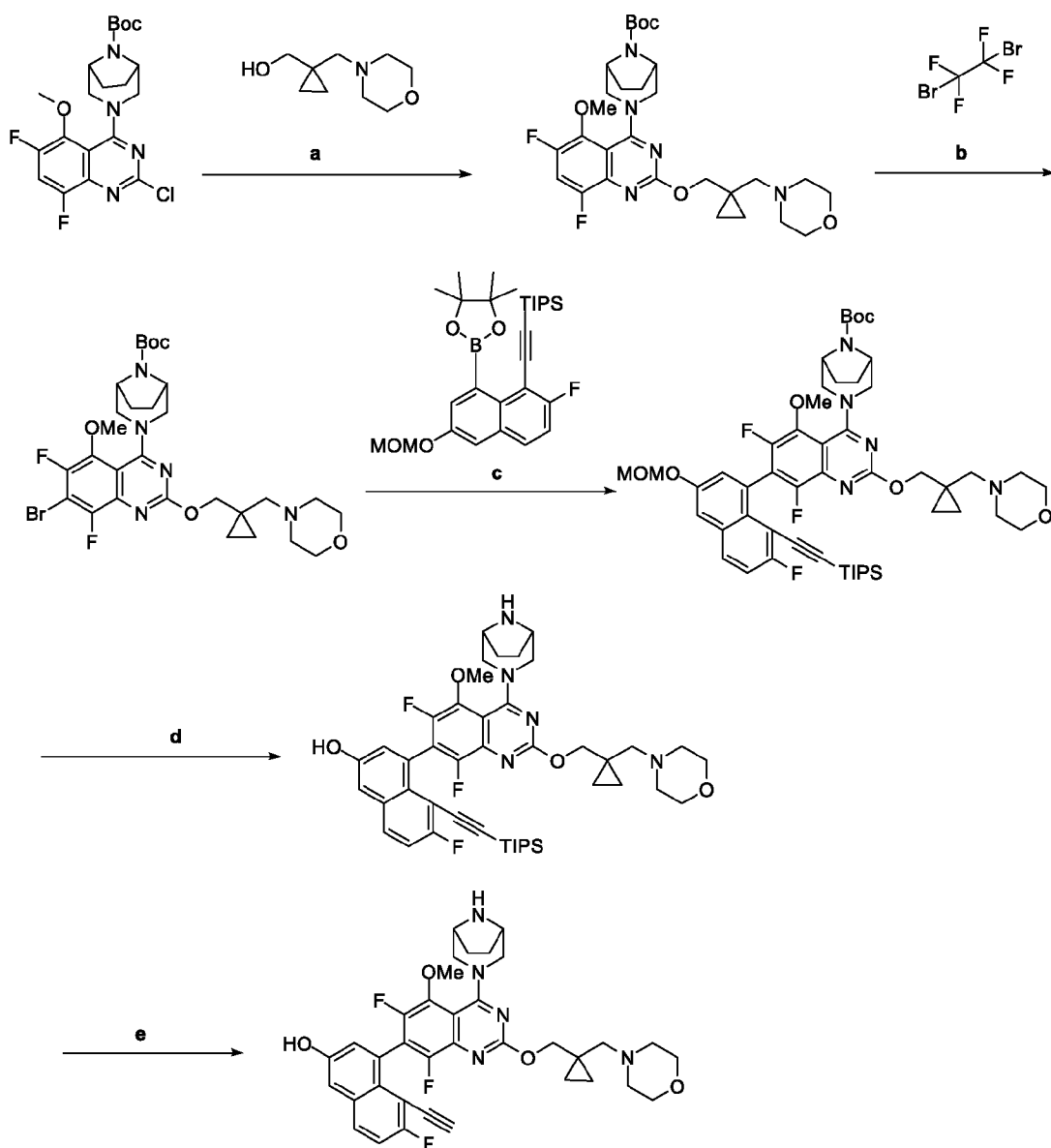
[00451] To a solution of compound 4-(4-(((1-(dimethylamino)cyclobutyl)methyl)amino)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (80 mg, crude) in DMF (1 mL) was added CsF (148.3 mg, 1.0 mmol, 10.0 eq) at room temperature. The reaction was stirred at 40 °C for 1 h. The mixture was concentrated to give a crude. The crude was purified by Prep-HPLC (acetonitrile with 0.1% FA in water, 10% to 50%) to give 4-(4-(((1-(dimethylamino)cyclobutyl)methyl)amino)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy quinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol 2,2,2-trifluoroacetate (1:1) (20.5 mg, 33.8%, yield of two steps) as a white solid. ^1H NMR (300 MHz, CD_3OD): δ 7.87 (dd, $J=9.0, 5.7$ Hz, 1H), 7.39 – 7.27 (m, 2H), 7.14 – 7.10 (m, 1H), 5.45 (d, $J=52.8$ Hz, 1H), 4.65 – 4.43 (m, 2H), 4.15 – 4.08 (m, 3H), 4.04 – 3.87 (m, 2H), 3.82 – 3.56 (m, 3H), 3.52 – 3.45 (m, 1H), 3.37 – 3.32 (m, 1H), 2.61 – 2.51 (m, 1H), 2.50 – 2.44 (m, 6H), 2.44 – 2.32 (m, 3H), 2.31 – 2.12 (m, 3H), 2.11 – 1.98 (m, 1H), 1.97 – 1.80 (m, 4H). ^{19}F NMR (300 MHz, CD_3OD): δ -76.905, -111.240, -133.75, -136.329, -174.218. LCMS: 664.3 ($M+H^+$)

Example 35

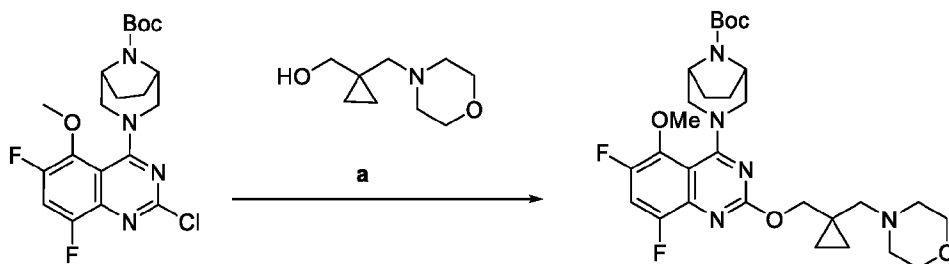
4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-5-methoxy-2-((1-(morpholinomethyl)cyclopropyl)methoxy)quinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



Synthetic scheme:

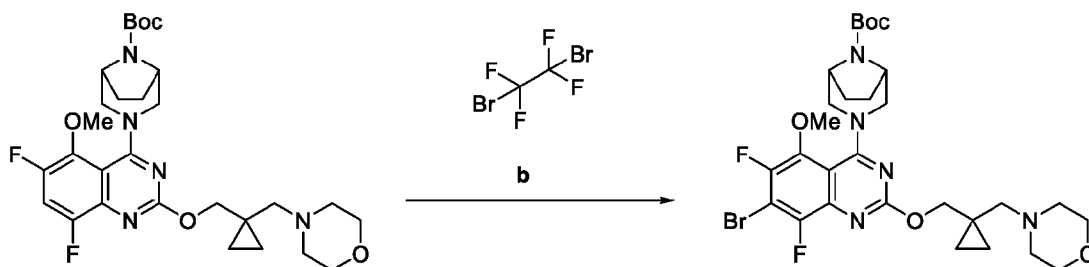


Step 1: Synthesis of tert-butyl 3-(6,8-difluoro-5-methoxy-2-((1-(morpholinomethyl)cyclopropyl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



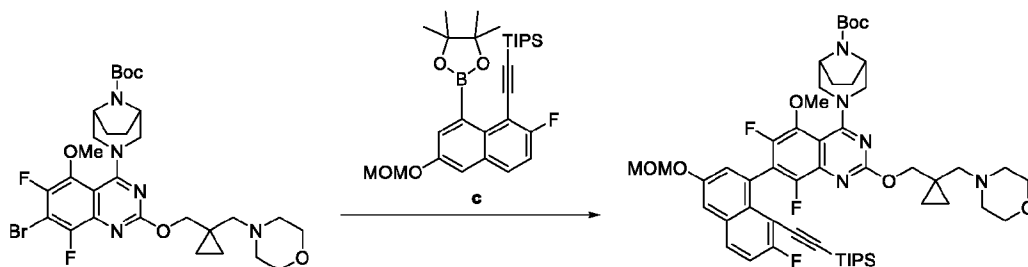
[00452] To a solution of compound tert-butyl 3-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (260 mg, 0.59 mmol, 1.0 eq) in 1,4-Dioxane (5.00 mL) was added (1-(morpholinomethyl)cyclopropyl)methanol (150 mg, 0.88 mmol, 1.5 eq), Cs₂CO₃ (477 mg, 1.46 mmol, 2.5 eq) and Ruphos-Pd-G3 (49 mg, 0.06 mmol, 0.1 eq). The reaction mixture was stirred at 100 °C for 15 h under nitrogen atmosphere. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The organic phase was washed with brine (15 mL), dried with Na₂SO₄, filtered and concentrated to give residue. The residue was purified by silica gel column chromatography (Petroleum ether: EtOAc = 3: 1) to give tert-butyl 3-(6,8-difluoro-5-methoxy-2-((1-(morpholinomethyl)cyclopropyl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (170 mg, 50.1%) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 7.26 – 7.20 (m, 1H), 4.37 – 4.04 (m, 6H), 3.79 (s, 3H), 3.68 – 3.60 (m, 4H), 3.40 (d, *J* = 12.6 Hz, 2H), 2.46 (s, 4H), 2.40 (s, 2H), 1.90 – 1.73 (m, 4H), 1.49 (s, 9H), 0.71 – 0.39 (m, 4H). LCMS: 576.3 (M+H⁺).

Step 2: Synthesis of tert-butyl 3-(7-bromo-6,8-difluoro-5-methoxy-2-((1-(morpholinomethyl)cyclopropyl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00453] To a solution of tert-butyl 3-(6,8-difluoro-5-methoxy-2-((1-(morpholinomethyl)cyclopropyl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (170 mg, 0.30 mmol, 1.0 eq) in THF (3.00 mL) was added *n*-BuLi 2.5M in THF (0.42 mL, 1.03 mmol, 3.5 eq) dropwise at -65 °C. The reaction mixture was stirred at -65 °C for 1 h. Then a solution of 1,2-dibromo-1,1,2,2-tetrafluoroethane (153 mg, 0.59 mmol, 2.0 eq) was added dropwise at -65 °C. The reaction mixture was stirred at -65 °C for 2 h. The residue was quenched with aqueous NH₄Cl (10 mL) and extracted with EtOAc (10 mL x 3). The organic phase was washed with brine (10 mL), dried with Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-TLC (Petroleum ether: EtOAc = 3: 1) to give tert-butyl 3-(7-bromo-6,8-difluoro-5-methoxy-2-((1-(morpholinomethyl)cyclopropyl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (150 mg, 77.6%) as a yellow solid. LCMS: 654.2, 656.2 (M+H⁺).

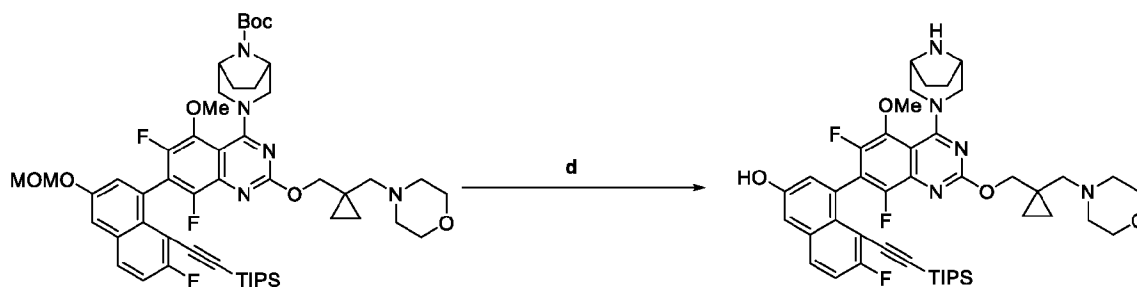
Step 3: Synthesis of tert-butyl (1R,5S)-3-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methoxy-2-((1-(morpholinomethyl)cyclopropyl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00454] To a solution of tert-butyl 3-(7-bromo-6,8-difluoro-5-methoxy-2-((1-(morpholinomethyl)cyclopropyl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (280 mg, 0.43 mmol, 1.0 eq) in Toluene (5 mL) and H₂O (1 mL) was added ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (439 mg, 0.86 mmol, 2.0 eq), K₃PO₄ (182 mg, 0.86 mmol, 2.0 eq), Tris(dibenzylideneacetone)dipalladium (117 mg, 0.13 mmol, 0.3 eq) and 3-(*tert*-butyl)-4-(2,6-dimethoxyphenyl)-2,3-dihydrobenzo[d][1,3]oxaphosphole (22 mg, 0.06 mmol, 0.15 eq). The reaction mixture was heated at MW 120 °C for 2 h. The mixture was diluted with water (15 mL) and extracted with EtOAc (15 mL x 3). The organic phase was washed with brine (10 mL), dried with Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by silica gel

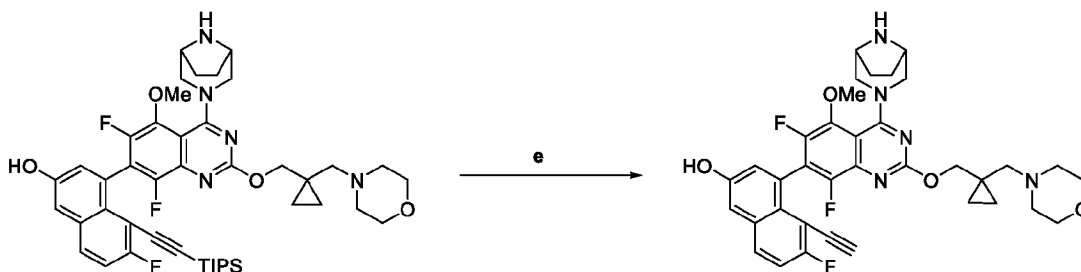
column chromatography (Petroleum ether: EtOAc = 3: 1) to give tert-butyl (1R,5S)-3-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methoxy-2-((1-(morpholinomethyl)cyclopropyl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (160 mg, 39.0%) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 7.78 (dd, J = 9.0, 5.7 Hz, 1H), 7.51 (d, J = 2.4 Hz, 1H), 7.33 – 7.27 (m, 1H), 7.22 – 7.18 (m, 1H), 5.29 (s, 2H), 4.47 – 4.19 (m, 6H), 3.95 (d, J = 2.7 Hz, 3H), 3.70 – 3.66 (m, 3H), 3.52 (s, 4H), 2.48 (s, 4H), 2.44 – 2.41 (m, 2H), 2.15 – 1.74 (m, 5H), 1.50 (s, 9H), 1.29 – 1.21 (m, 4H), 0.90 – 0.82 (m, 18H), 0.71 – 0.65 (m, 4H). LCMS: 960.4 (M+H⁺).

Step 4: Synthesis of 4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-5-methoxy-2-((1-(morpholinomethyl)cyclopropyl)methoxy)quinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol



[00455] To a solution of tert-butyl 3-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methoxy-2-((1-(morpholinomethyl)cyclopropyl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.10 mmol, 1.0 eq) in DCM (2.00 mL) was added HCl/dioxane (4 N, 2 mL) dropwise at 0 °C. Then the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to give 4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-5-methoxy-2-((1-(morpholinomethyl)cyclopropyl)methoxy)quinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (85 mg, crude) as a yellow solid. LCMS: 816.4 (M+H⁺).

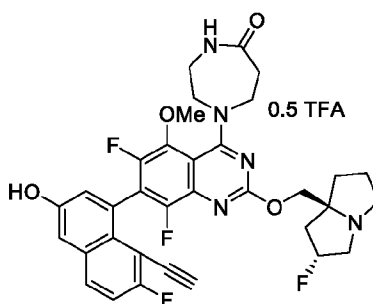
Step 5: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-5-methoxy-2-((1-(morpholinomethyl)cyclopropyl)methoxy)quinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



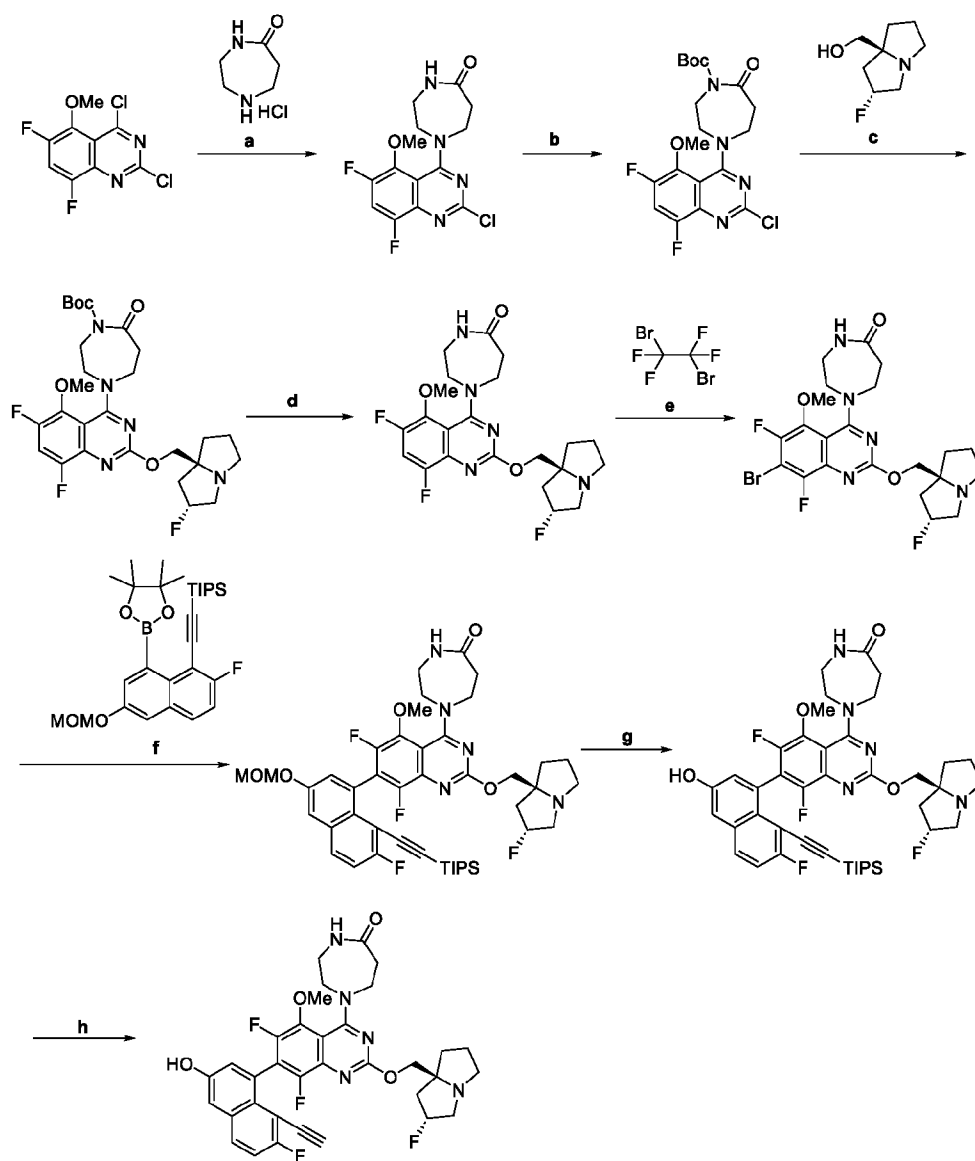
[00456] To a solution of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-5-methoxy-2-((1-(morpholinomethyl)cyclopropyl)methoxy)quinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (85 mg, 0.10 mmol, 1.0 eq) in DMF (3 mL) was added CsF (474 mg, 3.12 mmol, 30.0 eq). Then the reaction mixture was stirred at 40 °C for 15 h. The mixture was diluted with water (7 mL) and extracted with EtOAc (7 mL x 3). The organic phase was washed with water (10 mL x 3) and brine (10 mL), dried with Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC (0.1% FA in H₂O/ACN) to give 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-5-methoxy-2-((1-(morpholinomethyl)cyclopropyl)methoxy)quinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol (22 mg, 33.0% for 2 steps) as a white solid. ¹H NMR (300 MHz, CD₃OD): δ 8.46 (s, 1H), 7.87 (dd, *J* = 9.0, 5.7 Hz, 1H), 7.39 – 7.26 (m, 2H), 7.16 – 7.08 (m, 1H), 4.53 – 4.36 (m, 3H), 4.21 – 4.07 (m, 3H), 3.91 (s, 3H), 3.70 (s, 5H), 3.59 – 3.47 (m, 1H), 3.40 (s, 1H), 2.76 – 2.50 (m, 6H), 2.36 – 2.04 (m, 4H), 0.79 – 0.51 (m, 4H). ¹⁹F NMR (300 MHz, CD₃OD): δ -111.278, -131.757, -137.308. LCMS: 660.2 (M+H⁺).

Example 36

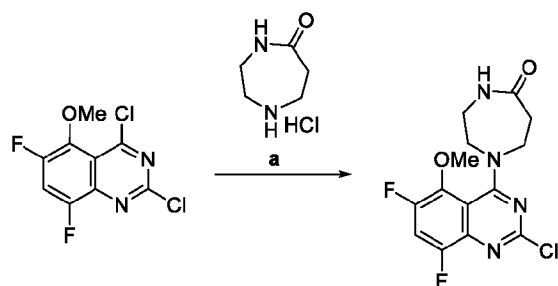
1-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1,4-diazepan-5-one trifluoroacetate



Synthetic scheme:



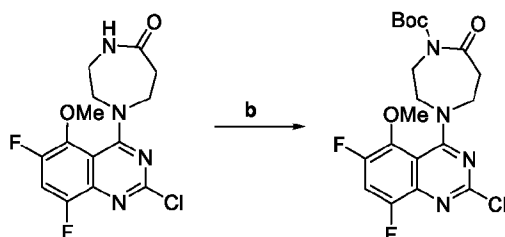
Step 1: Synthesis of 1-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-1,4-diazepan-5-one



[00457] To a solution of compound 2,4-dichloro-6,8-difluoro-5-methoxyquinazoline (500 mg, 1.9 mmol, 1.0 eq) and DIEA (733 mg, 5.68 mmol, 3.0 eq) in DCM (10 mL) was added

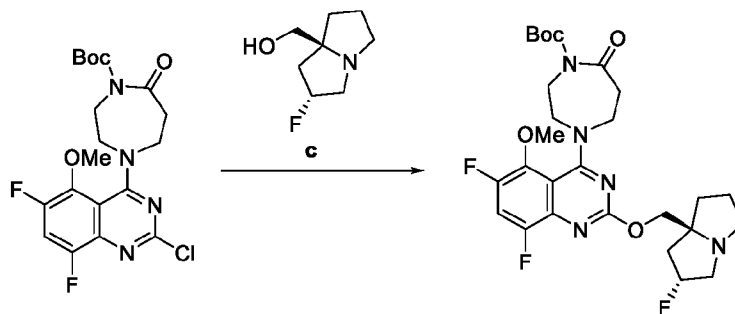
compound 1,4-diazepan-5-one hydrochloride (313 mg, 2.08 mmol, 1.1 eq) at -40 °C. The reaction mixture was stirred at room temperature for 2 h under nitrogen atmosphere. The mixture was quenched with water (30 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with H₂O (20 mL), brine (20 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (DCM: MeOH = 100: 1) to give compound 1-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-1,4-diazepan-5-one (500 mg, 77.2%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 7.38 (t, *J* = 10.0 Hz, 1H), 6.25 (s, 1H), 3.88 (s, 3H), 3.86 – 3.77 (m, 4H), 3.54 – 3.42 (m, 2H), 2.87 – 2.78 (m, 2H). LCMS: 343.0 (M+H⁺).

Step 2: Synthesis of tert-butyl 4-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-7-oxo-1,4-diazepane-1-carboxylate



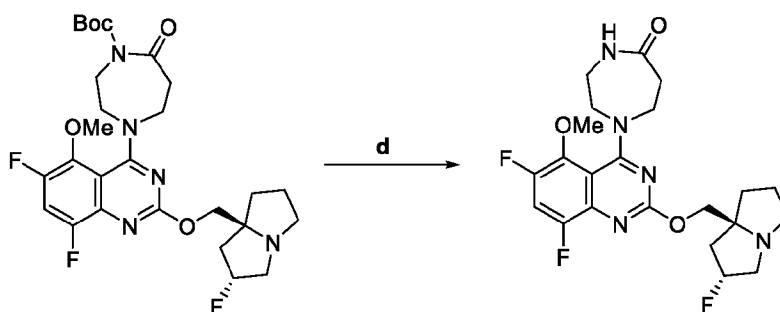
[00458] To a solution of compound 1-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-1,4-diazepan-5-one (500 mg, 1.46 mmol, 1.0 eq) in THF (10 mL) was added Boc₂O (383 mg, 1.75 mmol, 1.2 eq), TEA (444 mg, 4.39 mmol, 3.0 eq) and DMAP (18 mg, 0.15 mmol, 0.1 eq). The reaction mixture was stirred at room temperature for 3 h under nitrogen atmosphere. The mixture was quenched with water (30 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with H₂O (20 mL), brine (20 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (DCM: MeOH = 100: 1) to give compound tert-butyl 4-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-7-oxo-1,4-diazepane-1-carboxylate (500 mg, 77.4%) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 7.38 (dd, *J* = 11.1, 9.3 Hz, 1H), 4.09 – 4.00 (m, 2H), 3.89 (s, 3H), 3.86 – 3.75 (m, 4H), 3.08 – 2.96 (m, 2H), 1.52 (s, 9H). LCMS: 442.8 (M+H⁺).

Step 3: Synthesis of tert-butyl 4-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-7-oxo-1,4-diazepane-1-carboxylate



[00459] To a solution of compound tert-butyl 4-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-7-oxo-1,4-diazepane-1-carboxylate (400 mg, 0.9 mmol, 1.0 eq) in dioxane (8 mL) was added ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (216 mg, 1.36 mmol, 1.5 eq), Cs₂CO₃ (884 mg, 2.7 mmol, 3.0 eq) and SPhos Pd G4 (72 mg, 0.09 mmol, 0.1 eq) at room temperature. The reaction was stirred at 100 °C for 2 h. The mixture was partitioned between EtOAc (20 mL) and water (30 mL). The layers were separated. The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic layers were washed with H₂O (20 mL), brine (20 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (Dichloromethane: Methanol = 60: 1) to give compound tert-butyl 4-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-7-oxo-1,4-diazepane-1-carboxylate (240 mg, 46.9%) as a yellow solid. LCMS: 566.3 (M+H⁺).

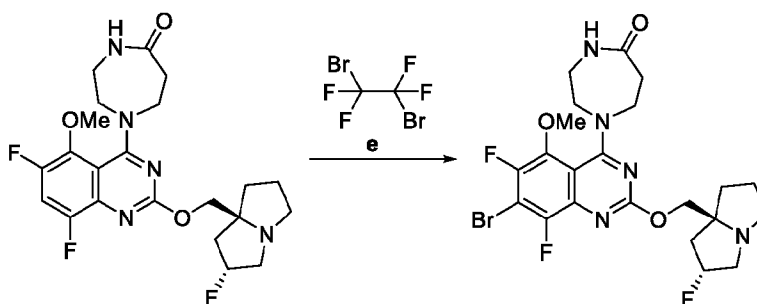
Step 4: Synthesis of 1-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1,4-diazepan-5-one



[00460] To a solution of compound tert-butyl 4-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-7-oxo-1,4-diazepane-1-carboxylate (300 mg, 0.53 mmol, 1.0 eq) in DCM (3 mL) was added TFA (3 mL). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was evaporated to dryness. The residue was quenched with sodium bicarbonate aqueous solution (30 mL) and extracted with

ethyl acetate (20 mL x 3). The combined organic layers were washed with H₂O (20 mL), brine (20 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (Dichloromethane: Methanol = 80: 1) to give compound 1-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1,4-diazepan-5-one (240 mg, 97.2%) as a yellow solid. LCMS: 466.2 (M+H⁺).

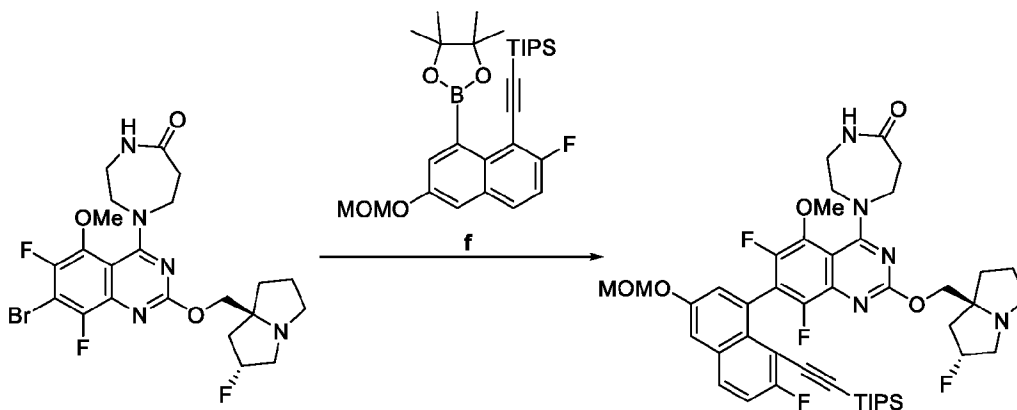
Step 5: Synthesis of 1-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1,4-diazepan-5-one



[00461] To a solution of compound 1-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1,4-diazepan-5-one (140 mg, 0.3 mmol, 1.0 eq) in THF (3 mL) was added LDA (2.0 M, 0.3 mL, 0.6 mmol, 2.0 eq) dropwise at -65 °C. The reaction mixture was stirred at -65 °C for 0.5 h under nitrogen atmosphere.

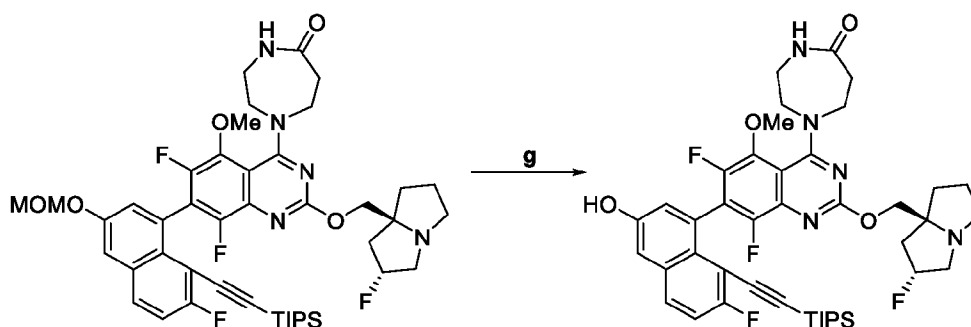
Compound 1,2-dibromo-1,1,2,2-tetrafluoroethane (155 mg, 0.6 mmol, 2.0 eq) was added to the mixture. The reaction mixture was stirred at -65 °C for 0.5 h under nitrogen atmosphere. The reaction mixture was quenched with ammonium chloride aqueous solution (30 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with H₂O (20 mL), brine (20 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (Dichloromethane: Methanol = 80: 1) to give compound 1-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1,4-diazepan-5-one (70 mg, 42.8%) as a yellow solid. LCMS: 544.0, 546.1 (M+H⁺).

Step 6: Synthesis of 1-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1,4-diazepan-5-one



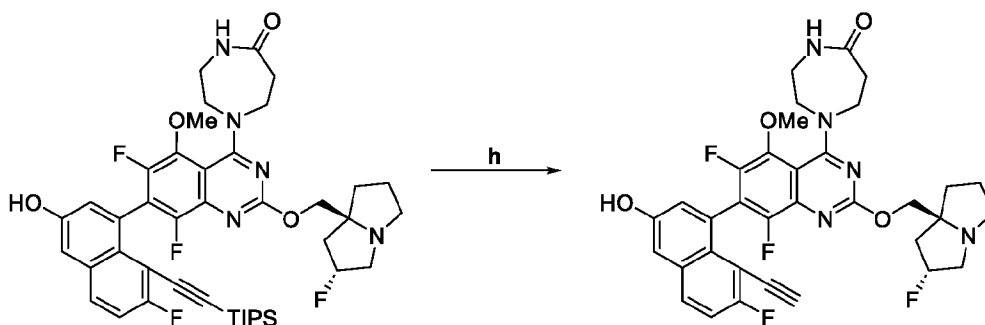
[00462] To a solution of compound 1-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1,4-diazepan-5-one (70 mg, 0.13 mmol, 1.0 eq) in PhMe (2 mL) and H₂O (0.4 mL) was added compound ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (132 mg, 0.26 mmol, 2.0 eq), K₃PO₄ (82 mg, 0.39 mmol, 3.0 eq), rac-BI-DIME (6 mg, 0.019 mmol, 0.15 eq) and Pd₂(dba)₃ (35 mg, 0.039 mmol, 0.3 eq). The reaction mixture was heated under microwave irradiation at 120 °C for 1 h under nitrogen atmosphere. The reaction mixture was poured into water (10 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with H₂O (10 mL), brine (10 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (Dichloromethane: Methanol = 60: 1) to give compound 1-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1,4-diazepan-5-one (35 mg, 32.0%) as a yellow solid. LCMS: 850.3 (M+H⁺).

Step 7: Synthesis of 1-(6,8-difluoro-7-(7-fluoro-3-hydroxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1,4-diazepan-5-one



[00463] To a solution of compound 1-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1,4-diazepan-5-one (85 mg, 0.1 mmol, 1.0 eq) in DCM (1 mL) was added TFA (1 mL). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure to give a crude compound 1-(6,8-difluoro-7-(7-fluoro-3-hydroxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1,4-diazepan-5-one (60 mg, crude) as a yellow solid. LCMS: 806.3 (M+H⁺).

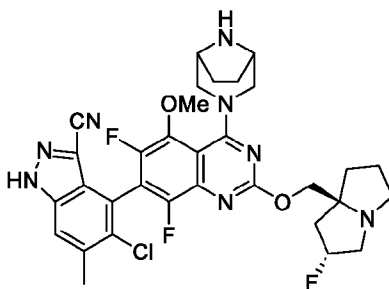
Step 8: Synthesis of 1-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1,4-diazepan-5-one trifluoroacetate (1:0.5)



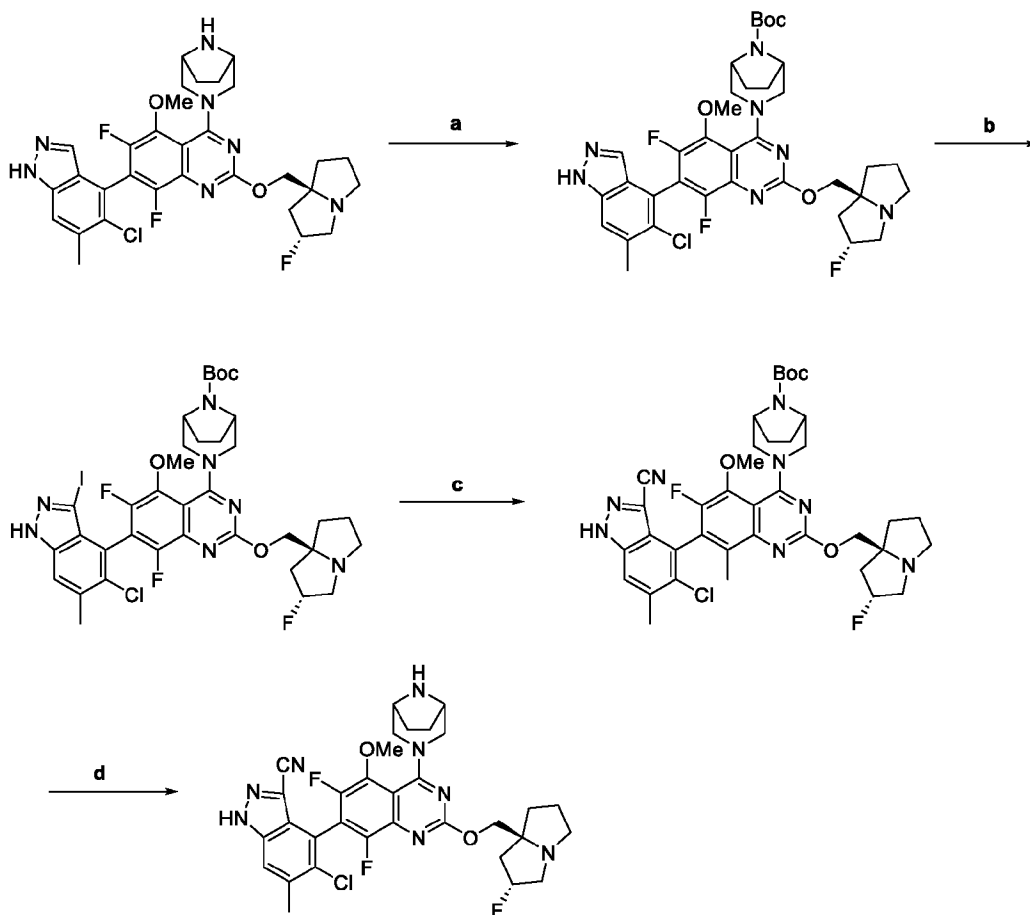
[00464] To a solution of compound 1-(6,8-difluoro-7-(7-fluoro-3-hydroxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1,4-diazepan-5-one (60 mg, crude) in DMF (1 mL) was added CsF (113 mg, 0.75 mmol, 10.0 eq) at room temperature. The reaction was stirred at 40 °C for 1 h. The mixture was concentrated to give a crude. The crude was purified by Prep-HPLC (acetonitrile with 0.1% FA in water, 10% to 60%) to give 1-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1,4-diazepan-5-one 2,2,2-trifluoroacetate (1:0.5) (31.5 mg, 41.2% for two steps) as a white solid. ¹H NMR (400 MHz, CD₃OD): δ 7.87 (dd, *J* = 8.8, 5.6 Hz, 1H), 7.41 – 7.27 (m, 2H), 7.21 – 7.05 (m, 1H), 6.32 – 6.17 (m, 2H), 5.74 – 5.65 (m, 1H), 5.48 (d, *J* = 52.8, 1H), 4.66 – 4.43 (m, 2H), 4.10 (s, 3H), 3.93 – 3.55 (m, 7H), 3.52 (s, 1H), 3.37 – 3.31 (m, 2H), 2.65 – 2.45 (m, 2H), 2.40 – 2.31 (m, 1H), 2.30 – 2.17 (m, 2H), 2.13 – 1.98 (m, 1H). ¹⁹F NMR (400 MHz, CD₃OD): δ -76.920, -111.255, -134.138, -136.595, -174.168. LCMS: 650.2 (M+H⁺).

Example 37

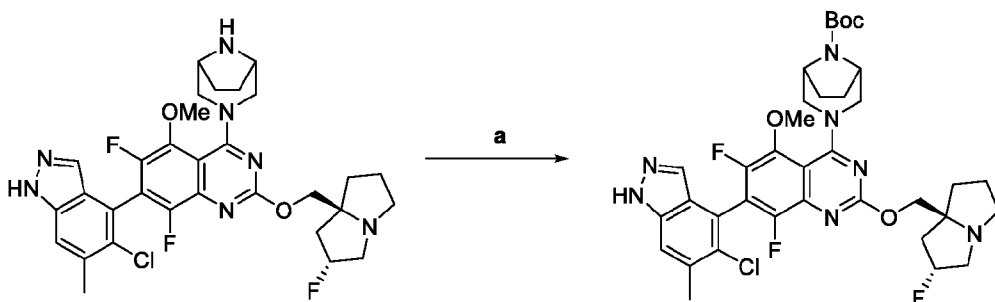
4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-chloro-6-methyl-1H-indazole-3-carbonitrile formate



Synthetic scheme:

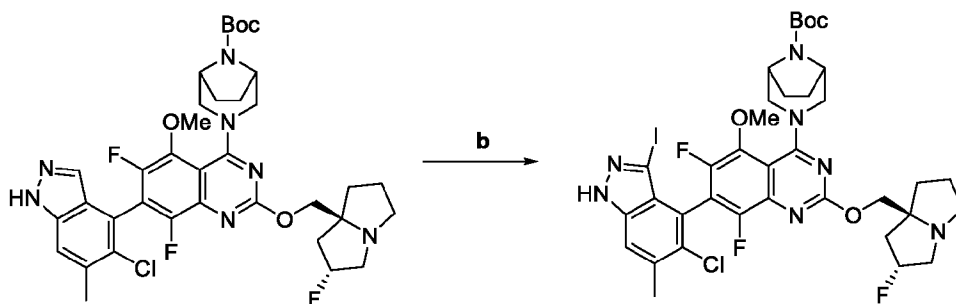


Step 1: Synthesis of tert-butyl 3-(7-(5-chloro-6-methyl-1H-indazol-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



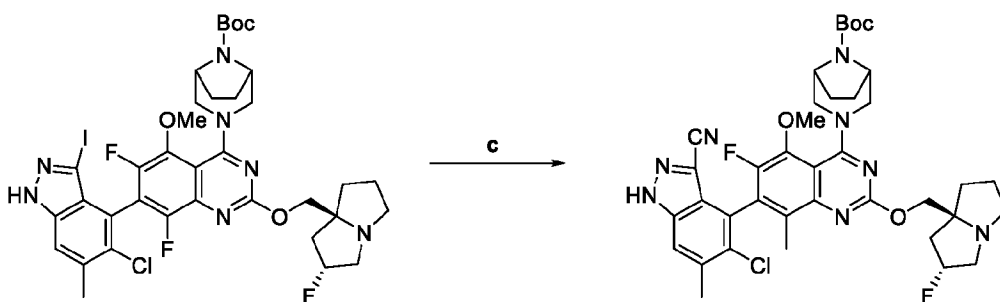
[00465] To a solution of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(5-chloro-6-methyl-1H-indazol-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline (700 mg, 1.1 mmol, 1.0 eq) in THF (7.0 mL) was added Boc_2O (240 mg, 1.1 mmol, 1.0 eq), NaHCO_3 (277 mg, 3.3 mmol, 3.0 eq) and H_2O (7.0 mL) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1 h. The mixture was diluted with water (20 mL) and extracted with DCM (20 mL x 3). The organic phase was washed with brine (20 mL), dried with Na_2SO_4 , filtered and concentrated to give a crude. The crude was purified by silica gel column chromatography (DCM : MeOH = 40 : 1) to give tert-butyl (1R,5S)-3-(7-(5-chloro-6-methyl-1H-indazol-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (350 mg, 43.1%) as a yellow solid. LCMS: 728.2 ($\text{M}+\text{H}^+$).

Step 2: Synthesis of tert-butyl 3-(7-(5-chloro-3-iodo-6-methyl-1H-indazol-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00466] To a solution of tert-butyl 3-(7-(5-chloro-6-methyl-1H-indazol-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (350 mg, 0.48 mmol, 1.0 eq) in DMF (5.0 mL) was added KOH (81 mg 1.44 mmol, 3.0 eq) and I₂ (488 mg, 1.92 mmol, 4.0 eq) under nitrogen atmosphere. Then the reaction mixture was stirred at room temperature for 15 h. The mixture was diluted with water (10 mL) and extracted with DCM (10 mL x 3). The organic phase was washed with water (10 mL x 3) and brine (10 mL), dried with Na₂SO₄, filtered and concentrated to give a crude. The crude was purified by silica gel column chromatography (DCM : MeOH = 30 : 1) to give tert-butyl 3-(7-(5-chloro-3-iodo-6-methyl-1H-indazol-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (140 mg, 34.1%) as a yellow solid. LCMS: 853.5 (M+H⁺).

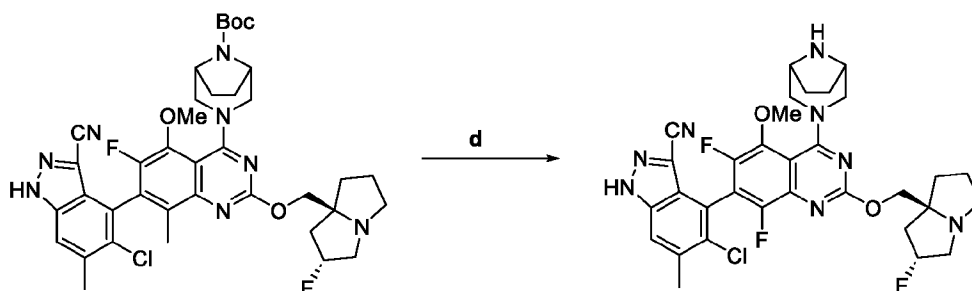
Step 3: Synthesis of tert-butyl 3-(7-(5-chloro-3-cyano-6-methyl-1H-indazol-4-yl)-6-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-8-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00467] To a solution of tert-butyl 3-(7-(5-chloro-3-iodo-6-methyl-1H-indazol-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (140 mg, 0.16 mmol, 1.0 eq) in DMAc (4.0 mL) was added Zn(CN)₂ (67 mg, 0.57 mmol, 3.0 eq) and Pd(PPh₃)₄ (66 mg, 0.06 mmol, 0.3 eq) at room temperature. The reaction mixture was heated under microwave irradiation at 160 °C for 30 min. The mixture was diluted with water (10 mL) and extracted with DCM (10 mL x 3). The organic phase was washed with water (10 mL x 3) and brine (10 mL), dried with Na₂SO₄, filtered and concentrated to give a crude. The crude was purified by silica gel column chromatography (DCM : MeOH = 20 : 1) to give tert-butyl 3-(7-(5-chloro-3-cyano-6-methyl-1H-indazol-4-yl)-6-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-

yl)methoxy)-5-methoxy-8-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (24 mg, 19.4%) as a yellow solid. LCMS: 753.3 (M+H⁺).

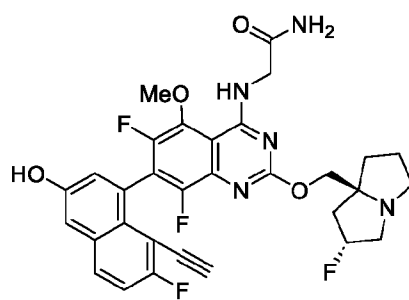
Step 4: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-chloro-6-methyl-1H-indazole-3-carbonitrile formate (1:1)



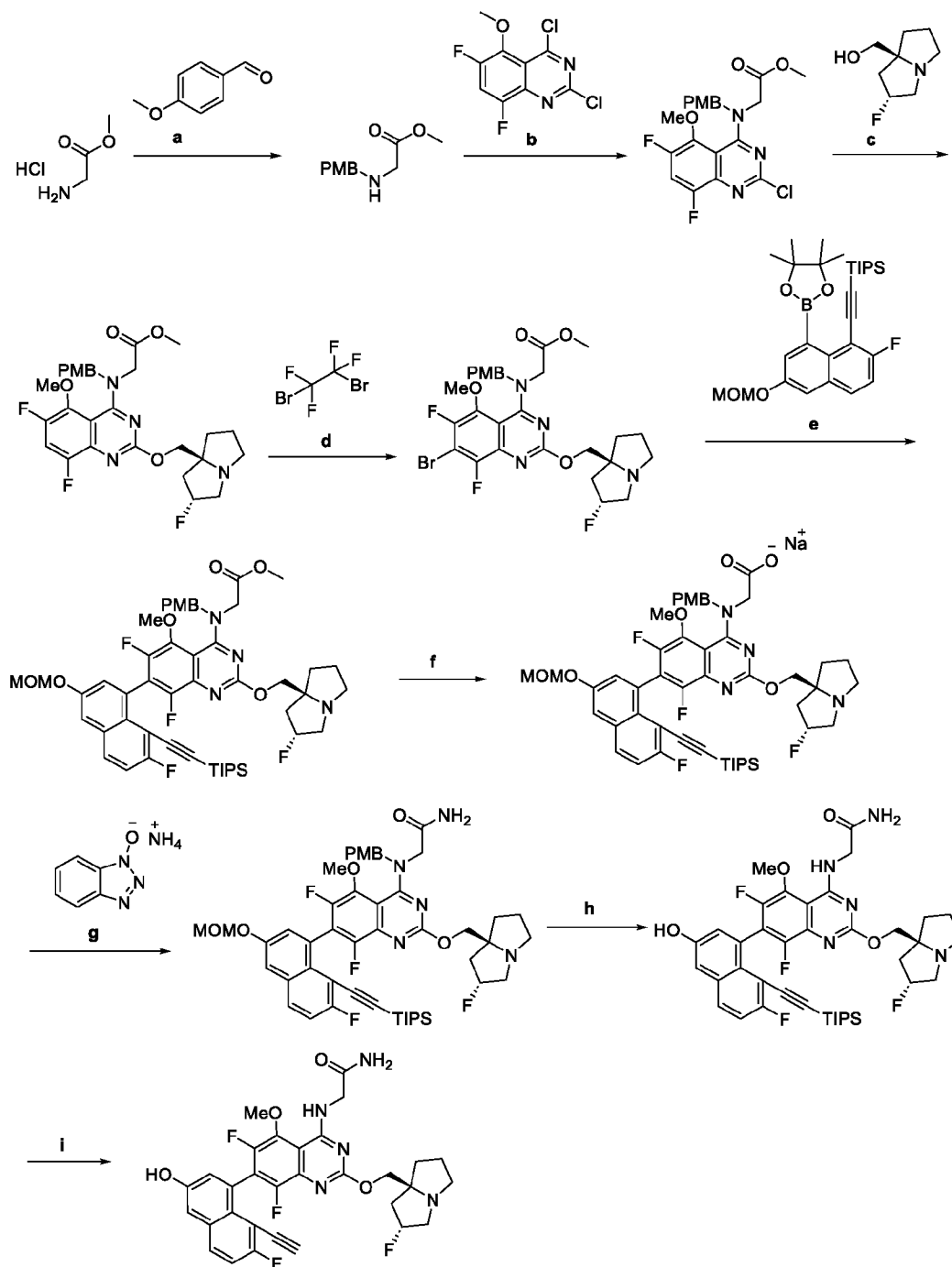
[00468] To a solution of tert-butyl 3-(7-(5-chloro-3-cyano-6-methyl-1H-indazol-4-yl)-6-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-8-methylquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (24 mg, 0.03 mmol, 1.0 eq) in DCM (1.0 mL) was added HCl in dioxane (0.5 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to give a crude. The mixture was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 10% to 60%) to give 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-chloro-6-methyl-1H-indazole-3-carbonitrile formate (1:1) (4.1 mg, 19.7%) as white solid. ¹H NMR (400 MHz, CD₃OD): δ 8.52 (s, 1H), 7.84 (s, 1H), 5.41 (d, *J* = 52.4, 1H), 4.53 – 4.27 (m, 4H), 3.99 – 3.95 (m, 2H), 3.95 – 3.91 (m, 3H), 3.69 – 3.46 (m, 5H), 3.25 – 3.12 (m, 1H), 2.64 (s, 3H), 2.55 – 2.23 (m, 3H), 2.18 – 2.09 (m, 2H), 2.06 – 1.91 (m, 5H). ¹⁹F NMR (400 MHz, CD₃OD): δ -131.3039, -138.409, -173.856. LCMS: 653.2 (M+H⁺).

Example 38

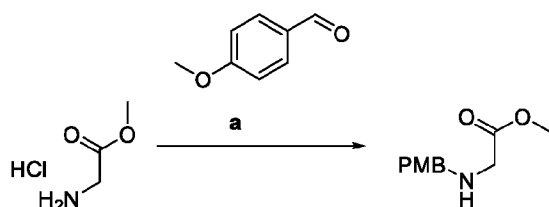
2-((7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)amino)acetamide 2,2,2-trifluoroacetate



Synthetic scheme:

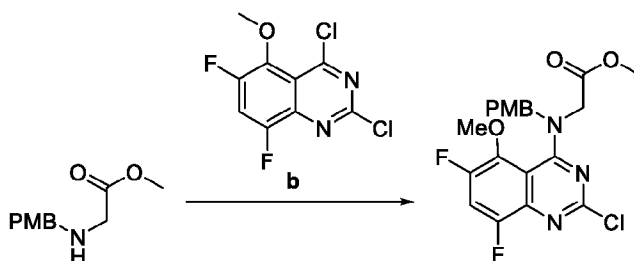


Step 1: Synthesis of methyl (4-methoxybenzyl)glycinate



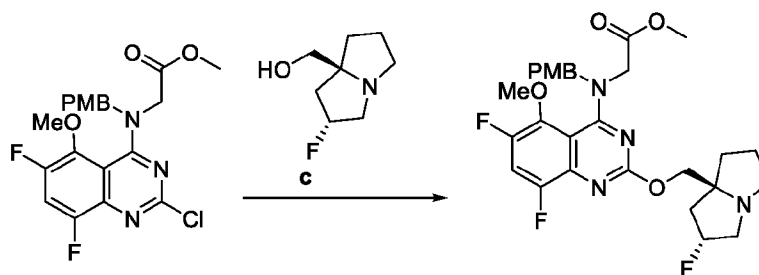
[00469] To a solution of compound methyl glycinate hydrochloride (1.0 g, 8.0 mmol, 1.0 eq) in MeOH (20 mL) was added compound 4-methoxybenzaldehyde (1.1 g, 8.0 mmol, 1.0 eq) and TEA (1.6 g, 16.0 mmol, 2.0 eq). The reaction was stirred at room temperature for 15 h. NaBH₄ (605 mg, 16.0 mmol, 2.0 eq) was added to the mixture. The reaction was stirred at room temperature for 2 h. The mixture was quenched with ammonium chloride aqueous solution (0.5 mL) and dried with Na₂SO₄. The mixture was filtered and the filtrate was concentrated to give crude compound methyl (4-methoxybenzyl)glycinate (2.2 g, crude) as a white solid. LCMS: 210.1 (M+H⁺).

Step 2: methyl N-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-N-(4-methoxybenzyl)glycinate



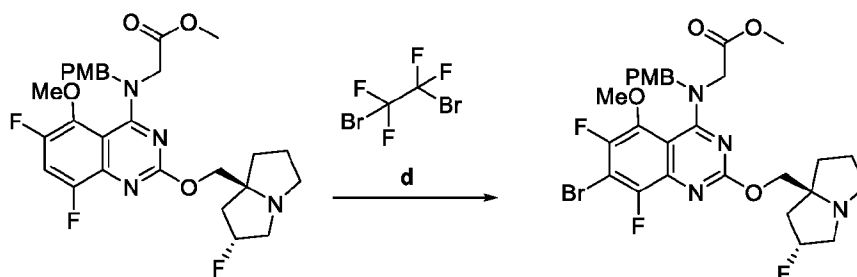
[00470] To a solution of compound 2,4-dichloro-6,8-difluoro-5-methoxyquinazoline (500 mg, 1.9 mmol, 1.0 eq) and DIEA (733 mg, 5.68 mmol, 3.0 eq) in DCM (10 mL) was added compound methyl (4-methoxybenzyl)glycinate (436 mg, 2.08 mmol, 1.1 eq) at -40 °C. The reaction mixture was stirred at room temperature for 2 h under nitrogen atmosphere. The mixture was quenched with water (30 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with H₂O (20 mL), brine (20 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (DCM: MeOH = 100: 1) to give compound methyl N-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-N-(4-methoxybenzyl)glycinate (400 mg, 48.3%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 7.39 – 7.31 (m, 1H), 7.25 – 7.19 (m, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.87 (s, 2H), 4.11 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H). LCMS: 438.1 (M+H⁺).

Step 3: Synthesis of methyl N-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-(4-methoxybenzyl)glycinate



[00471] To a solution of compound methyl N-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-N-(4-methoxybenzyl)glycinate (400 mg, 0.92 mmol, 1.0 eq) in dioxane (8 mL) was added ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (218 mg, 1.37 mmol, 1.5 eq), Cs₂CO₃ (894 mg, 2.7 mmol, 3.0 eq) and RuPhos Pd G3 (77 mg, 0.092 mmol, 0.1 eq) at room temperature. The reaction was stirred at 100 °C for 3 h. The mixture was partitioned between EtOAc (20 mL) and water (30 mL). The layers were separated. The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic layers were washed with H₂O (20 mL), brine (20 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (Dichloromethane: Methanol = 60: 1) to give compound methyl N-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-(4-methoxybenzyl)glycinate (320 mg, 62.4%) as a yellow solid. LCMS: 561.2 (M+H⁺).

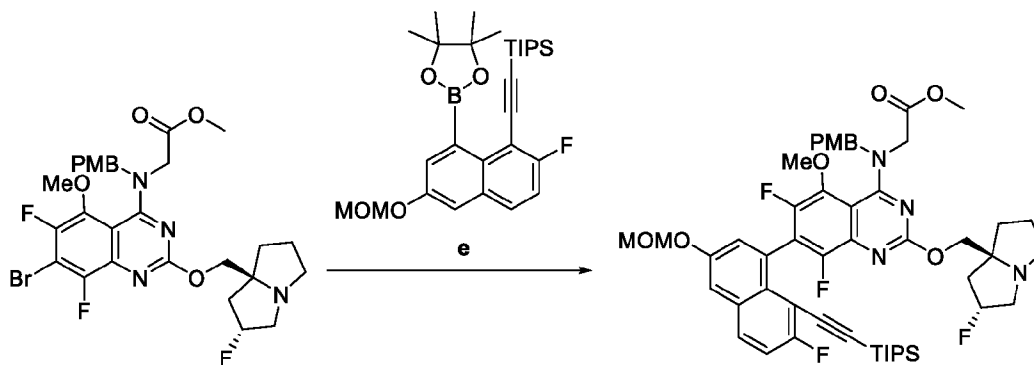
Step 4: Synthesis of methyl N-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-(4-methoxybenzyl)glycinate



[00472] To a solution of compound methyl N-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-(4-methoxybenzyl)glycinate (300 mg, 0.54 mmol, 1.0 eq) in THF (5 mL) was added LDA (2.0 M, 0.55 mL, 1.07 mmol, 2.0 eq) dropwise at -78 °C. The reaction mixture was stirred at -78 °C for 0.5 h under nitrogen atmosphere. Compound 1,2-dibromo-1,1,2,2-tetrafluoroethane (276 mg, 1.07 mmol, 2.0 eq) was added to the mixture. The reaction mixture was stirred at -78 °C for 0.5 h under nitrogen

atmosphere. The reaction mixture was quenched with ammonium chloride aqueous solution (30 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with H₂O (20 mL), brine (20 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (Dichloromethane: Methanol = 80: 1) to give compound methyl N-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-(4-methoxybenzyl)glycinate (184 mg, 53.8%) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 7.20 – 7.11 (m, 2H), 6.83 (d, *J* = 8.7, 2H), 5.23 (d, *J* = 52.2, 1H), 4.81 (s, 2H), 4.25 – 4.12 (m, 1H), 4.08 (s, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 3.74 (s, 3H), 3.37 – 3.05 (m, 3H), 3.05 – 2.82 (m, 1H), 2.31 – 2.19 (m, 1H), 2.19 – 2.03 (m, 2H), 2.02 – 1.78 (m, 3H). LCMS: 639.1, 641.1 (M+H⁺).

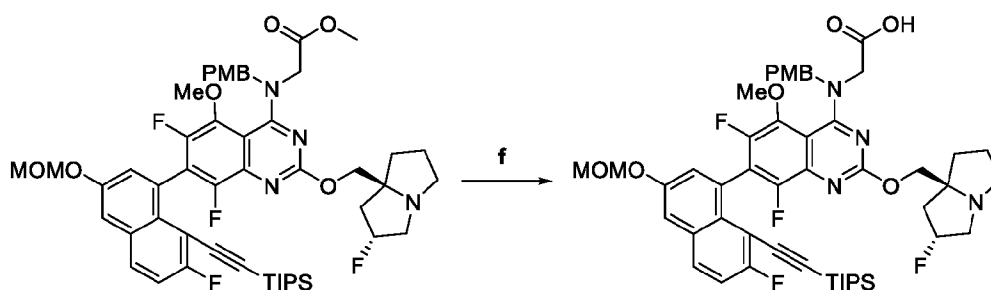
Step 5: Synthesis of N-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-(4-methoxybenzyl)glycinate



[00473] To a solution of compound methyl N-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-(4-methoxybenzyl)glycinate (150 mg, 0.24 mmol, 1.0 eq) in PhMe (4 mL) and H₂O (0.8 mL) was added compound ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (241 mg, 0.47 mmol, 2.0 eq), K₃PO₄ (150 mg, 0.71 mmol, 3.0 eq), rac-BI-DIME (12 mg, 0.035 mmol, 0.15 eq) and Pd₂(dba)₃ (65 mg, 0.071 mmol, 0.3 eq). The reaction mixture was heated under microwave irradiation at 120 °C for 1 h under nitrogen atmosphere. The reaction mixture was poured into water (10 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with H₂O (10 mL), brine (10 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (Dichloromethane: Methanol = 60: 1) to give

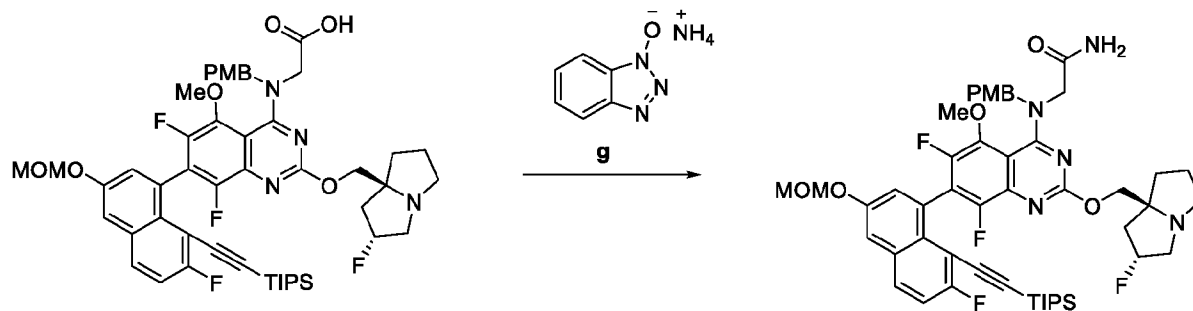
compound N-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-(4-methoxybenzyl)glycinate (130 mg, 58.6%) as a yellow solid. LCMS: 945.3 ($M+H^+$).

Step 6: Synthesis of compound sodium N-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-(4-methoxybenzyl)glycinate



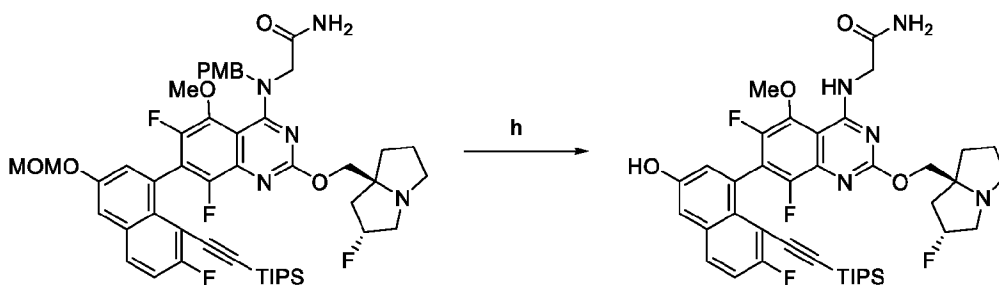
[00474] To a solution of compound N-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-(4-methoxybenzyl)glycinate (100 mg, 0.11 mmol, 1.0 eq) in THF (1.0 mL) was added MeOH (1.0 mL), H₂O (1.0 mL) and NaOH (6 mg, 0.16 mmol, 1.5 eq). The reaction mixture was stirred at room temperature for 2 h. The mixture was quenched with water (20 mL) and extracted with EtOAc (10 mL x 2). The combined organic layers were washed with H₂O (10 mL), brine (10 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by Prep-TLC (DCM: MeOH = 8: 1) to give compound N-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-(4-methoxybenzyl)glycine (100 mg, 99.2%) as a white solid. LCMS: 931.3 ($M+H^+$).

Step 7: Synthesis of compound 2-(((6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)(4-methoxybenzyl)amino)acetamide



[00475] To a solution of compound N-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-(4-methoxybenzyl)glycine (100 mg, 0.11 mmol, 1.0 eq) in DMF (2 mL) was added compound ammonium 1H-benzo[d][1,2,3]triazol-1-olate (48 mg, 0.32 mmol, 3.0 eq) and EDCI (60 mg, 0.32 mmol, 3.0 eq). Then the reaction mixture was stirred at room temperature for 4 h. The mixture was added with water (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic phases were washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by Prep-TLC (DCM: MeOH = 10: 1) to give compound 2-(((6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)(4-methoxybenzyl)amino)acetamide (50 mg, 51.2%) as a yellow solid. LCMS: 930.3 (M+H⁺).

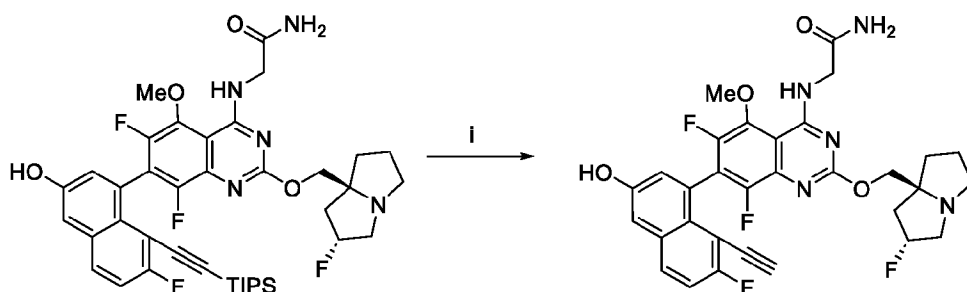
Step 8: Synthesis of 2-(((6,8-difluoro-7-(7-fluoro-3-hydroxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)amino)acetamide



[00476] To a solution of compound 2-(((6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)(4-methoxybenzyl)amino)acetamide (50 mg, 0.054 mmol, 1.0 eq) in DCM (1 mL) was added TFA (1 mL). The reaction mixture was stirred at

room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to give a crude compound 2-((6,8-difluoro-7-(7-fluoro-3-hydroxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)amino)acetamide (39 mg, crude) as a yellow solid. LCMS: 766.3 ($M+H^+$).

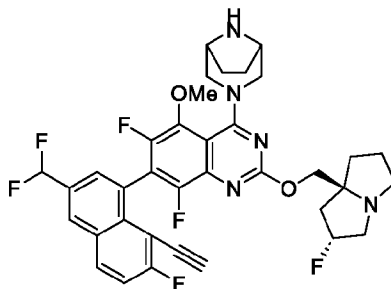
Step 9: Synthesis of 2-((7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)amino)acetamide 2,2,2-trifluoroacetate (1:0.7)



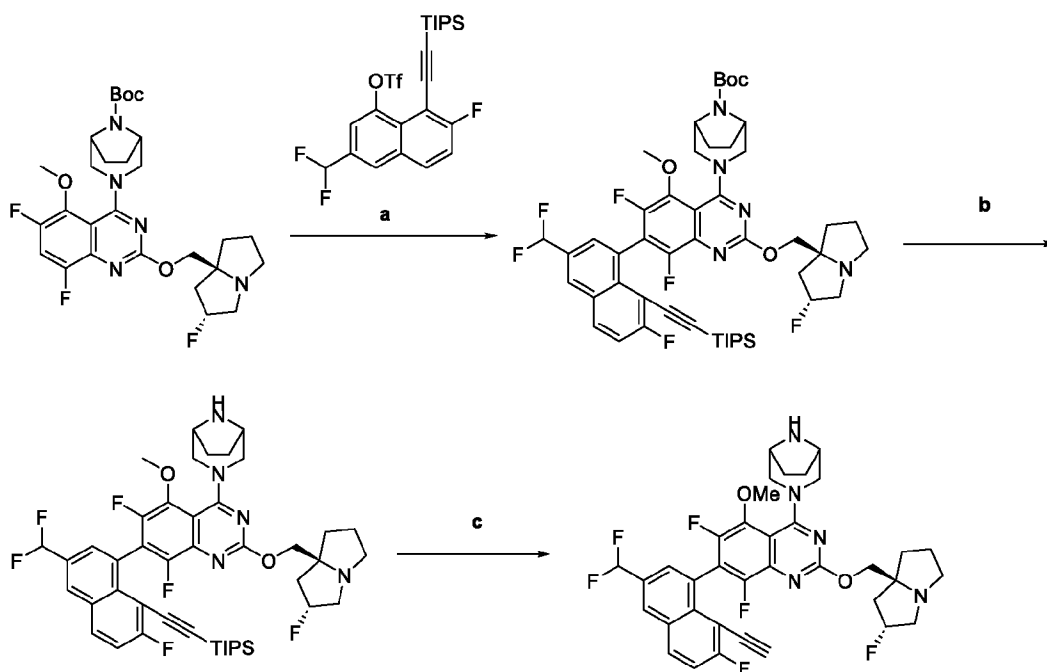
[00477] To a solution of compound 2-((6,8-difluoro-7-(7-fluoro-3-hydroxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)amino)acetamide (60 mg, crude) in DMF (1 mL) was added CsF (88 mg, 0.54 mmol, 10.0 eq) at room temperature. The reaction was stirred at 40 °C for 1 h. The mixture was concentrated to give a crude. The crude was purified by Prep-HPLC (acetonitrile with 0.1% FA in water, 10% to 50%) to give 2-((7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)amino)acetamide 2,2,2-trifluoroacetate (1:0.7) (9.1 mg, 23.4% for two steps) as a white solid. ^1H NMR (300 MHz, CD_3OD): δ 7.87 (dd, J = 9.0, 5.7 Hz, 1H), 7.41 – 7.27 (m, 2H), 7.14 (d, J = 2.4 Hz, 1H), 5.51 (d, J = 52.8, 1H), 4.67 – 4.56 (m, 2H), 4.41 – 4.25 (m, 2H), 4.18 (d, J = 2.1 Hz, 3H), 3.90 – 3.74 (m, 3H), 3.56 – 3.48 (m, 1H), 3.47 – 3.35 (m, 1H), 2.65 – 2.56 (m, 1H), 2.55 – 2.48 (m, 1H), 2.42 – 2.22 (m, 3H), 2.16 – 1.99 (m, 1H). ^{19}F NMR (300 MHz, CD_3OD): δ -76.920, -111.237, -134.379, -136.044, -174.360. LCMS: 610.3 ($M+H^+$).

Example 39

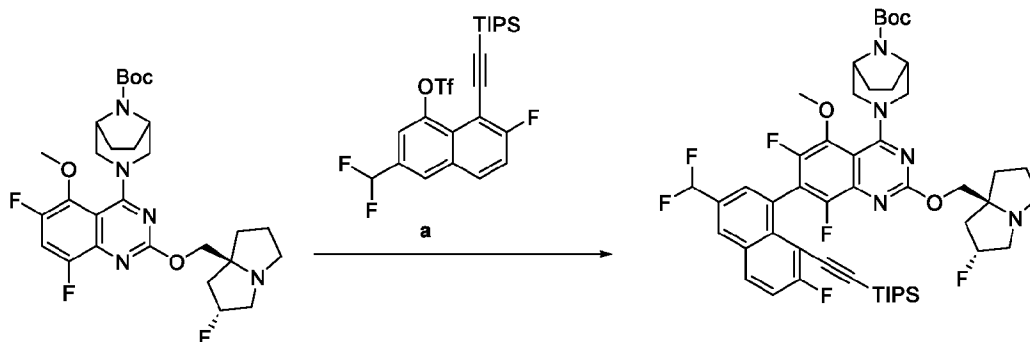
4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(3-(difluoromethyl)-8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline formate (1:0.2)



Synthetic scheme:

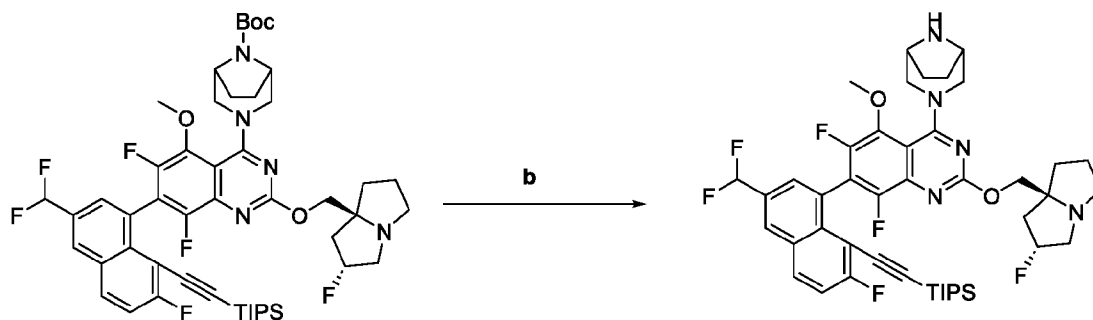


Step 1: Synthesis of tert-butyl 3-(7-(3-(difluoromethyl)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00478] To a solution of 3-(difluoromethyl)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate (140 mg, 0.25 mmol, 1.0 eq) in THF (2 mL) was added $(\text{TMP})_2\text{Zn} \cdot \text{MgCl}_2 \cdot \text{LiCl}$ (2.0 mL, 1.1 mmol, 4.4 eq) dropwise. The reaction mixture was stirred at 50 °C for 2 h. To the mixture was added a solution of tert-butyl (1R,5S)-3-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (104 mg, 0.19 mmol, 0.8 eq) and CPhos Pd G3 (21 mg, 0.02 mmol, 0.10 eq) in dioxane (2 mL). The reaction mixture was stirred at 80 °C for 12 h. The mixture was filtered and the filtrate was concentrated to give a residue. The residue was purified by silica gel column chromatography (DCM : MeOH = 40 : 1) to give tert-butyl (1R,5S)-3-(7-(3-(difluoromethyl)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (140 mg, 55.9%) as a yellow solid. LCMS: 938.1 ($\text{M} + \text{H}^+$).

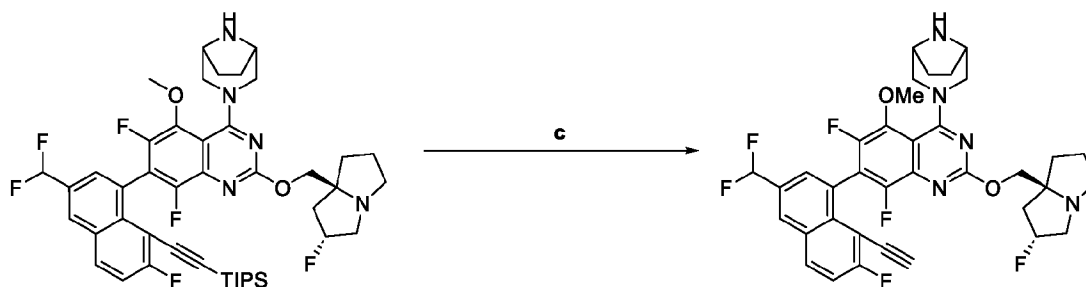
Step 2: Synthesis of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(3-(difluoromethyl)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline



[00479] To a solution of tert-butyl 3-(7-(3-(difluoromethyl)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-

pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.11 mmol, 1.0 eq) in DCM (2 mL) was added HCl/Dioxane (0.6 mL, 2.4 mmol, 20.0 eq) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h under N₂. The mixture was concentrated to give 4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(3-(difluoromethyl)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline (120 mg, crude) as a yellow solid. LCMS: 838.0 (M+H⁺).

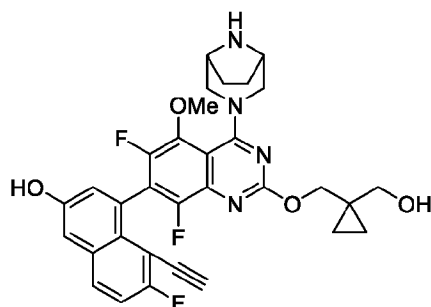
Step 3: Synthesis of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(3-(difluoromethyl)-8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline formate (1:0.2)



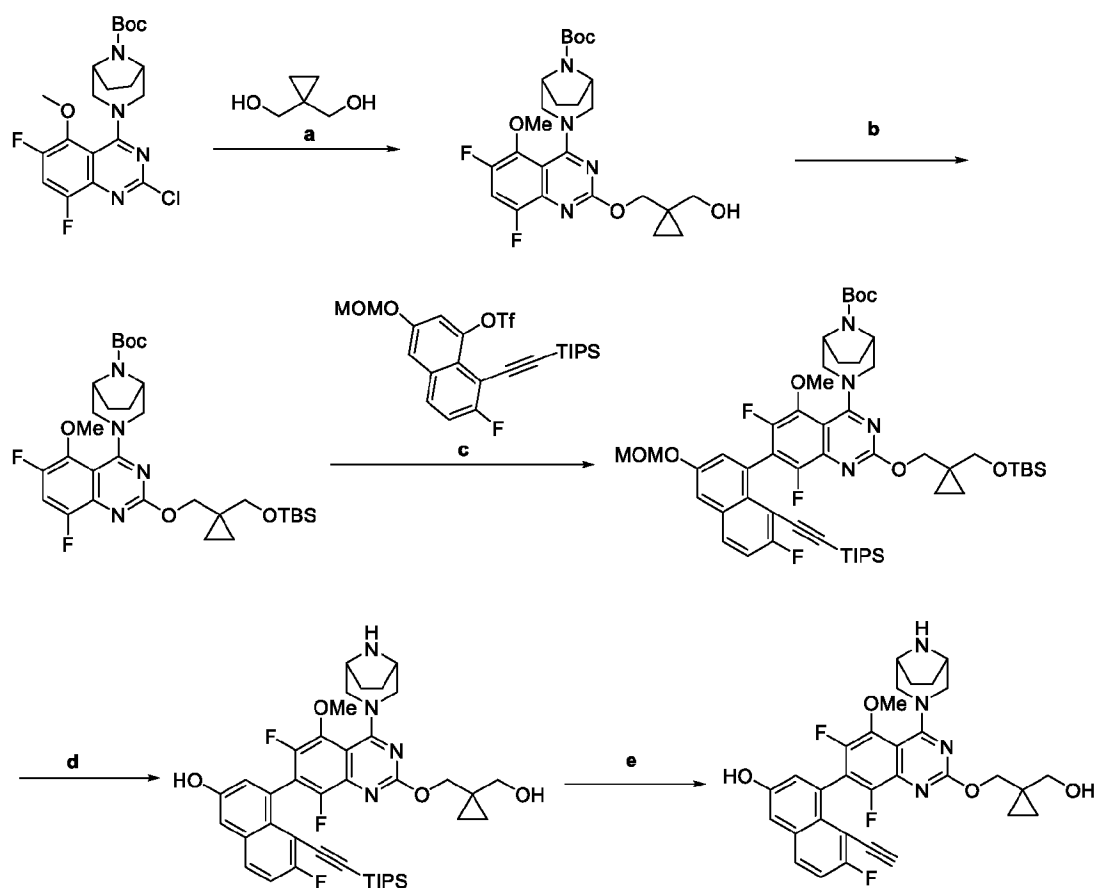
[00480] To a solution of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(3-(difluoromethyl)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline (120 mg, 0.14 mmol, 1.0 eq) in DMF (1.5 mL) was added CsF (425.3 mg, 2.8 mmol, 20.0 eq). The mixture was stirred at 50 °C for 3 h. The mixture was filtered off and the filtrate was concentrated to give a crude. The crude was purified by Prep-HPLC (ACN with 0.1% FA in water, 15% to 50%) to give 4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(3-(difluoromethyl)-8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline formate (1:0.2) (17 mg, 22.1%, two steps yield) as a white solid. ¹H NMR (400 MHz, CD₃OD): δ 8.33 (brs, 0.2H), 8.25 – 8.21 (m, 1H), 7.70 (s, 1H), 7.55 (t, *J* = 8.8 Hz, 1H), 7.01 (t, *J* = 55.6 Hz, 1H), 5.33 (d, *J* = 53.6 Hz, 1H), 4.91 – 4.89 (m, 2H), 4.47 (s, 1H), 4.35 – 4.22 (m, 2H), 4.04 (s, 1H), 3.87 (s, 3H), 3.78 – 3.71 (m, 2H), 3.67 – 3.61 (m, 1H), 3.55 – 3.51 (m, 1H), 3.44 – 3.37 (m, 2H), 3.07 – 3.03 (m, 1H), 2.47 – 2.14 (m, 3H), 2.05 – 1.99 (m, 3H), 1.88 – 1.79 (m, 4H). ¹⁹F NMR (400 MHz, CD₃OD): δ -104.058, -112.561, -132.624, -138.539, -173.763. LCMS: 682.2 (M+H⁺).

Example 40

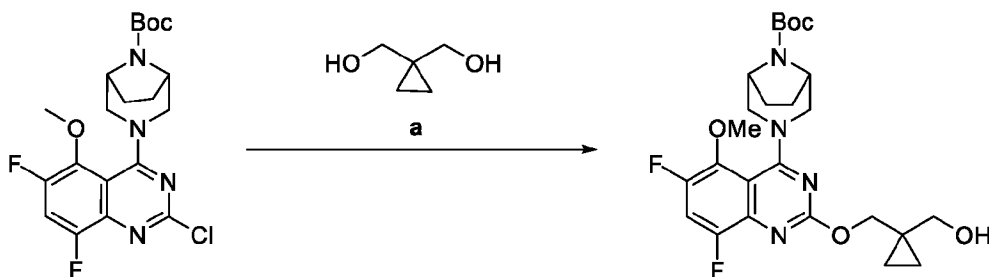
4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-((1-(hydroxymethyl)cyclopropyl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate



Synthetic scheme:

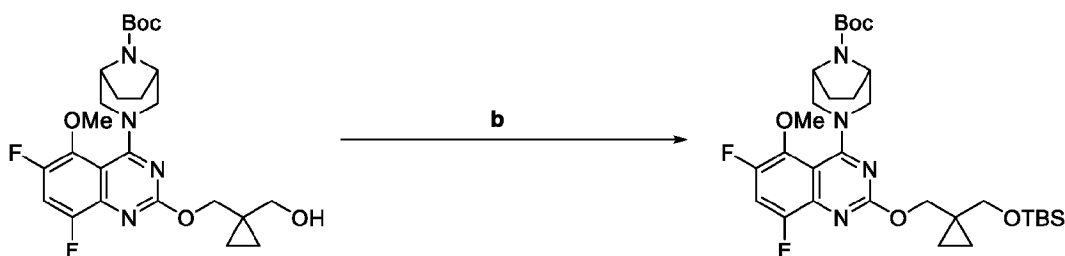


Step 1: Synthesis of tert-butyl 3-(6,8-difluoro-2-((1-(hydroxymethyl)cyclopropyl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00481] To a solution of tert-butyl 3-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.7 g, 3.9 mmol, 1.0 eq) in DMF (15 mL) and THF (15 mL) was added cyclopropane-1,1-diyl dimethanol (394 mg, 3.9 mmol, 1.0 eq) and Cs_2CO_3 (3.8 g, 11.6 mmol, 3.0 eq) at room temperature. The reaction mixture was stirred at 40 °C for 3 h under N_2 . The mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with H_2O (15 mL x 3), brine (15 mL), dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by silica gel column chromatography (DCM/MeOH=15:1) to give tert-butyl 3-(6,8-difluoro-2-((1-(hydroxymethyl)cyclopropyl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.9 g, 97.4%) as a white solid. ^1H NMR (300 MHz, CDCl_3): δ 7.29 (t, J = 9.9 Hz, 1H), 4.43 (s, 2H), 4.40 – 4.01 (m, 4H), 3.82 (s, 3H), 3.53 – 3.33 (m, 4H), 1.98 – 1.62 (m, 4H), 1.49 (s, 9H), 0.73 – 0.53 (m, 4H). LCMS: 507.2 ($\text{M}+\text{H}^+$).

