

## TETRACYCLIC DERIVATIVES, COMPOSITIONS AND METHODS THEREOF

### Priority Claims and Related Applications

[0001] This application claims the benefit of priority to U.S. Provisional Application Nos. 63/534,797, filed August 25, 2023, and 63/627,442, filed January 31, 2024, the entire content of each 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 tetracyclic compounds and derivatives thereof 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 EnsemVersion 4).

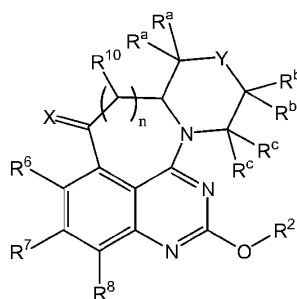
[0005] Despite extensive efforts over the past thirty years to develop inhibitors of KRas to treat cancer, no KRas(G12D) inhibitor has been clinically demonstrated with sufficient safety and/or efficacy to warrant regulatory approval. (McCormick **2015** *Clin Cancer Res.* 21 (8):1797-1801; Sun et al. **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 modulate the activity of KRas. Compounds of the invention are 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

$n$  is 1 or 2;

$X$  is  $CR^{x1}R^{x2}$ , wherein each of  $R^{x1}$  and  $R^{x2}$  is independently selected from H, halo and unsubstituted or substituted  $C_{1-3}$  alkyl;

$Y$  is  $NH$ ,  $NR^y$ ,  $CH_2NH$ ,  $CH_2NR^y$ ,  $NHCH_2$  or  $NR^yCH_2$ , wherein  $R^y$  is unsubstituted or substituted  $C_{1-4}$  alkyl,  $P(O)(OCH_3)_2$ ,  $C(O)OR^w$ ,  $C(O)R^w$ , wherein  $R^w$  is H or unsubstituted or substituted  $C_{1-6}$  alkyl;

$R^2$  is  $(CH_2)_iR^{2'}$ , wherein  $i$  is an integer selected from 1-6, and  $(CH_2)_i$  is optionally substituted, wherein  $R^{2'}$  is selected from the group consisting of H, halogen, CN, OH,  $C(O)NRR'$ , unsubstituted or substituted  $C_{1-6}$  alkyl, unsubstituted or substituted 3- to 6-membered carbocyclic ring, unsubstituted or substituted 4- to 6-membered heterocyclic ring and unsubstituted or substituted aryl 7- to 9-membered bicyclic heterocyclic ring;

$R^6$  is selected from the group consisting of H, halogen, CN, OR, unsubstituted or substituted  $C_{1-4}$  alkyl, unsubstituted or substituted  $C_{1-4}$  alkoxy,  $C(O)NRR'$ ,  $NRR'$ ,  $S(O)_2CH_3$ , unsubstituted or substituted 3- to 6-membered carbocyclic or heterocyclic ring, and unsubstituted or substituted 5- to 6-membered heteroaryl;

$R^7$  is an unsubstituted or substituted 6- to 10-membered unsaturated monocyclic or bicyclic ring, comprising 0-5 heteroatoms selected from N, O and S;

$R^8$  is H, halo, unsubstituted or substituted  $C_{1-4}$  alkyl, OR or  $NRR'$ ;

$R^a$ ,  $R^b$  and  $R^c$ :

each is independently selected from H, halo, unsubstituted or substituted  $C_{1-3}$  alkyl and OR; or

one  $R^a$  and one  $R^b$ , or one  $R^a$  and one  $R^c$ , together with Y and the carbon atoms they are bonded respectively, form a 4- to 7-membered heterocyclic ring;

each  $R^{10}$  is independently H, halo or  $C_{1-4}$  alkyl; or  $R^{10}$ 's, together with the carbon atoms they are bonded respectively, form a cyclopropyl or cyclobutyl group; and

each of R and  $R'$  is independently selected from H, unsubstituted or substituted  $C_{1-4}$  alkyl, or unsubstituted or substituted 3- 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.

[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 modulating (*e.g.*, inhibiting or reducing) 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.

#### Brief Description of the Drawings

[0017] **FIG. 1** shows racemic mixture of **Intermediates 3** and **4**.

[0018] **FIG. 2** shows trace of **Intermediate 3** prepared from **Intermediate 1** matches peak 1.

[0019] **FIG. 3** shows trace of **Intermediate 3** prepared from the known chiral starting material, tert-butyl (*1S,2S,5R*)-2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate, also matches peak 1.

[0020] **FIG. 4:** Spike experiment further confirms the stereochemistry of **Intermediate 3** from both reactions to be the same.

#### Definitions

[0021] 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.

[0022] As used herein, “at least” a specific value is understood to be that value and all values greater than that value.

[0023] 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.

[0024] 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.

[0025] 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.

[0026] 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.

[0027] The terms “disease”, “disorder” and “condition” are used interchangeably unless indicated otherwise.

[0028] 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.

[0029] 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.

[0030] 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.

[0031] 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.

[0032] 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.

[0033] 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.

[0034] 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.

[0035] 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 to 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, -CH<sub>2</sub>CN, -O-C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, -OC<sub>1</sub>-C<sub>6</sub> alkenyl, -OC<sub>1</sub>-C<sub>6</sub> alkynyl, -C<sub>1</sub>-C<sub>6</sub>

alkenyl, -C<sub>1</sub>-C<sub>6</sub> alkynyl, -OH, -OP(O)(OH)<sub>2</sub>, -OC(O)C<sub>1</sub>-C<sub>6</sub> alkyl, -C(O)C<sub>1</sub>-C<sub>6</sub> alkyl, -OC(O)OC<sub>1</sub>-C<sub>6</sub> alkyl, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, -NHC(O)C<sub>1</sub>-C<sub>6</sub> alkyl, -C(O)NHC<sub>1</sub>-C<sub>6</sub> alkyl, -S(O)<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, -S(O)NHC<sub>1</sub>-C<sub>6</sub> alkyl, and S(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>.

[0036] 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.

[0037] 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.

[0038] 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.

[0039] 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.

[0040] 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.

[0041] 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.

[0042] 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.

[0043] 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.

[0044] 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.

[0045] 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.

[0046] 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).

[0047] 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.

[0048] 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.

[0049] 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.

[0050] 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.

[0051] 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.”

[0052] 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.

[0053] 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, “C<sub>1-4</sub> alkyl” is intended to encompass, C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub>, C<sub>4</sub>, C<sub>1-3</sub>, C<sub>1-2</sub>, C<sub>2-4</sub>, C<sub>3-4</sub> and C<sub>2-3</sub> alkyl groups.

[0054] 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.*, C<sub>1-10</sub> 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 C<sub>1-6</sub> 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<sup>x</sup>)<sub>3</sub>, -OR<sup>x</sup>, -SR<sup>x</sup>, -OC(O)-R<sup>x</sup>, -N(R<sup>x</sup>)<sub>2</sub>, -C(O)R<sup>x</sup>, -C(O)OR<sup>x</sup>, -OC(O)N(R<sup>x</sup>)<sub>2</sub>, -C(O)N(R<sup>x</sup>)<sub>2</sub>, -N(R<sup>x</sup>)C(O)OR<sup>x</sup>, -N(R<sup>x</sup>)C(O)R<sup>x</sup>, -N(R<sup>x</sup>)C(O)N(R<sup>x</sup>)<sub>2</sub>, -N(R<sup>x</sup>)C(NR<sup>x</sup>)N(R<sup>x</sup>)<sub>2</sub>, -N(R<sup>x</sup>)S(O)<sub>t</sub>N(R<sup>x</sup>)<sub>2</sub> (where t is 1 or 2), -P(=O)(R<sup>x</sup>)(R<sup>x</sup>), or -O-P(=O)(OR<sup>x</sup>)<sub>2</sub> wherein each R<sup>x</sup> 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. 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.

[0055] 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-C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, -C<sub>1</sub>-C<sub>6</sub> alkenyl, -OC<sub>1</sub>-C<sub>6</sub> alkynyl, -C<sub>1</sub>-C<sub>6</sub> alkenyl, -C<sub>1</sub>-C<sub>6</sub> alkynyl, -OH, -OP(O)(OH)<sub>2</sub>, -OC(O)C<sub>1</sub>-C<sub>6</sub> alkyl, -C(O)C<sub>1</sub>-C<sub>6</sub> alkyl, -OC(O)OC<sub>1</sub>-

C<sub>6</sub>alkyl, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, -S(O)<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, -S(O)NHC<sub>1</sub>-C<sub>6</sub>alkyl, and S(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>. 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.

[0056] The term “halogen” or “halo” refers to fluorine (F), chlorine (Cl), bromine (Br) and iodine (I).

[0057] 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, benzimidazoliny, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnoliny, 6,7-dihydro-5H-pyrrolo[1,2- a]imidazole, furanyl, furazanyl, imidazoliny, imidazolyl, 1H-indazolyl, indolenyl, indoliny, indoliziny, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindoliny, isoindolyl, isoquinoliny, isothiazolyl, isoxazolyl, methylenedioxyphenyl, naphthyridiny, octahydroisoquinoliny, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidiny, oxazolyl, oxazolidiny, pyrimidinyl, phenanthridiny, phenanthroliny, phenaziny, phenothiaziny, phenoxathiiny, phenoxaziny, phthalaziny, piperonyl, pteridiny, puriny, pyranly, pyraziny, pyrazolidiny, pyrazoliny, pyrazolyl, pyridaziny, pyridoazole, pyridoimidazole, pyridothiazole, pyridiny, pyridyl, pyrimidinyl, pyrroliny, 2H-pyrroly, pyrroly, quinazoliny, quinoliny, 4H-quinoliziny, quinoxaliny, quinuclidiny, tetrahydroisoquinoliny, tetrahydroquinoliny, tetrazolyl, 6H-1,2,5-thiadiaziny, 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.

[0058] 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<sub>1</sub>Z<sub>2</sub>, and (NZ<sub>1</sub>Z<sub>2</sub>)carbonyl. The term "NZ<sub>1</sub>Z<sub>2</sub>" as used herein, means two groups, Z<sub>1</sub> and Z<sub>2</sub>, which are appended to the parent molecular moiety through a nitrogen atom. Z<sub>1</sub> and Z<sub>2</sub> are each independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, and formyl. Representative examples of NZ<sub>1</sub>Z<sub>2</sub> include, but are not limited to, amino, methylamino, acetylamino, and acetylmethylamino.

[0059] As used herein, the term "alkoxy" refers to an -O-alkyl radical.

[0060] 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<sub>3-13</sub> 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<sub>3-8</sub> cycloalkyl radical. In some embodiments, "cycloalkyl" can be a C<sub>3-5</sub> cycloalkyl radical. Illustrative examples of cycloalkyl groups include, but are not limited to the following moieties: C<sub>3-6</sub> carbocyclyl groups include, without limitation, cyclopropyl (C<sub>3</sub>), cyclobutyl (C<sub>4</sub>), cyclopentyl (C<sub>5</sub>), cyclopentenyl (C<sub>5</sub>), cyclohexyl (C<sub>6</sub>), cyclohexenyl (C<sub>6</sub>), cyclohexadienyl (C<sub>6</sub>) and the like. Examples of C<sub>3-7</sub> carbocyclyl groups include norbornyl (C<sub>7</sub>). Examples of C<sub>3-8</sub> carbocyclyl groups include the aforementioned C<sub>3-7</sub> carbocyclyl groups as well as cycloheptyl (C<sub>7</sub>), cycloheptadienyl (C<sub>7</sub>), cycloheptatrienyl (C<sub>7</sub>), cyclooctyl (C<sub>8</sub>), bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, and the like. Examples of C<sub>3-13</sub> carbocyclyl groups include the

aforementioned C<sub>3-8</sub> 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<sup>a</sup>)<sub>3</sub>, -OR<sup>a</sup>, -SR<sup>a</sup>, -OC(O)-R<sup>a</sup>, -N(R<sup>a</sup>)<sub>2</sub>, -C(O)R<sup>a</sup>, -C(O)OR<sup>a</sup>, -OC(O)N(R<sup>a</sup>)<sub>2</sub>, -C(O)N(R<sup>a</sup>)<sub>2</sub>, -N(R<sup>a</sup>)C(O)OR<sup>a</sup>, -N(R<sup>a</sup>)C(O)R<sup>a</sup>, -N(R<sup>a</sup>)C(O)N(R<sup>a</sup>)<sub>2</sub>, -N(R<sup>a</sup>)C(NR<sup>a</sup>)N(R<sup>a</sup>)<sub>2</sub>, -N(R<sup>a</sup>)S(O)<sub>t</sub>N(R<sup>a</sup>)<sub>2</sub> (where t is 1 or 2), -P(=O)(R<sup>a</sup>)(R<sup>a</sup>), or -O-P(=O)(OR<sup>a</sup>)<sub>2</sub> where each R<sup>a</sup> 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.

[0061] 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.*

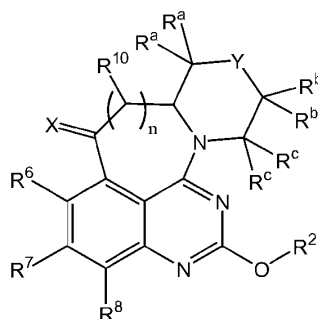
[0062] As used herein, the terms "heterocycle", "heterocyclic" or "heterocyclo" refer to fully saturated or partially unsaturated cyclic groups, for example, 3 to 7 membered monocyclic, 7 to 12 membered bicyclic, or 10 to 15 membered spirocyclic or tricyclic ring systems, which have at least one heteroatom (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, aziridiny, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidiny, pyrrolidinonyl, piperidiny, piperaziny, imidazolidiny, imidazopyridiny, thiazolidiny, dithianyl, trithianyl, dioxolanyl, oxazolidiny, oxazolidinonyl, decahydroquinoliny, piperidonyl, 4-piperidinonyl, quinuclidiny, thiomorpholiny, thiomorpholiny 1,1-dioxide, morpholiny, azepanyl, oxazepanyl, azabicyclohexanyls, 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]oxaziny, octahydroindoliziny, oxaazaspiroonanyls, oxaazaspirooctanyls, diazaspiroonanyls, oxaazabicycloheptanyls, hexahydropyrroliziny 4(1H)-oxide, and tetrahydro- 2H-thiopyranyl 1-oxide and tetrahydro-2H-thiopyranyl 1,1-dioxide.

### Detailed Description of the Invention

[0063] 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.

[0064] 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

$n$  is 1 or 2;

$X$  is  $CR^{x1}R^{x2}$ , wherein each of  $R^{x1}$  and  $R^{x2}$  is independently selected from H, halo and unsubstituted or substituted  $C_{1-3}$  alkyl;

$Y$  is NH,  $NR^y$ ,  $CH_2NH$ ,  $CH_2NR^y$ ,  $NHCH_2$  or  $NR^yCH_2$ , wherein  $R^y$  is unsubstituted or substituted  $C_{1-4}$  alkyl,  $P(O)(OCH_3)_2$ ,  $C(O)OR^w$ ,  $C(O)R^w$ , wherein  $R^w$  is H or unsubstituted or substituted  $C_{1-6}$  alkyl;

$R^2$  is  $(CH_2)_iR^{2'}$ , wherein  $i$  is an integer selected from 1-6, and  $(CH_2)_i$  is optionally substituted, wherein  $R^{2'}$  is selected from the group consisting of H, halogen, CN, OH,  $C(O)NRR'$ , unsubstituted or substituted  $C_{1-6}$  alkyl, unsubstituted or substituted 3- to 6-membered carbocyclic ring, unsubstituted or substituted 4- to 6-membered heterocyclic ring and unsubstituted or substituted aryl 7- to 9-membered bicyclic heterocyclic ring;

$R^6$  is selected from the group consisting of H, halogen, CN, OR, unsubstituted or substituted  $C_{1-4}$  alkyl, unsubstituted or substituted  $C_{1-4}$  alkoxy,  $C(O)NRR'$ ,  $NRR'$ ,  $S(O)_2CH_3$ , unsubstituted or substituted 3- to 6-membered carbocyclic or heterocyclic ring, and unsubstituted or substituted 5- to 6-membered heteroaryl;

$R^7$  is an unsubstituted or substituted 6- to 10-membered unsaturated monocyclic or bicyclic ring, comprising 0-5 heteroatoms selected from N, O and S;

$R^8$  is H, halo, unsubstituted or substituted  $C_{1-4}$  alkyl, OR or  $NRR'$ ;

$R^a$ ,  $R^b$  and  $R^c$ :

each is independently selected from H, halo, unsubstituted or substituted  $C_{1-3}$  alkyl and OR; or

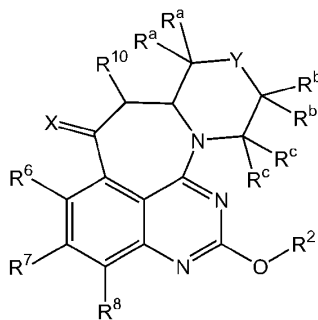
one  $R^a$  and one  $R^b$ , or one  $R^a$  and one  $R^c$ , together with  $Y$  and the carbon atoms they are bonded respectively, form a 4- to 7-membered heterocyclic ring;

each  $R^{10}$  is independently H, halo or  $C_{1-4}$  alkyl; or  $R^{10}$ 's, together with the carbon atoms they are bonded respectively, form a cyclopropyl or cyclobutyl group; and

each of  $R$  and  $R'$  is independently selected from H, unsubstituted or substituted  $C_{1-4}$  alkyl, or unsubstituted or substituted 3- to 6-membered carbocyclic ring, or where  $R$  and  $R'$  are

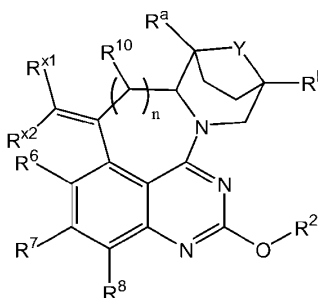
attached to the same N atom, together form an unsubstituted or substituted 4- to 6-membered heterocyclic ring.