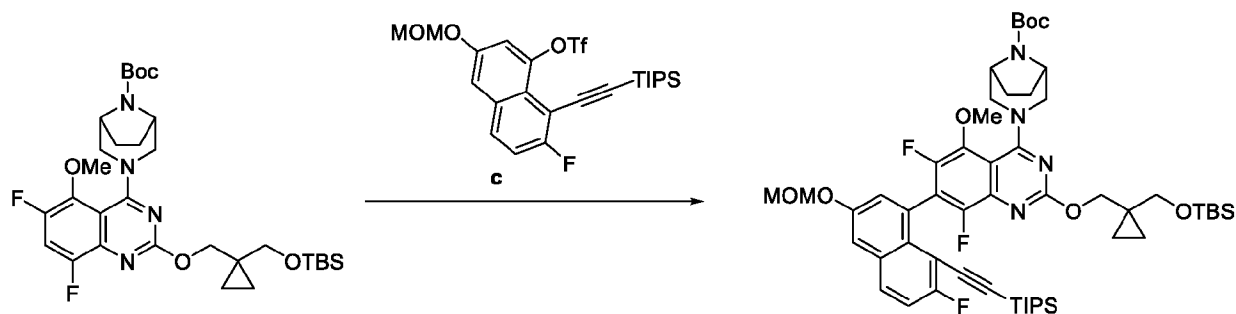
Step 2: Synthesis of tert-butyl 3-(2-((1-(((tert-butyldimethylsilyl)oxy)methyl)cyclopropyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00482] To a mixture of tert-butyl 3-(6,8-difluoro-2-((1-(hydroxymethyl)cyclopropyl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.9 g, 3.8 mmol, 1.0 eq) in DMF (20 mL) was added Imidazole (511 mg, 7.5 mmol, 2.0 eq) and TBSCl (678 mg, 4.5 mmol, 1.2 eq). The mixture was stirred at room temperature for 3 h. The mixture was diluted with H_2O (30 mL) and extracted

with EtOAc (30 mL x 3). The combined organic layers were washed with H₂O (20 mL x 3), brine (20 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (Petroleum ether / EtOAc = 5:1) to give tert-butyl 3-(2-((1-(((tert-butyldimethylsilyl)oxy)methyl)cyclopropyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.5 g, 64.4%) as a white solid. ¹H NMR (300 MHz, CDCl₃): δ 7.24 (t, *J* = 10.5 Hz, 1H), 4.40 – 3.99 (m, 6H), 3.79 (s, 3H), 3.67 (s, 2H), 3.42 (d, *J* = 12.9 Hz, 2H), 1.95 – 1.68 (m, 4H), 1.49 (s, 9H), 0.85 (s, 9H), 0.66 – 0.53 (m, 4H), -0.01 (s, 6H).

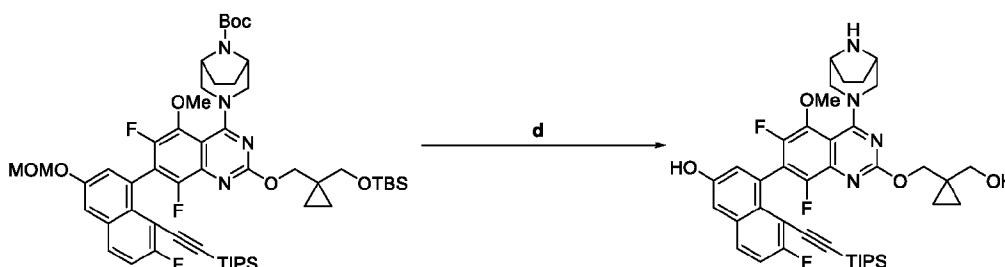
Step 3: Synthesis of tert-butyl 3-(2-((1-(((tert-butyldimethylsilyl)oxy) methyl) cyclopropyl)methoxy)-6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl) ethynyl)naphthalen-1-yl)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00483] To a solution of tert-butyl 3-(2-((1-(((tert-butyldimethylsilyl)oxy)methyl)cyclopropyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (500 mg, 0.81 mmol, 1.0 eq) in THF (5 mL) was added 0.4 M (TMP)₂Zn·MgCl₂·LiCl (8.9 mL, 3.5 mmol, 4.4 eq). The reaction mixture was stirred at 70 °C for 2 h under N₂. To the reaction mixture was added a solution of 7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate (600 mg, 1.1 mmol, 1.3 eq) and CPhos Pd G4 (66 mg, 0.08 mmol, 0.1 eq) in dioxane (6 mL). The reaction mixture was stirred at 80 °C for 12 h. The reaction was quenched with aq. NaHCO₃ solution (10 mL). The mixture was filtered through a Celite pad, and washed with EtOAc (5 mL). The filtrate was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated to give a crude. The crude was purified by silica gel column chromatography (Petroleum ether / EtOAc = 5:1) to give tert-butyl 3-(2-((1-(((tert-butyldimethylsilyl)oxy) methyl) cyclopropyl)methoxy)-6,8-difluoro-7-

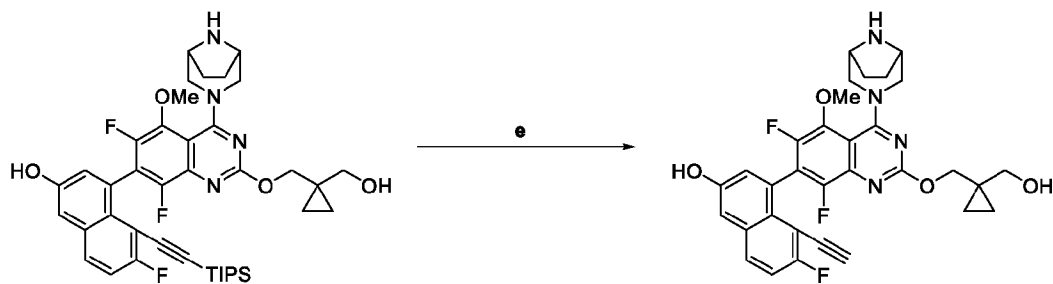
(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo [3.2.1]octane-8-carboxylate (100 mg, 12.3%) as a colorless oil. ¹H NMR (300 MHz, methanol-*d*₄): δ 7.89 (dd, *J* = 9.3, 5.7 Hz, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.34 (t, *J* = 8.7 Hz, 1H), 7.16 (d, *J* = 2.7 Hz, 1H), 5.28 (s, 2H), 4.65 – 4.18 (m, 6H), 3.95 (d, *J* = 3.0 Hz, 3H), 3.82 (s, 1H), 3.65 (s, 2H), 3.57 – 3.40 (m, 4H), 2.18 – 1.78 (m, 4H), 1.51 – 1.37 (m, 12H), 1.17 – 0.98 (m, 4H), 0.95 – 0.75 (m, 27H), 0.01 (s, 6H).

Step 4: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-((1-(hydroxymethyl)cyclopropyl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol



[00484] To a solution of tert-butyl 3-(2-((1-(((tert-butyl)dimethylsilyl)oxy)methyl)cyclopropyl)methoxy)-6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.10 mmol, 1.0 eq) in DCM (1 mL) was added HCl in dioxane (0.3 mL, 1.2 mmol, 12.1 eq) at room temperature. The mixture was stirred at room temperature for 2 h. The reaction was adjusted to pH~8 with NH₃-H₂O. The mixture was concentrated to give a residue. The residue was re-dissolved in DCM / MeOH (10:1, 5 mL). The filtrate was collected by filtration and concentrated to give 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-((1-(hydroxymethyl)cyclopropyl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (85 mg, crude) as a yellow solid. LCMS: 747.2 (M + H⁺).

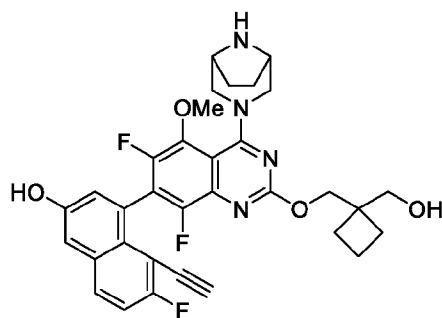
Step 5: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-((1-(hydroxymethyl)cyclopropyl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate (1:0.2)



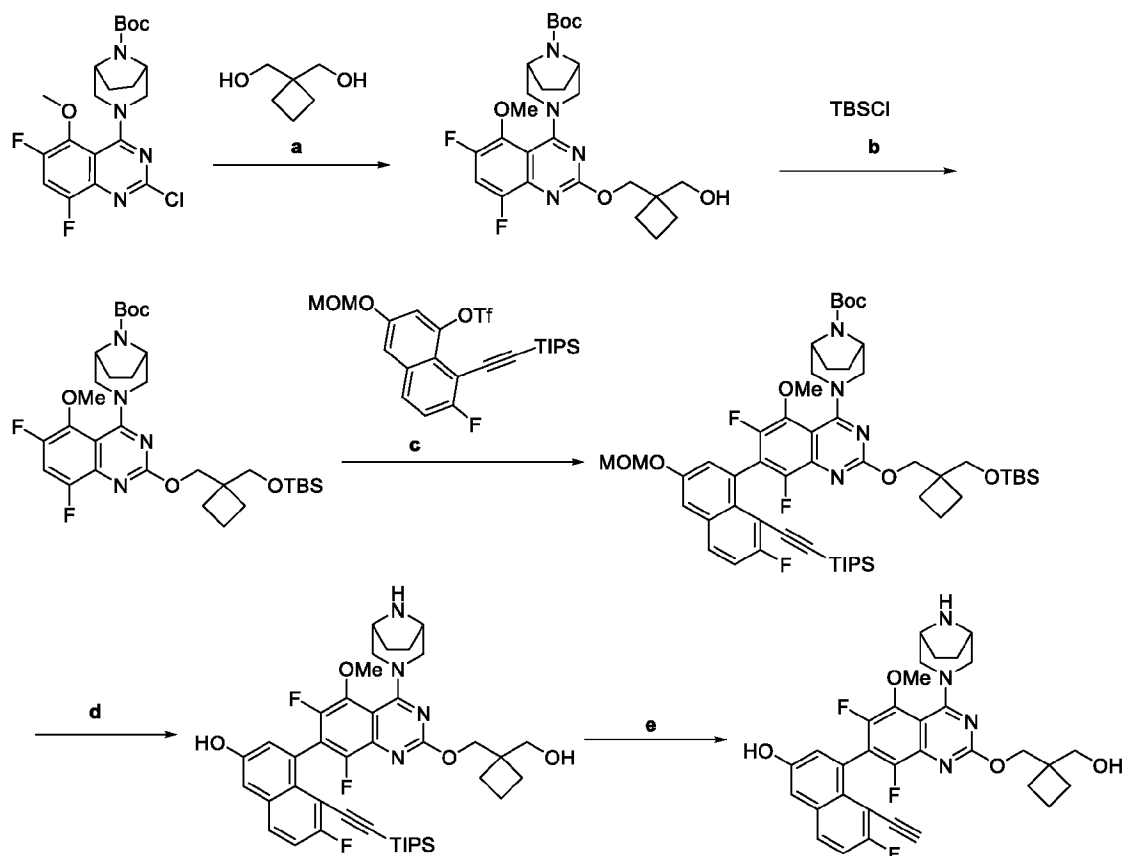
[00485] To a mixture of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-((1-(hydroxymethyl)cyclopropyl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl) ethynyl)naphthalen-2-ol (85 mg, 0.11 mmol, 1.0 eq) in DMF (2 mL) was added CsF (259 mg, 1.7 mmol, 15.0 eq). The mixture was stirred at 45 °C for 2 h. The filtrate was collected by filtration and concentrated to give a crude. The crude was purified by Prep-HPLC (ACN with 0.1% FA in water, 5% to 45%) to give 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-((1-(hydroxymethyl)cyclopropyl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate (1:0.2) (10 mg, 17.0% for two steps) as a white solid. ¹H NMR (400 MHz, CD₃OD): δ 7.86 (dd, J = 8.8, 6.0 Hz, 1H), 7.42 – 7.28 (m, 2H), 7.13 (s, 1H), 4.55 – 4.35 (m, 3H), 4.18 – 4.02 (m, 1H), 4.00 – 3.80 (m, 5H), 3.72 – 3.60 (m, 1H), 3.58 – 3.54 (m, 2H), 3.50 – 3.40 (m, 1H), 3.39 (s, 1H), 2.28 – 1.82 (m, 4H), 0.72 – 0.52 (m, 4H). ¹⁹F NMR (400 MHz, CD₃OD): δ -111.340, -132.245, -137.948. LCMS: 591.2 (M+H⁺).

Example 41

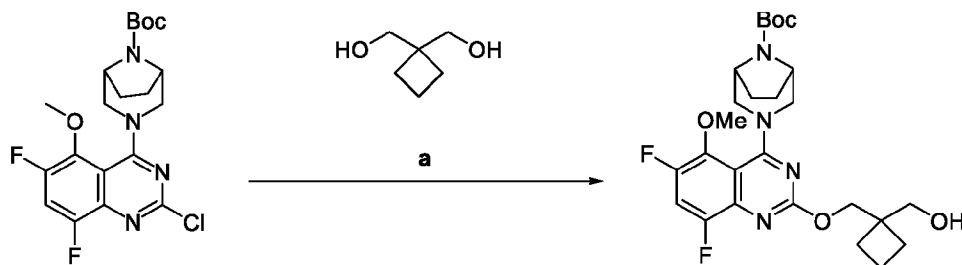
4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-((1-(hydroxymethyl)cyclobutyl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



Synthetic scheme:



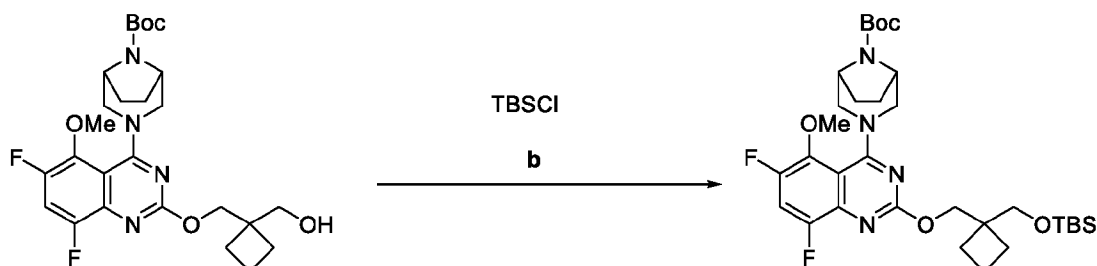
Step 1: Synthesis of tert-butyl 3-(6,8-difluoro-2-((1-(hydroxymethyl)cyclobutyl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00486] To a solution of cyclobutane-1,1-diylmethanol (554 mg, 4.77 mmol, 3.0 eq) in THF (7 mL) and DMF (7 mL) was added Cs₂CO₃ (1.55 g, 4.77 mmol, 3.0 eq), tert-butyl 3-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (700 mg, 1.59 mmol, 1.0 eq) at room temperature. The reaction mixture was stirred at 40 °C for 2 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give a residue. The crude product was purified by column chromatography (Petroleum ether: EtOAc = 10: 1) to give tert-butyl 3-(6,8-difluoro-2-((1-(hydroxymethyl)cyclobutyl)methoxy)-5-

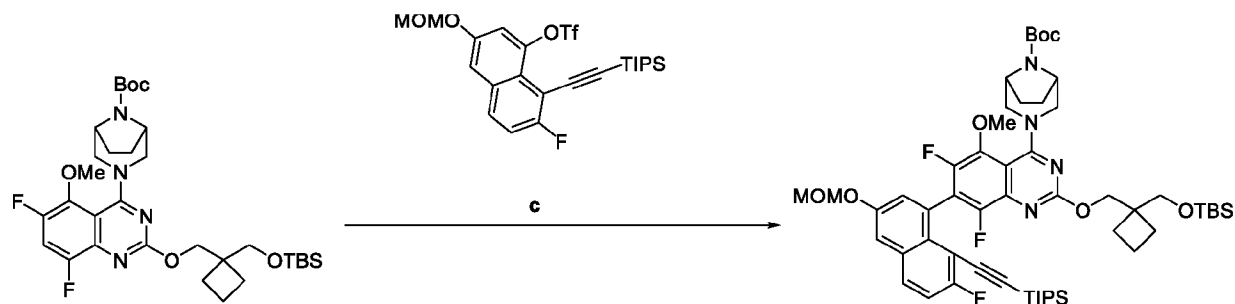
methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (760 mg, 91.8%) as a yellow liquid. LCMS: m/z 521.3 ($M+H^+$).

Step 2: Synthesis of tert-butyl 3-(2-((1-(((tert-butyldimethylsilyl)oxy)methyl)cyclobutyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



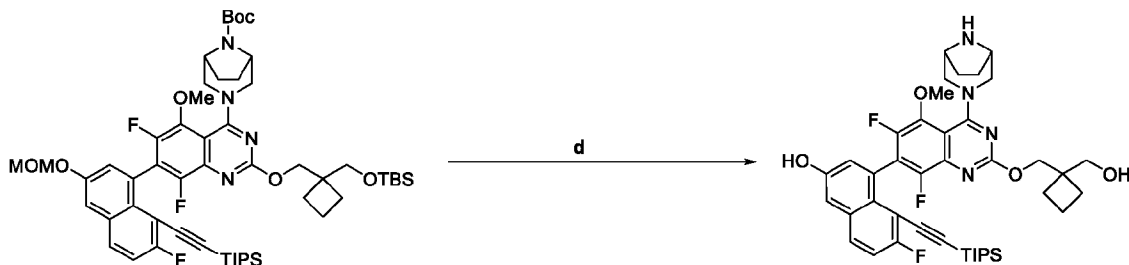
[00487] To a solution of tert-butyl 3-(6,8-difluoro-2-((1-(hydroxymethyl)cyclobutyl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (760 mg, 1.46 mmol, 1.0 eq) in DMF (8.8 mL) was added Imidazole (199 mg, 2.92 mmol, 2.0 eq) and TBSCl (264 mg, 1.75 mmol, 1.2 eq) at room temperature. The reaction mixture was stirred at room temperature for 3 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated to give a residue. The crude product was purified by column chromatography (Petroleum ether: EtOAc = 30: 1) to give tert-butyl 3-(2-((1-(((tert-butyldimethylsilyl)oxy)methyl)cyclobutyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (720 mg, 77.6%) as a colourless liquid. LCMS: m/z 635.3 ($M+H^+$).

Step 3: Synthesis of tert-butyl 3-(2-((1-(((tert-butyldimethylsilyl)oxy)methyl)cyclobutyl)methoxy)-6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00488] To a solution of tert-butyl 3-(2-((1-(((tert-butyldimethylsilyl)oxy)methyl)cyclobutyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (120 mg, 0.19 mmol, 1.0 eq) in THF (2.4 mL) was added (TMP)₂ZnMgCl₂LiCl (0.4M, 2.85 mL, 1.14 mmol, 6.0 eq) under N₂ atmosphere. The reaction mixture was stirred at 50 °C for 2 h. Then 7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate (123 mg, 0.23 mmol, 1.2 eq), CPhos Pd G3 (15 mg, 0.019 mmol, 0.1 eq) and 1,4-dioxane (2.4 mL) were added to the reaction mixture. The reaction mixture was stirred at 80 °C for overnight. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give a residue. The crude product was purified by prep-TLC (Petroleum ether: EtOAc = 5: 1) to give tert-butyl 3-(2-((1-(((tert-butyldimethylsilyl)oxy)methyl)cyclobutyl)methoxy)-6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (80 mg, 51.9%) as a yellow liquid. LCMS: m/z 453.1 (M-TBS)/2+H⁺).

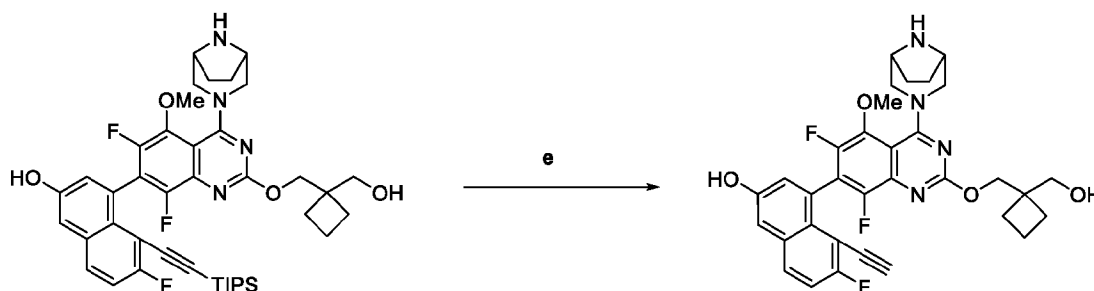
Step 4: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-((1-(hydroxymethyl)cyclobutyl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol



[00489] To a solution of tert-butyl 3-(2-((1-(((tert-butyldimethylsilyl)oxy)methyl)cyclobutyl)methoxy)-6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (60 mg, 0.059 mmol, 1.0 eq) in ACN (2.4 mL) was added HCl/Dioxane (0.47 mL) at 0 °C under N₂ atmosphere. The reaction mixture was stirred at 0 °C for 2 h. Then the reaction mixture was concentrated in vacuo to give 4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-((1-(hydroxymethyl)cyclobutyl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (crude) as a

yellow liquid, which was used directly for the next step without any further purification. LCMS: m/z 761.3 ($M+H^+$).

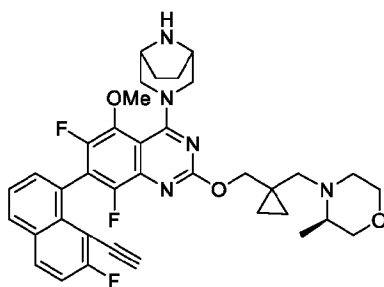
Step 5: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-((1-(hydroxymethyl)cyclobutyl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



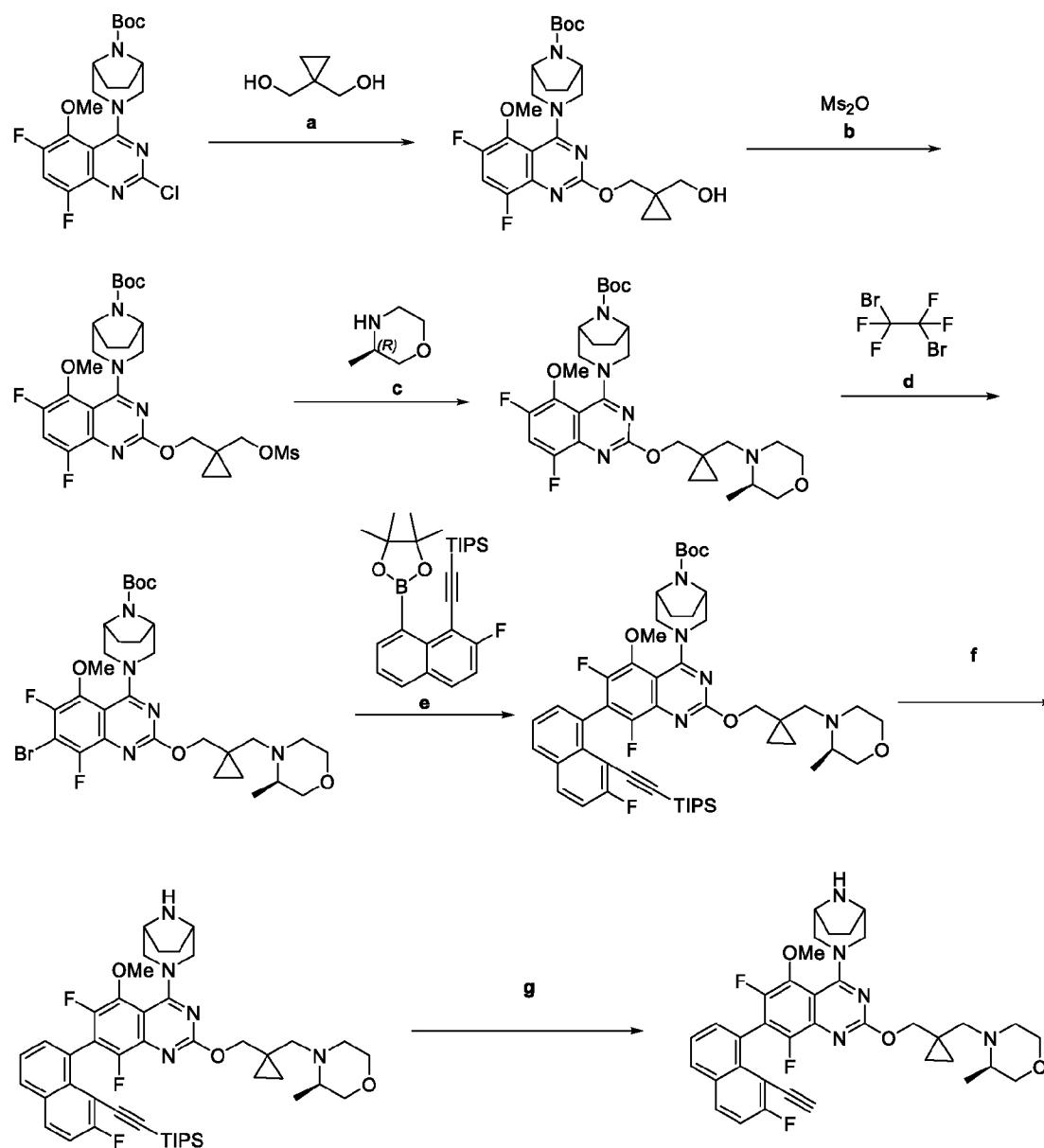
[00490] To a solution of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-((1-(hydroxymethyl)cyclobutyl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((trisopropylsilyl)ethynyl)naphthalen-2-ol (crude) in DMF (6.0 mL) was added CsF (134 mg, 0.885 mmol, 15.0 eq). The reaction mixture was stirred at 40 °C for 6 h. Then the reaction mixture was filtered, and the filtrate was purified by Prep-HPLC (acetonitrile with 0.1% FA in water, 20% to 65%) to give 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-((1-(hydroxymethyl)cyclobutyl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol (1.0 mg, with 1.3 FA salt, 2.6% for two steps) as a white solid. ^1H NMR (400 MHz, CD_3OD): δ 8.50 (s, 1H), 7.90-7.80 (m, 1H), 7.37 – 7.27 (m, 2H), 7.12 (d, J = 2.4 Hz, 1H), 5.35-5.25 (m, 1H), 4.57 (s, 1H), 4.50-4.30 (m, 3H), 4.20-3.90 (m, 3H), 3.90 (s, 3H), 3.67 (s, 2H), 3.65-3.55 (m, 1H), 3.52 – 3.42 (m, 2H), 2.09 – 1.82 (m, 10H). LCMS: m/z 605.2 ($M+H^+$).

Example 42

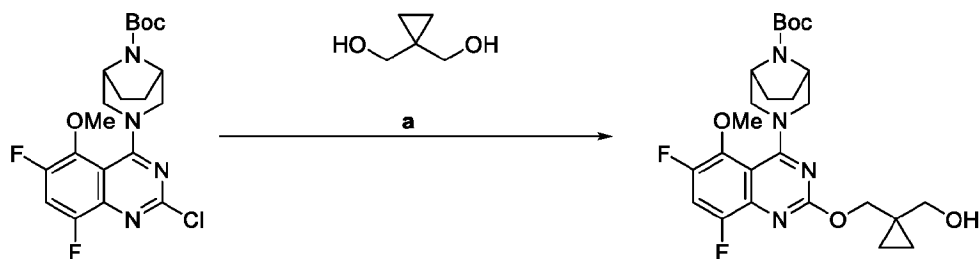
(3R)-4-((1-(((4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-5-methoxyquinazolin-2-yl)oxy)methyl)cyclopropyl)methyl)-3-methylmorpholine



Synthetic scheme:

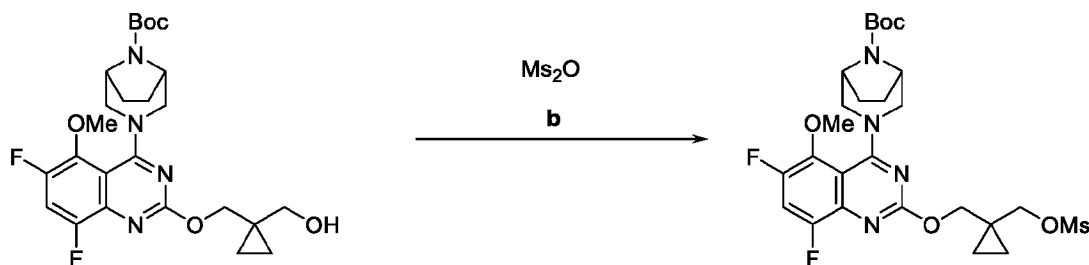


Step 1: Synthesis of tert-butyl 3-(6,8-difluoro-2-((1-(hydroxymethyl)cyclopropyl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00491] To a solution of tert-butyl 3-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (500 mg, 1.13 mmol, 1.0 eq) in THF (5 mL) and DMF (5 mL) was added Cs_2CO_3 (1.1 g, 3.40 mmol, 3.0 eq) and SM-2 (348 mg, 3.40 mmol, 3.0 eq) at room temperature. The reaction mixture was stirred at room temperature for 0.5 h and then stirred at 40 °C for 2 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated to give a residue to give tert-butyl 3-(6,8-difluoro-2-((1-(hydroxymethyl)cyclopropyl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (660 mg, crude) as a yellow solid, which was directly used in the next step without purification. LCMS: m/z 507.1 ($\text{M}+\text{H}^+$).

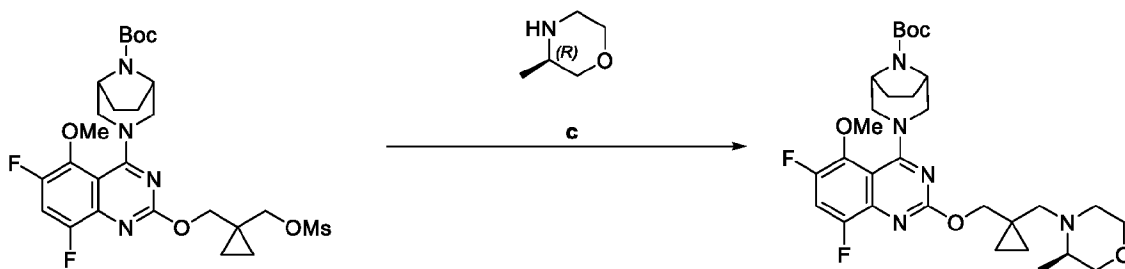
Step 2: Synthesis of tert-butyl 3-(6,8-difluoro-5-methoxy-2-((1-(((methylsulfonyl)oxy)methyl)cyclopropyl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00492] To a solution of tert-butyl 3-(6,8-difluoro-2-((1-(hydroxymethyl)cyclopropyl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (575 mg, 1.14 mmol, 1.0 eq) in DCM (5.8 mL) was added TEA (345 mg, 3.41 mmol, 3.0 eq) and the mixture was stirred at room temperature for 5 min. Then to the mixture was added methanesulfonyl anhydride (395 mg, 2.27 mmol, 2.0 eq) at 0 °C and stirred at room temperature for 1 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated to give a residue to give tert-butyl (1R,5S)-3-(6,8-difluoro-5-methoxy-2-((1-(((methylsulfonyl)oxy)methyl)cyclopropyl)methoxy)quinazolin-4-yl)-3,8-

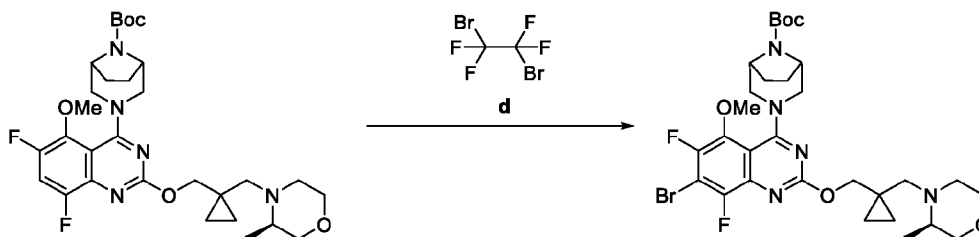
diazabicyclo[3.2.1]octane-8-carboxylate (620 mg, crude) as a yellow solid, which was directly used in the next step without purification. LCMS: m/z 585.2 ($M+H^+$).

Step 3: Synthesis of tert-butyl 3-(6,8-difluoro-5-methoxy-2-((1-(((R)-3-methylmorpholino)methyl)cyclopropyl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00493] To a solution of tert-butyl 3-(6,8-difluoro-5-methoxy-2-((1-(((methylsulfonyl)oxy)methyl) cyclopropyl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (620 mg, 1.06 mmol, 1.0 eq) in DMF (8.7 mL) was added 3R-3-methylmorpholine (128.7 mg, 1.27 mmol, 1.2 eq), KI (229 mg, 1.38 mmol, 1.3 eq) and NaHCO_3 (267 mg, 3.18 mmol, 3.0 eq), and the mixture was stirred at 85 °C for 3 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (20 mL x 3), dried over Na_2SO_4 and concentrated to afford the crude product. The residue was purified by silica gel column chromatography (petroleum ether / EtOAc = 7:1) to give tert-butyl 3-(6,8-difluoro-5-methoxy-2-((1-(((R)-3-methylmorpholino)methyl)cyclopropyl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (290 mg, 49.8% yield for 3 steps) as a yellow oil. LCMS: m/z 590.3 ($M+H^+$).

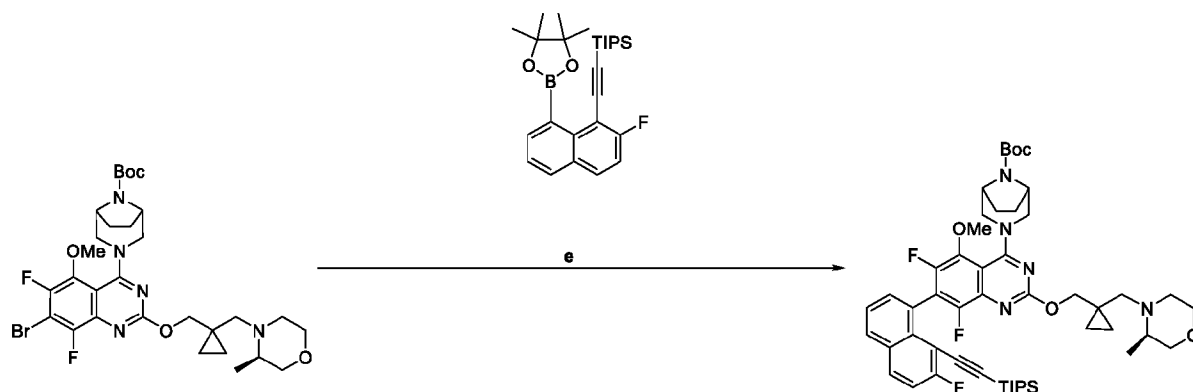
Step 4: Synthesis of tert-butyl 3-(7-bromo-6,8-difluoro-5-methoxy-2-((1-(((R)-3-methylmorpholino)methyl)cyclopropyl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00494] The solution of tert-butyl 3-(6,8-difluoro-5-methoxy-2-((1-(((R)-3-methylmorpholino) methyl)cyclopropyl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (290 mg, 0.49 mmol, 1.0 eq) in THF (4.0 mL) was

added LDA (2M THF solution) (1.5 mL, 3.00 mmol, 6.0 eq) at -65 °C and stirred at the same temperature for 0.5 h under N₂ atmosphere. Then the mixture was added 1,2-dibromotetrafluoroethane (1.02 g, 3.94 mmol, 8.0 eq) at -65 °C and stirred at the same temperature for 2 h under N₂ atmosphere. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give a residue. The crude product was purified by prep-TLC (petroleum ether/EtOAc = 2: 1) to give tert-butyl 3-(7-bromo-6,8-difluoro-5-methoxy-2-((1-(((R)-3-methylmorpholino)methyl)cyclopropyl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (200 mg, 60.8%) as a yellow liquid. LCMS: m/z 670.2, 668.2 (M+H⁺).

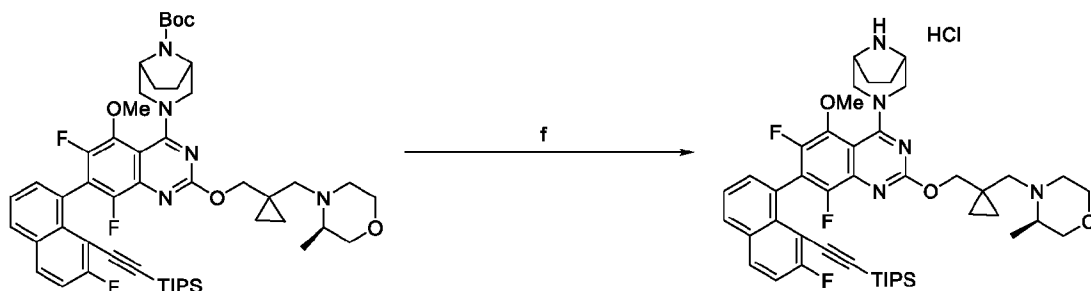
Step 5: Synthesis of tert-butyl 3-(6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methoxy-2-((1-(((R)-3-methylmorpholino)methyl)cyclopropyl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00495] To tert-butyl 3-(7-bromo-6,8-difluoro-5-methoxy-2-((1-(((R)-3-methylmorpholino)methyl)cyclopropyl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (75 mg, 0.11 mmol, 1.0 eq), ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (61 mg, 0.14 mmol, 1.2 eq), Cs₂CO₃ (110 mg, 0.34 mmol, 3.0 eq) and cataCXium A Pd G3 (16 mg, 0.02 mmol, 0.2 eq) in the microwave tube was added Toluene (3.8 mL) and water (0.8 mL). The tube was irradiated under microwave at 120 °C for 2 h under N₂. Upon completion, the mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phases were dried over Na₂SO₄ and concentrated to give a residue. The crude product was purified by prep-TLC (petroleum ether/EtOAc = 2: 1) to give tert-butyl 3-(6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methoxy-2-((1-(((R)-3-methylmorpholino)methyl)cyclopropyl)methoxy)quinazolin-4-yl)-3,8-

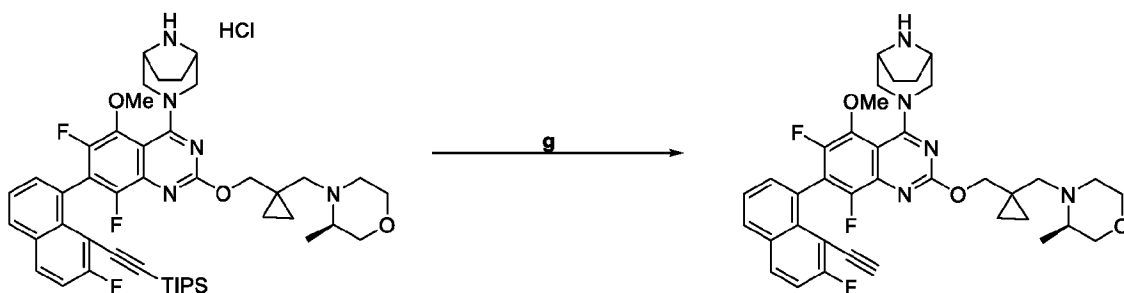
diazabicyclo[3.2.1]octane-8-carboxylate (92 mg, 90.2%) as a yellow liquid. LCMS: m/z 914.4 ($M+H^+$).

Step 6: Synthesis of (3R)-4-((1-(((4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methoxyquinazolin-2-yl)oxy)methyl)cyclopropyl)methyl)-3-methylmorpholine hydrochloride



[00496] To a solution of tert-butyl 3-(6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methoxy-2-((1-((R)-3-methylmorpholino)methyl)cyclopropyl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (40 mg, 0.04 mmol, 1.0 eq) in ACN (4.0 mL) was added HCl/dioxane(4M) (0.35 mL, 1.40 mmol, 32.0 eq) at 0 °C under N_2 atmosphere. Then the reaction was stirred at 0 °C for 1 h. Then the mixture was concentrated to give a residue to afford (3R)-4-((1-(((4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methoxyquinazolin-2-yl)oxy)methyl)cyclopropyl)methyl)-3-methylmorpholine hydrochloride (36 mg, crude) as a yellow solid, which was directly used in the next step without purification. LCMS: m/z 814.4 ($M-HCl+H^+$).

Step 7: Synthesis of (3R)-4-((1-(((4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-5-methoxyquinazolin-2-yl)oxy)methyl)cyclopropyl)methyl)-3-methylmorpholine

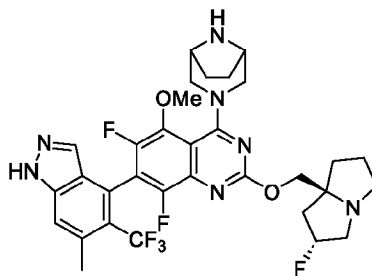


[00497] To a solution of (3R)-4-((1-(((4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methoxyquinazolin-2-

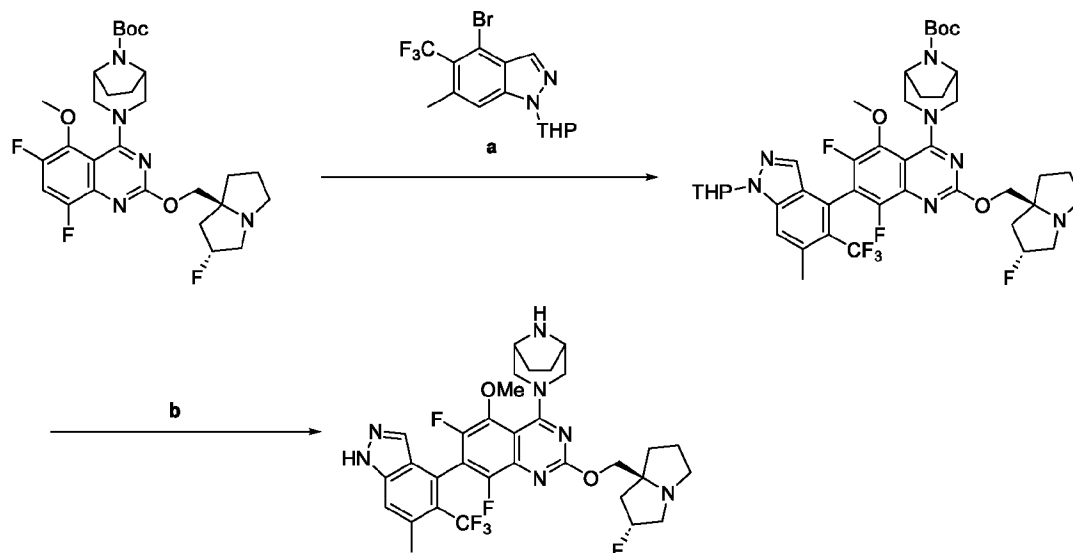
yl)oxy)methyl)cyclopropyl)methyl)-3-methylmorpholine hydrochloride (36 mg, 0.04 mmol, 1.0 eq) in DMF (1.0 mL) was added CsF (100 mg, 0.66 mmol, 15 eq) at 40 °C under N₂ atmosphere. Then the reaction was stirred at 40 °C for 3 h. The product was filtered to give a crude. The crude was purified by Prep-HPLC (acetonitrile with 0.1% FA in water, 20% to 60%) to give (3R)-4-((1-(((4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-5-methoxyquinazolin-2-yl)oxy)methyl)cyclopropyl)methyl)-3-methylmorpholine (13 mg, with 1.0 FA salt, 45.2% yield for 2 steps) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.29 – 8.16 (m, 3H), 7.75 – 7.58 (m, 3H), 4.56 (dd, *J* = 27.2, 10.8 Hz, 1H), 4.21-4.15 (m, 1H), 4.05 (d, *J* = 6.8 Hz, 1H), 3.98 – 3.77 (m, 2H), 3.70 (s, 3H), 3.68 – 3.37 (m, 7H), 3.36 – 3.14 (m, 3H), 3.07 – 2.88 (m, 2H), 2.35 – 2.22 (m, 1H), 2.17 – 2.06 (m, 1H), 1.92 – 1.76 (m, 1H), 1.75 – 1.51 (m, 4H), 0.90 – 0.78 (m, 3H), 0.72 – 0.60 (m, 1H), 0.57 – 0.43 (m, 2H), 0.38 – 0.28 (m, 1H). LCMS: *m/z* 658.2 (M+H⁺)

Example 43

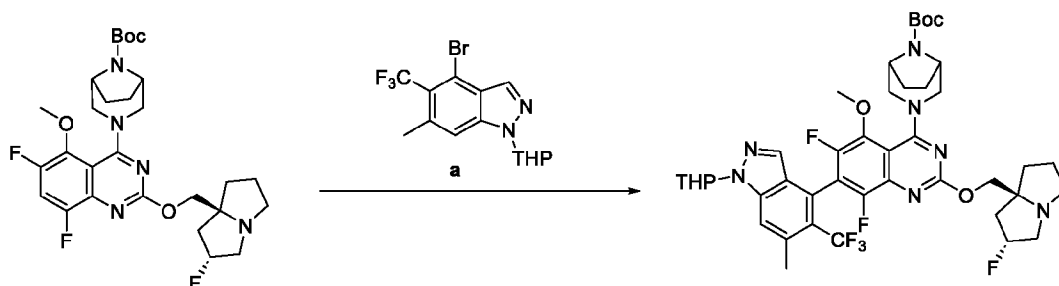
4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-7-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)quinazoline formate



Synthetic scheme:



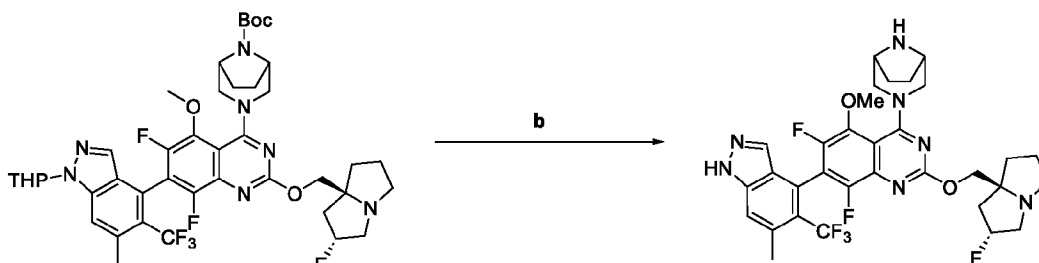
Step 1: Synthesis of tert-butyl 3-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-7-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00498] To a solution of compound tert-butyl 3-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (200 mg, 0.36 mmol, 1.0 eq) in THF (3 mL) was added (TMP)₂Zn·MgCl₂·LiCl (2.7 mL, 1.1 mmol, 3.0 eq, 0.4 M in THF) under nitrogen atmosphere. The reaction was stirred at 50 °C for 2 h. To the reaction was added 4-bromo-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazole (154 mg, 0.43 mmol, 1.2 eq) and RuPhos Pd G2 (28 mg, 0.04 mmol, 0.1 eq) in dioxane (2 mL) under nitrogen atmosphere. The reaction was stirred at 100 °C for 12 h. The residue was partitioned between EtOAc (20 mL) and water (20 mL). The layers were separated. The aqueous layer was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over MgSO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (dichloromethane:

methanol = 10: 1) to give tert-butyl 3-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-7-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (50 mg, 16.7%) as a yellow solid. LCMS: 846.2 (M+H⁺).

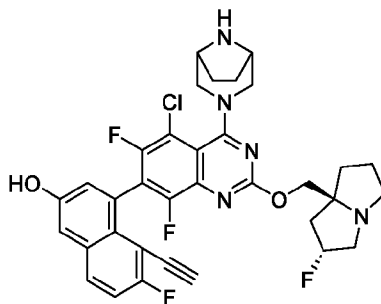
Step 2: Synthesis of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-7-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)quinazoline formate (1:0.7)



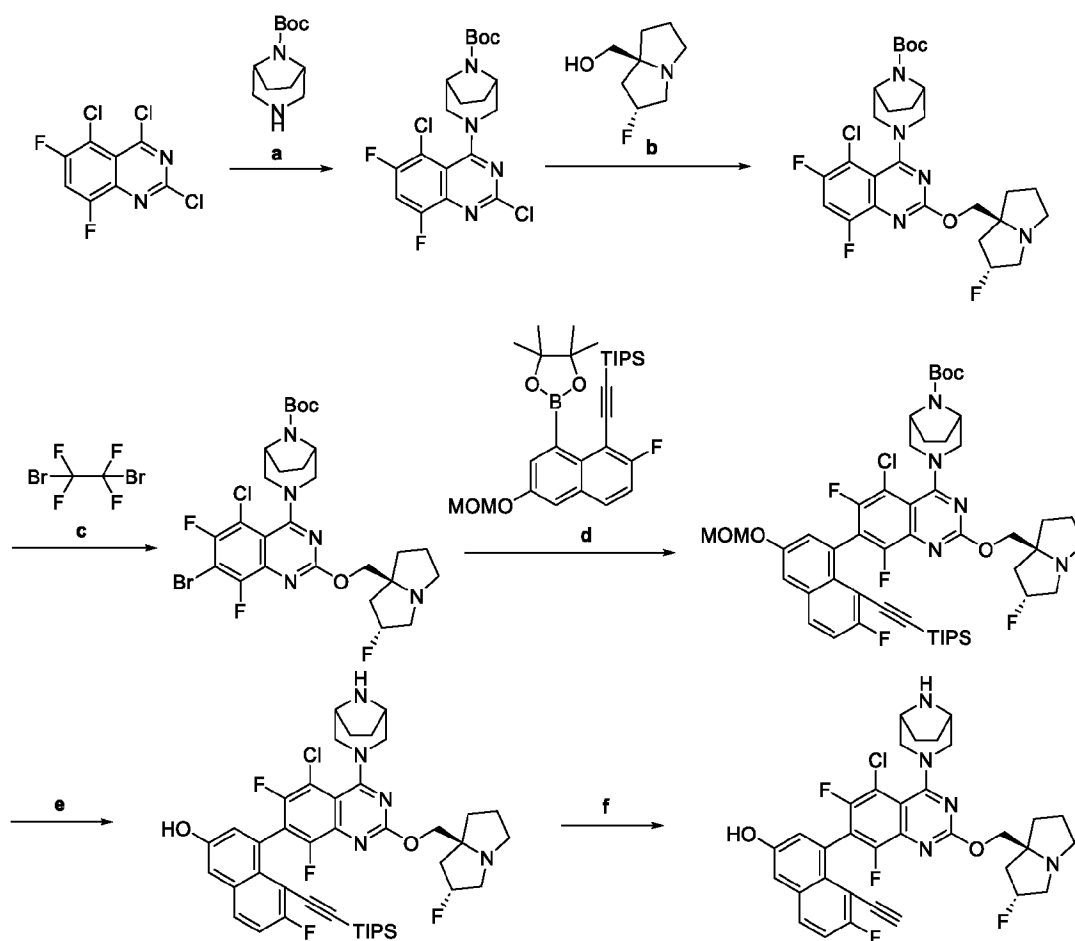
[00499] To a solution of tert-butyl 3-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-7-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (50 mg, 0.06 mmol, 1.0 eq) in DCM (4 mL) was added HCl in dioxane (2 mL, 4 N in dioxane). Then the reaction mixture was stirred at room temperature for 1 h. The mixture was concentrated and purified by prep-HPLC (acetonitrile with 0.1% FA in water, 20% to 60%) to give 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-7-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)quinazoline formate (1:0.7) (15.0 mg, 38.4%) as a white solid. ¹H NMR (400 MHz, CD₃OD): δ 8.50 (s, 0.7H), 7.71 (s, 1H), 7.67 (s, 1H), 5.43 (d, J = 53.2 Hz, 1H), 4.52 – 4.38 (m, 3H), 4.36 – 4.24 (m, 1H), 4.08 – 3.98 (m, 2H), 3.92 (s, 3H), 3.74 – 3.44 (m, 5H), 3.27 – 3.17 (m, 1H), 2.72 (s, 3H), 2.58 – 2.22 (m, 3H), 2.22 – 2.09 (m, 3H), 2.09 – 1.95 (m, 4H). ¹⁹F NMR (400 MHz, CD₃OD): δ -56.602, -132.678, -138.326, -173.890. LCMS: 662.3 (M+H⁺).

Example 44

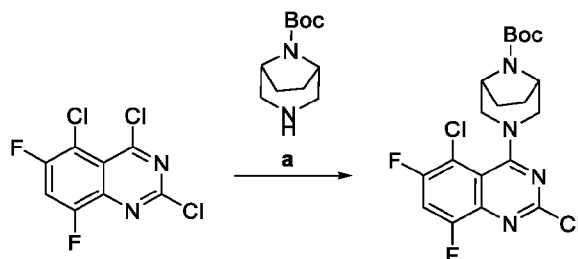
4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-chloro-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate



Synthetic scheme:

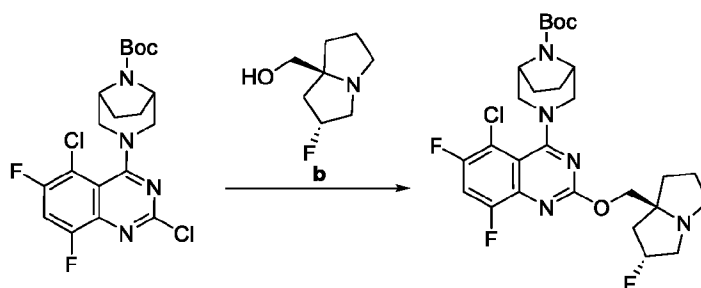


Step 1: Synthesis of tert-butyl 3-(2,5-dichloro-6,8-difluoroquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00500] To a solution of 2,4,5-trichloro-6,8-difluoroquinazoline (1.1 g, 4.08 mmol, 1.0 eq) in DCM (11.0 mL) was added tert-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.3 g, 6.12 mmol, 1.5 eq) and DIEA (4.6 g, 35.51 mmol, 8.7 eq) at -40 °C. The mixture was stirred for 2 h at -40 °C. The mixture was diluted with water (10 mL) and extracted with DCM (20 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by silica gel column chromatography (Petroleum ether / EtOAc = 4 / 1) to afford tert-butyl (1R,5S)-3-(2,5-dichloro-6,8-difluoroquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.3 g, 72.2 %) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 7.35 (t, *J* = 8.7 Hz, 1H), 4.42 – 3.96 (m, 4H), 3.96 – 3.47 (m, 2H), 1.93 – 1.69 (m, 2H), 1.56 – 1.53 (m, 2H), 1.51 (s, 9H). LCMS: 445.0 (M+H⁺).

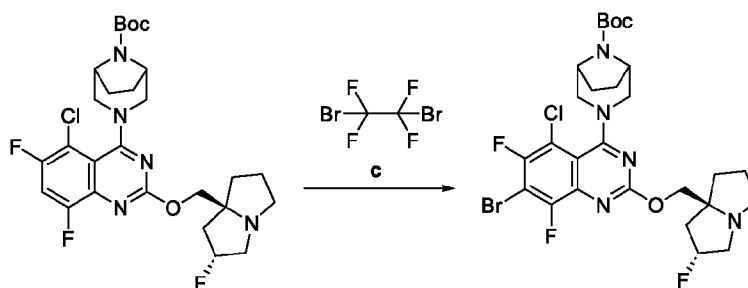
Step 2: Synthesis of tert-butyl 3-(5-chloro-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00501] To a solution of tert-butyl 3-(2,5-dichloro-6,8-difluoroquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (500 mg, 1.13 mmol, 1.0 eq) in THF (5.0 mL) and DMF (5.0 mL) was added ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (233 mg, 1.46 mmol, 1.3 eq), Cs₂CO₃ (1.1 g, 3.38 mmol, 3.0 eq) and DABCO (126 mg, 1.13 mmol, 1.0 eq). The reaction mixture was stirred at room temperature for 15 h under nitrogen atmosphere. The mixture was diluted with water (15 mL) and extracted with EtOAc (20 mL x 3). The organic phases were washed with brine (20 mL), dried with Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by silica gel column chromatography (DCM : MeOH = 100 :

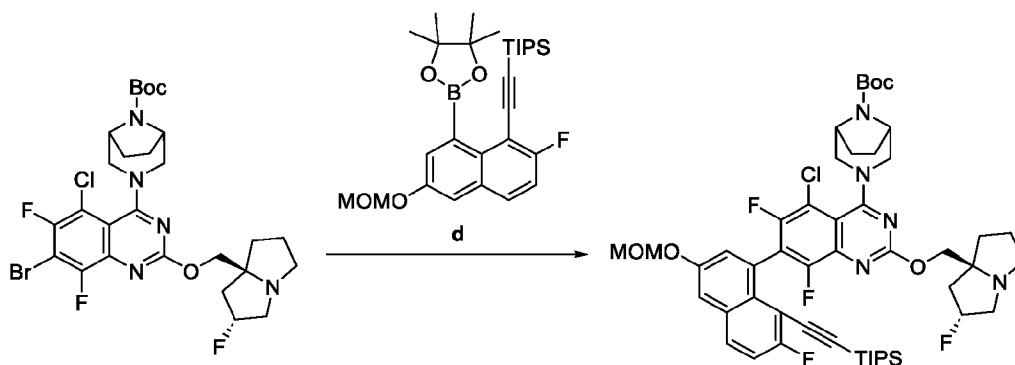
1) to give tert-butyl 3-(5-chloro-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (500 mg, 78.3%) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 7.25 – 7.18 (m, 1H), 5.40 – 5.13 (m, 1H), 4.43 – 3.96 (m, 5H), 3.87 – 3.45 (m, 2H), 3.35 – 3.07 (m, 3H), 3.03 – 2.89 (m, 1H), 2.37 – 2.06 (m, 3H), 2.02 – 1.68 (m, 5H), 1.68 – 1.53 (m, 2H), 1.50 (s, 9H), 1.36 – 1.24 (m, 1H). LCMS: 568.2 (M+H⁺).

Step 3: Synthesis of tert-butyl 3-(7-bromo-5-chloro-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



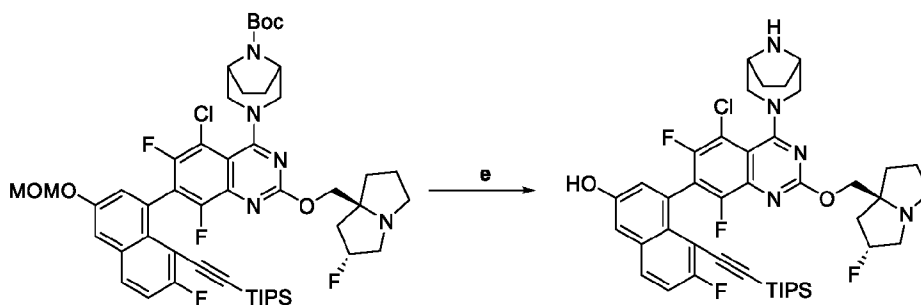
[00502] To a solution of tert-butyl 3-(5-chloro-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (500 mg, 0.88 mmol, 1.0 eq) in THF (5 mL) was added LDA (2.0 M, 0.88 mL, 1.76 mmol, 2.0 eq) dropwise at -65 °C. The reaction mixture was stirred at -65 °C for 0.5 h under nitrogen atmosphere. 1,2-dibromo-1,1,2,2-tetrafluoroethane (455 mg, 1.76 mmol, 2.0 eq) was added to the mixture. The reaction mixture was stirred at -65 °C for 0.5 h under nitrogen atmosphere. The reaction mixture was quenched with ammonium chloride aqueous solution (30 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with H₂O (20 mL), brine (20 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (Dichloromethane : Methanol = 100 : 1) to give tert-butyl 3-(7-bromo-5-chloro-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (333 mg, 58.6%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 5.27 (d, *J* = 54.0 Hz, 1H), 4.38 – 3.98 (m, 5H), 3.80 – 3.50 (m, 2H), 3.34 – 3.06 (m, 3H), 3.04 – 2.85 (m, 1H), 2.37 – 2.04 (m, 3H), 2.01 – 1.69 (m, 5H), 1.67 – 1.53 (m, 2H), 1.50 (s, 9H), 1.33 – 1.25 (m, 1H). LCMS: 646.1, 648.1 (M+H⁺).

Step 4: Synthesis of tert-butyl 3-(5-chloro-6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



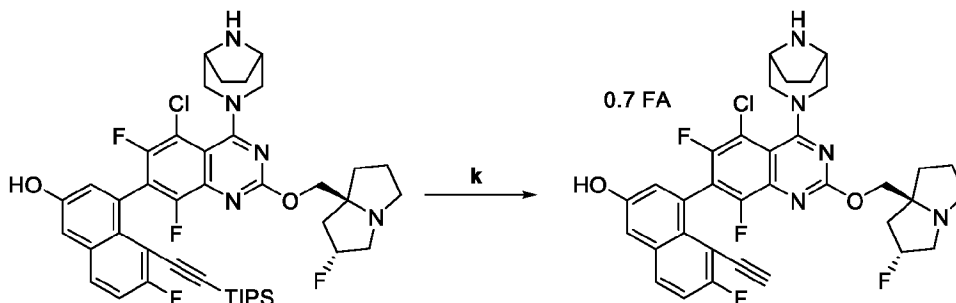
[00503] To a solution of tert-butyl 3-(7-bromo-5-chloro-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.16 mmol, 1.0 eq) in toluene (2 mL) and H₂O (0.4 mL) was added compound ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (159 mg, 0.31 mmol, 2.0 eq), K₃PO₄ (99 mg, 0.47 mmol, 3.0 eq), rac-BI-DIME (8 mg, 0.023 mmol, 0.15 eq) and Pd₂(dba)₃ (43 mg, 0.047 mmol, 0.3 eq). The reaction mixture was heated under microwave irradiation at 120 °C for 1 h under nitrogen atmosphere. The reaction mixture was poured into water (10 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with H₂O (10 mL), brine (10 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (Dichloromethane : Methanol = 60 : 1) to give tert-butyl 3-(5-chloro-6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (88 mg, 59.7%) as a yellow solid. LCMS: 952.2 (M+H⁺).

Step 5: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-chloro-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol



[00504] To a solution of tert-butyl 3-(5-chloro-6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (50 mg, 0.05 mmol, 1.0 eq) in DCM (2.0 mL) was added HCl in dioxane (1.0 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to give 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-chloro-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (43 mg, crude) as a yellow solid. LCMS: 808.2 ($M+H^+$).

Step 6: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-chloro-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate (1:0.7)

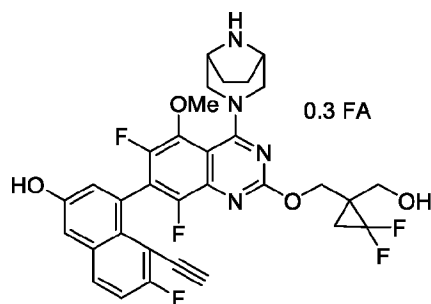


[00505] To a solution of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-chloro-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (43 mg, 0.05 mmol, 1.0 eq) in DMF (1.0 mL) was added CsF (190 mg 1.25 mmol, 25.0 eq). Then the reaction mixture was stirred at 40 °C for 30 min. The mixture was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 10% to 50%) to give 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-chloro-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-5-ethynyl-6-

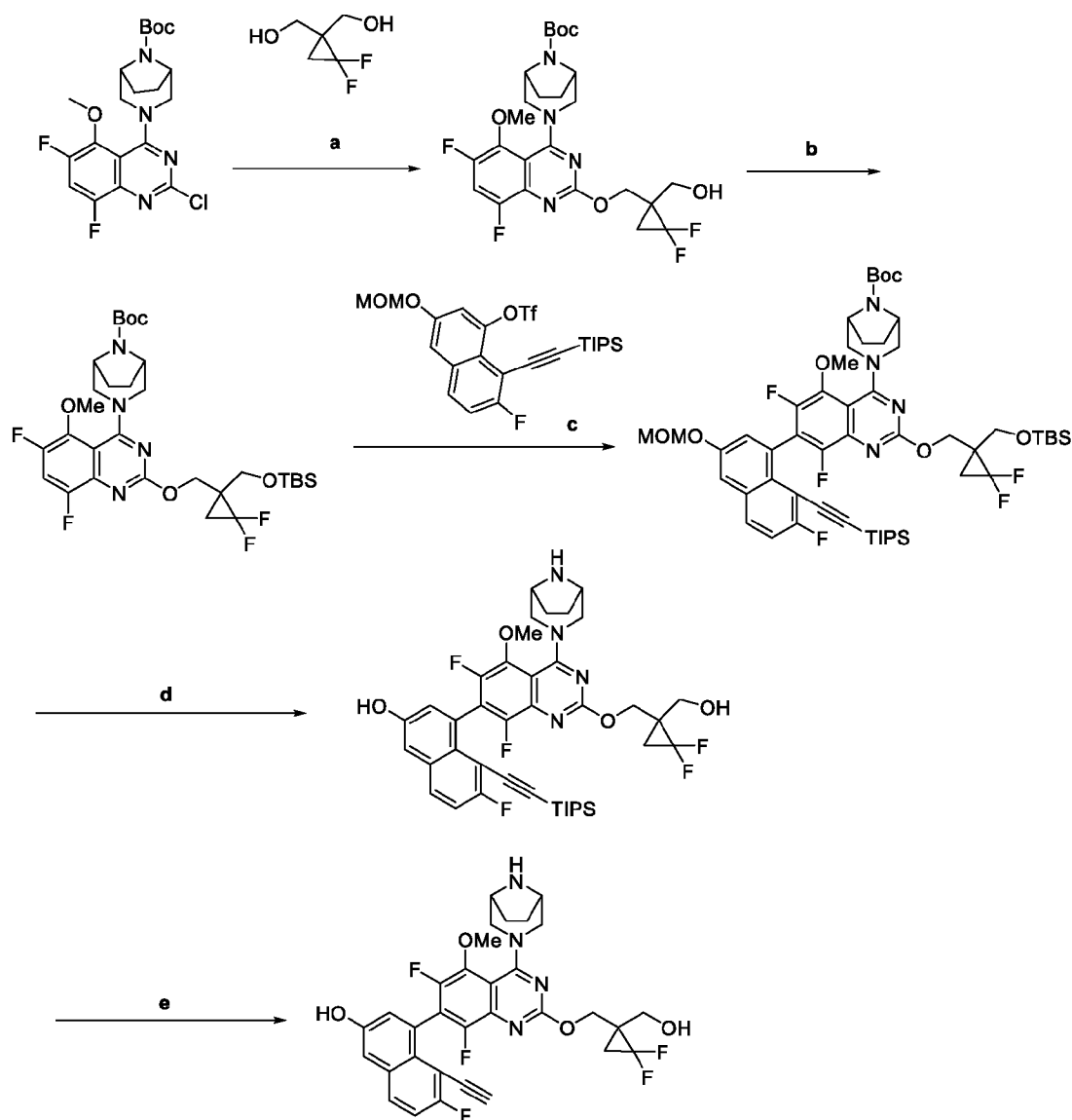
fluoronaphthalen-2-ol formate (1:0.7) (17.6 mg, 51.4% yield of two steps) as a white solid. ^1H NMR (400 MHz, CD_3OD): δ 8.52 (brs, 0.7H), 7.94 – 7.83 (m, 1H), 7.41 – 7.29 (m, 2H), 7.19 – 7.11 (m, 1H), 5.37 (d, $J = 53.6$ Hz, 1H), 4.84 – 4.42 (m, 1H), 4.41 – 4.30 (m, 2H), 4.26 – 4.03 (m, 1H), 4.03 – 3.87 (m, 1H), 3.86 – 3.54 (m, 3H), 3.52 – 3.33 (m, 4H), 3.18 – 3.07 (m, 1H), 2.47 – 2.18 (m, 3H), 2.15 – 2.03 (m, 2H), 2.02 – 1.27 (m, 5H). ^{19}F NMR (400 MHz, CD_3OD): δ -111.093, -118.281, -127.324, -173.779. LCMS: 652.2 ($\text{M} + \text{H}^+$).

Example 45

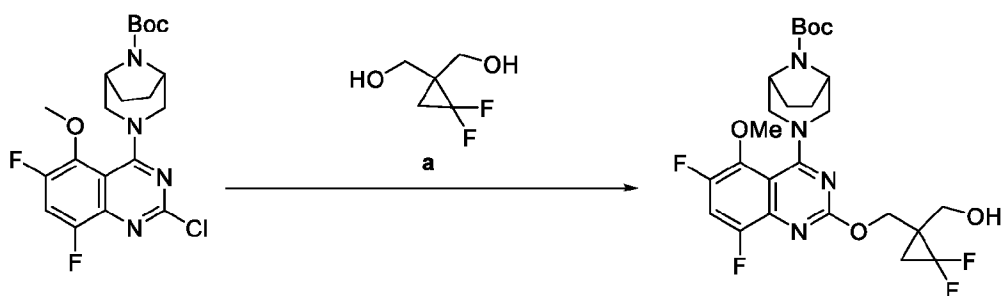
4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-((2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-6,8-difluoro-5-methoxy quinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate



Synthesis scheme



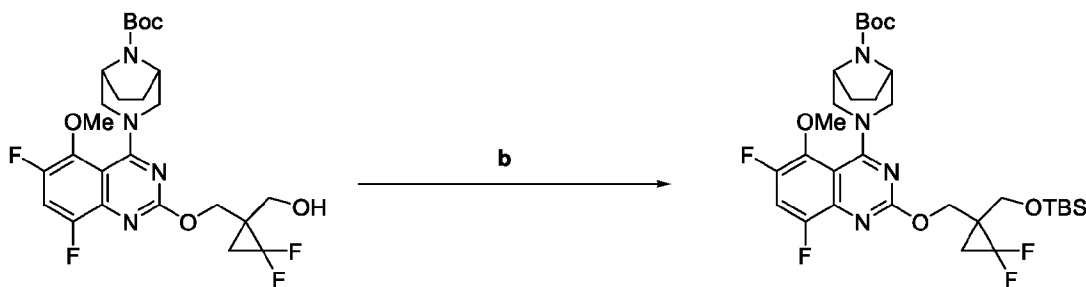
Step 1: Synthesis of tert-butyl 3-(2-((2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00506] To a solution of tert-butyl 3-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.0 g, 2.27 mmol, 1.0 eq) in THF (5 mL) and DMF (5

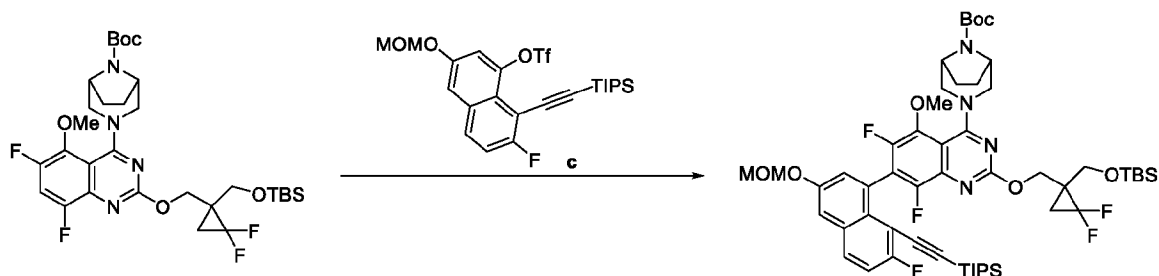
mL) was added (2,2-difluorocyclopropane-1,1-diyl)dimethanol (376.5 mg, 2.72 mmol, 1.2 eq), DABCO (254.5 mg, 2.27 mmol, 1.0 eq) and Cs_2CO_3 (2.2 g, 6.81 mmol, 3.0 eq). The reaction mixture was stirred at room temperature for 15 h under N_2 . The mixture was added with water (20 mL) and extracted with EtOAc (25 mL x 2). The combined organic phases were washed with water (15 mL x 3), brine (15 mL), dried over Na_2SO_4 and concentrated to give a residue. The residue was purified by silica gel chromatography (Petroleum ether: Ethyl acetate ~ 10: 1 to 1: 1) to give tert-butyl 3-(2-((2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (730 mg, 59.2%) as a yellow solid. LCMS: 543.2 ($\text{M}+\text{H}^+$).

Step 2: Synthesis of tert-butyl 3-(2-((1-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-difluorocyclopropyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



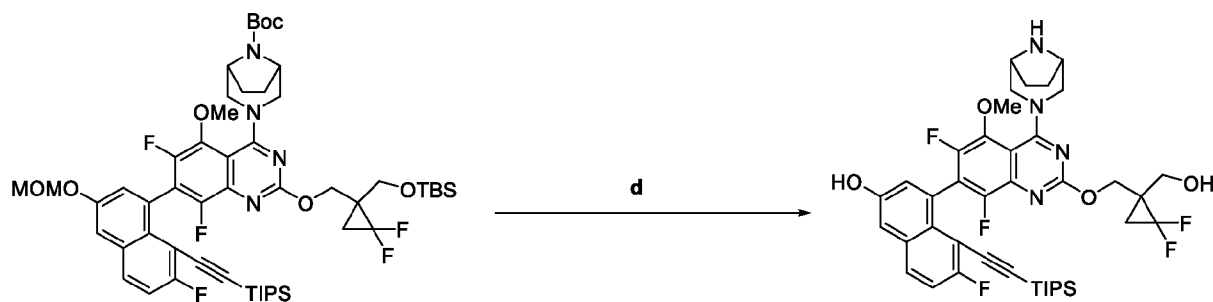
[00507] To a solution of tert-butyl 3-(2-((2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (730 mg, 1.34 mmol, 1.0 eq) in DMF (8 mL) was added TBSCl (245 mg, 1.60 mmol, 1.2 eq) and Imidazole (182 mg, 2.68 mmol, 2.0 eq) at 0 °C. The reaction mixture was stirred at room temperature for 12 h under N_2 . The mixture was diluted with water (15 mL) and extracted with EtOAc (20 mL x 3). The combined organic phases were washed with water (15 mL x 3), brine (15 mL), dried over Na_2SO_4 and concentrated to give a residue. The residue was purified by column chromatography (Petroleum ether: Ethyl acetate = 5: 1) to give tert-butyl 3-(2-((1-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-difluorocyclopropyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (620 mg, 70.2%) as a yellow solid. LCMS: 657.2 ($\text{M}+\text{H}^+$).

Step 3: Synthesis of tert-butyl 3-(2-((1-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-difluorocyclopropyl)methoxy)-6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



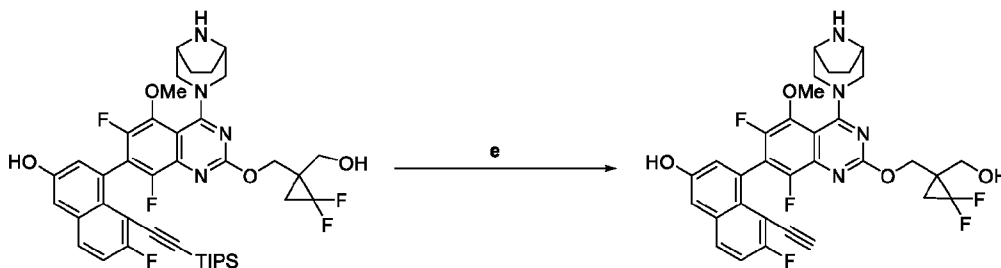
[00508] To a solution of tert-butyl 3-(2-((1-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-difluorocyclopropyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.15 mmol, 1.0 eq) in THF (2 mL) was added (TMP)₂Zn.MgCl₂.LiCl (1 mL, 0.90 mmol, 6.0 eq) dropwise. The reaction mixture was stirred at 50 °C for 2 h under N₂. To the mixture was added a solution of 7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate (97 mg, 0.18 mmol, 1.2 eq) and CPhos Pd G4 (12 mg, 0.01 mmol, 0.1 eq) in Dioxane (2 mL). The reaction mixture was stirred at 50 °C for 12 h. The mixture was filtered and the filtrate was concentrated to give a residue. The residue was purified by silica gel column chromatography (Petroleum ether: Ethyl acetate = 5: 1) to give tert-butyl 3-(2-((1-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-difluorocyclopropyl)methoxy)-6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (110 mg, 69.4%) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 7.76 – 7.71 (m, 1H), 7.46 (d, *J* = 2.7 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.15 (s, 1H), 5.24 (s, 2H), 4.58 – 4.52 (m, 1H), 4.45 – 4.39 (m, 1H), 4.24 – 4.25 (m, 2H), 3.90 (s, 3H), 3.80 – 3.65 (m, 3H), 3.47 (s, 3H), 3.27 – 3.23 (m, 1H), 2.02 – 1.97 (m, 1H), 1.85 – 1.78 (m, 2H), 1.46 (s, 9H), 1.20 (s, 2H), 1.13 – 1.03 (m, 2H), 0.83 – 0.78 (m, 29H), 0.65 – 0.58 (m, 2H), 0.01 (s, 6H).

Step 4 Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-((2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol



[00509] To a solution of tert-butyl 3-(2-((1-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-difluorocyclopropyl)methoxy)-6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (110 mg, 0.10 mmol, 1.0 eq) in DCM (2 mL) was added HCl/Dioxane (0.6 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h under N₂. The mixture was concentrated to give 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-((2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (100 mg, crude) as a yellow solid. LCMS: 783.2 (M+H⁺).

Step 5 Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-((2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate (1:0.3)

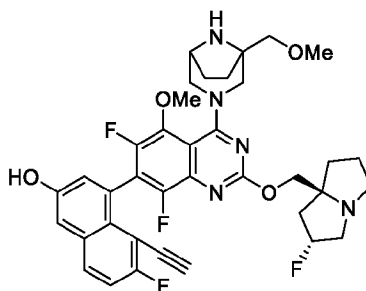


[00510] To a solution of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-((2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (100 mg, 0.12 mmol, 1.0 eq) in DMF (2.0 mL) was added CsF (364 mg, 2.40 mmol, 20.0 eq). The mixture was stirred at 50 °C for 3 h. The mixture was concentrated to give a crude. The crude was purified by Prep-HPLC (ACN with 0.1% FA in water, 15% to 50%) to give 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-((2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate (1:0.3) (30.7 mg, 46.8%, two steps yield) as a white solid. ¹H

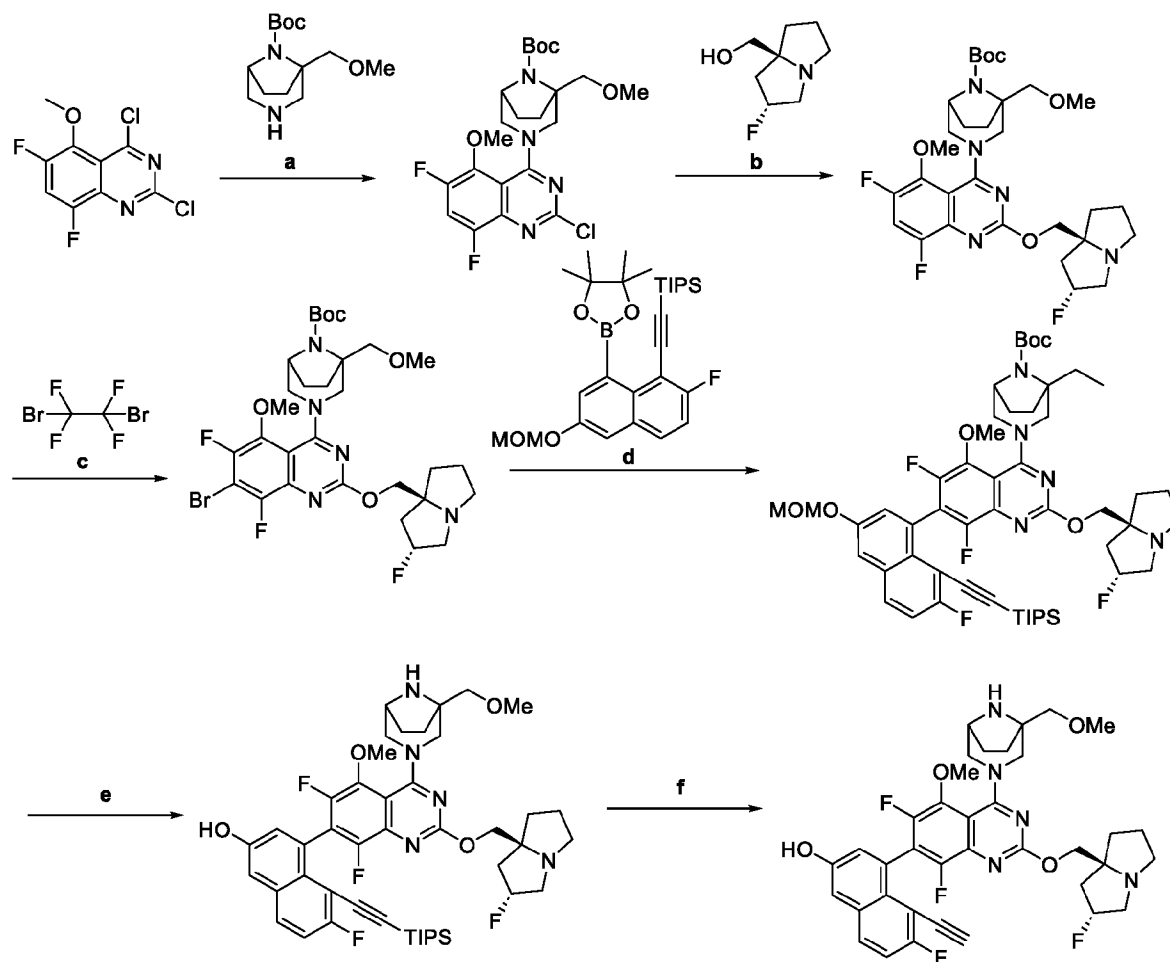
NMR (300 MHz, CD₃OD): δ 7.86 (dd, J = 9.3, 5.7 Hz, 1H), 7.41 – 7.30 (m, 2H), 7.12 (d, J = 2.4 Hz, 1H), 4.76 – 4.65 (m, 1H), 4.56 – 4.52 (m, 1H), 4.50 – 4.41 (m, 1H), 4.15 – 4.02 (m, 1H), 3.88 (s, 3H), 3.84 – 3.78 (m, 4H), 3.63 (d, J = 13.5 Hz, 1H), 3.45 (d, J = 13.5 Hz, 1H), 3.37 (s, 1H), 2.20 – 2.06 (m, 1H), 2.00 – 1.89 (m, 3H), 1.65 – 1.48 (m, 2H). ¹⁹F NMR (300 MHz, CD₃OD): δ -111.324, -132.329, -137.853, -138.60 (d, J_{F-F} = 171.9 Hz, J_{F-H} = 6.0 Hz, 1F), -140.34 (d, J_{F-F} = 172.2 Hz, 1F). LCMS: 627.3 (M+H⁺).

Example 46

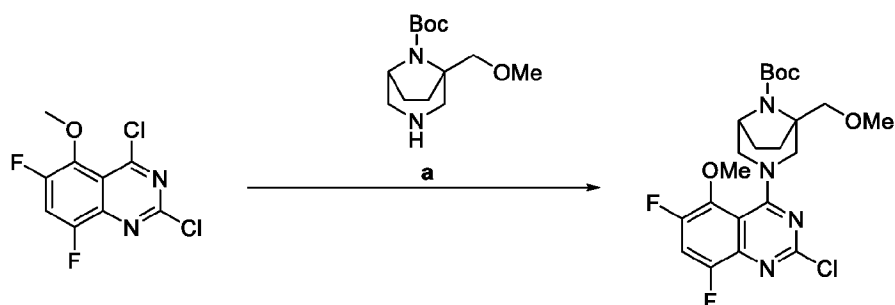
4-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-4-(1-(methoxymethyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)quinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



Synthetic scheme:



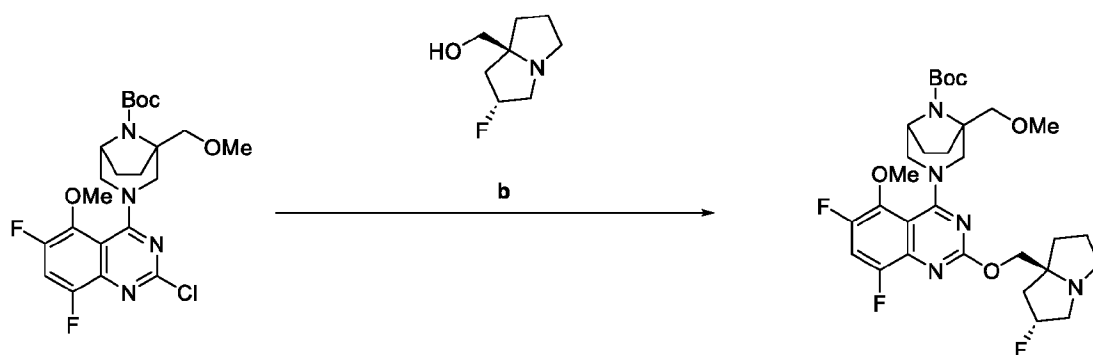
Step 1: Synthesis of tert-butyl 3-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-1-(methoxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00511] To a solution of 2,4-dichloro-6,8-difluoro-5-methoxyquinazoline (476 mg, 1.80 mmol, 1.5 eq) in DCM (10 mL) was added DIEA (1.4 g, 10.47 mmol, 8.7 eq) and tert-butyl 1-(methoxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (600 mg, crude, 1.20 mmol, 1.0 eq) in DCM (4.5 mL) dropwise at -40 °C under argon. After that, the reaction mixture was stirred for 2 h at -40 °C. Then the reaction mixture was quenched with water (20 mL) and extracted with

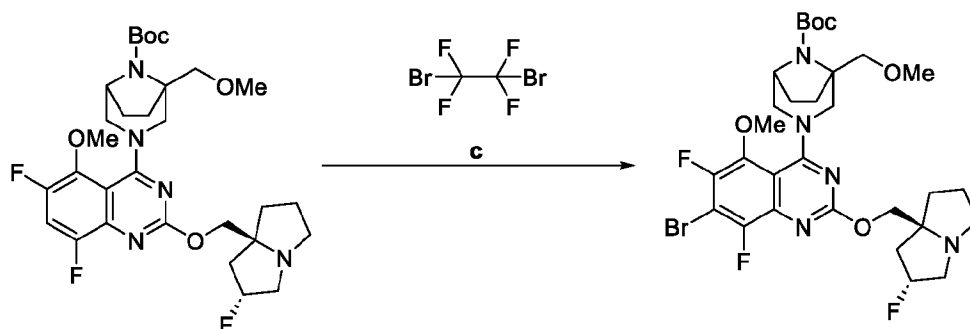
DCM (20 mL x 3). The organic layer was washed with brine (50 mL), dried over Na₂SO₄ and concentrated to give the residue, which was purified by silica gel column chromatography (petroleum ether/EtOAc = 20: 1) to give tert-butyl 3-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-1-(methoxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (386 mg, yield 66.2% for two steps) as a yellow solid. LCMS: m/z 484.8 (M+H⁺).

Step 2: Synthesis of compound tert-butyl 3-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1-(methoxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



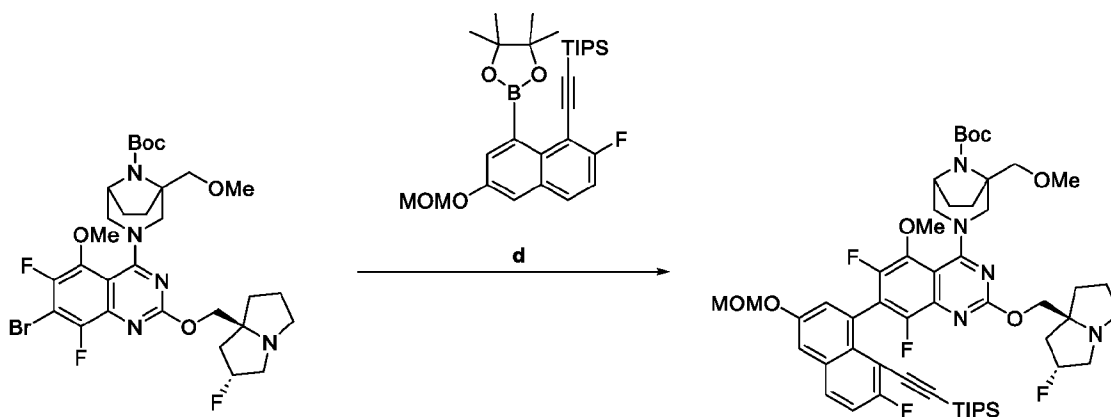
[00512] To a solution of tert-butyl 3-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-1-(methoxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (400 mg, 0.82 mmol, 1.0 eq), ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl) methanol (171 mg, 1.07 mmol, 1.3 eq) in THF (4.8 mL) and DMF (4.8 mL) was added DABCO (93 mg, 0.82 mmol, 1.0 eq) and Cs₂CO₃ (806 mg, 2.47 mmol, 3.0 eq) at room temperature under N₂ atmosphere. The reaction mixture was stirred at room temperature for 12 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with water (30 mL x 3) and brine (30 mL), dried over Na₂SO₄ and concentrated to give a residue. The crude product was purified by silica gel column chromatography (DCM/MeOH = 10: 1) to give tert-butyl 3-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1-(methoxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (250 mg, 49.9%) as a yellow solid. LCMS: m/z 608.3 (M+H⁺).

Step 3: Synthesis of tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1-(methoxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



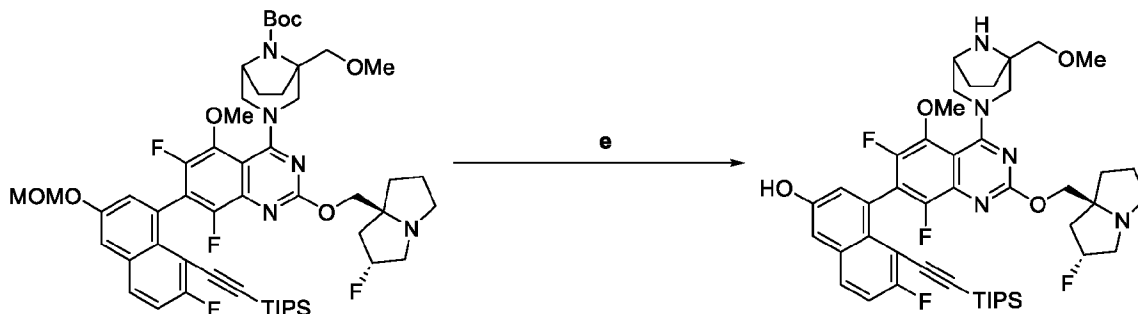
[00513] To a solution of tert-butyl 3-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1-(methoxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (105 mg, 0.17 mmol, 1.0 eq) in THF (3.5 mL) was added LDA (2N in THF, 0.52 mL, 1.04 mmol, 6.0 eq) at -65 °C under N₂ atmosphere. The reaction mixture was stirred at -65 °C for 0.5 h. Then the mixture was added 1,2-dibromo-1,1,2,2-tetrafluoroethane (360 mg, 1.38 mmol, 8.0 eq) and stirred at 25 °C for 15 h. The mixture was quenched with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (30 mL), dried over Na₂SO₄ and concentrated to give a residue. The crude product was purified by silica gel column chromatography (DCM/MeOH = 10: 1) to give tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1-(methoxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (90 mg, 75.8%) as a yellow liquid. LCMS: m/z 686.2, 688.2 (M+H⁺).

Step 4: Synthesis of tert-butyl 3-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1-(methoxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00514] Tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1-(methoxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (90 mg, 0.13 mmol, 1.0 eq), ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (81 mg, 0.16 mmol, 1.2 eq), cataCXium A Pd G3 (19 mg, 0.026 mmol, 0.2 eq) and Cs_2CO_3 (128 mg, 0.39 mmol, 3.0 eq) were placed in the reaction bottle. A solution of PhMe/ H_2O (5: 1, 6.0 mL) was added at room temperature. The mixture was stirred under microwave irradiation at 100 °C for 1 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated to give a residue. The crude product was purified by prep-TLC (DCM/MeOH = 10: 1) to give tert-butyl 3-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-(((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1-(methoxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (90 mg, 69.2%) as a yellow liquid. LCMS: m/z 992.4 ($\text{M}+\text{H}^+$).

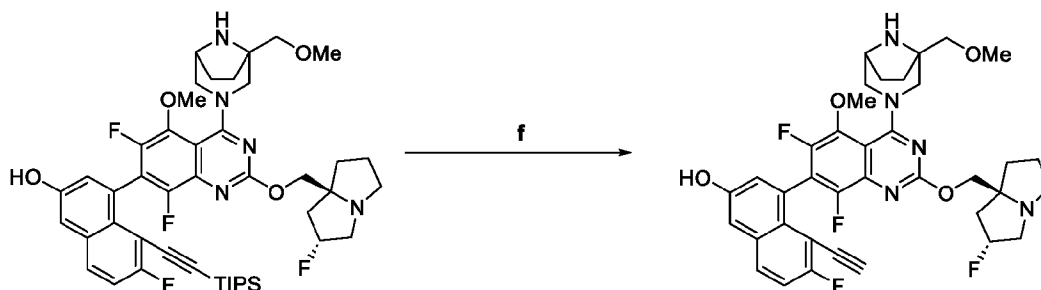
Step 5: Synthesis of 4-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-4-(1-(methoxymethyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)quinazolin-7-yl)-6-fluoro-5-(((triisopropylsilyl)ethynyl)naphthalen-2-ol



[00515] To a solution of tert-butyl 3-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-(((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1-(methoxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (90 mg, 0.09 mmol, 1.0 eq) in ACN (3.6 mL) was added 4N HCl/Dioxane (0.9 mL) at 0 °C under N_2 atmosphere. The reaction mixture was stirred at 0 °C for 4 h. Then the reaction mixture was concentrated in vacuo to give 4-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-4-(1-

(methoxymethyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)quinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (90 mg, crude) as a yellow liquid, which was used directly for the next step without any further purification. LCMS: m/z 848.3 ($M+H^+$).

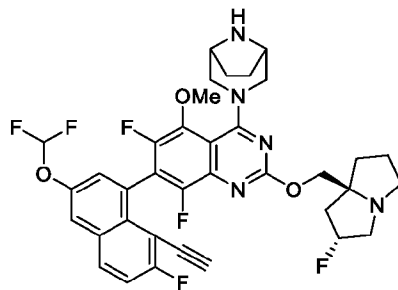
Step 6: Synthesis of 4-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-4-(1-(methoxymethyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)quinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



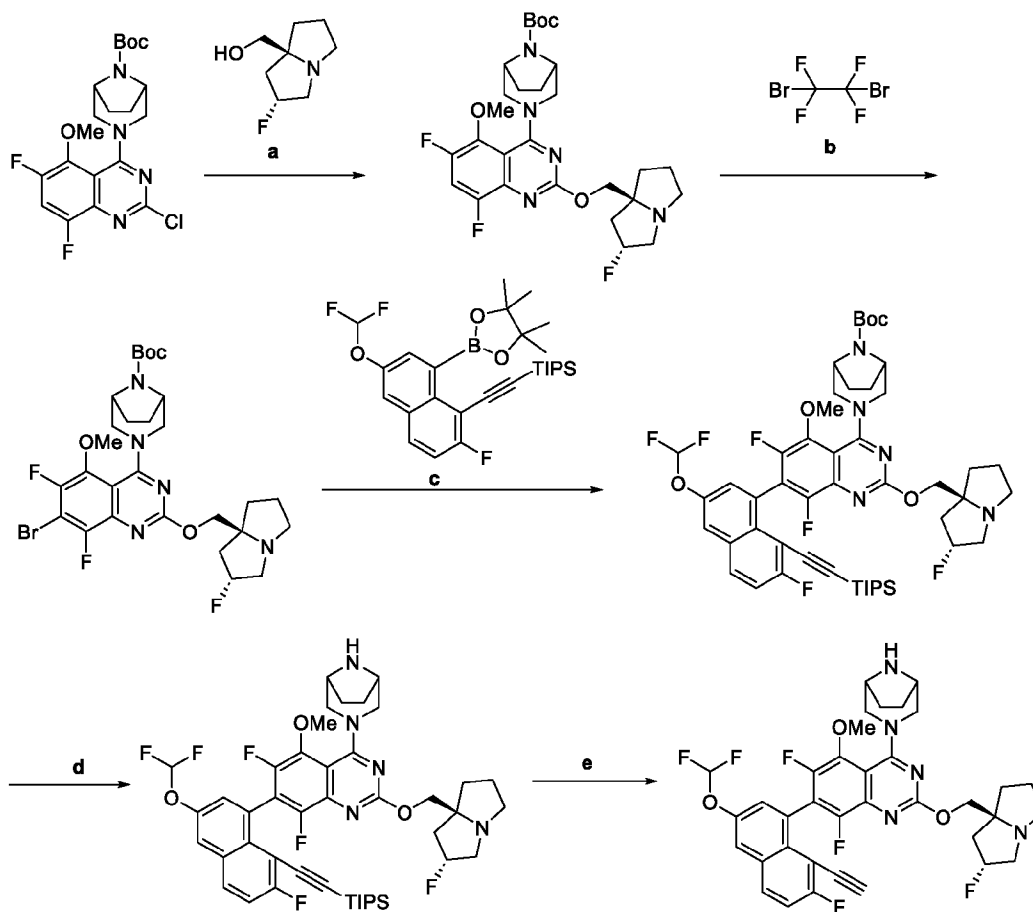
[00516] To a solution of 4-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-4-(1-(methoxymethyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)quinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (90 mg, 0.09 mmol, 1.0 eq) in DMF (1.0 mL) was added CsF (207 mg, 1.36 mmol, 15.0 eq). The reaction mixture was stirred at 40 °C for 6 h. Then the reaction mixture was filtered and the filtrate was concentrated to give a residue, which was purified by Prep-HPLC (acetonitrile in water with 0.1% FA, 10% to 26%) to give 4-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-4-(1-(methoxymethyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)quinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol (20.2 mg, with 0.68 FA salt, 30.7% for two steps) as a white solid. ^1H NMR (400 MHz, $DMSO-d_6$): δ 10.21 (brs, 1H), 8.00 (dd, $J = 8.8, 2.8$ Hz, 1H), 7.48 (t, $J = 8.8$ Hz, 1H), 7.41 (d, $J = 2.0$ Hz, 1H), 7.19 (s, 1H), 5.28 (d, $J = 54.2$ Hz, 1H), 4.18 – 3.86 (m, 4H), 3.76 (s, 3H), 3.65 – 3.51 (m, 1H), 3.50 – 3.17 (m, 9H), 3.15–3.03 (m, 2H), 3.01 (s, 1H), 2.90 – 2.78 (m, 1H), 2.12 (s, 1H), 2.10 – 1.94 (m, 2H), 1.92 – 1.50 (m, 6H), 1.50 – 1.32 (m, 1H). LCMS: m/z 692.2 ($M+H^+$).

Example 47

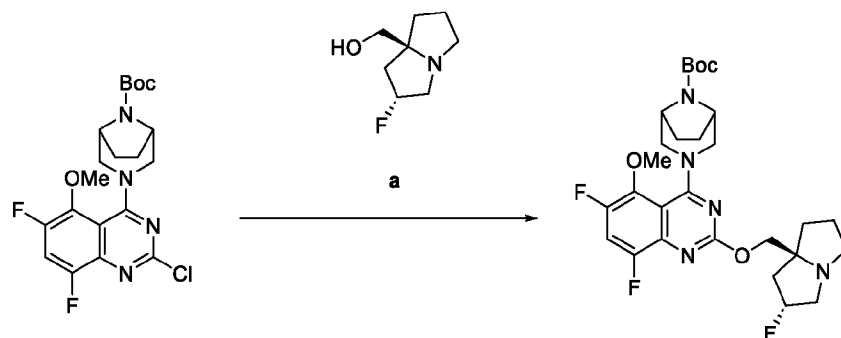
4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(3-(difluoromethoxy)-8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline



Synthetic scheme:

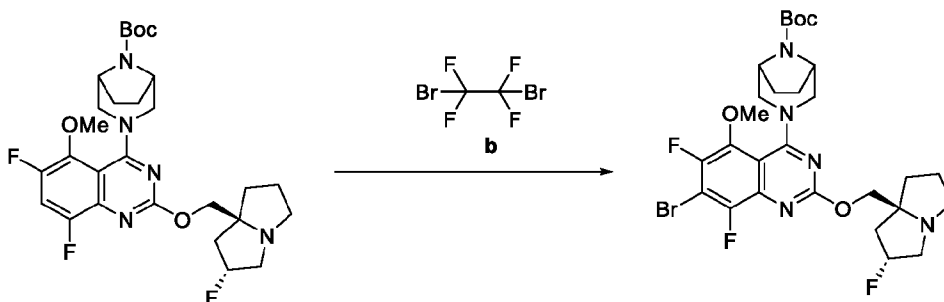


Step 1: Synthesis of tert-butyl 3-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00517] To a solution of tert-butyl 3-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (400 mg, 0.91 mmol, 1.0 eq), ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (174 mg, 1.09 mmol, 1.2 eq) in THF (4 mL) and DMF (4 mL) was added DABCO (102 mg, 0.91 mmol, 1.0 eq) and Cs_2CO_3 (889 mg, 2.73 mmol, 3.0 eq) at room temperature under N_2 atmosphere. The reaction mixture was stirred at room temperature for 15 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated to give a residue. The crude product was purified by column chromatography (DCM: MeOH = 30: 1) to give tert-butyl 3-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (430 mg, 83.8%) as a yellow solid. LCMS: m/z 564.2 ($\text{M}+\text{H}^+$).

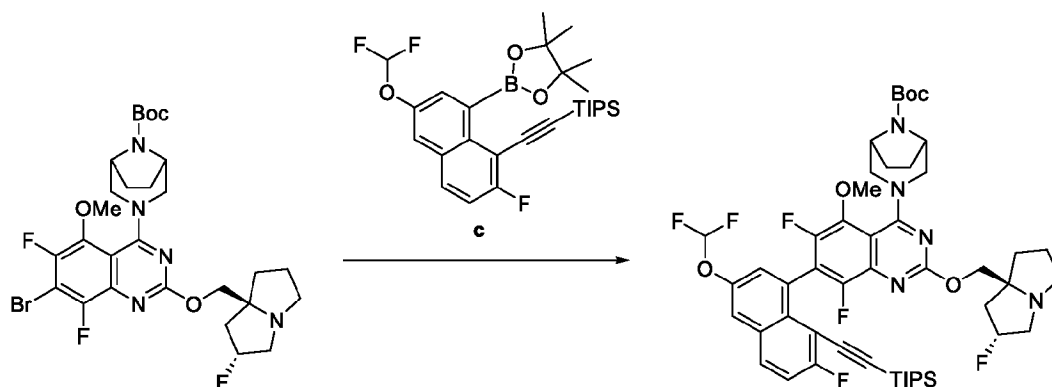
Step 2: Synthesis of tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00518] To a solution of tert-butyl 3-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (400 mg, 0.71 mmol, 1.0 eq) in THF (13.4 mL) was added LDA (2N, 2.13 mL, 4.26

mmol, 6.0 eq) at $-65\text{ }^{\circ}\text{C}$ under N_2 atmosphere. The reaction mixture was stirred at $-65\text{ }^{\circ}\text{C}$ for 0.5 h. Then 1,2-dibromo-1,1,2,2-tetrafluoroethane (1.5 g, 5.68 mmol, 8.0 eq) was added to the reaction mixture and stirred at $-65\text{ }^{\circ}\text{C}$ for 2 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated to give a residue. The crude product was purified by column chromatography (DCM: MeOH = 10: 1) to give tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (440 mg, 96.4%) as a yellow liquid. LCMS: m/z 642.2 ($\text{M}+\text{H}^+$).

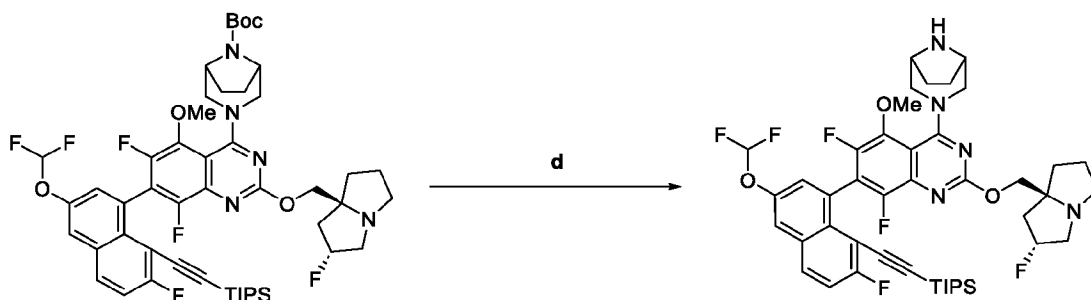
Step 3: Synthesis of tert-butyl 3-(7-(3-(difluoromethoxy)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00519] Tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (70 mg, 0.11 mmol, 1.0 eq), ((6-(difluoromethoxy)-2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (67 mg, 0.13 mmol, 1.2 eq), Cxium A Pd G3 (16 mg, 0.022 mmol, 0.2 eq) and Cs_2CO_3 (108 mg, 0.33 mmol, 3.0 eq) were placed in the reaction bottle. A solution of PhMe/ H_2O (5/1, 4.32 mL) was added at room temperature. The mixture was stirred with microwave reactor at $120\text{ }^{\circ}\text{C}$ for 2 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated to give a residue. The crude product was purified by prep-TLC (DCM: MeOH = 10: 1) to give tert-butyl 3-(7-(3-(difluoromethoxy)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-

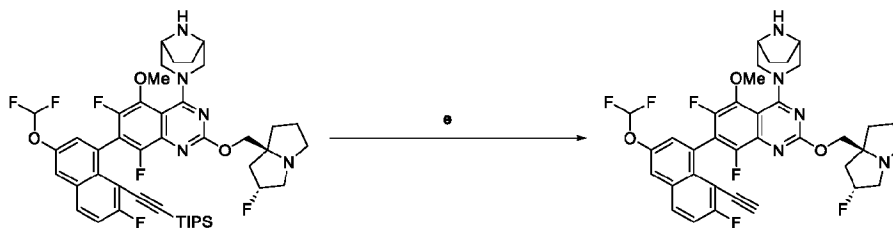
diazabicyclo[3.2.1]octane-8-carboxylate (80 mg, 76.2%) as a yellow liquid. LCMS: m/z 954.3 ($M+H^+$).

Step 4: Synthesis of (bicyclo[3.2.1]octan-3-yl)-7-(3-(difluoromethoxy)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline



[00520] To a solution of tert-butyl 3-(7-(3-(difluoromethoxy)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (60 mg, 0.063 mmol, 1.0 eq) in ACN (2.4 mL) was added HCl/Dioxane (4M, 0.51 mL) at 0 °C under N_2 atmosphere. The reaction mixture was stirred at 0 °C for 2 h. Then the reaction mixture was concentrated in vacuo to give (bicyclo[3.2.1]octan-3-yl)-7-(3-(difluoromethoxy)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline (crude) as a yellow liquid, which was used directly for the next step without any further purification. LCMS: m/z 854.3 ($M+H^+$).

Step 5: Synthesis of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(3-(difluoromethoxy)-8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline

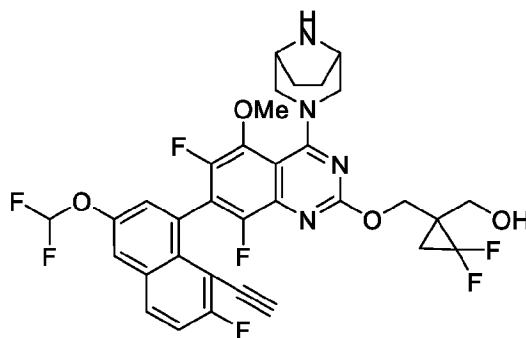


[00521] To a solution of (bicyclo[3.2.1]octan-3-yl)-7-(3-(difluoromethoxy)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline (crude) in DMF (1.5 mL) was added CsF

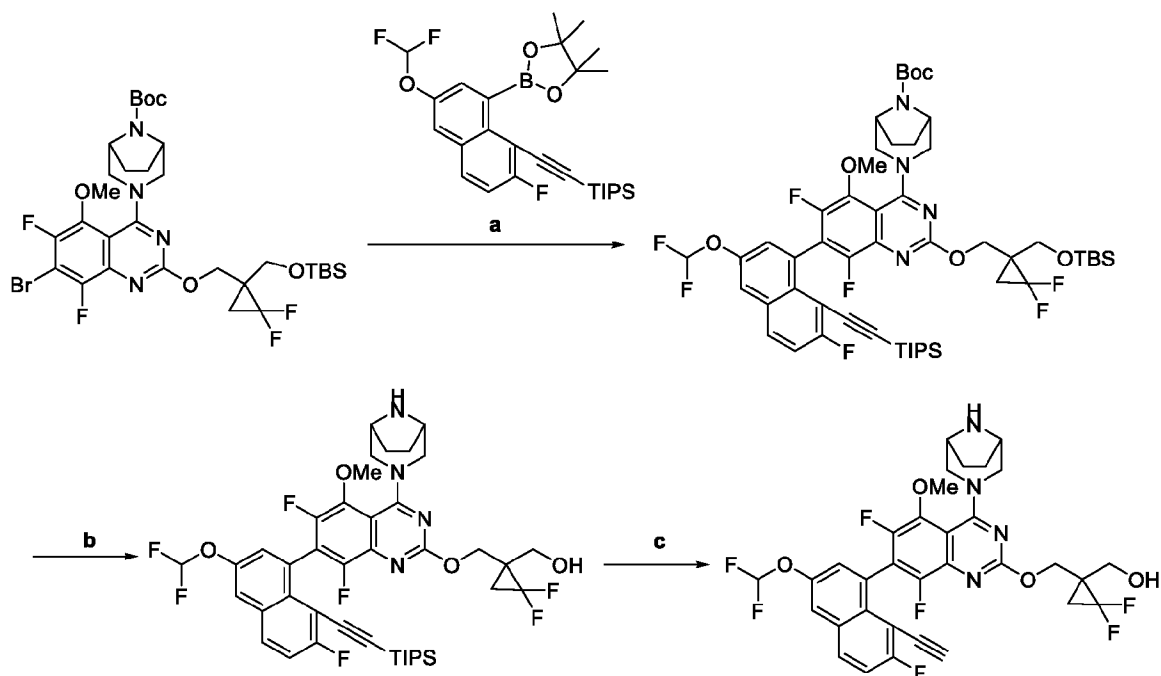
(144 mg, 0.945 mmol, 15.0 eq). The reaction mixture was stirred at 40 °C for 6 h. Then the reaction mixture was filtered, and the filtrate was purified by Prep-HPLC (acetonitrile with 0.1% FA in water, 15% to 50%) to give 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(3-(difluoromethoxy)-8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline (19.6 mg, with 0.8 FA salt, 41.8% for two steps) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.37 – 8.17 (m, 2H), 8.03 (d, *J* = 2.0 Hz, 1H), 7.74 – 7.21 (m, 3H), 5.27 (d, *J* = 52.0 Hz, 1H), 4.30-3.90 (m, 4H), 3.77 (s, 4H), 3.60-3.20 (m, 6H), 3.10-2.90 (m, 3H), 3.01 (s, 1H), 2.90-2.70 (m, 1H), 2.20-1.51 (m, 10H). LCMS: *m/z* 698.2 (M+H⁺).

Example 48

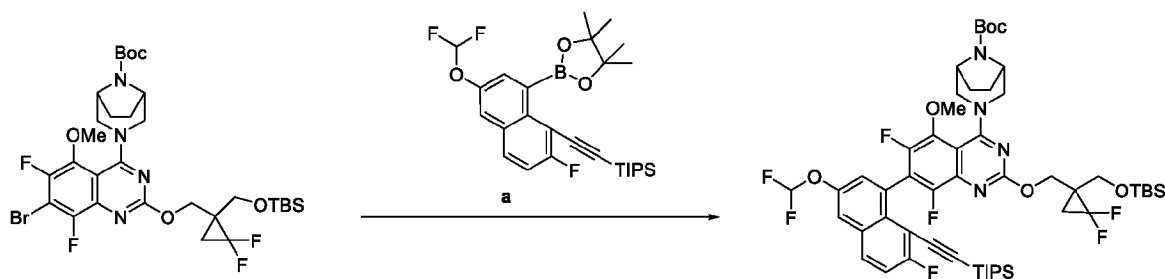
(1-(((4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(3-(difluoromethoxy)-8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-5-methoxyquinazolin-2-yl)oxy)methyl)-2,2-difluorocyclopropyl)methanol formate



Synthetic scheme:



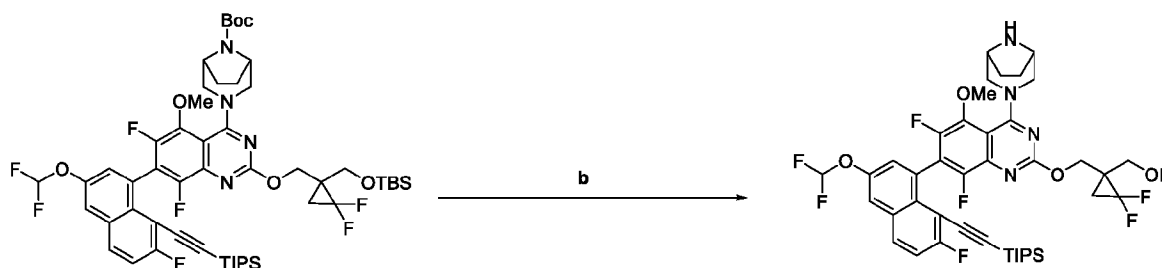
Step 1: Synthesis of tert-butyl 3-(2-((1-(((tert-butyl(dimethyl)silyl)oxy)methyl)-2,2-difluorocyclopropyl)methoxy)-7-(3-(difluoromethoxy)-7-fluoro-8-(((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00522] To a solution of tert-butyl 3-(7-bromo-2-((1-(((tert-butyl(dimethyl)silyl)oxy)methyl)-2,2-difluorocyclopropyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.13 mmol, 1.0 eq) and ((6-(difluoromethoxy)-2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (84.5 mg, 0.16 mmol, 1.2 eq) in toluene (1.5 mL) and H₂O (0.3 mL) was added K₃PO₄ (55.1 mg, 0.26 mmol, 2.0 eq), rac-BI-DIME (8.6 mg, 0.026 mmol, 0.2 eq) and Pd₂(dba)₃ (18.3 mg, 0.02 mmol, 0.15 eq). The mixture was heated under microwave irradiation at 120 °C for 1 h under N₂. The reaction mixture was partitioned between EtOAc (5 mL) and H₂O (3 mL). The layers were separated. The aqueous layer was extracted with EtOAc (5 mL x 3). The

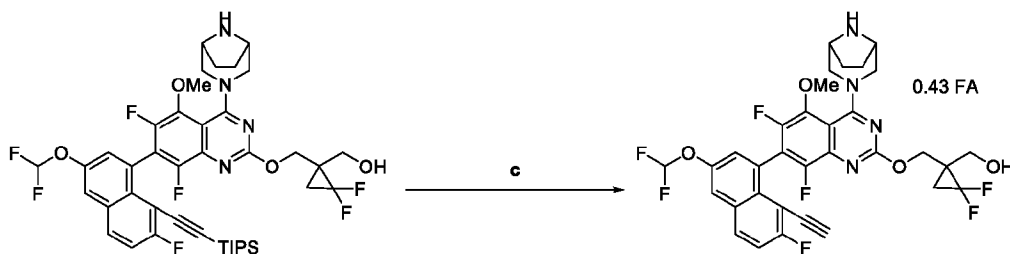
combined organic layers were washed with brine (3 mL), dried over Na₂SO₄ and concentrated to give a crude. The crude was purified by Prep-TLC (DCM: MeOH ~ 15: 1) to give tert-butyl 3-(2-((1-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-difluorocyclopropyl)methoxy)-7-(3-(difluoromethoxy)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (52 mg, 36.4%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 7.85 (dd, *J* = 9.2, 6.0 Hz, 1H), 7.63 (d, *J* = 2.2 Hz, 1H), 7.38 (t, *J* = 8.8 Hz, 1H), 7.27 (s, 1H), 6.63 (t, *J* = 73.2 Hz, 1H), 4.63 – 4.53 (m, 1H), 4.49 – 4.40 (m, 1H), 4.30 (s, 2H), 3.96 (s, 3H), 3.88 – 3.83 (m, 1H), 3.84 – 3.79 (m, 1H), 3.59 – 3.30 (m, 2H), 2.12 – 2.01 (m, 1H), 1.98 – 1.89 (m, 2H), 1.78 – 1.63 (m, 1H), 1.50 (s, 9H), 1.39 – 1.33 (m, 1H), 1.29 – 1.25 (m, 1H), 0.95 – 0.88 (m, 29H), 0.72 – 0.63 (m, 3H), 0.04 (s, 6H).

Step 2: Synthesis of (1-(((4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(3-(difluoromethoxy)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-5-methoxyquinazolin-2-yl)oxy)methyl)-2,2-difluorocyclopropyl)methanol



[00523] To a solution of tert-butyl 3-(2-((1-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-difluorocyclopropyl)methoxy)-7-(3-(difluoromethoxy)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (52 mg, 0.05 mmol, 1.0 eq) in DCM (1.0 mL) was added HCl/Dioxane (0.3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h under N₂. The mixture was concentrated to give (1-(((4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(3-(difluoromethoxy)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-5-methoxyquinazolin-2-yl)oxy)methyl)-2,2-difluorocyclopropyl)methanol (45 mg, crude) as a yellow solid. LCMS: 833.0 (M+H⁺).

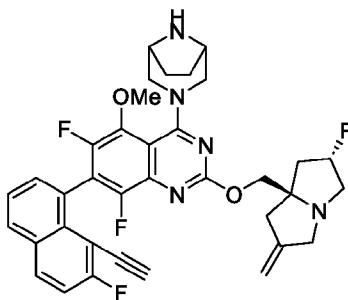
Step 3: Synthesis of (1-(((4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(3-(difluoromethoxy)-8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-5-methoxyquinazolin-2-yl)oxy)methyl)-2,2-difluorocyclopropyl)methanol formate(1:0.43)



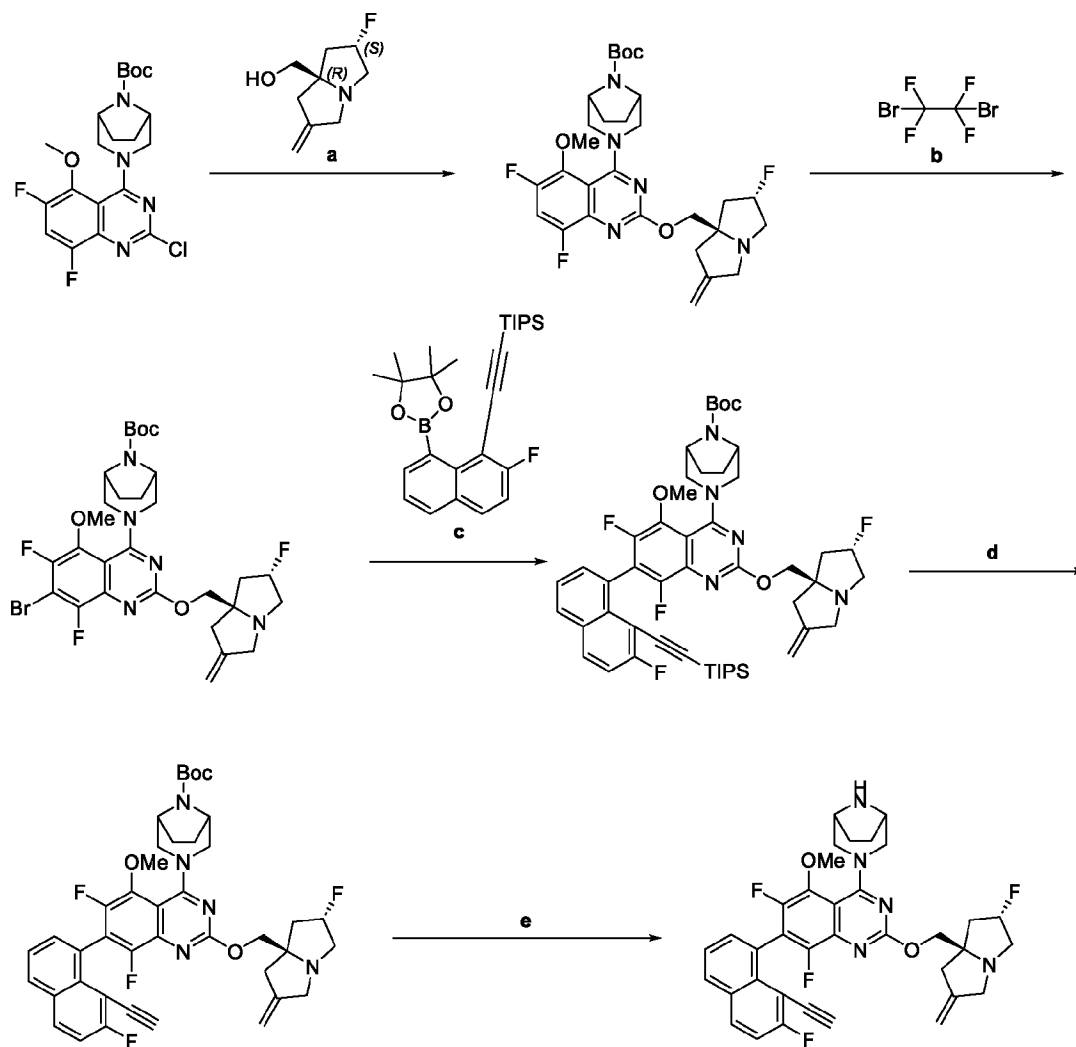
[00524] To a solution of (1-(((4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(3-(difluoromethoxy)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-5-methoxyquinazolin-2-yl)oxy)methyl)-2,2-difluorocyclopropyl)methanol (45 mg, 0.54 mmol, 1.0 eq) in DMF (2.0 mL) was added CsF (1.6 g, 10.4 mmol, 20.0 eq). The mixture was stirred at 50 °C for 4 h. The mixture was concentrated to give a crude. The crude was purified by Prep-HPLC (ACN with 0.1% FA in water, 15% to 50%) to give (1-(((4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(3-(difluoromethoxy)-8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-5-methoxyquinazolin-2-yl)oxy)methyl)-2,2-difluorocyclopropyl)methanol formate(1:0.43) (22.4 mg, 62.4%, two steps yield) as a white solid. ¹H NMR (400 MHz, CD₃OD): δ 8.52 (brs, 0.43H), 8.10 (dd, *J* = 9.2, 6.0 Hz, 1H), 7.86 (d, *J* = 2.4 Hz, 1H), 7.49 (t, *J* = 8.8 Hz, 1H), 7.42 (d, *J* = 2.4 Hz, 1H), 7.05 (t, *J* = 73.4 Hz, 1H), 4.71 – 4.66 (m, 1H), 4.60 – 4.48 (m, 2H), 4.12 (d, *J* = 13.6 Hz, 1H), 4.01 (d, *J* = 17.4 Hz, 2H), 3.90 (s, 3H), 3.78 (s, 2H), 3.69 (d, *J* = 13.6 Hz, 1H), 3.58 – 3.46 (m, 2H), 2.29 – 2.12 (m, 1H), 2.08– 1.90 (m, 3H), 1.64 – 1.53 (m, 1H), 1.52– 1.43 (m, 1H). ¹⁹F NMR (400 MHz, CD₃OD): δ -84.083, -107.016, -131.938, -137.726, -138.620 (d, *J*_{F-F} = 172.4 Hz, *J*_{F-H} = 5.6 Hz, 1F), -140.322 (d, *J*_{F-F} = 172.4 Hz, 1F). LCMS: 677.0 (M+H⁺).

Example 49

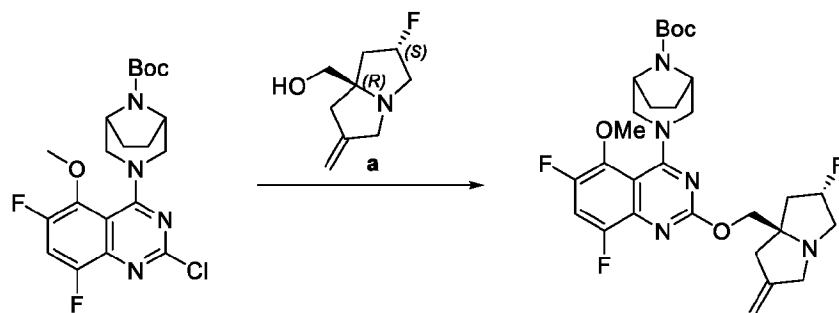
4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline formate



Synthesis scheme



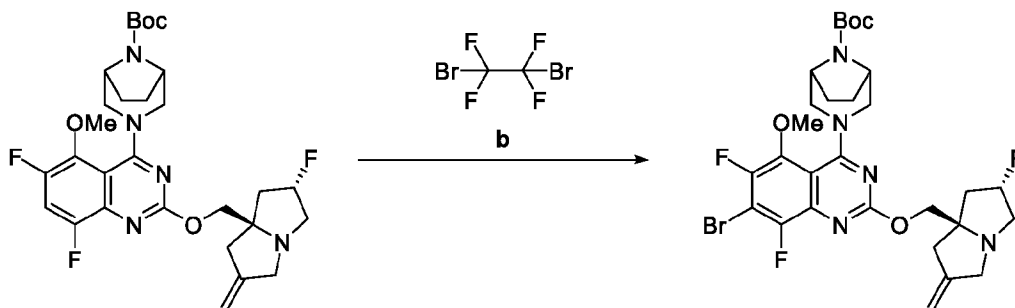
Step 1: Synthesis of tert-butyl 3-(6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00525] To a solution of tert-butyl 3-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (270 mg, 0.61 mmol, 1.0 eq) in THF (3 mL) and DMF

(3 mL) was added ((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (136 mg, 0.80 mmol, 1.3 eq), DABCO (69 mg, 0.61 mmol, 1.0 eq) and Cs₂CO₃ (598 mg, 1.84 mmol, 3.0 eq). The reaction mixture was stirred at room temperature for 15 h under N₂. The reaction mixture was partitioned between EtOAc (5 mL) and water (5 mL). The layers were separated. The aqueous layer was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated to give a crude. The crude was purified by Prep-TLC (petroleum ether / EtOAc = 1:1) to give tert-butyl 3-(6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (300 mg, 85.2%) as a green solid. ¹H NMR (400 MHz, CDCl₃): δ 7.23 (t, *J* = 10.8 Hz, 1H), 5.32 (d, *J* = 54.0 Hz, 1H), 4.97 (s, 2H), 4.40 – 4.01 (m, 6H), 3.97 – 3.84 (m, 1H), 3.78 (s, 3H), 3.66 – 3.57 (m, 1H), 3.53 – 3.30 (m, 3H), 3.20 – 3.11 (m, 1H), 2.88 – 2.68 (m, 2H), 2.44 – 2.23 (m, 2H), 1.92 – 1.80 (m, 2H), 1.76 – 1.63 (m, 2H), 1.49 (s, 9H). LCMS: 576.3 (M+H⁺).

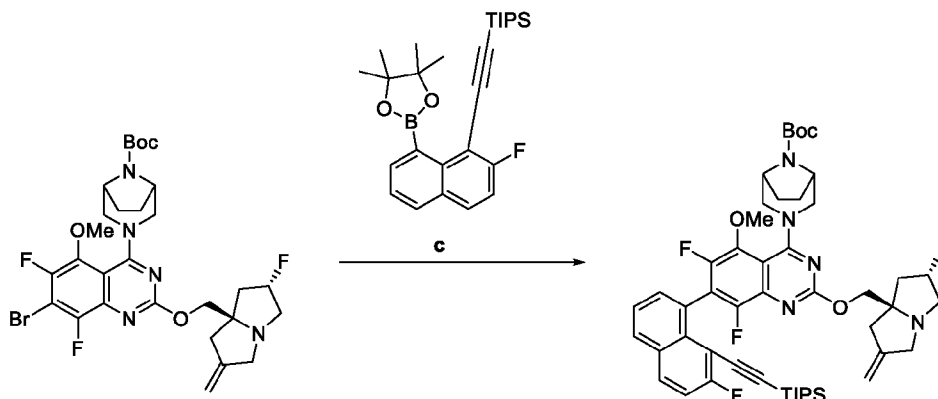
Step 2: Synthesis of tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00526] To a solution of tert-butyl 3-(6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (80 mg, 0.14 mmol, 1.0 eq) in THF (2 mL) was added LDA (0.2 mL, 0.3 mmol, 2.0 eq) at -78 °C under N₂ atmosphere. The mixture was stirred at -78 °C for 30 min. The mixture was added 1,2-dibromo-1,1,2,2-tetrafluoroethane (108 mg, 0.42 mmol, 3.0 eq) at the same temperature, and stirred for 2 h. The reaction was quenched with water (5 mL). The mixture was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with H₂O (5 mL), brine (5 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by Prep-TLC (DCM / MeOH = 15:1) to give tert-butyl 3-(7-bromo-6,8-

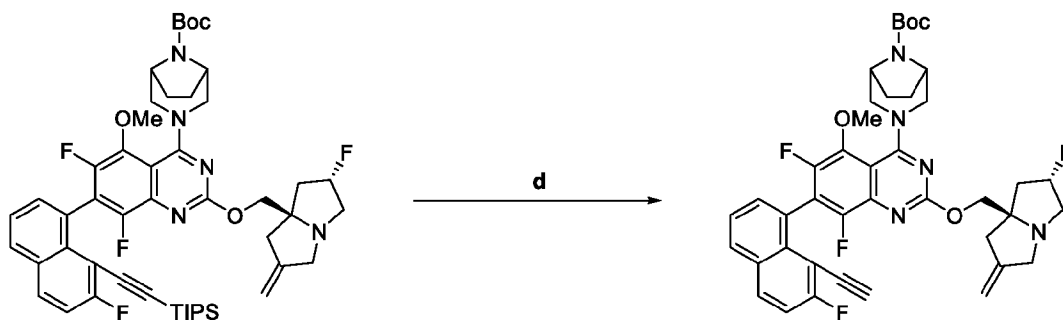
difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (60 mg, 65.9%) as a green solid. LCMS: 654.2, 656.1 ($M+H^+$).

Step 3: Synthesis of tert-butyl 3-(6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



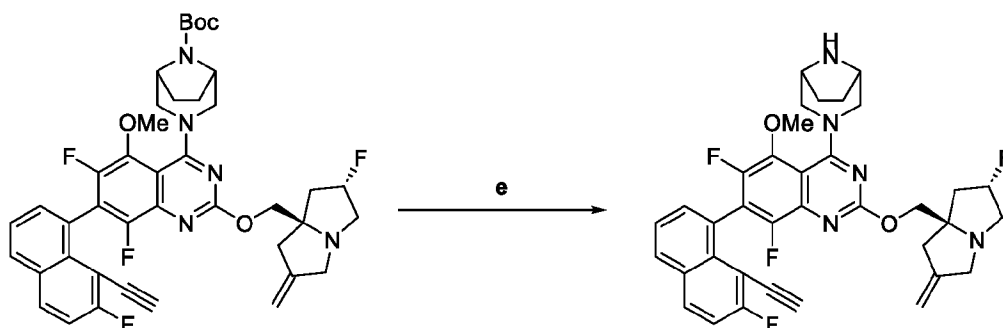
[00527] To a solution of tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (70 mg, 0.11 mmol, 1.0 eq) and ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (73 mg, 0.16 mmol, 1.5 eq) in Toluene (1.5 mL) and H₂O (0.3 mL) was added K₃PO₄ (45 mg, 0.21 mmol, 2.0 eq), rac-BI-DIME (7 mg, 0.03 mmol, 0.3 eq) and Pd₂(dba)₃ (15 mg, 0.02 mmol, 0.15 eq). The mixture was heated under microwave irradiation at 120 °C for 1 h under N₂. The reaction mixture was partitioned between EtOAc (5 mL) and H₂O (5 mL). The layers were separated. The aqueous layer was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄ and concentrated to a crude. The crude was purified by Prep-TLC (DCM / MeOH = 15:1) to give tert-butyl 3-(6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (50 mg, 51.9%) as a white solid. LCMS: 900.3 ($M+H^+$).

Step 4: Synthesis of tert-butyl 3-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00528] To a mixture of tert-butyl 3-(6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (50 mg, 0.06 mmol, 1.0 eq) in DMF (1 mL) was added CsF (253 mg, 1.67 mmol, 30.0 eq). The mixture was stirred at 50 °C for 2 h. The filtrate was collected by filtration and concentrated to give a residue. The residue was re-dissolved in DCM/MeOH (10/1, 5 mL), filtered and concentrated to give tert-butyl 3-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (45 mg, crude) as a yellow solid. LCMS: 744.3 (M+H⁺).

Step 5: Synthesis of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline formate (1:1)

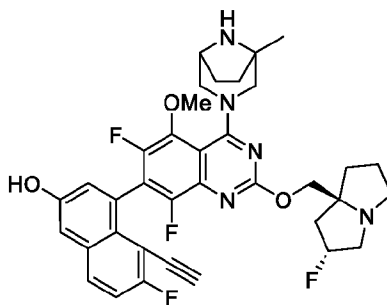


[00529] To a solution of tert-butyl 3-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (45 mg, 0.06 mmol, 1.0 eq) in DCM (1 mL) was added TFA (0.1 mL, 0.6 mmol, 10.0 eq) at 0 °C. The mixture was stirred at room temperature for 1 h. The reaction was adjusted pH~8 with NH₃•H₂O. The mixture

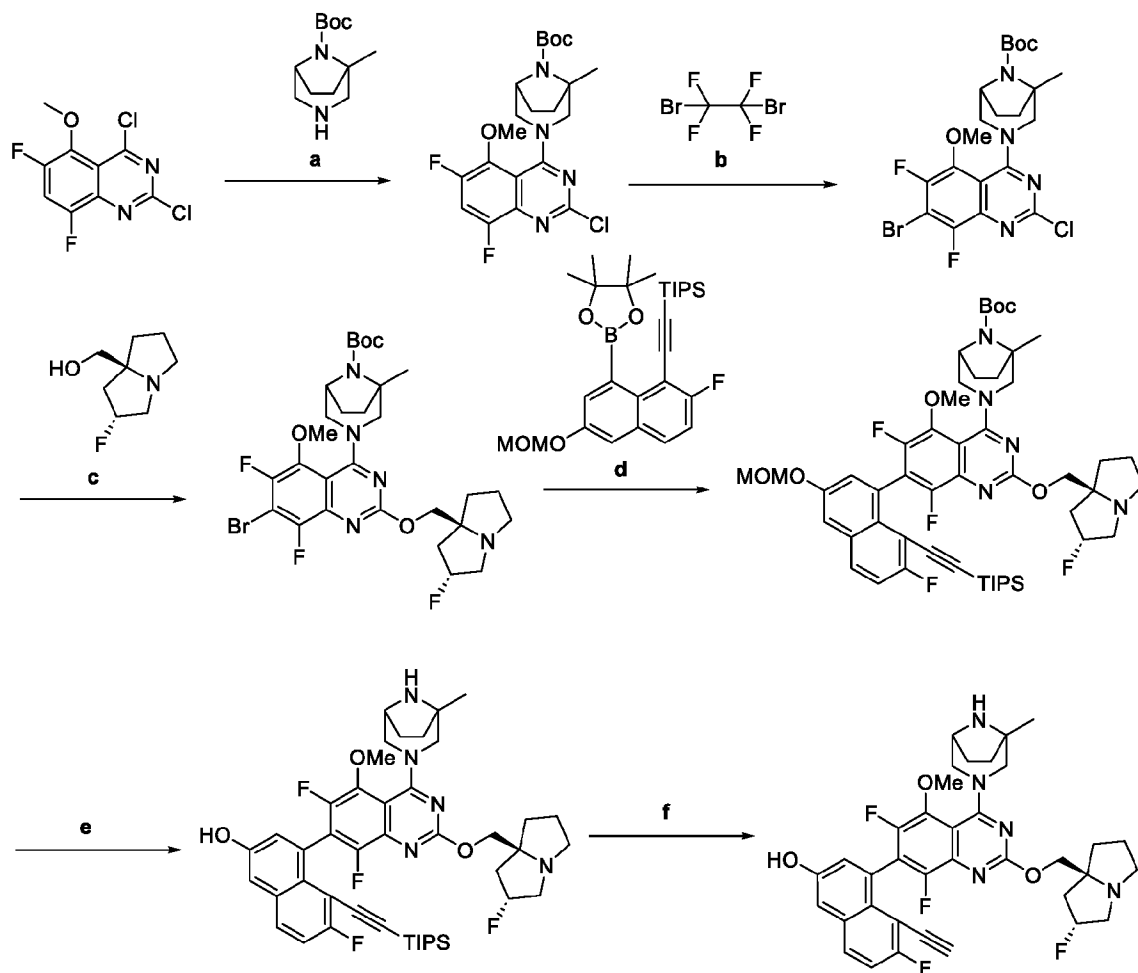
was concentrated to give a crude. The crude was purified by Prep-HPLC (ACN with 0.1% FA in water, 5% to 35%) to give 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline formate (1:1) (16 mg, 41.2% for two steps) as a white solid. ¹H NMR (400 MHz, CD₃OD): δ 8.20 – 8.08 (m, 2H), 7.66 (t, J = 7.2 Hz, 1H), 7.56 (d, J = 7.2 Hz, 1H), 7.46 (t, J = 8.8 Hz, 1H), 5.39 (d, J = 53.6 Hz, 1H), 5.04 (s, 2H), 4.63 – 4.48 (m, 1H), 4.45 – 4.30 (m, 2H), 4.24 – 4.07 (m, 3H), 4.02 – 3.92 (m, 1H), 3.91 (s, 3H), 3.82 – 3.57 (m, 2H), 3.65 – 3.43 (m, 3H), 3.42 – 3.25 (m, 1H), 2.92 – 2.76 (m, 2H), 2.53 – 2.23 (m, 3H), 2.21 – 2.01 (m, 3H). ¹⁹F NMR (400 MHz, CD₃OD): -106.358, -131.969, -136.594, -173.647. LCMS: 644.3 (M+H⁺).

Example 50

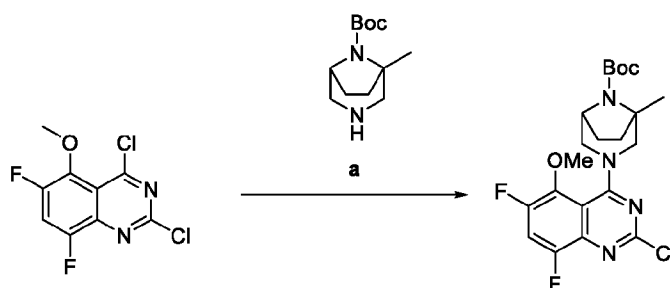
4-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-4-(1-methyl-3,8-diazabicyclo [3.2.1]octan-3-yl)quinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate



Synthetic scheme:



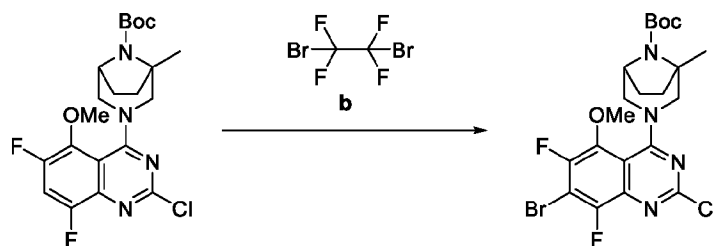
Step 1: Synthesis of *tert*-butyl 3-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-1-methyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of 2,4-dichloro-6,8-difluoro-5-methoxyquinazoline (1.4 g, 5.3 mmol, 1.2 eq) in DCM (15 mL) was added DIEA (5.0 g, 38.4 mmol, 8.7 eq) and *tert*-butyl 1-methyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.0 g, crude, 4.4 mmol, 1.0 eq) in DCM (4 mL) at -40 °C under argon. After that, the reaction mixture was stirred for 1 h at -40 °C. Then the reaction mixture was quenched with water (20 mL) and separated. The aqueous layer was

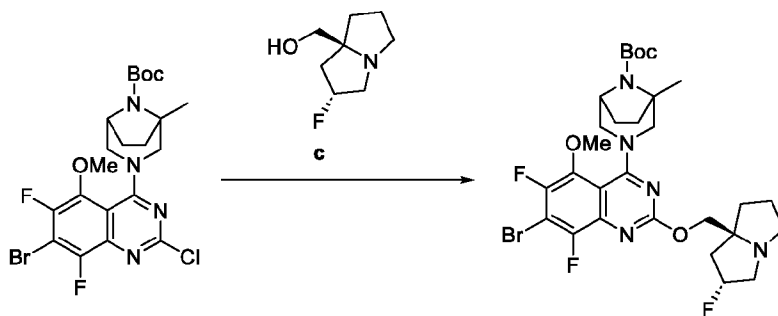
extracted with DCM (20 mL x 3). The organic layers were washed with brine (20 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by silica gel column chromatography (petroleum ether / EtOAc = 20:1) to give tert-butyl 3-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-1-methyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (231 mg, 25.5% for two steps) as a yellow solid. LCMS: 455.1 (M+H⁺).

Step 2: Synthesis of tert-butyl 3-(7-bromo-2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-1-methyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



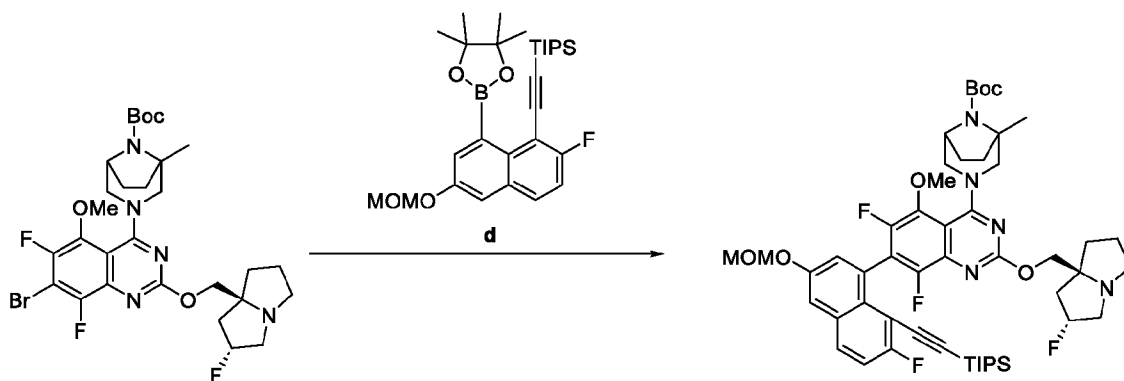
[00530] To a solution of tert-butyl 3-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-1-methyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (60 mg, 0.13 mmol, 1.0 eq) in THF (2 mL) was added LDA (0.4 mL, 0.80 mmol, 6.0 eq) at -65 °C under N₂ atmosphere. The mixture was stirred at -65 °C for 30 min. The mixture was added 1,2-dibromo-1,1,2,2-tetrafluoroethane (103 mg, 0.40 mmol, 3.0 eq) at the same temperature, and stirred for 2 h. The reaction was quenched with water (5 mL). The mixture was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄ and concentrated to give a crude. The crude product was purified by prep-TLC (petroleum ether / EtOAc = 2:1) to give tert-butyl 3-(7-bromo-2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-1-methyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (51 mg, 72.4%) as a green solid. LCMS: 533.0, 535.0 (M+H⁺).

Step 3: Synthesis of tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1-methyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00531] A solution of tert-butyl 3-(7-bromo-2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-1-methyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (90 mg, 0.17 mmol, 1.0 eq), ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (35 mg, 0.22 mmol, 1.3 eq), DABCO (19 mg, 0.17 mmol, 1.0 eq) and Cs_2CO_3 (165 mg, 0.51 mmol, 3.0 eq) in THF (1.0 mL) and DMF (1.0 mL) was stirred at room temperature for 15 h under nitrogen atmosphere. The mixture was added H_2O (2 mL). The resulting mixture was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with H_2O (3 mL x 3), brine (3 mL), dried over Na_2SO_4 and concentrated to give a crude. The crude product was purified by silica gel column chromatography (DCM / MeOH = 15:1) to give tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1-methyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (90 mg, 81.1%) as a white solid. LCMS: 656.2, 658.2 ($\text{M}+\text{H}^+$).

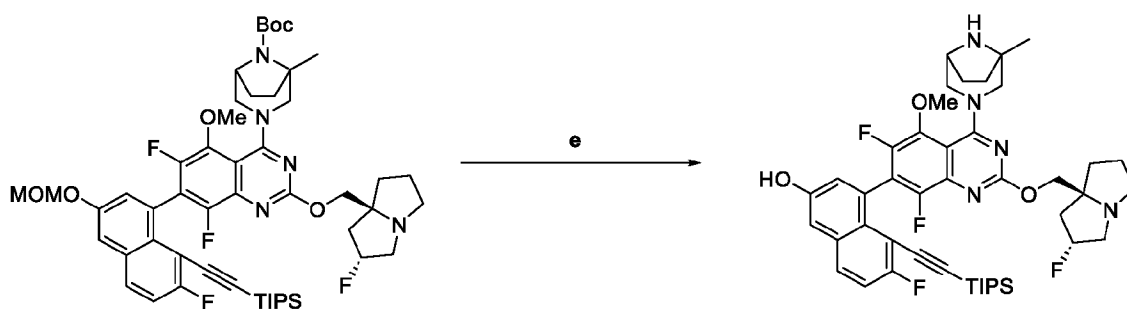
Step 4: Synthesis of tert-butyl 3-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1-methyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00532] To a solution of tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1-methyl-3,8-diazabicyclo

[3.2.1]octane-8-carboxylate (45 mg, 0.07 mmol, 1.0 eq) and ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (53 mg, 0.10 mmol, 1.5 eq) in Toluene (1.5 mL) and H₂O (0.3 mL) was added K₃PO₄ (19 mg, 0.14 mmol, 2.0 eq), rac-BI-DIME (5 mg, 0.01 mmol, 0.2 eq) and Pd₂(dba)₃ (9 mg, 0.01 mmol, 0.15 eq). The mixture was heated under microwave irradiation at 120 °C for 1 h under N₂. The reaction mixture was partitioned between EtOAc (5 mL) and H₂O (3 mL). The layers were separated. The aqueous layer was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (3 mL), dried over Na₂SO₄ and concentrated to a crude. The crude was purified by Prep-TLC (DCM / MeOH = 15:1) to give tert-butyl 3-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1-methyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (25 mg, 37.7%) as a white solid. LCMS: 962.4 (M+H⁺).

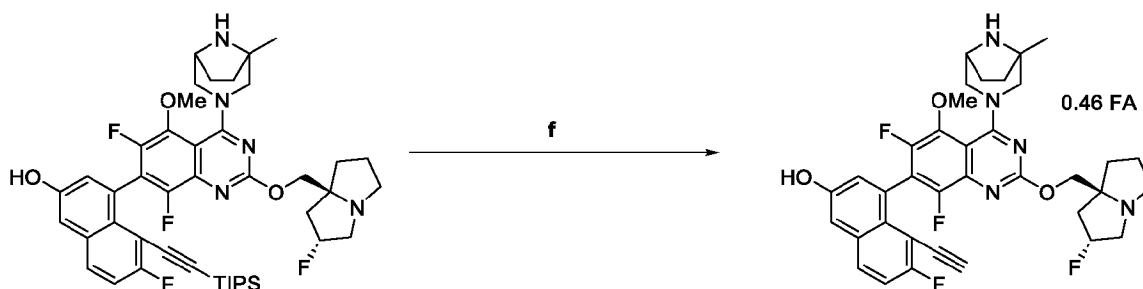
Step 5: Synthesis of 4-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-4-(1-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)quinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol



[00533] To a solution of tert-butyl 3-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-1-methyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (35 mg, 0.04 mmol, 1.0 eq) in DCM (1 mL) was added HCl in dioxane (0.3 mL, 1.2 mmol, 33.3 eq) at room temperature. The mixture was stirred at room temperature for 1 h. The reaction was adjusted to pH~8 with NH₃-H₂O. The mixture was concentrated to give a residue. The residue was re-dissolved in DCM/MeOH (10:1, 5 mL). The filtrate collected by filtration was concentrated to give 4-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-4-(1-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)quinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol

fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (30 mg, crude) as a yellow solid. LCMS: 818.3 ($M+H^+$).

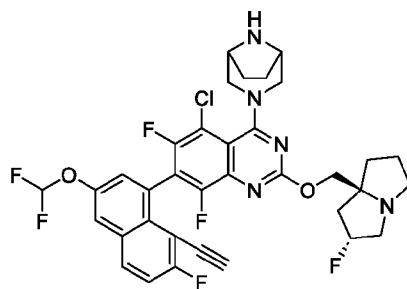
Step 6: Synthesis of 4-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-4-(1-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)quinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate (1:0.46)



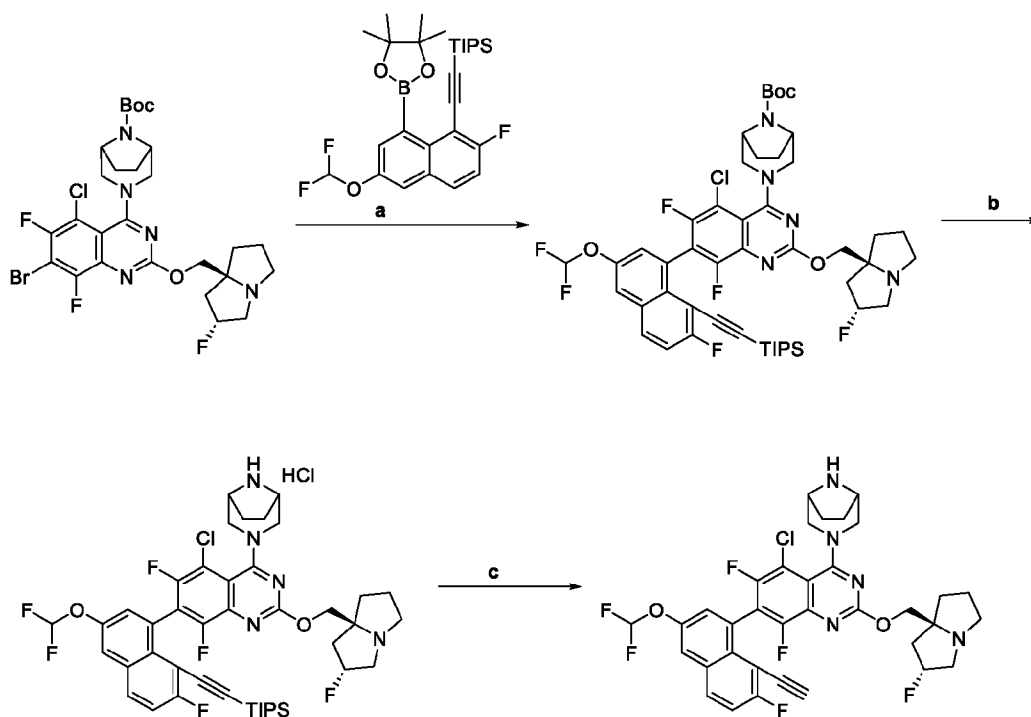
[00534] To a mixture of 4-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-4-(1-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)quinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (30 mg, 0.04 mmol, 1.0 eq) in DMF (1 mL) was added CsF (85 mg, 0.56 mmol, 15.0 eq). The mixture was stirred at 50 °C for 2 h. The filtrate collected by filtration was concentrated to give a crude. The crude was purified by Prep-HPLC (ACN with 0.1% FA in water, 5% to 35%) to give 4-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-4-(1-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)quinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate (1:0.46) (21 mg, 81.7% for two steps) as a white solid. ^1H NMR (400 MHz, CD_3OD): δ 8.51 (brs, 0.46H), 7.87 (dd, J = 9.2, 5.6 Hz, 1H), 7.40 – 7.28 (m, 2H), 7.13 (s, 1H), 5.38 (d, J = 52.8 Hz, 1H), 4.59 – 4.29 (m, 3H), 4.09 – 3.93 (m, 1H), 3.88 (s, 3H), 3.87 – 3.77 (m, 1H), 3.72 – 3.34 (m, 6H), 3.21 – 3.10 (m, 1H), 2.50 – 1.55 (m, 10H), 1.42 (d, J = 12.4 Hz, 3H). ^{19}F NMR (400 MHz, CD_3OD): δ -111.267, -132.701, -137.411, -173.935. LCMS: 662.2 ($M+H^+$).

Example 51

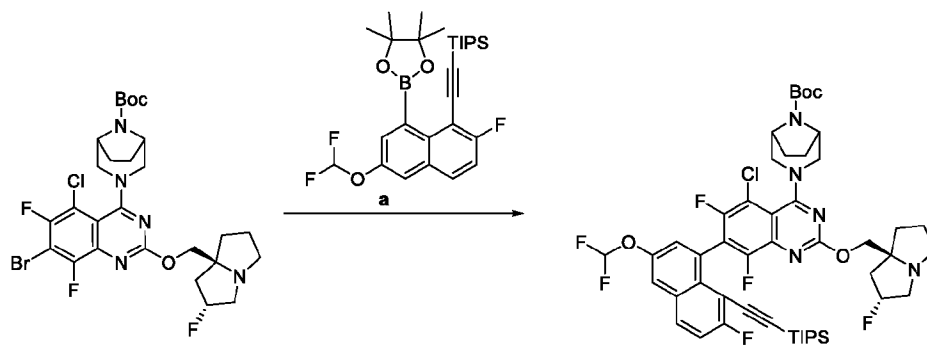
4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-chloro-7-(3-(difluoromethoxy)-8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazoline formate



Synthetic scheme:

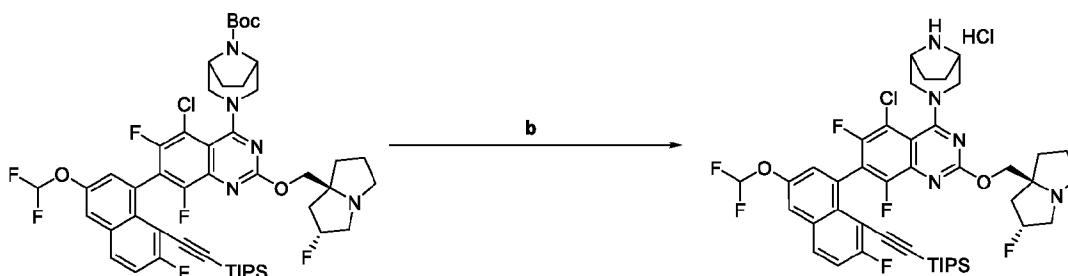


Step 1: Synthesis of tert-butyl 3-(5-chloro-7-(3-(difluoromethoxy)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



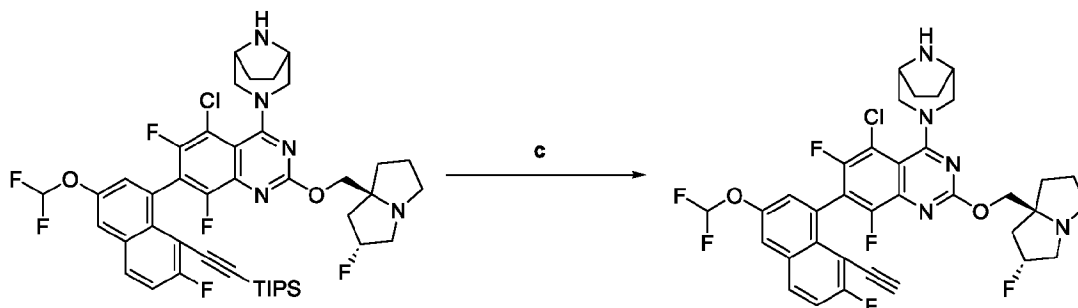
[00535] To a solution of tert-butyl 3-(7-bromo-5-chloro-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (110 mg, 0.17 mmol, 1.0 eq) in toluene (2.0 mL) was added ((6-(difluoromethoxy)-2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (97 mg, 0.19 mmol, 1.2 eq), K_3PO_4 (108 mg, 0.51 mmol, 3.0 eq), rac-BI-DIME (8 mg, 0.02 mmol, 0.15 eq), $Pd_2(dba)_3$ (47 mg, 0.05 mmol, 0.3 eq) and H_2O (0.4 mL) at room temperature. The reaction mixture was heated under microwave irradiation under nitrogen atmosphere at 120 °C for 1 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The organic phase was washed with brine (10 mL), dried with Na_2SO_4 , filtered and concentrated to give a crude. The crude was purified by prep-TLC (DCM : MeOH = 15 : 1) to give tert-butyl 3-(5-chloro-7-(3-(difluoromethoxy)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (120 mg, 73.5%) as a yellow solid. LCMS: 958.2 ($M+H^+$).

Step 2: Synthesis of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-chloro-7-(3-(difluoromethoxy)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazoline hydrochloride



[00536] To a solution of tert-butyl 3-(5-chloro-7-(3-(difluoromethoxy)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (110 mg, 0.11 mmol, 1.0 eq) in DCM (2.0 mL) was added HCl in dioxane (1.0 mL, 4M in dioxane). Then the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to give 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-chloro-7-(3-(difluoromethoxy)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazoline hydrochloride (110 mg, crude) as a yellow solid. LCMS: 858.1 ($M+H^+$).

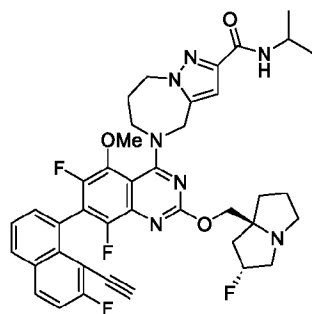
Step 3: Synthesis of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-chloro-7-(3-(difluoromethoxy)-8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazoline formate (1:0.6)



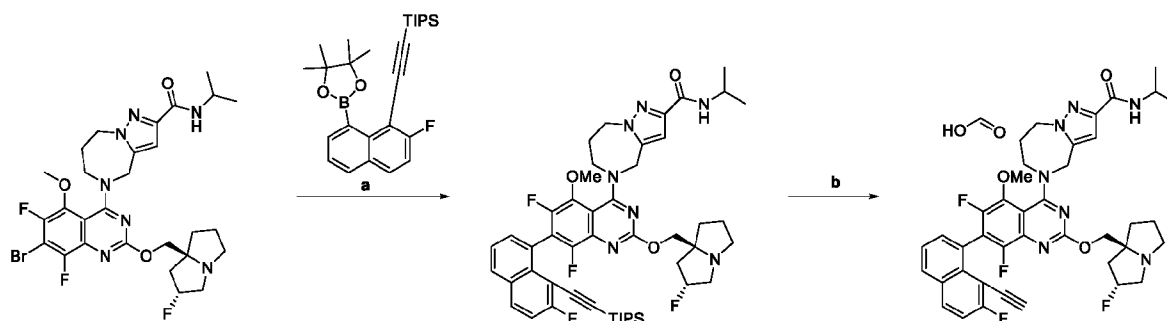
[00537] To solution of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-chloro-7-(3-(difluoromethoxy)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazoline hydrochloride (110 mg, 0.13 mmol, 1.0 eq) in DMF (1.0 mL) was added CsF (494 mg, 3.25 mmol, 25 eq). The reaction mixture was stirred at 40 °C for 30 min. The mixture was diluted by MeOH (1.0 mL) and purified by prep-HPLC (acetonitrile with 0.1% FA in water, 10% to 60%) to give 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-chloro-7-(3-(difluoromethoxy)-8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazoline formate (1:0.6) (37.9 mg, 45.2% yield for two steps) as white solid. ¹H NMR (400 MHz, CD₃OD): δ 8.51 (s, 0.6H), 8.11 (dd, *J* = 9.2, 5.6 Hz, 1H), 7.88 (d, *J* = 2.4 Hz, 1H), 7.60 – 7.43 (m, 2H), 7.06 (t, *J* = 73.6 Hz, 1H), 5.37 (d, *J* = 52.8 Hz, 1H), 4.70 – 4.30 (m, 3H), 4.25 – 4.05 (m, 1H), 4.05 – 3.89 (m, 1H), 3.88 – 3.58 (m, 3H), 3.55 – 3.33 (m, 4H), 3.20 – 3.06 (m, 1H), 2.50 – 2.28 (m, 2H), 2.28 – 2.15 (m, 1H), 2.14 – 2.02 (m, 2H), 2.02 – 1.40 (m, 5H). ¹⁹F NMR (300 MHz, CD₃OD): δ -84.149, -106.822, -118.688, -127.162, -173.784. LCMS: 702.0 (M+H⁺).

Example 52

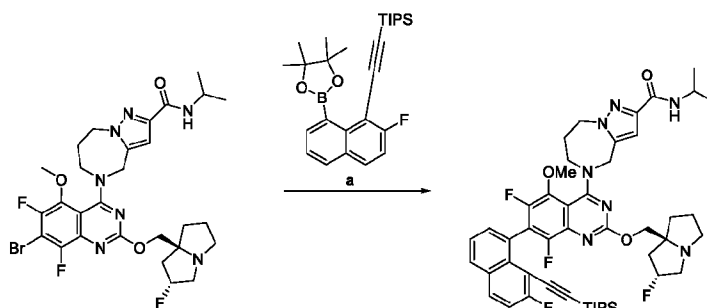
5-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide formate



Synthesis scheme



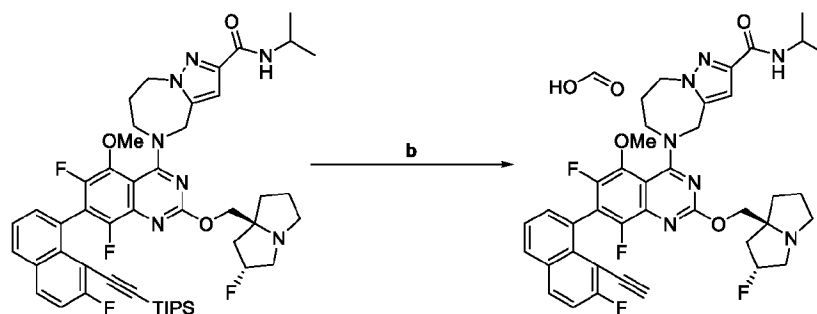
Step 1: Synthesis of 5-(6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



[00538] To a solution of compound 5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (25 mg, 0.038 mmol, 1.0 eq) in PhMe (2 mL) and H₂O (0.4 mL) was added ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (35 mg, 0.077 mmol, 2.0 eq), K₃PO₄ (24 mg, 0.12 mmol, 3.0 eq), rac-BI-DIME (2 mg, 0.0058 mmol, 0.15 eq) and Pd₂(dba)₃ (11 mg, 0.012 mmol, 0.3 eq). The reaction mixture was stirred at 100 °C for 15 h under nitrogen atmosphere. The reaction mixture was poured into water (10 mL). The aqueous layer was extracted with ethyl

acetate (10 mL x 3). The combined organic layers were washed with H₂O (10 mL), brine (10 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (Dichloromethane: Methanol = 60: 1) to give 5-(6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (17 mg, 49.3%) as a yellow solid. LCMS: 898.1 (M+H⁺).

Step 2: Synthesis of 5-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide formate (1:0.3)

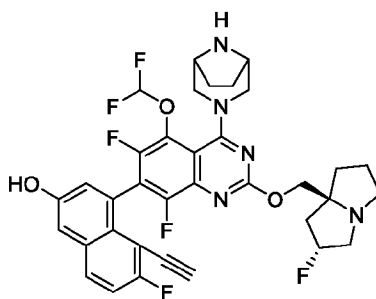


[00539] To a solution of 5-(6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (20 mg, 0.022 mmol, 1.0 eq) in DMF (1 mL) was added CsF (34 mg, 0.22 mmol, 10.0 eq) at room temperature. The reaction was stirred at 40 °C for 1 h. The mixture was filtered and concentrated to give residue. The residue was purified by Prep-HPLC (acetonitrile with 0.1% FA in water, 10% to 60%) to give 5-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide formate (1:0.3) (5.4 mg, 32.7%) as a white solid. ¹H NMR (400 MHz, CD₃OD): δ 8.53 (brs, 0.3H), 8.20 – 8.03 (m, 2H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 8.8 Hz, 1H), 6.58 (s, 1H), 5.33 (d, *J* = 53.6 Hz, 1H), 5.05 (s, 2H), 4.53 – 4.33 (m, 2H), 4.29 – 4.01 (m, 5H), 3.82 (s, 3H), 3.49 – 3.40 (m, 1H), 3.39 – 3.37 (m, 2H), 3.36 – 3.31 (m, 1H), 3.13 – 3.02 (m, 1H), 2.42 – 2.09 (m, 5H),

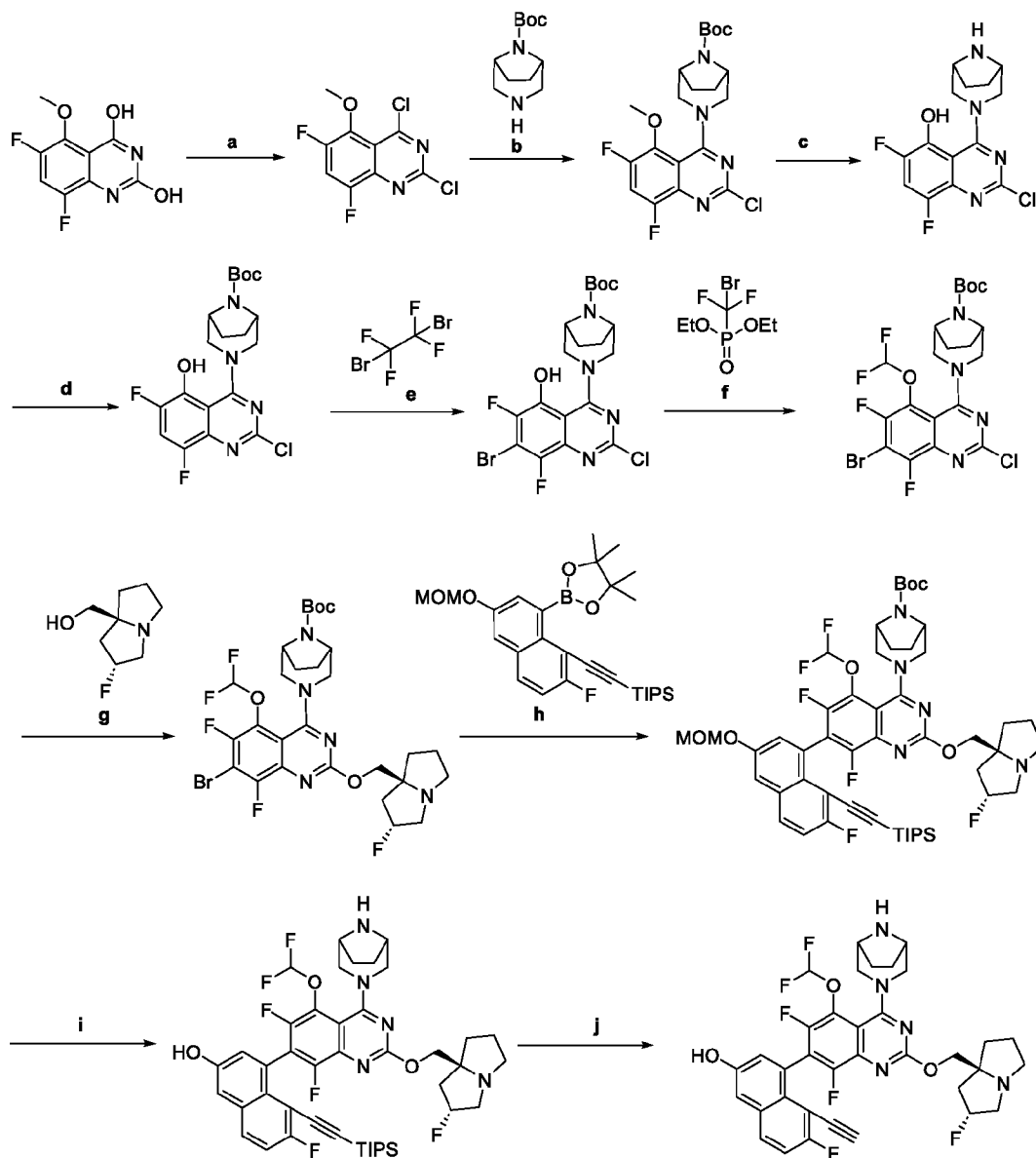
2.09 – 1.97 (m, 2H), 1.97 – 1.79 (m, 1H), 1.23 (d, $J = 6.4$ Hz, 6H). ^{19}F NMR (400 MHz, CD_3OD): -106.428, -132.193, -137.810, -173.542. LCMS: 742.0 ($\text{M}+\text{H}^+$).