[0065] In certain embodiments of (I), n is 1, having the structure of Formula (II):



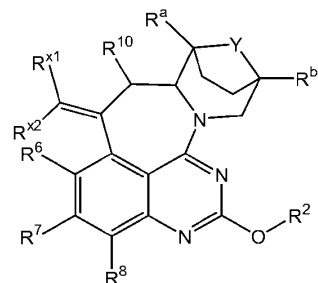
(II)

[0066] In certain embodiments of (I), one R<sup>a</sup> and one R<sup>b</sup>, wherein together with Y and the carbon atoms they are respectively bonded to, form a 5-membered heterocyclic ring, having the structure of Formula (I<sup>A</sup>):



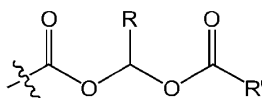
(I<sup>A</sup>)

[0067] In certain embodiments of (II), one R<sup>a</sup> and one R<sup>b</sup>, wherein together with Y and the carbon atoms they are respectively bonded to, form a 5-membered heterocyclic ring, having the structure of Formula (II<sup>A</sup>):



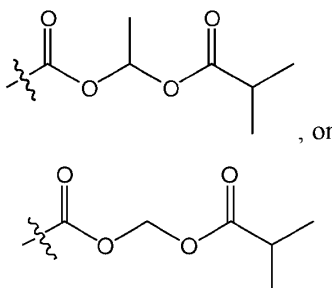
(II<sup>A</sup>)

- [0068] In certain embodiments of (I<sup>A</sup>) or (II<sup>A</sup>), one of R<sup>a</sup> and R<sup>b</sup> is CH<sub>3</sub> and the other is H.
- [0069] In certain embodiments of (I<sup>A</sup>) or (II<sup>A</sup>), each of R<sup>a</sup> and R<sup>b</sup> is H.
- [0070] In certain embodiments of (I)-(II<sup>A</sup>), each of R<sup>x1</sup> and R<sup>x2</sup> is independently selected from H, F and Cl.
- [0071] In certain embodiments of (I)-(II<sup>A</sup>), each of R<sup>x1</sup> and R<sup>x2</sup> is H.
- [0072] In certain embodiments of (I)-(II<sup>A</sup>), one of R<sup>x1</sup> and R<sup>x2</sup> is H and the other is F or Cl.
- [0073] In certain embodiments of (I)-(II<sup>A</sup>), each of R<sup>x1</sup> and R<sup>x2</sup> is F or Cl.
- [0074] In certain embodiments of (I)-(II<sup>A</sup>), at least one of R<sup>x1</sup> and R<sup>x2</sup> is an unsubstituted or substituted C<sub>1-3</sub> alkyl.
- [0075] In certain embodiments of (I)-(II<sup>A</sup>), Y is NH.
- [0076] In certain embodiments of (I)-(II<sup>A</sup>), Y is NR<sup>y</sup>.
- [0077] In certain embodiments, R<sup>y</sup> is P(O)(OCH<sub>3</sub>)<sub>2</sub>.
- [0078] In certain embodiments, R<sup>y</sup> is C(O)OR, wherein R is an unsubstituted or substituted C<sub>1-4</sub> alkyl.
- [0079] In certain embodiments, R<sup>y</sup> comprises:



wherein each of R and R' is selected from H or substituted or unsubstituted C<sub>1-6</sub> alkyl or substituted or unsubstituted 3- to 6-membered carbocycle.

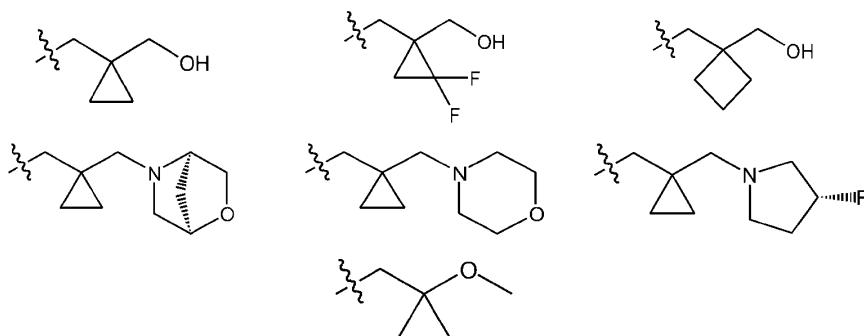
- [0080] In certain embodiments, R<sup>y</sup> comprises:



- [0081] In certain embodiments of (I)-(II<sup>A</sup>), R<sup>6</sup> is H.
- [0082] In certain embodiments of (I)-(II<sup>A</sup>), R<sup>6</sup> is F.
- [0083] In certain embodiments of (I)-(II<sup>A</sup>), R<sup>6</sup> is Cl.

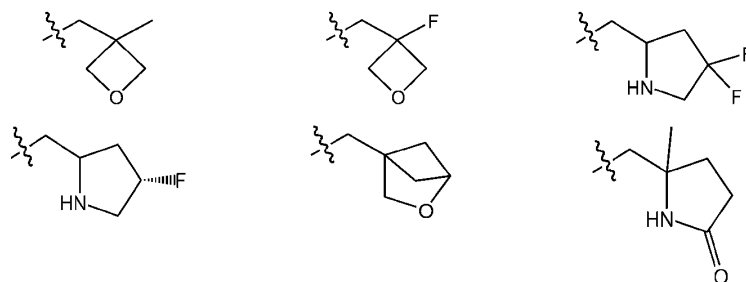
- [0084] In certain embodiments of (I)-(II<sup>A</sup>), R<sup>6</sup> is C<sub>1-3</sub> alkyl or C<sub>3-4</sub> cycloalkyl.
- [0085] In certain embodiments of (I)-(II<sup>A</sup>), R<sup>6</sup> is CH<sub>2</sub>F, CHF<sub>2</sub> or CF<sub>3</sub>.
- [0086] In certain embodiments of (I)-(II<sup>A</sup>), R<sup>6</sup> is CN, S(O)<sub>2</sub>R, NRR', OR or C(O)NRR'.
- [0087] In certain embodiments of (I)-(II<sup>A</sup>), each R<sup>e</sup> is H.
- [0088] In certain embodiments of (I)-(II<sup>A</sup>), *i* is 1.
- [0089] In certain embodiments of (I)-(II<sup>A</sup>), R<sup>2'</sup> is a C<sub>3-6</sub> carbocyclic or heterocyclic ring substituted with 0-5 R<sup>2A</sup>, wherein each R<sup>2A</sup> is independently selected from D, halo, OC<sub>1-3</sub> alkyl or C<sub>1-3</sub> alkyl, wherein the C<sub>1-3</sub> alkyl is optionally substituted with one or more of halo, OH, NRR', CN and CONRR'.
- [0090] In certain embodiments of (I)-(II<sup>A</sup>), R<sup>2'</sup> is C<sub>3-5</sub> carbocyclic ring substituted with 0-5 R<sup>2A</sup>.

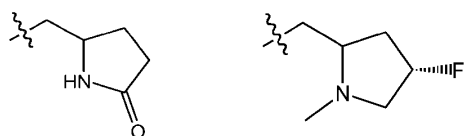
- [0091] Non-limiting examples of R<sup>2</sup> include:



- [0092] In certain embodiments of (I)-(II<sup>A</sup>), R<sup>2'</sup> is C<sub>3-5</sub> heterocyclic ring substituted with 0-5 R<sup>2A</sup>.

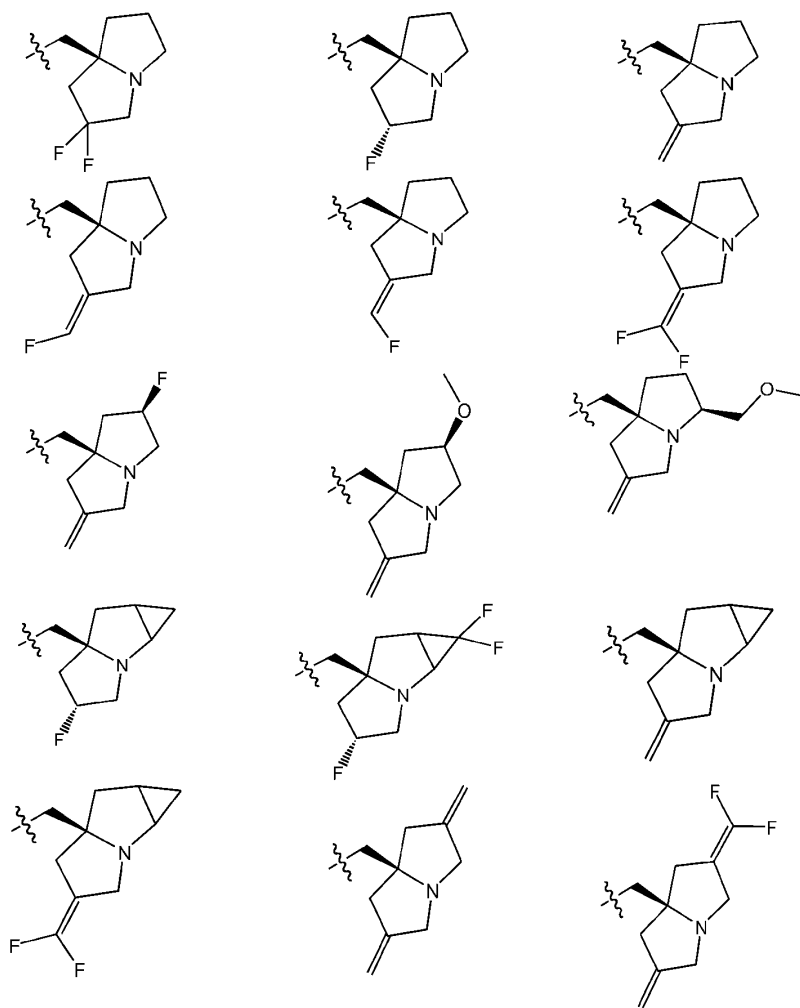
- [0093] Non-limiting examples of R<sup>2</sup> also include:

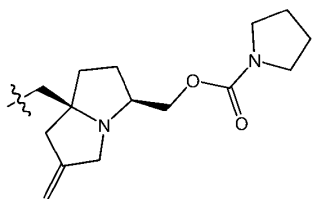




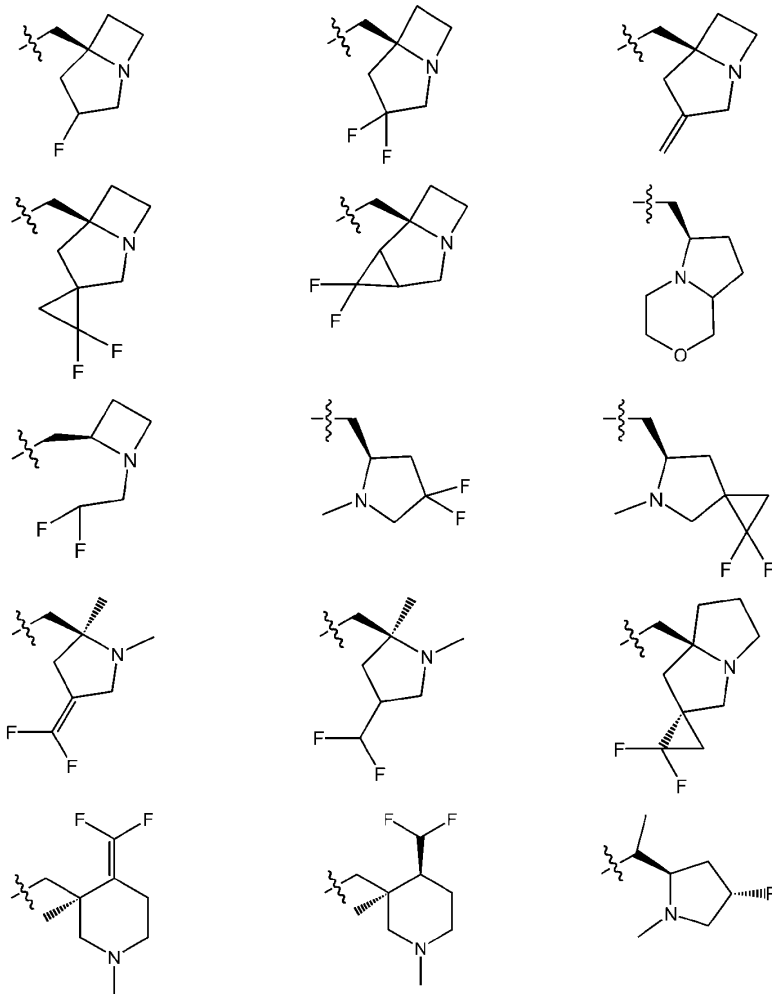
[0094] In certain embodiments of (I)-(II<sup>A</sup>), R<sup>2</sup> is a bicyclic, unsubstituted or substituted C<sub>6-10</sub> heterocyclic ring.

[0095] Non-limiting examples of R<sup>2</sup> also include:



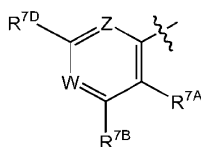


[0096] Non-limiting examples of R<sup>2</sup> further include:



[0097] In certain embodiments of (I)-(II<sup>A</sup>), R<sup>7</sup> is an unsubstituted or substituted 6-membered aryl or heteroaryl ring, comprising 0-5 heteroatoms selected from N, O and S.

[0098] In certain embodiments, R<sup>7</sup> has the structural formula:



wherein

Z is N or CR<sup>7E</sup>;

W is N or CR<sup>7C</sup>;

R<sup>7A</sup> is H, halo or substituted or unsubstituted C<sub>1-3</sub> alkyl;

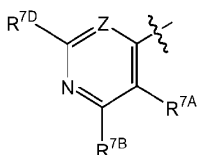
R<sup>7B</sup> is H, halo or substituted or unsubstituted C<sub>1-3</sub> alkyl;

R<sup>7C</sup> is H or halo;

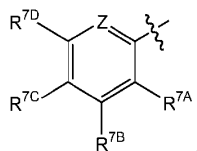
R<sup>7D</sup> is H, NRR', halo or OR; and

R<sup>7E</sup> is H or halo.

[0099] In certain embodiments, W is N, and R<sup>7</sup> has the structural formula:



[00100] In certain embodiments, W is CR<sup>7C</sup>, and R<sup>7</sup> has the structural formula:



[00101] In certain embodiments, Z is N.

[00102] In certain embodiments, Z is CH.

[00103] In certain embodiments, Z is CF.

[00104] In certain embodiments, R<sup>7D</sup> is NH<sub>2</sub>.

[00105] In certain embodiments, R<sup>7D</sup> is OH.

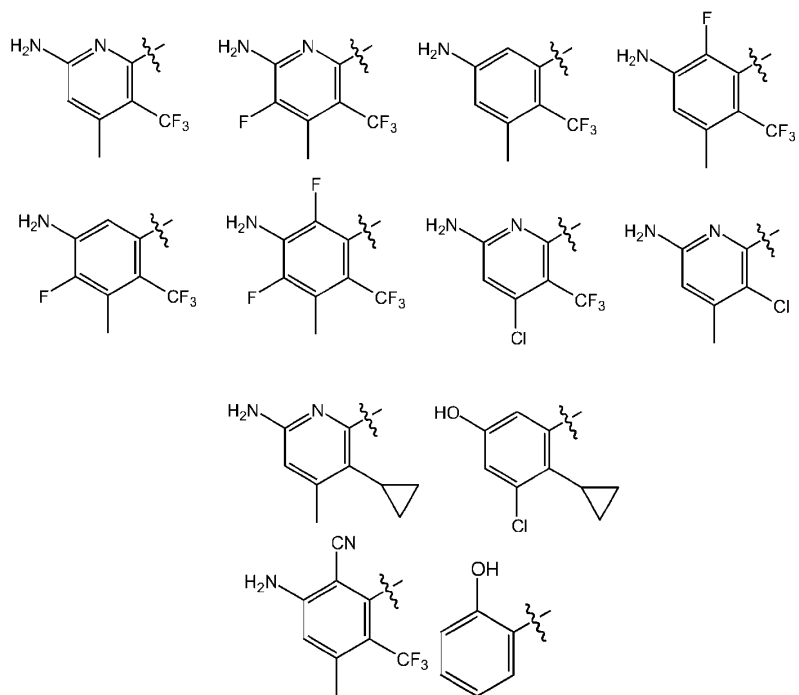
[00106] In certain embodiments, R<sup>7A</sup> is CF<sub>3</sub>.

[00107] In certain embodiments, R<sup>7A</sup> is cyclopropyl.

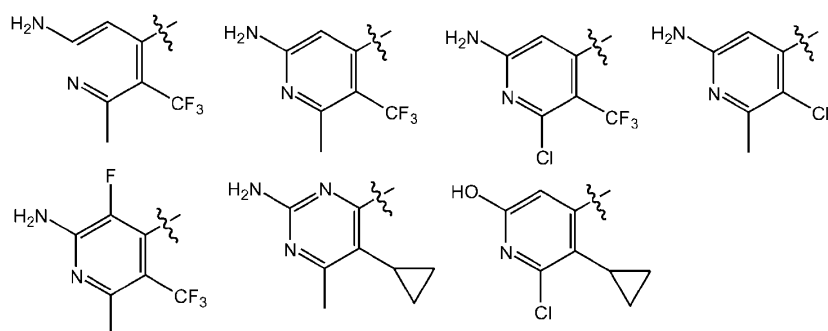
[00108] In certain embodiments, R<sup>7B</sup> is CH<sub>3</sub> or Cl.

[00109] In certain embodiments, R<sup>7C</sup> is F or H.

[00110] Non-limiting examples of R<sup>7</sup> include:



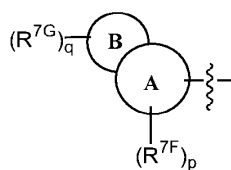
[00111] Non-limiting examples of  $\mathbb{R}^7$  also include:



[00112] In certain embodiments of (I)-(II<sup>A</sup>), R<sup>7</sup> is an unsubstituted or substituted 9- or 10-membered bicyclic aryl or heteroaryl ring, comprising 0-5 heteroatoms selected from N, O and S.

[00113] In certain embodiments,  $R^7$  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 carbocyclic, heterocyclic, aryl or heteroaryl ring with 0-3 heteroatoms selected from N, O and S;

each of  $R^{7F}$  and  $R^{7G}$  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,  $(CH_2)_kNRR'$ ,  $(CH_2)_kC(=O)NRR'$ ,  $(CH_2)_kOC(=O)R$ ,  $(CH_2)_kOC(=O)OR$ ;

each of  $p$  and  $q$  is independently 0, 1, 2 or 3; and

each  $k$  is independently 0, 1 or 2.

[00114] In certain embodiments, Ring A is a 6-membered aryl ring.

[00115] In certain embodiments, Ring A is a 6-membered heteroaryl ring.

[00116] In certain embodiments, Ring B is a 5-membered heterocyclic ring.

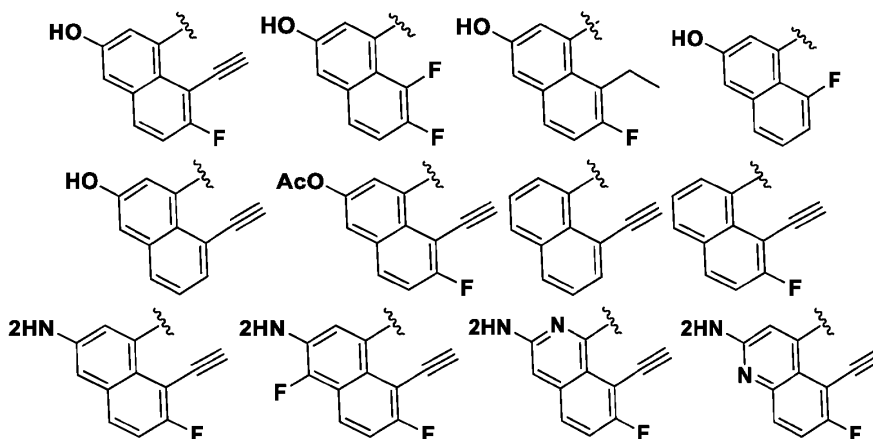
[00117] In certain embodiments, Ring B is a 6-membered heterocyclic ring.

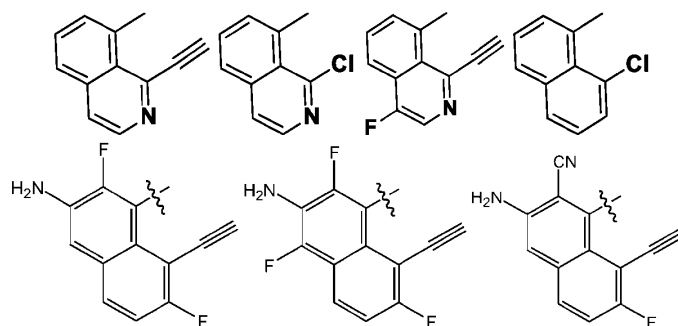
[00118] In certain embodiments, Ring B is a 5-membered heteroaryl ring.

[00119] In certain embodiments, Ring B is a 6-membered heteroaryl ring.

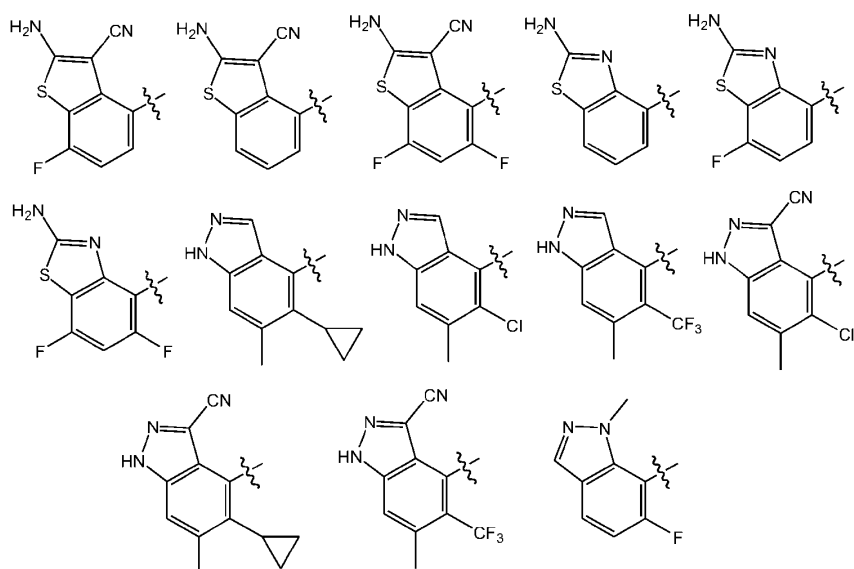
[00120] In certain embodiments, Ring B is a 6-membered aryl ring.

[00121] Non-limiting examples of  $R^7$  include:

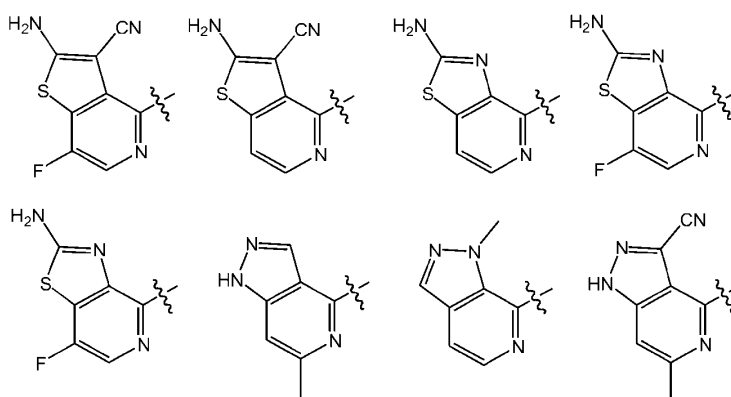




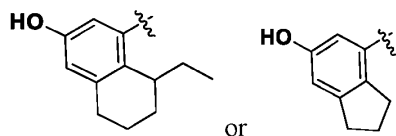
[00122] Non-limiting examples of  $R^7$  include:



[00123] Non-limiting examples of  $R^7$  also include:



[00124] Non-limiting examples of  $R^7$  further include:

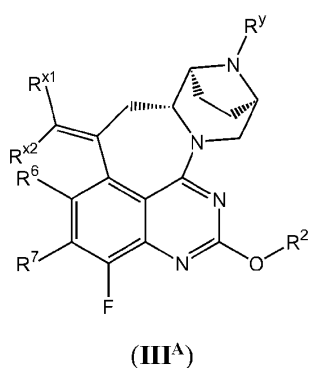


[00125] In certain embodiments of (I)-(II<sup>A</sup>),  $R^{10}$  is H.

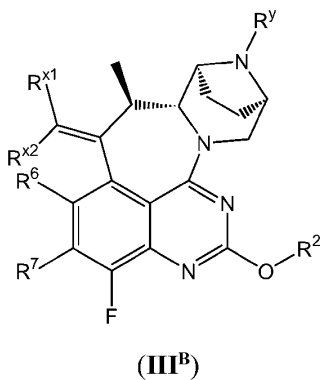
[00126] In certain embodiments of (I)-(II<sup>A</sup>),  $R^{10}$  is CH<sub>3</sub>.

[00127] In certain embodiments of (I)-(II<sup>A</sup>),  $R^8$  is F.

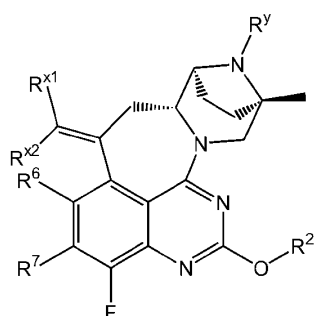
[00128] In certain embodiments of (I)-(II<sup>A</sup>), the compound has the structural formula (III<sup>A</sup>):



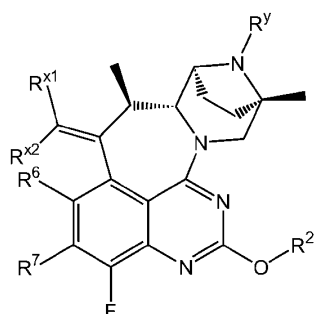
[00129] In certain embodiments of (I)-(II<sup>A</sup>), the compound has the structural formula (III<sup>B</sup>):



[00130] In certain embodiments of (I)-(II<sup>A</sup>), the compound has the structural formula (III<sup>C</sup>):

(III<sup>C</sup>)

[00131] In certain embodiments of (I)-(II<sup>A</sup>), the compound has the structural formula (III<sup>D</sup>):

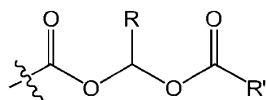
(III<sup>D</sup>)

[00132] In certain embodiments of (III<sup>A</sup>)-(III<sup>D</sup>), R<sup>6</sup> is F.

[00133] In certain embodiments of (III<sup>A</sup>)-(III<sup>D</sup>), R<sup>6</sup> is Cl.

[00134] In certain embodiments of (III<sup>A</sup>)-(III<sup>D</sup>), R<sup>y</sup> is H.

[00135] In certain embodiments of (III<sup>A</sup>)-(III<sup>D</sup>), R<sup>y</sup> comprises:



wherein each of R and R' is selected from H or substituted or unsubstituted C<sub>1-6</sub> alkyl or substituted or unsubstituted 3- to 6-membered carbocycle

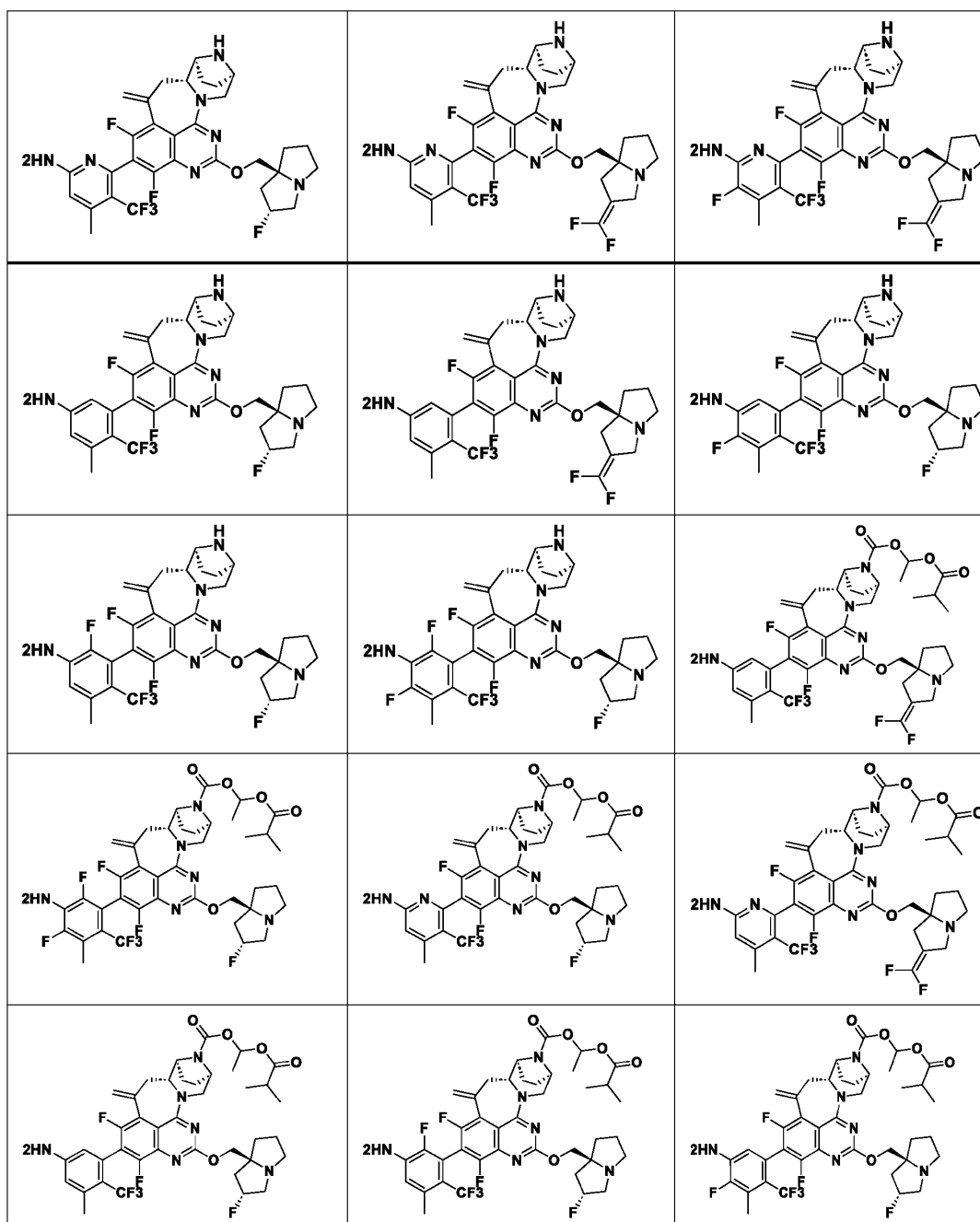
[00136] In certain embodiments of (III<sup>A</sup>)-(III<sup>D</sup>), R<sup>x2</sup> is H.

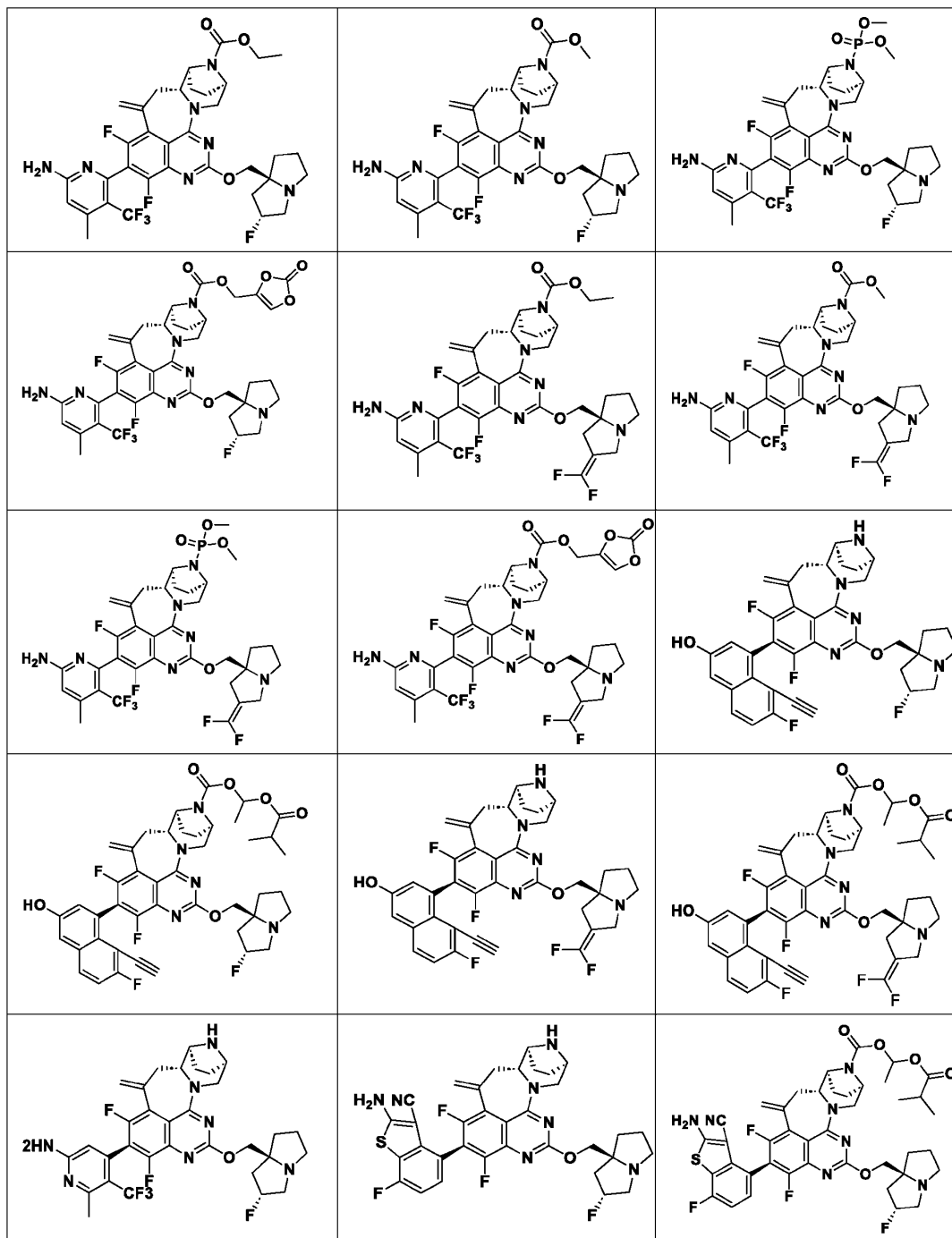
[00137] In certain embodiments of (III<sup>A</sup>)-(III<sup>D</sup>), R<sup>x1</sup> is H.