Example 53

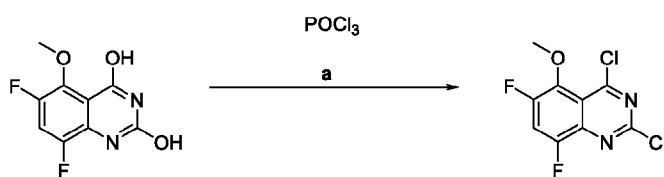
4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-(difluoromethoxy)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



Synthesis scheme



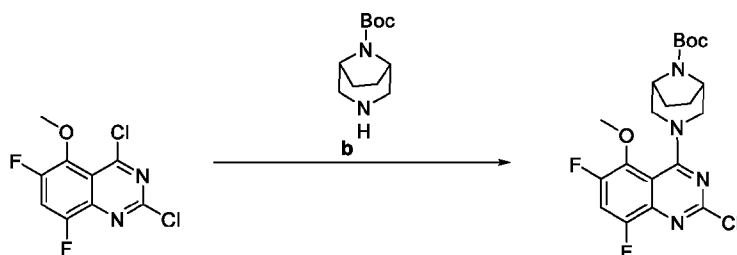
Step 1: Synthesis of 2,4-dichloro-6,8-difluoro-5-methoxyquinazoline



[00540] A solution of 6,8-difluoro-5-methoxyquinazoline-2,4-diol (500 mg, 2.19 mmol, 1.0 eq) and DIEA (592 mg, 4.58 mmol, 2.1 eq) in POCl₃ (8 mL) was stirred at 110 °C for 2 h under nitrogen atmosphere. The mixture was concentrated to give compound 2,4-dichloro-6,8-difluoro-

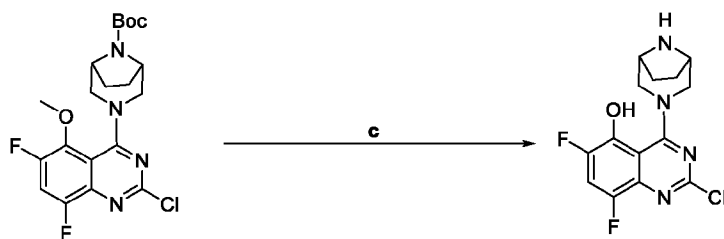
5-methoxyquinazoline (crude) as a brown solid, which was used directly for the next step without any further purification.

Step 2: Synthesis of tert-butyl 3-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00541] To a solution of 2,4-dichloro-6,8-difluoro-5-methoxyquinazoline (2.33 g, 8.8 mmol, 1.0 eq) in DCM (25 mL) was added DIEA (9.9 g, 76.56 mmol, 8.7 eq) and *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2.43 g, 11.44 mmol, 1.3 eq) at -40 °C. The reaction mixture was stirred at room temperature overnight under nitrogen atmosphere. The mixture was concentrated to give a residue. The residue was partitioned between DCM (10 mL) and water (20 mL). The layers were separated. The aqueous layer was extracted with DCM (10 mL x 3). The combined organic layers were washed brine (10 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (Petroleum ether: EtOAc = 5: 1) to give compound *tert*-butyl 3-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (860 mg, 22.2% for two steps) as a yellow solid. LCMS: *m/z* 441.1 (M+H⁺).

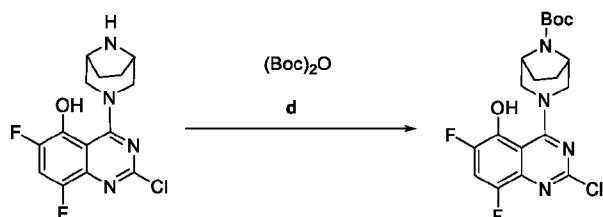
Step 3: Synthesis of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-chloro-6,8-difluoroquinazolin-5-ol



[00542] A solution of *tert*-butyl 3-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1 g, 2.27 mmol, 1.0 eq) in DCM (3.5 mL) was added BBr₃ (11.4 g, 45.36 mmol, 20.0 eq) at -60 °C. The reaction mixture was stirred at room temperature overnight. The mixture was concentrated to give crude. The crude was adjusted to

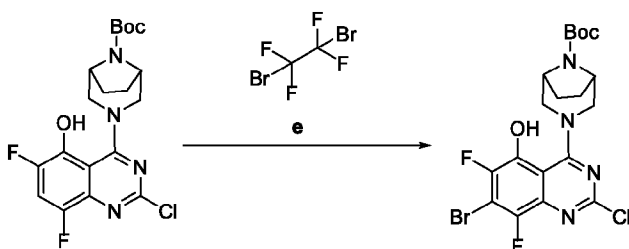
pH ~ 8 with solid NaHCO_3 , which was used directly for the next step without any further purification. LCMS: m/z 327.1 ($M+H^+$).

Step 4: Synthesis of tert-butyl 3-(2-chloro-6,8-difluoro-5-hydroxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00543] To a solution of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-chloro-6,8-difluoroquinazolin-5-ol (738 mg, 2.26 mmol, 1.0 eq) in THF/ H_2O (1/1, 80 mL) was added $(\text{Boc})_2\text{O}$ (592 mg, 2.71 mmol, 1.2 eq), NaHCO_3 (570 mg, 6.78 mmol, 3.0 eq) at 0 °C. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with H_2O (20 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to give a residue. The crude product was purified by silica gel column chromatography (Petroleum ether: EtOAc = 3: 1) to give compound tert-butyl 3-(2-chloro-6,8-difluoro-5-hydroxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (900 mg, 93.4% for two steps) as a yellow solid. LCMS: m/z 427.1 ($M+H^+$).

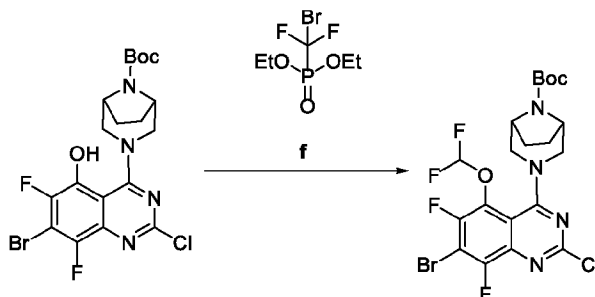
Step 5: Synthesis of tert-butyl 3-(7-bromo-2-chloro-6,8-difluoro-5-hydroxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00544] To a solution of tert-butyl 3-(2-chloro-6,8-difluoro-5-hydroxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (450 mg, 1.05 mmol, 1.0 eq) in THF (5 mL) was added LDA (2M in THF, 3.2 mL, 6.32 mmol, 6.0 eq) at -65 °C under N_2 atmosphere. After 30 min, the reaction mixture was added 1,2-dibromo-1,1,2,2-tetrafluoroethane (2.19 g, 8.43 mmol, 8.0 eq). The reaction mixture was stirred at -65 °C for 3 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10

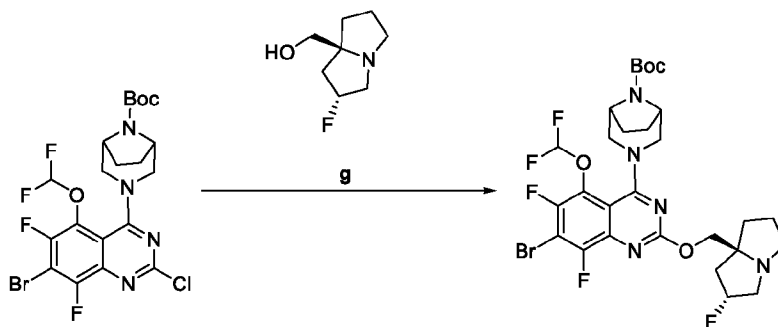
mL), dried over Na_2SO_4 and concentrated to give a residue. The crude product was purified by silica gel column chromatography (Petroleum ether: EtOAc = 5: 1) to give tert-butyl 3-(7-bromo-2-chloro-6,8-difluoro-5-hydroxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (180 mg, 33.9%) as a yellow solid. LCMS: m/z 505.1, 507.0 ($\text{M}+\text{H}^+$).

Step 6: Synthesis of tert-butyl 3-(7-bromo-2-chloro-5-(difluoromethoxy)-6,8-difluoroquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



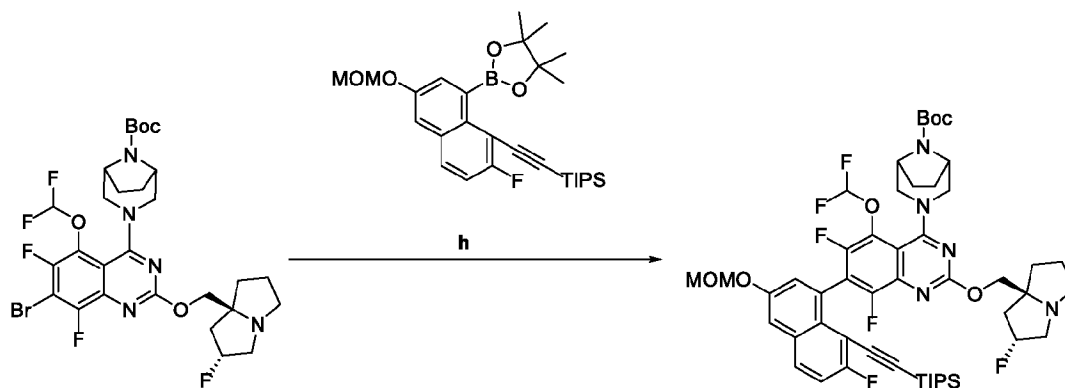
[00545] To a solution of tert-butyl 3-(7-bromo-2-chloro-6,8-difluoro-5-hydroxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (220 mg, 0.44 mmol, 1.0 eq) in ACN/ H_2O (1/1, 4.4 mL) was added KOH (488 mg, 8.7 mmol, 20.0 eq), diethyl (bromodifluoromethyl)phosphonate (235 mg, 0.87 mmol, 2.0 eq). The reaction mixture was stirred at room temperature for 2 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated to give a residue. The crude product was purified by silica gel column chromatography (Petroleum ether: EtOAc = 3: 1) to give tert-butyl 3-(7-bromo-2-chloro-5-(difluoromethoxy)-6,8-difluoroquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (190 mg, 77.3%) as a yellow solid. LCMS: m/z 555.0, 557.0 ($\text{M}+\text{H}^+$).

Step 7: Synthesis of tert-butyl 3-(7-bromo-5-(difluoromethoxy)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00546] To a solution of tert-butyl 3-(7-bromo-2-chloro-5-(difluoromethoxy)-6,8-difluoroquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (50 mg, 0.090 mmol, 1.0 eq) and ((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl) methanol (17.2 mg, 0.108 mmol, 1.2 eq) in DMF/THF (1/1, 2.0 mL) was added DABCO (10 mg, 0.090 mmol, 1.0 eq), Cs₂CO₃ (87.9 mg, 0.27 mmol, 3.0 eq). The reaction mixture was stirred at room temperature overnight under N₂ atmosphere. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give a residue. The crude product was purified by prep-TLC (DCM: MeOH = 10: 1) to give tert-butyl 3-(7-bromo-5-(difluoromethoxy)-6,8-difluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (28 mg, 44.4%) as a yellow solid. LCMS: *m/z* 678.1, 680.1 (M+H⁺).

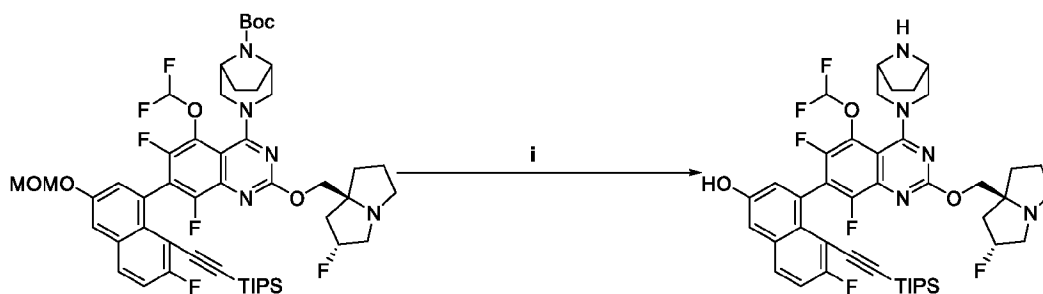
Step 8: Synthesis of tert-butyl 3-(5-(difluoromethoxy)-6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00547] To a solution of tert-butyl 3-(7-bromo-5-(difluoromethoxy)-6,8-difluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (28 mg, 0.041 mmol, 1.0 eq) in toluene/H₂O (5/1, 1.2 mL) was added ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl) ethynyl) triisopropylsilane (25.1 mg, 0.049 mmol, 1.2 eq), cataCxiu A Pd G3 (5.8 mg, 0.008 mmol, 0.2 eq) and Cs₂CO₃ (40.1 mg, 0.123 mmol, 3.0 eq). The sealed vial was irradiated in the microwave at 120 °C for 1.5 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL),

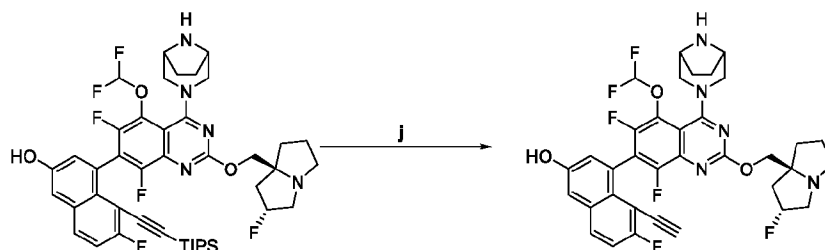
dried over Na_2SO_4 and concentrated to give a residue. The crude product was purified by prep-TLC (DCM: MeOH = 10: 1) to give tert-butyl 3-(5-(difluoromethoxy)-6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (21 mg, 51.2%) as a yellow solid. LCMS: m/z 984.1 ($\text{M}+\text{H}^+$).

Step 9: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-(difluoromethoxy)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol



[00548] To a solution of tert-butyl 3-(5-(difluoromethoxy)-6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (21 mg, 0.021 mmol, 1.0 eq) in ACN (1.5 mL) was added HCl/dioxane (0.3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. Then the reaction mixture was concentrated in vacuo to afford 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-(difluoromethoxy)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (crude) as a yellow solid, which was used directly for the next step without any further purification. LCMS: m/z 840.1 ($\text{M}+\text{H}^+$).

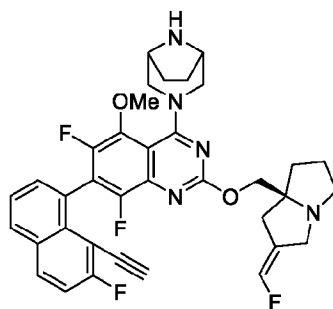
Step 10: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-(difluoromethoxy)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



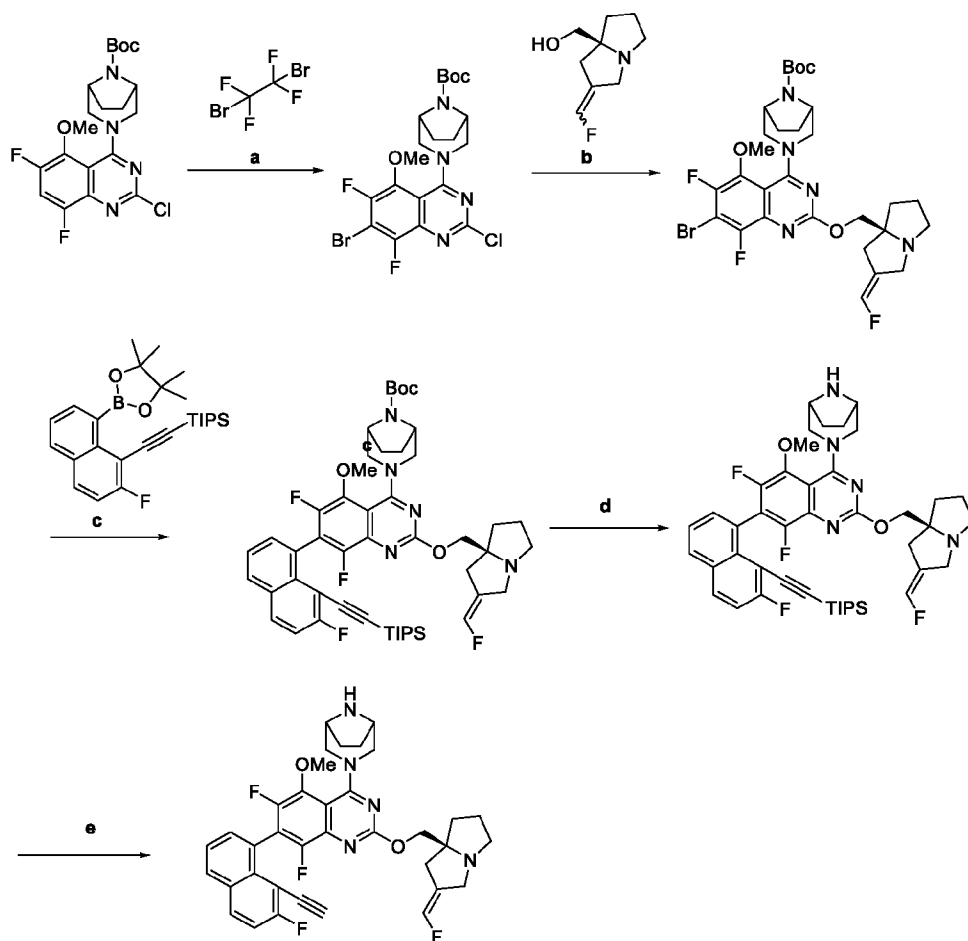
[00549] To a solution of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-(difluoromethoxy)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (crude) in DMF (1 mL) was added CsF (47.8 mg, 0.315 mmol, 15.0 eq). The reaction mixture was stirred at 40 °C for 2 h. Then the reaction mixture was filtered and the filtrate was purified by Prep-HPLC (0.1% FA) to afford 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-(difluoromethoxy)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol (4 mg, 0.005 mmol, with 0.6 FA salt, 27.4% yield for two steps) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.27 (s, 1H), 8.23 (s, 0.6H), 8.01 (dd, *J* = 9.2, 6.0 Hz, 1H), 7.57 – 7.33 (m, 2H), 7.21 (s, 1H), 6.89 (t, *J* = 76.0 Hz, 1H), 5.28 (d, *J* = 52.0 Hz, 1H), 4.19 – 3.82 (m, 4H), 3.60–3.30 (m, 7H), 3.14 – 2.97 (m, 4H), 2.83 (s, 1H), 2.14 – 1.70 (m, 6H), 1.58 (s, 2H). LCMS: *m/z* 684.2 (M+H⁺).

Example 54

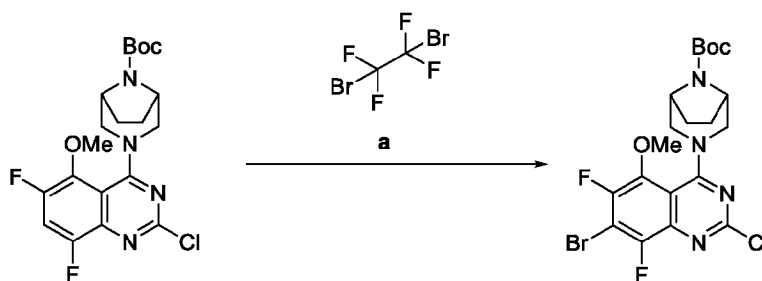
4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro naphthalen-1-yl)-6,8-difluoro-2-(((S,Z)-2-(fluoromethylene) tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy quinazoline



Synthetic scheme:



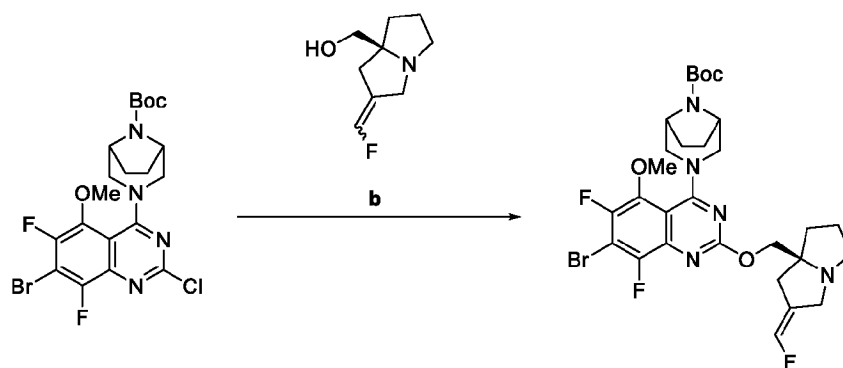
Step 1: Synthesis of tert-butyl 3-(7-bromo-2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00550] To a solution of tert-butyl 3-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (500 mg, 1.13 mmol, 1.0 eq) in THF (7 mL) under N₂ atmosphere was added LDA (3.4 mL, 6.80 mmol, 6.0 eq) at -65 °C under N₂ atmosphere and the reaction mixture was stirred for 40 minutes at -65 °C. Then the 1,2-Dibromotetrafluoroethane (2.36 g, 9.07 mmol, 8.0 eq) was added at -65 °C. The reaction was stirred at -65 °C for 2 h under N₂ atmosphere. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x

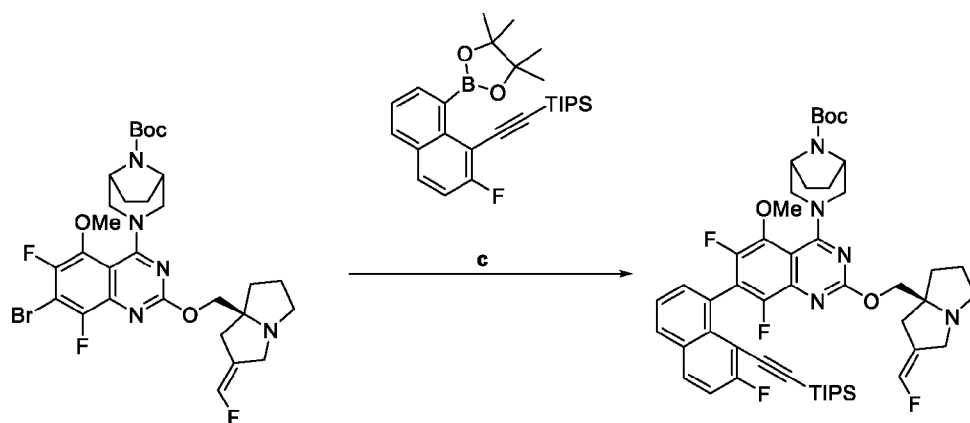
3). The combined organic phase was washed with brine (10 mL), dried over Na₂SO₄ and concentrated to afford the crude product. The crude product was purified by column chromatography on silica gel (eluted with petroleum ether: EtOAc = 20: 1) to give tert-butyl 3-(7-bromo-2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (325 mg, 55.1%) as a yellow solid. LCMS: m/z 519.0, 521.1 (M+H⁺).

Step 2: Synthesis of tert-butyl 3-(7-bromo-6,8-difluoro-2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



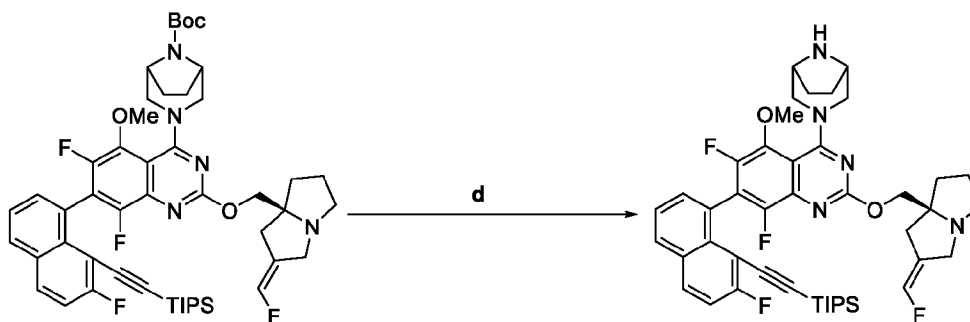
[00551] To a solution of tert-butyl 3-(7-bromo-2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (200 mg, 0.39 mmol, 1.0 eq) in THF (2.0 mL) and DMF (2.0 mL) was added (*S*)-2-(2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (79 mg, 0.46 mmol, 1.2 eq), Cs₂CO₃ (414 mg, 1.27 mmol, 3.3 eq) and DABCO (48 mg, 0.42 mmol, 1.1 eq), the reaction mixture was stirred at room temperature for overnight under N₂ atmosphere. The mixture was diluted with water (5 mL) and extracted with EtOAc (5 mL x 3). The combined organic phase was washed with water (20 mL) and brine (20 mL), dried over Na₂SO₄ and concentrated to give a residue. The crude product was purified by prep-TLC (DCM: MeOH = 10: 1) to give tert-butyl 3-(7-bromo-6,8-difluoro-2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (45 mg, 17.9%) as a yellow solid. LCMS: m/z 654.1, 656.2 (M+H⁺).

Step 3: Synthesis of tert-butyl 3-(6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



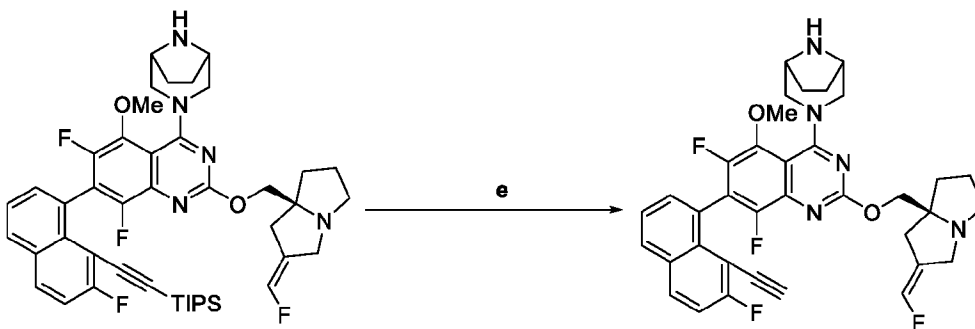
[00552] A solution of tert-butyl 3-(7-bromo-6,8-difluoro-2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (45 mg, 0.069 mmol, 1.0 eq) in Toluene (2.25 mL) was taken into the microwave tube. Then cataCXium A Pd G3 (0.01 mg, 0.014 mmol, 0.2 eq), Cs₂CO₃ (67 mg, 0.21 mmol, 3.0 eq), ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (38 mg, 0.08 mmol, 1.2 eq) and water (0.45 mL) were added to the microwave tube. Then the reaction mixture was heated under microwave irradiation at 120 °C for 1.5 hours. Upon completion, the mixture was diluted with water (5 mL) and extracted with EtOAc (5 mL x 3). The combined organic phase was washed with brine (20 mL x 3), dried over Na₂SO₄ and concentrated to afford the crude product. The crude product was purified by prep-TLC (DCM: MeOH = 10: 1) to give tert-butyl (1R,5S)-3-(6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (27 mg, 43.5%) as a yellow solid. LCMS: m/z 900.2 (M+H⁺).

Step 4: Synthesis of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline



[00553] To a solution of tert-butyl 3-(6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (35 mg, 0.039 mmol, 1.0 eq) in ACN (0.35 mL) was added Hydrochloric acid/Dioxane (4 M) (0.32 mL, 1.25 mmol, 32.11 eq) at 0 °C and the reaction mixture was stirred for 1 h under N₂ atmosphere. Upon completion, the mixture was concentrated to afford the crude product 4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline (30 mg, 96.6%) as a yellow solid, which was continue used for the next step without purification. LCMS: m/z 800.1 (M+H⁺).

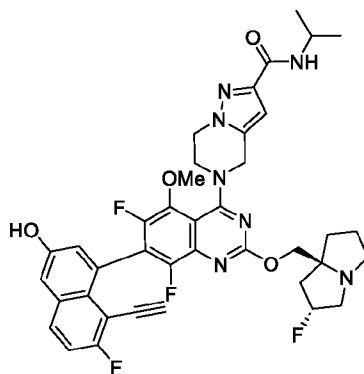
Step 5: Synthesis of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline

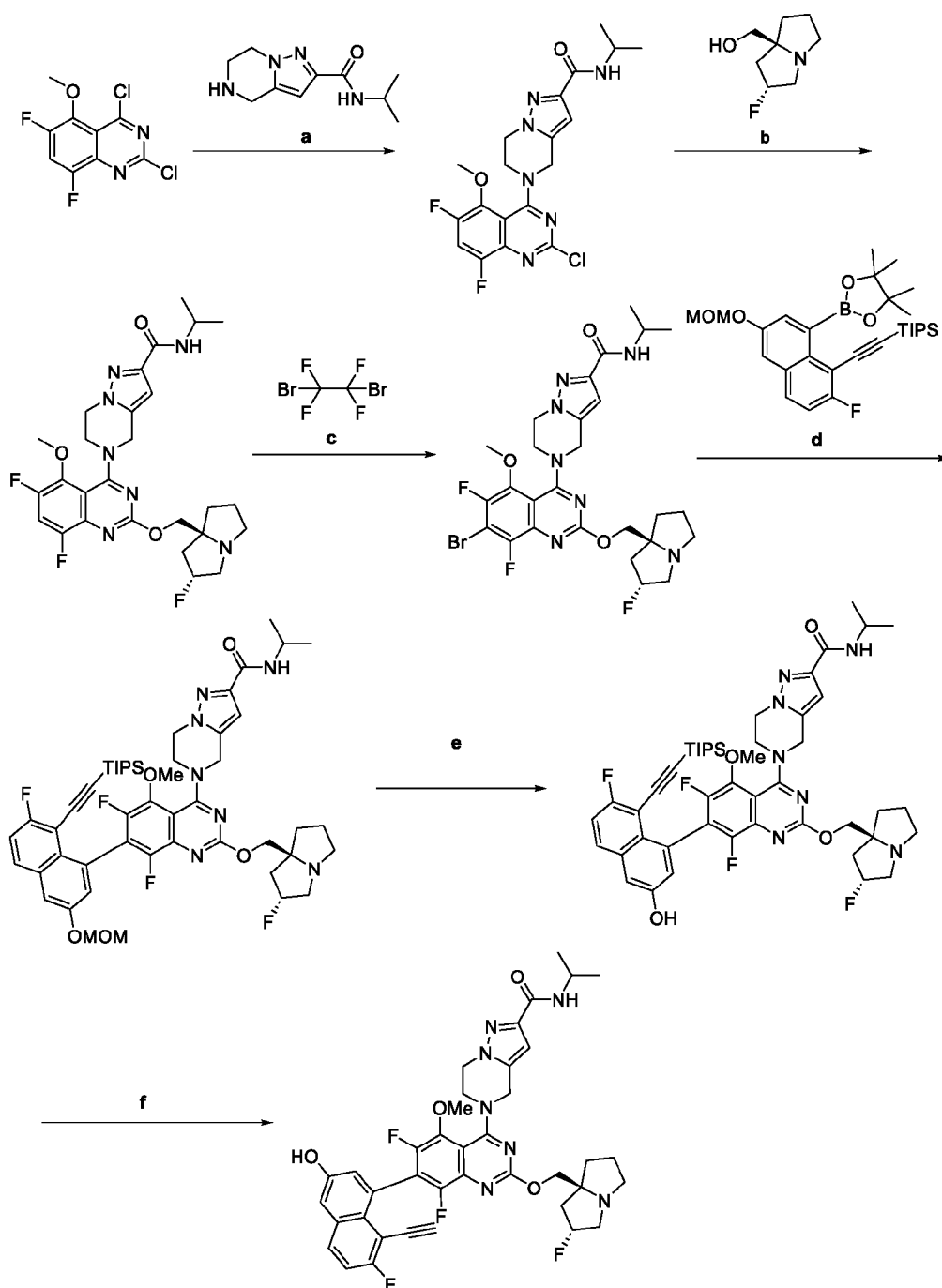


[00554] To a solution of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline (31 mg, 0.039 mmol, 1.0 eq) in DMF (0.9 mL) was added CsF (90 mg, 0.59 mmol, 15.0 eq) at 40 °C under N₂ atmosphere. Then the reaction was stirred at 40 °C for 4 h. Upon completion, the mixture was filtered to give a crude. The crude was purified by Prep-HPLC (acetonitrile with 0.1% FA in water, 25% to 45%) to give 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline (5 mg, with 0.6 FA salt, 20.5%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.38 – 8.06 (m, 3H), 7.76 – 7.53 (m, 3H), 6.75 (dd, *J* = 84.0, 8.0 Hz, 1H), 4.20-3.90 (m, 4H), 3.76 (s, 3H), 3.70- 2.95 (m, 9H), 2.56-2.50 (m, 2H), 2.33-2.25 (m, 1H), 2.00 – 1.57 (m, 8H). LCMS: m/z 644.0 (M+H⁺).

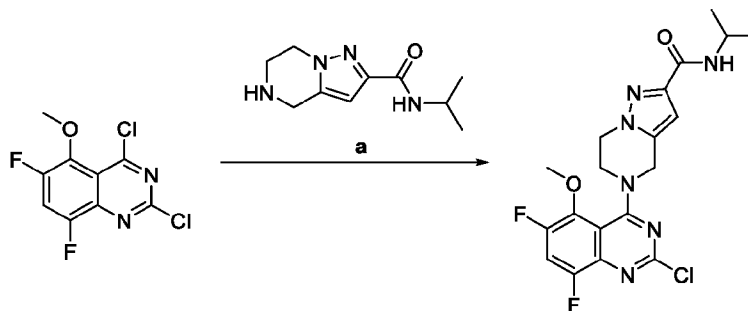
Example 55

5-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide formate



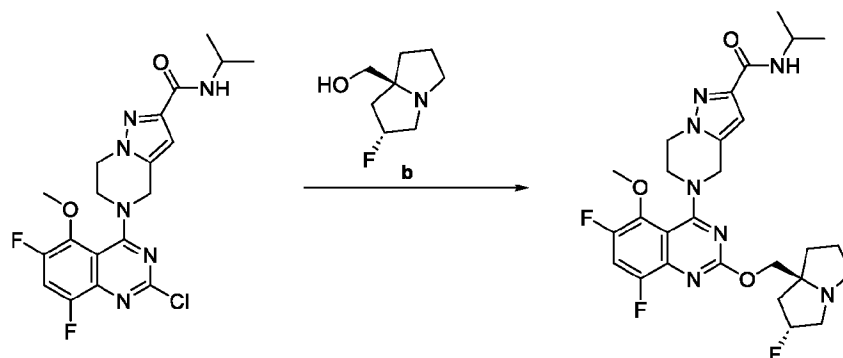


Step 1: Synthesis of 5-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-N-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide



[00555] To a solution of N-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide (350 mg, 1.7 mmol, 1.0 eq) in DCM (2 mL) was added DIEA (869 mg, 6.7 mmol, 4.0 eq). The reaction mixture was stirred at -20 °C for 1 h under nitrogen atmosphere. Then the reaction was added 2,4-dichloro-6,8-difluoro-5-methoxyquinazoline (445 mg, 1.7 mmol, 1.0 eq) in DCM (1 mL). The reaction mixture was stirred at -20 °C for 1 h under nitrogen atmosphere. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The organic phases were washed with brine (10 mL), dried with Na₂SO₄, filtered and concentrated to give a crude. The crude product was purified by prep-TLC (DCM : MeOH = 15 : 1) to give 5-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-N-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide (480 mg, 65.2% yield of two steps) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 7.43 (t, *J* = 9.2 Hz, 1H), 6.68 – 6.62 (m, 2H), 4.84 (s, 2H), 4.47 (t, *J* = 5.2 Hz, 2H), 4.35 – 4.17 (m, 1H), 4.08 (t, *J* = 5.2 Hz, 2H), 3.88 (s, 3H), 1.25 (d, *J* = 6.4 Hz, 6H). LCMS: 437.1 (M+H⁺).

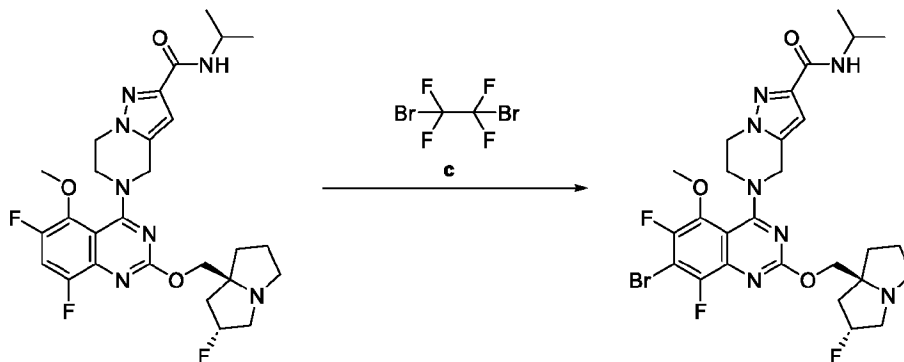
Step 2: Synthesis of 5-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide



[00556] To a solution of 5-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-N-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide (480 mg, 1.1 mmol, 1.0 eq) in dioxane

(10 mL) was added Cs_2CO_3 (1.07 g, 3.3 mmol, 3.0 eq), ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (263 mg, 1.7 mmol, 1.5 eq) and S-Phos Pd G4 (87 mg, 0.11 mmol, 0.1 eq). The reaction mixture was stirred at 100 °C for 12 h under nitrogen atmosphere. The mixture was quenched by the addition of water (20 mL) and then extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to give crude. The residue was purified by silica gel column chromatography (DCM : MeOH = 30 : 1) to give 5-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide (560 mg, 90.1%) as a yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 7.32 (t, J = 10.0 Hz, 1H), 6.69 – 6.62 (m, 2H), 5.34 (d, J = 52.4 Hz, 1H), 4.85 – 4.75 (m, 2H), 4.46 – 4.42 (m, 2H), 4.40 – 4.33 (m, 1H), 4.29 – 4.23 (m, 1H), 4.03 – 3.94 (m 2H), 3.81 (s, 3H), 3.48 (s, 1H), 3.37 – 3.27 (m, 1H), 3.05 (s, 1H), 2.45 – 2.15 (m, 3H), 2.10 – 1.92 (m, 3H), 1.81 – 1.48 (m, 2H), 1.25 (d, J = 6.4 Hz, 6H). LCMS: 560.2 ($\text{M}+\text{H}^+$).

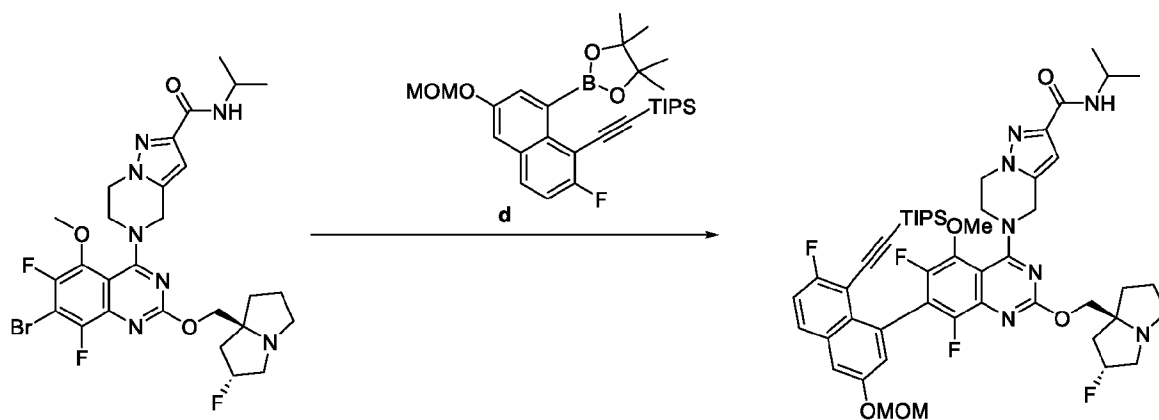
Step 3: Synthesis of 5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide



[00557] To a solution of 5-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide (350 mg, 0.63 mmol, 1.0 eq) in THF (4 mL) was added LDA (2M) (1.9 mL 3.8 mmol, 6.0 eq, 2.0M in hexane/THF). Then the reaction mixture was stirred at -65 °C for 30 min. Then the reaction mixture was added 1,2-dibromo-1,1,2,2-tetrafluoroethane (982 mg, 3.78 mmol, 6.0 eq). The crude was partitioned between EtOAc (10 mL) and water (10 mL). The layers were separated. The aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over MgSO_4 and evaporated to dryness.

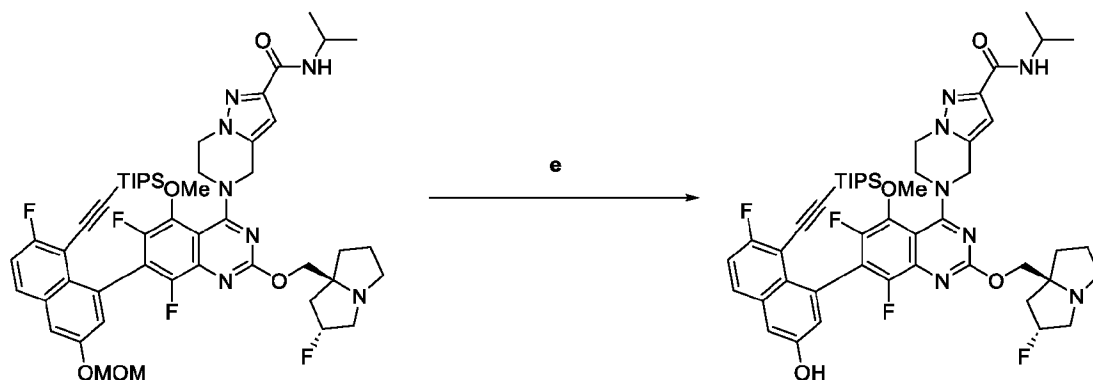
The crude product was purified by silica gel column chromatography (DCM : MeOH = 40 : 1) to give 5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide (90 mg, 22.5%) as a yellow solid. LCMS: 637.9, 640.0 (M+H⁺).

Step 4: Synthesis of 5-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-(((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide



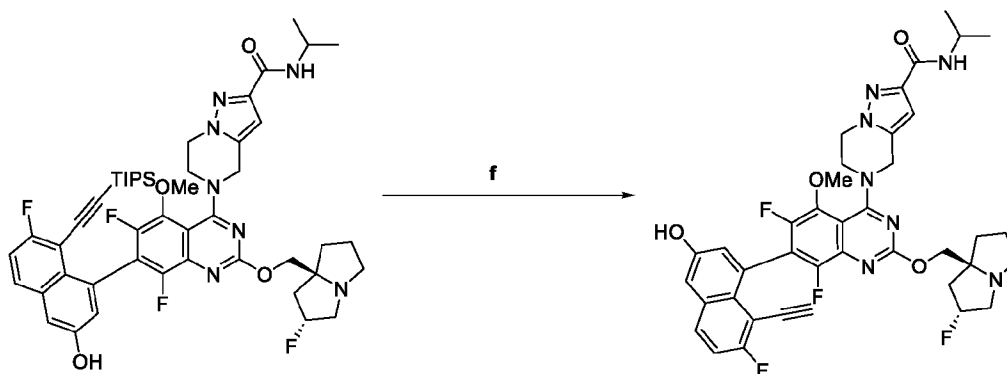
[00558] To a solution of 5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide (50 mg, 0.08 mmol, 1.0 eq) in toluene (2.0 mL) and H₂O (0.4 mL) was added K₃PO₄ (51 mg 0.24 mmol, 3.0 eq), *rac*-BI-DIME (4 mg, 0.01 mmol, 0.15 eq), Pd₂(dba)₃ (22 mg, 0.024 mmol, 0.3 eq) and ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (62 mg, 0.12 mmol, 1.5 eq) under nitrogen atmosphere. The reaction mixture was heated under microwave irradiation under nitrogen atmosphere at 120 °C for 1 h. The mixture was diluted with water (5 mL) and extracted with EtOAc (5 mL x 3). The organic phases were washed with brine (5 mL), dried with Na₂SO₄, filtered and concentrated to give a crude. The crude was purified by prep-TLC (DCM : MeOH = 15 : 1) to give 5-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-(((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide (45 mg, 60.8%) as a yellow solid. LCMS: 944.1 (M+H⁺).

Step 5: Synthesis of 5-(6,8-difluoro-7-(7-fluoro-3-hydroxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide



[00559] To a solution of 5-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl) ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide (45 mg, 0.05 mmol, 1.0 eq) in DCM (1.0 mL) was added HCl in dioxane (0.5 mL, 4 M in dioxane) at room temperature. Then the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure to give 5-(6,8-difluoro-7-(7-fluoro-3-hydroxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide (40 mg, crude) as a white solid. LCMS: 900.1 (M+H⁺).

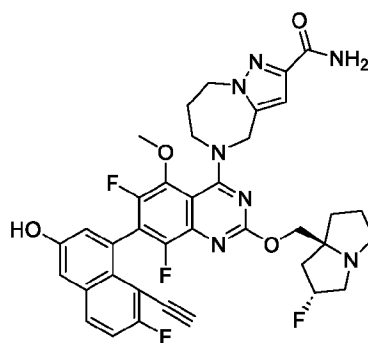
Step 6: Synthesis of 5-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide formate



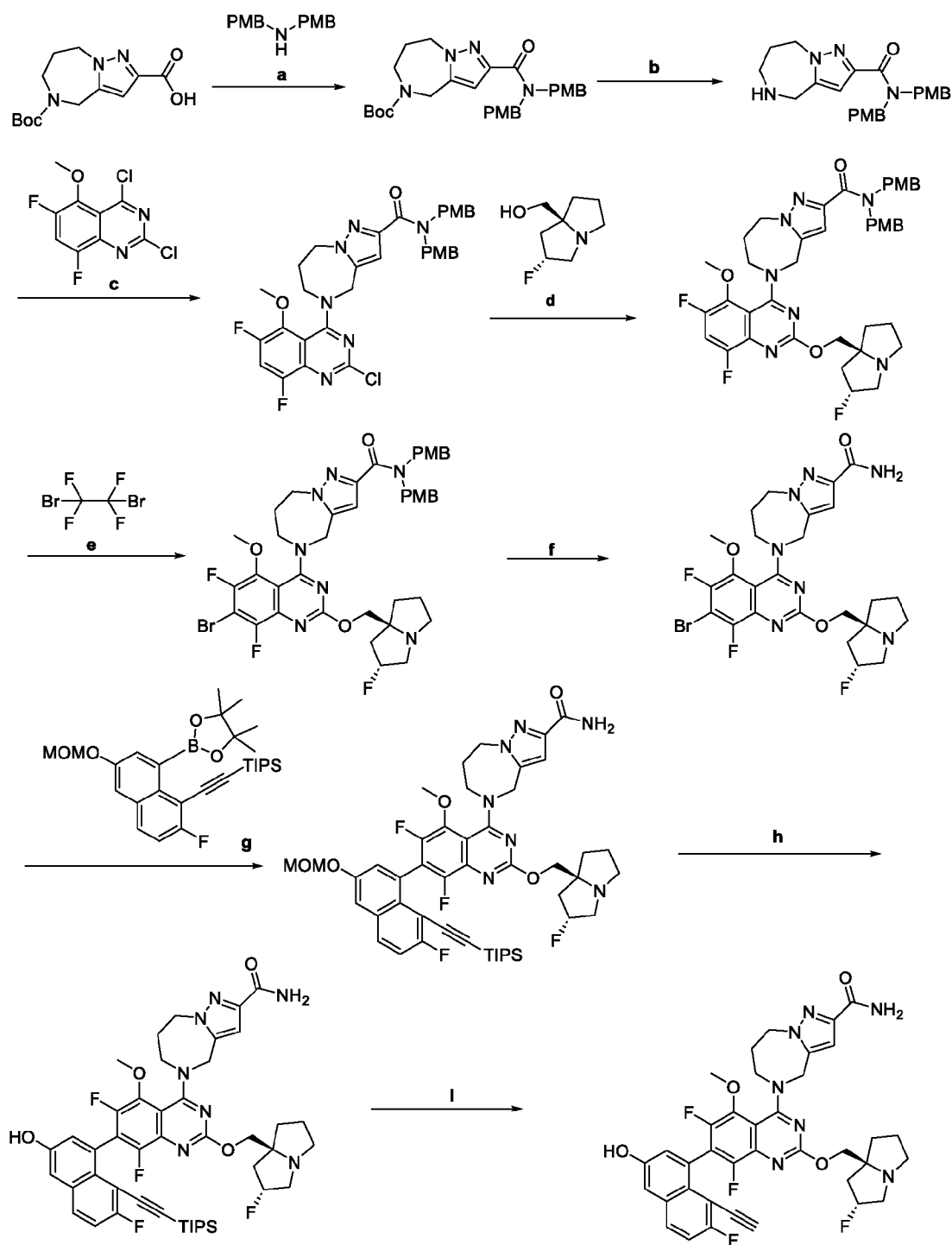
[00560] To a solution of 5-(6,8-difluoro-7-(7-fluoro-3-hydroxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide (40 mg, 0.04 mmol, 1.0 eq) in DMF (1 mL) was added CsF (152 mg, 1.0 mmol, 25.0 eq). The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was filtered and diluted by MeOH (1.0 mL). The mixture was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 10% to 60%) to give 5-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide formate (1:0.2) (10.0 mg, 28.2% yield for two steps) as a white solid. ¹H NMR (400 MHz, CD₃OD): δ 8.54 (brs, 0.2H), 7.91 – 7.80 (m, 1H), 7.40 – 7.28 (m, 2H), 7.15 (d, *J* = 2.0 Hz, 1H), 6.63 (s, 1H), 5.34 (d, *J* = 53.6 Hz, 1H), 4.92 (s, 2H), 4.58 – 4.42 (m 2H), 4.40 – 4.13 (m, 4H), 4.09 – 3.98 (m, 1H), 3.86 (s, 3H), 3.42 – 3.31 (m, 4H), 3.15 – 3.00 (m, 1H), 2.44 – 2.24 (m, 3H), 2.20 – 2.10 (m, 2H), 1.99 – 1.86 (m, 1H), 1.25 (d, *J* = 6.4 Hz, 6H). ¹⁹F NMR (400 MHz, CD₃OD): δ -111.255, -131.740, -136.720, -173.697. LCMS: 744.4 (M+H⁺).

Example 56

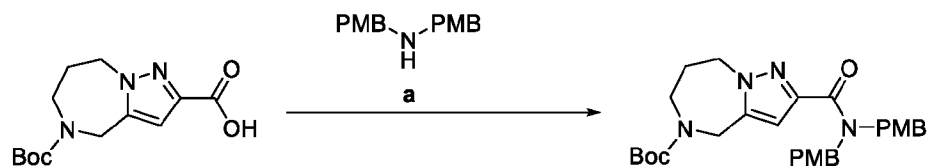
5-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide formate



Synthetic scheme:

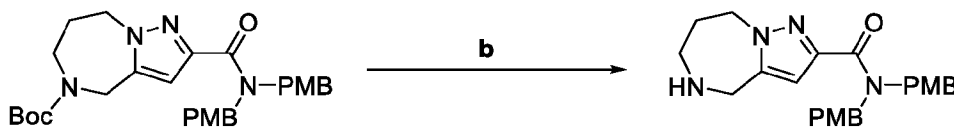


Step 1: Synthesis of tert-butyl 2-(bis(4-methoxybenzyl)carbamoyl)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate



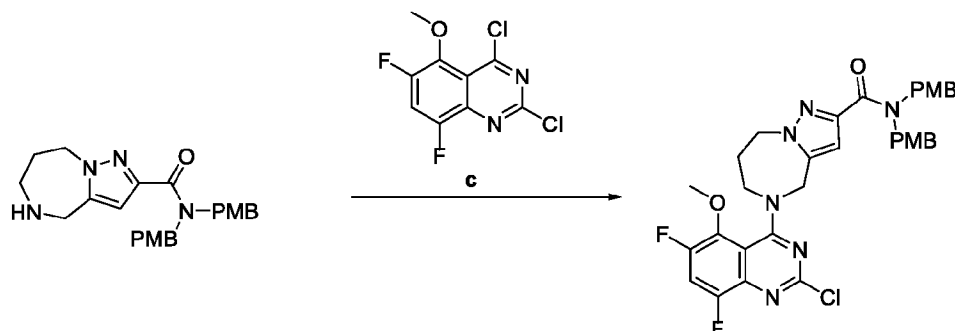
[00561] To a solution of 5-(tert-butoxycarbonyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxylic acid (2.0 g, 7.11 mmol, 1.0 eq) in THF (12.0 mL) was added bis(4-methoxybenzyl)amine (1.83 g, 7.11 mmol, 1.0 eq), HATU (5.40 g, 14.2 mmol, 2.0 eq) and TEA (4.32 g, 42.7 mmol, 6.0 eq). Then the mixture was stirred at room temperature for 2 h. The mixture was diluted with water (30 mL) and extracted with EtOAc (20 mL x 3). The combined organic phases were washed with brine (30 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by flash silica gel column chromatography (eluted with EtOAc in Petroleum ether = 5%) to give tert-butyl 2-(bis(4-methoxybenzyl)carbamoyl)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate (3.0 g, 81.1%) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 7.25 – 7.13 (m, 4H), 6.90 – 6.82 (m, 4H), 6.59 (s, 1H), 4.97 – 4.71 (m, 2H), 4.62 – 4.31 (m, 6H), 3.81 (s, 3H), 3.80 (s, 3H), 3.70 (s, 2H), 1.96 – 1.85 (m, 2H), 1.38 (s, 9H). LCMS: 521.2 (M+H⁺).

Step 2: Synthesis of N,N-bis(4-methoxybenzyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



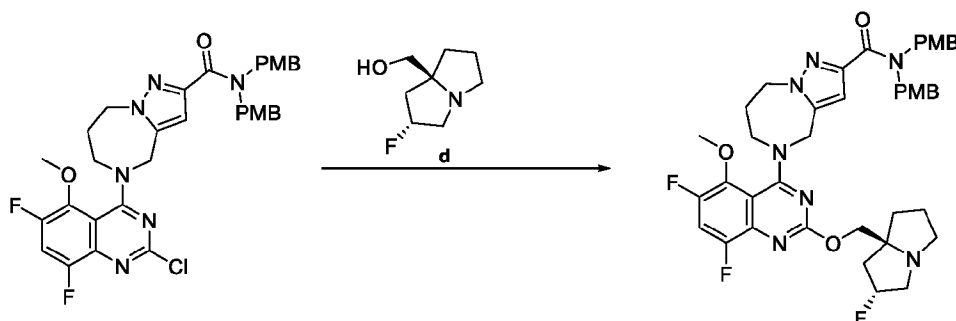
[00562] To a solution of tert-butyl 2-(bis(4-methoxybenzyl)carbamoyl)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate (3.0 g, 5.76 mmol, 1.0 eq) in DCM (18.0 mL) was added HCl (4M in Dioxane) (5.0 mL). The mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated to give N,N-bis(4-methoxybenzyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (2.4 g, crude) as a white solid. LCMS: 421.1 (M+H⁺).

Step 3: Synthesis of 5-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-N,N-bis(4-methoxybenzyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



[00563] To a solution of 2,4-dichloro-6,8-difluoro-5-methoxyquinazoline (1.51 g, 5.71 mmol, 1.0 eq) and DIEA (3.69 g, 28.5 mmol, 5.0 eq) in DCM (10.0 mL) was added dropwise a solution of N,N-bis(4-methoxybenzyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (2.4 g, crude) in DCM (5.0 mL) at -20 °C under N₂. The mixture was stirred at -20 °C for 2 h. The mixture was diluted with water (30 mL) and extracted with DCM (30 mL x 3). The combined organic phases were washed with brine (40 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by silica gel chromatography (DCM: MeOH = 80: 1) to give 5-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-N,N-bis(4-methoxybenzyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (2.89 g, 77.3% for two steps) as a white solid. LCMS: 649.0 (M+H⁺).

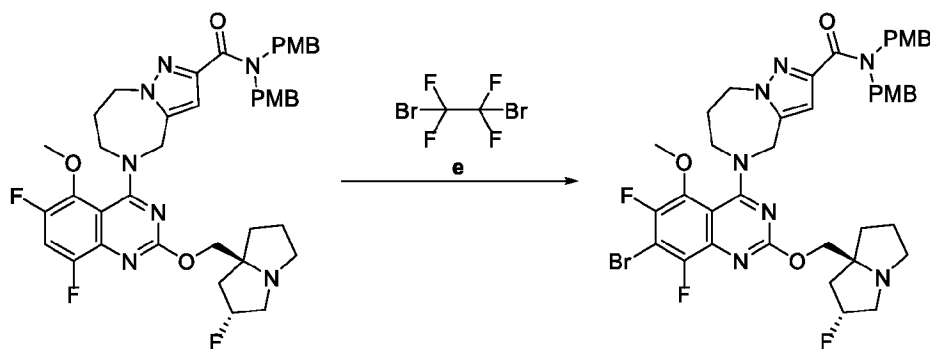
Step 4: Synthesis of 5-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N,N-bis(4-methoxybenzyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



[00564] To a solution of 5-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-N,N-bis(4-methoxybenzyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (520 mg, 0.80 mmol, 1.0 eq) in 1,4-Dioxane (5.0 mL) was added ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (191 mg, 1.20 mmol, 1.5 eq), Cs₂CO₃ (783 mg, 2.40 mmol, 3.0 eq) and S-Phos Pd G4 (63.5 mg, 0.08 mmol, 0.1 eq). Then the reaction mixture was stirred at

100 °C for 12 h. The mixture was diluted with water (15 mL) and extracted with EtOAc (20 mL x 3). The combined organic phases were washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by silica gel chromatography (DCM: MeOH = 50: 1) to give 5-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N,N-bis(4-methoxybenzyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (500 mg, 80.8%) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 7.32 – 7.26 (m, 1H), 7.23 – 7.14 (m, 4H), 6.90 – 6.81 (m, 4H), 6.61 (s, 1H), 5.28 (d, *J* = 53.1 Hz, 1H), 4.97 – 4.74 (m, 4H), 4.52 (s, 2H), 4.43 – 4.31 (m, 2H), 4.30 – 4.04 (m, 2H), 3.94 – 3.84 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.68 – 3.58 (m, 3H), 3.39 – 2.89 (m, 4H), 2.33 – 1.89 (m, 8H). LCMS: 772.2 (M+H⁺).

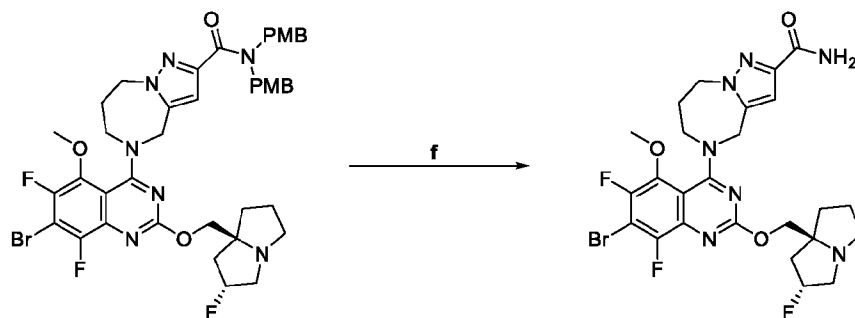
Step 5: Synthesis of 5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N,N-bis(4-methoxybenzyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



[00565] To a solution of 5-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N,N-bis(4-methoxybenzyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (260 mg, 0.337 mmol, 1.0 eq) in THF (5.0 mL) was added dropwise *n*-BuLi 2.5M in THF (0.2 mL, 0.506 mmol, 1.5 eq) at -78 °C. The reaction mixture was stirred at -78 °C for 1 h. Then 1,2-dibromo-1,1,2,2-tetrafluoroethane (96 mg, 0.371 mmol, 1.1 eq) was added and the reaction mixture was stirred at -78 °C for 1.5 h. The mixture was diluted with water (15 mL) and extracted with EtOAc (10 mL x 3). The combined organic phases were washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by silica gel chromatography (eluted with DCM: MeOH = 10: 1) to give 5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N,N-bis(4-methoxybenzyl)-5,6,7,8-tetrahydro-4H-

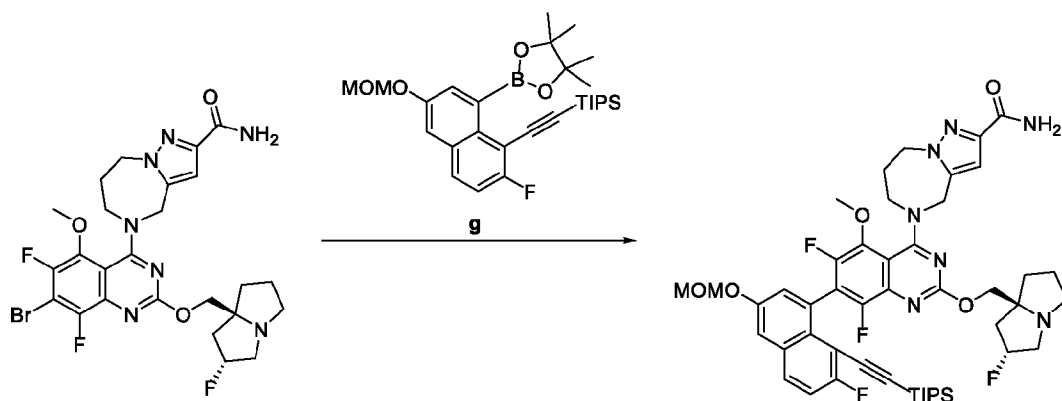
pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (200 mg, 69.7%) as a yellow solid. LCMS: 850.1, 852.1 (M+H⁺).

Step 6: Synthesis of 5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



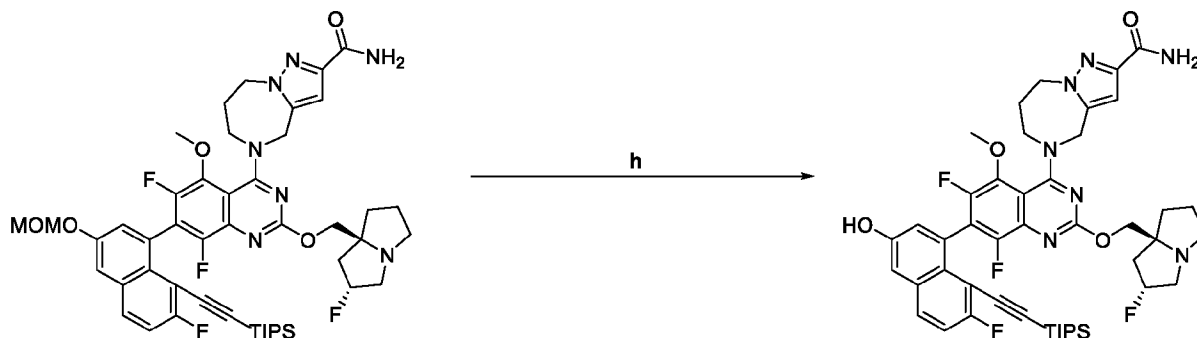
[00566] A solution of 5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N,N-bis(4-methoxybenzyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (120 mg, 0.141 mmol, 1.0 eq) in TFA (0.5 mL) was stirred at 50 °C for 12 h. The mixture was quenched by the addition of saturated aqueous Na₂CO₃ solution (5 mL) and then extracted with DCM: MeOH = 10: 1 (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by silica gel chromatography (eluted with DCM: MeOH = 10: 1) to give 5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (70 mg, 81.3%) as a white solid. LCMS: 610.2, 612.2 (M + H⁺).

Step 7: Synthesis of 5-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-(((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



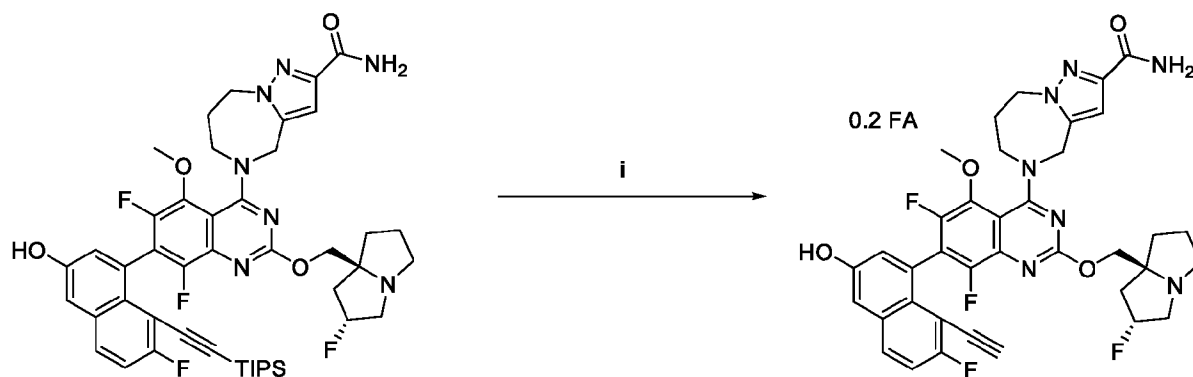
[00567] To a solution of 5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (30 mg, 0.049 mmol, 1.0 eq) and ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (28 mg, 0.054 mmol, 1.1 eq) in toluene (1.5 mL) and H₂O (0.3 mL) was added Pd₂(dba)₃ (7 mg, 0.007 mmol, 0.15 eq), rac-BI-DIME (5 mg, 0.015 mmol, 0.3 eq) and K₃PO₄ (21 mg, 0.10 mmol, 2.0 eq). The mixture was heated under microwave irradiation at 120 °C for 2.5 h. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (15 mL x 3). The organic phase was washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-TLC (DCM: MeOH = 10: 1) to give 5-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-(((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (21 mg, 46.6%) as a yellow solid. LCMS: 916.3 (M+H⁺).

Step 8: Synthesis of 5-(6,8-difluoro-7-(7-fluoro-3-hydroxy-8-(((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



[00568] To a solution of 5-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (20 mg, 0.022 mmol, 1.0 eq) in DCM (2 mL) was added HCl (4M in Dioxane) (0.5 mL). The mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure to give 5-(6,8-difluoro-7-(7-fluoro-3-hydroxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (19 mg, crude) as a white solid. LCMS: 872.4 (M+H⁺).

Step 9: Synthesis of 5-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide formate (1:0.2)

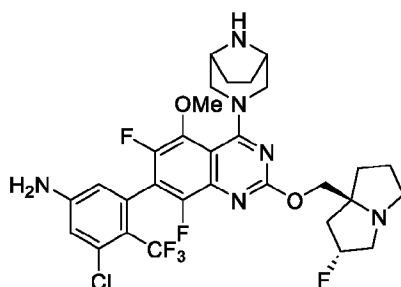


[00569] To a solution of 5-(6,8-difluoro-7-(7-fluoro-3-hydroxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (19 mg, 0.022 mmol, 1.0 eq) in DMF (3 mL) was added CsF (16.7 mg, 0.11 mmol, 5.0 eq). The mixture was stirred at 40 °C for 2 h. The mixture was

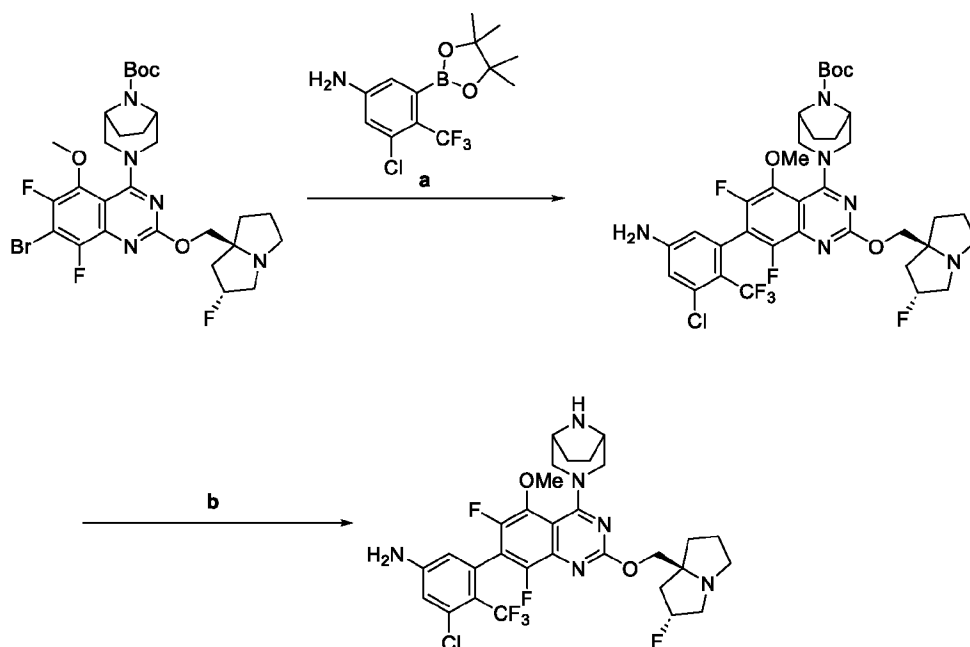
concentrated to give a residue. The residue was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 30% to 40%) to give 5-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide formate (1:0.2) (7 mg, 44.2% for two steps) as a white solid. ^1H NMR (400 MHz, CD_3OD): δ 8.53 (s, 0.2H), 7.86 (dd, $J = 9.2, 6.0$ Hz, 1H), 7.36 – 7.29 (m, 2H), 7.16 – 7.12 (m, 1H), 6.75 – 6.70 (m, 1H), 5.36 (d, $J = 53.6$ Hz, 1H), 5.05 (s, 2H), 4.52 – 4.36 (m, 2H), 4.29 – 4.19 (m, 2H), 4.16 – 4.02 (m, 2H), 3.82 (s, 3H), 3.54 – 3.34 (m, 4H), 3.17 – 3.08 (m, 1H), 2.40 – 1.95 (m, 8H). ^{19}F NMR (400 MHz, CD_3OD): -111.304, -132.388, -137.697, -173.621. LCMS: 715.9 ($\text{M}+\text{H}^+$).

Example 57

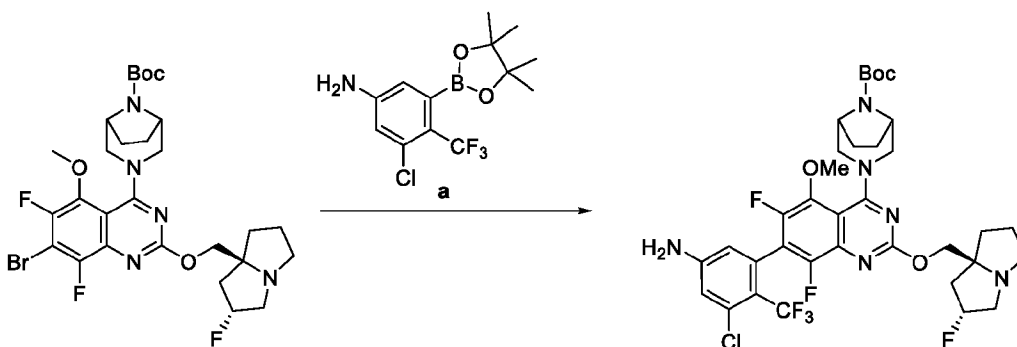
3-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-chloro-4-(trifluoromethyl)aniline formate



Synthetic scheme



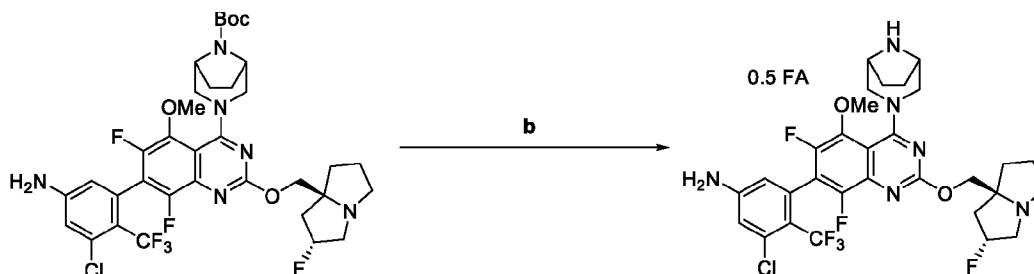
Step 1: Synthesis of tert-butyl 3-(7-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00570] To a solution of tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (110 mg, 0.17 mmol, 1.0 eq) in dioxane (5 mL) and H₂O (1 mL) was added 3-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline (165 mg, 0.51 mmol, 3.0 eq), CsF (78 mg, 0.51 mmol, 3.0 eq) and Pd(dtbpf)Cl₂ (22 mg, 0.03 mmol, 0.2 eq). The reaction mixture was stirred at 90 °C for 15 h under nitrogen atmosphere. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The organic phase was washed with brine (10 mL), dried with Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by silica gel column chromatography (DCM: MeOH = 15: 1) to give tert-

butyl (1R,5S)-3-(7-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (70 mg, 54.0%) as a yellow solid. LCMS: 757.4 (M+H⁺).

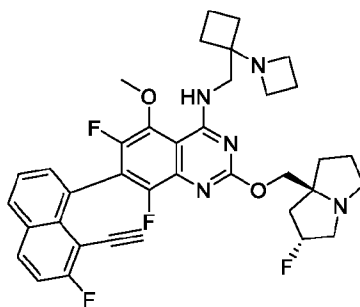
Step 2: Synthesis of 3-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-chloro-4-(trifluoromethyl)aniline formate (1:0.5)



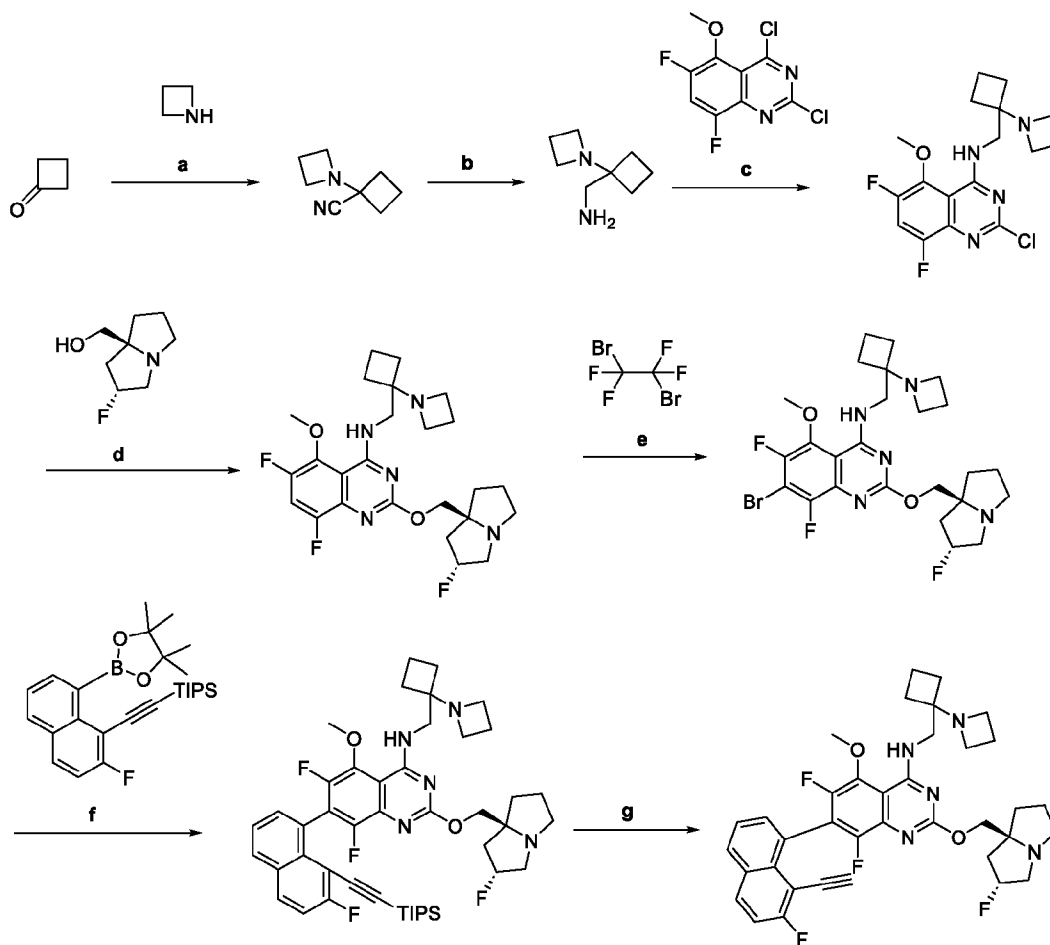
[00571] To a solution of tert-butyl 3-(7-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (70 mg, 0.09 mmol, 1.0 eq) in DCM (3.0 mL) was added HCl in dioxane (1.5 mL). Then the reaction mixture was stirred at room temperature for 1 h. The mixture was concentrated and purified by prep-HPLC (acetonitrile with 0.1% FA in water, 5% to 60%) to give 3-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-chloro-4-(trifluoromethyl)aniline formate (1:0.5) (29.6 mg, 48.8%) as a white solid. ¹H NMR (300 MHz, CD₃OD): δ 8.49 (brs, 0.5H), 6.91 (s, 1H), 6.44 (d, *J* = 2.1, 1H), 5.41 (d, *J* = 52.5 Hz, 1H), 4.47 – 4.31 (m, 3H), 4.27 – 4.14 (m, 1H), 4.02 – 3.90 (m, 2H), 3.87 (s, 3H), 3.66–3.45 (m, 5H), 3.26 – 3.16 (m, 1H), 2.56 – 2.32 (m, 2H), 2.31 – 2.21 (m, 1H), 2.20 – 2.05 (m, 3H), 2.05 – 1.93 (m, 4H). ¹⁹F NMR (300 MHz, CD₃OD): δ -56.412, -133.325, -138.457, -173.896. LCMS: 656.9 (M+H⁺).

Example 58

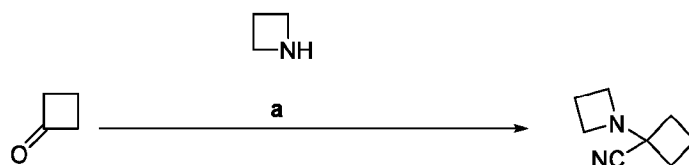
N-((1-(azetidin-1-yl)cyclobutyl)methyl)-7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-amine



Synthetic scheme:



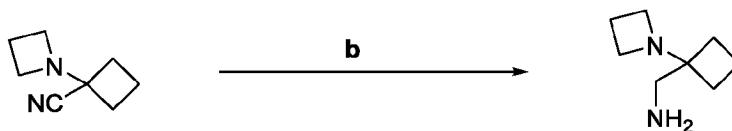
Step 1: Synthesis of 1-(azetidin-1-yl)cyclobutane-1-carbonitrile



[00572] To a solution of azetidine (4.1 g, 71.28 mmol, 5.0 eq) in Acetic acid (23 mL) at 0 °C under argon, cyclobutanone (1.0 g, 14.27 mmol, 1.0 eq) and TMSCN (3.5 g, 35.28 mmol, 2.5 eq)

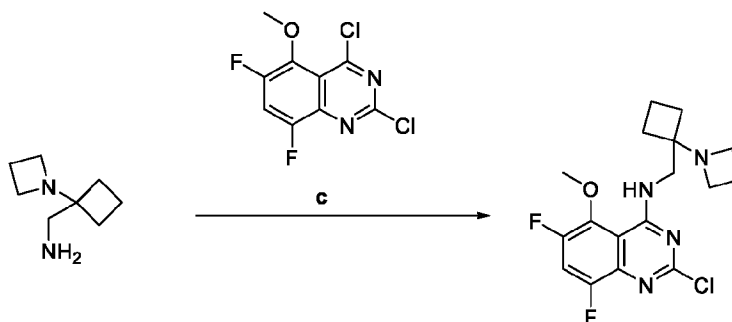
was added dropwise. The mixture was stirred at 25 °C for 12 h, diluted with DCM (100 mL) and added 32% sodium hydroxide solution to adjust pH to 9 (~35 mL). The mixture was extracted with DCM (100 mL x 2). The combined organic phases were dried over sodium sulfate, filtered and carefully evaporated. The residue was purified by silica gel column chromatography (petroleum ether / EtOAc = 10:1) to give the 1-(azetidin-1-yl)cyclobutane-1-carbonitrile (1.3 g, 66.7%) as a yellow liquid. LCMS: m/z 137.2 ($M+H^+$).

Step 2: Synthesis of (1-(azetidin-1-yl)cyclobutyl)methanamine



[00573] The solution of 1-(azetidin-1-yl)cyclobutane-1-carbonitrile (600 mg, 4.40 mmol, 1.0 eq) in THF (18 mL) was cooled to 0 °C under argon and added LAH (1.0 g, 26.35 mmol, 6.0 eq) dropwise. After that, the reaction mixture was stirred for 3 h at 0 °C. Then the reaction mixture was quenched with $Na_2SO_4 \cdot 10H_2O$ (8.5 g, 26.39 mmol, 6.0 eq) and stirred for 1 h at 25 °C. Then the mixture was filtered and the filtrate was concentrated to afford the (1-(azetidin-1-yl)cyclobutyl)methanamine (450 mg, crude) as a yellow oil. LCMS: m/z 141.3 ($M+H^+$).