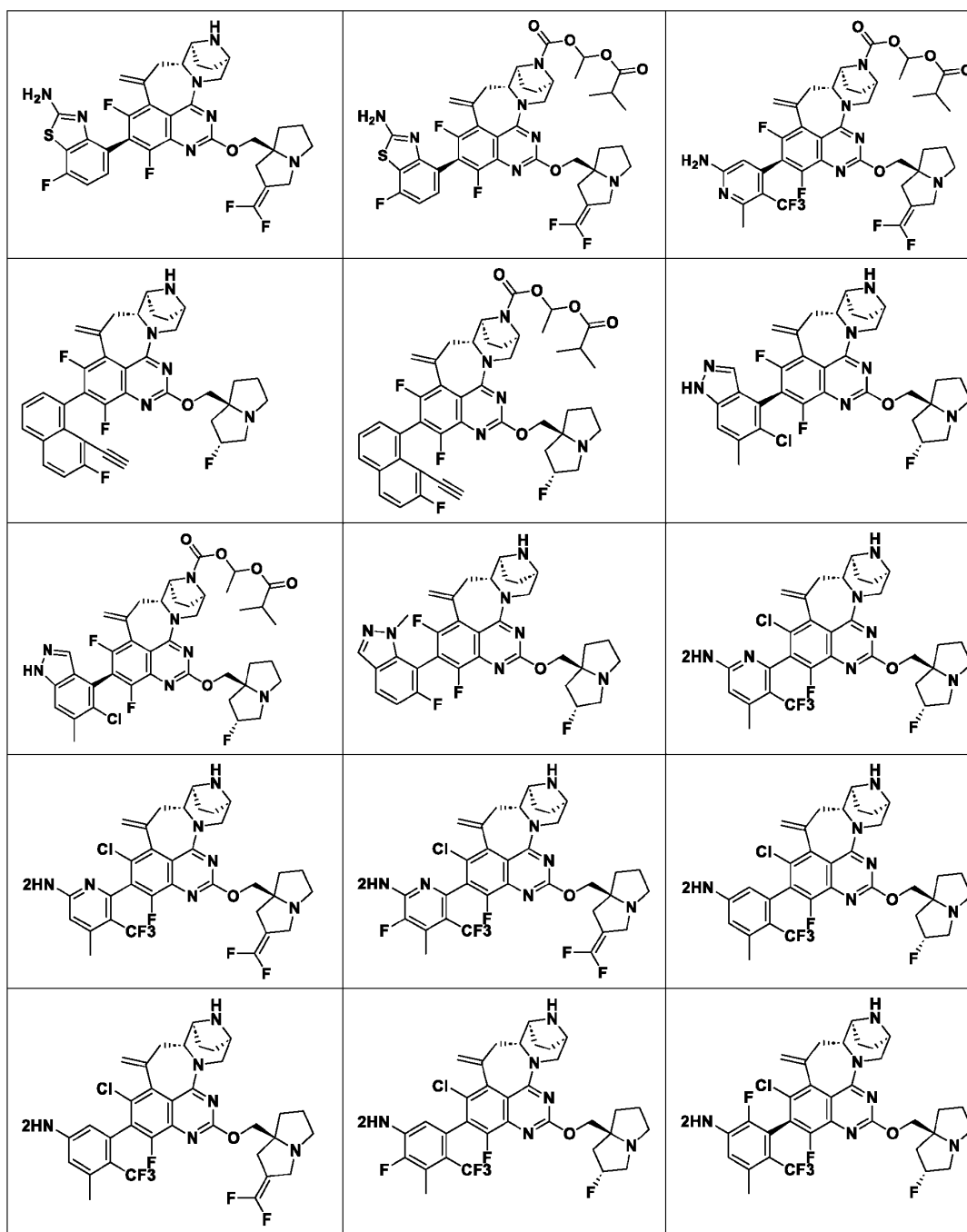
[00138] In certain embodiments of (III<sup>A</sup>)-(III<sup>D</sup>), one of R<sup>x1</sup> and R<sup>x2</sup> is F.

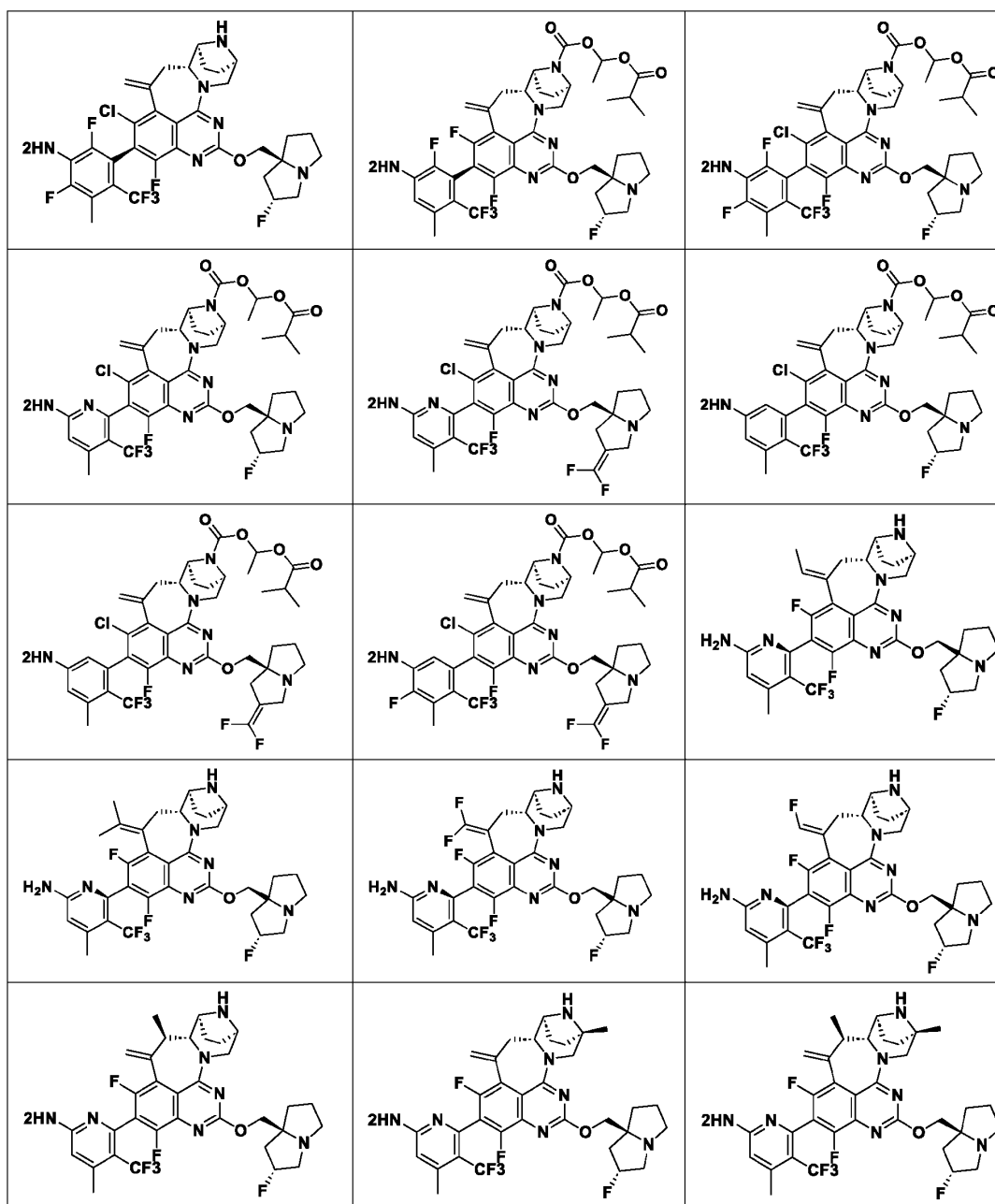
[00139] Non-limiting examples of compounds of the invention include those listed in **Table 1**.

**Table 1. Exemplary Compounds**

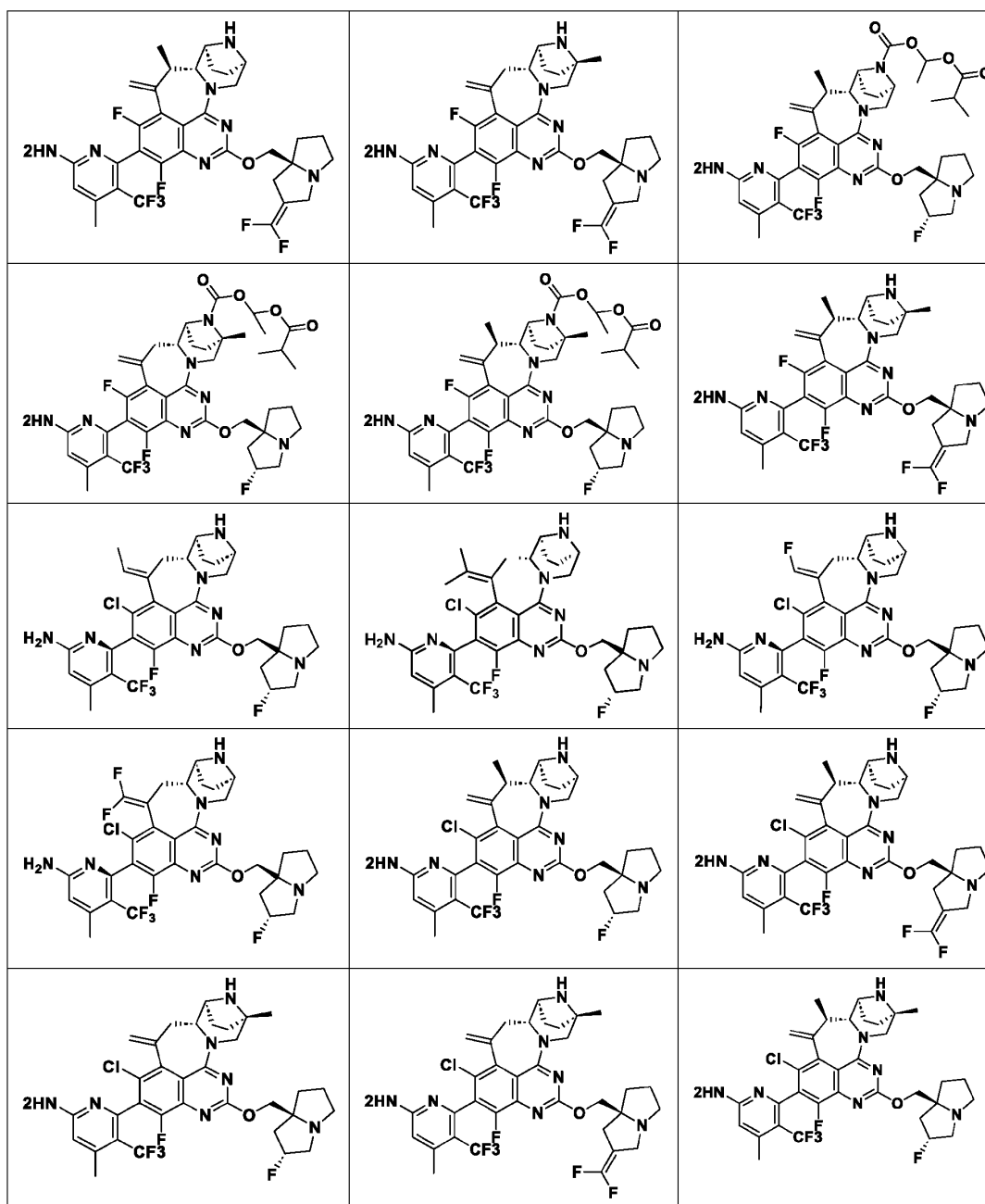


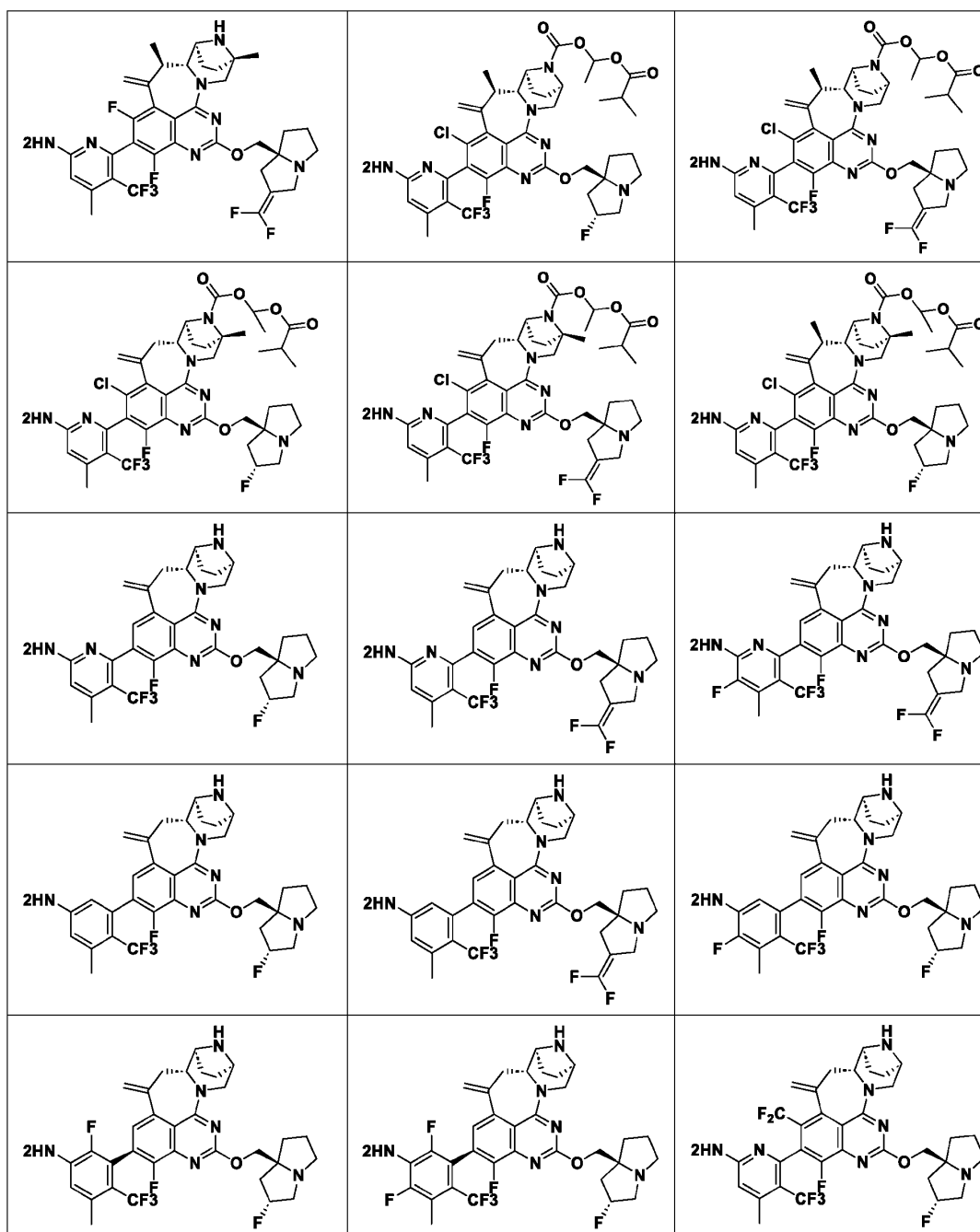


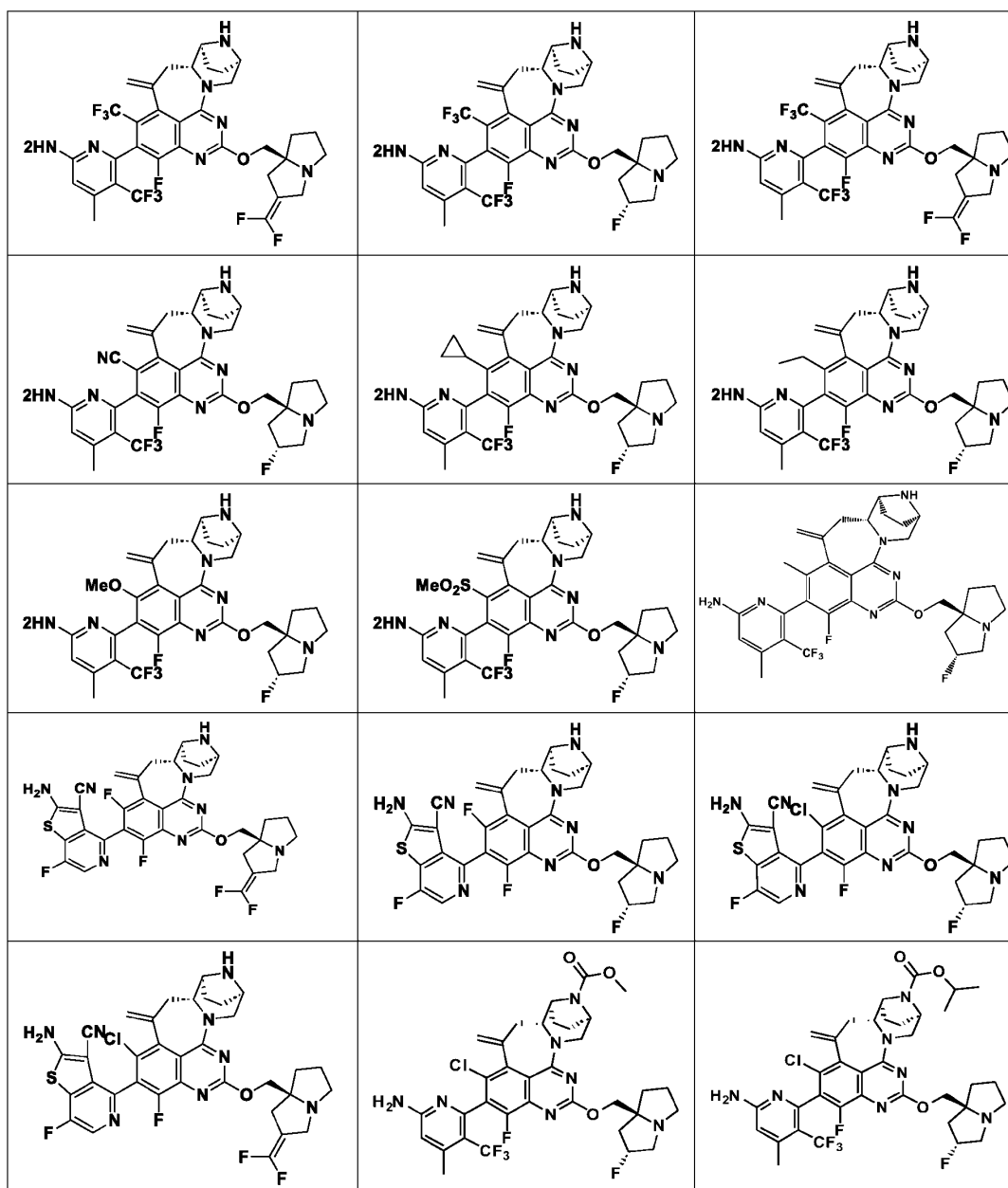


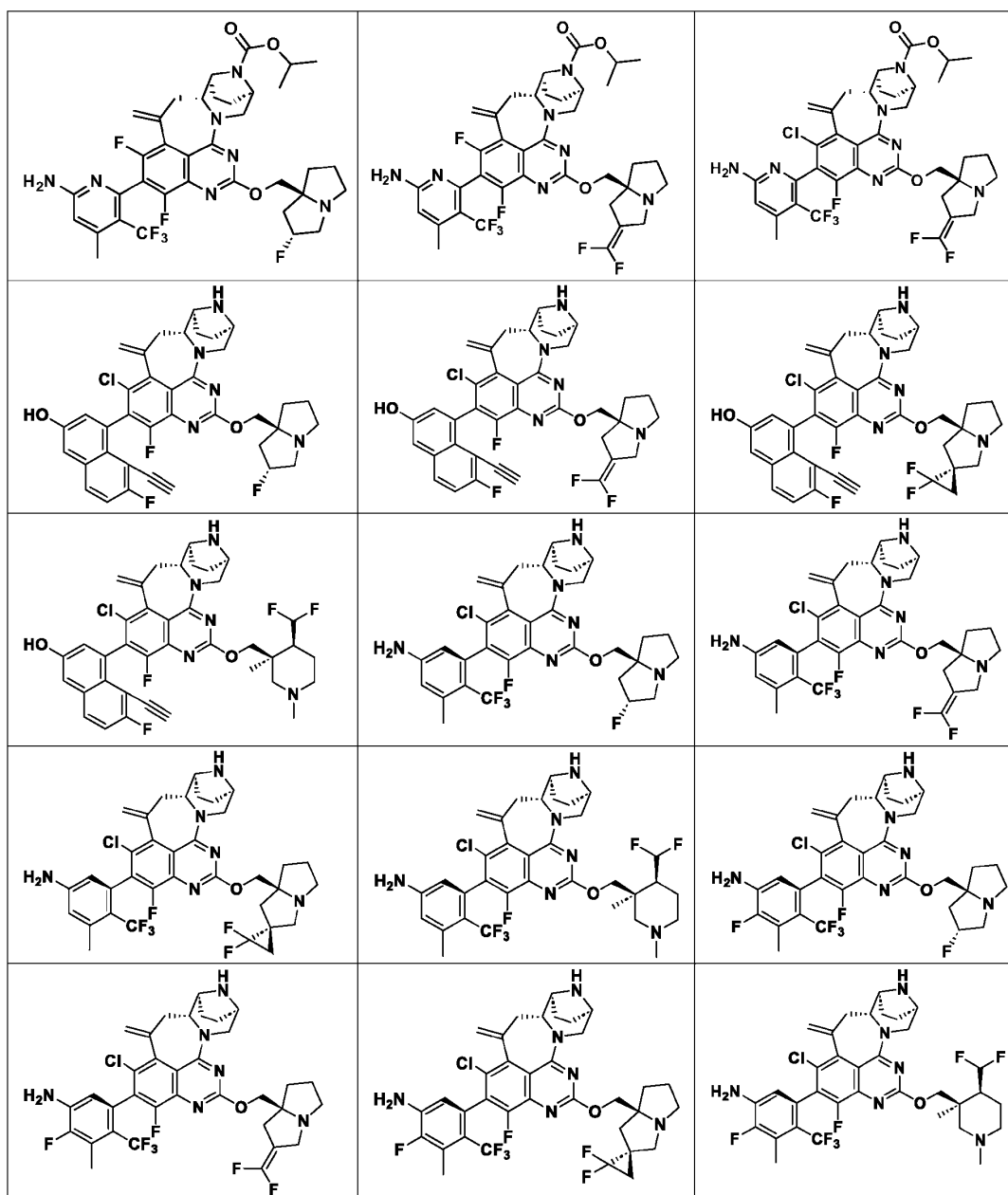


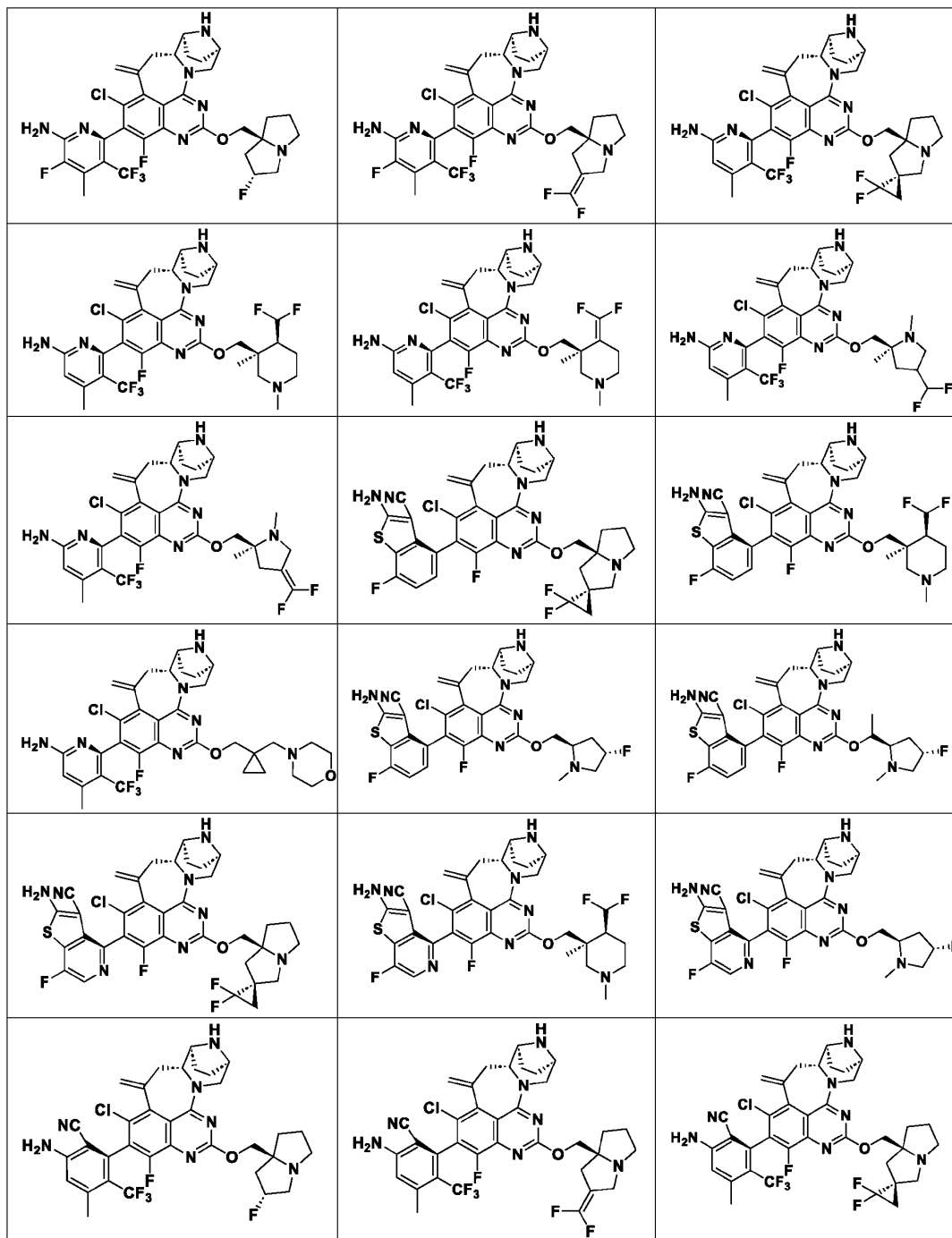


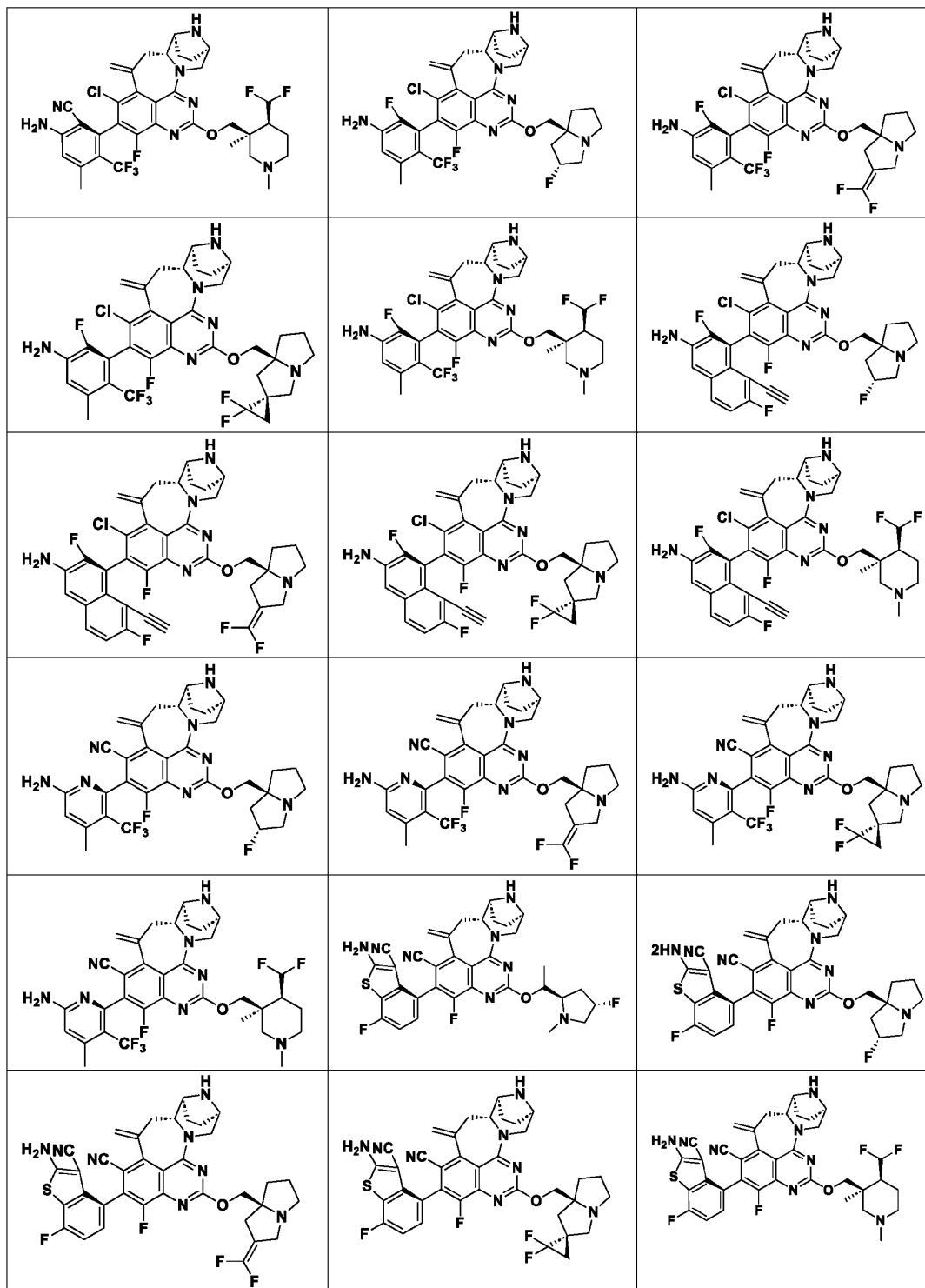


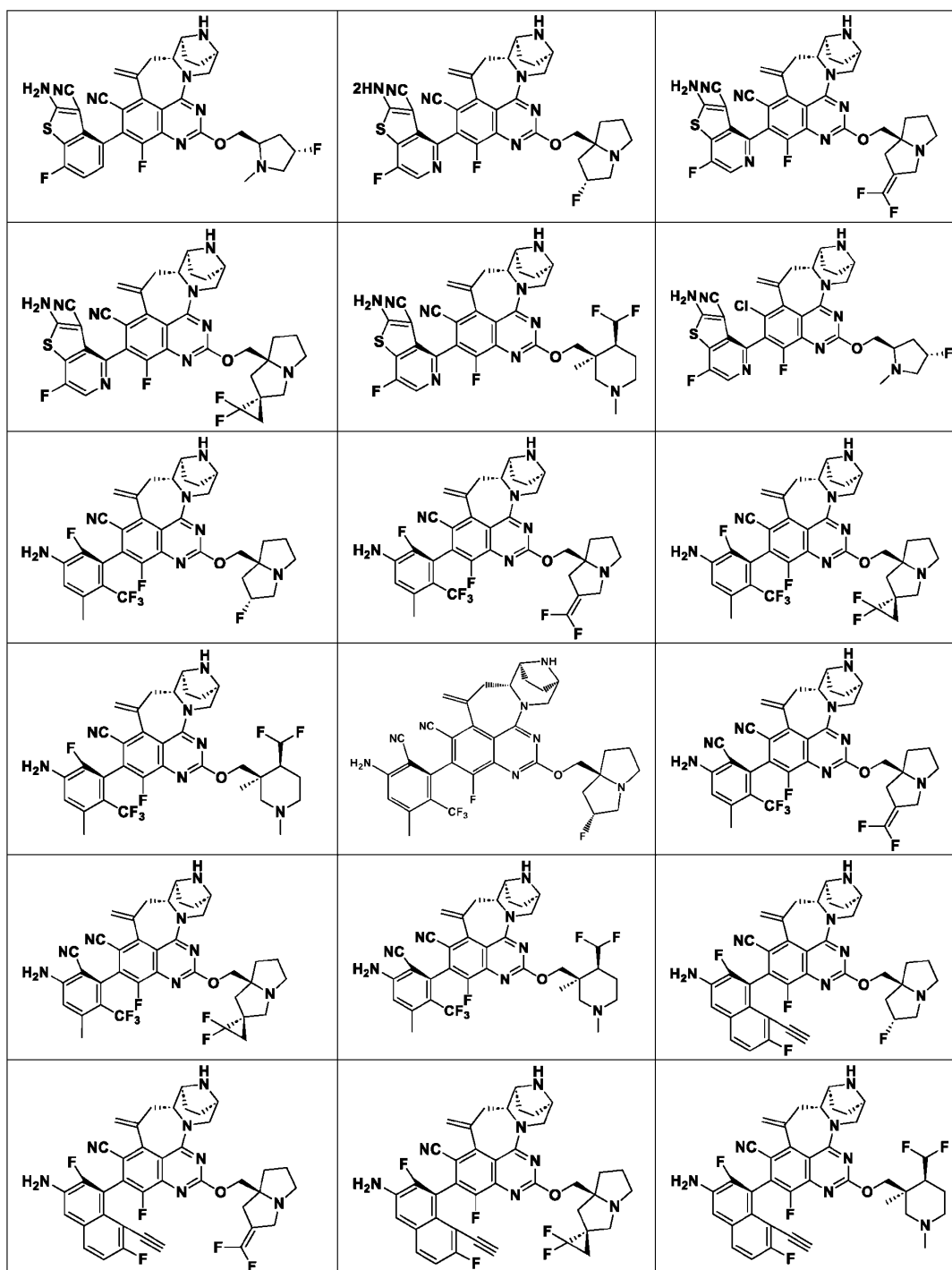


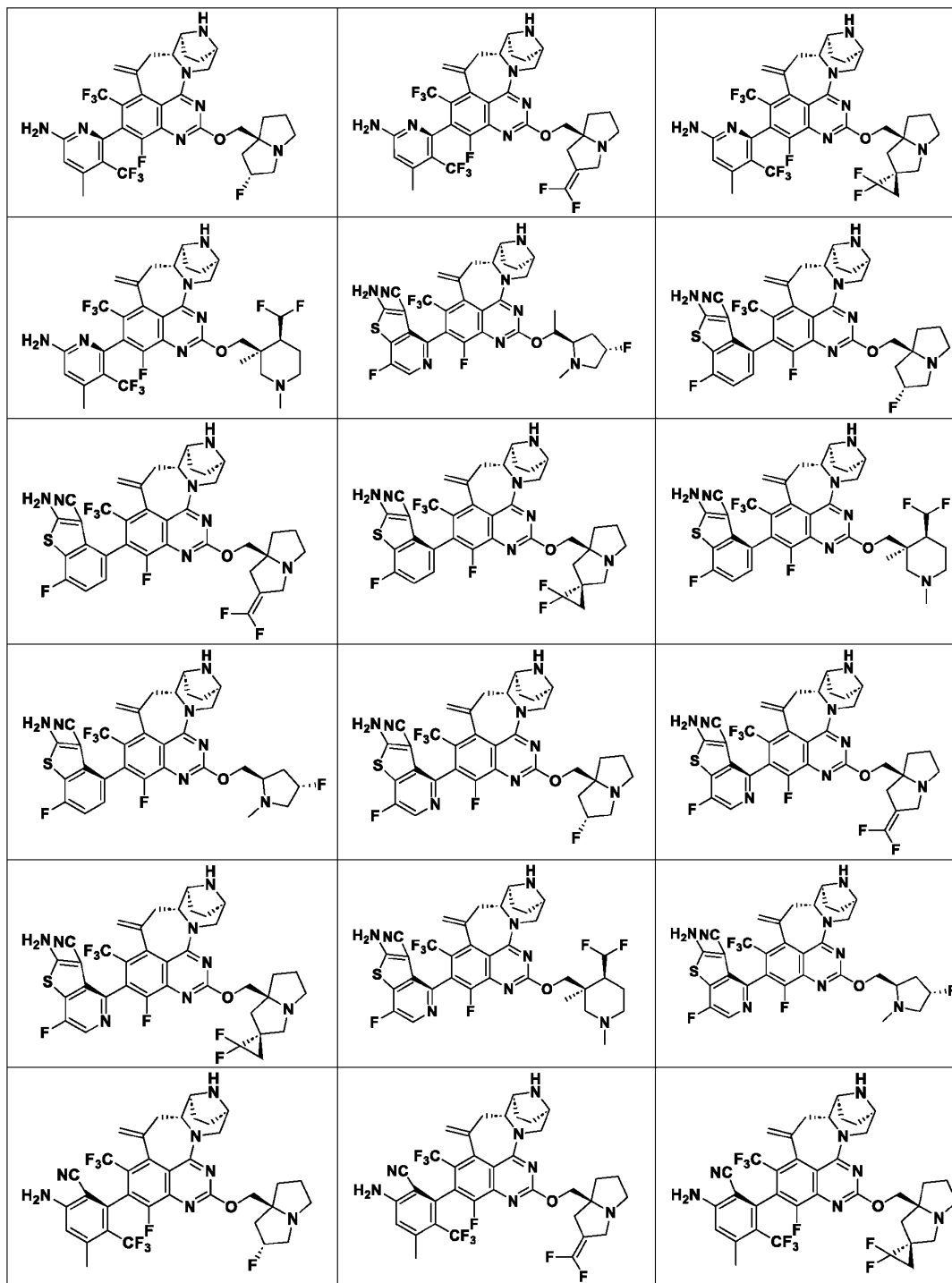




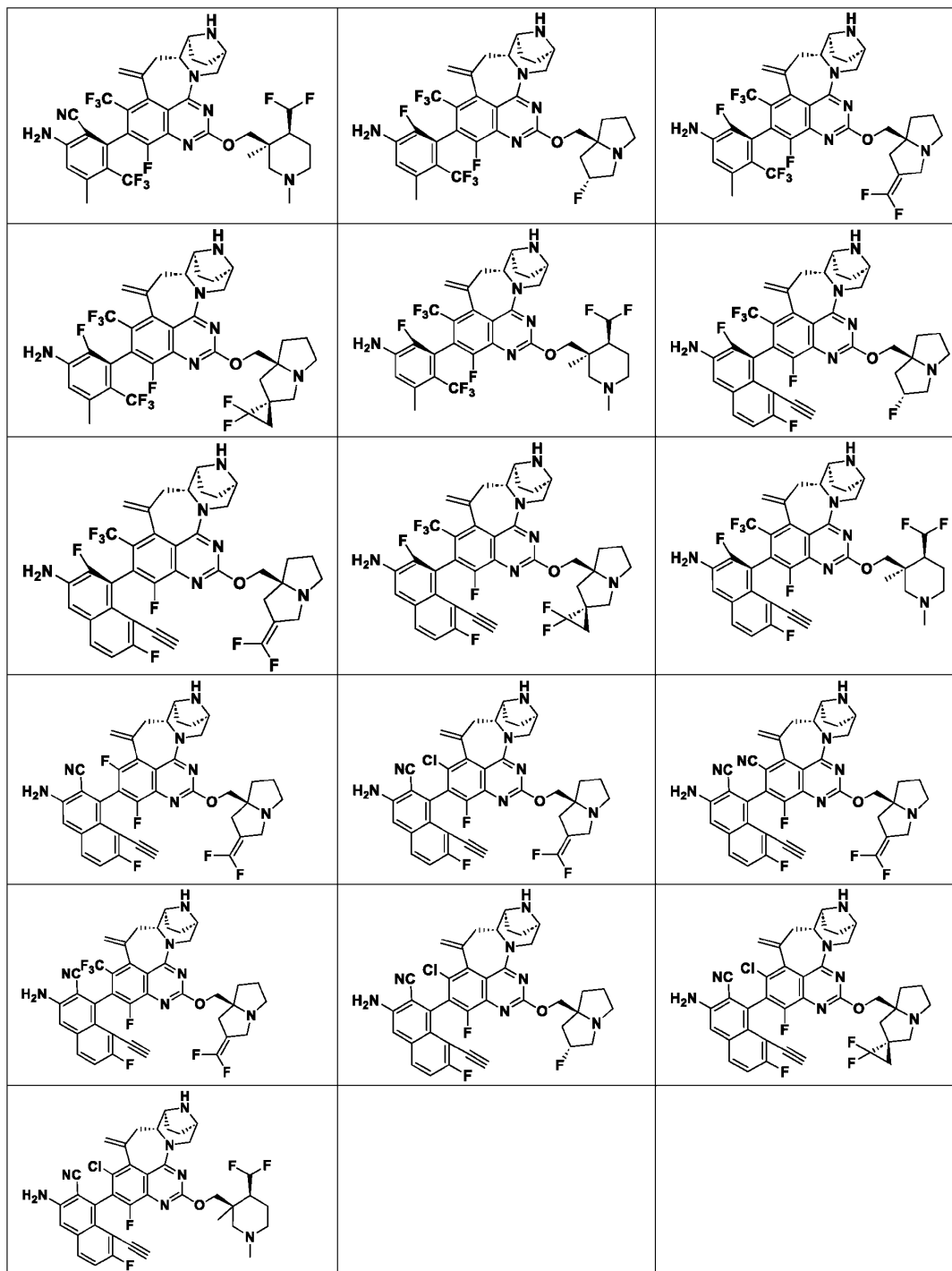












- [00140] In certain embodiments, compounds of the invention are selected from **Table 2**.
- [00141] In certain embodiments, compounds of the invention have one or more deuterium atoms in place of hydrogen atoms.
- [00142] In certain embodiments, compounds of the invention have one deuterium atom in place of a hydrogen atom.
- [00143] In another aspect, the invention generally relates to a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable excipient, carrier, or diluent.
- [00144] In certain embodiments, a pharmaceutical composition of the invention is suitable for oral administration.
- [00145] In yet another aspect, the invention generally relates to a unit dosage form comprising a pharmaceutical composition comprising a compound disclosed herein.
- [00146] In certain embodiments, the unit dosage form is in the form of a tablet or capsule.
- [00147] 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.
- [00148] In yet another aspect, the invention generally relates to a method for modulating (*e.g.*, inhibiting or reducing) KRas(G12D) activity in a cell, comprising contacting the cell with a compound disclosed herein.
- [00149] 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.
- [00150] 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.
- [00151] 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.
- [00152] 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.

[00153] In certain embodiments, the cancer is selected from the group consisting of carcinoma, squamous carcinoma, adenocarcinoma, sarcoma, leukemia, neuroma, melanoma, and lymphoma.

[00154] 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.

[00155] 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.

[00156] 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.

[00157] In certain embodiments, the subject has a mutation of KRAS, HRAS and/or NRAS.

[00158] 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.

[00159] 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.

[00160] 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.

[00161] 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.

[00162] 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.

[00163] 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.

[00164] 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.

[00165] 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.

[00166] 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.

[00167] 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.

[00168] 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.

[00169] 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.

[00170] 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.

[00171] 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.

[00172] 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.

[00173] 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.

[00174] 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.

[00175] In certain embodiments, the method further comprises administering a chemotherapeutic agent to the subject.

[00176] 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.

[00177] 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, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiolesterol, mepitiolesterol, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglutone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestabucil; bisantrene; edatrexate; 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<sup>®</sup> 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<sup>®</sup> (paclitaxel; Bristol-Myers Squibb Oncology, Princeton, N.J.), ABRAXANE<sup>®</sup> (Cremophor-free), albumin-engineered nanoparticle formulations of paclitaxel (American Pharmaceutical Partners, Schaumburg, Ill.), and TAXOTERE<sup>®</sup> (doxetaxel; Rhone-Poulenc Rorer, Antony, France); chlorambucil; GEMZAR<sup>®</sup> (gemcitabine); 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; NAVELBINE<sup>®</sup> (vinorelbine); novantrone; teniposide; edatrexate; daunomycin; aminopterin; capecitabine (XELODA<sup>®</sup>); 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.

[00178] 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).

[00179] 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.

[00180] 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.

[00181] 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.

[00182] 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  $^2\text{H}$ ,  $^3\text{H}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$ ,  $^{18}\text{O}$ ,  $^{17}\text{O}$ ,  $^{31}\text{P}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{18}\text{F}$ , and  $^{36}\text{Cl}$ , respectively.