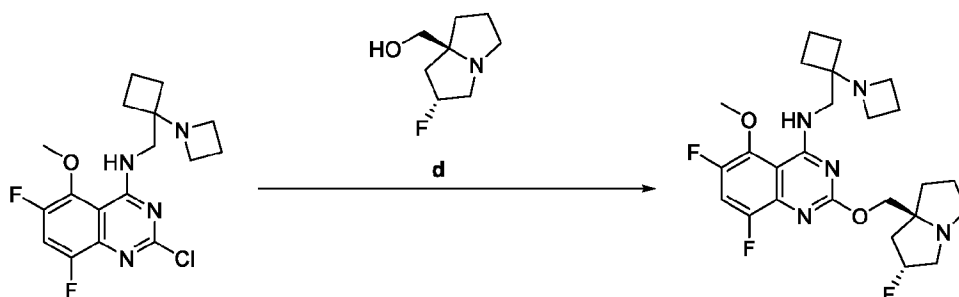
Step 3: Synthesis of N-((1-(azetidin-1-yl)cyclobutyl)methyl)-2-chloro-6,8-difluoro-5-methoxyquinazolin-4-amine



[00574] To a solution of 2,4-dichloro-6,8-difluoro-5-methoxyquinazoline (300 mg, 1.13 mmol, 1.0 eq) in DCM (3 mL) cooled to -40 °C under argon, was added DIEA (1.44 g, 11.10 mmol, 8.7 eq) and (1-(azetidin-1-yl)cyclobutyl)methanamine (215 mg, 1.53 mmol, 1.2 eq) in DCM (1 mL) dropwise. After that, the reaction mixture was stirred for 2 h at -40 °C. Then the reaction mixture was quenched with water (10 mL) and extracted with DCM (10 mL x 3). The organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated to give the

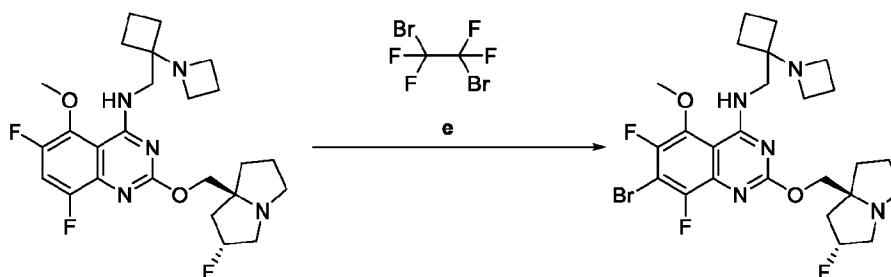
residue, which was purified by silica gel column chromatography (petroleum ether/EtOAc = 20:1) to give N-((1-(azetidin-1-yl)cyclobutyl)methyl)-2-chloro-6,8-difluoro-5-methoxyquinazolin-4-amine (300 mg, 71.9%) as a yellow solid. LCMS: m/z 369.1 ($M+H^+$).

Step 4: Synthesis of N-((1-(azetidin-1-yl)cyclobutyl)methyl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-amine



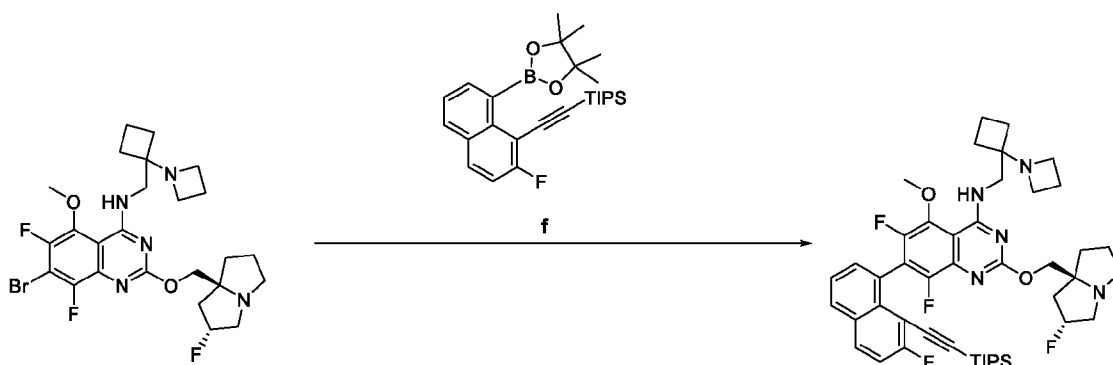
[00575] To a solution of N-((1-(azetidin-1-yl)cyclobutyl)methyl)-2-chloro-6,8-difluoro-5-methoxyquinazolin-4-amine (200 mg, 0.54 mmol, 1.0 eq), ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl) methanol (173 mg, 1.08 mmol, 2.0 eq) in THF (2.4 mL) and DMF (2.4 mL) was added DABCO (61 mg, 0.54 mmol, 1.0 eq) and Cs_2CO_3 (530 mg, 1.63 mmol, 3.0 eq) at room temperature under N_2 atmosphere. The reaction mixture was stirred at room temperature for 36 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with water (30 mL x 3) and brine (30 mL), dried over Na_2SO_4 and concentrated to give a residue. The crude product was purified by silica gel column chromatography (DCM / MeOH = 10:1) to give N-((1-(azetidin-1-yl)cyclobutyl)methyl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-amine (120 mg, 45.0%) as a yellow solid. LCMS: m/z 492.3 ($M+H^+$).

Step 5: Synthesis of N-((1-(azetidin-1-yl)cyclobutyl)methyl)-7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-amine



[00576] To a solution of N-((1-(azetidin-1-yl)cyclobutyl)methyl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-amine (120 mg, 0.24 mmol, 1.0 eq) in THF (4.8 mL) was added LDA (2N, 0.73 mL, 1.46 mmol, 6.0 eq) at -65 °C under N₂ atmosphere. The reaction mixture was stirred at -65 °C for 0.5 h. Then the mixture was added 1,2-dibromo-1,1,2,2-tetrafluoroethane (507 mg, 1.953 mmol, 8.0 eq) and stirred at 25 °C for 12 h. The mixture was quenched with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (30 mL), dried over Na₂SO₄ and concentrated to give a residue. The crude product was purified by silica gel column chromatography (DCM / MeOH = 10:1) to give N-((1-(azetidin-1-yl)cyclobutyl)methyl)-7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-amine (110 mg, 79.0%) as a yellow liquid. LCMS: m/z 570.1, 572.2 (M+H⁺).

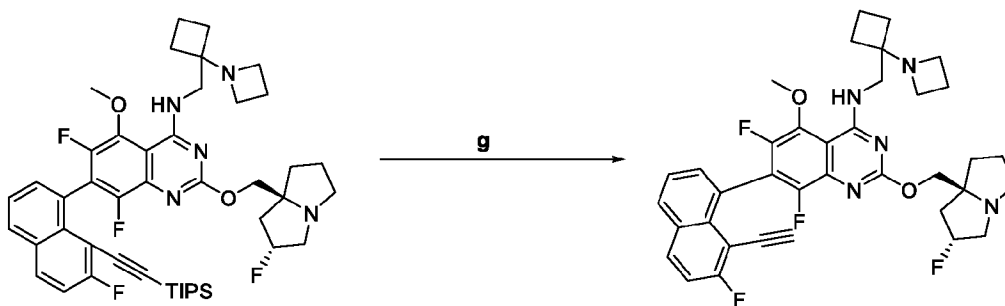
Step 6: Synthesis of N-((1-(azetidin-1-yl)cyclobutyl)methyl)-6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-amine



[00577] N-((1-(azetidin-1-yl)cyclobutyl)methyl)-7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-amine (120 mg, 0.21 mmol, 1.0 eq), ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (143 mg, 0.32 mmol, 1.5 eq), cataCXium A Pd G3 (31 mg, 0.06 mmol, 0.2 eq) and Cs₂CO₃ (206 mg, 0.63 mmol, 3.0 eq) were placed in the reaction bottle. A solution of PhMe / H₂O (5:1, 6.0 mL) was added at room temperature. The mixture was stirred under microwave irradiation at 120 °C for 1.5 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give a residue. The crude product was purified by

prep-TLC (DCM / MeOH = 10:1) to give N-((1-(azetidin-1-yl)cyclobutyl)methyl)-6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-amine (120 mg, 70.0%) as a yellow liquid. LCMS: m/z 816.4 ($M+H^+$).

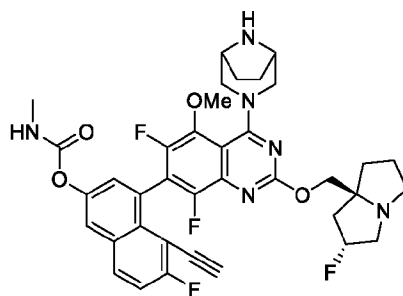
Step 7: Synthesis of N-((1-(azetidin-1-yl)cyclobutyl)methyl)-7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-amine



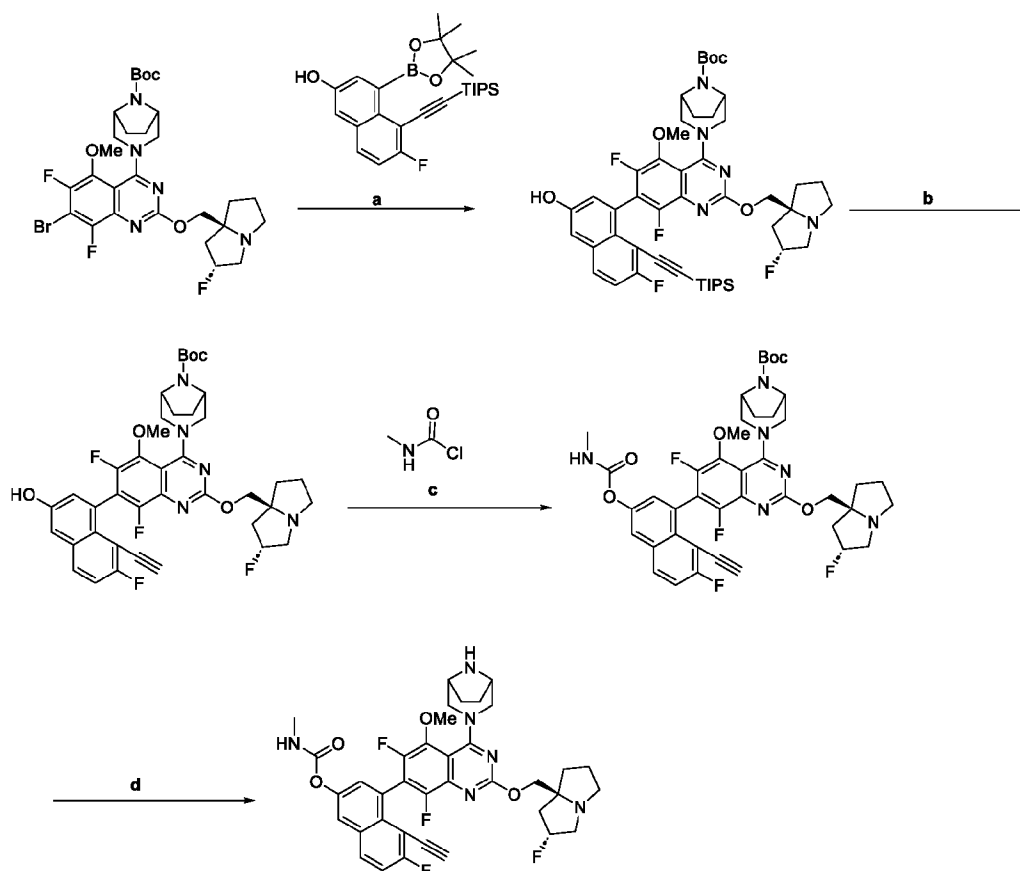
[00578] To a solution of N-((1-(azetidin-1-yl)cyclobutyl)methyl)-6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-amine (100 mg, 0.12 mmol, 1.0 eq) in DMF (1.0 mL) was added CsF (279 mg, 1.84 mmol, 15.0 eq). The reaction mixture was stirred at 40 °C for 12 h. Then the reaction mixture was filtered and the filtrate was concentrated to give a residue, which was purified by Prep-HPLC (acetonitrile in water with 0.1% FA, 15% to 36%) to give N-((1-(azetidin-1-yl)cyclobutyl)methyl)-7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-amine (34.2 mg, with 0.27 FA salt, 41.5%) as a white solid. ^1H NMR (400 MHz, DMSO- d_6): δ 8.70 (s, 1H), 8.27-8.21 (m, 2H), 7.72-7.61 (m, 3H), 5.28 (d, J = 56.0 Hz, 1H), 4.26 (s, 1H), 4.08-4.04 (m, 1H), 4.02 (s, 3H), 4.00-3.90 (m, 1H), 3.59-3.55 (m, 2H), 3.47-3.44 (m, 2H), 3.30-3.20 (m, 3H), 3.20-3.05 (m, 2H), 3.03 (s, 1H), 2.84-2.82 (m, 1H), 2.25-2.13 (m, 3H), 2.05-1.98 (m, 4H), 1.86-1.63 (m, 7H). LCMS: m/z 660.3 ($M+H^+$).

Example 59

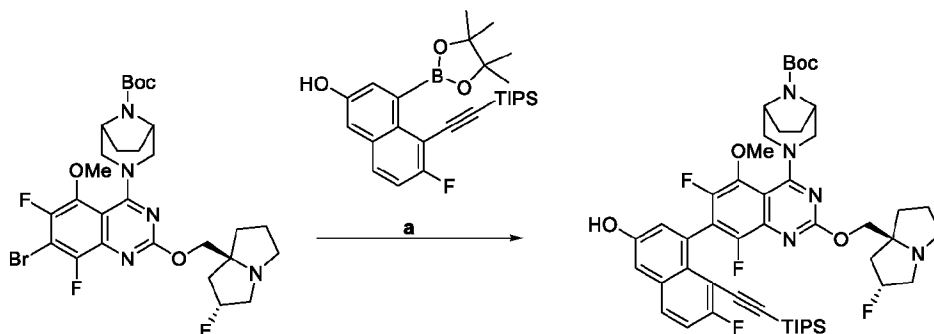
4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-yl methylcarbamate



Synthetic scheme:

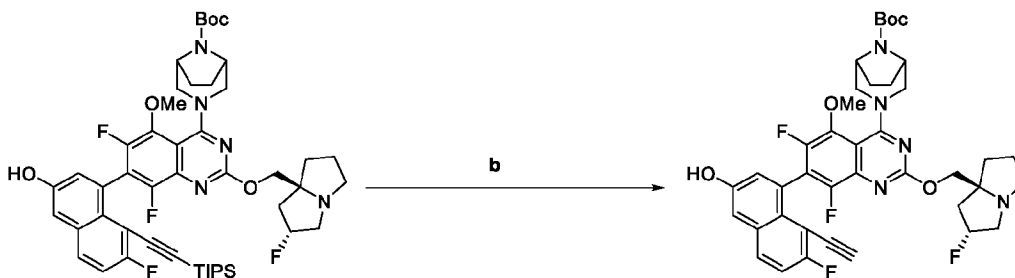


Step 1: tert-butyl 3-(6,8-difluoro-7-(7-fluoro-3-hydroxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00579] tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (150 mg, 0.23 mmol, 1.0 eq), 6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (131 mg, 0.28 mmol, 1.2 eq), Cxium A Pd G3 (34 mg, 0.046 mmol, 0.2 eq) and Cs₂CO₃ (225 mg, 0.69 mmol, 3.0 eq) were placed in the reaction bottle. A solution of PhMe/H₂O (5/1, 9.0 mL) was added at room temperature. The mixture was stirred with microwave reactor at 120 °C for 2 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give a residue. The crude product was purified by prep-TLC (DCM: MeOH = 10: 1) to give tert-butyl 3-(6,8-difluoro-7-(7-fluoro-3-hydroxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (130 mg, 62.5%) as a yellow liquid. LCMS: 904.4 ([M+H]⁺).

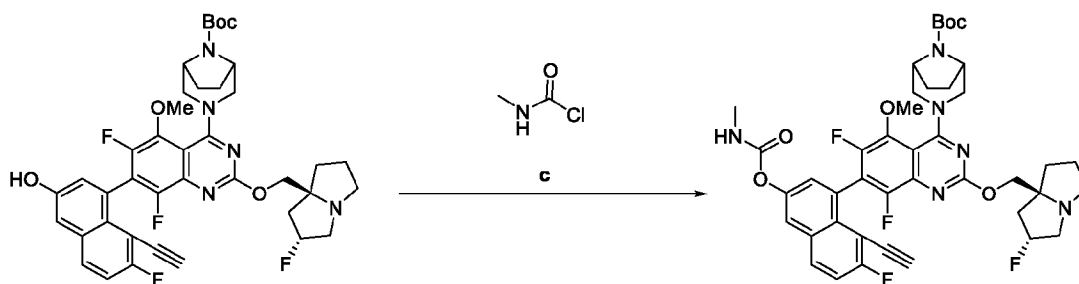
Step 2: Synthesis of tert-butyl 3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00580] To a solution of tert-butyl 3-(6,8-difluoro-7-(7-fluoro-3-hydroxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

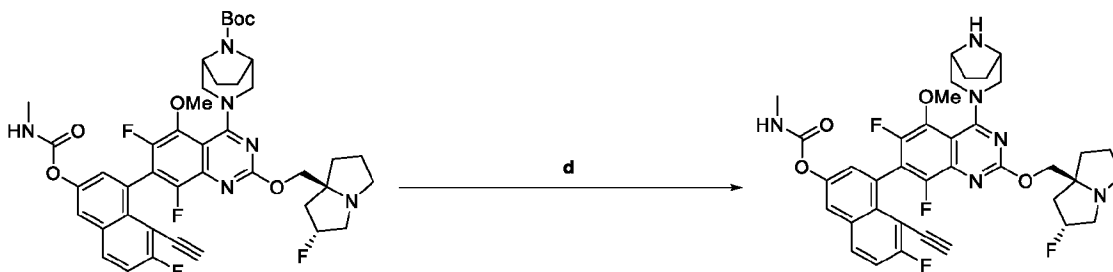
(100 mg, 0.11 mmol, 1.0 eq) in DMF (1.0 mL) was added CsF (251 mg, 1.65 mmol, 15.0 eq). The reaction mixture was stirred at 40 °C for 2 h. The mixture was diluted with water (5 mL) and extracted with EtOAc (5 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give tert-butyl (1R,5S)-3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (110 mg, crude) as a yellow liquid. LCMS: 748.3 (M+H⁺).

Step 3: Synthesis of tert-butyl 3-(7-(8-ethynyl-7-fluoro-3-((methylcarbamoyl)oxy)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00581] To a solution of tert-butyl 3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (crude), methylcarbamic chloride (62 mg, 0.66 mmol, 6.0 eq) in DCM (1.1 mL) was added DIEA (128 mg, 0.99 mmol, 9.0 eq) at room temperature under N₂ atmosphere. The reaction mixture was stirred at 30 °C for 15 h. The mixture was diluted with water (5 mL) and extracted with DCM (5 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give tert-butyl 3-(7-(8-ethynyl-7-fluoro-3-((methylcarbamoyl)oxy)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, crude) as a yellow liquid. LCMS: 805.3 (M+H⁺).

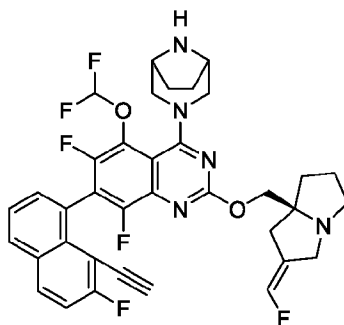
Step 4: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-yl methylcarbamate



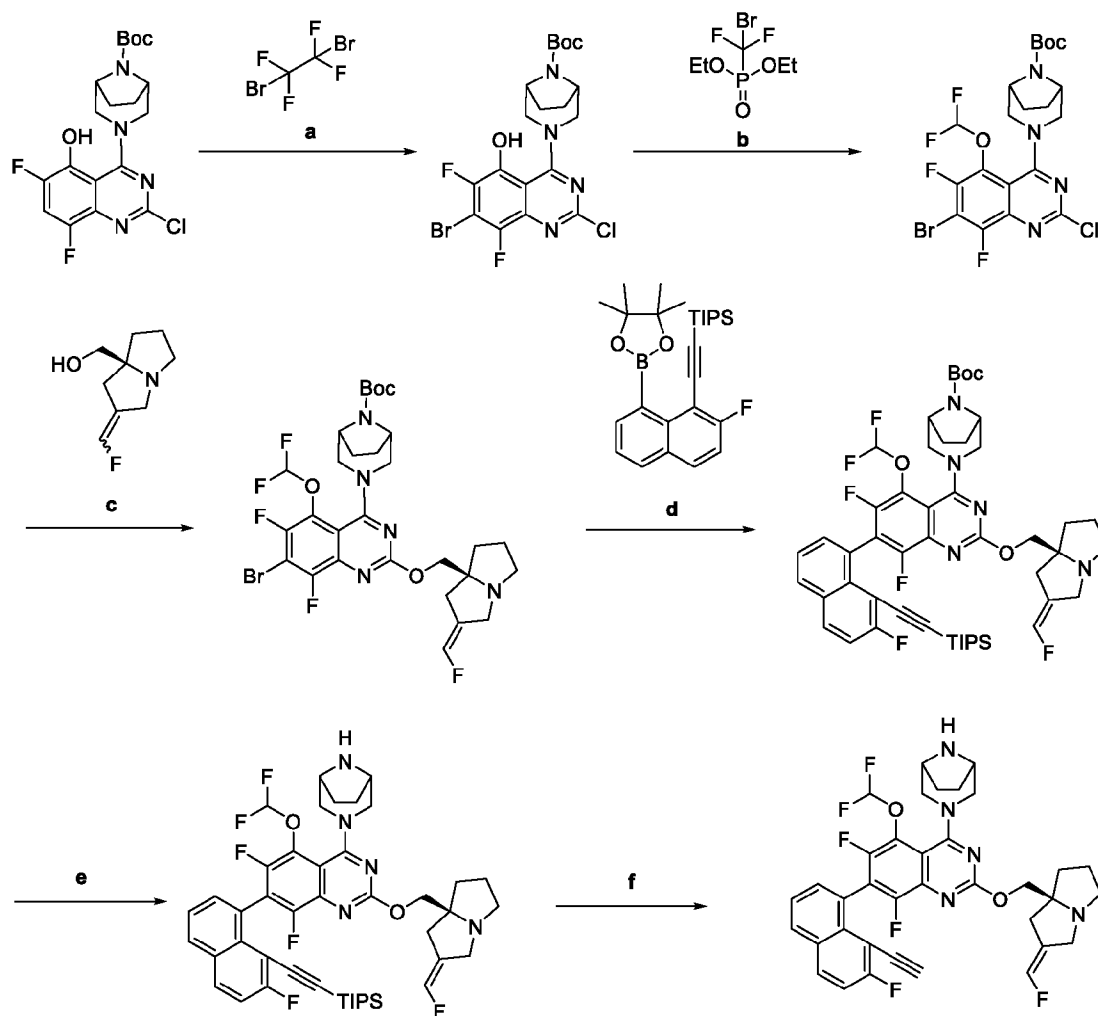
[00582] To a solution of tert-butyl 3-(7-(8-ethynyl-7-fluoro-3-((methylcarbamoyl)oxy)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (crude) in ACN (4.4 mL) was added HCl/Dioxane (0.88 mL) at 0 °C under N₂ atmosphere. The reaction mixture was stirred at 0 °C for 4 h. Then the reaction mixture was filtered and the filtrate was purified by Prep-HPLC (acetonitrile with 0.1% FA in water, 15% to 30%) to give 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-yl methylcarbamate (15.1 mg, with 0.65 FA salt, 18.2% for three steps) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.26 – 8.15 (m, 2H), 7.98 (d, *J* = 2.4 Hz, 1H), 7.80-7.70 (m, 1H), 7.64 (t, *J* = 9.2 Hz, 1H), 5.28 (d, *J* = 54.8 Hz, 1H), 4.16 (s, 1H), 4.10-3.90 (m, 4H), 3.90-3.60 (m, 8H), 3.15-3.00 (m, 4H), 2.90-2.80 (m, 1H), 2.75-2.65 (m, 3H), 2.12 (s, 1H), 2.05 (s, 1H), 2.00 (s, 1H), 1.90-1.60 (m, 8H). LCMS: 705.3 (M+H⁺).

Example 60

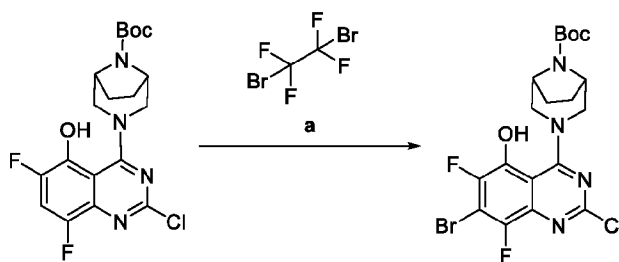
4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-(difluoromethoxy)-7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazoline



Synthesis scheme



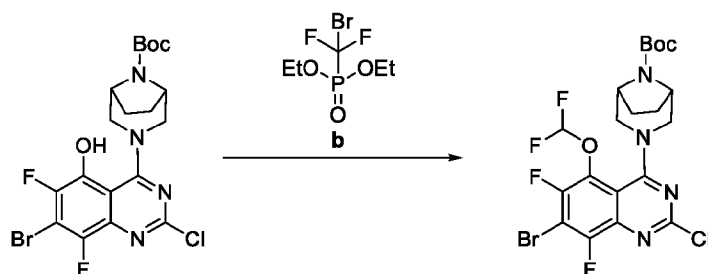
Step 1: Synthesis of tert-butyl 3-(7-bromo-2-chloro-6,8-difluoro-5-hydroxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00583] To a solution of tert-butyl 3-(2-chloro-6,8-difluoro-5-hydroxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (450 mg, 1.05 mmol, 1.0 eq) in THF (5 mL) was added LDA (2 M in THF, 3.2 mL, 6.32 mmol, 6.0 eq) at -65 °C under N₂ atmosphere. After 30 min, the reaction mixture was added 1,2-dibromo-1,1,2,2-tetrafluoroethane (2.19 g, 8.43 mmol, 8.0

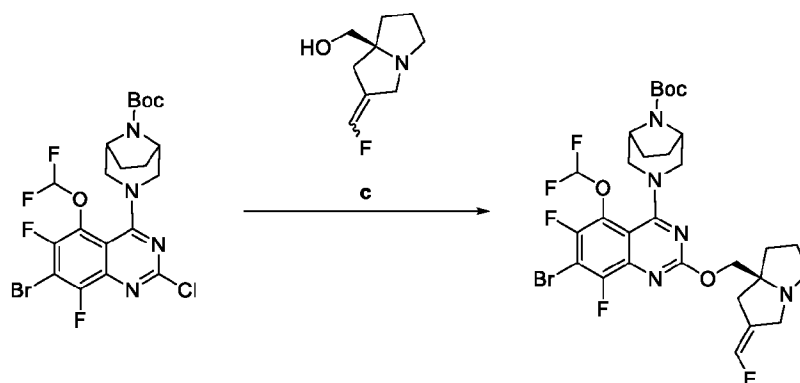
eq). The reaction mixture was stirred at -65 °C for 3 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give a residue. The crude product was purified by silica gel column chromatography (Petroleum ether: EtOAc = 5: 1) to give tert-butyl 3-(7-bromo-2-chloro-6,8-difluoro-5-hydroxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (180 mg, 33.9%) as a yellow solid. LCMS: m/z 505.1, 507.0 (M+H⁺).

Step 2: Synthesis of tert-butyl 3-(7-bromo-2-chloro-5-(difluoromethoxy)-6,8-difluoroquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



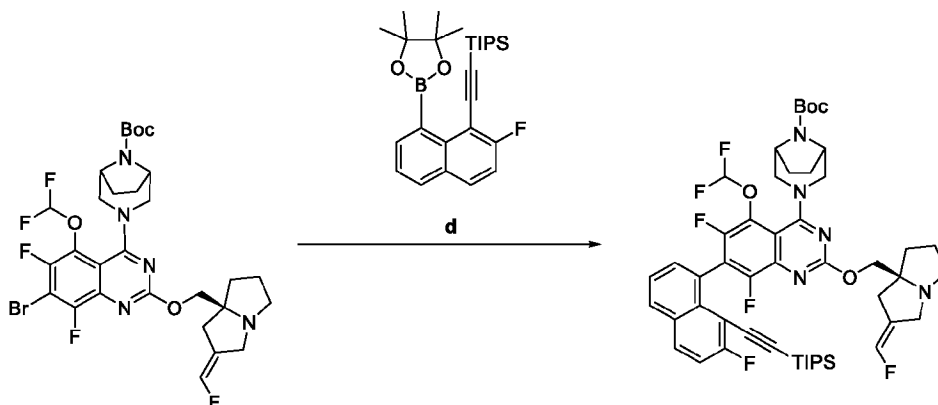
[00584] To a solution of tert-butyl 3-(7-bromo-2-chloro-6,8-difluoro-5-hydroxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (220 mg, 0.44 mmol, 1.0 eq) in ACN/H₂O (1/1, 4.4 mL) was added KOH (488 mg, 8.7 mmol, 20.0 eq), diethyl (bromodifluoromethyl)phosphonate (235 mg, 0.87 mmol, 2.0 eq). The reaction mixture was stirred at room temperature for 1 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give a residue. The crude product was purified by silica gel column chromatography (Petroleum ether: EtOAc = 3: 1) to give tert-butyl 3-(7-bromo-2-chloro-5-(difluoromethoxy)-6,8-difluoroquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (190 mg, 77.3%) as a yellow solid. LCMS: m/z 557.0 (M+H⁺).

Step 3: Synthesis of tert-butyl 3-(7-bromo-5-(difluoromethoxy)-6,8-difluoro-2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00585] To a solution of tert-butyl 3-(7-bromo-2-chloro-5-(difluoromethoxy)-6,8-difluoroquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (190 mg, 0.34 mmol, 1.0 eq) in DMSO (5.0 mL) was added (S)-(2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (117 mg, 0.68 mmol, 2.0 eq), KF (40 mg, 0.68 mmol, 2.0 eq). The reaction mixture was stirred at 100 °C for 5 h under N₂ atmosphere. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give a residue. The crude product was purified by prep-TLC (DCM: MeOH = 5: 1) to give tert-butyl 3-(7-bromo-5-(difluoromethoxy)-6,8-difluoro-2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (60 mg, 25.6%) as a yellow solid. LCMS: m/z 690.1 (M+H⁺).

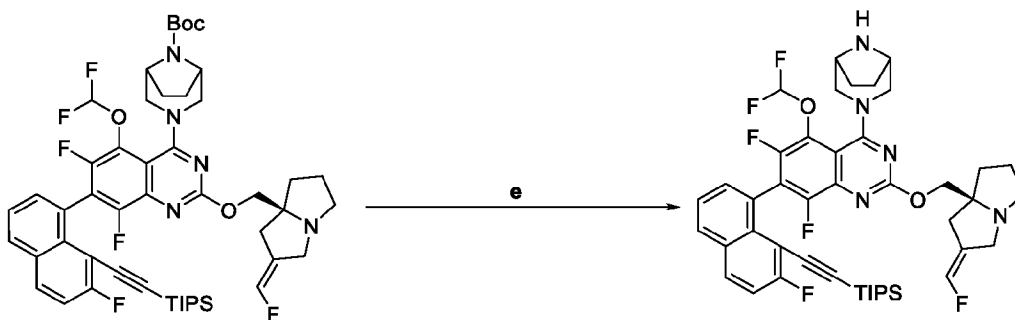
Step 4: Synthesis of tert-butyl 3-(5-(difluoromethoxy)-6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00586] To a solution of tert-butyl 3-(7-bromo-5-(difluoromethoxy)-6,8-difluoro-2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-

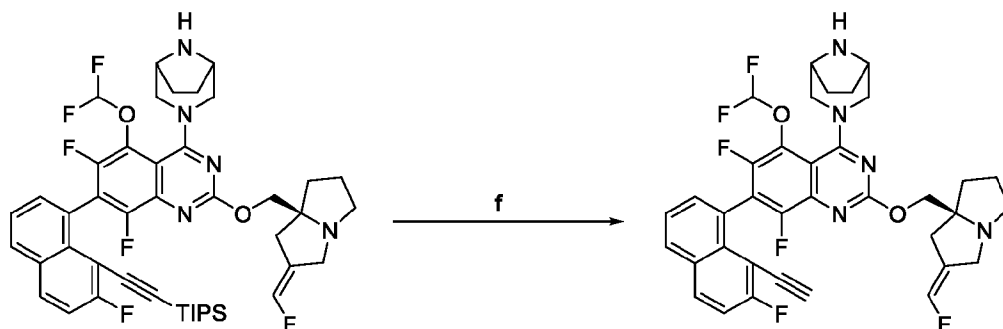
diazabicyclo[3.2.1]octane-8-carboxylate (50 mg, 0.072 mmol, 1.0 eq) in toluene/H₂O (5/1, 3.6 mL) was added ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) naphthalen-1-yl) ethynyl) triisopropylsilane (39 mg, 0.086 mmol, 1.2 eq), cataCium A Pd G3 (10 mg, 0.014 mmol, 0.2 eq), Cs₂CO₃ (70 mg, 0.216 mmol, 3.0 eq). The sealed vial was irradiated under the microwave at 120 °C for 1.5 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give a residue. The crude product was purified by prep-TLC (DCM: MeOH = 10: 1) to give tert-butyl 3-(5-(difluoromethoxy)-6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (40 mg, 59.7%) as a yellow solid. LCMS: 936.5 (M+H⁺).

Step 5: Synthesis of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-(difluoromethoxy)-6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazoline



[00587] To a solution of tert-butyl 3-(5-(difluoromethoxy)-6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (30 mg, 0.032 mmol, 1.0 eq) in ACN (1.5 mL) was added HCl/dioxane (0.3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. Then the reaction mixture was concentrated in vacuo to afford 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-(difluoromethoxy)-6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazoline (crude) as a yellow solid, which was used directly for the next step without any further purification. LCMS: m/z 836.3 (M+H⁺).

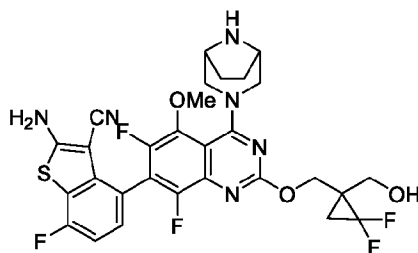
Step 6: Synthesis of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-(difluoromethoxy)-7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazoline



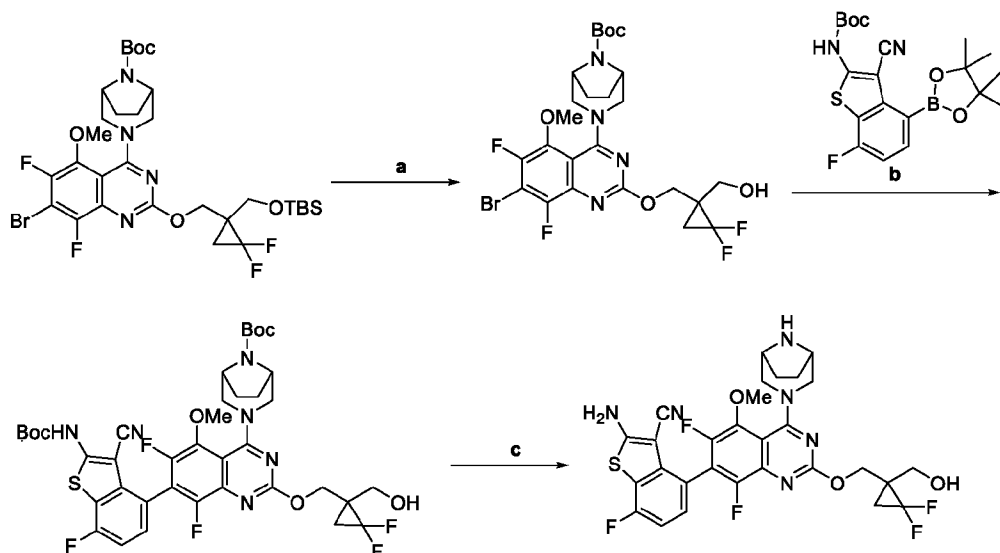
[00588] To a solution of 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-(difluoromethoxy)-6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazoline (crude) in DMF (1 mL) was added CsF (75 mg, 0.495 mmol, 15.0 eq). The reaction mixture was stirred at 40 °C for 4 h. Then the reaction mixture was filtered and the filtrate was purified by Prep-HPLC (0.1% FA) to afford 4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-(difluoromethoxy)-7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazoline formate (1: 0.5) (3.6 mg, 0.005 mmol, 16.5% for two steps) as a yellow solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.34 – 8.17 (m, 2H), 7.82 – 7.53 (m, 3H), 7.20–6.50 (m, 2H), 4.13 – 3.87 (m, 3H), 3.70 (d, *J* = 14.4 Hz, 2H), 3.47 (m, 3H), 3.10–2.90 (m, 2H), 2.75–2.70 (m, 1H), 2.60–2.20 (m, 6H), 2.06 – 1.51 (m, 9H). LCMS: *m/z* 680.2 (M+H⁺).

Example 61

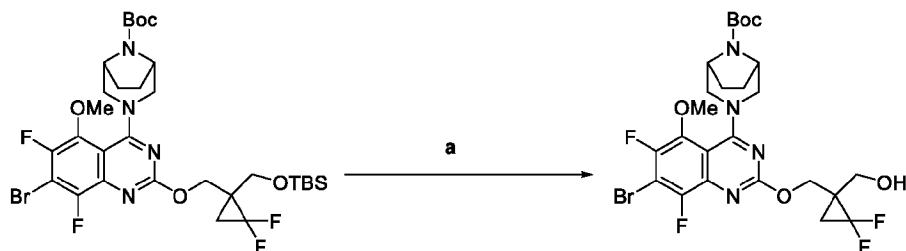
4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-((2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile hydrochloride



Synthetic scheme:

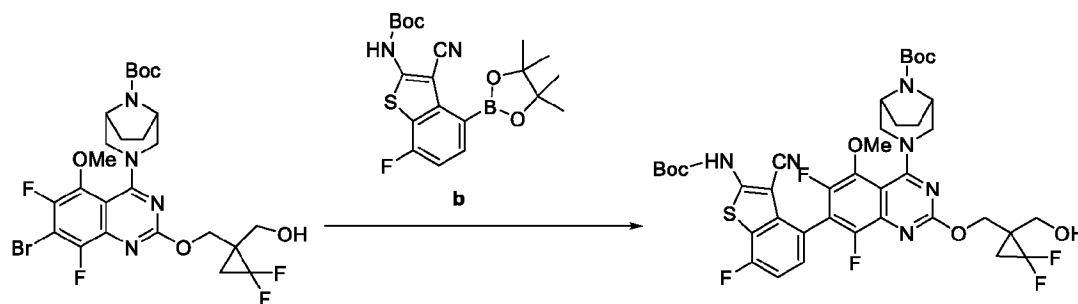


Step 1: Synthesis of tert-butyl 3-(7-bromo-2-((2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



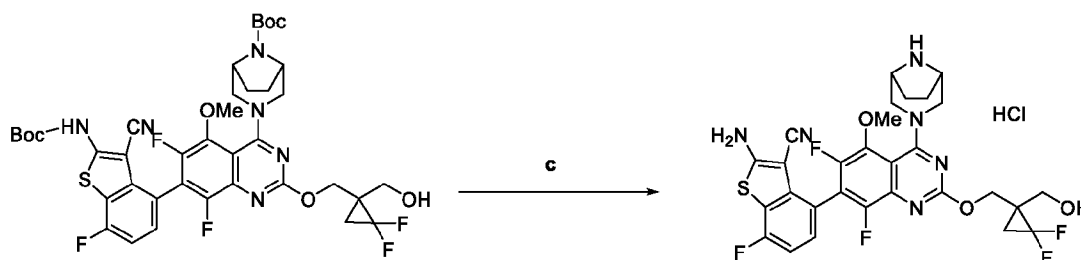
[00589] To a solution of tert-butyl 3-(7-bromo-2-((1-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-difluorocyclopropyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.14 mmol, 1.0 eq) in DMF (2.0 mL) was added CsF (425 mg, 2.8 mmol, 20.0 eq). The mixture was stirred at 50 °C for 2.5 h. The mixture was concentrated to give a crude. The crude was purified by Prep-TLC (Petroleum ether: EtOAc = 5: 1) to give tert-butyl 3-(7-bromo-2-((2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (70 mg, 82.9%) as a yellow solid. LCMS: 620.8, 622.8 (M+H⁺).

Step 2: Synthesis of tert-butyl 3-(7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-((2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00590] To a solution of tert-butyl 3-(7-bromo-2-((2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (60 mg, 0.09 mmol, 1.0 eq) and tert-butyl (3-cyano-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophen-2-yl)carbamate (45 mg, 0.10 mmol, 1.2 eq) in toluene (1.5 mL) was added Cs₂CO₃ (59 mg, 0.18 mmol, 2.0 eq), (CAS: 2816930-70-6) (6 mg, 0.10 mmol, 0.12 eq) and Pd₂(dba)₃ (4 mg, 0.004 mmol, 0.05 eq). The mixture was stirred at 100 °C for 4 h under N₂. The reaction mixture was partitioned between EtOAc (5 mL) and H₂O (3 mL). The layers were separated. The aqueous layer was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (3 mL), dried over Na₂SO₄ and concentrated to a crude. The crude was purified by Prep-TLC (DCM: MeOH ~ 15: 1) to give tert-butyl (3-(7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-((2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (35 mg, 43.4%) as a yellow solid. LCMS: 833.2 (M+H⁺).

Step 3: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-((2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile hydrochloride

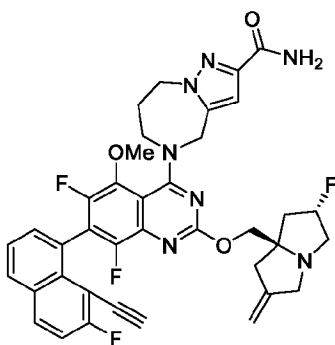


[00591] To a solution of tert-butyl 3-(7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-((2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (35 mg, 0.04

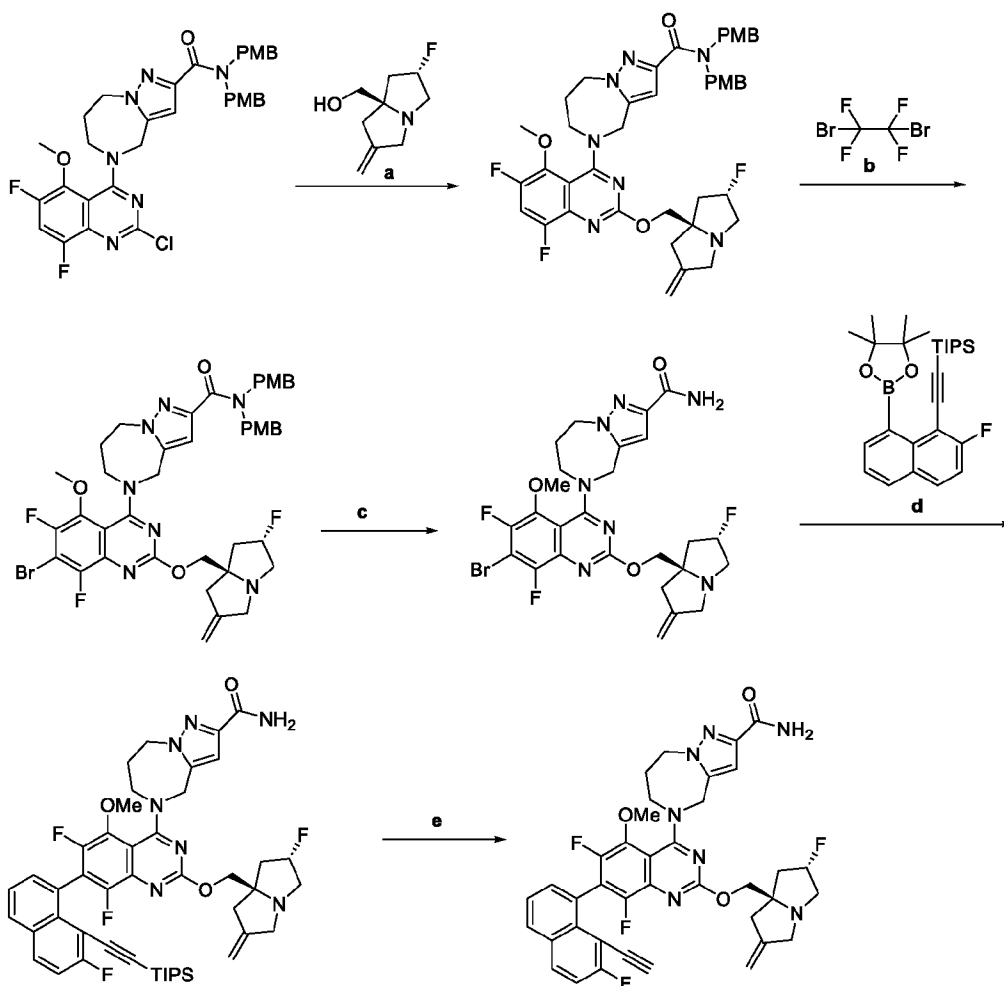
mmol, 1.0 eq) in DCM (1.0 mL) was added 4 M HCl/Dioxane (0.3 mL, 1.2 mmol, 30.0 eq) at 0 °C. The reaction mixture was stirred at room temperature for 3 h under N₂. The mixture was concentrated to give a crude. The crude was purified by Prep-HPLC (ACN with 0.1% FA in water, 15% to 50%) to give 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-((2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-6,8-difluoro-5-methoxyquinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile hydrochloride (1:1) (2 mg, 7.5%) as a white solid. ¹H NMR (300 MHz, CD₃OD): δ 7.30 (dd, *J* = 8.4, 5.1 Hz, 1H), 7.07 – 7.01 (m, 1H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.55 (d, *J* = 11.7 Hz, 1H), 4.32 (d, *J* = 15.0 Hz, 2H), 3.95 (s, 2H), 3.90 (s, 3H), 3.78 (s, 2H), 3.61 – 3.53 (m, 2H), 2.05 – 1.99 (m, 4H), 1.59 – 1.46 (m, 2H). ¹⁹F NMR (300 MHz, CD₃OD): δ -118.270, -132.403, -138.153, -138.613 (d, *J*_{F-F} = 171.9 Hz, *J*_{F-H} = 3.3 Hz, 1F), -140.359 (d, *J*_{F-F} = 172.2 Hz, 1F). LCMS: 632.8 (M+H⁺).

Example 62

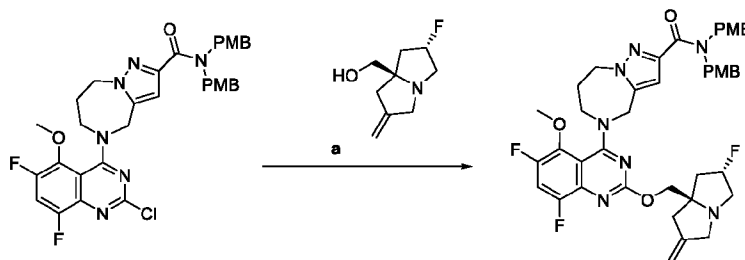
5-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



Synthetic scheme:



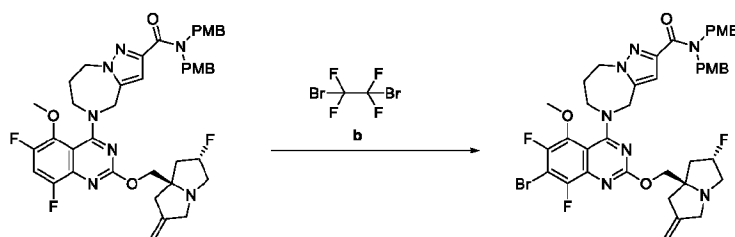
Step 1: Synthesis of 5-(6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N,N-bis(4-methoxybenzyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



[00592] A solution of compound 5-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-N,N-bis(4-methoxybenzyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (500 mg, 0.77 mmol, 1.0 eq), compound ((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-

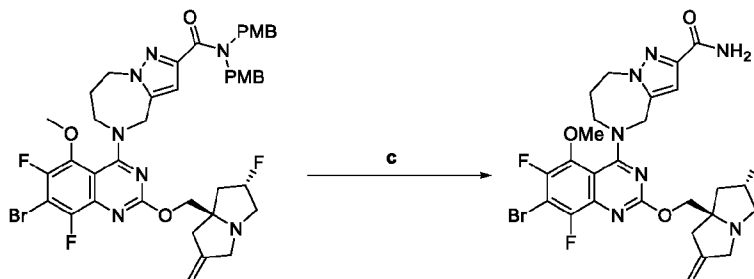
7a(5H)-yl)methanol (171 mg, 1.0 mmol, 1.3 eq), DABCO (86 mg, 0.77 mmol, 1.0 eq) and Cs_2CO_3 (753 mg, 2.31 mmol, 3.0 eq) in THF (3.0 mL) and DMF (3.0 mL) was stirred at room temperature for 15 h under nitrogen atmosphere. The mixture was added H_2O (12 mL), extracted with EtOAc (5 mL x 3). The combined organic layers were washed with H_2O (5 mL x 3), brine (5 mL), dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by silica gel column chromatography (DCM: MeOH = 10: 1) to give compound 5-(6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N,N-bis(4-methoxybenzyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (480 mg, 79.5%) as a green solid. LCMS: 784.3 ($\text{M}+\text{H}^+$).

Step 2: Synthesis of 5-(7-bromo-6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N,N-bis(4-methoxybenzyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



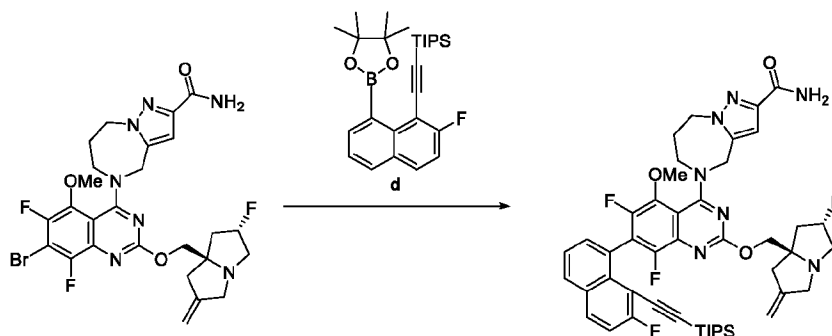
[00593] To a solution of compound 5-(6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N,N-bis(4-methoxybenzyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (280 mg, 0.36 mmol, 1.0 eq) in THF (3 mL) was added LDA (0.6 mL, 1.1 mmol, 3.0 eq) at -78°C under N_2 atmosphere. The mixture was stirred at -78°C for 30 min. The mixture was added 1,2-dibromo-1,1,2,2-tetrafluoroethane (102 mg, 0.39 mmol, 1.1 eq) at the same temperature, and stirred for 2 h. The reaction was quenched with water (5 mL). The mixture was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by prep-TLC (DCM: MeOH = 10: 1) to give compound 5-(7-bromo-6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N,N-bis(4-methoxybenzyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (190 mg, 61.7%) as a green solid. LCMS: 862.2, 864.2 ($\text{M}+\text{H}^+$).

Step 3: Synthesis of 5-(7-bromo-6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



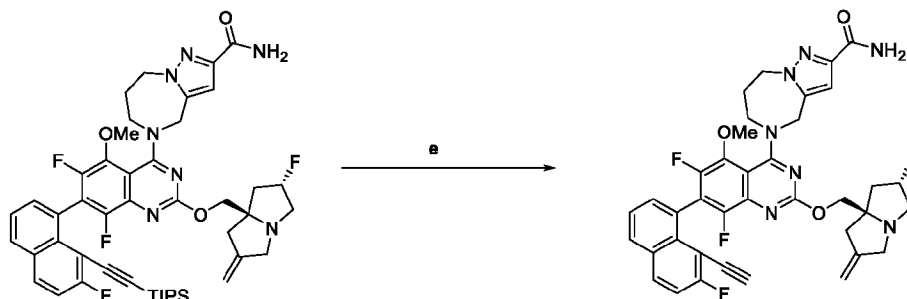
[00594] A solution of compound 5-(7-bromo-6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N,N-bis(4-methoxybenzyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (48 mg, 0.06 mmol, 1.0 eq) in TFA (2 mL) was stirred at 50 °C for 15 h under nitrogen atmosphere. The reaction evaporated to dryness. The crude product was purified by prep-TLC (DCM: MeOH = 10: 1) to give compound 5-(7-bromo-6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (30 mg, 86.1%) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 6.69 (s, 1H), 5.49 – 5.19 (m, 2H), 4.95 (s, 2H), 4.89 – 4.77 (m, 2H), 4.45 – 4.34 (m, 2H), 4.21 – 4.11 (m, 1H), 3.94 – 3.75 (m, 2H), 3.67 (s, 3H), 3.61 – 3.53 (m, 1H), 3.48 – 3.29 (m, 1H), 3.22 – 3.04 (m, 1H), 2.73 (s, 2H), 2.51 – 1.94 (m, 5H). LCMS: 622.1, 624.1 (M+H⁺).

Step 4: Synthesis of 5-(6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



[00595] To a solution of 5-(7-bromo-6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (30 mg, 0.048 mmol, 1.0 eq) and ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (33 mg, 0.072 mmol, 1.5 eq) in PhMe (1.0 mL) and H₂O (0.25 mL) was added K₃PO₄ (20 mg, 0.10 mmol, 2.0 eq), rac-BI-DIME (3 mg, 0.01 mmol, 0.2 eq) and Pd₂(dba)₃ (6 mg, 0.007 mmol, 0.15 eq). The mixture was heated under microwave irradiation at 120 °C for 1.5 h under N₂. The reaction mixture was partitioned between EtOAc (5 mL) and H₂O (3 mL). The layers were separated. The aqueous layer was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (3 mL), dried over Na₂SO₄ and concentrated to a crude. The crude was purified by Prep-TLC (DCM: MeOH ~ 15: 1) to give 5-(6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (13 mg, 31.1%) as a white solid. LCMS: 868.3 (M+H⁺).

Step 5: Synthesis of 5-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

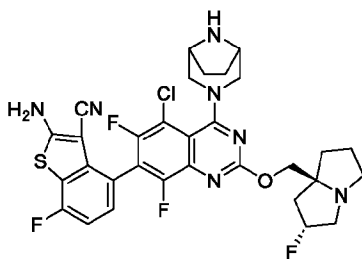


[00596] To a mixture of 5-(6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (10 mg, 0.012 mmol, 1.0 eq) in DMF (1 mL) was added CsF (55 mg, 0.36 mmol, 30.0 eq). The mixture was stirred at 50 °C for 2 h. The filtrate collected by filtration was concentrated to give a crude. The crude was purified by Prep-HPLC (ACN with 0.1% FA in water) to give 5-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-

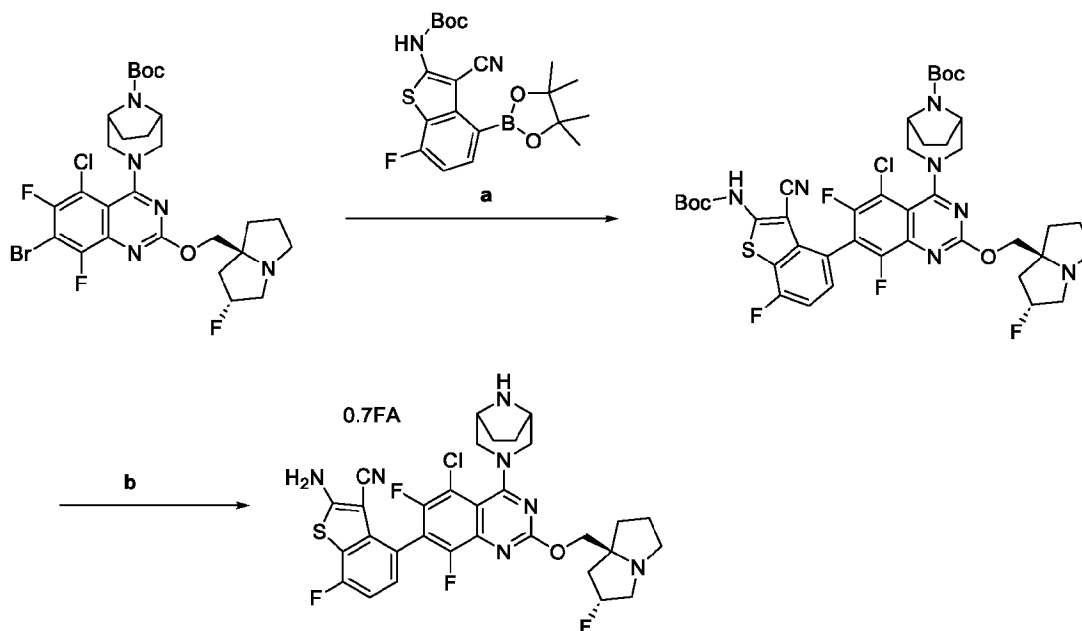
pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (4 mg, 46.8%) as a white solid. ^1H NMR (400 MHz, CD_3OD): δ 8.11 (d, $J = 7.6$ Hz, 2H), 7.65 (t, $J = 7.6$ Hz, 1H), 7.60 – 7.54 (m, 1H), 7.45 (t, $J = 8.8$ Hz, 1H), 6.69 (s, 1H), 5.35 (d, $J = 54.0$ Hz, 1H), 5.10 – 4.98 (m, 4H), 4.58 – 4.38 (m, 2H), 4.20 (s, 2H), 4.14 – 4.01 (m, 2H), 3.94 – 3.83 (m, 1H), 3.80 (s, 3H), 3.72 – 3.64 (m, 1H), 3.58 – 3.36 (m, 3H), 2.82 – 2.72 (m, 2H), 2.45 – 2.13 (m, 4H). ^{19}F NMR (400 MHz, CD_3OD): δ -106.439, -132.135, -137.785, -173.253. LCMS: 712.2 ($\text{M}+\text{H}^+$).

Example 63

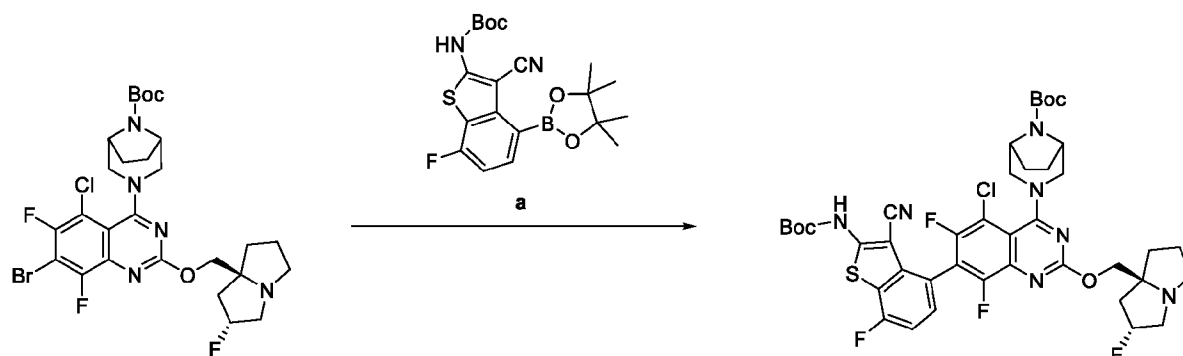
4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-chloro-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile formate



Synthetic scheme:

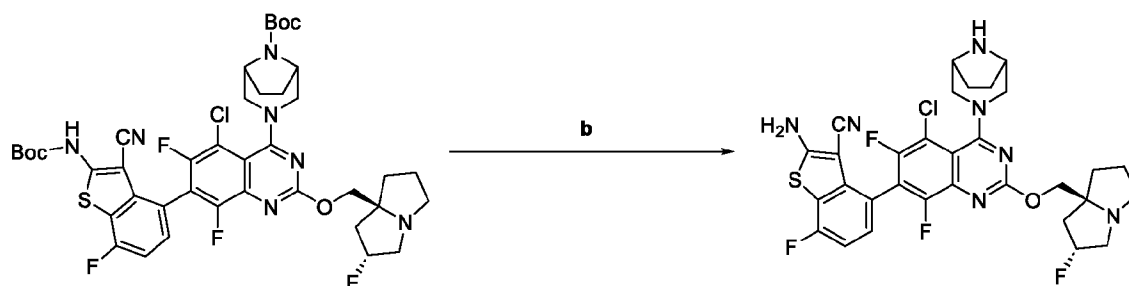


Step 1: Synthesis of tert-butyl 3-(7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-5-chloro-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00597] To a solution of tert-butyl 3-(7-bromo-5-chloro-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (150 mg, 0.23 mmol, 1.0 eq) in dioxane (6 mL) and H₂O (2 mL) was added tert-butyl (3-cyano-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophen-2-yl)carbamate (117 mg, 0.28 mmol, 1.2 eq), K₃PO₄ (99 mg, 0.46 mmol, 3.0 eq) and Pd(dtbpf)Cl₂ (15 mg, 0.02 mmol, 0.1 eq). The reaction mixture was stirred at 90 °C for 4 h under nitrogen atmosphere. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The organic phase was washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by silica gel column chromatography (DCM / MeOH = 15:1) to give tert-butyl 3-(7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-5-chloro-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (55 mg, 27.6%) as a yellow solid. LCMS: 858.1 (M+H⁺).

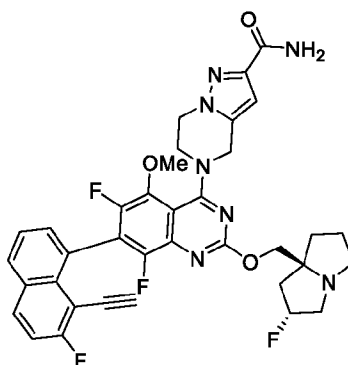
Step 2: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-chloro-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile formate (1:0.7)



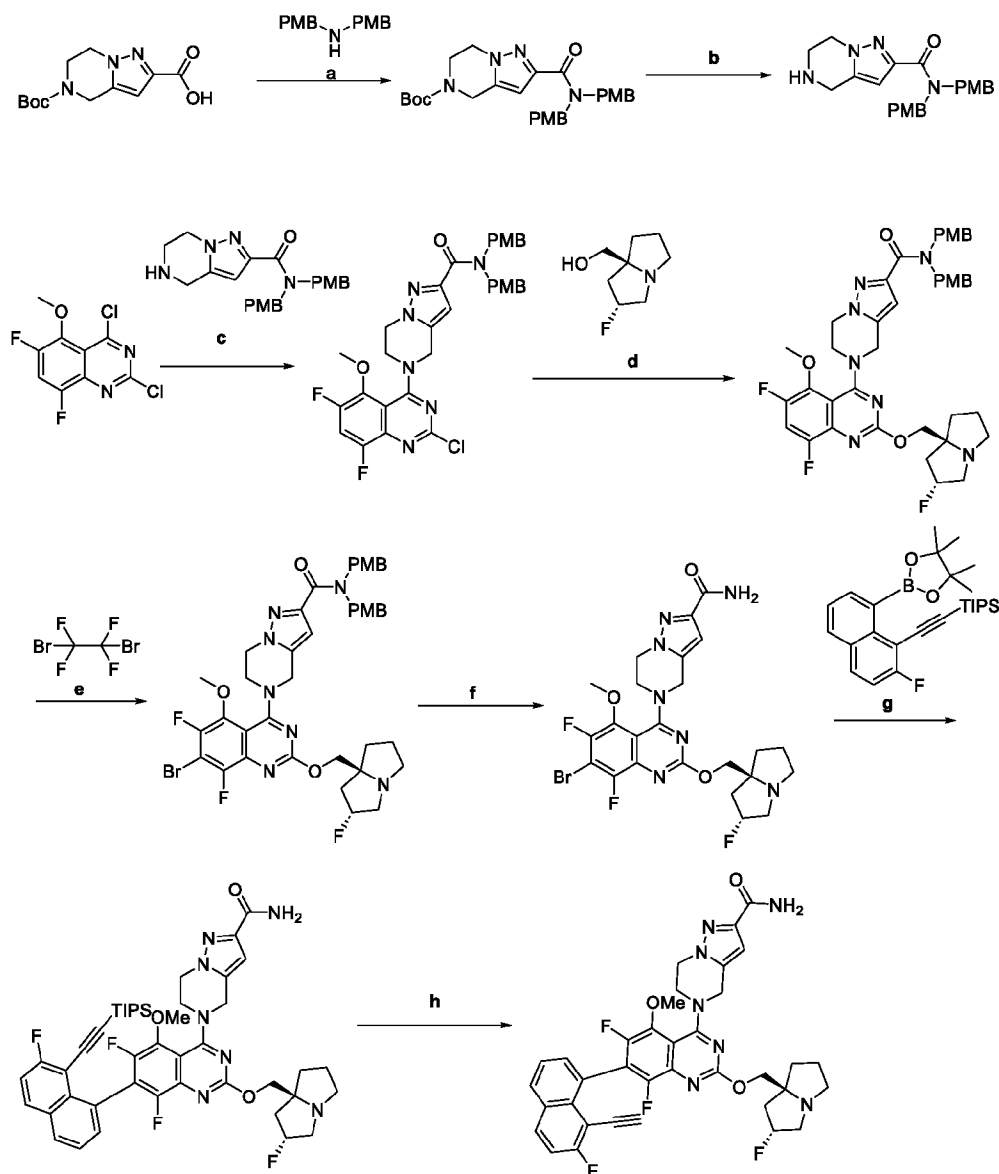
[00598] To a solution of tert-butyl 3-(7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-5-chloro-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (55 mg, 0.06 mmol, 1.0 eq) in DCM (3.0 mL) was added HCl in dioxane (1.5 mL, 4M in dioxane). Then the reaction mixture was stirred at room temperature for 1 h. The mixture was concentrated and purified by prep-HPLC (acetonitrile with 0.1% FA in water, 5% to 60%) to give 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-chloro-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile formate (1:0.7) (2.3 mg, 5.4%) as a white solid. ¹H NMR (400 MHz, CD₃OD): δ 8.55(s, 1H), 7.33 (dd, *J* = 8.4, 5.2 Hz, 1H), 7.07 (t, *J* = 8.8 Hz, 1H), 5.38 (d, *J* = 53.2 Hz, 1H), 4.78 – 4.50 (m, 1H), 4.48 – 4.28 (m, 2H), 4.18 – 4.00 (m, 1H), 4.00 – 3.85 (m, 1H), 3.85 – 3.74 (m, 1H), 3.74 – 3.58 (m, 2H), 3.56 – 3.37 (m, 3H), 3.24 – 3.08 (m, 1H), 2.55 – 2.17 (m, 3H), 2.17 – 2.04 (m, 2H), 2.03 – 1.92 (m, 1H), 1.92 – 1.62 (m, 3H), 1.60 – 1.40 (m, 1H). ¹⁹F NMR (400 MHz, CD₃OD): -117.829, -119.858, -127.801, -173.818. LCMS: 658.1 (M+H⁺).

Example 64

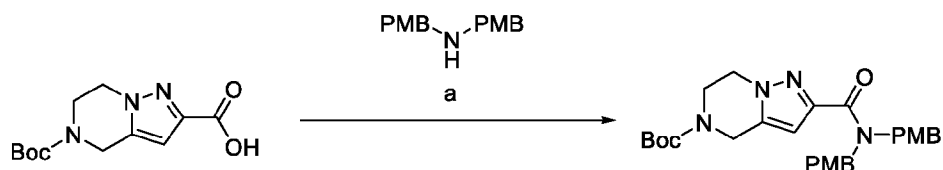
5-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide



Synthetic scheme:



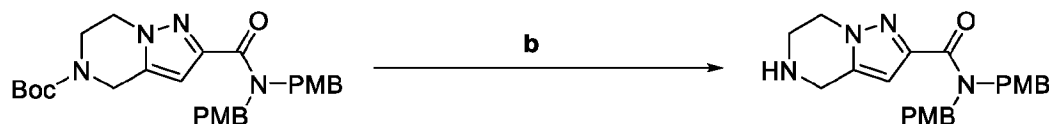
Step 1: Synthesis of tert-butyl 2-(bis(4-methoxybenzyl)carbamoyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate



[00599] To a solution of compound 5-(tert-butoxycarbonyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (250 mg, 0.94 mmol, 1.0 eq) in THF (3.0 mL) was added

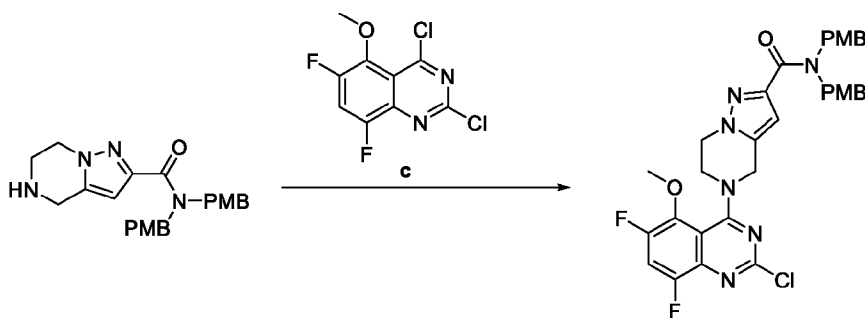
compound bis(4-methoxybenzyl)amine (241 mg, 0.94 mmol, 1.0 eq), DIEA (725 mg, 5.6 mmol, 6.0 eq) and HATU (712 mg, 1.9 mmol, 2.0 eq) at room temperature. The reaction was stirred at room temperature for 2 h. The mixture was partitioned between EtOAc (20 mL) and water (30 mL). The layers were separated. The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic layers were washed with H₂O (20 mL), brine (20 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (Dichloromethane: Methanol = 200:1) to give compound tert-butyl 2-(bis(4-methoxybenzyl)carbamoyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (400 mg, 84.4%) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 7.24 – 7.11 (m, 4H), 6.94 – 6.80 (m, 4H), 6.53 (s, 1H), 4.85 (s, 2H), 4.65 (s, 2H), 4.55 (s, 2H), 4.22 – 4.10 (m, 2H), 3.87 (t, J = 5.4 Hz, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 1.49 (s, 9H). LCMS: 507.1 (M+H⁺).

Step 2: Synthesis of N,N-bis(4-methoxybenzyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide



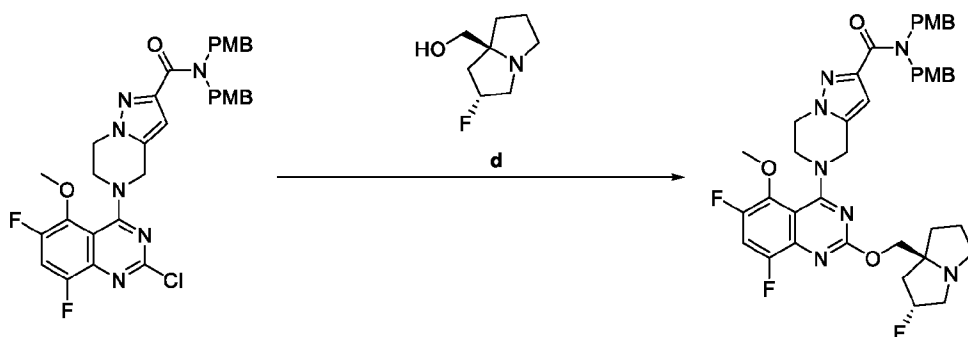
[00600] To a solution of compound tert-butyl 2-(bis(4-methoxybenzyl)carbamoyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (400 mg, 0.79 mmol, 1.0 eq) in DCM (4.0 mL) was added HCl in dioxane (4 M, 4.0 mL, 15.8 mmol, 20.0 eq). The reaction was stirred at room temperature for 2 h. The mixture was concentrated to give a crude. The crude was diluted with NaHCO₃ aqueous solution (30 mL) and extracted with EtOAc (20 mL x 3). The combined organic phases were washed with brine (30 mL), dried over Na₂SO₄ and concentrated to give crude compound *N,N*-bis(4-methoxybenzyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide (360 mg, crude) as a yellow solid. LCMS: 407.0 (M+H⁺).

Step 3: Synthesis of 5-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-N,N-bis(4-methoxybenzyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide



[00601] To a solution of N,N-bis(4-methoxybenzyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide (510 mg, 1.3 mmol, 1.0 eq) in DCM (10.0 mL) was added 2,4-dichloro-6,8-difluoro-5-methoxyquinazoline (331 mg, 1.3 mmol, 1.0 eq) and DIEA (1.3 g, 10.0 mmol, 8.0 eq) at -20 °C. The reaction mixture was stirred at room temperature for 2 h under nitrogen atmosphere. The reaction mixture was quenched with water (20 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with H₂O (10 mL), brine (10 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (Dichloromethane: Methanol = 150: 1) to give 5-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-N,N-bis(4-methoxybenzyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide (400 mg, 50.0% for 2 steps) as a yellow solid. LCMS: 635.0 (M+H⁺).

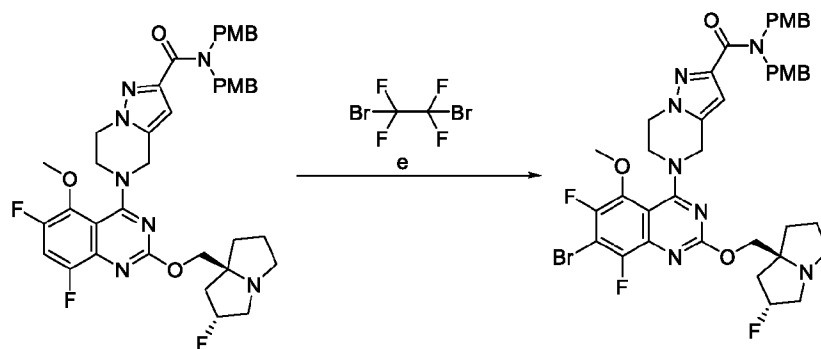
Step 4: Synthesis of 5-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N,N-bis(4-methoxybenzyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide



[00602] To a solution of 5-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-N,N-bis(4-methoxybenzyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide (500 mg, 0.80 mmol, 1.0 eq) in dioxane (16 mL) was added Cs₂CO₃ (782 mg, 2.4 mmol, 3.0 eq), ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (191 mg, 1.2 mmol, 1.5 eq) and S-Phos Pd G4 (63 mg, 0.08 mmol, 0.1 eq) at room temperature. The reaction mixture was stirred at 100 °C

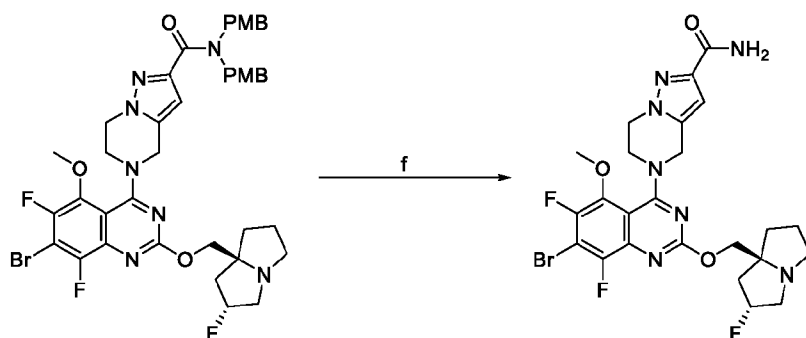
for 3 h under nitrogen atmosphere. The mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 3). The organic phase was washed with brine (20 mL), dried with Na₂SO₄, filtered and concentrated to give a crude. The crude was purified by silica gel column chromatography (DCM: MeOH = 40 : 1) to give 5-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N,N-bis(4-methoxybenzyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide (320 mg, 53.6%) as a yellow solid. LCMS: 758.5 (M+H⁺).

Step 5: Synthesis of 5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N,N-bis(4-methoxybenzyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide



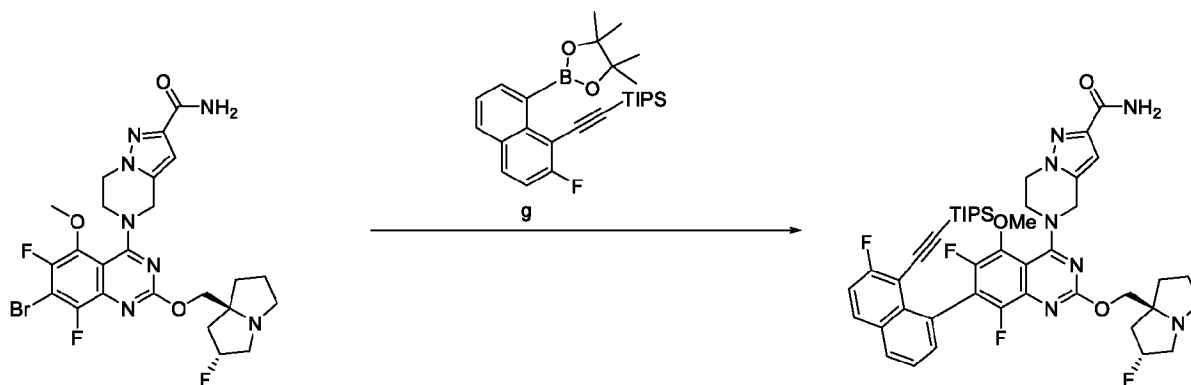
[00603] To a solution of 5-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N,N-bis(4-methoxybenzyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide (280 mg, 0.37 mmol, 1.0 eq) in THF (3 mL) was added *n*-BuLi (0.22 mL, 0.56 mmol, 1.5 eq, 2.5 M in hexane/THF) at -78 °C under nitrogen atmosphere. Then the reaction mixture was stirred at -78 °C for 1 h. Then to the mixture was added 1,2-dibromo-1,1,2,2-tetrafluoroethane (106 mg, 0.41 mmol, 1.1 eq) in THF (2 mL). Then the reaction mixture was stirred at -78 °C for 1 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The organic phase was washed with brine (10 mL), dried with Na₂SO₄, filtered and concentrated to give a crude. The crude was purified by prep-TLC (DCM: MeOH = 15: 1) to give 5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N,N-bis(4-methoxybenzyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide (110 mg, 34.9%) as a yellow solid. LCMS: 836.1, 838.1 (M+H⁺).

Step 6: Synthesis of 5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide



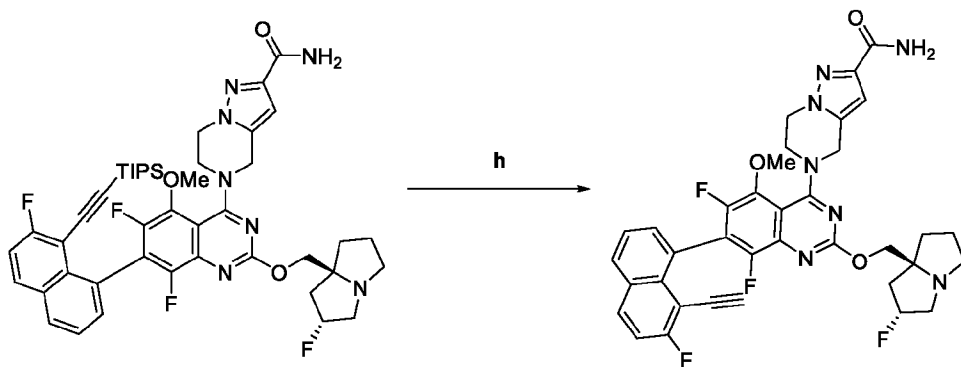
[00604] A solution of 5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-N,N-bis(4-methoxybenzyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide (110 mg, 0.13 mmol, 1.0 eq) in TFA (1 mL) and stirred at 50 °C for 15 h. The mixture was concentrated to give a crude. The crude was diluted with aqueous sodium bicarbonate solution (10 mL) and extracted with EtOAc (10 mL x 3). The organic phase was washed with brine (10 mL), dried with Na₂SO₄, filtered and concentrated to give a crude. The crude was purified by prep-TLC (DCM : MeOH = 15:1) to give 5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide (60 mg, 76.6%) as a yellow solid. LCMS: 596.1, 598.0 (M+H⁺).

Step 7: Synthesis of 5-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide



[00605] To a solution of 5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide (50 mg, 0.08 mmol, 1.0 eq) in toluene (2 mL) was added ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (54 mg, 0.12 mmol, 1.5 eq), rac BI-DIME (3mg, 0.01 mmol, 0.15 eq), Pd₂(dba)₃ (18 mg, 0.02 mmol, 0.3 eq) and H₂O (0.4 mL). The reaction mixture was heated under microwave irradiation under nitrogen atmosphere at 130 °C for 1 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The organic phase was washed with brine (10 mL), dried with Na₂SO₄, filtered and concentrated to give a crude. The crude was purified by prep-TLC (DCM : MeOH = 15 : 1) to give 5-(6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide (28 mg, 39.6%) as a yellow solid. LCMS: 842.0 (M+H⁺).

Step 8: Synthesis of 5-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide

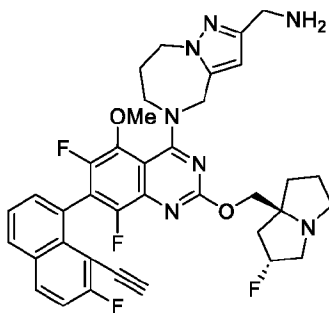


[00606] To solution of 5-(6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxamide (28 mg, 0.03 mmol, 1.0 eq) in DMF (1 mL) was added CsF (114 mg, 0.75 mmol, 25.0 eq). The reaction mixture was stirred at room temperature for 3 h. The mixture was diluted by MeOH (1.0 mL) and purified by prep-HPLC (acetonitrile with 0.1% FA in water, 10% to 60%) to give 5-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-

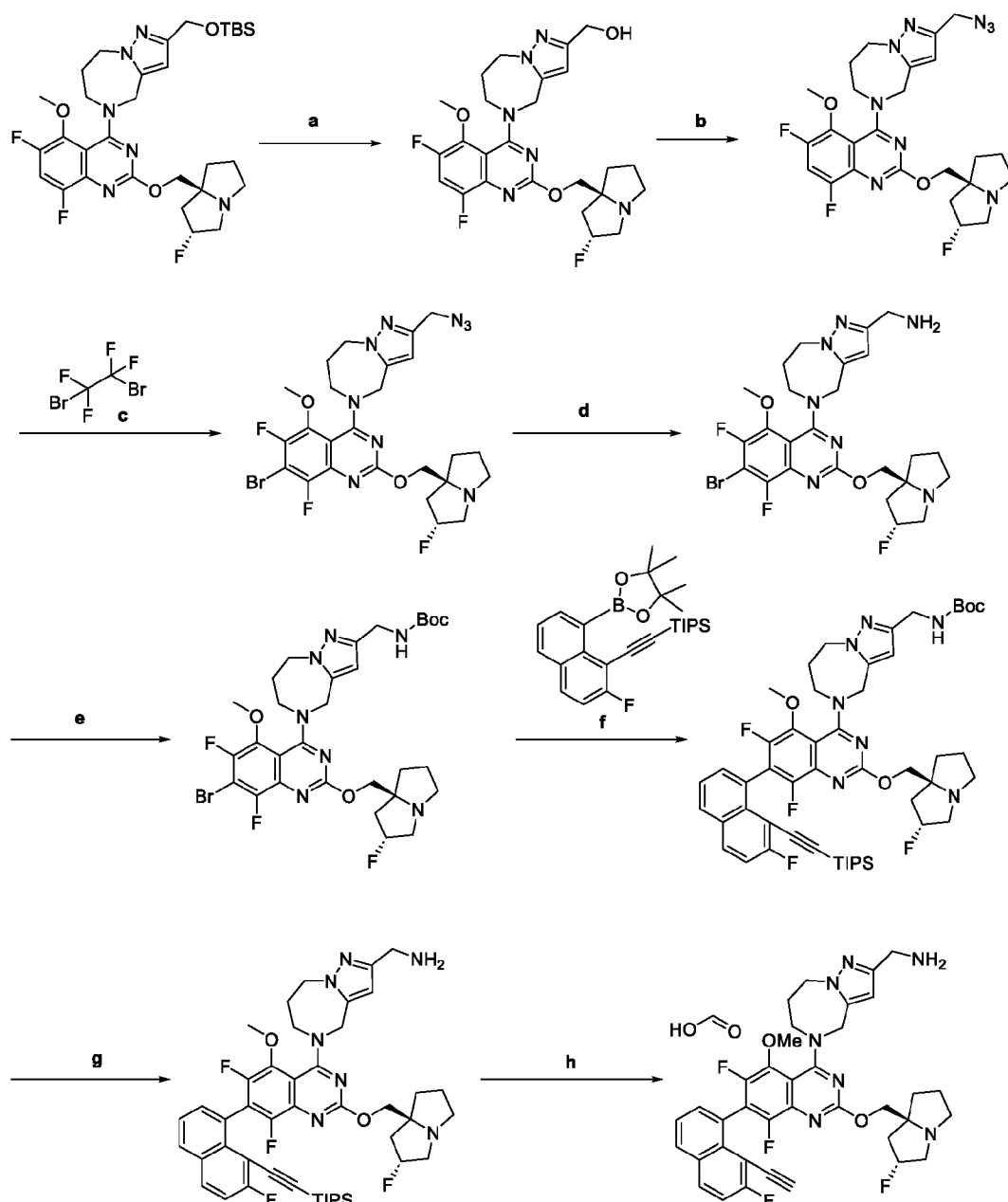
carboxamide (9.3 mg, 40.8%) as a white solid. ^1H NMR (300 MHz, CD_3OD): δ 8.17 – 8.08 (m, 2H), 7.71 – 7.63 (m, 1H), 7.62 – 7.55 (m, 1H), 7.50 – 7.41 (m, 1H), 6.66 (s, 1H), 5.31 (d, J = 54.0 Hz, 1H), 4.94 (s, 2H), 4.61 – 4.41 (m, 2H), 4.40 – 4.18 (m, 3H), 4.12 – 3.98 (m, 1H), 3.87 (s, 3H), 3.50 (s, 1H), 3.30 – 3.19 (m, 3H), 3.10 – 3.01 (m, 1H), 2.41 – 2.11 (m, 3H), 2.07 – 1.86 (m, 3H). ^{19}F NMR (300 MHz, CD_3OD): δ -106.434, -131.589, -136.896, -173.659. LCMS: 686.1 ($\text{M}+\text{H}^+$).