[00183] By isotopically-labeling the presently disclosed compounds, the compounds may be useful in drug and/or substrate tissue distribution assays. Tritiated ( $^3\text{H}$ ) and carbon-14 ( $^{14}\text{C}$ ) labeled compounds are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium ( $^2\text{H}$ ) 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.

[00184] Further, substitution of normally abundant hydrogen ( $^1\text{H}$ ) 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  $^{12}\text{C}$  with  $^{13}\text{C}$ . (See, WO 2007/005643, WO 2007/005644, WO 2007/016361, and WO 2007/016431.)

[00185] 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.

[00186] 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.

[00187] 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.

[00188] 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.

[00189] 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.

[00190] 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.

[00191] 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.

[00192] 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.

[00193] 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

[00194] The following examples are given for the purpose of illustrating the invention, but not for limiting the scope or spirit of the invention.

[00195] 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.

### Abbreviations

---

Ac = Acetyl

AcO = Acetate

---

---

Ac<sub>2</sub>O = Acetic anhydride

Ar = Aryl

B<sub>2</sub>Pin<sub>2</sub> = bis(pinacolato)diboron

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

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

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, Triethylendiamine

DAST = Diethylaminosulphur trifluoride

dba = Dibenzylideneacetone

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

DCC = 1,3-Dicyclohexylcarbodiimide

DCM = Dichloromethane

DEAD = Diethyl azodicarboxylate

DIBAL = Diisobutylaluminium hydride

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                                               |
| DMSO              | = Dimethylsulphoxide                                                                             |
| DPA               | = Diisopropylamine                                                                               |
| Ddpb              | = 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<br>hydrochloride                                 |
| Eq                | = equivalent                                                                                     |
| ESI or ES         | = Electrospray ionization                                                                        |
| Et                | = ethyl                                                                                          |
| Et <sub>2</sub> O | = Diethyl ether                                                                                  |
| EtOAc             | = Ethyl acetate                                                                                  |
| 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                                                                                      |

---

---

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)Cl<sub>2</sub> = [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium  
Pd(PPh<sub>3</sub>)<sub>4</sub> = tetrakis(triphenylphosphine)palladium  
Ph = Phenyl  
Piv = Pivaloyl, 2,2-dimethylacetyl  
PMB = p-Methoxybenzyl  
PPTS = Pyridinium p-toluensulphonate  
n-Pr = n-Propyl

---



---

Pr = Propyl

i-Pr or iPr = isopropyl

PTC = Phase transfer catalyst

PTSA = p-Toluenesulphonic acid

Pv = Pivaloyl, 2,2-dimethylacetyl

Py = Pyridine

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

RT = room temperature

SFC = supercritical fluid chromatography

SEM = 2-(Trimethylsilyl)ethoxymethyl

TBAF = Tetrabutylammonium fluoride

TBDMS = tert-Butyldimethylsilyl

TBDPS = tert-Butyldiphenylsilyl

TBS = tert-Butyldimethylsilyl

TEA = Triethylamine

TES = Triethylsilyl

Tf = Trifluoromethanesulfonyl

TfO = Trifluoromethanesulfonate

Tf<sub>2</sub>O = Trifluoromethanesulfonyl anhydride

TfOH = Trifluoromethanesulfonic acid

TFA = Trifluoroacetic acid

TFAA = Trifluoroacetic anhydride

THF = Tetrahydrofuran

THP = Tetrahydropyranyl

TIPS = Triisopropylsilyl

TMEDA = N,N,N',N'-Tetramethylethylenediamine

TMG = Tetramethylguanidine

TMS = Trimethylsilyl

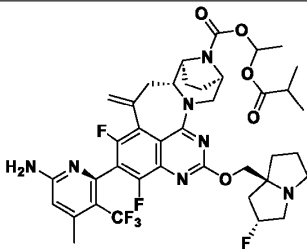
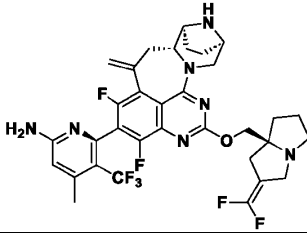
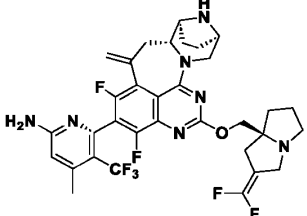
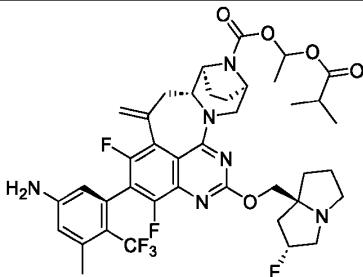
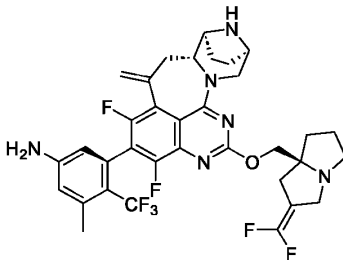
Tol = p-Tolyl

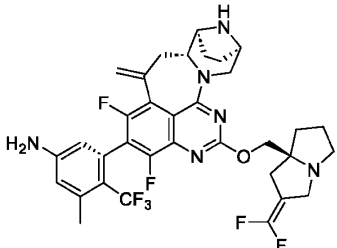
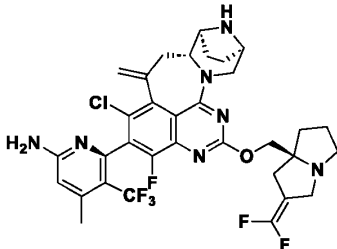
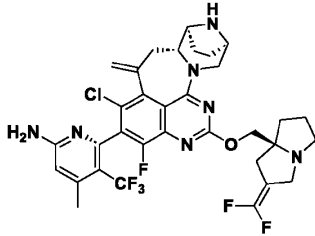
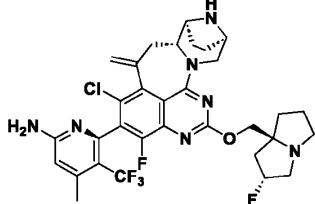
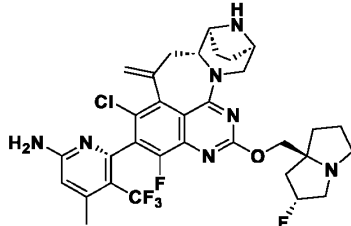
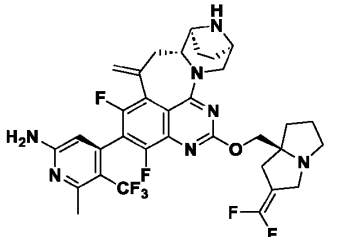
TPS = Tripropylsilyl

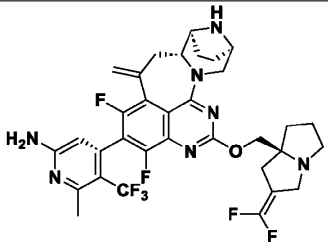
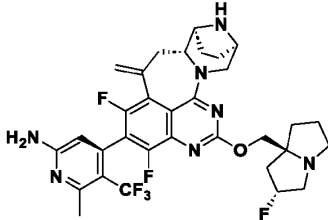
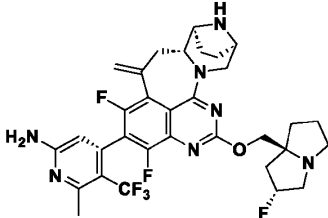
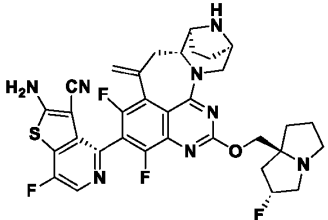
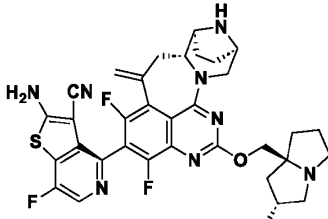
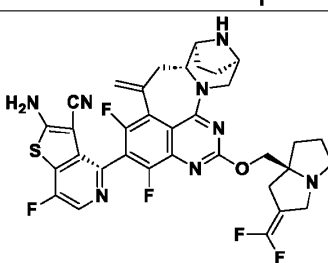
Tr = Trityl, triphenylmethyl