Example 65

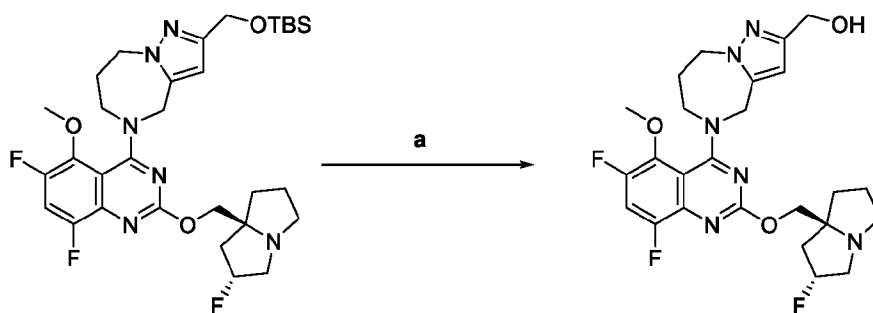
(5-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methanamine formate



Synthetic scheme:

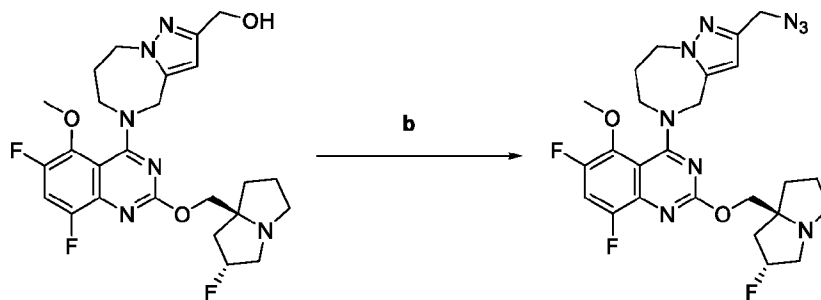


Step 1: Synthesis of (5-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methanol



[00607] To a solution of 2-(((tert-butyldimethylsilyl)oxy)methyl)-5-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine (200 mg, 0.32 mmol, 1.0 eq) in DCM (2 mL) was added HCl in dioxane (4 M, 1.6 mL, 6.3 mmol, 20.0 eq). The mixture was concentrated, added with NaHCO₃ aqueous solution (30 mL) and extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (30 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by Prep-TLC (dichloromethane: methanol = 10 : 1) to give (5-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methanol (140 mg, 85.4%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 7.34 – 7.28 (m, 1H), 6.24 (brs, 1H), 5.26 (d, *J* = 53.6 Hz, 1H), 4.86 – 4.74 (m, 2H), 4.61 (s, 2H), 4.30 – 4.19 (m, 2H), 4.09 – 3.99 (m, 1H), 3.96 – 3.83 (m, 3H), 3.79 – 3.72 (m, 3H), 3.41 – 3.15 (m, 3H), 3.04 – 2.91 (m, 1H), 2.39 – 2.08 (m, 5H), 2.05 – 1.79 (m, 4H). LCMS: 519.2 (M+H⁺).

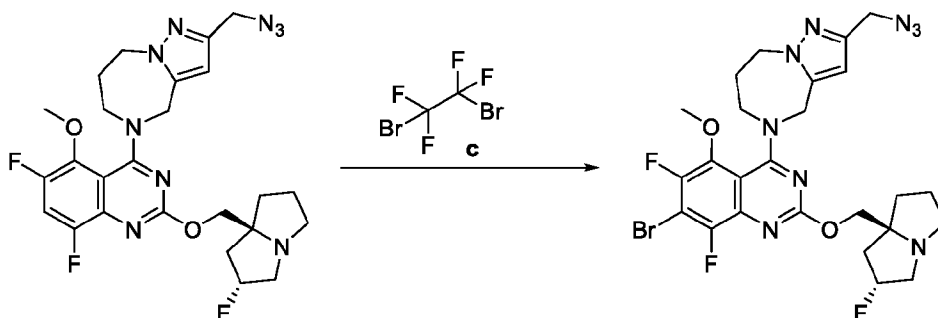
Step 2: Synthesis of 2-(azidomethyl)-5-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine



[00608] To a solution of (5-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-

a][1,4]diazepin-2-yl)methanol (140 mg, 0.27 mmol, 1.0 eq) in dioxane (1.0 mL) and toluene (1.0 mL) was added DPPA (372 mg, 1.4 mmol, 5.0 eq) and DBU (206 mg, 1.4 mmol, 5.0 eq) at room temperature. The reaction was stirred at 30 °C for 15 h. The mixture was partitioned between EtOAc (20 mL) and water (30 mL). The layers were separated. The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic layers were washed with H₂O (20 mL), brine (20 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (dichloromethane: methanol = 150 : 1) to give 2-(azidomethyl)-5-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine (133 mg, 90.6%) as a yellow solid. LCMS: 544.3 (M+H⁺).

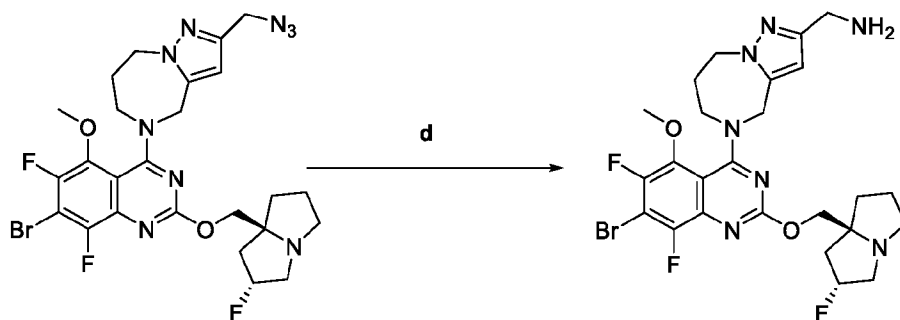
Step 3: Synthesis of 2-(azidomethyl)-5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine



[00609] To a solution of 2-(azidomethyl)-5-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine (180 mg, 0.33 mmol, 1.0 eq) in THF (4.0 mL) was added LDA (2.0M, 0.5 mL, 0.99 mmol, 3.0 eq) dropwise at -65 °C. The reaction mixture was stirred at -65 °C for 0.5 h under nitrogen atmosphere. To the mixture was added 1,2-dibromo-1,1,2,2-tetrafluoroethane (256 mg, 0.99 mmol, 3.0 eq). The reaction mixture was stirred at -65 °C for 0.5 h under nitrogen atmosphere. The reaction mixture was quenched with ammonium chloride aqueous solution (20 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with H₂O (10 mL), brine (10 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (dichloromethane: methanol = 150: 1) to give 2-(azidomethyl)-5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-

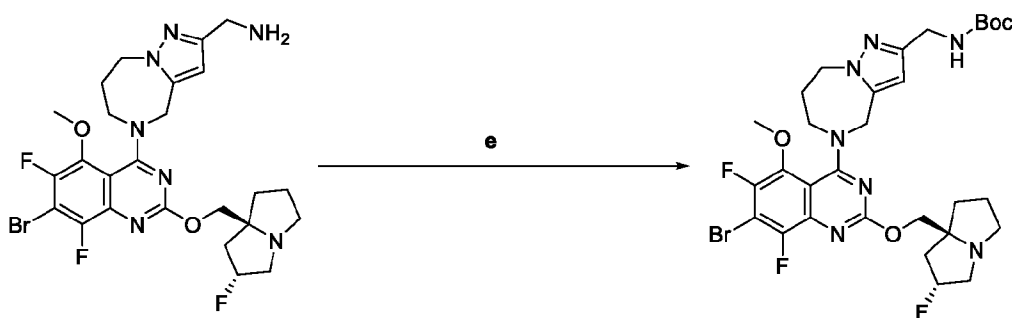
7a(5H-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine (90 mg, 43.7%) as a yellow solid. LCMS: 621.9, 623.9 (M+H⁺).

Step 4: Synthesis of (5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methanamine



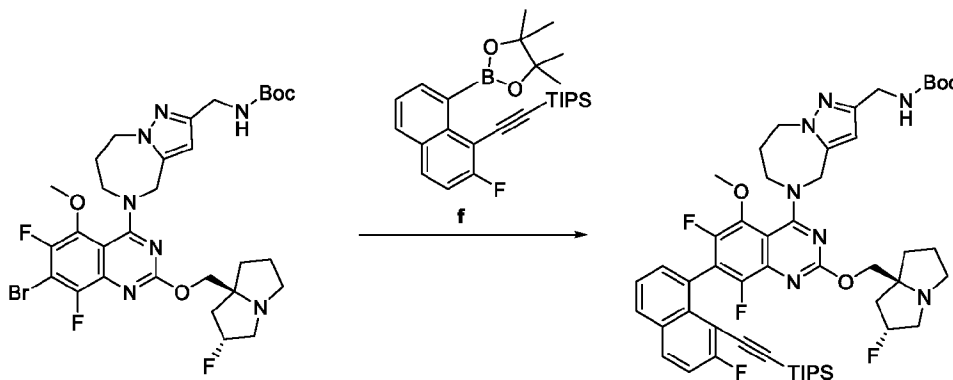
[00610] To a solution of 2-(azidomethyl)-5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine (70 mg, 0.11 mmol, 1.0 eq) in THF (2.5 mL) and H₂O (0.5 mL) was added PPh₃ (59 mg, 0.23 mmol, 2.0 eq). The reaction mixture was stirred at 35 °C for 24 h under nitrogen atmosphere. The reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with H₂O (10 mL), brine (10 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (dichloromethane: methanol = 30: 1) to give (5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methanamine (30 mg, 44.7%) as a yellow solid. LCMS: 596.3, 598.3 (M+H⁺).

Step 5: Synthesis of tert-butyl ((5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methyl)carbamate



[00611] To a solution of (5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methanamine (30 mg, 0.05 mmol, 1.0 eq) in DCM (2.0 mL) was added Boc_2O (33 mg, 0.15 mmol, 3.0 eq), TEA (25 mg, 0.25 mmol, 5.0 eq) and DMAP (1 mg, 0.008 mmol, 0.16 eq). The reaction mixture was stirred at room temperature for 15 h. The reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (10 mL x 2). The combined organic layers were washed with H_2O (10 mL), brine (10 mL), dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by silica gel column chromatography (Dichloromethane: Methanol = 60 : 1) to give tert-butyl ((5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methyl)carbamate (25 mg, 71.3%) as a yellow solid. LCMS: 696.2, 698.1 ($\text{M}+\text{H}^+$).

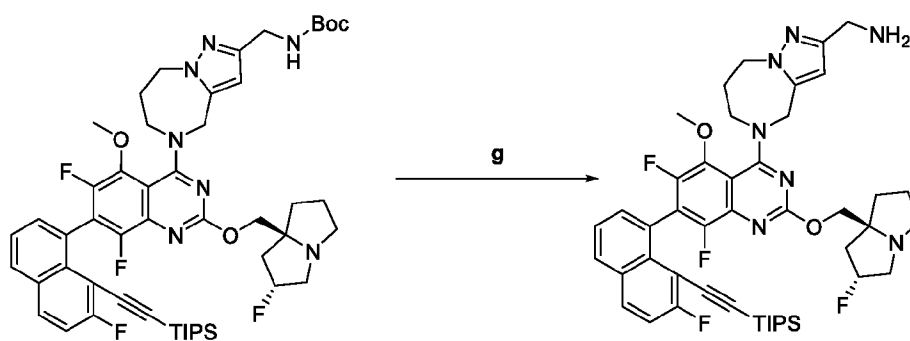
Step 6: Synthesis of tert-butyl ((5-(6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methyl)carbamate



[00612] To a solution of tert-butyl ((5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methyl)carbamate (13 mg, 0.02 mmol, 1.0 eq) in toluene (2 mL) and H_2O (0.4 mL) was added ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (17 mg, 0.04 mmol, 2.0 eq), K_3PO_4 (12 mg, 0.06 mmol, 3.0 eq), rac-BI-DIME (1 mg, 0.003 mmol, 0.15 eq) and $\text{Pd}_2(\text{dba})_3$ (5 mg, 0.006 mmol, 0.3 eq). The mixture was stirred at 100 °C for 15 h under nitrogen atmosphere. The reaction mixture was poured into water (10 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3).

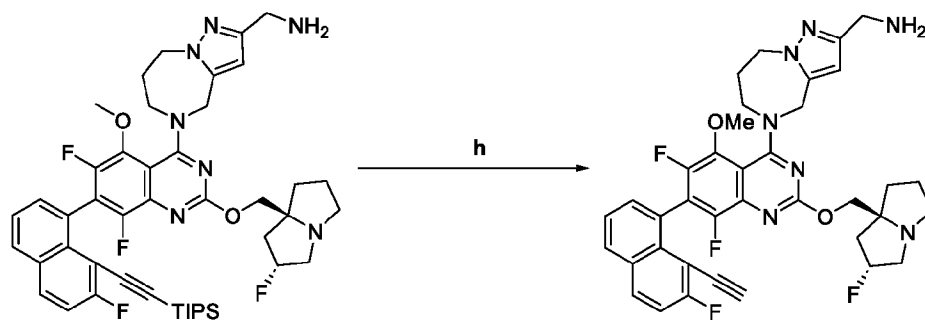
The combined organic layers were washed with H₂O (10 mL), brine (10 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (Dichloromethane: Methanol = 40 : 1) to give tert-butyl ((5-(6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methyl)carbamate (10 mg, 56.8%) as a yellow solid. LCMS: 942.0 (M+H⁺).

Step 7: Synthesis of (5-(6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methanamine



[00613] A solution of tert-butyl ((5-(6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methyl)carbamate (20 mg, 0.02 mmol, 1.0 eq) and HCl in Dioxane (1 mL) in DCM (1 mL) was stirred at room temperature for 1 h. The mixture was concentrated to give a crude (5-(6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methanamine (13 mg, crude) as a yellow solid. LCMS: 842.0 (M+H⁺).

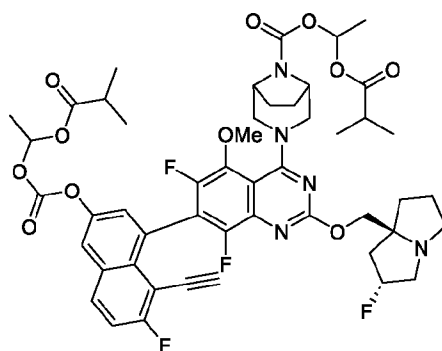
Step 8: Synthesis of (5-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methanamine formate (1:1)



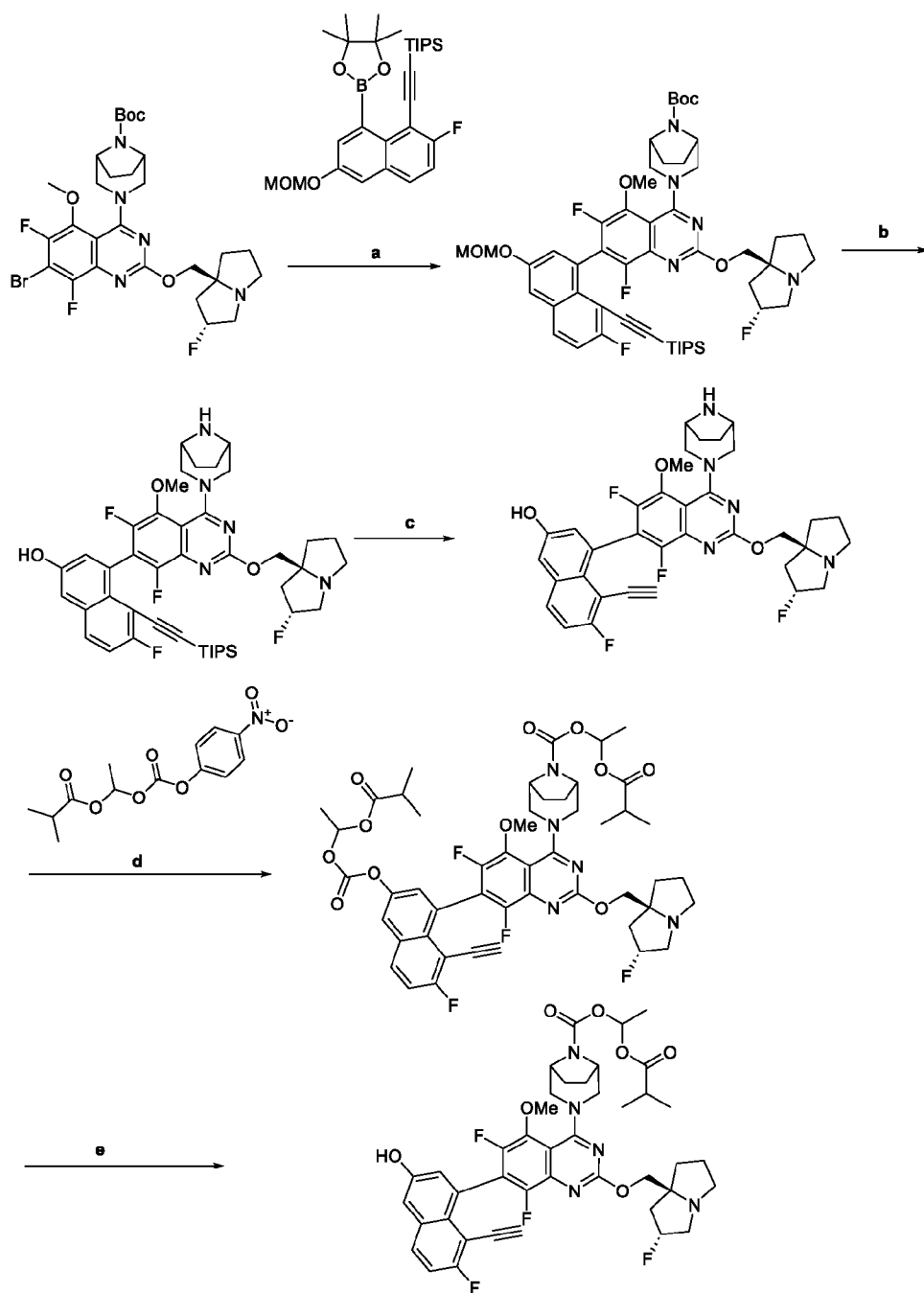
[00614] To a solution of (5-(6,8-difluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methanamine (13 mg, 0.02 mmol, 1.0 eq) in DMF (1 mL) was added CsF (23 mg, 0.15 mmol, 10.0 eq) at room temperature. The reaction was stirred at 40 °C for 1 h. The mixture was filtered and concentrated to give a residue. The residue was purified by Prep-HPLC (acetonitrile with 0.1% FA in water, 10% to 60%) to give (5-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methanamine formate (1:1) (1.6 mg, 10.3% for two steps) as a white solid. ¹H NMR (400 MHz, CD₃OD): δ 8.52 (brs, 1H), 8.12 (d, *J* = 6.4 Hz, 2H), 7.73 – 7.63 (m, 1H), 7.57 (d, *J* = 6.8 Hz, 1H), 7.42 – 7.35 (m, 1H), 6.29 (s, 1H), 5.34 (d, *J* = 54.4 Hz, 1H), 5.18 – 4.94 (m, 3H), 4.55 – 4.34 (m, 2H), 4.29 – 4.19 (m, 2H), 4.03 (s, 3H), 3.78 (s, 3H), 3.57 – 3.37 (m, 3H), 3.16 – 2.97 (m, 1H), 2.47 – 1.79 (m, 8H). ¹⁹F NMR (400 MHz, CD₃OD): δ -106.399, -132.137, -137.619, -173.656. LCMS: 686.2 (M+H⁺).

Example 66

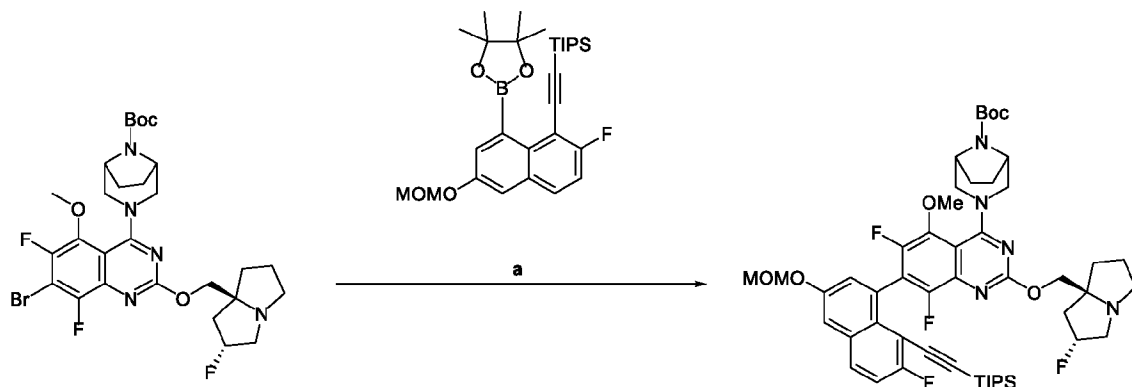
1-(Isobutyryloxy)ethyl 3-(7-(8-ethynyl-7-fluoro-3-(((1-(isobutyryloxy) ethoxy)carbonyl)oxy)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



Synthesis scheme

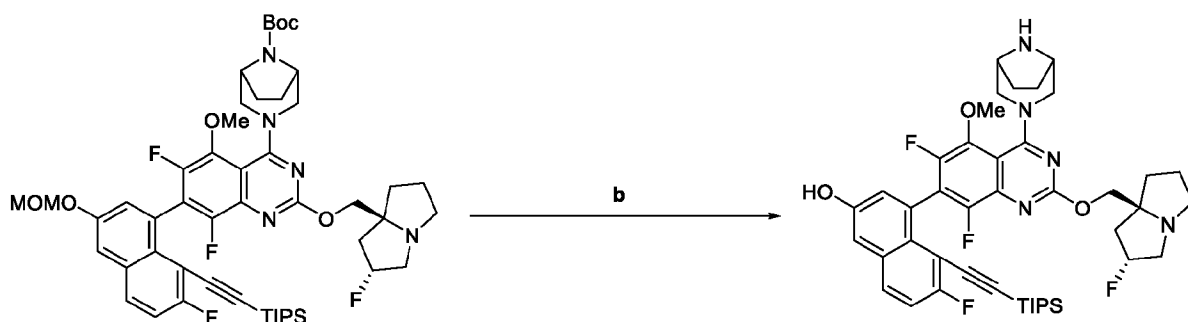


Step 1: Synthesis of tert-butyl 3-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



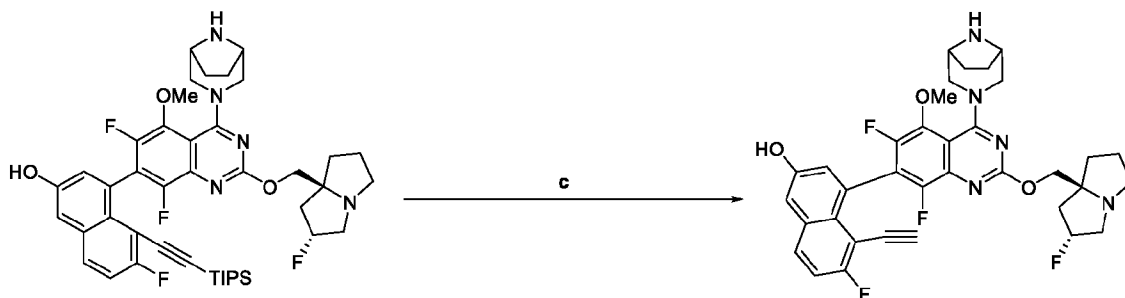
[00615] A tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (200 mg, 0.31 mmol, 1.0 eq), ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (191 mg, 0.37 mmol, 1.2 eq), Cs_2CO_3 (304 mg, 0.93 mmol, 3.0 eq) and cataCXium A Pd G3 (45 mg, 0.06 mmol, 0.2 eq) in the microwave tube, Toluene (6.2 mL) and water (1.2 mL) was added. Then the reaction mixture was heated under microwave irradiation at 120 °C for 1.5 hours. Upon completion, the mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was dried over Na_2SO_4 and concentrated to give a residue. The crude product was purified by prep-TLC (DCM: MeOH = 20: 1) to give tert-butyl 3-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-(((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (280 mg, 94.9%) as a yellow liquid. LCMS: m/z 948.2 ($\text{M}+\text{H}^+$)

Step 2: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-(((triisopropylsilyl)ethynyl)naphthalen-2-ol



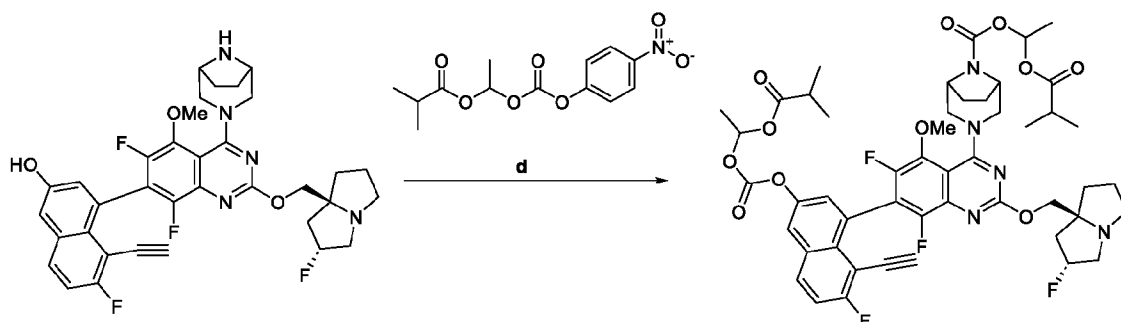
[00616] To a solution of tert-butyl 3-(6,8-difluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (80 mg, 0.08 mmol, 1.0 eq) in ACN (1.2 mL) was added Hydrochloric acid/Dioxane (4 M) (0.68 mL, 2.7 mmol, 32.11 eq) at 0 °C and the reaction mixture was stirred for 2 h under N₂ atmosphere. Upon completion, the mixture was concentrated to give a residue to afford the crude product 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (67 mg, 98.8%) as a yellow solid which was continue used for the next step without purification. LCMS: m/z 804.1 (M+H⁺).

Step 3: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



[00617] To a solution of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (68 mg, 0.08 mmol, 1.0 eq) in DMF (2.1 mL) was added CsF (191 mg, 1.26 mmol, 15.0 eq) at 40 °C under N₂ atmosphere. Then the reaction was stirred at 40 °C for 4 h. Upon completion, the mixture was filtered and the filtrate was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with water (30 mL) and brine (30 mL x 3), dried over Na₂SO₄ and concentrated to afford the crude product 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol (48 mg, 88.1%) as a yellow solid, which was continue used for the next step without purification. LCMS: m/z 648.3 (M+H⁺).

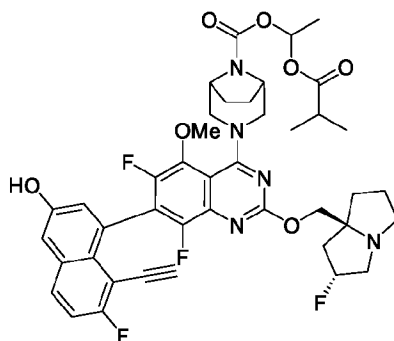
Step 4: Synthesis of 1-(isobutyryloxy)ethyl 3-(7-(8-ethynyl-7-fluoro-3-(((1-(isobutyryloxy)ethoxy)carbonyl)oxy)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



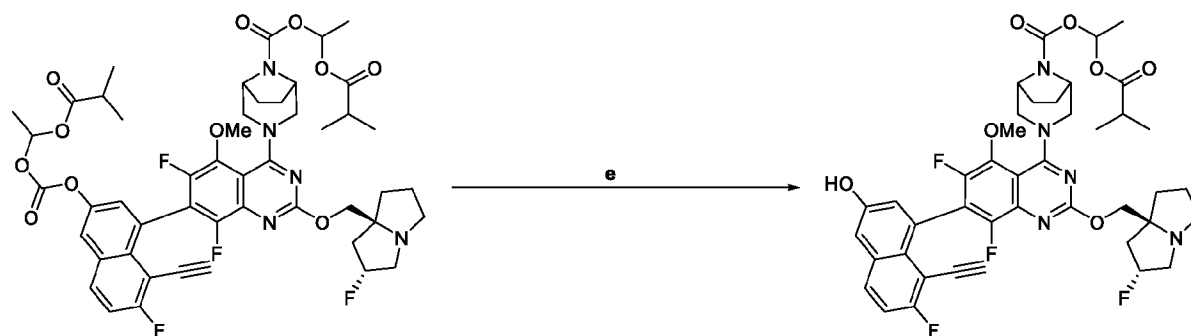
[00618] To a solution of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol (110 mg, 0.17 mmol, 1.0 eq) in DCM (3.0 mL) was added Propanoic acid, 2-Methyl-, 1-[[[(4-nitrophenoxy)carbonyl]oxy]ethyl ester (101 mg, 0.34 mmol, 2.0 eq), DIEA (66 mg, 0.51 mmol, 3.0 eq), and the reaction mixture was stirred at room temperature for overnight under N₂ atmosphere. Upon completion, the mixture was concentrated to give a residue. The crude product was purified by prep-TLC (DCM: MeOH = 10: 1) to give 1-(isobutyryloxy)ethyl (1R,5S)-3-(7-(8-ethynyl-7-fluoro-3-(((1-(isobutyryloxy)ethoxy)carbonyl)oxy)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 61.2%) as a yellow liquid. ¹H NMR (400 MHz, DMSO) (with 0.1 FA) δ 8.27 (dd, *J* = 9.2, 6.0 Hz, 1H), 8.18 (d, *J* = 2.4 Hz, 1H), 7.76-7.63 (m, 2H), 6.80-6.70 (m, 2H), 5.41 (d, *J* = 66.4 Hz, 1H), 4.40-4.20 (m, 2H), 4.16 (s, 1H), 3.98-3.90 (br, 1H), 3.79 (s, 3H), 3.47 (d, *J* = 13.2 Hz, 1H), 2.65-2.55 (m, 1H), 2.0-1.60 (m, 10H), 1.66 (s, 1H), 1.55 (d, *J* = 5.2 Hz, 3H), 1.47 (d, *J* = 5.2 Hz, 3H), 1.10 (dd, *J* = 6.8, 2.8 Hz, 12H). LCMS: *m/z* 964.3 (M+H⁺).

Example 67

1-(Isobutyryloxy)ethyl 3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



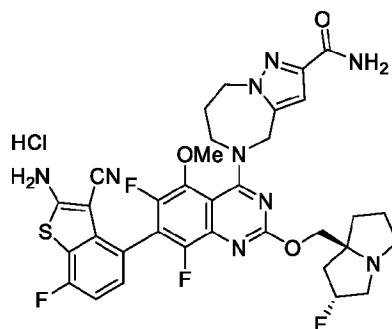
Step 1: Synthesis of 1-(isobutyryloxy)ethyl 3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



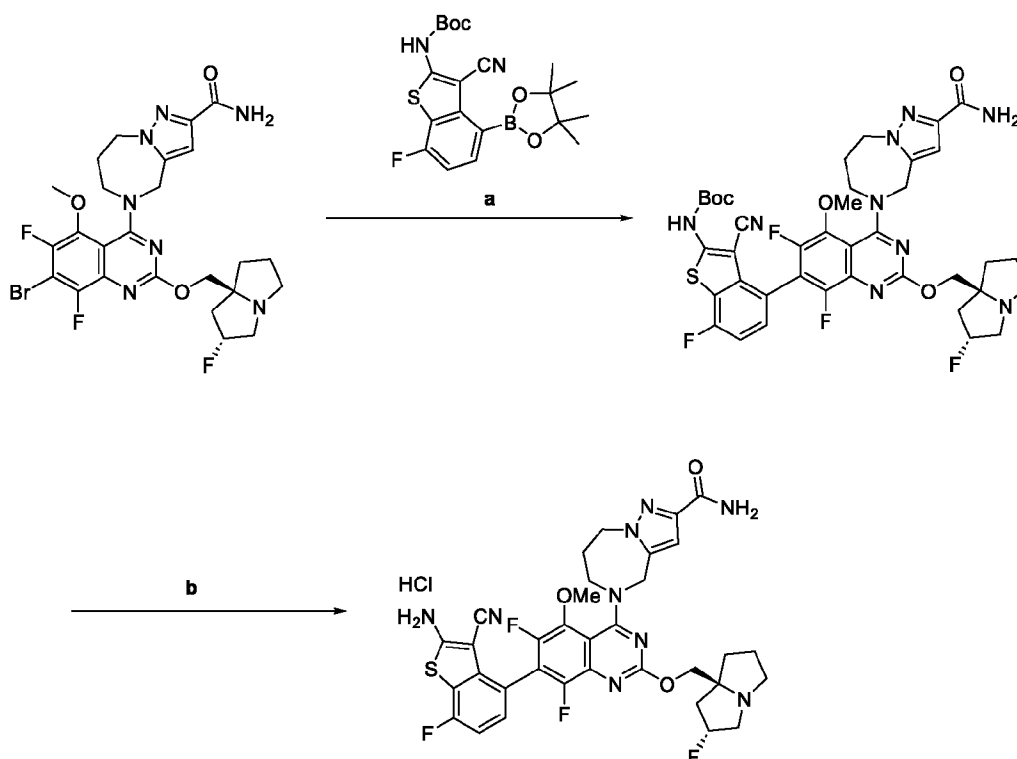
[00619] To a solution of 1-(isobutyryloxy)ethyl 3-(7-(8-ethynyl-7-fluoro-3-(((1-(isobutyryloxy)ethoxy)carbonyl)oxy)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (70 mg, 0.073 mmol, 1.0 eq) in ACN (1 mL) was added the Ammonium hydroxide (204 mg, 5.8 mmol, 80.0 eq) and the reaction mixture was stirred at room temperature for overnight under N₂ atmosphere. Upon completion, the mixture was purified by Prep-HPLC (acetonitrile with 0.1% FA in water, 30% to 56%) to give 1-(isobutyryloxy)ethyl 3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (21 mg, with 0.3 FA, 35.6%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.22 (s, 1H), 7.99 (t, *J* = 6.4 Hz, 1H), 7.48 (t, *J* = 8.4 Hz, 1H), 7.42 (s, 1H), 7.17 (s, 1H), 6.73 (s, 1H), 5.27 (d, *J* = 53.2 Hz, 1H), 4.31 (d, *J* = 20.0 Hz, 2H), 4.09-3.95 (m, 3H), 3.77 (s, 3H), 3.43 (d, *J* = 12.4 Hz, 1H), 3.15-3.05 (m, 2H), 3.01 (s, 1H), 2.83 (s, 1H), 2.67 (s, 1H), 2.33 (s, 1H), 2.12 (s, 1H), 2.03-1.90 (m, 3H), 1.90-1.60 (m, 8H), 1.46 (s, 3H), 1.09 (s, 6H). LCMS: 806.2 ([M+H]⁺).

Example 68

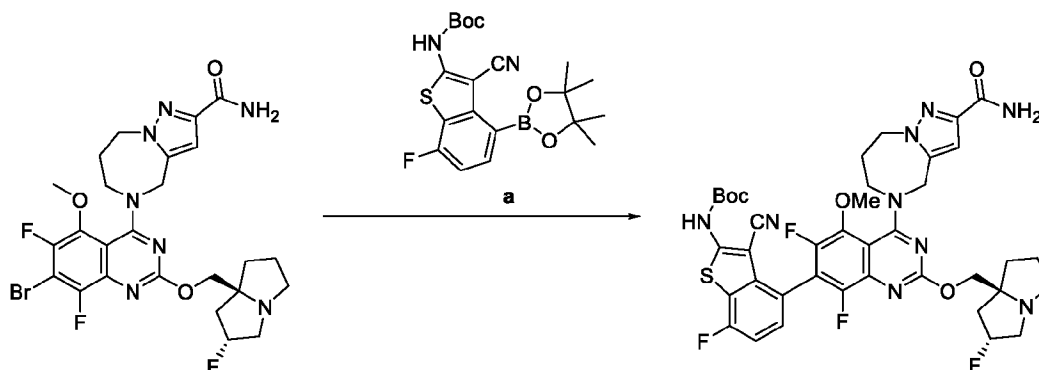
5-(7-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide hydrochloride (1:1)



Synthesis scheme

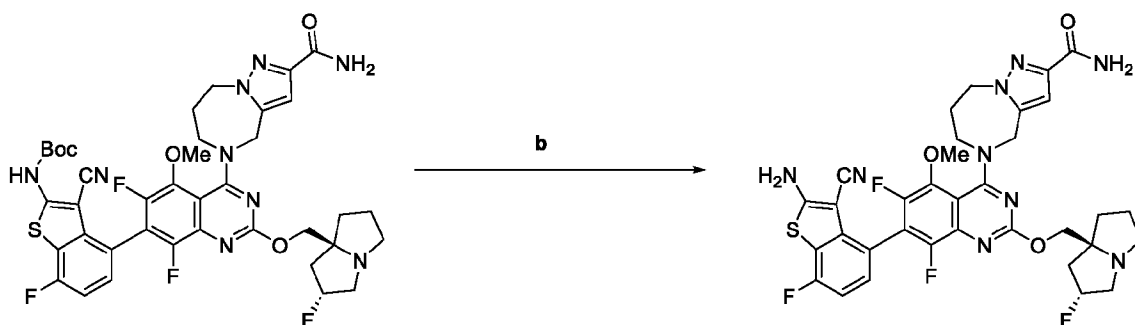


Step 1 Synthesis of tert-butyl (4-(4-(2-carbamoyl-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5(6H)-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate



[00620] To a solution of 5-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (40 mg, 0.06 mmol, 1.0 eq) and tert-butyl (3-cyano-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophen-2-yl)carbamate (29 mg, 0.07 mmol, 1.2 eq) in Dioxane (1.0 mL) and H₂O (0.2 mL) was added K₃PO₄ (29 mg, 0.14 mmol, 2.0 eq), rac-BI-DIME (4 mg, 0.01 mmol, 0.2 eq) and Pd₂(dba)₃ (9 mg, 0.01 mmol, 0.15 eq). The mixture was stirred at 100 °C for 12 h under N₂. The reaction mixture was concentrated to give a crude. The crude was purified by Prep-TLC (DCM / MeOH = 15:1) to give tert-butyl (4-(4-(2-carbamoyl-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5(6H)-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate (15 mg, 27.8%) as a yellow solid. LCMS: 822.0 (M+H⁺).

Step 2 Synthesis of 5-(7-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide hydrochloride (1:1)

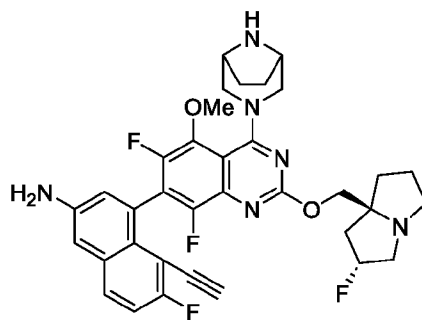


[00621] To a solution of tert-butyl (4-(4-(2-carbamoyl-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5(6H)-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate (15

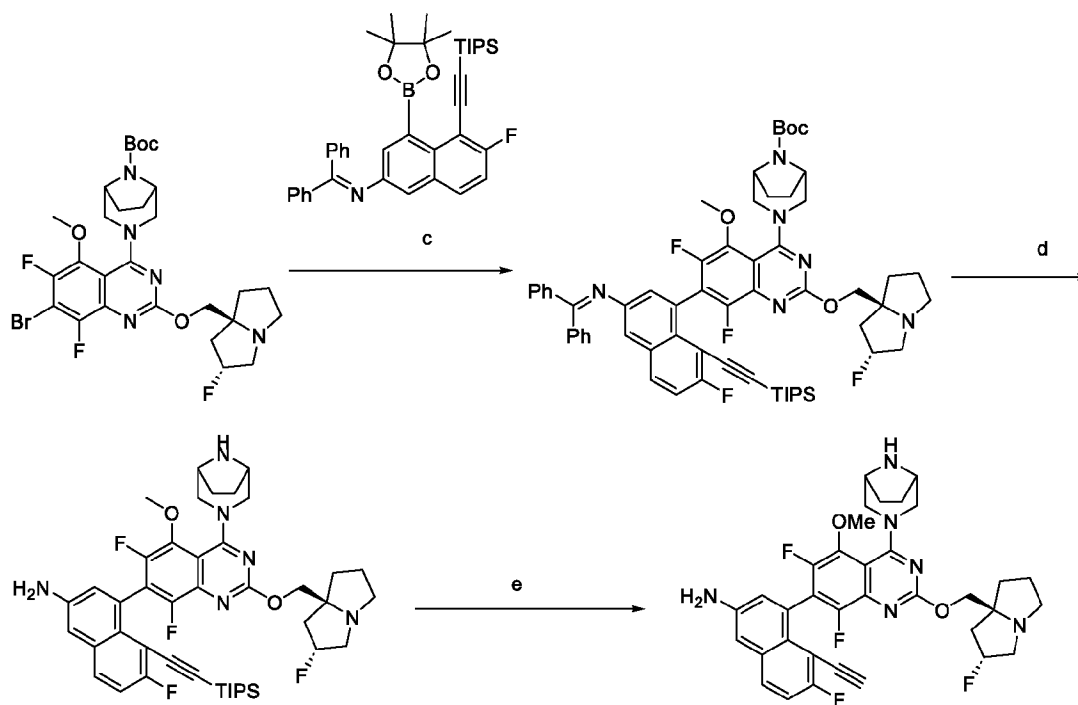
mg, 0.02 mmol, 1.0 eq) in DCM (1.0 mL) was added 4 M HCl/Dioxane (0.3 mL, 1.2 mmol, 66.0 eq). The reaction mixture was stirred at 40 °C for 2 h under N₂. The mixture was concentrated to give a crude. The crude was purified by Prep-HPLC (ACN with 0.1% FA in water, 5% to 35%) to give 5-(7-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide hydrochloride (1:1) (1.7 mg, 12.3%) as a white solid. ¹H NMR (400 MHz, CD₃OD): δ 7.36 – 7.26 (m, 1H), 7.04 (t, *J* = 8.8 Hz, 1H), 6.72 (s, 1H), 5.48 – 5.12 (m, 1H), 5.03 (s, 2H), 4.57 (s, 1H), 4.47 – 4.33 (m, 2H), 4.31 – 4.16 (m, 2H), 4.15 – 4.00 (m, 2H), 3.85 (s, 3H), 3.47 – 3.36 (m, 1H), 3.12 (s, 1H), 2.47 – 1.83 (m, 10H). ¹⁹F NMR (400 MHz, CD₃OD): δ -118.302, -132.791, -138.139, -173.702. LCMS: 722.2 (M+H⁺).

Example 69

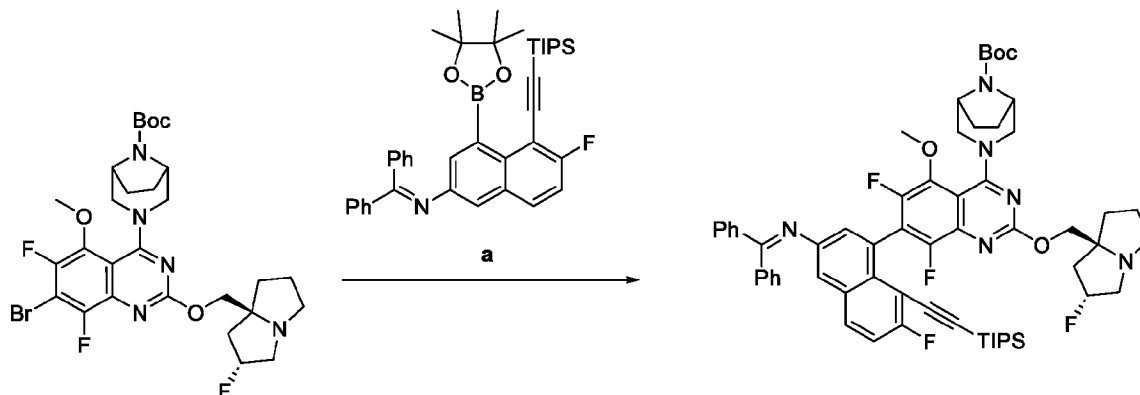
4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-amine hydrochloride



Synthesis scheme



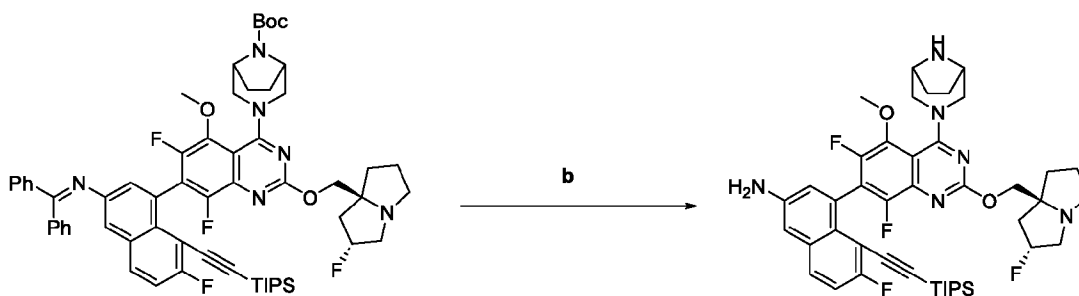
Step 1: Synthesis of tert-butyl 3-(7-(3-((diphenylmethylene)amino)-7-fluoro-8-((triisopropylsilyl) ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00622] To a solution of tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.16 mmol, 1.0 eq) and N-(6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)-1,1-diphenylmethanimine (118 mg, 0.19 mmol, 1.2 eq) in PhMe (1.0 mL) and H₂O (0.25 mL) was added K₃PO₄ (66 mg, 0.31 mmol, 2.0 eq), rac-BI-DIME (10 mg, 0.03 mmol, 0.2 eq) and Pd₂(dba)₃ (21 mg, 0.02 mmol,

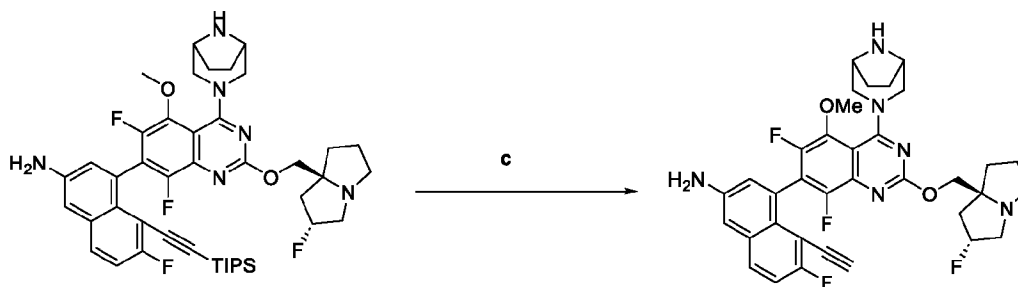
0.15 eq). The mixture was heated under microwave irradiation at 120 °C for 1 h under N₂. The reaction mixture was partitioned between EtOAc (5 mL) and H₂O (3 mL). The layers were separated. The aqueous layer was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (3 mL), dried over Na₂SO₄ and concentrated to a crude. The crude was purified by Prep-TLC (DCM / MeOH = 15 / 1) to give tert-butyl 3-(7-(3-((diphenylmethylene)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (55 mg, 33.0 %) as a white solid. LCMS: 534.3 (M/2+H⁺).

Step 2: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-amine



[00623] To a solution of tert-butyl 3-(7-(3-((diphenylmethylene)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.09 mmol, 1.0 eq) in DCM (2 mL) was added 4 M HCl/Dioxane (0.5 mL, 1.8 mmol, 20.0 eq) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated to give 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-amine (90 mg, crude) as a yellow solid. LCMS: 803.3 (M+H⁺).

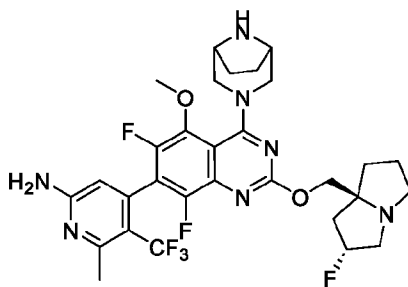
Step 3: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-amine hydrochloride (1:1)



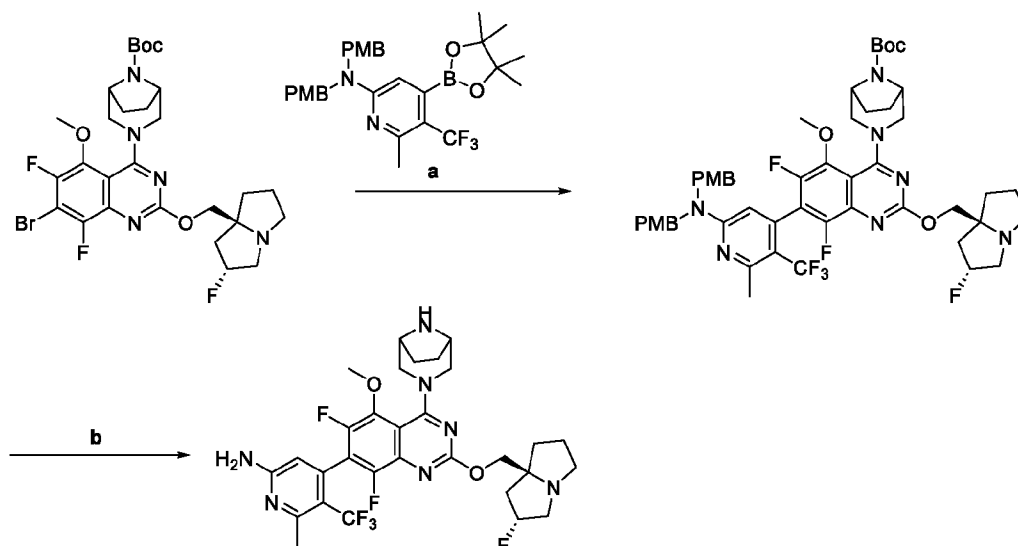
[00624] To a solution of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((trisopropylsilyl)ethynyl)naphthalen-2-amine (90 mg, 0.11 mmol, 1.0 eq) in DMF (1.5 mL) was added CsF (510 mg, 3.4 mmol, 30.0 eq). The mixture was stirred at 50 °C for 2 h. The mixture was filtered off and the filtrate was concentrated to give a crude. The crude was purified by Prep-HPLC (ACN with 0.1% FA in water, 15% to 50%) to give 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-amine hydrochloride (1:1) (15 mg, 21.3 %, two steps yield) as a white solid. ¹H NMR (400 MHz, CD₃OD): δ 7.81 – 7.71 (m, 1H), 7.31 – 7.26 (m, 1H), 7.18 (s, 1H), 7.05 (s, 1H), 5.36 (d, *J* = 54.4 Hz, 1H), 4.51 – 4.30 (m, 3H), 4.14 – 4.02 (m, 1H), 3.88 (s, 3H), 3.89 – 3.84 (m, 2H), 3.70 – 3.65 (m, 1H), 3.50 – 3.45 (m, 5H), 3.19 – 3.09 (m, 1H), 2.45 – 1.90 (m, 10H). ¹⁹F NMR (400 MHz, CD₃OD): δ -113.071, -132.522, -137.336, -173.884. LCMS: 647.3 (M+H⁺).

Example 70

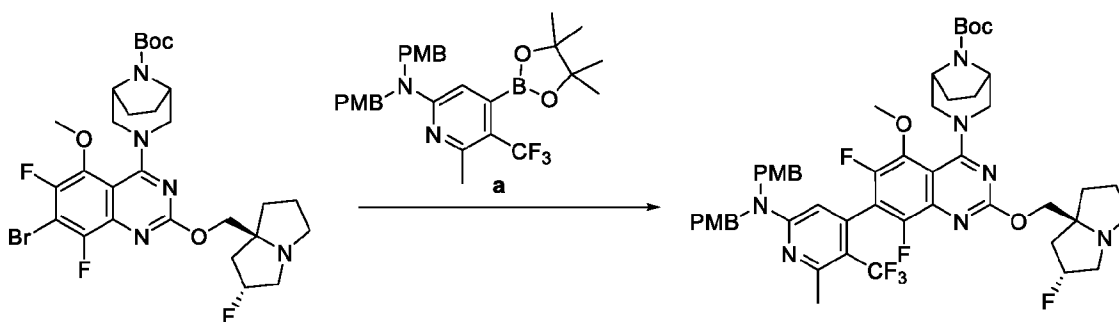
4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine formate



Synthetic scheme:



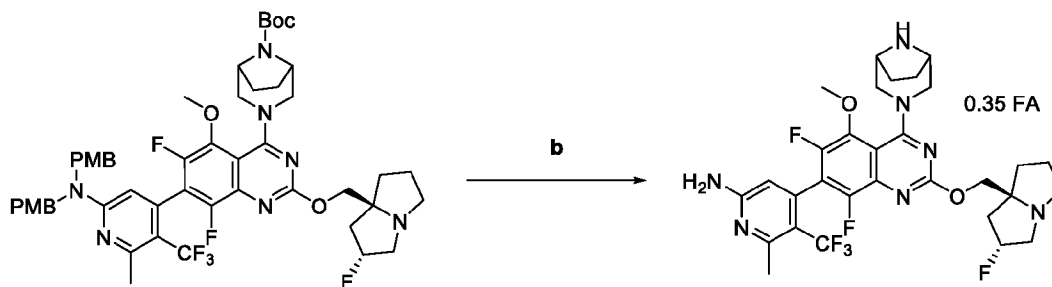
Step 1: Synthesis of tert-butyl 3-(7-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00625] To a solution of tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (50 mg, 0.08 mmol, 1.0 eq) in dioxane (1 mL) and H₂O (0.2 mL) was added N,N-bis(4-methoxybenzyl)-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)pyridin-2-amine (63 mg, 0.12 mmol, 1.5 eq), K₂CO₃ (32 mg, 0.23 mmol, 3.0 eq) and Pd(PPh₃)₄ (9 mg, 0.01 mmol, 0.1 eq). The reaction mixture was stirred at 100 °C for 5 h under N₂. The reaction mixture was partitioned between EtOAc (5 mL) and H₂O (3 mL). The layers were separated. The aqueous layer was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (3 mL), dried over Na₂SO₄ and concentrated to a crude. The crude was purified by Prep-TLC (DCM / MeOH = 15:1) to give tert-butyl (1R,5S)-3-(7-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-6,8-difluoro-2-

(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (15 mg, 19.7%) as a white solid. LCMS: 978.3 ($M+H^+$).

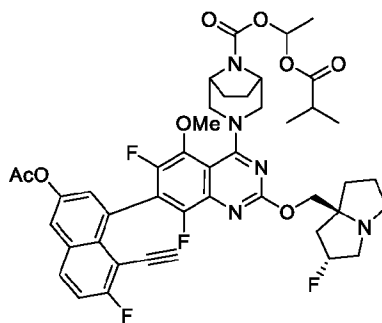
Step 2: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine formate (1:0.35)



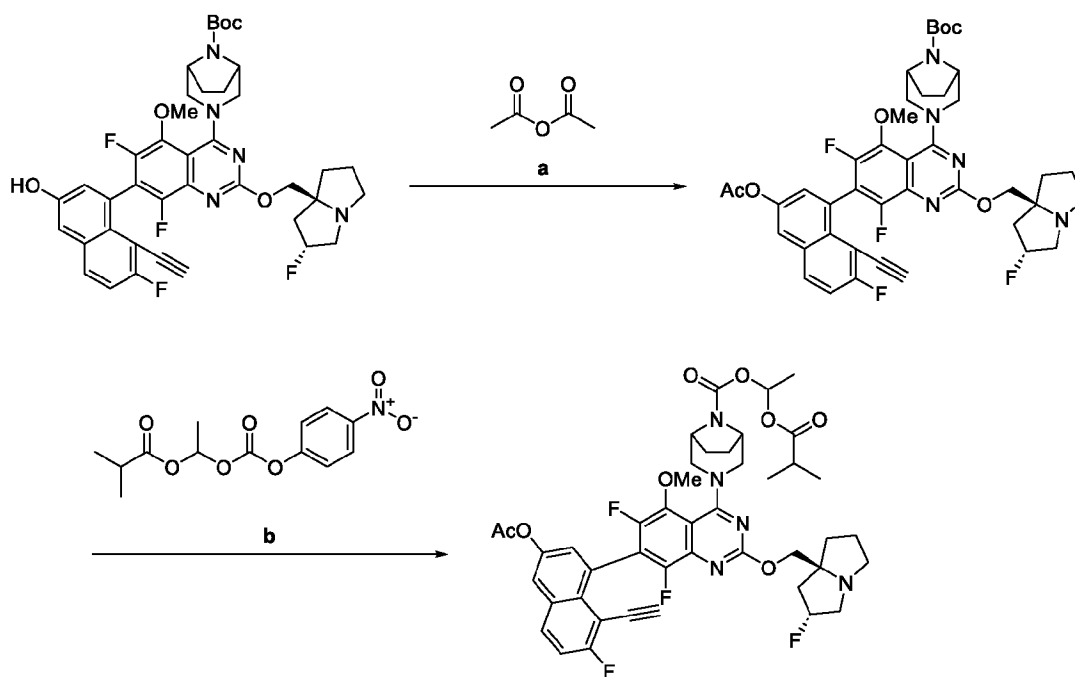
[00626] A solution of tert-butyl 3-(7-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (15 mg, 0.02 mmol, 1.0 eq) in TFA (2 mL) was stirred at 50 °C for 2 h. The mixture was concentrated to give a crude. The crude was purified by Prep-HPLC (ACN with 0.1% FA in water, 5% to 35%) to give 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine formate (1:0.35) (1.9 mg, 18.9%) as a white solid. ^1H NMR (400 MHz, CD_3OD): δ 8.55 (brs, 0.35H), 6.31 (s, 1H), 5.34 (d, J = 53.6 Hz, 1H), 4.58 (s, 1H), 4.39 – 4.20 (m, 4H), 4.19 – 4.00 (m, 1H), 3.85 (s, 3H), 3.73 (s, 2H), 3.65 – 3.44 (m, 3H), 3.19 – 3.03 (m, 1H), 2.55 (s, 3H), 2.47 – 1.73 (m, 10H). ^{19}F NMR (400 MHz, CD_3OD): δ -55.814, -133.384, -139.653, -173.705. LCMS: 638.2 ($M+H^+$).

Example 71

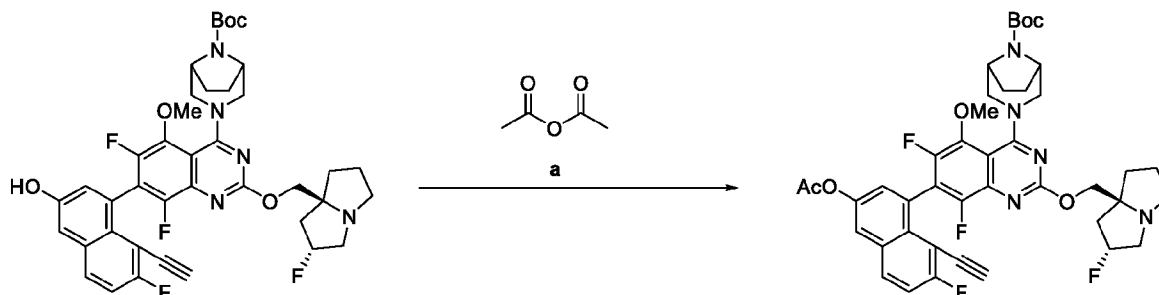
1-(Isobutyryloxy)ethyl 3-(7-(3-acetoxy-8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



Synthesis scheme



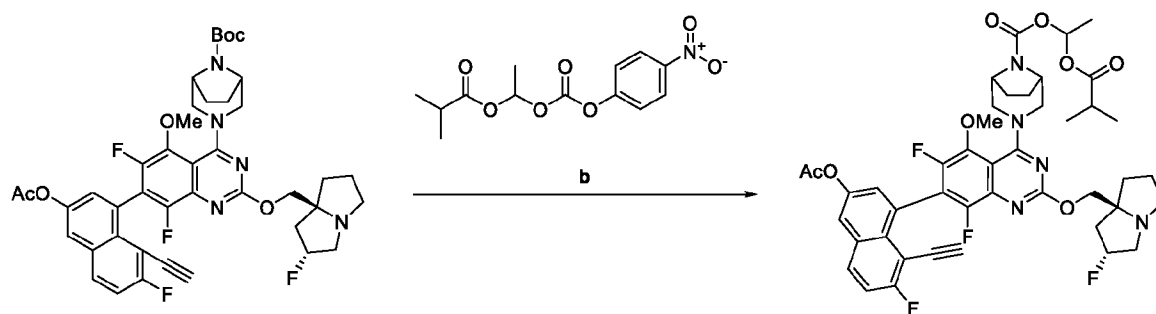
Step 1: Synthesis of tert-butyl 3-(7-(3-acetoxy-8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00627] To a solution of tert-butyl 3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-

methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (25 mg, 0.034 mmol, 1.0 eq) in DCM (0.5 mL) was added TEA (10 mg, 0.10 mmol, 3.0 eq) and Acetic anhydride (4 mg, 0.041 mmol, 1.2 eq) at 0 °C under N₂ atmosphere. The reaction mixture was stirred at room temperature for 2 h. Then the reaction mixture was concentrated in vacuo to give tert-butyl (1R,5S)-3-(7-(3-acetoxy-8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (40 mg, crude) as a yellow liquid, which was used directly for the next step without any further purification. LCMS: *m/z* 790.3 (M+H⁺).

Step 2: Synthesis of 1-(isobutyryloxy)ethyl 3-(7-(3-acetoxy-8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

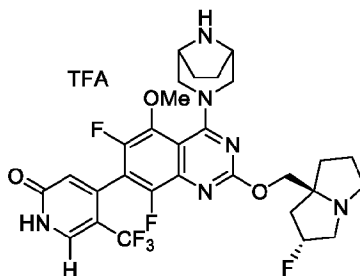


[00628] To a solution of tert-butyl 3-(7-(3-acetoxy-8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (40 mg, crude) in ACN (1.0 mL) was added HCl/Dioxane (0.28 mL) at 0 °C under N₂ atmosphere. The reaction mixture was stirred at 0 °C for 2 h. Then to the reaction mixture was added 1-(((4-nitrophenoxy)carbonyl)oxy)ethyl isobutyrate (12 mg, 0.041 mmol, 1.2 eq) and DIEA (154 mg, 1.19 mmol, 35.11 eq) at room temperature. The reaction mixture was stirred at room temperature for 2 h. Then the reaction mixture was filtered and the filtrate was purified by Prep-HPLC (acetonitrile with 0.1% FA in water, 50% to 70%) to give 1-(isobutyryloxy)ethyl 3-(7-(3-acetoxy-8-ethynyl-7-fluoronaphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (3.1 mg, 10.7% for two steps) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.93 (s, 1H), 8.24 (t, *J* = 7.2 Hz, 1H), 8.04 (s, 1H), 7.68 (t, *J* = 8.8 Hz, 1H), 7.57 (s, 1H), 7.29 – 6.97 (m, 1H), 6.74 (s, 1H), 5.56 (d, *J* = 53.2 Hz, 1H), 4.70–.50 (m, 2H), 4.32 (d, *J* = 20.0 Hz,

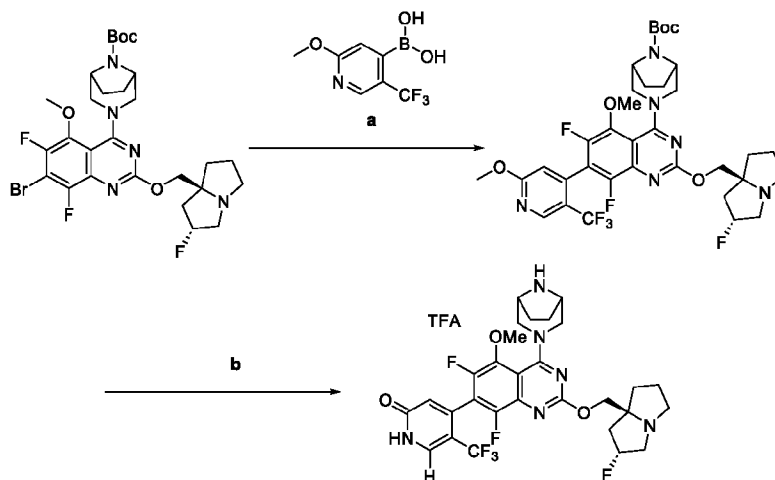
2H), 4.14 (s, 1H), 3.80 (s, 6H), 3.34 – 3.29 (m, 1H), 2.67 (s, 1H), 2.35-2.25 (m, 5H), 2.17 (s, 2H), 2.01 (s, 2H), 1.85 (s, 3H), 1.64 (s, 1H), 1.47 (d, $J = 3.6$ Hz, 3H), 1.24 (s, 2H), 1.09 (s, 6H).
LCMS: m/z 848.3 ($M+H^+$).

Example 72

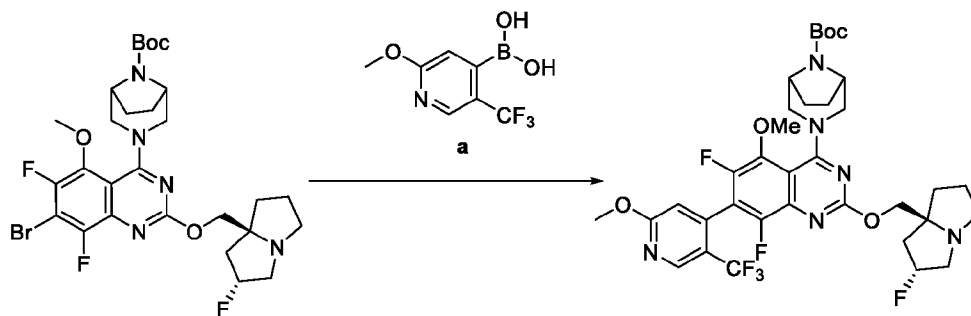
4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-(trifluoromethyl)pyridin-2(1H)-one 2,2,2-trifluoroacetate (1:1)



Synthesis scheme

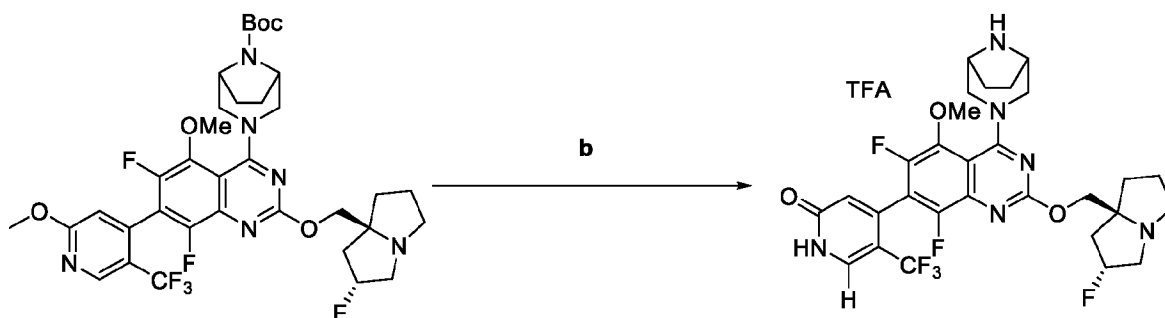


Step 1 Synthesis of tert-butyl 3-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-7-(2-methoxy-5-(trifluoromethyl)pyridin-4-yl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00629] To a solution of tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (200 mg, 0.31 mmol, 1.0 eq) in toluene (2 mL) was added (2-methoxy-5-(trifluoromethyl)pyridin-4-yl)boronic acid (138 mg, 0.62 mmol, 2.0 eq), Cs₂CO₃ (303 mg, 0.93 mmol, 3.0 eq), cataCXium A Pd G3 (44 mg, 0.06 mmol, 0.2 eq) and H₂O (0.4 mL) at room temperature. The reaction mixture was heated under microwave irradiation under nitrogen atmosphere at 120 °C for 1 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The organic phase was washed with brine (10 mL), dried with Na₂SO₄, filtered and concentrated to give a crude. The crude was purified by prep-TLC (DCM : MeOH = 15 : 1) to give tert-butyl 3-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-7-(2-methoxy-5-(trifluoromethyl)pyridin-4-yl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (35 mg, 15.2%) as a yellow solid. LCMS: 738.9 (M+H⁺).

Step 2 Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-(trifluoromethyl)pyridin-2(1H)-one 2,2,2-trifluoroacetate (1:1)

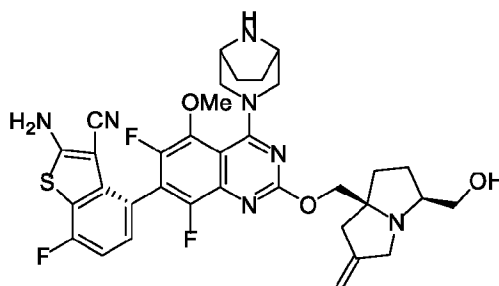


[00630] To a solution of tert-butyl 3-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxy-7-(2-methoxy-5-(trifluoromethyl)pyridin-4-yl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (35 mg, 0.05 mmol, 1.0 eq) in

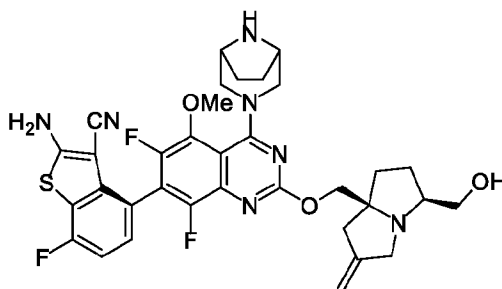
EtOH (0.5 mL) was added HBr (40% in water) (0.5 mL). Then the reaction mixture was stirred at 80 °C for 1 h. The mixture was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 10% to 60%) to give 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-(trifluoromethyl)pyridin-2(1H)-one trifluoroacetate (1:1) (2.0 mg, 6.8%) as white solid. ¹H NMR (300 MHz, CD₃OD): δ 12.71 (brs, 1H), 10.85 (s, 1H), 9.35 – 9.01 (m, 2H), 8.14 (s, 1H), 6.60 (s, 1H), 5.57 (d, *J* = 54.0 Hz, 1H), 4.55 (s, 2H), 4.26 – 4.02 (m, 4H), 3.90 – 3.71 (m, 6H), 3.66 – 3.54 (m, 3H), 2.75 – 2.54 (m, 2H), 2.37 – 2.01 (m, 5H), 1.97 – 1.88 (m, 3H). ¹⁹F NMR (300 MHz, CD₃OD): δ -59.327, -73.830, -130.018, -136.785, -173.036. LCMS: 625.2 (M + H⁺).

Example 73

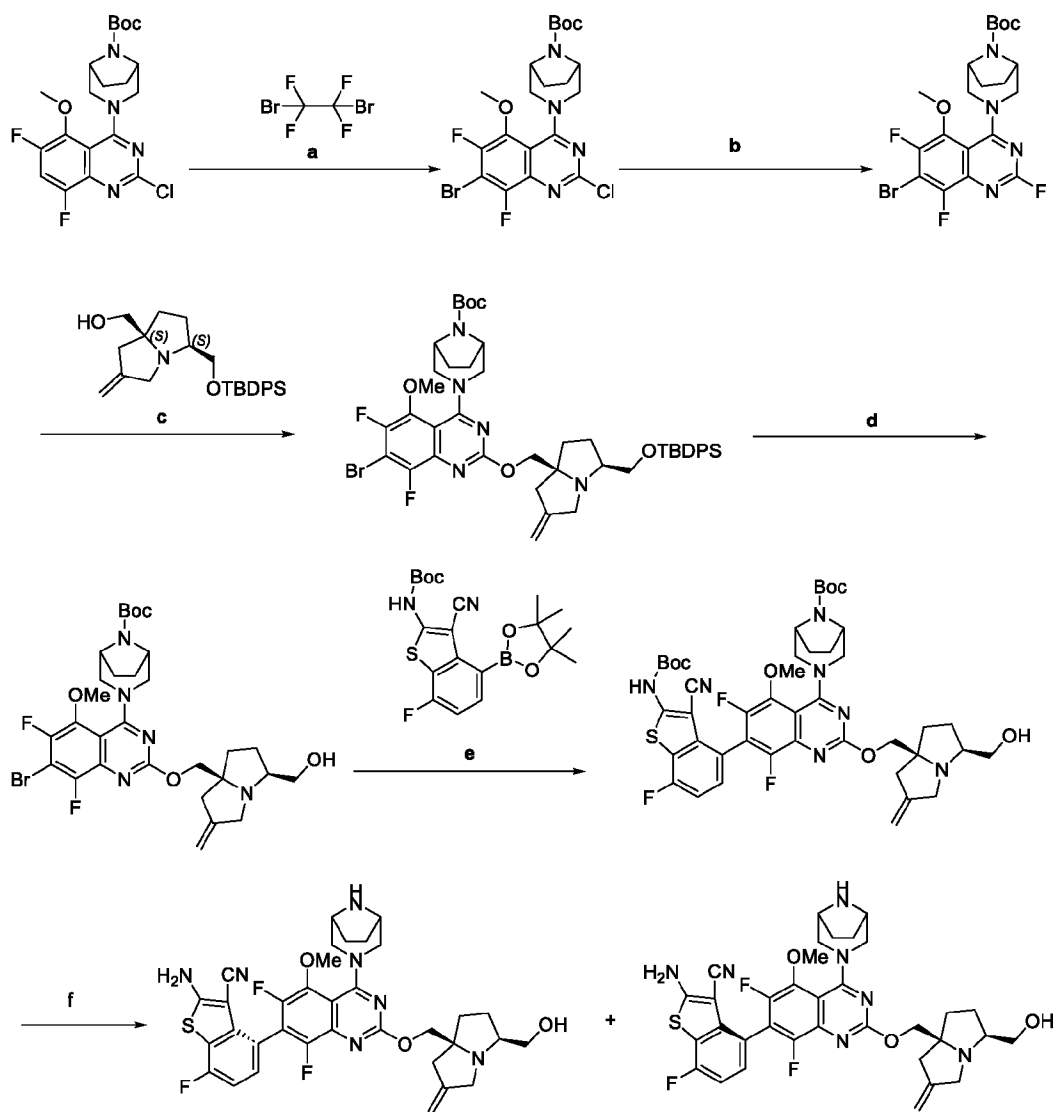
4-((S)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((5S,7aS)-5-(hydroxymethyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile



4-((R)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((5S,7aS)-5-(hydroxymethyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile

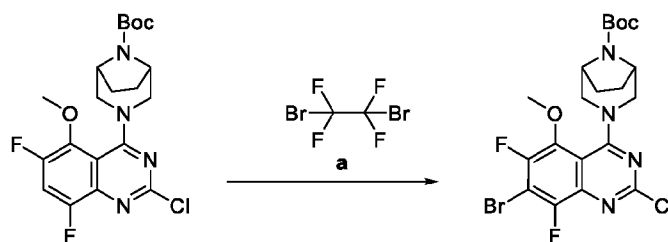


Synthetic scheme:



the two isomers (*R* or *S*) cannot be confirmed

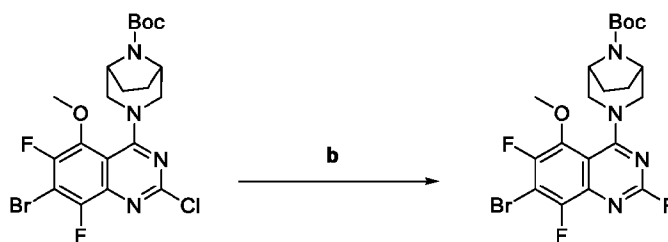
Step 1: Synthesis of tert-butyl 3-(7-bromo-2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00631] To a solution of tert-butyl 3-(2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2.0 g, 4.5 mmol, 1.0 eq) in THF (20 mL) was added

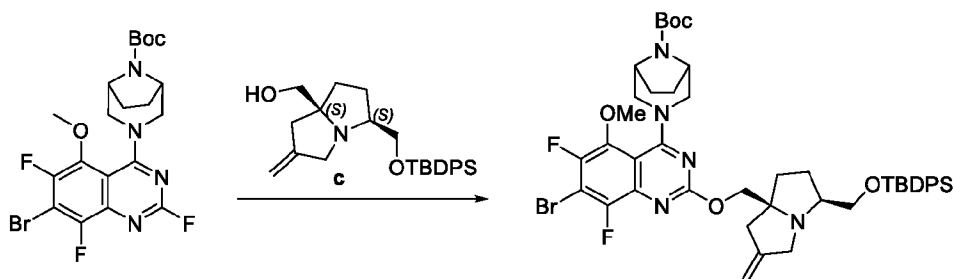
LDA (2M) (6.8 mL, 13.5 mmol, 3.0 eq) at -65 °C under N₂ atmosphere. The mixture was stirred at -65 °C for 30 min. The mixture was added 1,2-dibromo-1,1,2,2-tetrafluoroethane (3.5 g, 13.5 mmol, 3.0 eq) at the same temperature, and stirred for 2.5 h. The reaction was quenched with H₂O (15 mL). The mixture was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄ and evaporated to dryness to give a crude. The crude product was purified by silica gel column chromatography (Petroleum ether: EtOAc = 10: 1) to give compound tert-butyl 3-(7-bromo-2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.6 g, 68.1%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 4.32 – 4.11 (m, 4H), 3.85 (s, 3H), 3.51 – 3.49 (m, 2H), 1.87 – 1.84 (m, 2H), 1.60 – 1.55 (m, 2H), 1.50 (s, 9H). LCMS: 519.0, 521.1 (M+H⁺).

Step 2: Synthesis of tert-butyl 3-(7-bromo-2,6,8-trifluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



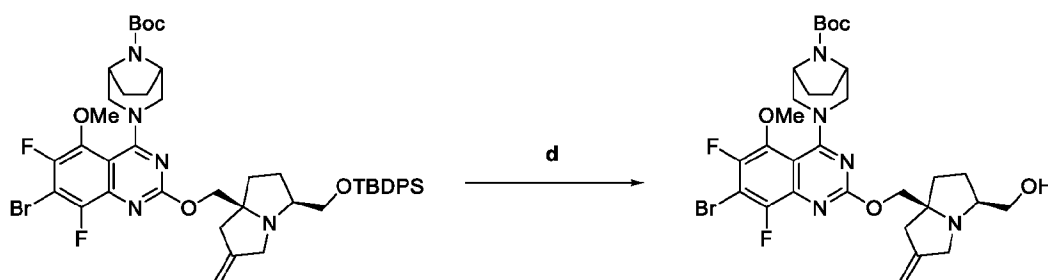
[00632] To a solution of tert-butyl 3-(7-bromo-2-chloro-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (600 mg, 1.15 mmol, 1.0 eq) in DMSO (6 mL) was added KF (1.3 g, 23.0 mmol, 20.0 eq). The reaction mixture was stirred at 110 °C for 15 h under N₂. The mixture was quenched with H₂O (15 mL). The resulting mixture was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with H₂O (5 mL x 3), brine (5 mL), dried over Na₂SO₄ and concentrated to give crude product. The crude product was purified by silica gel column chromatography (Petroleum ether: EtOAc = 5: 1) to give tert-butyl 3-(7-bromo-2,6,8-trifluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (520 mg, 89.5%) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 4.28 – 4.13 (m, 4H), 3.86 (s, 3H), 3.54 – 3.51 (m, 2H), 1.85 – 1.83 (m, 2H), 1.62 – 1.60 (m, 2H), 1.50 (s, 9H). LCMS: 503.0, 505.0 (M+H⁺).

Step 3: Synthesis of tert-butyl 3-(7-bromo-2-(((5S,7aS)-5-(((tert-butyl)diphenylsilyl)oxy)methyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



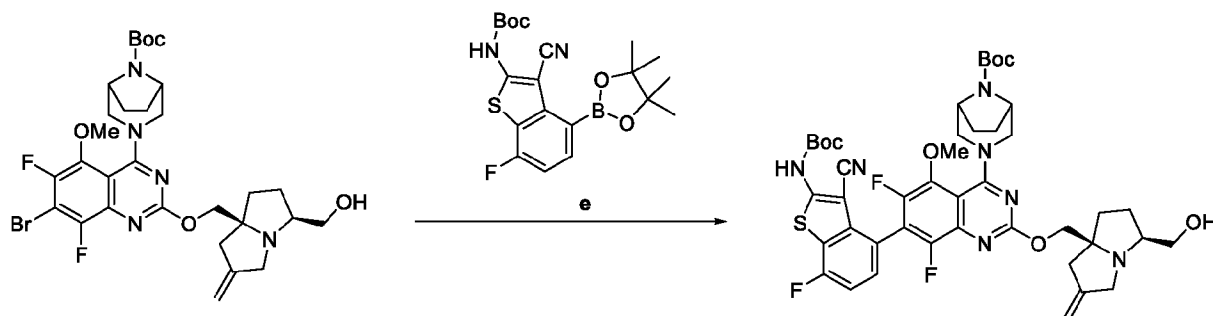
[00633] To a solution of tert-butyl 3-(7-bromo-2,6,8-trifluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (834 mg, 1.7 mmol, 1.4 eq) in THF (4 mL) was added 60% NaH (142 mg, 3.6 mmol, 3.0 eq) at 0 °C under N₂. The reaction mixture was stirred at the same temperature for 0.5 h. To the mixture was added (5S,7aS)-5-(((tert-butyl)diphenylsilyl)oxy)methyl-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (500 mg, 1.2 mmol, 1.0 eq) in THF (2 mL) at 0 °C under N₂. The reaction mixture was stirred at 0 °C for 2.5 h. The reaction was quenched by the addition of H₂O (5 mL). The mixture was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄ and concentrated to give crude product. The crude product was purified by silica gel column chromatography (DCM: MeOH = 15: 1) to give tert-butyl 3-(7-bromo-2-(((5S,7aS)-5-(((tert-butyl)diphenylsilyl)oxy)methyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (330 mg, 36.6%) as a white solid. ¹H NMR (300 MHz, CDCl₃): δ 7.71 (t, *J* = 6.6 Hz, 4H), 7.48 – 7.35 (m, 6H), 4.86 (s, 2H), 4.24 (brs, 2H), 4.12 – 4.00 (m, 4H), 3.79 (s, 3H), 3.62 – 3.51 (m, 3H), 3.40 (d, *J* = 7.8 Hz, 2H), 3.27 (d, *J* = 14.1 Hz, 1H), 2.99 – 2.89 (m, 1H), 2.73 (d, *J* = 15.3 Hz, 1H), 2.33 (d, *J* = 15.3 Hz, 1H), 2.21 (d, *J* = 6.0 Hz, 1H), 2.11–1.95 (m, 1H), 1.81 (s, 2H), 1.75 – 1.60 (m, 4H), 1.49 (s, 9H), 1.06 (s, 9H). LCMS: 904.2, 906.2 (M+H⁺).