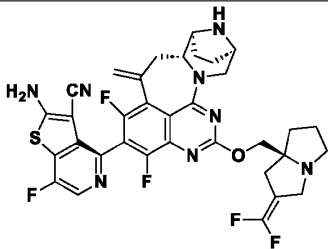
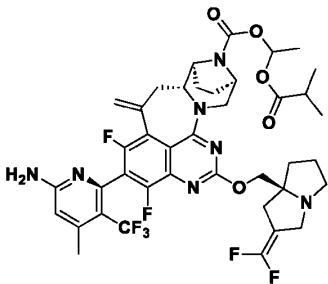
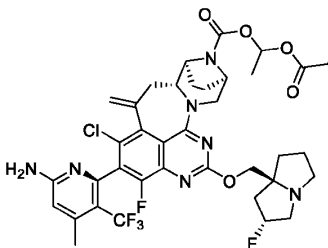
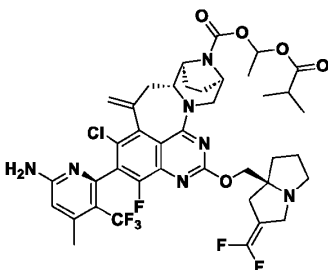
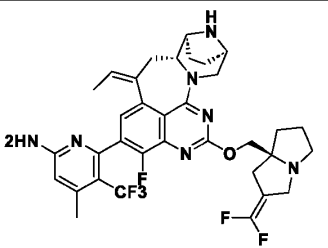
---

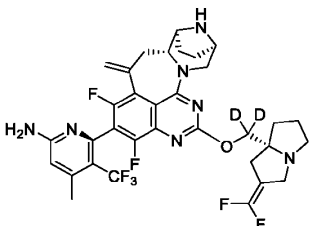
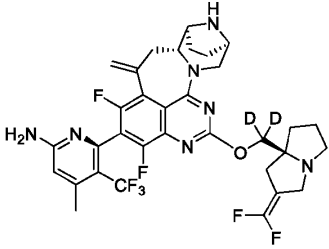
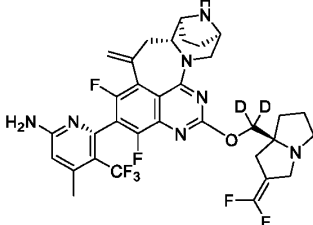
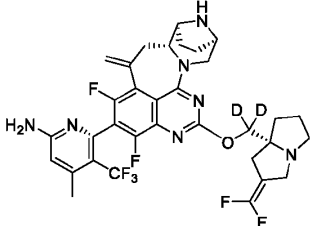
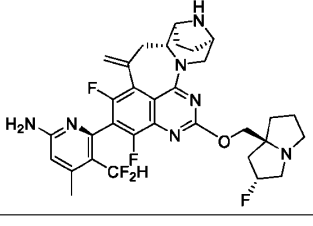
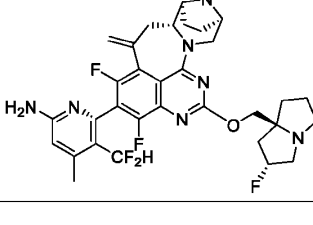


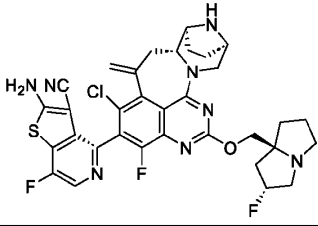
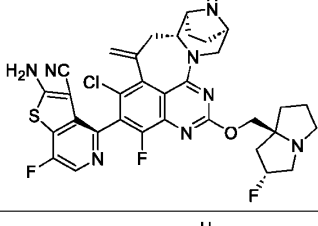
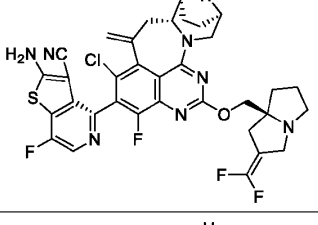
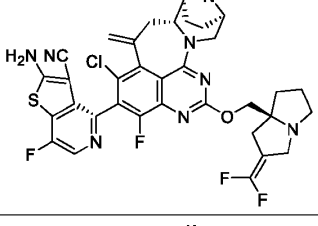
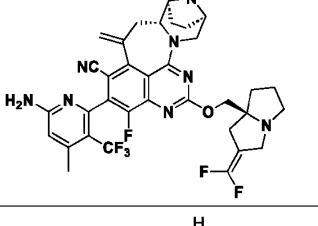
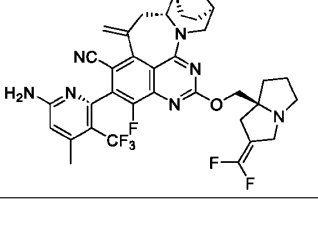
|   |                                                                                     |
|---|-------------------------------------------------------------------------------------|
| 5 |    |
| 6 |    |
| 7 |   |
| 8 |  |
| 9 |  |

|    |                                                                                      |
|----|--------------------------------------------------------------------------------------|
| 10 |     |
| 11 |     |
| 12 |   |
| 13 |  |
| 14 |  |
| 15 |   |

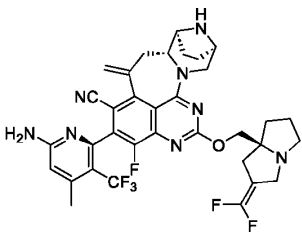
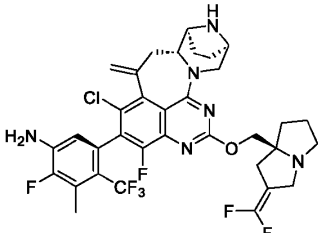
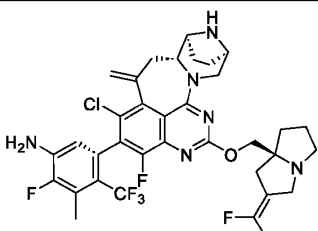
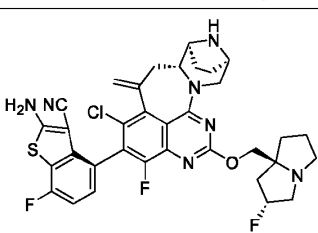
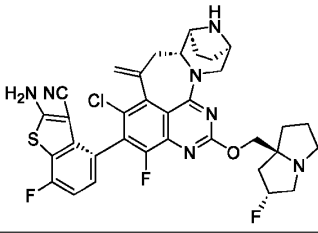
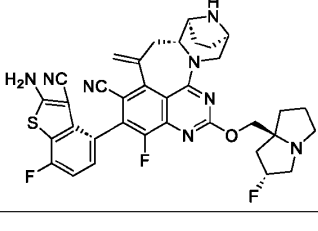
|    |                                                                                     |
|----|-------------------------------------------------------------------------------------|
| 16 |    |
| 17 |    |
| 18 |   |
| 19 |  |
| 20 |  |
| 21 |  |

|    |                                                                                     |
|----|-------------------------------------------------------------------------------------|
| 22 |    |
| 23 |    |
| 24 |   |
| 25 |  |
| 26 |  |

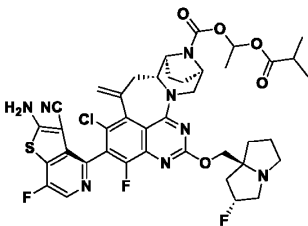
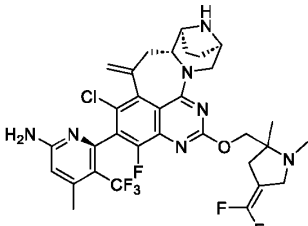
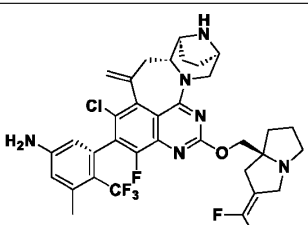
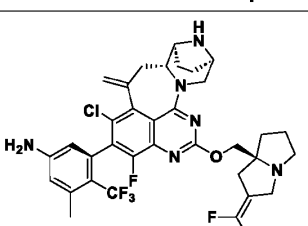
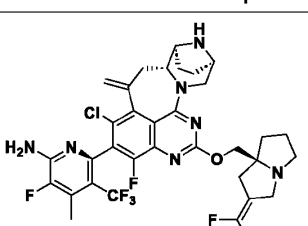
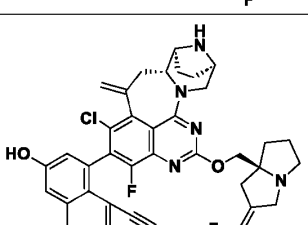
|    |                                                                                     |
|----|-------------------------------------------------------------------------------------|
| 27 |    |
| 28 |    |
| 29 |   |
| 30 |  |
| 31 |  |
| 32 |  |

|    |                                                                                     |
|----|-------------------------------------------------------------------------------------|
| 33 |    |
| 34 |    |
| 35 |   |
| 36 |  |
| 37 |  |
| 38 |  |

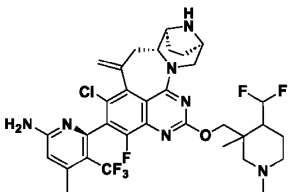
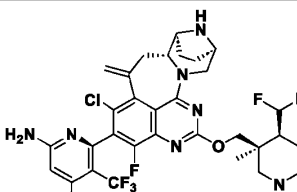
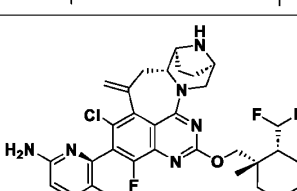
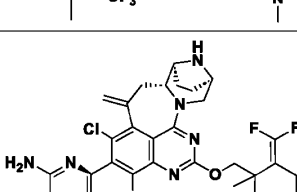
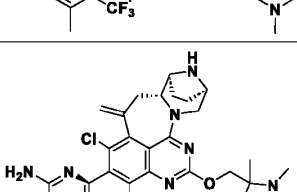
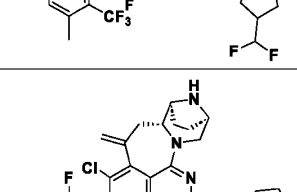


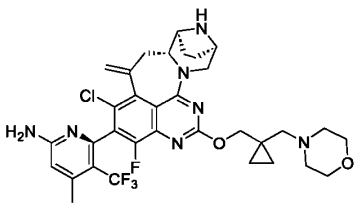
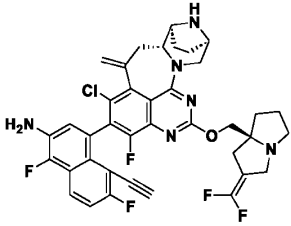
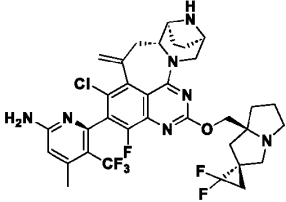
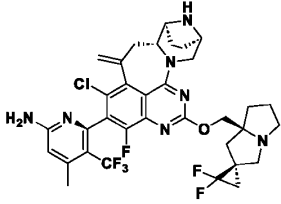
|    |                                                                                     |
|----|-------------------------------------------------------------------------------------|
| 39 |    |
| 40 |    |
| 41 |   |
| 42 |  |
| 43 |  |
| 44 |  |

|    |  |
|----|--|
| 45 |  |
| 46 |  |
| 47 |  |
| 48 |  |
| 49 |  |
| 50 |  |

|    |                                                                                     |
|----|-------------------------------------------------------------------------------------|
| 51 |    |
| 52 |    |
| 53 |   |
| 54 |  |
| 55 |  |
| 56 |  |

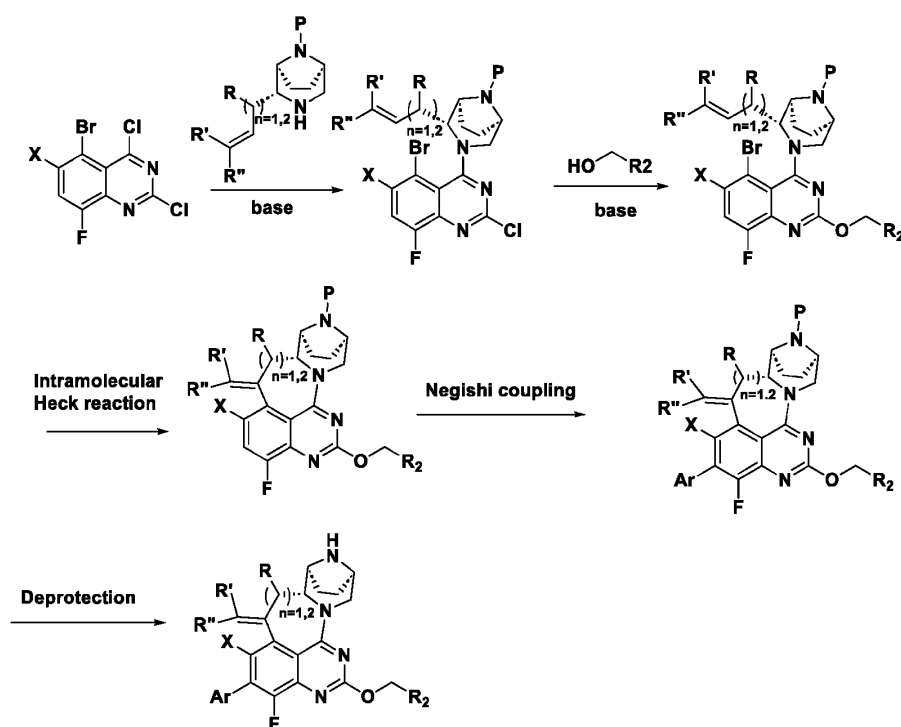
|    |  |
|----|--|
| 57 |  |
| 58 |  |
| 59 |  |
| 60 |  |
| 61 |  |
| 62 |  |

|    |                                                                                     |
|----|-------------------------------------------------------------------------------------|
| 63 |    |
| 64 |    |
| 65 |    |
| 66 |   |
| 67 |  |
| 68 |  |

|    |                                                                                     |
|----|-------------------------------------------------------------------------------------|
| 69 |    |
| 70 |    |
| 71 |   |
| 72 |  |

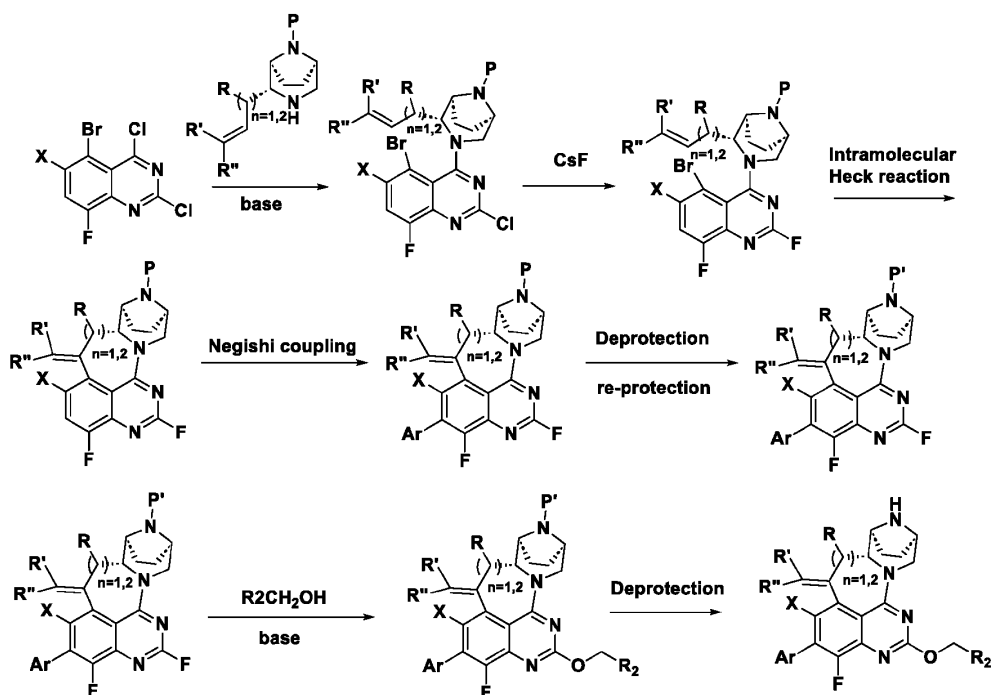
## General Synthetic Schemes

*Scheme 1*



[00196] **Scheme 1** illustrates one general procedure for preparing the compounds of disclosure using metal-catalyzed reactions. Displacement of 4-chloro group of 1,3-disubstituted quinazoline with a protected alpha-allyl bridged piperazine or amine provides 2-chloro-4-amine-substituted quinazoline alkene intermediate. Then 2-chloro group was displaced with an appropriate alcohol to provide an ether substituted quinazoline intermediate. This intermediate goes through intramolecular Heck reaction between aryl bromide and alkene to form the quinazoline fused seven-member or eight-member ring with an *exo*-alkene group. After deprotonation and zincate formation, Pd-catalyzed Negishi coupling with a suitable aryl halide affords the desired aryl-aryl coupling product. After the removal of all the protecting groups, the product was purified and submitted to SFC separation to give the desired diastereomer.