Step 4: Synthesis of tert-butyl 3-(7-bromo-6,8-difluoro-2-(((5S,7aS)-5-(hydroxymethyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00634] To a solution of tert-butyl 3-(7-bromo-2-(((5S,7aS)-5-(((tert-butyl)diphenylsilyl)oxy)methyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (300 mg, 0.33 mmol, 1.0 eq) in DMF (5.0 mL) was added CsF (1 g, 6.6 mmol, 20.0 eq). The mixture was stirred at 50 °C for 15 h. The resulting mixture was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with H₂O (5 mL x 3), brine (5 mL x 2), dried over Na₂SO₄ and concentrated to give crude product. The crude was purified by Prep-TLC (DCM: MeOH = 15: 1) to give tert-butyl 3-(7-bromo-6,8-difluoro-2-(((5S,7aS)-5-(hydroxymethyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (180 mg, 81.4%) as a yellow solid. LCMS: 666.2, 668.2 (M+H⁺).

Step 5: Synthesis of tert-butyl 3-(7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6,8-difluoro-2-(((5S,7aS)-5-(hydroxymethyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

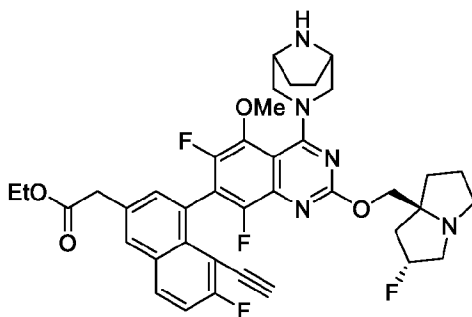


[00635] To a solution of tert-butyl 3-(7-bromo-6,8-difluoro-2-(((5S,7aS)-5-(hydroxymethyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (85 mg, 0.13 mmol, 1.0 eq) and tert-butyl (3-cyano-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophen-2-yl)carbamate (107 mg, 0.25 mmol, 2.0 eq) in PhMe (1.0 mL) and H₂O (0.2 mL) was added K₃PO₄ (54 mg, 0.25 mmol, 2.0 eq), rac-BI-DIME (8 mg, 0.03 mmol, 0.2 eq) and Pd₂(dba)₃ (17 mg, 0.02 mmol, 0.15 eq). The mixture was stirred at 120 °C for 1 h by microwave under N₂. The reaction mixture was concentrated to give a crude. The crude was purified by Prep-TLC (DCM: MeOH ~ 15: 1) to give tert-butyl 3-(7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6,8-difluoro-2-(((5S,7aS)-5-(hydroxymethyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-

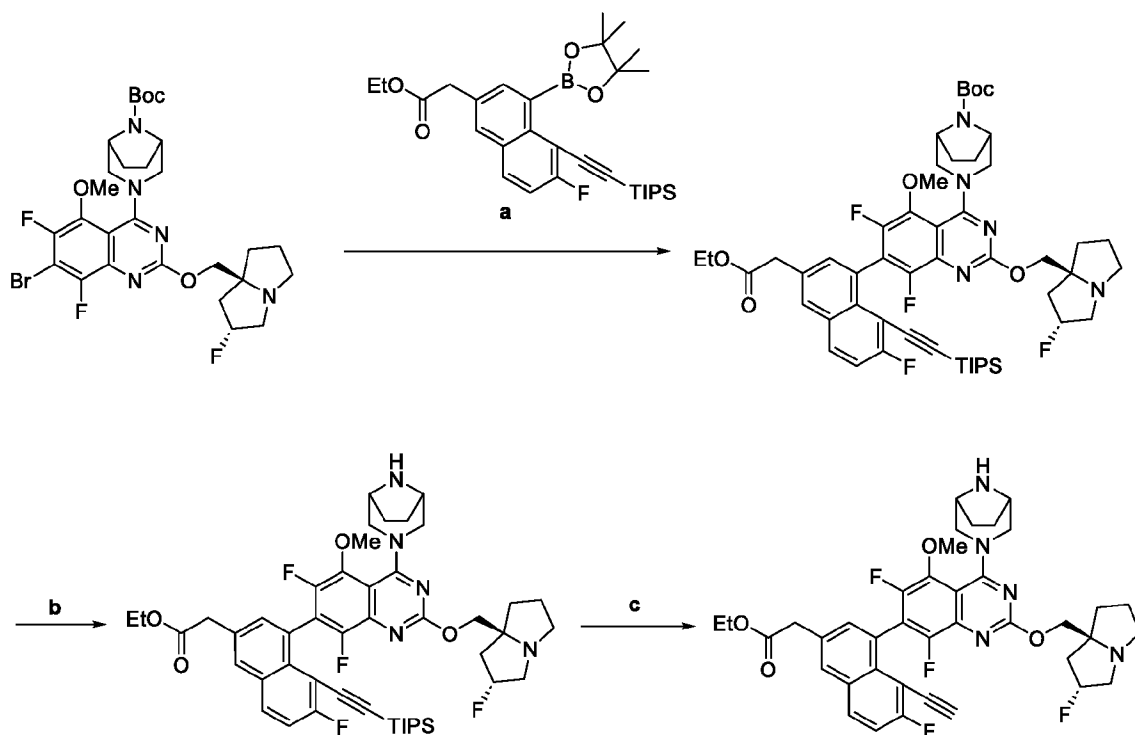
yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (35 mg, 31.2%) as a yellow solid. LCMS: 678.3 (M+H⁺).

Example 74

ethyl 2-(4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-yl)acetate

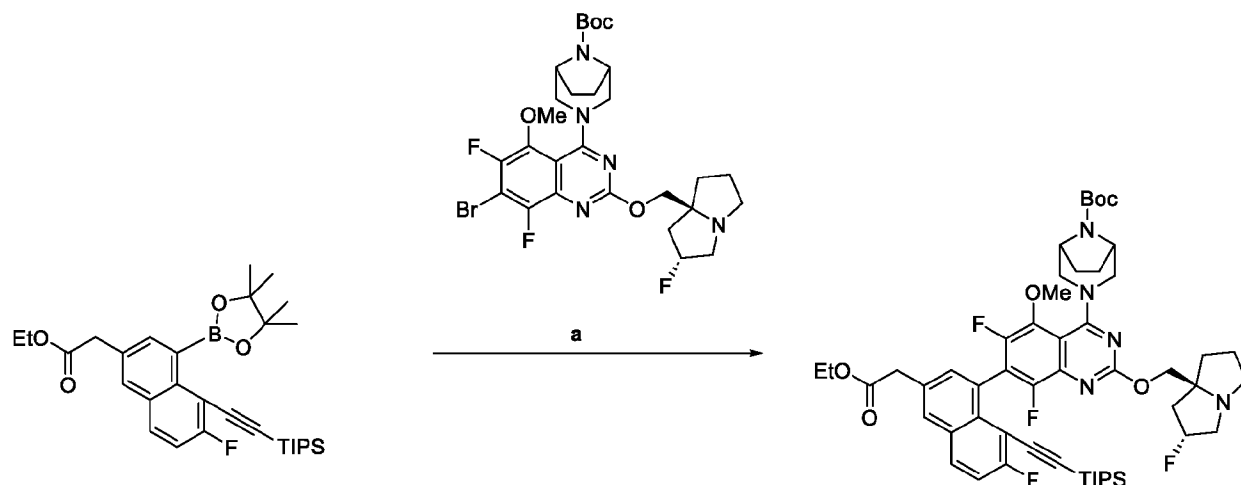


Synthesis scheme



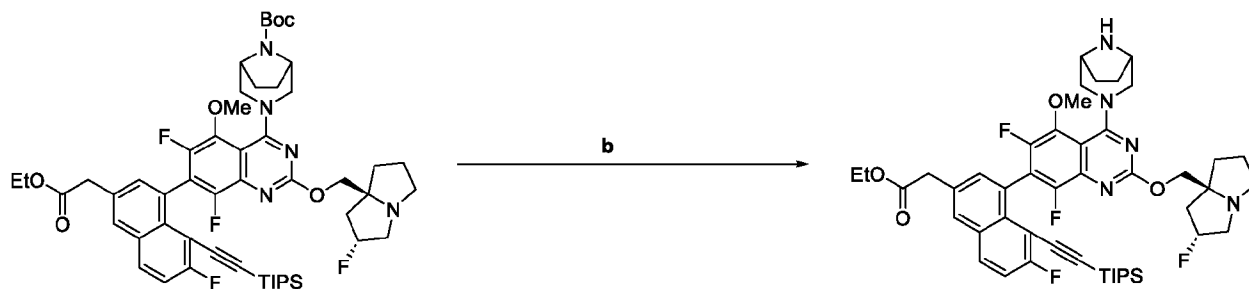
Step 1: Synthesis of tert-butyl 3-(7-(3-(2-ethoxy-2-oxoethyl)-7-fluoro-8-(((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-

1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



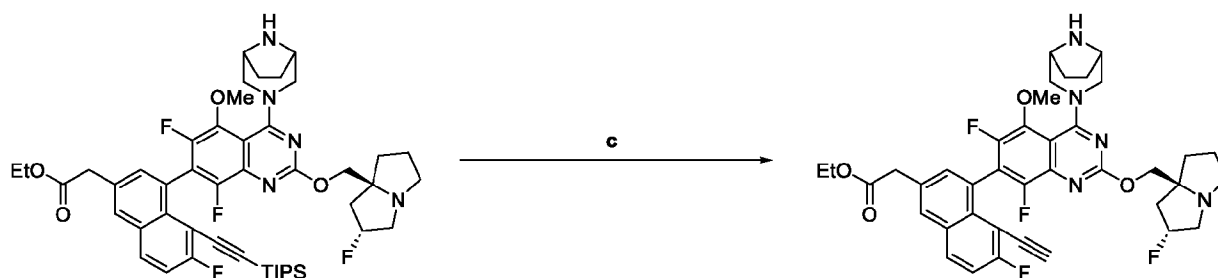
[00636] Tert-butyl 3-(7-bromo-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (160 mg, 0.25 mmol, 1.0 eq), ethyl 2-(6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)acetate (162 mg, 0.30 mmol, 1.2 eq), cataCXium A Pd G3 (36 mg, 0.05 mmol, 0.2 eq) and Cs_2CO_3 (244 mg, 0.75 mmol, 3.0 eq) were placed in the reaction bottle. A solution of PhMe/ H_2O (5/1, 9.6 mL) was added at room temperature. The mixture was stirred in microwave reactor at 120 °C for 1.5 h. The mixture was diluted with water (10 mL) and extracted with DCM: MeOH = 10: 1 (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated to give a residue. The crude product was purified by prep-TLC (DCM: MeOH = 15: 1) to give tert-butyl 3-(7-(3-(2-ethoxy-2-oxoethyl)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (110 mg, 45.2%) as a yellow liquid. LCMS: m/z 974.4 ($\text{M}+\text{H}^+$).

Step 2: Synthesis of ethyl 2-(4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)acetate



[00637] To a solution of tert-butyl 3-(7-(3-(2-ethoxy-2-oxoethyl)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (30 mg, 0.031 mmol, 1.0 eq) in ACN (1.0 mL) was added HCl/Dioxane (0.25 mL) at 0 °C under N₂ atmosphere. The reaction mixture was stirred at 0 °C for 2 h. Then the reaction mixture was concentrated in vacuo to give ethyl 2-(4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)acetate (50 mg, crude) as a yellow liquid, which was used directly for the next step without any further purification. LCMS: m/z 874.4 (M+H⁺).

Step 3: Synthesis of ethyl 2-(4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-yl)acetate formate (1: 0.4)

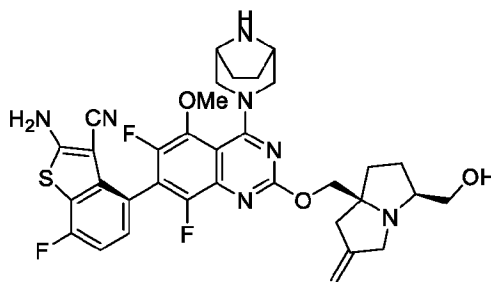


[00638] To a solution of ethyl 2-(4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)acetate (50 mg, crude) in DMF (0.5 mL) was added CsF (71 mg, 0.465 mmol, 15.0 eq). The reaction mixture was stirred at 40 °C for 6 h. Then the reaction mixture was filtered and the filtrate was purified by Prep-HPLC (acetonitrile with 0.1% FA in water, 15% to 41%) to give ethyl 2-(4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-

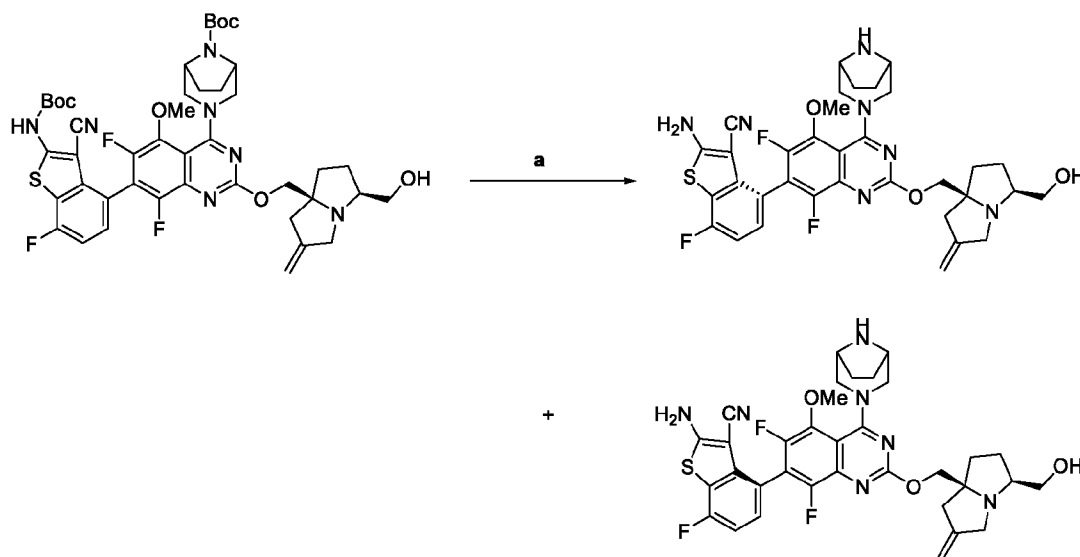
methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-yl)acetate (2.6 mg, with 0.4 FA, 11.0% for two steps) as a white solid. ^1H NMR (400 MHz, CH_3CN): δ 8.20 (s, 0.4H), 8.12-8.05 (m, 1H), 7.99 (s, 1H), 7.53 (s, 1H), 7.45 (t, $J = 8.8$ Hz, 1H), 5.26 (d, $J = 54.4$ Hz, 1H), 4.30-4.05 (m, 6H), 3.96 (d, $J = 9.6$ Hz, 1H), 3.85 (s, 2H), 3.79 (s, 3H), 3.52 (d, $J = 14.4$ Hz, 2H), 3.42 (d, $J = 12.8$ Hz, 1H), 3.33 (d, $J = 12.8$ Hz, 1H), 3.23 (s, 1H), 3.15 (d, $J = 7.6$ Hz, 2H), 3.08 (s, 1H), 2.91 (s, 1H), 2.20-2.10 (m, 6H), 1.90 – 1.79 (m, 4H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS: m/z 718.3 ($\text{M}+\text{H}^+$).

Example 75

4-((R)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((5S,7aS)-5-(hydroxymethyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile



Step 1: Synthesis of 4-((S)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((5S,7aS)-5-(hydroxymethyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile & 4-((R)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((5S,7aS)-5-(hydroxymethyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-2-

amino-7-fluorobenzo[b]thiophene-3-carbonitrile

the two isomers (R or S) cannot be confirmed

[00639] To a solution of tert-butyl 3-(7-(2-(((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6,8-difluoro-2-(((5S,7aS)-5-(hydroxymethyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (20 mg, 0.02 mmol, 1.0 eq) in DCM (2 mL) was added 4 N HCl/dioxane (1.5 mL, 6.0 mmol, 26.0 eq) at room temperature. Then the reaction mixture was stirred at 40 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 10% to 50%) to give 4-((S)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((5S,7aS)-5-(hydroxymethyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile (1.1 mg, 6.4%, the faster peak) as a white solid and 4-((R)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((5S,7aS)-5-(hydroxymethyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile (1.1 mg, 6.4%, the slower peak) as a white solid, the two isomers (*R* or *S*) cannot be confirmed.

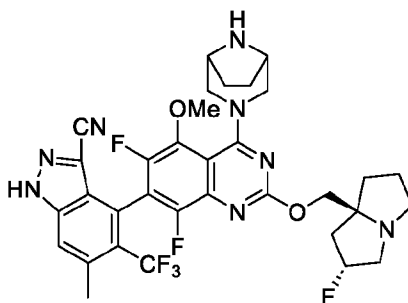
[00640] 4-((S)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((5S,7aS)-5-(hydroxymethyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile (peak 1): ¹H NMR (300 MHz, CD₃OD): 7.39 – 7.28 (m, 1H), 7.12 – 6.95 (m, 1H), 5.31 (s, 2H), 4.69 (d, *J* = 12.9 Hz,

1H), 4.54 (d, $J = 14.7$ Hz, 1H), 4.39 (d, $J = 15.0$ Hz, 2H), 4.25 – 4.04 (m, 3H), 3.97 (d, $J = 1.2$ Hz, 3H), 3.95 – 3.56 (m, 6H), 2.98 (d, $J = 15.9$ Hz, 1H), 2.81 (d, $J = 16.8$ Hz, 1H), 2.59 – 2.48 (m, 1H), 2.28 – 1.96 (m, 7H). ^{19}F NMR (300 MHz, CD_3OD): δ -117.767 -132.883, -135.857. LCMS: 678.2 ($\text{M}+\text{H}^+$).

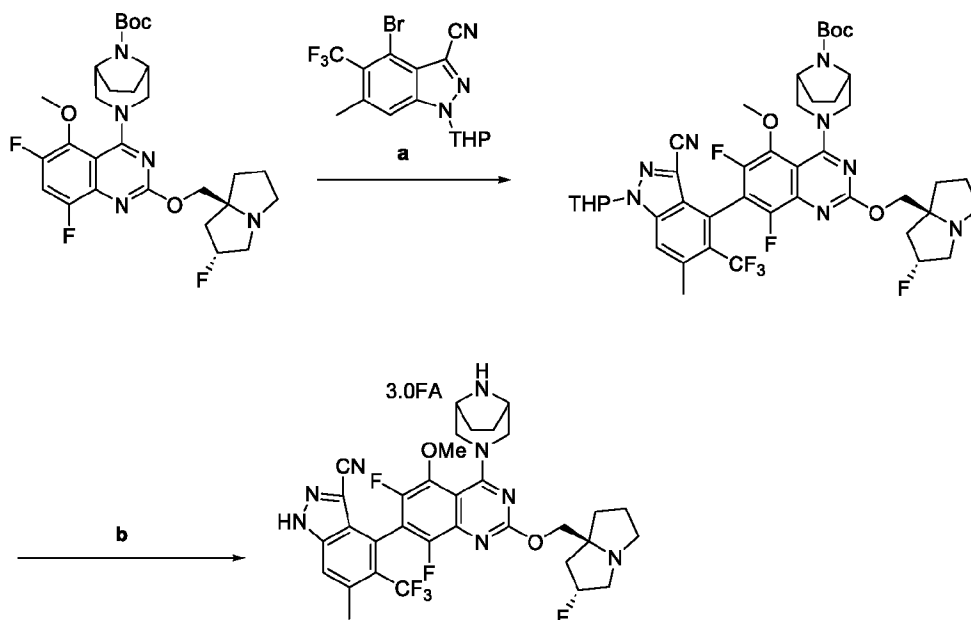
[00641] 4-((R)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((5S,7aS)-5-(hydroxymethyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile (peak 2): ^1H NMR (300 MHz, CD_3OD): δ 7.39 – 7.28 (m, 1H), 7.12 – 7.00 (m, 1H), 5.19 (s, 2H), 4.66 (d, $J = 12.6$ Hz, 1H), 4.45 (d, $J = 11.7$ Hz, 2H), 4.30 (d, $J = 14.7$ Hz, 1H), 4.12 – 4.08 (m, 1H), 4.07 – 4.01 (m, 2H), 3.93 (s, 3H), 3.90 – 3.82 (m, 1H), 3.78 – 3.50 (m, 5H), 2.87 (d, $J = 15.9$ Hz, 1H), 2.67 (d, $J = 15.6$ Hz, 1H), 2.44 – 2.35 (m, 1H), 2.19 – 1.96 (m, 7H). ^{19}F NMR (300 MHz, CD_3OD): δ -118.032, -132.714, -137.276 LCMS: 678.2 ($\text{M}+\text{H}^+$).

Example 76

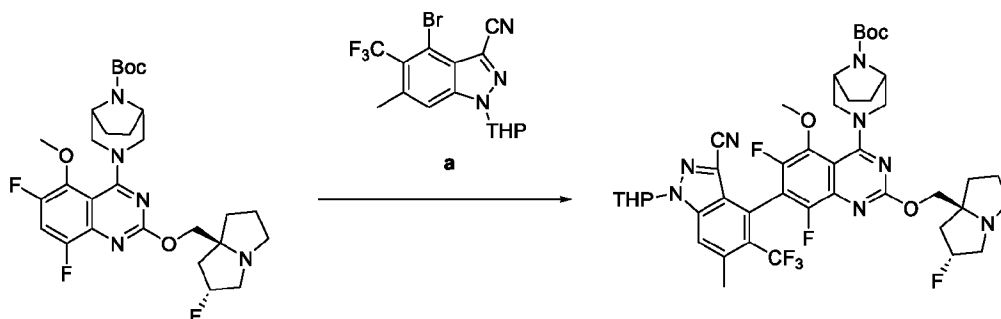
4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-methyl-5-(trifluoromethyl)-1H-indazole-3-carbonitrile formate



Synthetic scheme



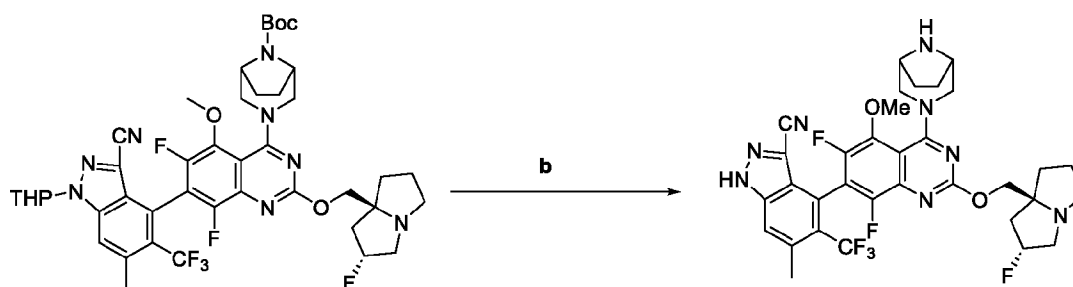
Step 1: Synthesis of tert-butyl 3-(7-(3-cyano-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00642] To a solution of compound 4-bromo-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazole-3-carbonitrile (30 mg x 6, 0.05 mmol, 1.0 eq) in THF (1 mL x 6) was added (TMP)₂Zn•MgCl₂•LiCl (0.8 mL x 6, 0.32 mmol, 6.0 eq, 0.4 M in THF) under nitrogen atmosphere. The reaction was stirred at 50 °C for 2 h. To the reaction was added tert-butyl 3-(6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (25 mg x 6, 0.06 mmol, 1.2 eq) and RuPhos Pd G2 (4 mg x 6, 0.005 mmol, 0.1 eq) in dioxane (2 mL x 6) under nitrogen atmosphere. The mixture was heated under microwave irradiation at 120 °C for 30 min. The residue was partitioned between EtOAc (20 mL) and water (20 mL). The layers were separated.

The aqueous layer was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over MgSO₄ and evaporated to dryness. The crude product was purified by prep-TLC (DCM : methanol = 10 : 1) to give tert-butyl 3-(7-(3-cyano-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (20 mg, 7.2%) as a yellow solid. LCMS: 871.3 (M+H⁺).

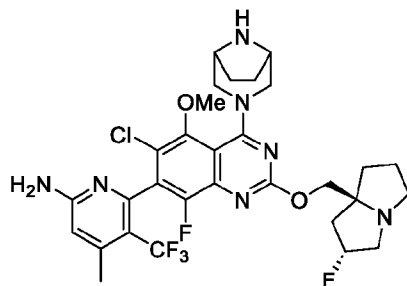
Step 2: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-methyl-5-(trifluoromethyl)-1H-indazole-3-carbonitrile formate (1:3)



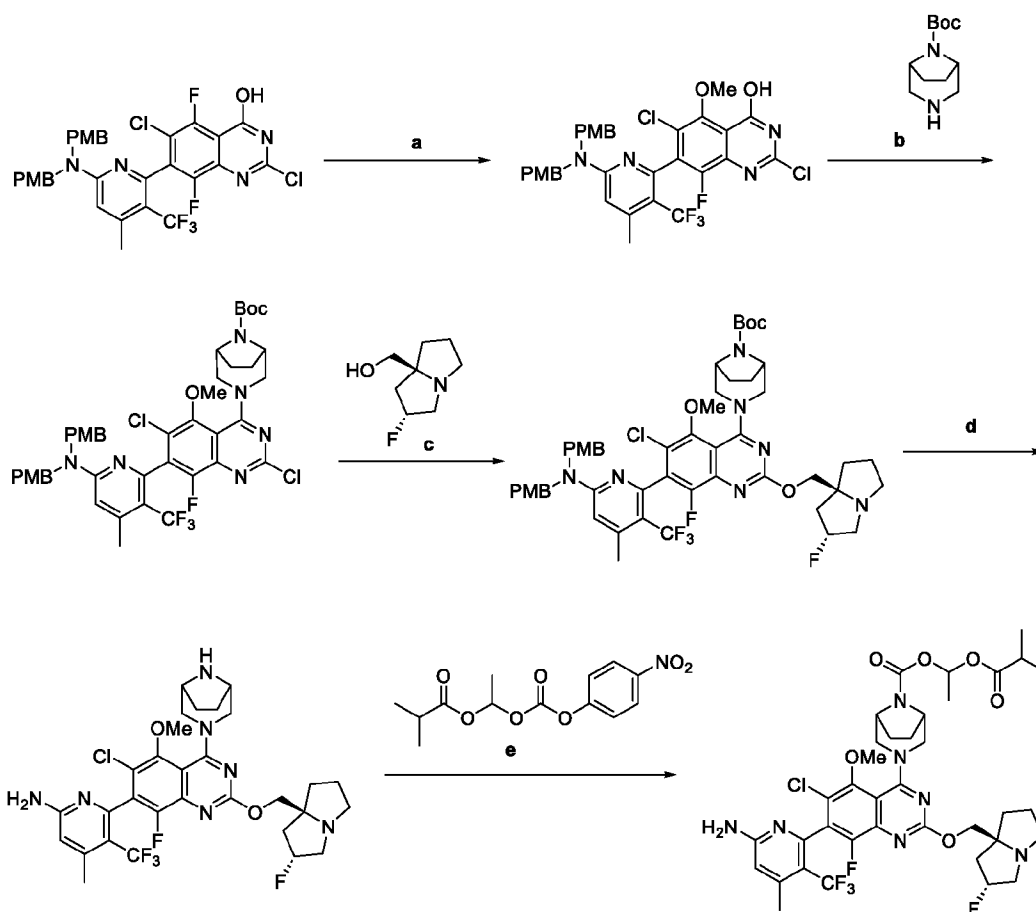
[00643] To a solution of tert-butyl 3-(7-(3-cyano-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (20 mg, 0.02 mmol, 1.0 eq) in DCM (1 mL) was added TFA (0.5 mL). Then the reaction mixture was stirred at room temperature for 1 h. The mixture was concentrated and purified by prep-HPLC (acetonitrile with 0.1% FA in water, 10% to 50%) to give 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-methyl-5-(trifluoromethyl)-1H-indazole-3-carbonitrile formate (1:3) (1.3 mg, 6.8%) as a white solid. ¹H NMR (400 MHz, CD₃OD): δ 8.47 (brs, 3H), 8.00 (s, 1H), 5.41 (d, *J* = 51.2 Hz, 1H), 4.58 (s, 2H), 4.53 – 4.34 (m, 3H), 4.33 – 4.18 (m, 1H), 4.06 – 3.90 (m, 5H), 3.76 – 3.44 (m, 5H), 3.29 – 3.17 (m, 1H), 2.71 (s, 3H), 2.47 – 2.35 (m, 2H), 2.34 – 2.23 (m, 2H), 2.20 – 2.11 (m, 3H), 2.07 – 1.90 (m, 3H). ¹⁹F NMR (400 MHz, CD₃OD): δ -57.566, -131.421, -137.280, -173.957. LCMS: 687.2 (M+H⁺).

Example 77

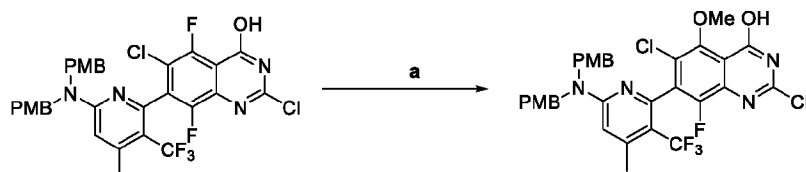
6-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine 2,2,2-trifluoroacetate (1:1)



Synthetic scheme:

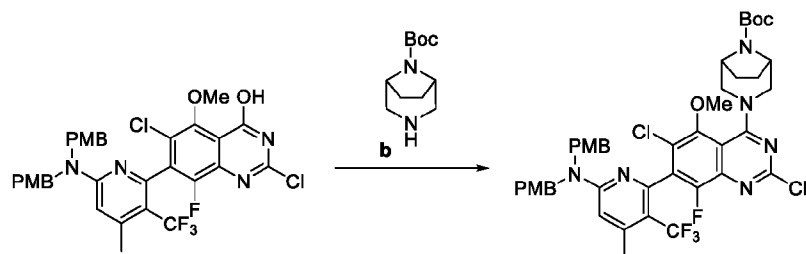


Step 1: Synthesis of 7-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-2,6-dichloro-8-fluoro-5-methoxyquinazolin-4-ol



[00644] To a solution of MeOH (34 mg, 1.1 mmol, 2.0 eq) in DMF (4 mL) was added NaH (105 mg, 2.6 mmol, 5.0 eq) at 0 °C under N₂. The reaction mixture was stirred at the same temperature for 0.5 h. To the mixture was added 7-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-2,6-dichloro-5,8-difluoroquinazolin-4-ol (350 mg, 0.53 mmol, 1.0 eq) in DMF (0.5 mL) at 0 °C under N₂. The reaction mixture was stirred at 65 °C for 2 h. The reaction was quenched by the addition of water (5 mL). The mixture was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄ and concentrated to give crude product. The crude product was purified by silica gel column chromatography (DCM: MeOH = 15: 1) to give 7-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-2,6-dichloro-8-fluoro-5-methoxyquinazolin-4-ol (300 mg, 84.3%) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 10.38 (brs, 1H), 7.13 (d, *J* = 8.8 Hz, 4H), 6.84 (d, *J* = 8.8 Hz, 4H), 6.42 (s, 1H), 4.92 – 4.51 (m, 4H), 3.99 (s, 3H), 3.80 (s, 6H), 2.41 (q, *J* = 1.6 Hz, 3H). LCMS: 677.1 (M+H⁺).

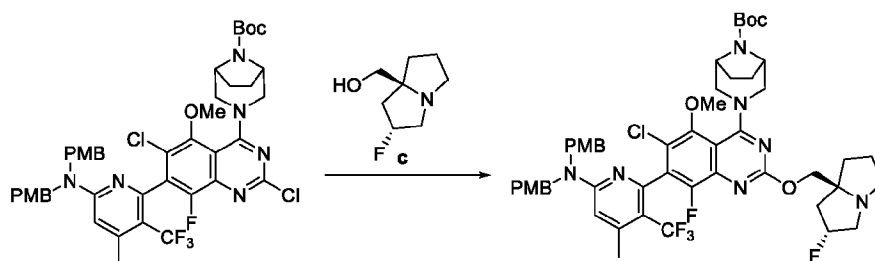
Step 2 Synthesis of tert-butyl 3-(7-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-2,6-dichloro-8-fluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00645] To a solution of 7-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-2,6-dichloro-8-fluoro-5-methoxyquinazolin-4-ol (300 mg, 0.44 mmol, 1.0 eq) in DCM (5 mL) was added tert-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (122 mg, 0.58 mmol, 1.3 eq), DIEA (172 mg, 1.3 mmol, 3.0 eq) and BOP-Cl (451 mg, 1.8 mmol, 4.0 eq). The reaction mixture was stirred at room temperature for 15 h. The mixture was washed with water (2 mL), brine (2 mL), dried over Na₂SO₄ and concentrated to give a crude. The crude

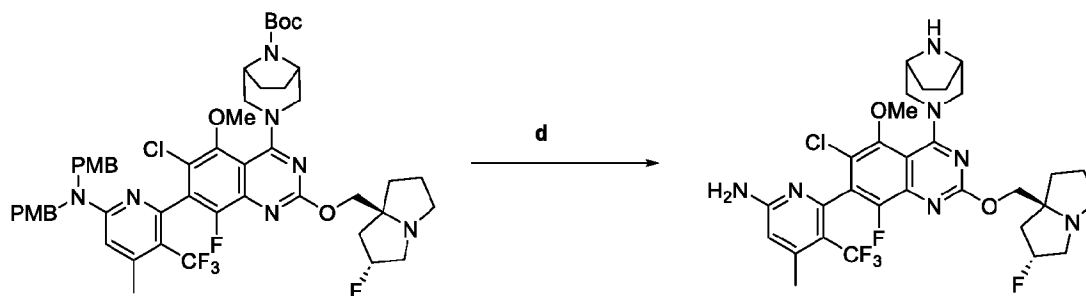
was purified by silica gel column chromatography (Petroleum ether: EtOAc = 1: 1) to give tert-butyl 3-(7-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-2,6-dichloro-8-fluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (230 mg, 59.6%) as a yellow solid. LCMS: 436.0 ($M/2+H^+$).

Step 3 Synthesis of tert-butyl 3-(7-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00646] A solution of compound tert-butyl 3-(7-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-2,6-dichloro-8-fluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (200 mg, 0.23 mmol, 1.0 eq), ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (40 mg, 0.25 mmol, 1.1 eq), DABCO (26 mg, 0.23 mmol, 1.0 eq), and CS_2CO_3 (224 mg, 0.69 mmol, 3.0 eq) in THF (2 mL) and DMF (2 mL) was stirred at room temperature for 15 h under nitrogen atmosphere. The mixture was added H_2O (5 mL), extracted with EtOAc (5 mL x 3). The combined organic layers were washed with H_2O (2 mL x 3), brine (5 mL), dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by silica gel column chromatography (DCM: MeOH = 15: 1) to give tert-butyl 3-(7-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (180 mg, 78.9%) as a yellow solid. LCMS: 994.3 ($M+H^+$).

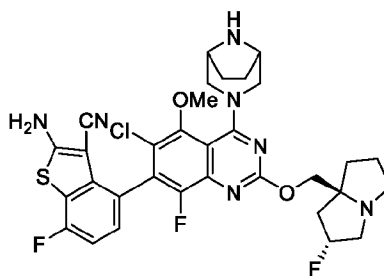
Step 4: Synthesis of 6-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine 2,2,2-trifluoroacetate (1:1)



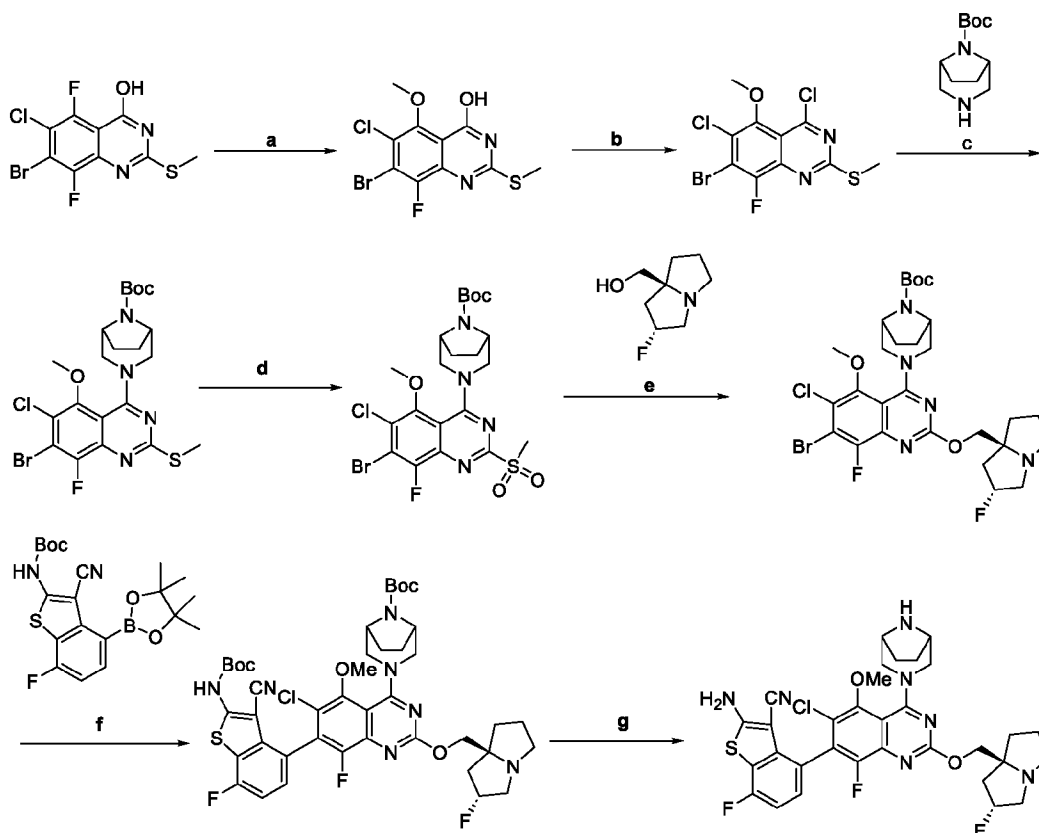
[00647] A solution of tert-butyl 3-(7-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (180 mg, 0.18 mmol, 1.0 eq) in TFA (4 mL) was stirred at 50 °C for 2 h. The mixture was concentrated to give a crude. The crude was purified by Prep-HPLC (ACN with 0.1% FA in water, 15% to 80%) to give 6-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine 2,2,2-trifluoroacetate (1:1) (90 mg, 66.2%) as a white solid. ¹H NMR (300 MHz, CD₃OD): δ 6.60 (s, 1H), 5.30 (d, *J* = 52.2 Hz, 1H), 4.54 – 4.06 (m, 4H), 3.98 – 3.86 (m, 2H), 3.73 (s, 3H), 3.69 – 3.41 (m, 5H), 3.21 – 3.11 (m, 1H), 2.44 (s, 3H), 2.40 – 1.88 (m, 10H). ¹⁹F NMR (300 MHz, CD₃OD): δ -56.584, -76.940, -132.327, -173.856. LCMS: 654.2 (M + H⁺).

Example 78

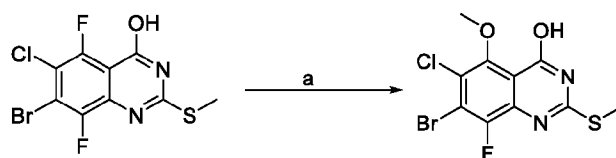
4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile



Synthetic scheme

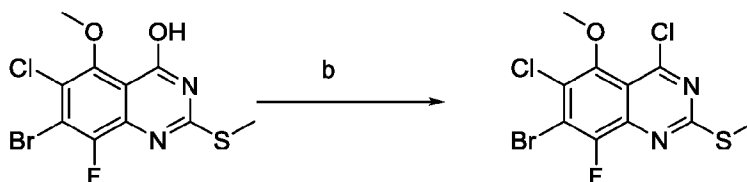


Step 1: Synthesis of 7-bromo-6-chloro-8-fluoro-5-methoxy-2-(methylthio)quinazolin-4-ol



[00648] To a solution of MeOH (74.5 mg, 2.33 mmol, 1.5 eq) in DMF (5.3 mL) was added NaH (60%, 362 mg, 9.05 mmol, 5.8 eq) at 0 °C. After 30 min, the mixture was added 7-bromo-6-chloro-5,8-difluoro-2-(methylthio)quinazolin-4-ol (530 mg, 1.55 mmol, 1.0 eq). The mixture was stirred at room temperature for 30 min. The mixture was diluted with saturated NH₄Cl solution (10 mL) and extracted with DCM (10 mL x 3). The organic layer was washed with brine (10 mL x 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give the crude product 7-bromo-6-chloro-8-fluoro-5-methoxy-2-(methylthio)quinazolin-4-ol (300 mg, crude) as a brown solid. LCMS: m/z 352.8, 354.9 (M+H⁺).

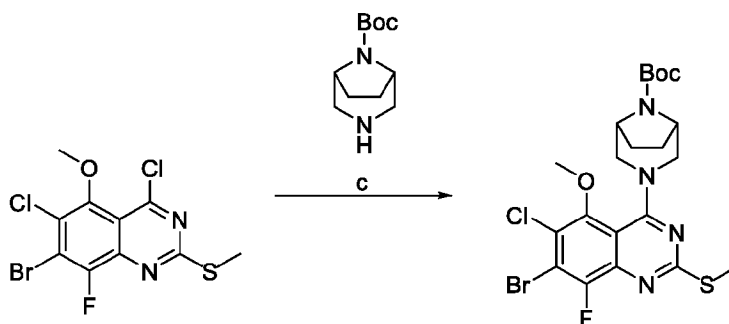
Step 2: Synthesis of 7-bromo-4,6-dichloro-8-fluoro-5-methoxy-2-(methylthio)quinazoline



[00649] To a solution of 7-bromo-6-chloro-8-fluoro-5-methoxy-2-(methylthio)quinazolin-4-ol (280 mg, 0.79 mmol, 1.0 eq) in POCl_3 (2.2 mL) was added DIEA (512 mg, 3.96 mmol, 5.0 eq). The mixture was stirred at 90 °C for 1 h under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to give the crude product 7-bromo-4,6-dichloro-8-fluoro-5-methoxy-2-(methylthio)quinazoline (crude) as a brown solid.

LCMS: no signal

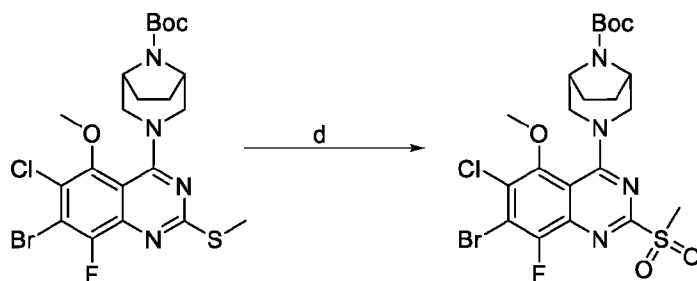
Step 3: Synthesis of tert-butyl 3-(7-bromo-6-chloro-8-fluoro-5-methoxy-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00650] To a solution of 7-bromo-4,6-dichloro-8-fluoro-5-methoxy-2-(methylthio)quinazoline (crude, 0.79 mmol, 1.0 eq) in DCM (4 mL) was added DIEA (684 mg, 5.29 mmol, 6.7 eq) and tert-butyl(1R,5S)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (168 mg, 0.79 mmol, 1.0 eq) at -40 °C. The mixture was stirred at -40 °C for 1 h under nitrogen atmosphere. The mixture was diluted with H_2O (10 mL) and extracted with DCM (10 mL x 3). The organic layer was washed with brine (10 mL x 2), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give the crude product, which was purified by pre-TLC (petroleum ether: EtOAc = 3: 1) to afford tert-butyl (1R,5S)-3-(7-bromo-6-chloro-8-fluoro-5-methoxy-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (250 mg, 57.6% for two steps) as a yellow solid.

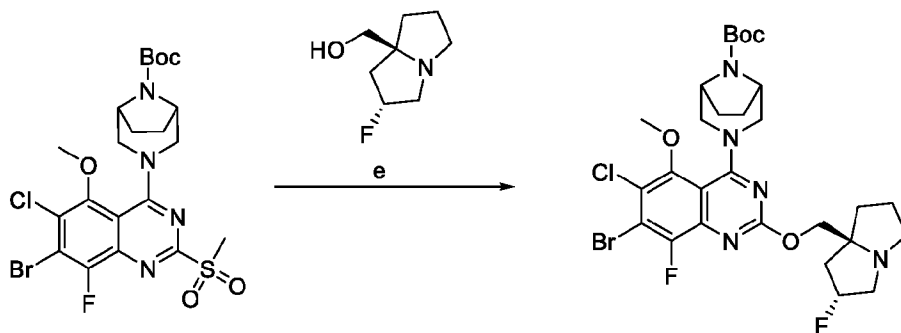
LCMS: m/z 547.1, 549.0 ($\text{M}+\text{H}^+$).

Step 4: Synthesis of tert-butyl 3-(7-bromo-6-chloro-8-fluoro-5-methoxy-2-(methylsulfonyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00651] To a solution of tert-butyl 3-(7-bromo-6-chloro-8-fluoro-5-methoxy-2-(methylthio)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (220 mg, 0.40 mmol, 1.0 eq) in DCM (4.65 mL) was added *m*-CPBA (75%, 230 mg, 1.0 mmol, 2.5 eq) at 0 °C under N₂ atmosphere. The reaction mixture was stirred at room temperature for 2 h. The mixture was diluted with saturated sodium sulfite solution (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was dried over Na₂SO₄ and concentrated to give a crude product, which was purified by pre-TLC (Petroleum ether: EtOAc = 1: 1) to afford tert-butyl 3-(7-bromo-6-chloro-8-fluoro-5-methoxy-2-(methylsulfonyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (170 mg, 73.3%) as a yellow liquid. LCMS: *m/z* 579.1, 581.0 (M+H⁺).

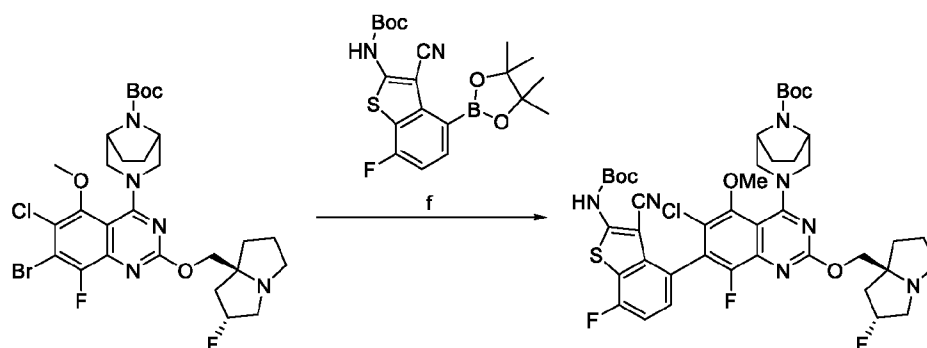
Step 5: Synthesis of tert-butyl 3-(7-bromo-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00652] To a solution of compound tert-butyl 3-(7-bromo-6-chloro-8-fluoro-5-methoxy-2-(methylsulfonyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (130 mg, 0.224 mmol, 1.0 eq) and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (107 mg, 0.672 mmol, 3.0 eq) in THF (6.5 mL) was added LiHMDS (1M, 0.672 mL, 0.672 mmol, 3.0 eq) at 0 °C under N₂ atmosphere. The reaction mixture was stirred at 0 °C for 1 h. The mixture was diluted with water (5 mL) and extracted with EtOAc (5 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give a residue. The

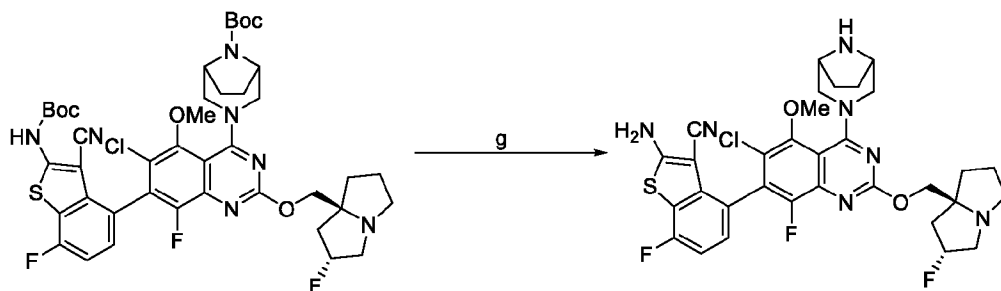
crude product was purified by pre-TLC (Petroleum ether: EtOAc = 50: 1) to afford tert-butyl 3-(7-bromo-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo [3.2.1] octane-8-carboxylate (110 mg, 74.6%) as a yellow liquid. LCMS: m/z 658.2, 660.1 (M+H⁺).

Step 6: Synthesis of tert-butyl 3-(7-(2-(((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00653] To a solution of tert-butyl 3-(7-bromo-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (60 mg, 0.091 mmol, 1.0 eq) in dioxane/H₂O (3/1, 3.2 mL) was added tert-butyl (3-cyano-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophen-2-yl)carbamate (45.8 mg, 0.11 mmol, 1.2-eq), Pd(dtpbf)Cl₂ (11.8 mg, 0.018 mmol, 0.2 eq), K₃PO₄ (34.8 mg, 0.164 mmol, 1.8 eq). The sealed vial was irradiated in the microwave at 100 °C for 1 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give a residue. The crude product was purified by pre-TLC (DCM: MeOH = 10: 1) to afford tert-butyl 3-(7-(2-(((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (40 mg, 50.5%) as a yellow solid. LCMS: m/z 658.1 (M+H⁺).

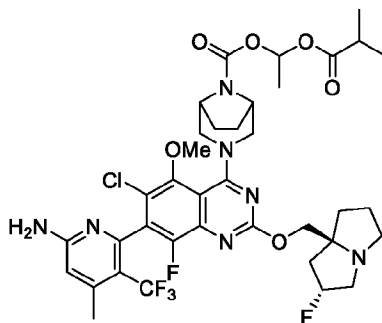
Step 7: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile



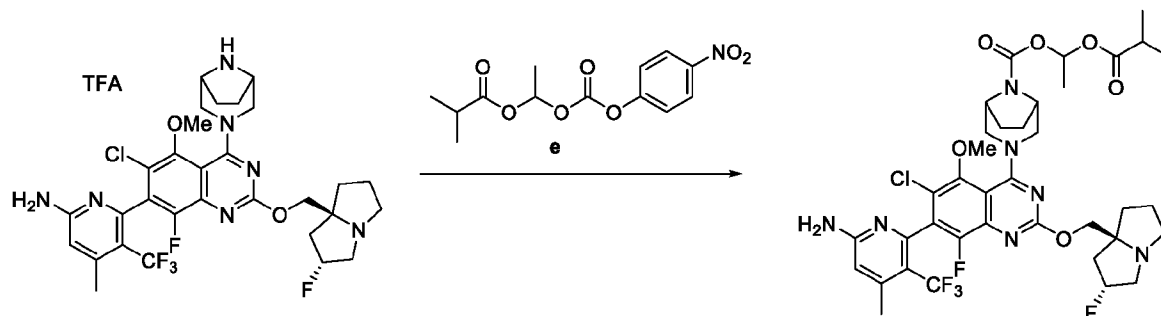
[00654] To a solution of tert-butyl 3-(7-(2-(((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.115 mmol, 1.0 eq) in ACN (5 mL) was added HCl/dioxane (4 M, 0.92 mL, 3.677 mmol, 32.0 eq) at 0 °C under nitrogen atmosphere. The mixture was stirred at room temperature overnight. The reaction mixture was concentrated to give crude product, which was purified by pre-HPLC (0.1% FA) to afford 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile (5.8 mg, with 0.37 FA, 7.1%) as a white solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.09 (s, 2H), 7.37 – 7.23 (m, 1H), 7.14 (t, *J* = 8.8 Hz, 1H), 5.27 (d, *J* = 52.2 Hz, 1H), 4.03 (dd, *J* = 30 Hz, 10.9 Hz, 2H), 3.64 (s, 3H), 3.48 (s, 4H), 3.15-3.05 (m, 5H), 2.83 (s, 1H), 2.13 (s, 1H), 2.03 (s, 2H), 1.87 – 1.72 (m, 4H), 1.56 (s, 3H). LCMS: *m/z* 670.2 (M+H⁺).

Example 79

1-(Isobutyryloxy)ethyl 3-(7-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



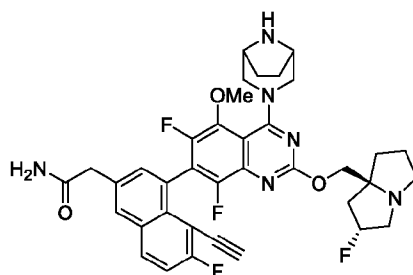
Step 1: Synthesis of 1-(isobutyryloxy)ethyl 3-(7-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



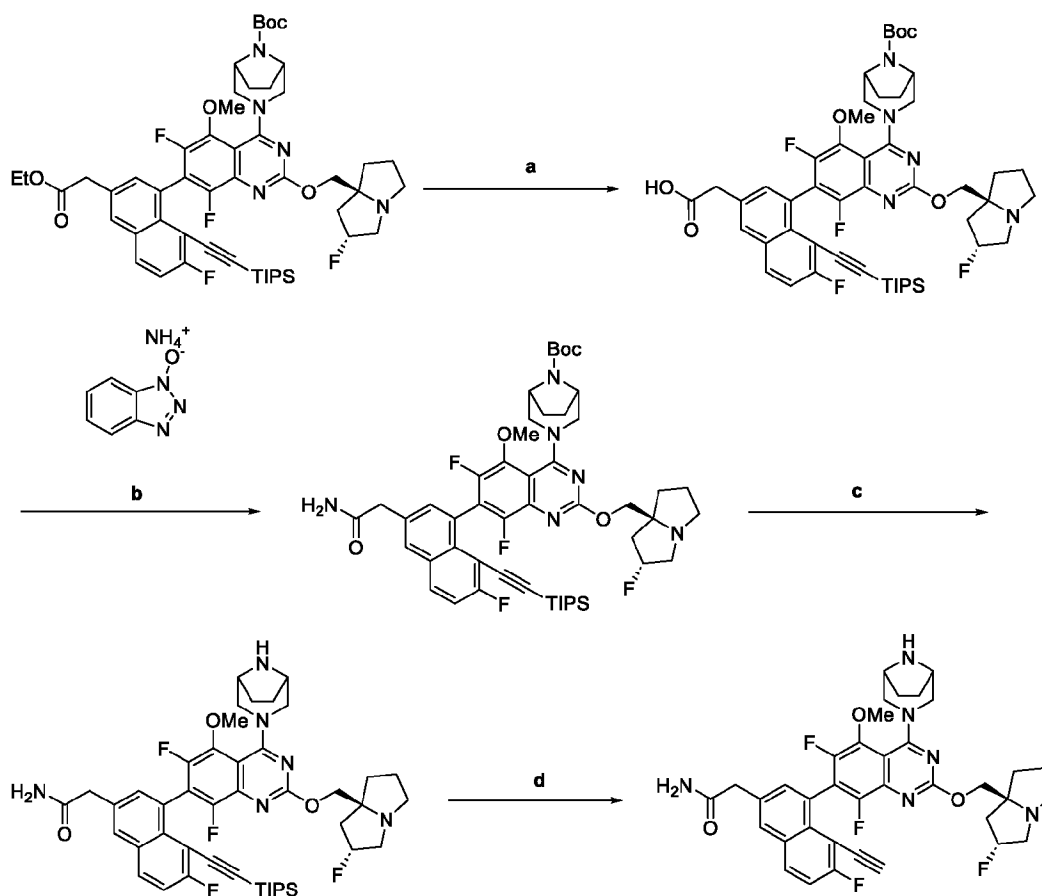
[00655] To a solution of 6-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (60 mg, 0.08 mmol, 1.0 eq) in DCM (2 mL) was added 1-(((4-nitrophenoxy)carbonyl)oxy)ethyl isobutyrate (28 mg, 0.09 mmol, 1.2 eq) and DIEA (31 mg, 0.24 mmol, 3.0 eq). The mixture was stirred at room temperature for 15 h. The mixture was purified by prep-TLC (DCM: MeOH ~ 10: 1) to give a crude. The crude was purified by Prep-HPLC (ACN with 0.1% FA in water, 20% to 80%) to give 1-(isobutyryloxy)ethyl 3-(7-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (16 mg, 24.6%) as a white solid. ¹H NMR (400 MHz, CD₃OD): δ 6.82 (q, *J* = 5.6 Hz, 1H), 6.60 (s, 1H), 5.36 (d, *J* = 53.2 Hz, 1H), 4.68 – 4.13 (m, 6H), 3.70 (s, 3H), 3.65 – 3.31 (m, 5H), 3.17 – 3.07 (m, 1H), 2.68 – 2.50 (m, 1H), 2.44 (d, *J* = 1.2 Hz, 3H), 2.42 – 1.74 (m, 10H), 1.52 (d, *J* = 5.6 Hz, 3H), 1.26 – 1.13 (m, 6H). ¹⁹F NMR (400 MHz, CD₃OD): δ -56.590, -132.578, -173.746. LCMS: 812.2 (M+H⁺).

Example 80

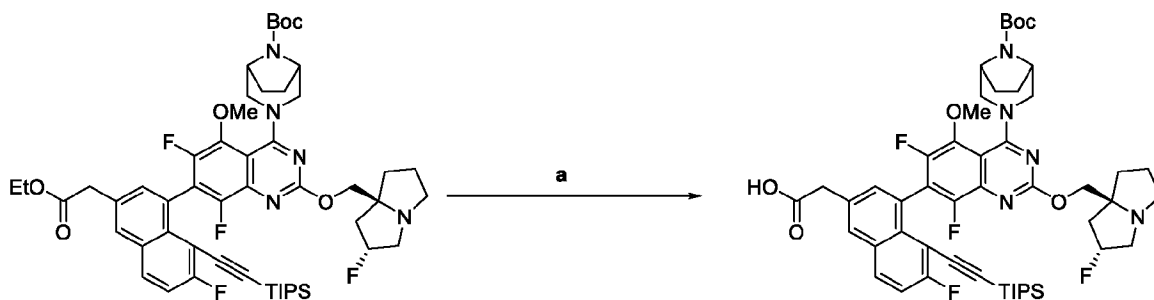
2-(4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-yl)acetamide



Synthetic scheme

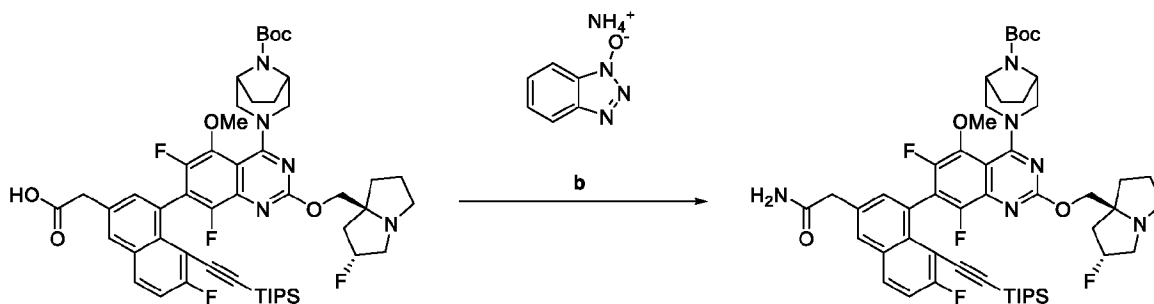


Step 1: Synthesis of 2-(4-(4-(8-(tert-butoxycarbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)acetic acid



[00656] To a solution of tert-butyl 3-(7-(3-(2-ethoxy-2-oxoethyl)-7-fluoro-8-((triisopropylsilyl) ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (60 mg, 0.062 mmol, 1.0 eq) in THF (2 mL) was added 1 N LiOH solution (1 mL). The reaction mixture was heated at 40 °C for 1.5 h. The mixture was diluted with water (10 mL) and adjusted to pH~ 7 with 1N HCl (5 mL), extracted with DCM: MeOH = 10: 1 (10 mL x 3). The organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford 2-(4-(4-(8-(tert-butoxycarbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)acetic acid (80 mg, crude) as a yellow liquid, which was used directly for the next step without any further purification. LCMS: m/z 946.4 ([M+H]⁺).

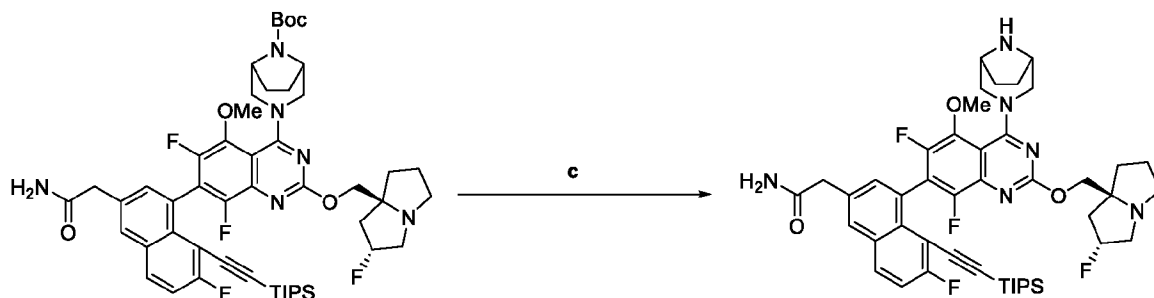
Step 2: Synthesis of tert-butyl 3-(7-(3-(2-amino-2-oxoethyl)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00657] To a solution of 2-(4-(4-(8-(tert-butoxycarbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)acetic acid (80

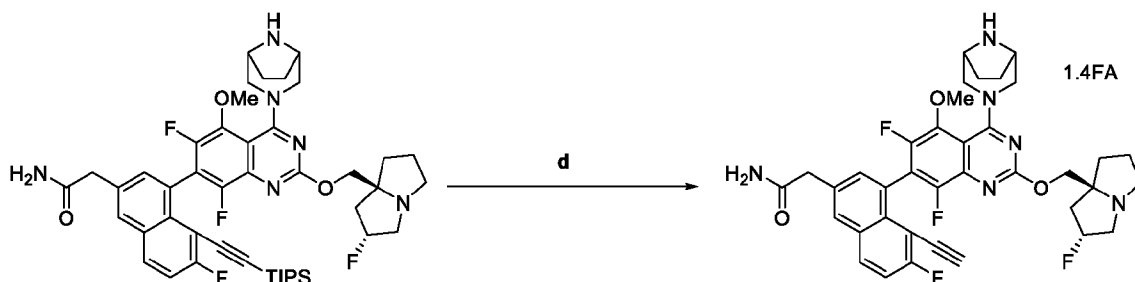
mg, crude) in DMF (1.2 mL) was added ammonium 1H-benzo[d][1,2,3]triazol-1-olate (29 mg, 0.19 mmol, 3.0 eq) and EDCI (36 mg, 0.19 mmol, 3.0 eq) at room temperature under N₂ atmosphere. The reaction mixture was stirred at room temperature for 1.5 h. The mixture was diluted with water (10 mL) and extracted with DCM: MeOH = 10: 1 (10 mL x 3). The organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford tert-butyl 3-(7-(3-(2-amino-2-oxoethyl)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (140 mg, crude) as a yellow liquid, which was used directly for the next step without any further purification. LCMS: m/z 945.4 (M+H⁺).

Step 3: Synthesis of 2-(4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)acetamide



[00658] To a solution of tert-butyl 3-(7-(3-(2-amino-2-oxoethyl)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (140 mg, crude) in ACN (2.0 mL) was added HCl/Dioxane (4 M, 0.5 mL) at 0 °C under N₂ atmosphere. The reaction mixture was stirred at 0 °C for 2h and concentrated under reduced pressure to give the crude product 2-(4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)acetamide (70 mg, crude) as a yellow liquid, which was used directly for the next step without any further purification. LCMS: m/z 845.4 (M+H⁺).

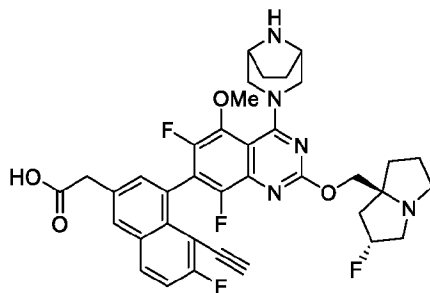
Step 4: Synthesis of 2-(4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-yl)acetamide



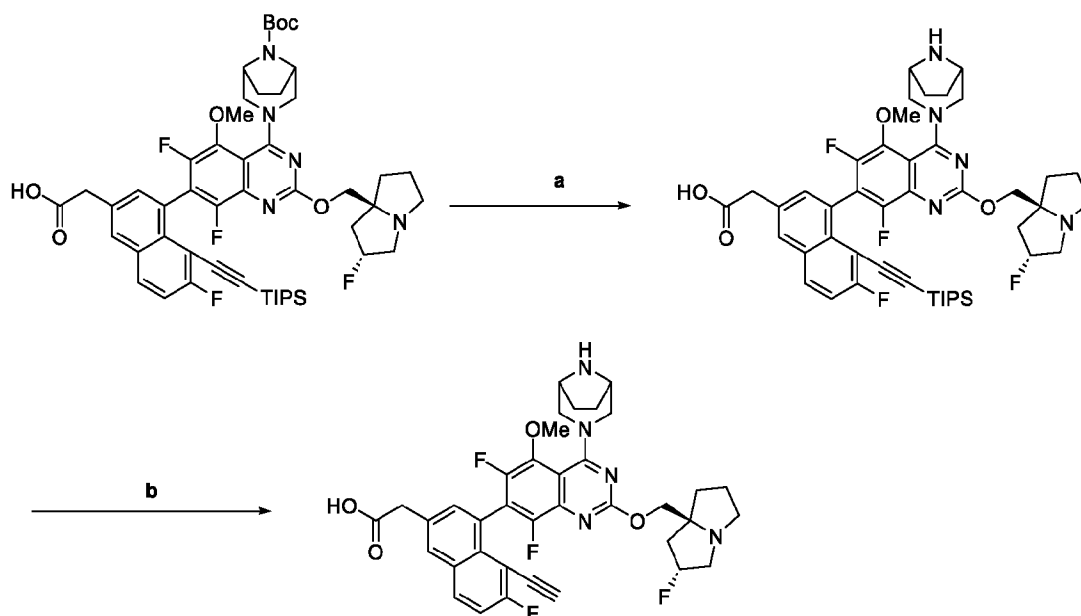
[00659] To a solution of 2-(4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)acetamide (70 mg, crude) in DMF (1.0 mL) was added CsF (141 mg, 0.93 mmol, 15.0 eq). The reaction mixture was stirred at 40 °C for 4 h. Then the reaction mixture was filtered and the filtrate was purified by Prep-HPLC (acetonitrile with 0.1% FA in water, 10% to 30%) to give 2-(4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-yl)acetamide formate (8.1 mg, with 1.4 FA, 17.3% for four steps) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.23 (s, 1.4H), 8.19 (dd, *J* = 9.2, 6.0 Hz, 1H), 8.04 (s, 1H), 7.70-7.50 (m, 3H), 7.00 (s, 1H), 5.28 (d, *J* = 54.4 Hz, 1H), 4.18 (s, 1H), 4.12-4.02 (m, 2H), 3.98 (d, *J* = 10.0 Hz, 1H), 3.77 (s, 4H), 3.61 (s, 3H), 3.47 (d, *J* = 12.4 Hz, 2H), 3.29 (d, *J* = 12.4 Hz, 2H), 3.18-3.02 (m, 2H), 3.01 (s, 1H), 2.90-2.80 (m, 1H), 2.32 – 1.94 (m, 4H), 1.85 – 1.74 (m, 4H), 1.69 (s, 2H). LCMS: *m/z* 689.3 ([*M*+*H*)⁺).

Example 81

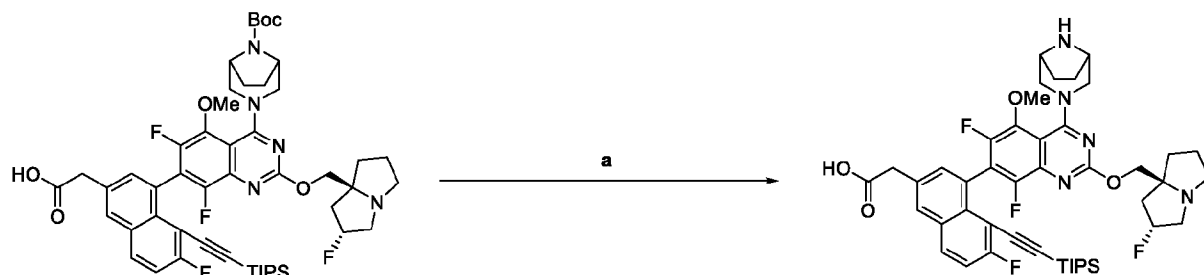
2-(4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-yl)acetic acid



Synthetic scheme



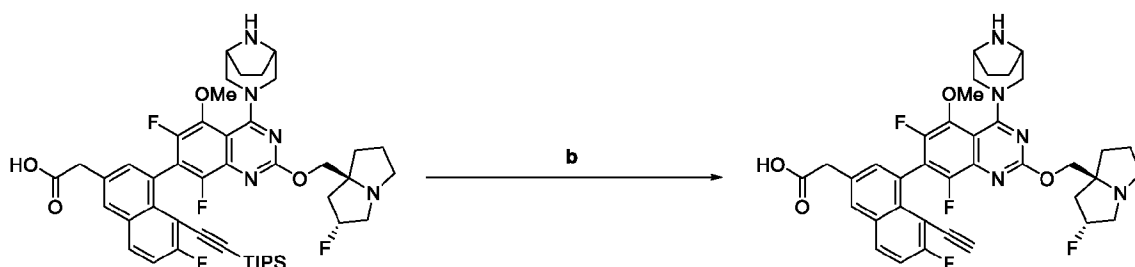
Step 1: Synthesis of 2-(4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)acetic acid



[00660] To a solution of 2-(4-(4-(8-(tert-butoxycarbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)acetic acid (59 mg, 0.062 mmol, 1.0 eq) in ACN (2.0 mL) was added HCl/Dioxane (4 M, 0.5 mL) at 0 °C under

N₂ atmosphere. The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give the crude product 2-(4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)acetic acid (50 mg, crude) as a yellow liquid, which was used directly for the next step without any further purification. LCMS: m/z 846.4 (M+H⁺).

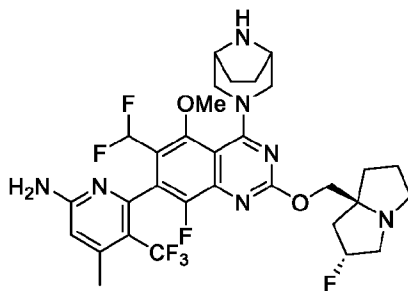
Step 2: Synthesis of 2-(4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-yl)acetic acid formate



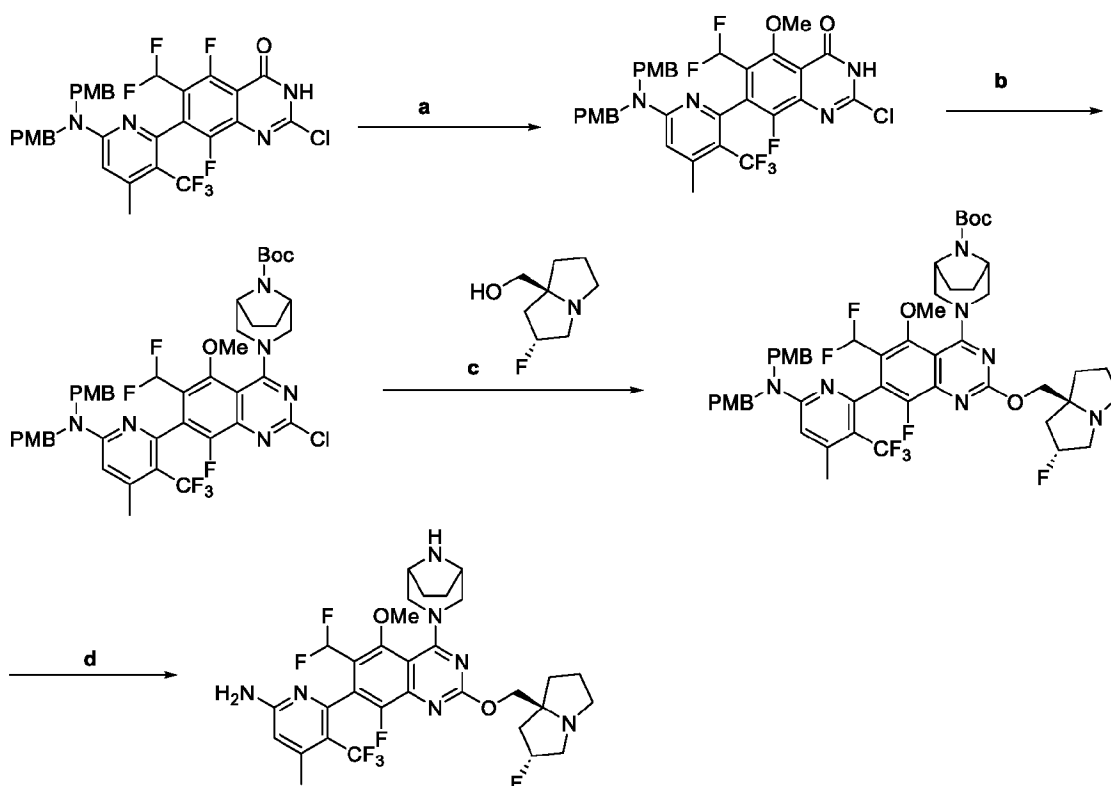
[00661] To a solution of 2-(4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)acetic acid (50 mg, crude) in DMF (1.0 mL) was added CsF (141 mg, 0.93 mmol, 15.0 eq). The reaction mixture was stirred at 40 °C for 6 h. Then the reaction mixture was filtered and the filtrate was purified by Prep-HPLC (acetonitrile with 0.1% FA in water, 20% to 30%) to give 2-(4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-yl)acetic acid (12.1 mg, with 0.3 FA, 27.7% for two steps) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.25 (s, 0.3H), 8.18 (dd, *J* = 9.2, 6.0 Hz, 1H), 8.06 (s, 1H), 7.63 – 7.52 (m, 2H), 5.27 (d, *J* = 53.6 Hz, 1H), 4.18 (d, *J* = 9.2 Hz, 1H), 4.10–4.05 (m, 2H), 3.97 (d, *J* = 10.4 Hz, 1H), 3.78 (s, 2H), 3.76 (s, 3H), 3.57 (d, *J* = 16.0 Hz, 2H), 3.45 (d, *J* = 12.4 Hz, 2H), 3.26 (d, *J* = 12.0 Hz, 2H), 3.15–3.05 (m, 2H), 3.01 (s, 1H), 2.90–2.75 (m, 1H), 2.22 – 1.93 (m, 4H), 1.85–1.75 (m, 4H), 1.70–1.60 (m, 2H). LCMS: m/z 690.2 ([M+H]⁺).

Example 82

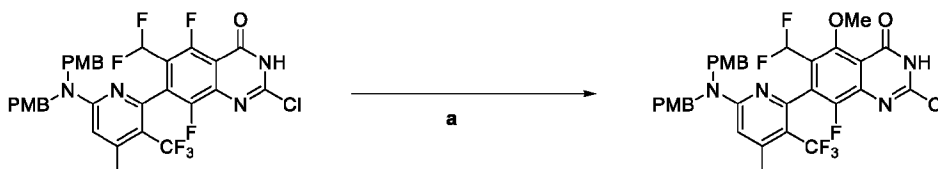
6-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(difluoromethyl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine 2,2,2-trifluoroacetate



Synthetic scheme:

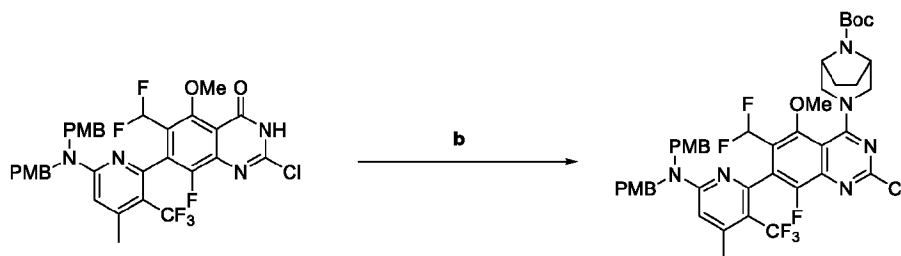


Step 1: Synthesis of 7-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-2-chloro-6-(difluoromethyl)-8-fluoro-5-methoxyquinazolin-4(3H)-one



[00662] To a solution of MeOH (7 mg, 0.22 mmol, 1.5 eq) in DMF (2.0 mL) was added NaH (60%, 29 mg, 0.74 mmol, 5.0 eq). The mixture was stirred at room temperature for 0.5 h. Compound 7-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-2-chloro-6-(difluoromethyl)-5,8-difluoroquinazolin-4(3H)-one (100 mg, 0.15 mmol, 1.0 eq) was added to the mixture. The mixture was stirred at room temperature for 15 h. The reaction mixture was quenched with saturated ammonium chloride aqueous solution (10 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with H₂O (10 mL), brine (10 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (Dichloromethane: Methanol = 100: 1) to give compound 7-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-2-chloro-6-(difluoromethyl)-8-fluoro-5-methoxyquinazolin-4(3H)-one (100 mg, 98.3%) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 7.06 – 7.01 (m, 4H), 6.80 – 6.75 (m, 4H), 6.74 – 6.54 (m, 1H), 6.34 (s, 1H), 4.67 – 4.58 (m, 2H), 4.58 – 4.49 (m, 2H), 3.94 (s, 3H), 3.72 (s, 6H), 2.33 (s, 3H). LCMS: 693.2 (M+H⁺).

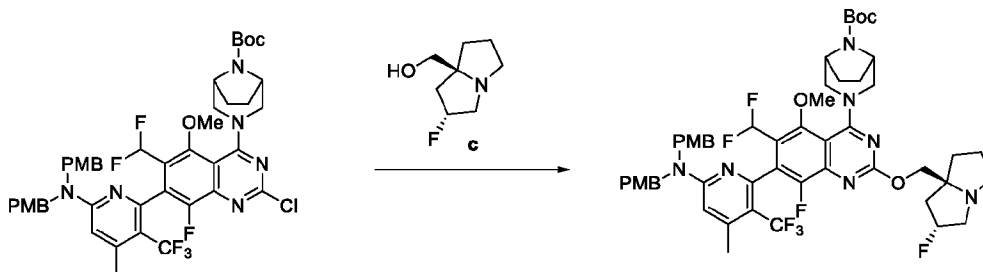
Step 2: Synthesis of tert-butyl 3-(7-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-2-chloro-6-(difluoromethyl)-8-fluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00663] To a solution of compound 7-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-2-chloro-6-(difluoromethyl)-8-fluoro-5-methoxyquinazolin-4(3H)-one (80 mg, 0.12 mmol, 1.0 eq) in DCM (2 mL) was added DIEA (224 mg, 1.7 mmol, 15.0 eq) and BOP-Cl (118 mg, 0.46 mmol, 4.0 eq). The mixture was stirred at room temperature for 15 h. The reaction mixture was quenched with water (10 mL). The aqueous layer was extracted with DCM (10 mL x 3). The combined organic layers were washed with H₂O (10 mL), brine (10 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (Dichloromethane: Methanol = 150: 1) to give compound tert-butyl 3-(7-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-2-chloro-

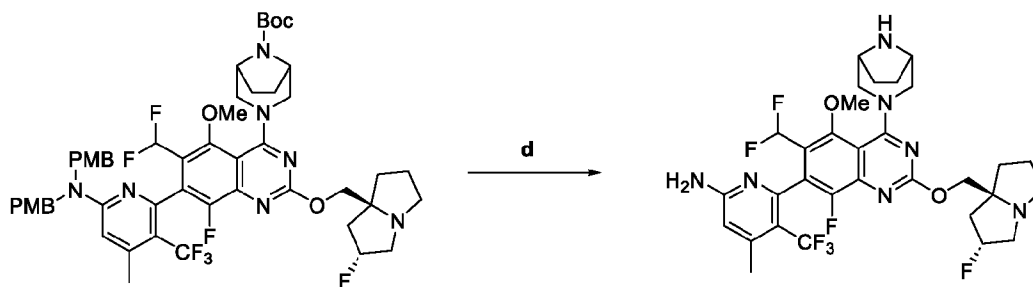
6-(difluoromethyl)-8-fluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (48 mg, 46.9%) as a yellow solid. LCMS: 444.0 ($M/2+H^+$).

Step 3: Synthesis of tert-butyl 3-(7-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-6-(difluoromethyl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00664] To a solution of compound tert-butyl 3-(7-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-2-chloro-6-(difluoromethyl)-8-fluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (40 mg, 0.045 mmol, 1.0 eq) in DMF (1 mL) and THF (1 mL) was added compound ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (8.6 mg, 0.054 mmol, 1.2 eq), CS_2CO_3 (44 mg, 0.14 mmol, 3.0 eq) and DABCO (5 mg, 0.045 mmol, 1.0 eq). The mixture was stirred at room temperature for 15 h. The reaction mixture was quenched with water (10 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with H_2O (10 mL), brine (10 mL), dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by silica gel column chromatography (Dichloromethane: Methanol = 60: 1) to give compound tert-butyl 3-(7-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-6-(difluoromethyl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (27 mg, 59.3%) as a yellow solid. LCMS: 505.8 ($M/2+H^+$).

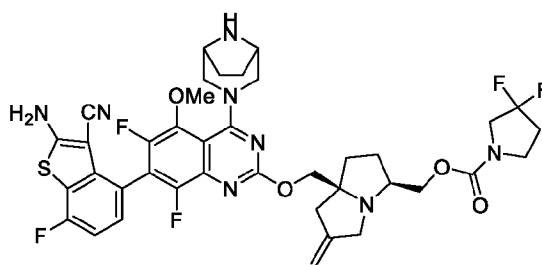
Step 4 Synthesis of 6-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(difluoromethyl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine 2,2,2-trifluoroacetate (1:1)



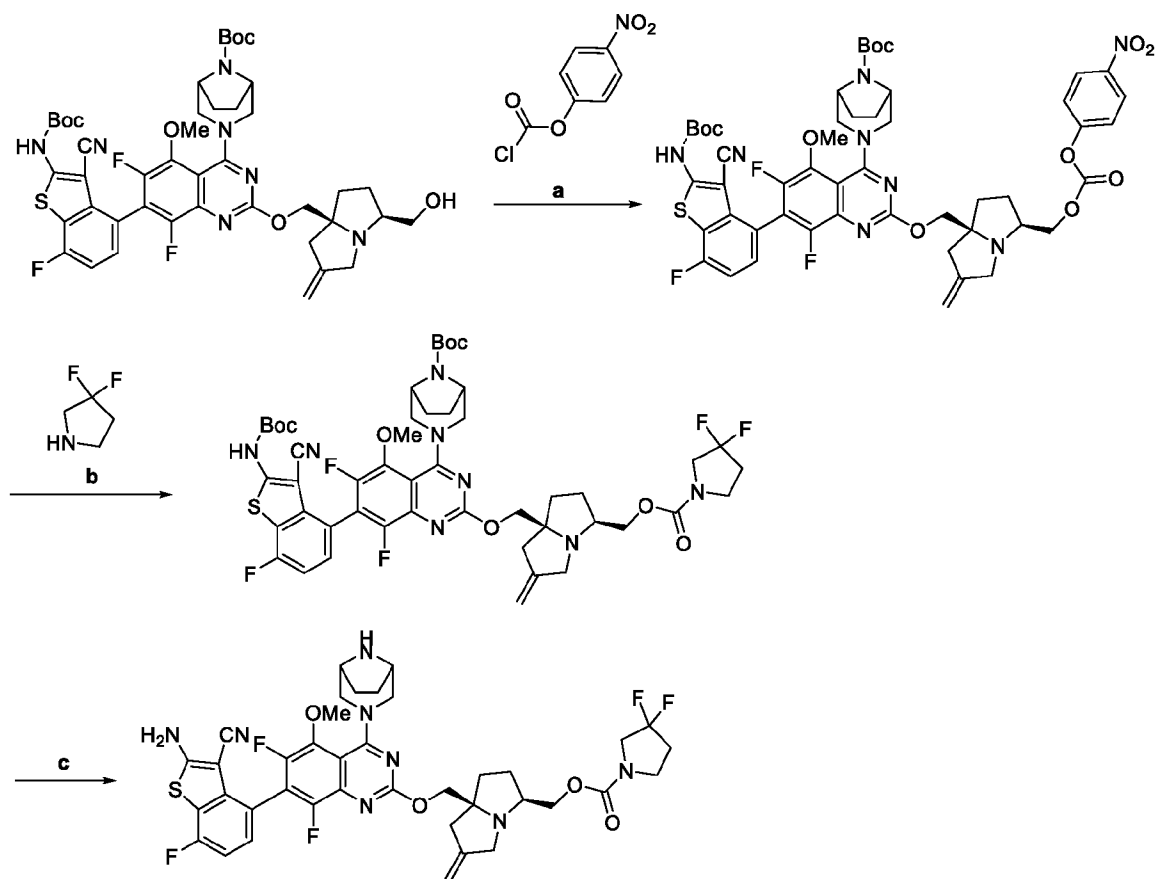
[00665] A solution of tert-butyl 3-(7-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-6-(difluoromethyl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (40 mg, 0.04 mmol, 1.0 eq) in TFA (1 mL) was stirred at 50 °C for 4 h. The mixture was concentrated to give a residue. The residue was purified by Prep-HPLC (acetonitrile with 0.1% FA in water, 10% to 60%) to give 6-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(difluoromethyl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine 2,2,2-trifluoroacetate (1:1) (12.2 mg, 39.3%) as a white solid. ¹H NMR (400 MHz, CD₃OD): δ 6.85 (t, *J*=53.6 Hz, 1H), 6.59 (s, 1H), 5.43 (d, *J*=52.8 Hz, 1H), 4.53 – 4.40 (m, 2H), 4.02 – 3.86 (m, 2H), 3.75 (s, 3H), 3.70 – 3.61 (m, 2H), 3.61 – 3.46 (m, 3H), 3.45 – 3.31 (m, 1H), 3.27 – 3.11 (m, 2H), 2.62 – 2.47 (m, 1H), 2.44 (s, 3H), 2.41 – 2.34 (m, 1H), 2.34 – 2.24 (m, 1H), 2.23 – 2.09 (m, 2H), 2.09 – 1.73 (m, 5H). ¹⁹F NMR (300 MHz, CD₃OD): δ -56.099, -76.927, -111.275, -134.677, -173.909. LCMS: 670.2 (M+H⁺).

Example 83

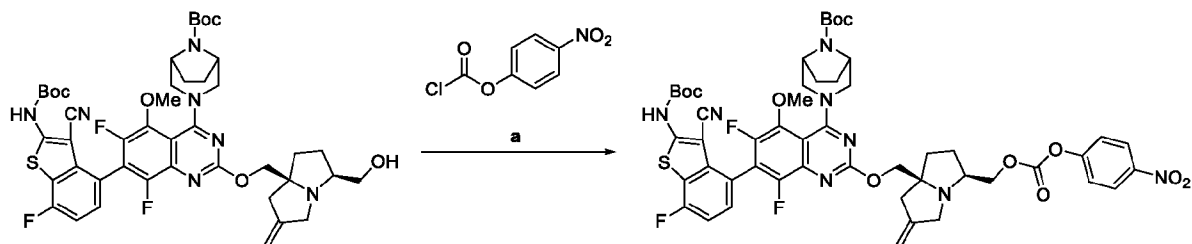
((3S,7aS)-7a-(((7-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-5-methoxyquinazolin-2-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 3,3-difluoropyrrolidine-1-carboxylate formate



Synthetic scheme:



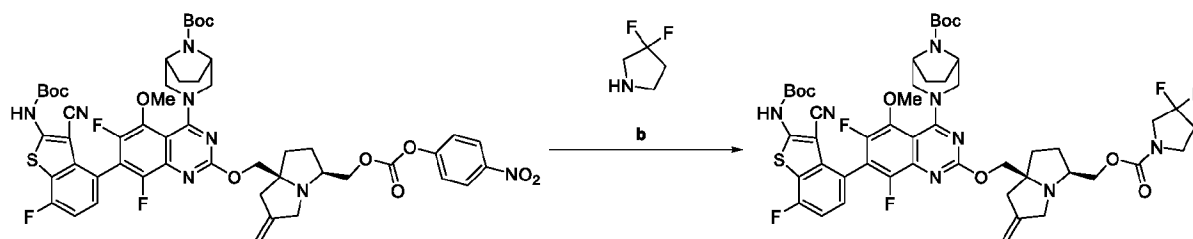
Step 1: Synthesis of tert-butyl 3-(7-(2-(((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6,8-difluoro-5-methoxy-2-(((5S,7aS)-2-methylene-5-(((4-nitrophenoxy)carbonyl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00666] To a solution of tert-butyl 3-(7-(2-(((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6,8-difluoro-2-(((5S,7aS)-5-(hydroxymethyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (40 mg, 0.04 mmol, 1.0 eq) in THF (1.5 mL) was added

4-nitrophenyl carbonochloridate (40 mg, 0.20 mmol, 5.0 eq) and TEA (24 mg, 0.24 mmol, 6.0 eq). The reaction mixture was stirred at 50 °C for 5 h under N₂. The reaction mixture was concentrated to give tert-butyl 3-(7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6,8-difluoro-5-methoxy-2-(((5S,7aS)-2-methylene-5-(((4-nitrophenoxy)carbonyl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (50 mg, crude) as a yellow oil.

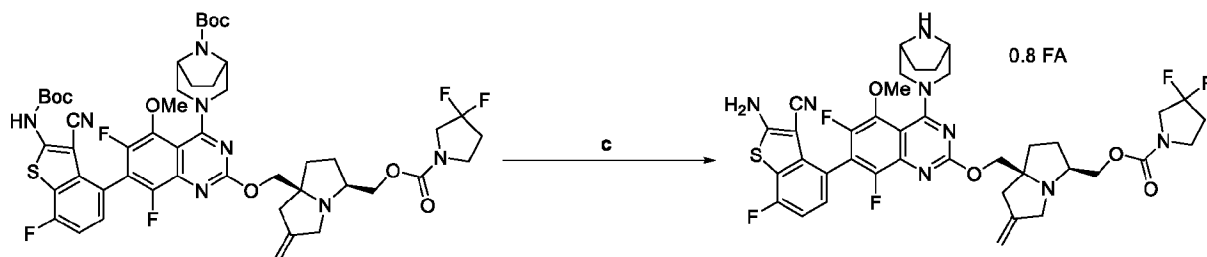
Step 2: Synthesis of tert-butyl 3-(7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-(((5S,7aS)-5-(((3,3-difluoropyrrolidine-1-carbonyl)oxy)methyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00667] To a solution of tert-butyl 3-(7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6,8-difluoro-5-methoxy-2-(((5S,7aS)-2-methylene-5-(((4-nitrophenoxy)carbonyl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (50 mg, 0.04 mmol, 1.0 eq) in THF (1.5 mL) was added 3,3-difluoropyrrolidine (25 mg, 0.24 mmol, 6.0 eq) and TEA (24 mg, 0.24 mmol, 6.0 eq). The reaction mixture was stirred at room temperature for 2 h under N₂. The reaction was quenched with H₂O (5 mL). The resulting mixture was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄ and concentrated to give a crude product. The crude was purified by Prep-TLC (DCM / MeOH = 10 / 1) to give tert-butyl 3-(7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-(((5S,7aS)-5-(((3,3-difluoropyrrolidine-1-carbonyl)oxy)methyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (12 mg, 26.1%, two steps yield) as a yellow solid. LCMS: 505.8 (M/2+H⁺).

Step 3: Synthesis of ((3S,7aS)-7a-(((7-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-5-methoxyquinazolin-2-yl)oxy)methyl)-6-

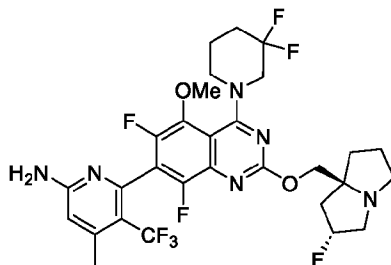
methylenehexahydro-1H-pyrrolizin-3-yl)methyl 3,3-difluoropyrrolidine-1-carboxylate formate (1:0.8)



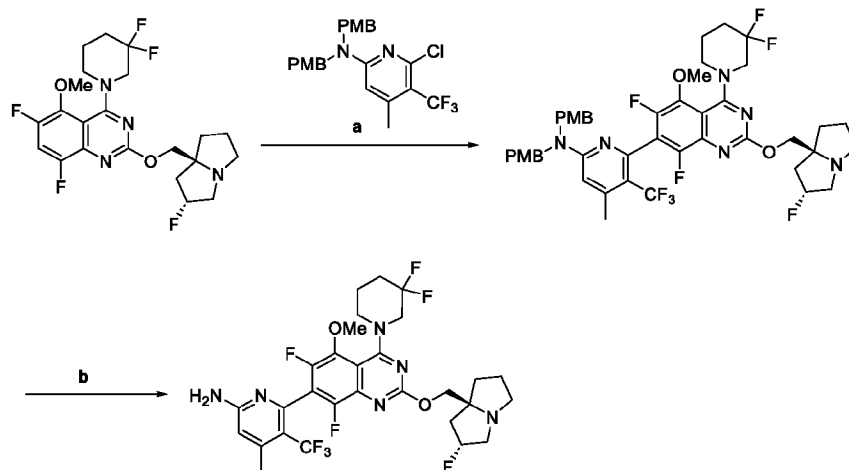
[00668] To a solution of tert-butyl 3-(7-(2-(((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-(((5S,7aS)-5-(((3,3-difluoropyrrolidine-1-carbonyl)oxy)methyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (12 mg, 0.01 mmol, 1.0 eq) in DCM (1.0 mL) was added TFA (0.3 mL). The reaction mixture was stirred at 40 °C for 2 h under N₂. The mixture was concentrated to give a crude. The crude was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 10% to 50%) to give ((3S,7aS)-7a-(((7-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-4-(3,8 diazabicyclo[3.2.1]octan-3-yl)-6,8-difluoro-5-methoxyquinazolin-2-yl)oxy) methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 3,3-difluoropyrrolidine-1-carboxylate formate (1:0.8) (4.6 mg, 47.9%) as a white solid. ¹H NMR (400 MHz, CD₃OD) δ 8.51 (brs, 1H), 7.30 – 7.28 (m, 1H), 7.04 (t, *J* = 8.8 Hz, 1H), 4.94 (s, 2H), 4.39 – 4.23 (m, 3H), 4.19 – 4.09 (m, 2H), 4.02 – 3.98 (m, 1H), 3.89 (s, 3H), 3.85 (s, 2H), 3.78 – 3.65 (m, 4H), 3.62 – 3.52 (m, 3H), 3.44 – 3.38 (m, 2H), 3.13 – 3.08 (m, 1H), 2.70 (d, *J* = 15.6 Hz, 1H), 2.41 (d, *J* = 15.6 Hz, 2H), 2.31 – 2.22 (m, 1H), 2.12 – 2.03 (m, 1H), 2.01 – 1.90 (s, 4H), 1.88 – 1.75 (m, 2H). ¹⁹F NMR (400 MHz, CD₃OD): δ -103.694, -118.368, -132.558, -138.794. LCMS: 811.2 (M+H⁺).

Example 84

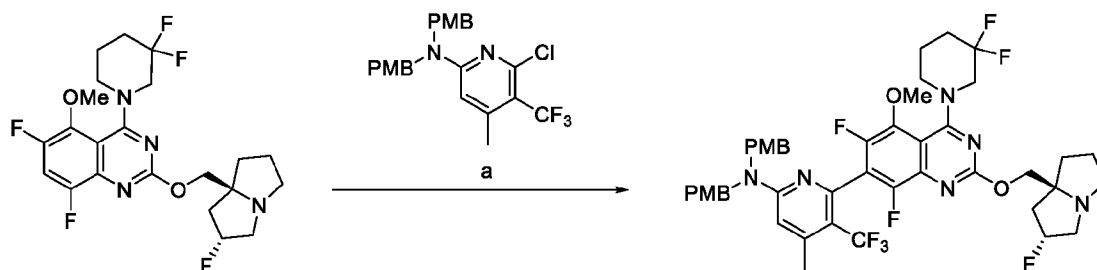
6-(4-(3,3-difluoropiperidin-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine 2,2,2-trifluoroacetate



Synthetic scheme:



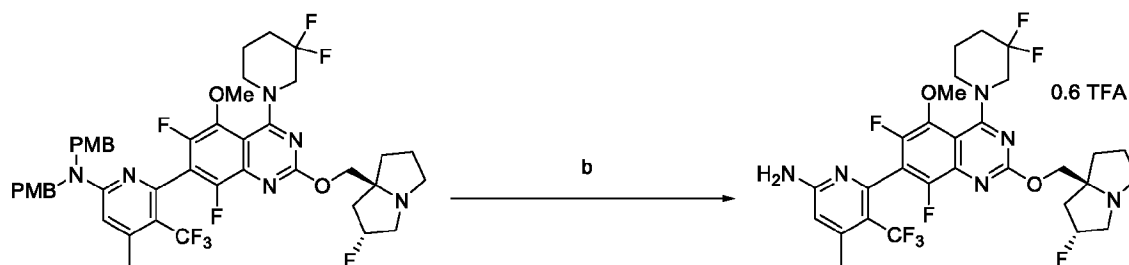
Step 1: Synthesis of 6-(4-(3,3-difluoropiperidin-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-N,N-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine



[00669] To a solution of 4-(3,3-difluoropiperidin-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline (60 mg, 0.13 mmol, 1.0 eq) in THF (2 mL) was added (TMP)₂Zn·MgCl₂·LiCl (0.4 M in THF) (1.9 mL, 0.76 mmol, 6.0 eq) dropwise. The reaction mixture was stirred at 50 °C for 2 h under N₂ atmosphere. To the mixture was added a solution of 6-chloro-N,N-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (69 mg, 0.15 mmol, 1.2 eq) and CPhos Pd G4 (10 mg, 0.012

mmol, 0.1 eq) in dioxane (2 mL). The reaction mixture was stirred at 80 °C for 12 h. The mixture was filtered and the filtrate was concentrated to give a residue. The residue was purified by silica gel column chromatography (DCM: MeOH = 15: 1) to give 6-(4-(3,3-difluoropiperidin-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-N,N-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (50 mg, 44.2%) as a yellow solid. LCMS: m/z 887.3 ($M+H^+$).

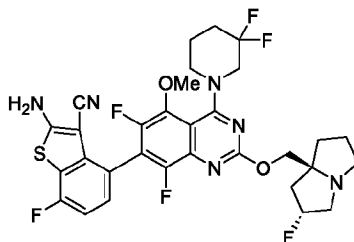
Step 2: Synthesis of 6-(4-(3,3-difluoropiperidin-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine 2,2,2-trifluoroacetate



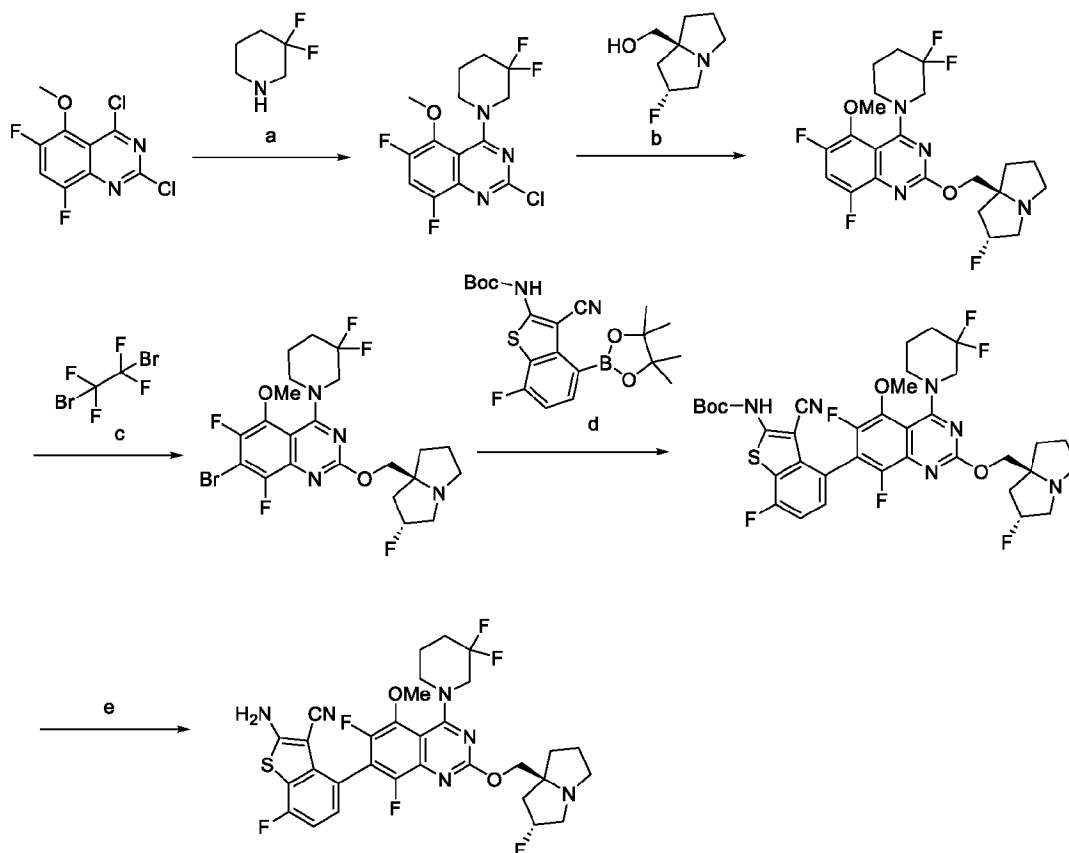
[00670] To a solution of 6-(4-(3,3-difluoropiperidin-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-N,N-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (50 mg, 0.056 mmol, 1.0 eq) in DCM (1 mL) was added TFA (0.2 mL) at 0 °C. The reaction mixture was stirred at 50 °C for 2 h under N_2 atmosphere. The mixture was concentrated to give a crude. The crude was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 10% to 50%) to give 6-(4-(3,3-difluoropiperidin-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine 2,2,2-trifluoroacetate (1:0.6) (13 mg, 30.3%) as a white solid. ^1H NMR (300 MHz, CD_3OD): δ 6.61 (s, 1H), 5.49 (d, J = 52.2 Hz, 1H), 4.65 – 4.45 (m, 2H), 3.98 – 3.56 (m, 10H), 2.74 – 1.94 (m, 14H). ^{19}F NMR (300 MHz, CD_3OD): δ -56.392, -76.941, -102.042, -134.245, -139.041, -174.089. LCMS: m/z 647.2 ($M+H^+$).

Example 85

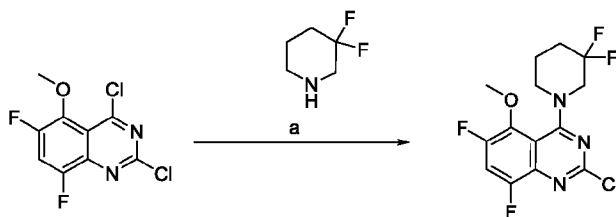
2-Amino-4-(4-(3,3-difluoropiperidin-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile 2,2,2-trifluoroacetate



Synthesis scheme



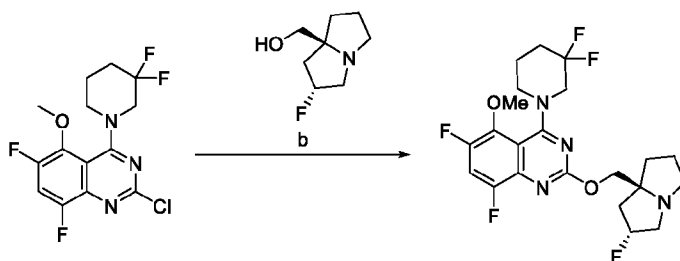
Step 1: Synthesis of 2-chloro-4-(3,3-difluoropiperidin-1-yl)-6,8-difluoro-5-methoxyquinazoline



[00671] To a solution of 2,4-dichloro-6,8-difluoro-5-methoxyquinazoline (600 mg, 2.2 mmol, 1.0 eq) and DIEA (851 mg, 6.6 mmol, 3.0 eq) in DCM (6 mL) was added 3,3-difluoropiperidine (338 mg, 2.8 mmol, 1.3 eq) at -40 °C. The reaction mixture was stirred at -40 °C for 2 h under

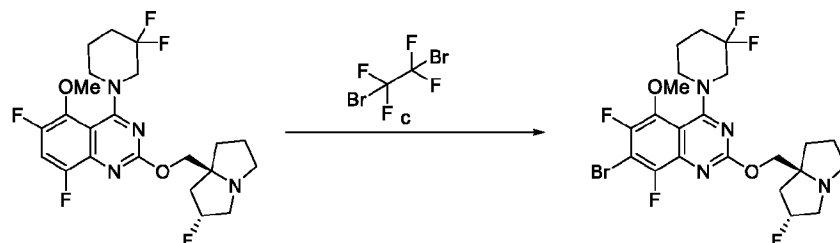
nitrogen atmosphere. The mixture was concentrated to give a residue. The residue was partitioned between DCM (10 mL) and water (5 mL). The layers were separated. The aqueous layer was extracted with DCM (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by prep-TLC (Petroleum ether: EtOAc = 15: 1) to give 2-chloro-4-(3,3-difluoropiperidin-1-yl)-6,8-difluoro-5-methoxyquinazoline (710 mg, 89.1%) as a yellow solid. LCMS: m/z 350.1 (M+H⁺).

Step 2: Synthesis of 4-(3,3-difluoropiperidin-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline



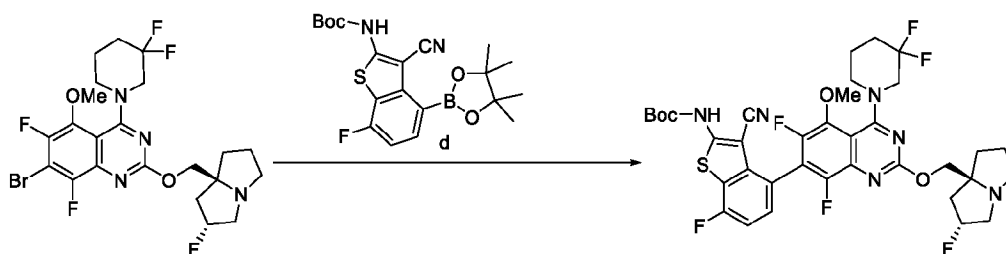
[00672] To a solution of 2-chloro-4-(3,3-difluoropiperidin-1-yl)-6,8-difluoro-5-methoxyquinazoline (710 mg, 2.0 mmol, 1.0 eq) in THF (5 mL) and DMF (5 mL) was added ((2R)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl) methanol (381 mg, 2.4 mmol, 1.2 eq), DABCO (224 mg, 2.0 mmol, 1.0 eq) and Cs₂CO₃ (1.9 g, 6.0 mmol, 3.0 eq). The reaction mixture was stirred at room temperature for 15 h under nitrogen atmosphere. The mixture was added H₂O (10 mL). The resulting mixture was extracted with EtOAc (15 mL x 3). The combined organic layers were washed with H₂O (10 mL x 3), brine (10 mL), dried over Na₂SO₄ and evaporated to dryness. The crude was purified by Prep-TLC (DCM: MeOH = 10: 1) to give 4-(3,3-difluoropiperidin-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline (870 mg, 90.6%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 7.27 (t, *J* = 10.0 Hz, 1H), 5.26 (d, *J* = 53.2 Hz, 1H), 4.24 (d, *J* = 10.0 Hz, 1H), 4.14 (d, *J* = 10.4 Hz, 1H), 3.90 – 3.74 (m, 5H), 3.42 (s, 2H), 3.29 – 3.21 (m, 2H), 3.20 – 3.12 (m, 1H), 2.99 – 2.93 (m, 1H), 2.26 (d, *J* = 4.0 Hz, 1H), 2.20 – 1.85 (m, 9H). LCMS: m/z 473.2 (M+H⁺).

Step 3: Synthesis of 7-bromo-4-(3,3-difluoropiperidin-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline



[00673] To a solution of 4-(3,3-difluoropiperidin-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline (460 mg, 0.97 mmol, 1.0 eq) in THF (5 mL) was added LDA (1.0 mL, 1.9 mmol, 2.0 eq) at -65 °C under N₂ atmosphere. The mixture was stirred at -65 °C for 30 min. The mixture was added 1,2-dibromo-1,1,2,2-tetrafluoroethane (373 mg, 1.4 mmol, 1.5 eq) at the same temperature, and stirred for 2.5 h. The reaction was quenched with water (5 mL). The mixture was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄ and evaporated to dryness. The reaction was repeated for two times. The crude product was purified by prep-TLC (DCM: MeOH = 12: 1) to give 7-bromo-4-(3,3-difluoropiperidin-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline (450 mg, 83.9%) as a yellow solid. LCMS: m/z 551.1, 553.1 (M+H⁺).

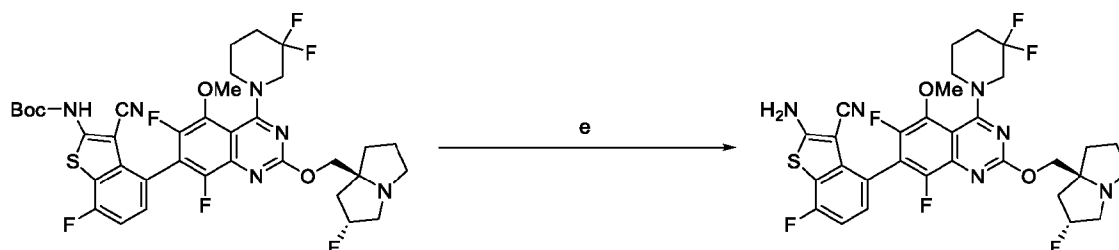
Step 4: Synthesis of tert-butyl (3-cyano-4-(4-(3,3-difluoropiperidin-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate



[00674] A solution of 7-bromo-4-(3,3-difluoropiperidin-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazoline (50 mg, 0.09 mmol, 1.0 eq), tert-butyl (3-cyano-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophen-2-yl)carbamate (56 mg, 0.13 mmol, 1.5 eq), K₃PO₄ (57 mg, 0.27 mmol, 3.0 eq) and Pd₂(dppf)Cl₂·DCM (8 mg, 0.01 mmol, 0.15 eq) in dioxane (2 mL) and H₂O (0.4 mL) was stirred at 110 °C for 1 h by microwave under nitrogen atmosphere. The mixture was concentrated to give the crude product. The crude product was purified by Prep-TLC (DCM:

MeOH = 12: 1) to give tert-butyl (3-cyano-4-(4-(3,3-difluoropiperidin-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate (20 mg, 28.9%) as a white solid. LCMS: m/z 763.2 ($M+H^+$).

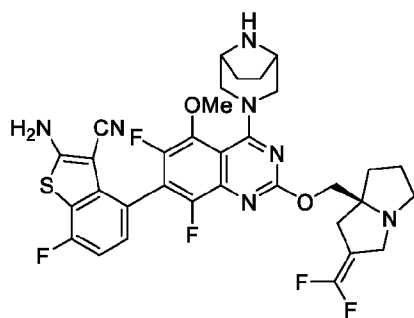
Step 5: Synthesis of 2-amino-4-(4-(3,3-difluoropiperidin-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile 2,2,2-trifluoroacetate (1:1)



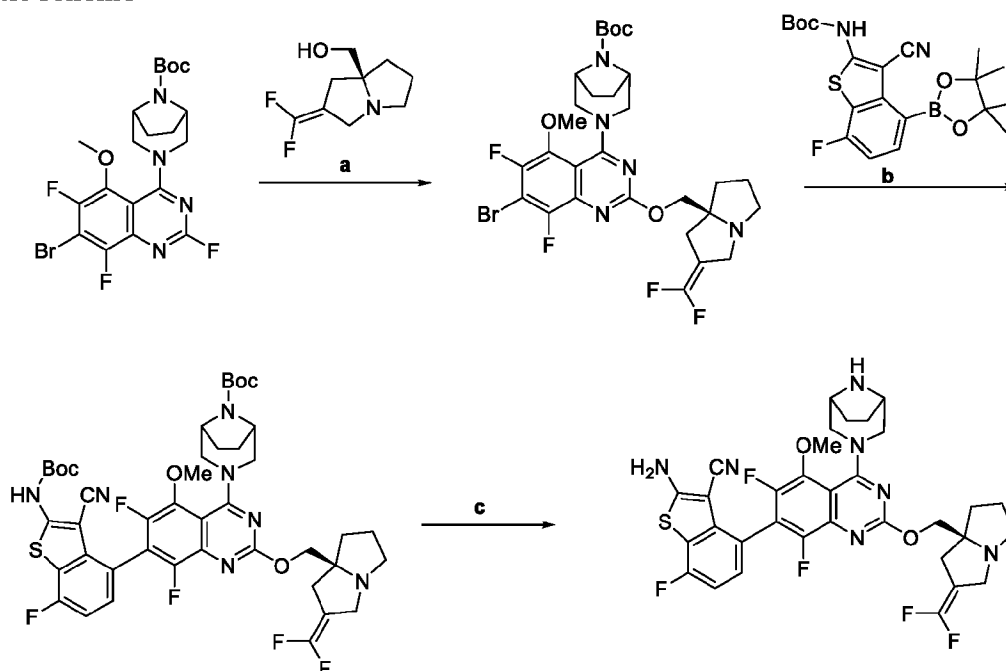
[00675] To a solution of tert-butyl (3-cyano-4-(4-(3,3-difluoropiperidin-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate (20 mg, 0.027 mmol, 1.0 eq) in DCM (1 mL) was added TFA (0.3 mL). The reaction mixture was stirred at 40 °C for 2 h under N_2 atmosphere. The mixture was concentrated to give a crude. The crude was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 10% to 50%) to give 2-amino-4-(4-(3,3-difluoropiperidin-1-yl)-6,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxyquinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile 2,2,2-trifluoroacetate (1:1) (1.8 mg, 8.8%) as a white solid. ^1H NMR (400 MHz, CD_3OD): δ 7.31 (dd, J = 8.4, 5.2 Hz, 1H), 7.06 (t, J = 8.8 Hz, 1H), 5.55 (d, J = 51.6 Hz, 1H), 4.69 – 4.50 (m, 6H), 3.99 – 3.81 (m, 6H), 3.52 – 3.45 (m, 1H), 2.80 – 1.95 (m, 10H). ^{19}F NMR (400 MHz, CD_3OD): δ -76.932, -101.334 (d, J_{F-F} = 256.8 Hz, 1F), -102.781 (d, J_{F-F} = 256.4 Hz, 1F), -118.018, -132.716, -136.502, -174.267. LCMS: m/z 663.2 ($M+H^+$).

Example 86

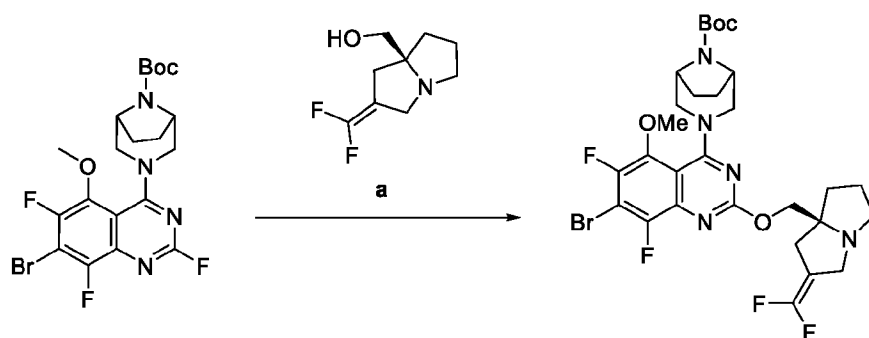
4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6,8-difluoro-5-methoxyquinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile



Synthetic scheme



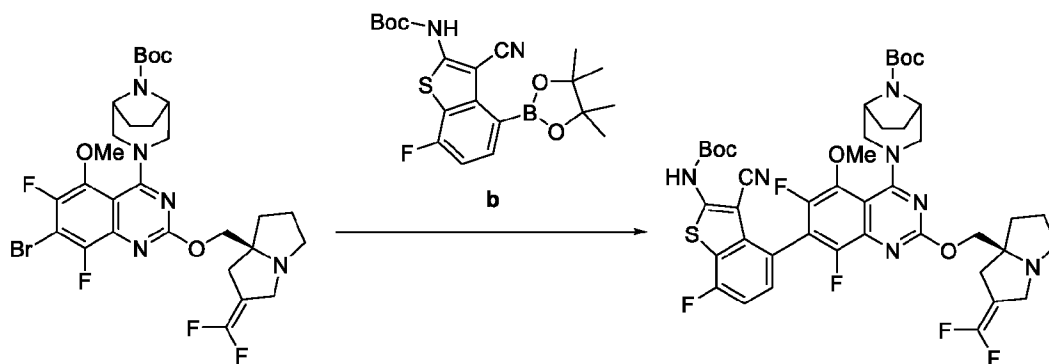
Step 1: Synthesis of tert-butyl 3-(7-bromo-2-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00676] To a solution of compound tert-butyl 3-(7-bromo-2,6,8-trifluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (150 mg, 0.30 mmol, 1.0

eq) in DMF (1.5 mL) and THF (1.5 mL) was added compound (S)-(2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (51 mg, 0.30 mmol, 0.9 eq), Cs₂CO₃ (292 mg, 0.90 mmol, 3.0 eq) and DABCO (34 mg, 0.30 mmol, 1.0 eq). The mixture was stirred at room temperature for 15 h. The reaction mixture was quenched with water (20 mL). The aqueous layer was extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with H₂O (20 mL), brine (20 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by Prep-TLC (Dichloromethane: Methanol = 15 : 1) to give compound tert-butyl 3-(7-bromo-2-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (78 mg, 38.9%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 4.33 – 4.07 (m, 5H), 3.81 (s, 3H), 3.49 – 3.32 (m, 3H), 3.26 – 3.11 (m, 1H), 2.86 – 2.75 (m, 1H), 2.71 – 2.58 (m, 1H), 2.45 – 2.34 (m, 1H), 2.21 – 2.11 (m, 1H), 1.98 – 1.88 (m, 2H), 1.88 – 1.77 (m, 3H), 1.74 – 1.60 (m, 4H), 1.49 (s, 9H). LCMS: 672.2, 674.2 (M+H⁺).

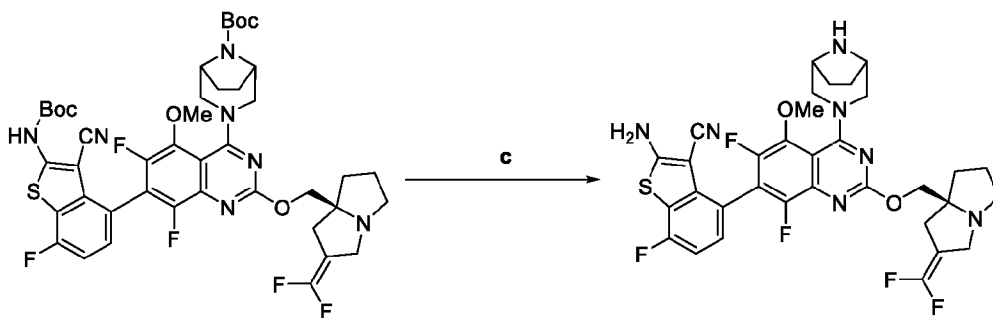
Step 2: Synthesis of tert-butyl 3-(7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00677] To a solution of compound tert-butyl 3-(7-bromo-2-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (78 mg, 0.12 mmol, 1.0 eq) in dioxane (3.0 mL) and H₂O (1.0 mL) was added compound tert-butyl (3-cyano-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophen-2-yl)carbamate (58 mg, 0.14 mmol, 1.2 eq), K₃PO₄ (49 mg, 0.23 mmol, 2.0 eq) and Pd(dtbpf)Cl₂ (8 mg, 0.01 mmol, 0.1 eq). The mixture was stirred at 90 °C for 3 h. The reaction mixture was quenched with water (20 mL).

The aqueous layer was extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with H₂O (20 mL), brine (20 mL), dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by Prep-TLC (Dichloromethane : Methanol = 15 : 1) to give compound tert-butyl 3-(7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (20 mg, 19.5%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 7.77 (brs, 1H), 7.46 – 7.35 (m, 1H), 7.16 (t, *J* = 8.0 Hz, 1H), 4.34 – 4.19 (m, 3H), 3.86 (s, 3H), 3.83 – 3.71 (m, 1H), 3.55 – 3.42 (m, 2H), 3.41 – 3.31 (m, 1H), 3.27 – 3.11 (m, 1H), 2.91 – 2.78 (m, 1H), 2.70 – 2.60 (m, 1H), 2.46 – 2.35 (m, 1H), 2.26 – 2.15 (m, 1H), 1.99 – 1.89 (m, 2H), 1.88 – 1.78 (m, 3H), 1.77 – 1.59 (m, 4H), 1.56 (s, 9H), 1.50 (s, 9H). LCMS: 442.7 (M/2+H⁺).

Step 3: Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6,8-difluoro-5-methoxyquinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile



[00678] A solution of tert-butyl 3-(7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6,8-difluoro-5-methoxyquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (23 mg, 0.03 mmol, 1.0 eq) in TFA (1.0 mL) and DCM (1.0 mL) was stirred at room temperature for 0.5 h. The mixture was concentrated to give a residue. The residue was purified by Prep-TLC (Dichloromethane : 0.1% NH₄OH in methanol = 5 : 1) to give 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6,8-difluoro-5-methoxyquinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile (8.9 mg, 50.0%) as a white solid. ¹H NMR (400 MHz, CD₃OD): δ 8.74 – 8.60 (m, 1H), 8.40 (t, *J* = 9.2 Hz, 1H), 5.60 – 5.36 (m, 3H), 5.23 – 5.08 (m, 4H), 5.06 – 4.93 (m, 2H), 4.68

– 4.56 (m, 1H), 4.40 – 4.30 (m, 1H), 4.06 – 3.97 (m, 1H), 3.96 – 3.88 (m, 1H), 3.76 – 3.64 (m, 1H), 3.43 – 3.34 (m, 3H), 3.25 – 3.01 (m, 6H), 2.66 – 2.48 (m, 2H). LCMS: 684.2 (M+H⁺).

Biological binding assays:

KRAS/SOS1-RAF1 HTRF binding assay

[00679] The test compounds were prepared as 10mM stock solution in 100% DMSO. The stock solution was then serially diluted 3-fold in 100% DMSO to 10 concentrations. 200nL of each diluted compound solution was transferred to 384-well plate in duplicate. To each well, 5 μ L of 10nM enzyme solution containing Biotin-KRAS G12D or WT protein with final concentration of 2.5 nM in the assay buffer (50mM HEPES, pH7.5, 50mM NaCl, 5mM MgCl₂, 1mM DTT, 0.1% BSA, 0.01% Triton X-100). For negative control, 5 μ L of assay buffer was added instead. The plate was incubated at room temperature for 20 min. 5 μ L of SOS1 and GTP (final concentration at 100 nM and 10 μ M, respectively) were subsequently added to each well to initiate the nucleotide exchange. After incubation at room temperature for 2 hours, 5 μ L of GST-RAF1 (final concentration at 8 nM) was added. All reactions were incubated at room temperature for 20 min and then 5 μ L of 1x anti-GST-XL665 and 1x Streptavidin-Tb were added for detection. After one-hour incubation at room temperature, all samples were subjected to read the TR-FRET signal on Envision with excitation at 340 nm and emission fluorescence at 615 nm and 665 nm. IC₅₀ values were then calculated by plotting dose-response curves and then using the XLfit application in Excel software.

KRAS(GMPPNP)-RAF1 HTRF binding assay

[00680] The test compounds were prepared as 10mM stock solution in 100% DMSO. The stock solution was then serially diluted 3-fold in 100% DMSO to 10 concentrations. 200nL of each diluted compound solution was transferred to 384-well plate in duplicate. To each well, 10 μ L of enzyme solution containing Biotin-KRAS G12D or WT protein with final concentration of 5 nM or 2 nM in the assay buffer (50mM HEPES, pH7.5, 50mM NaCl, 5mM MgCl₂, 1mM DTT, 0.1% BSA, 0.01% Triton X-100), respectively. For negative control, 10 μ L of assay buffer was added instead. The plate was incubated at room temperature for 20 min. 5 μ L of GST-RAF1 (final concentration at 8 nM) was subsequently added to each well. Then 5 μ L of 1x anti-GST-XL665 and 1x Streptavidin-Tb were added for detection. After one-hour incubation at room temperature, all samples were subjected to read the TR-FRET signal on Envision with excitation

at 340nm and emission fluorescence at 615 nm and 665 nm. IC₅₀ values were then calculated by plotting dose-response curves and then using the XLfit application in Excel software.

Table 2: Binding Assay Activities*

Example #	GDP HTRF Biochemical assay IC₅₀ (nm)	GDP HTRF G12D Biochemical assay IC₅₀ (nm)	GMPPNP G12D Biochemical assay IC₅₀ (nm)	GMPPNP WT Biochemical assay IC₅₀ (nm)
1	A	C	C	C
2	A	C	C	C
3	A	B	B	C
4	A	A	B	C
5	A	B	B	C
6	N	N	N	N
7	A	B	B	C
8	A	C	C	C
9	B	C	C	C
10	A	C	C	C
11	A	C	B	C
12	C	C	C	C
13	B	C	C	C
14	A	C	C	C
15	A	B	B	C
16	A	C	C	C
17	A	B	B	C
18	A	A	A	B

19	A	B	B	C
20	A	C	C	C
21	A	A	C	C
22	A	A	C	C
23	A	C	C	C
24	A	A	C	C
25	A	B	C	C
26	A	C	C	C
27	A	C	C	C
28	A	A	A	B
29	A	A	A	B
30	A	A	A	B
31	A	B	B	C
32	A	A	A	A
33	A	A	B	C
34	A	A	A	B
35	A	A	A	C
36	A	A	B	B
37	A	B	B	C
38	A	A	B	B
39	B	C	C	C
40	A	C	C	C

41	A	C	C	C
42	A	C	C	C
43	A	B	C	C
44	A	A	A	B
45	A	B	C	C
46	A	A	B	C
47	A	C	C	C
48	C	C	C	C
49	A	C	C	C
50	A	A	A	A
51	A	C	C	C
52	A	A	C	C
53	A	B	B	C
54	A	B	B	C
55	A	A	C	C
56	A	A	A	B
57	A	B	B	C
58	A	B	C	C
59	A	A	A	B
60	A	C	C	C
61	A	C	C	C
62	A	B	C	C

63	A	A	A	B
64	B	C	C	C
65	A	C	C	C
66	B	A	C	C
67	A	A	C	C
68	A	A	B	C
69	A	B	B	C
70	A	B	C	C
71	N	N	N	N
72	C	C	C	C
73	B	C	C	C
74	C	C	C	C
75	A	A	A	C
76	B	C	C	C
77	A	B	C	C
78	A	A	A	B
79	C	C	C	C
80	C	C	C	C
81	C	C	C	C
82	A	C	C	C
83	A	B	B	C
84	C	C	C	C

85	B	A	C	C

*A: < 100 nM; B: 100 nM – 1 μ M; C: >1 μ M; N: not tested

Cell base assay:

2D CTG proliferation assay

[00681] KRASG^{12D} mutant or WT cells were grown in culture media according to vendors' instructions. Cells were plated in clear bottom tissue culture treated 96-well plates at a density of 1000-2000 cells/well in a volume of 100 μ L and allowed to recover overnight. The edge wells were filled with cell culture media without cells. The plated cells were treated with a 3-fold 9-point serial dilution doses of test compounds, or DMSO control. Compounds were prepared as 10 mM DMSO stock solution and added to the cells with a HP D300 digital dispenser. The top final concentration varied from 10 to 1 μ M depending on the potency of the compounds, with the final concentration of DMSO to be 0.1%. Following 3 days of drug treatment, 100 μ L of Cell Titer-Glo (CTG) (Promega, G7570) reagent was added to the cells using a Multidrop Combi instrument. The plates were placed on an orbital shaker for 10 minutes to induce cell lysis, and further incubated at room temperature for 10 minutes to stabilize luminescent signal. The luminescence signal was read on Envision with a measurement time of 0.1 s.

[00682] Cell proliferation percent inhibition values were calculated using the following equation:

$$\text{Inhibition\%} = [1 - (T120_{\text{compound}} - T120_{\text{blank}}) / (T120_{\text{DMSO}} - T120_{\text{blank}})] \times 100\%.$$

T120_{compound}: the signals from compound-treated wells.

T120_{blank}: the signals from blank wells.

T120_{DMSO}: the signals from 0.5%DMSO-treated wells.

[00683] XLfit software (Fit model: Dose response one site/ ∞) 205 [fit = (A+((B-A)/(1+((C/x)^D))))]) was used for curve fitting and IC50 calculation.

Table 3. Cell Assay Activities

Example #	AGS Cells (nM)	MKN Cells (nM)
1	B	C

2	C	C
3	B	C
4	A	C
5	B	C
6	N	N
7	B	C
8	N	N
9	N	N
10	N	N
11	C	C
12	N	N
13	N	N
14	N	N
15	C	C
16	N	N
17	B	C
18	A	C
19	C	C
20	B	C
21	B	C
22	C	C
23	B	C

24	B	C
25	B	C
26	C	C
27	C	C
28	A	C
29	A	C
30	A	C
31	B	C
32	A	C
33	B	C
34	A	C
35	A	C
36	B	C
37	B	C
38	B	C
39	N	N
40	C	C
41	C	C
42	C	C
43	B	C
44	A	C
45	B	C

46	B	C
47	C	C
48	C	C
49	C	C
50	A	C
51	C	C
52	C	C
53	B	C
54	B	C
55	B	C
56	B	C
57	B	C
58	C	C
59	A	C
60	C	C
61	C	C
62	C	C
63	B	C
64	N	N
65	C	C
66	N	N
67	N	N

68	C	C
69	B	C
70	C	C
71	N	N
72	C	C
73	C	C
74	C	C
75	B	C
76	N	N
77	N	N
78	B	C
79	N	N
80	N	N
81	N	N
82	C	C
83	B	C
84	C	C
85	C	C

*A: < 100 nM; B: 100 nM – 1 uM; C: >1 uM; N: not tested

pERK Assay (Western Blot)

[00684] KRASG^{12D} mutant or WT cells were grown in culture media specified by the vendors. Cells were plated in tissue culture treated 6 well plates at a density of 0.5×10^6 cells/well in 3 mL of culture media and allowed to recover overnight. The plated cells were

treated with a 3-fold 9-point serial dilution doses of test compound, or DMSO. Compounds were prepared as 10 mM DMSO stock solution, and 3 μ L of the diluted compounds were added to the cells, with a final concentration of 0.1% DMSO. Following 3 hours of drug treatment, cells were lysed on the plate by adding 100 μ L of lysis buffer containing protease inhibitor and phosphatase inhibitor. Cells were scraped and transferred to 1.5 mL microcentrifuge tubes. Cell lysates were centrifuged at 13,000 x g for 15 minutes at 4°C. The protein concentrations were determined using the BCA kit. All sample supernatants were transferred to Eppendorf tubes and stored at -80 °C.

[00685] For Western blot, 15-20 μ g of protein was loaded into each well. Following electrophoresis, proteins were transferred to a filter membrane. The membrane was incubated in blocking buffer (LI-COR) for an hour at room temperature with rocking and was incubated overnight at 4 °C in primary antibodies diluted at 1:1000. On the second day, the primary antibodies were removed, and the membrane was washed 3 x 10 minutes in TBST and incubated in secondary antibodies for 45 min at room temperature. The membrane was washed again and imaged using ODYSSEY (LI-COR) to measure the signal intensity from the IRDye 800CW goat anti-mouse secondary antibodies (LICOR). The data was analyzed for the intensity of each protein band, including total ERK, and phosphorylated ERK (pERK).

[00686] The percentage of pERK was determined by dividing the signal output of pERK by the signal output of total ERK. Percent inhibition of phosphorylation of ERK in compound-treated samples compared to vehicle-treated control samples was determined by subtracting compound-treated pERK signal from vehicle-treated pERK signal then dividing by the vehicle-treated pERK signal and multiplying by 100.

[00687] Although the present invention has been described in detail with preferred embodiments, those of ordinary skill in the art should understand that modifications, variations, and equivalent replacements made to the present invention within the scope of the present invention belong to the protection of the present invention.

[00688] Applicant's disclosure is described herein in preferred embodiments with reference to the Figures, in which like numbers represent the same or similar elements. Reference throughout this specification to "one embodiment," "an embodiment," or similar language means that a particular feature, structure, or characteristic described in connection with the embodiment is

included in at least one embodiment of the present invention. Thus, appearances of the phrases “in one embodiment,” “in an embodiment,” and similar language throughout this specification may, but do not necessarily, all refer to the same embodiment.

[00689] The described features, structures, or characteristics of Applicant’s disclosure may be combined in any suitable manner in one or more embodiments. In the description, herein, numerous specific details are recited to provide a thorough understanding of embodiments of the invention. One skilled in the relevant art will recognize, however, that Applicant’s composition and/or method may be practiced without one or more of the specific details, or with other methods, components, materials, and so forth. In other instances, well-known structures, materials, or operations are not shown or described in detail to avoid obscuring aspects of the disclosure.

[00690] In this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural reference, unless the context clearly dictates otherwise.

[00691] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present disclosure, the preferred methods and materials are now described. Methods recited herein may be carried out in any order that is logically possible, in addition to a particular order disclosed.

Incorporation by Reference

[00692] References and citations to other documents, such as patents, patent applications, patent publications, journals, books, papers, web contents, have been made in this disclosure. All such documents are hereby incorporated herein by reference in their entirety for all purposes. Any material, or portion thereof, that is said to be incorporated by reference herein, but which conflicts with existing definitions, statements, or other disclosure material explicitly set forth herein is only incorporated to the extent that no conflict arises between that incorporated material and the present disclosure material. In the event of a conflict, the conflict is to be resolved in favor of the present disclosure as the preferred disclosure.

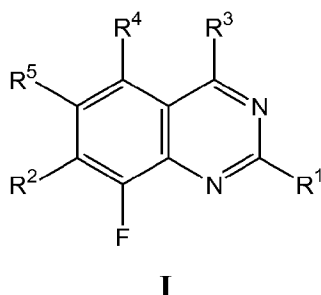
Equivalents

[00693] The representative examples are intended to help illustrate the invention, and are not intended to, nor should they be construed to, limit the scope of the invention. Indeed, various modifications of the invention and many further embodiments thereof, in addition to those shown and described herein, will become apparent to those skilled in the art from the full contents of this document, including the examples and the references to the scientific and patent literature included herein. The examples contain important additional information, exemplification and guidance that can be adapted to the practice of this invention in its various embodiments and equivalents thereof.

What is claimed is:

CLAIMS

1. A compound having the structural Formula I:



or a pharmaceutically acceptable form or an isotope derivative thereof,
wherein

R^1 is XR^{11} or $NR^{12}R^{13}$, wherein X is O, S or absent, R^{11} is $(CH_2)_iR^{14}$, and i is an integer selected from 0-6, wherein $(CH_2)_i$ is optionally substituted;

R^2 is an unsubstituted or substituted 6- to 10-membered unsaturated monocyclic or bicyclic ring, comprising 0-5 heteroatoms selected from N, O and S;

R^3 is $L-R^{3'}$, wherein

L is a single bond or $NR(CH_2)_k$, wherein k is an integer selected from 0-3;

and

$R^{3'}$ is an unsubstituted or substituted, 3- to 10-membered saturated or unsaturated monocyclic, bicyclic or bridged ring moiety that comprises 0-5 heteroatoms selected from N, O and S;

each of R^4 and R^5 is independently selected from the group consisting of H, halogen, CN, OH, unsubstituted or substituted C_{1-4} alkyl, unsubstituted or substituted C_{1-4} alkoxy, NO_2 , NRR' , $C(O)NRR'$, $NRC(O)R''$, $C(O)R''$, $OC(O)R''$, $C(O)OR$, unsubstituted or substituted 3- to 8-membered carbocycle, and unsubstituted or substituted 3- to 8-membered heterocycle, *provided that* (a) R^4 and R^5 are not H at the same time, and (b) where R^4 is H, R^5 is an unsubstituted or substituted 3- to 8-membered carbocycle, or unsubstituted or substituted 3- to 8-membered heterocycle;

each of R^{12} and R^{13} is independently selected from the group consisting of H, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted carbocyclic ring, and unsubstituted or substituted heterocyclic ring; or R^{12} and R^{13} , together with the N atom they are bound to, are joined to form an unsubstituted or substituted heterocyclic or heteroaryl ring;

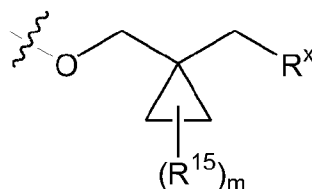
R^{14} is selected from the group consisting of H, halogen, CN, OH, NO_2 , unsubstituted or substituted C_{1-6} alkyl, NRR' , $C(O)NRR'$, $NRC(O)R''$, SO_2NRR' , $NR-SO_2R'$, $NRC(O)NRR'$, $C(O)CH_2$ -aryl, $C(O)OCH_2$ -aryl, $NRC(O)OCH_2$ -phenyl, $C(O)R''$, $OC(O)R''$, $C(O)OR$, unsubstituted or substituted 3- to 6-membered carbocyclic ring, unsubstituted or substituted 4- to 6-membered heterocyclic ring; unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl; and

each of R and R' is independently selected from H, unsubstituted or substituted C_{1-4} alkyl, or unsubstituted or substituted 4- to 6-membered carbocyclic ring, or where R and R' are attached to the same N atom, together form an unsubstituted or substituted 4- to 6-membered heterocyclic ring; and

R'' is H, unsubstituted or substituted C_{1-4} alkoxy, unsubstituted or substituted C_{1-4} alkyl, or unsubstituted or substituted 4- to 6-membered carbocyclic ring.

2. The compound of claim 1, wherein at least one of R^4 and R^5 is not H.
3. The compound of claim 2, wherein neither R^4 nor R^5 is H.
4. The compound of any one of claims 1-3, wherein R^4 is halogen, CN, OH, unsubstituted or substituted C_{1-4} alkyl, unsubstituted or substituted C_{1-4} alkoxy, NO_2 , NRR' , $C(O)NRR'$, $NRC(O)R''$, $C(O)R''$, $OC(O)R''$ or $C(O)OR$.
5. The compound of claim any one of 1-5, wherein R^5 is halogen, CN, OH, unsubstituted or substituted C_{1-4} alkyl, unsubstituted or substituted C_{1-4} alkoxy, NO_2 , NRR' , $C(O)NRR'$, $NRC(O)R''$, $C(O)R''$, $OC(O)R''$ or $C(O)OR$.
6. The compound of any one of claims 1-5, wherein R^5 is an unsubstituted or substituted 3- to 8-membered carbocycle.
7. The compound of any one of claims 1-5, wherein R^5 is an unsubstituted or substituted 3- to 8-membered heterocycle.
8. The compound of claim 1, wherein R^4 is H and R^5 is an unsubstituted or substituted 3- to 6-membered carbocycle.

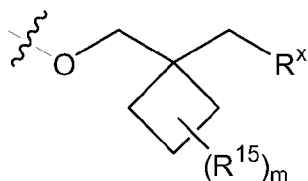
9. The compound of claim 1, wherein R^4 is H and R^5 is an unsubstituted or substituted 4- to 7-membered heterocycle.
10. The compound of any one of claims 1-3, wherein one of R^4 and R^5 is a halogen and the other is selected from halogen, CN, methyl and ethyl
11. The compound of any one of claims 1-3, wherein one of R^4 and R^5 is a halogen and the other is selected from OH, OCH_3 , $C(O)NH_2$ and $C(O)NHCH_3$.
12. The compound of any one of claims 1-3, wherein one of R^4 and R^5 is halogen, CN, methyl and ethyl and the other is an unsubstituted or substituted 3- to 8-membered carbocycle.
13. The compound of any one of claims 1-3, wherein one of R^4 and R^5 is halogen, CN, methyl and ethyl and the other is an unsubstituted or substituted 3- to 8-membered heterocycle.
14. The compound of any one of claims 1-3, wherein one of R^4 and R^5 is unsubstituted or substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.
15. The compound of any one of claims 1-3, wherein one of R^4 and R^5 is unsubstituted or substituted tetrahydrofuran, tetrahydropyran, cyclic sulfone, cyclic sulfonamide, cyclic amide, cyclic carbamate, azetidine, pyrrolidine, piperidine, pyrazole, imidazole, 1, 3-oxazole, 1,2-oxazole, 1,3-thiazole, 1, 2,4-triazole, 1,2,3-triazole, 1, 3,4-oxadiazole, 1,3,4-thiadiazole, furan, pyridine, pyrimidine, pyridazine, pyrazine, or triazine.
16. The compound of any one of claims 1-15, wherein R^1 is $X(CH_2)_iR^{14}$, wherein X is O.
17. The compound of claim 16, wherein R^{14} is a C_{3-6} carbocyclic ring substituted with 0-5 R^{15} , wherein each R^{15} is independently selected from D, halo, C_{1-3} alkyl optionally substituted with one or more of halo, OH, NRR' , CN, $CONRR'$ or SO_2NRR' .
18. The compound of claim 16 or 17, wherein i is 1.
19. The compound of any one of claims 16-18, wherein R^{14} is C_{3-4} cycloalkyl ring substituted with 0-5 R^{15} .
20. The compound of claim 19, wherein R^1 has the structure:



wherein R^x is OH, halo, NRR' , CN, $CONRR'$ or SO_2NRR' .

21. The compound of claim 20, wherein R^{15} is F, m is 0-2, and R^x is CH_2OH .

22. The compound of claim 19, wherein R^1 has the structure:



wherein R^x is OH, halo, NRR' , CN, $CONRR'$ or SO_2NRR' .

23. The compound of claim 22, wherein R^{15} is F, m is 0-2, and CH_2OH .

24. The compound of any one of claims 1-15, wherein R^1 is $NR^{12}R^{13}$.

25. The compound of any one of claims 1-15, wherein X is absent and R^1 is $(CH_2)_iR^{14}$.

26. The compound of claim 25, wherein R^{14} is NRR' .

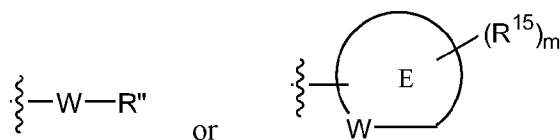
27. The compound of any one of claims 1-26, wherein R^{14} comprises one or more of amino, amide, sulfonamide, and carboxylic ester groups.

28. The compound of any one of claims 1-26, wherein R^{14} is a mono- or bicyclic, unsubstituted or substituted C_{4-10} heterocyclic ring.

29. The compound of claim 28, wherein R^{14} is a monocyclic, unsubstituted or substituted C_{4-7} heterocyclic ring.

30. The compound of claim 28, wherein R^{14} is a bicyclic, unsubstituted or substituted C_{6-10} heterocyclic ring.

31. The compound of any one of claims 1-26, wherein R^{14} has the structure of:



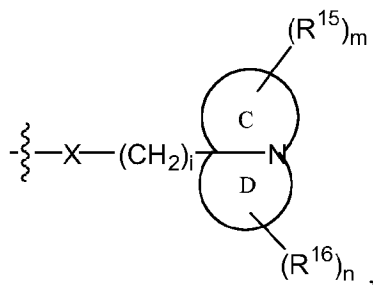
wherein

Ring E is a 4- to 7-membered unsubstituted or substituted monocyclic or bicyclic carbocyclic or heterocyclic ring;

W is O, S, N, NR, C(O), S(O)₂, NHC(O), C(O)NH, OC(O), C(O)O, S(O)₂NH, or NHS(O)₂; and

R^{15} is selected from the group consisting of halogen, OH, CN, C_{1-6} alkyl, C_{1-6} alkoxy, $=CRR'$, NRR' , $C(O)NRR'$, $NRC(O)R''$, $NRC(O)NRR'$, $C(O)R$, $C(O)OR$, $S(O)_2NRR'$, or $NRS(O)_2R$, $S(O)_2NRR'$ and $NRS(O)_2NRR'$.

32. The compound of any one of claims 1-15, wherein R^1 has the structure of:



wherein

each of Ring C and Ring D is a 4- to 7-membered heterocyclic ring;

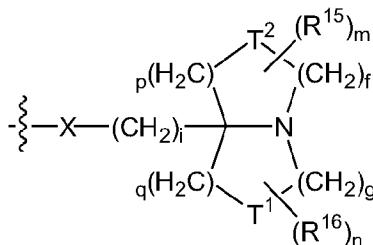
X is O or S;

each of R^{15} and R^{16} is independently selected from the group consisting of halogen, OH, CN, NRR' , $=CRR'$, C_{1-6} alkyl and C_{1-6} alkoxy;

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

each of m and n is independently 0, 1, 2 or 3.

33. The compound of claim 32, wherein R^1 has the structure of:



wherein

each of T^1 and T^2 is independently $CR^{17}R^{18}$, $C=CR^{17}R^{18}$, NR^{19} , O, S or $S(O)_2$;

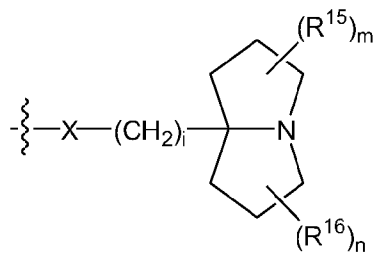
each of R^{17} and R^{18} is independently selected from the group consisting of: H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^{19} is selected from the group consisting of: H, C_{1-6} alkyl, and C_{1-6} alkoxy;

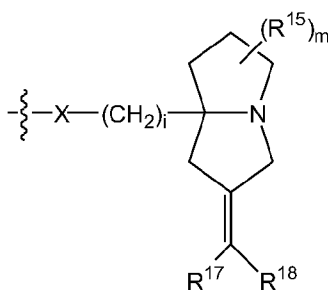
each of f , g , p and q is independently 0, 1, 2 or 3, provided that if one of f and p is 0, the other is not 0 and if one of g and q is 0, the other is not 0; and

each of m and n is independently 0, 1, 2 or 3.

34. The compound of claim 33, wherein each of T^1 and T^2 is $CR^{17}R^{18}$, each of f , g , p and q is 1, with R^1 having the structure of:

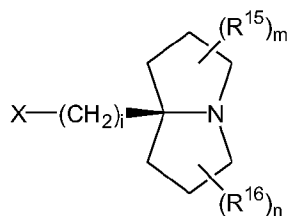


35. The compound of claim 33, wherein T^1 is $C=CR^{17}R^{18}$ and T^2 is $CR^{17}R^{18}$, each of f , g , p and q is 1, with R^1 having the structure of:

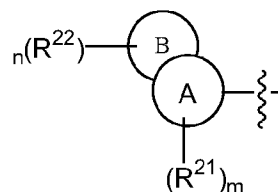


wherein each of R^{17} and R^{18} is independently H or halo.

36. The compound of claim 33-35, having a chirality as shown below:



37. The compound of claim 36, wherein m is 0, n is 1, and R^{16} is F.
38. The compound of any one of claims 32-37, wherein X is O.
39. The compound of claim 38, wherein i is 1.
40. The compound of any one of claims 1-39, wherein R^2 is an unsubstituted or substituted 6- to 10-membered unsaturated bicyclic ring, comprising 0-5 heteroatoms selected from N, O and S.
41. The compound of claim 40, wherein R^2 has the structure of:



wherein

Ring A is a 6-membered aryl or heteroaryl ring with 0-2 N atoms;

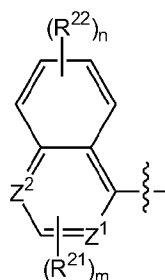
Ring B is a 5- or 6-membered aryl or heteroaryl with 0-3 heteroatoms selected from N, O and S;

each of R^{21} and R^{22} is independently selected from the group consisting of halogen, OH, CN, NRR' , unsubstituted or substituted C_{1-6} alkyl, and unsubstituted or substituted C_{1-6} alkoxy, $(CH_2)_xNRR'$, $(CH_2)_xC(=O)NRR'$, $(CH_2)_xOC(=O)R$, $(CH_2)_xOC(=O)OR$;

each of m and n is independently 0, 1, 2 or 3; and

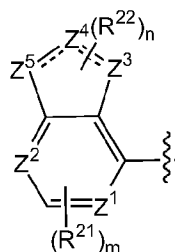
each x is independently 0, 1 or 2.

42. The compound of claim 41, wherein R^2 is:



wherein each of Z^1 and Z^2 is independently selected from CH and N.

43. The compound of claim 42, wherein each of Z^1 and Z^2 is CH.
44. The compound of claim 42, wherein Z^1 is CH and Z^2 is N.
45. The compound of claim 42, wherein Z^1 is Z and Z^2 is CH.
46. The compound of claim 42, wherein each of Z^1 and Z^2 is N.
47. The compound of claim 41, wherein R^2 is:



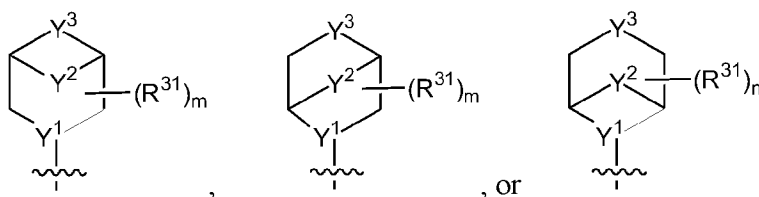
wherein

each of Z^1 and Z^2 is independently selected from CH and N; and

each of Z^3 , Z^4 and Z^5 is independently selected from CR'', N, NR, O or S,

provided that Ring B remains an aromatic ring, wherein R is H or a C₁₋₄ alkyl.

48. The compound of claim 47, wherein each of Z^1 and Z^2 is CH.
49. The compound of claim 47, wherein Z^1 is CH and Z^2 is N.
50. The compound of claim 47, wherein Z^1 is Z and Z^2 is CH.
51. The compound of claim 47, wherein each of Z^1 and Z^2 is N.
52. The compound of any one of claims 47-51, wherein each of Z^3 , Z^4 and Z^5 is not a heteroatom.
53. The compound of any one of claims 37-51, wherein at least one of Z^3 , Z^4 and Z^5 is a heteroatom.
54. The compound of any one of claims 1-53, wherein L is a single bond.
55. The compound of any one of claims 1-53, wherein L is a single bond and R^{31} is:



wherein

Y^1 is N or CR'';

Y^2 is (CH₂)_j, NR or CH₂OCH₂;

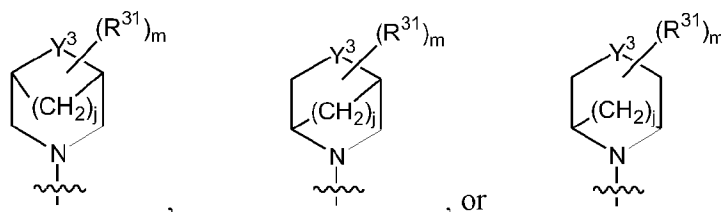
Y^3 is NR, CR'', O or S;

each R^{31} is independently selected from the group consisting of halogen, OH, NRR', C(O)NRR', unsubstituted or substituted C₁₋₆ alkyl, and unsubstituted or substituted C₁₋₆ alkoxy, NRC(O)R'', NRC(O)NRR', C(O)R'', and C(O)OR, S(O)₂NRR', NRS(O)₂R and NRS(O)₂NRR';

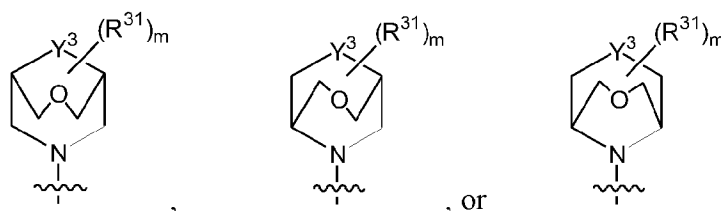
each j is independently 0, 1, 2 or 3; and

m is 0, 1, 2 or 3.

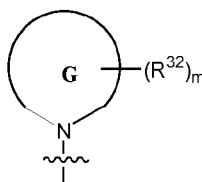
56. The compound of claim 55, wherein R^3 is:



57. The compound of claim 55 or 56, wherein Y^3 is NR.
58. The compound of claim 55 or 56, wherein Y^3 is CR^{''}.
59. The compound of claim 55 or 56, wherein Y^3 is O or S.
60. The compound of any one of claims 57-59, wherein j is 2.
61. The compound of claim 55, wherein R^3 is:



62. The compound of claim 61, wherein Y^3 is NR.
63. The compound of claim 61, wherein Y^3 is CR^{''}.
64. The compound of any one of claims 56-63, wherein m is 0.
65. The compound of any one of claims 56-63, wherein m is 1.
66. The compound of any one of claims 1-53, wherein L is a single bond and $R^{3'}$ is an unsubstituted or substituted, 3- to 10-membered saturated or unsaturated monocyclic that comprises 0-3 heteroatoms selected from N, O and S.
67. The compound of claim 66, wherein $R^{3'}$ is an unsubstituted or substituted, 6-membered saturated or unsaturated monocyclic that comprises 1-3 heteroatoms selected from N, O and S.
68. The compound of claim 67, wherein $R^{3'}$ has the structure:



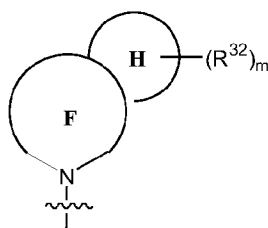
wherein

Ring G is a 5- to 7-membered heterocyclic ring with 1-3 heteroatoms selected from N, O and S;

each R^{32} is independently selected from the group consisting of halogen, OH, NRR' , $C(O)NRR'$, unsubstituted or substituted C_{1-6} alkyl, and unsubstituted or substituted C_{1-6} alkoxy, $NRC(O)R''$, $NRC(O)NRR'$, $C(O)R''$, and $C(O)OR$, $S(O)_2NRR'$, $NRS(O)_2R$ and $NRS(O)_2NRR'$; and

m is 0, 1, 2 or 3.

69. The compound of claim 68, wherein Ring G is 6-membered.
70. The compound of claim 66, wherein R^{31} is an unsubstituted or substituted, 10- to 12-membered saturated or unsaturated bicyclic that comprises 1-5 heteroatoms selected from N, O and S.
71. The compound of claim 70, wherein R^{31} has the structure:



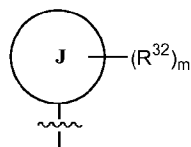
wherein

Rings F and H together form a hetero-bicyclic ring;

each R^{32} is independently selected from the group consisting of halogen, OH, NRR' , $C(O)NRR'$, unsubstituted or substituted C_{1-6} alkyl, and unsubstituted or substituted C_{1-6} alkoxy, $NRC(O)R''$, $NRC(O)NRR'$, $C(O)R''$, and $C(O)OR$, $S(O)_2NRR'$, $NRS(O)_2R$ and $NRS(O)_2NRR'$; and

m is 0, 1, 2 or 3.

72. The compound of claim 71, wherein Ring F is 7-membered and Ring H is 5-membered.
73. The compound of any one of claims 1-53, wherein L is $NR(CH_2)_k$ and R^3 is $NR(CH_2)_kR^{31}$.
74. The compound of claim 73, wherein k is 0.
75. The compound of claim 73, wherein k is 1.
76. The compound of any one of claims 73-75, wherein R^{31} is an unsubstituted or substituted, 3- to 6-membered monocyclic ring moiety that comprises 0-3 heteroatoms selected from N, O and S.
77. The compound of claim 76, wherein R^{31} has the structure:



wherein

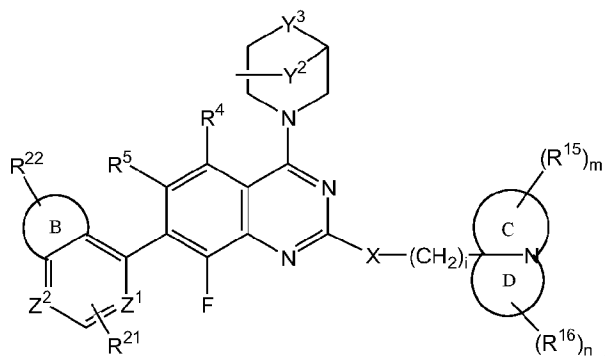
Ring J is a 5- to 7-membered carbocyclic or heterocyclic ring with 0-3 heteroatoms selected from N, O and S;

each R^{32} is independently selected from the group consisting of halogen, OH, NRR' , $C(O)NRR'$, unsubstituted or substituted C_{1-6} alkyl, and unsubstituted or substituted C_{1-6} alkoxy, $NRC(O)R''$, $NRC(O)NRR'$, $C(O)R''$, and $C(O)OR$, $S(O)_2NRR'$, $NRS(O)_2R$ and $NRS(O)_2NRR'$; and

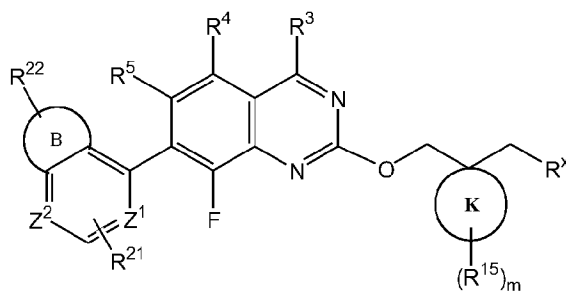
m is 0, 1, 2 or 3.

78. The compound of claim 77, wherein Ring J is 6-membered.

79. The compound of any one of claims 1-15, having the structural formula:



80. The compound of any one of claims 1-15, having the structural formula:



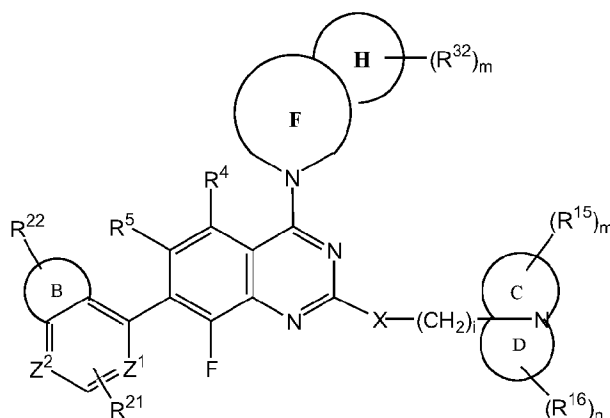
wherein

Ring K is a C_{3-4} cycloalkyl;

R^x is OH, halo, NRR' , CN, $CONRR'$ or SO_2NRR' ; and

m is 0, 1, 2 or 3.

81. The compound of any one of claims 1-15, having the structural formula:



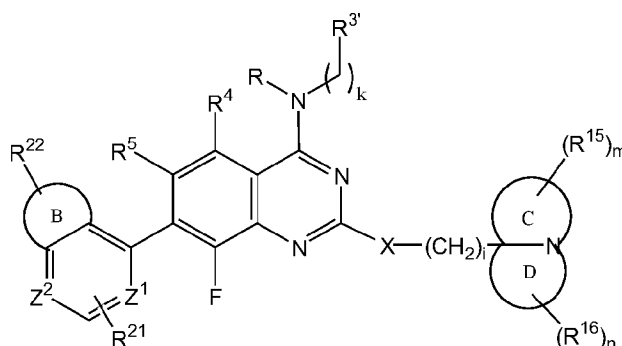
wherein

Rings F and H together form a hetero-bicyclic ring;

each R^{32} is independently selected from the group consisting of halogen, OH, NRR' , $C(O)NRR'$, unsubstituted or substituted C_{1-6} alkyl, and unsubstituted or substituted C_{1-6} alkoxy, $NRC(O)R''$, $NRC(O)NRR'$, $C(O)R''$, and $C(O)OR$, $S(O)_2NRR'$, $NRS(O)_2R$ and $NRS(O)_2NRR'$; and

m is 0, 1, 2 or 3.

82. The compound of any one of claims 1-15, having the structural formula:



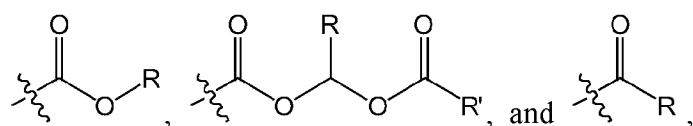
wherein

$R^{3'}$ is an unsubstituted or substituted, 3- to 6-membered monocyclic ring moiety that comprises 0-3 heteroatoms selected from N, O and S; and

k is 0, 1 or 2.

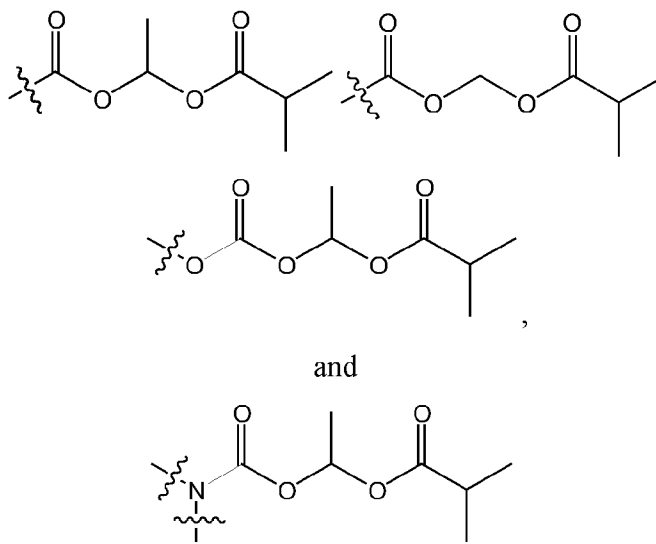
83. The compound of claim 1, selected from **Table 1**.
84. The compound of any of claims 1-83, having one or more deuterium atoms in place of hydrogen.

85. The compound of any of claims 1-83, having one deuterium atom in place of a hydrogen atom.
86. A pro-drug of a compound according to any of claims 1-85.
87. The pro-drug of claim 86, comprising an ester, a carbonate and/or a carbamate moiety.
88. The pro-drug of claim 86, wherein one or both of R^2 and R^3 comprises an ester, a carbonate and/or a carbamate moiety.
89. The pro-drug of any one of claims 86-88, wherein the ester, carbonate and carbamate moieties are selected from:



R or $R' = H$ or substituted or unsubstituted C_{1-6} alkyl or substituted or unsubstituted 3- to 6-membered carbocycle.

90. The pro-drug of any one of claims 86-89, wherein the ester, carbonate and carbamate moieties are selected from:



91. A pharmaceutical composition comprising a compound according to any one of claims 1-90 and a pharmaceutically acceptable excipient, carrier, or diluent.
92. The pharmaceutical composition of claim 91, being suitable for oral administration.
93. A unit dosage form comprising a pharmaceutical composition according to claim 91 or 92.
94. The unit dosage form of claim 93, being in the form of a tablet or capsule.

95. A method for inhibiting cell proliferation *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound according to any one of claims 1-90.
96. A method for inhibiting KRas(G12D) activity in a cell, comprising contacting the cell with a compound according to any one of claims 1-90.
97. A method for treating a disease or disorder mediated by a Ras mutant protein, comprising administering to a subject in need thereof a therapeutically effective amount of the compound according to any one of claims 1-90.
98. A method for treating or reducing cancer, or a related disease or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of the compound according to any one of claims 1-90.
99. The method of claim 98, wherein the cancer is selected from the group consisting of carcinoma, squamous carcinoma, adenocarcinoma, sarcoma, leukemia, neuroma, melanoma, and lymphoma.
100. The method of claim 98 or 99, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, lung cancer, endometrial cancer, appendix cancer, cholangiocarcinoma, bladder urothelial cancer, ovarian cancer, gastric cancer, breast cancer, bile duct cancer, and a hematologic malignancy.
101. The method of any one of claims 95-100, wherein the subject has a mutation of KRAS, HRAS and/or NRAS.
102. The method of any one of claims 95-101, wherein the subject being treated is further administered one or more of chemotherapy, radiotherapy, targeted therapy, immunotherapy, and hormonal therapy.
103. Use of the compound according to any one of claims 1-90, and a pharmaceutically acceptable excipient, carrier, or diluent, in preparation of a medicament for treating a disease or disorder.
104. The use of claim 103, wherein the disease or disorder is cancer.
105. The use of claim 104, wherein the cancer is selected from the group consisting of carcinoma, squamous carcinoma, adenocarcinoma, sarcoma, leukemia, neuroma, melanoma, and lymphoma.
106. The use of claim 105, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, lung cancer, endometrial cancer, appendix cancer,

cholangiocarcinoma, bladder urothelial cancer, ovarian cancer, gastric cancer, breast cancer, bile duct cancer, and a hematologic malignancy.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US23/25372

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. C07D 239/72; C07D 239/80; C07D 239/94; C07D 403/12; C07D 403/14; C07D 487/08 (2023.01)

ADD.

CPC - INV. C07D 239/72; C07D 239/80; C07D 239/94; C07D 403/12; C07D 403/14; C07D 487/08

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)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WO 2022/002102 A1 (INVENTISBIO CO., LTD.) 06 January 2022; paragraphs [5], [259], [262], [394], [401]	1-3, 4/1-3, 11/1-3 --- 8-9, 10/1-3, 12/1-3, 13/1-3, 14/1-3, 15/1-3, 83
Y	US 2021/0188869 A1 (ARAXES PHARMA LLC) 24 June 2021; paragraphs [0008], [0576], [0713], [0753]	8, 10/1-3, 12/1-3, 13/1-3, 14/1-3, 83
Y	US 2010/0234324 A1 (EGGENWEILER, H-M et al.) 16 September 2010; paragraphs [0311], [0314], [0422]	9, 13/1-3, 15/1-3
P,X	WO 2022/232331 A1 (AMGEN INC.) 03 November 2022; page 228, see Example 230; page 232, see Example 231	1-2

☐ Further documents are listed in the continuation of Box C.☐ 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

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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

17 August 2023 (17.08.2023)

Date of mailing of the international search report

SEP 11 2023

Name and mailing address of the ISA/

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Shane Thomas

Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US23/25372

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 5-7, 16-82, 84-106
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.