### Scheme 2

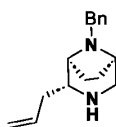


[00197] **Scheme 2** illustrates another procedure for preparing the compounds of disclosure. After the displacement of the 4-chloro group of 1,3-disubstituted quinazoline with a protected alpha-allyl bridged piperazine or amine, 2-Cl was transformed to 2-F by reacting with CsF. 2-F quinazoline alkene goes through intramolecular Heck reaction and Negishi coupling with suitable aryl halide to form 2-F-7-Aryl quinazoline fused seven-member or eight-member ring with an *exo*-alkene group. Amine protecting group sometimes has to be switched to another group if necessary. S<sub>N</sub>Ar replacement of 2-F with an appropriate alcohol affords an ether substituted quinazoline intermediate. Removal of all the protecting group provides the diastereomeric product mixture, which was separated by SFC to give the desired single diastereomer.

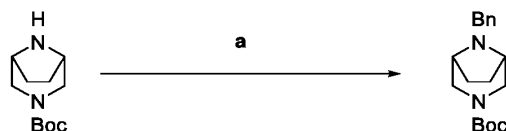
### Syntheses of Intermediates

#### Intermediate 1

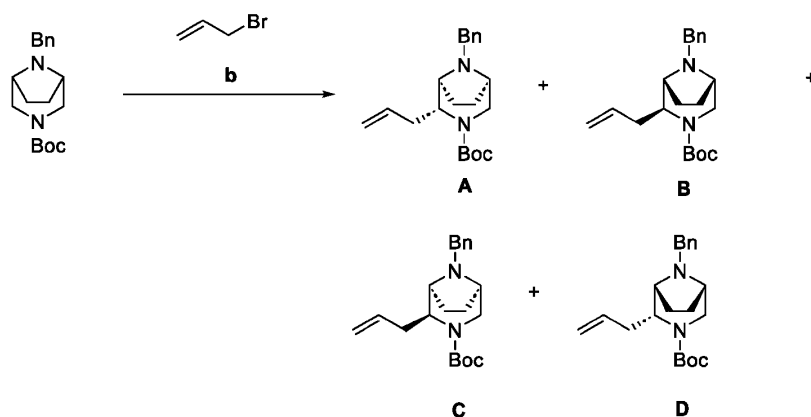
(1*R*,2*R*,5*S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octane





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

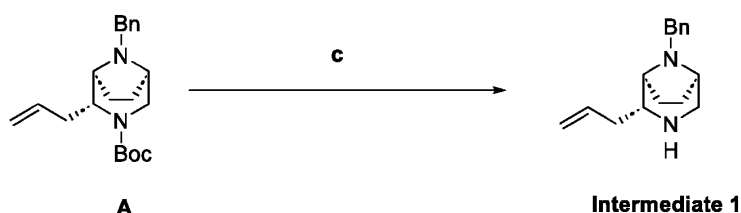
[00198] To a solution of tert-butyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate (15.0 g, 70.8 mmol, 1.0 eq) in DMF (245 mL) was added  $K_2CO_3$  (19.6 g, 141.5 mmol, 2.0 eq). Then the reaction was cooled to 0 °C and added BnBr (18.1 g, 106.1 mmol, 1.5 eq). The mixture was stirred at room temperature for 2 h. HPLC and TLC showed the complete reaction. The solution was diluted with water (750 mL) and extracted with EtOAc (150 mL x 3). The organic layers were separated, washed with water (50 mL), brine (50 mL) and dried over  $Na_2SO_4$ . After filtration and concentration under reduced pressure, the resulting crude product was purified by silica gel column chromatography (petroleum ether: EtOAc = 10: 1) to afford tert-butyl 8-benzyl-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (15.0 g, 70.2%) as a yellow oil. LCMS:  $m/z$  303.1 ( $M+H^+$ ).

**Step 2: Synthesis of tert-butyl (1*R*, 2*R*, 5*S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octane-3-carboxylate**

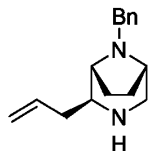
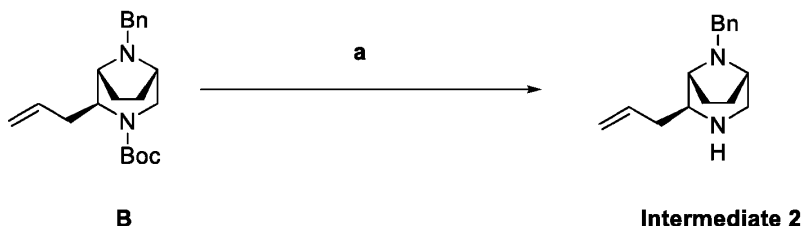
[00199] To a solution of tert-butyl 8-benzyl-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (40.0 g, 132.0 mmol, 1.0 eq) and *N,N,N',N'*-Tetramethylethylenediamine (30.7 g, 264.8 mmol, 2.0 eq) in THF (400 mL) was added *sec*-Butyllithium (264.8 mL, 264.8 mmol, 2.0 eq) dropwise at -78 °C under  $N_2$ . After stirring at -78 °C for 40 min. 3-bromoprop-1-ene (79.2 g, 661.6 mmol, 5.0 eq) in THF (80 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred overnight. Then the reaction was quenched by the addition of saturated aqueous

NaHCO<sub>3</sub> (300 mL). The aqueous layer was separated and extracted with EtOAc (500 mL x 3). The combined organic phase was washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to give a residue. The residue was purified by silica gel chromatography (eluted with petroleum ether: EtOAc = 30: 1) to afford the four diastereomers as two separable spots, each of which contains two enantiomers (Spot 1 contains compound **C** and compound **D**, less molar; Spot 2 contains compound **A** and compound **B**, more polar). The spot with higher polarity (spot 2, compound **A** and compound **B**) was the desired racemic mixture and collected as a yellow oil (9.6 g, 21.2%). The stereochemistry of A and B was later confirmed through **Intermediates 1** and **2**. Some of this oil (5 g, 14.6 mmol) was further separated by SFC to give the two pure enantiomers: *tert*-butyl (*1R,2R,5S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (Compound **A**; peak 1 in SFC, 1.2 g, 5.1%) as a yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.45-7.15 (m, 5H), 5.88-5.58 (m, 1H), 5.10-4.90 (m, 2H), 3.67-3.47 (m, 3H), 3.40 (dd, *J* = 12.1, 1.8 Hz, 1H), 3.28 (dd, *J* = 12.1, 3.8 Hz, 1H), 3.20-3.15 (m, 3H), 2.20-2.06 (m, 1H), 2.07 -1.90 (m, 2H), 1.88-1.69 (m, 1H), 1.65-1.55 (m, 1H), 1.45 (s, 9H). LCMS: *m/z* 343.1 (*M*+H<sup>+</sup>); and *tert*-butyl (*1R,2R,5S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (Compound **B**, peak 2 in SFC, 1.1 g, 4.7%) as a yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.45-7.15 (m, 5H), 5.88-5.58 (m, 1H), 5.10-4.90 (m, 2H), 3.67-3.47 (m, 3H), 3.40 (dd, *J* = 12.1, 1.8 Hz, 1H), 3.28 (dd, *J* = 12.1, 3.8 Hz, 1H), 3.20-3.15 (m, 3H), 2.20-2.06 (m, 1H), 2.07 -1.90 (m, 2H), 1.88-1.69 (m, 1H), 1.65-1.55 (m, 1H), 1.45 (s, 9H). LCMS: *m/z* 343.1 (*M*+H<sup>+</sup>).

**Step 3: Synthesis of (*1R, 2R, 5S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octane**



[00200] To a solution of *tert*-butyl (*1R,2R,5S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (compound **A**, 3.0 g, 8.8 mmol, 1.0 eq) in DCM (8 mL) was added TFA (15 mL). The mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure to give a crude product, (*1R, 2R, 5S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octane TFA salt as a yellow oil, which was used directly. LCMS: *m/z* 243.1 (*M*+H<sup>+</sup>).

**Intermediate 2****(1*R*,2*S*,5*S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octane****Step 1: Synthesis of (1*R*,2*S*,5*S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octane**

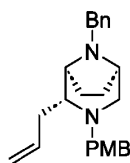
[00201] To a solution of tert-butyl (1*R*,2*S*,5*S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (Compound **B** from **Intermediate 1** synthesis step 2, 540 mg, 1.58 mmol, 1.0 eq) in DCM (5 mL) was added TFA (2.5 mL). The mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure to give (1*R*,2*S*,5*S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octane TFA salt as a yellow oil, which was used directly. LCMS:  $m/z$  243.1 ( $M+H^+$ ).

**Stereochemistry Determination of Intermediate 1 and 2**

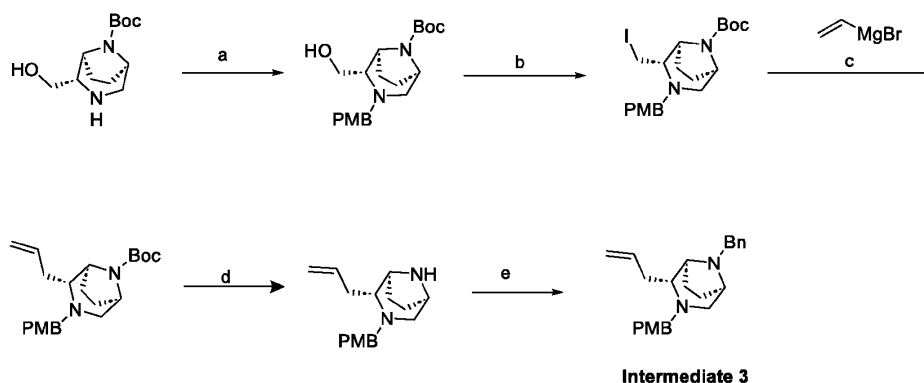
[00202] Stereochemistry of **Intermediate 1** and **Intermediate 2** was determined by chiral HPLC through derivatization to match a common product, **Intermediate 3**, (1*S*,2*R*,5*R*)-2-allyl-8-benzyl-3-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octane, which was prepared from the known chiral starting material, tert-butyl (1*S*,2*S*,5*R*)-2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate. The result showed that the derivative from **Intermediate 1** matches **Intermediate 3**.

**Intermediate 3**

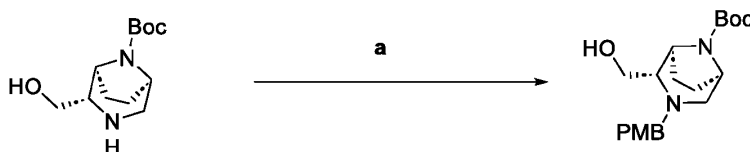
**(1*S*,2*R*,5*R*)-2-allyl-8-benzyl-3-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octane (Prepared as chiral standard from a commercially available enantiomeric pure starting material, tert-butyl (1*S*,2*S*,5*R*)-2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate)**



### Synthetic scheme

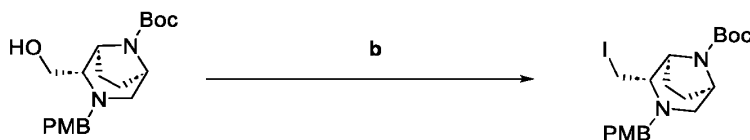


### Step 1: Synthesis of tert-butyl (1S,2S,5R)-2-(hydroxymethyl)-3-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[00203] To a solution of the known tert-butyl (1S,2S,5R)-2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (4.0 g, 16.5 mmol, 1.0 eq) in DCM (240 mL) was added TEA (3.3 g, 33.1 mmol, 2.0 eq) and 4-methoxybenzaldehyde (2.4 g, 17.3 mmol, 1.05 eq) at room temperature. After stirring at room temperature for 30 min, acetic acid (1.19 g, 19.8 mmol, 1.2 eq) and NaBH(OAc)<sub>3</sub> (10.5 g, 49.6 mmol, 3.0 eq) were added. The mixture was stirred overnight and cooled down to 0 °C. A solution of KHCO<sub>3</sub> (28 g in water 100 mL) was added. The two layers were separated, and the aqueous layer was extracted with DCM (50 x 2 mL). The combined organic layer was washed with 5% aqueous NaHCO<sub>3</sub> (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated to afford the crude product. The crude was purified by column chromatography on silica gel eluted with (Petroleum ether: EtOAc = 50: 1) to give tert-butyl (1S,2S,5R)-2-(hydroxymethyl)-3-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (3.2 g, 53.5%) as a white solid. LCMS: m/z 363.0 (M+H<sup>+</sup>).

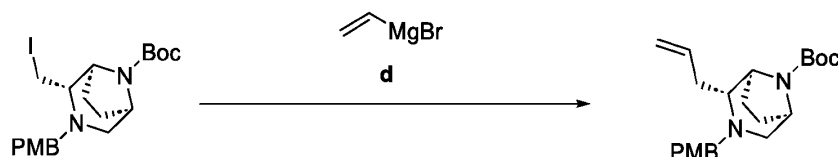
**Step 2: Synthesis of tert-butyl (1*S*,2*S*,5*R*)-3-(4-methoxybenzyl)-2-(((methylsulfonyl)oxy)methyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate**



[00204] To a solution of tert-butyl (1*S*,2*S*,5*R*)-2-(hydroxymethyl)-3-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (700 mg, 1.9 mmol, 1.0 eq) in THF (7 mL) was added TEA (587 mg, 5.8 mmol, 3.0 eq) at room temperature. The mixture was cooled to 0 °C and added Ms<sub>2</sub>O (505 mg, 2.9 mmol, 1.5 eq). The solution was stirred for 1h at room temperature. LCMS showed the reaction went to completion. LCMS: *m/z* 441.0 (M+H<sup>+</sup>).

To the above solution was added NaI (5.1 g, 34.2 mmol, 18.0 eq) at room temperature. The solution was heated at 50 °C overnight and cooled to room temperature. The mixture was filtered and the filtrate was concentrated to give the crude product, which was purified by silica gel chromatography (petroleum ether: EtOAc = 3: 1) to afford tert-butyl (1*S*,2*S*,5*R*)-2-(iodomethyl)-3-(4-methoxybenzyl)-3,8-diazabicyclo [3.2.1]octane-8-carboxylate (613 mg, 67.2 % for two steps) as a yellow oil. LCMS: *m/z* 472.9 (M+H<sup>+</sup>).

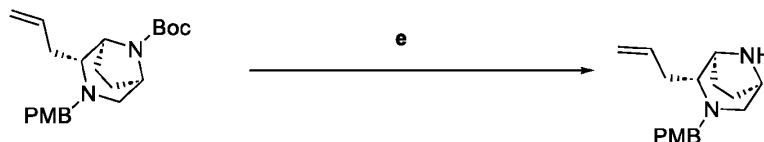
**Step 3: Synthesis of tert-butyl (1*S*,2*R*,5*R*)-2-allyl-3-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate**



[00205] To a solution of CuI (1.83 g, 9.63 mmol, 3.2 eq) in THF (6.7 mL) was added vinyl magnesium bromide (1 M, 18.06 mL, 18.06 mmol, 6.0 eq) at -40 °C under N<sub>2</sub> atmosphere. The reaction mixture was stirred at the same temperature for 30 min. Then tert-butyl (1*S*,2*S*,5*R*)-2-(iodomethyl)-3-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.42 g, 3.01 mmol, 1.0 eq) in THF (10 mL) was added. The reaction mixture was stirred at 10 °C for 2 h and diluted with EtOAc (35 mL), saturated ammonium chloride solution (35 mL) and ammonium hydroxide (7 mL). The mixture was extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (Petroleum ether: EtOAc = 5:

1) to afford tert-butyl (*1S,2R,5R*)-2-allyl-3-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (305 mg, 27.2%) as a yellow oil. LCMS: *m/z* 373.0 ( $[M+H]^+$ ).

**Step 4: Synthesis of (*1S,2R,5R*)-2-allyl-3-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octane**



[00206] To a solution of tert-butyl (*1S,2R,5R*)-2-allyl-3-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (215 mg, 0.58 mmol, 1.0 eq) in DCM (5.8 mL) was added TFA (1.45 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h, then concentrated under reduced pressure to give a crude TFA salt (240 mg) as a yellow oil, which was used directly for the next step without further purification. LCMS: *m/z* 273.1 ( $M+H^+$ ).

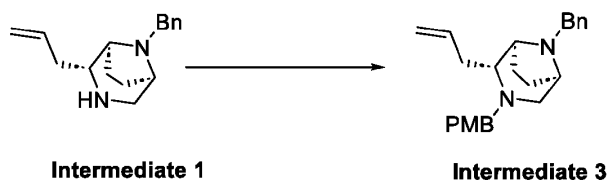
**Step 5: Synthesis of (*1S,2R,5R*)-2-allyl-8-benzyl-3-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octane**



**Intermediate 3**

[00207] To a solution of (*1S,2R,5R*)-2-allyl-3-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octane (240 mg, crude) and  $K_2CO_3$  (321 mg, 2.32 mmol, 4.0 eq) in DMF (7.25 mL) was added BnBr (149 mg, 0.87 mmol, 1.5 eq) at 0 °C under  $N_2$  atmosphere. The reaction was stirred at room temperature for 1.5 h, then diluted with  $H_2O$  (5 mL). The mixture was extracted with EtOAc (5 mL x 3). The combined organic layers were dried over  $Na_2SO_4$ , filtered, and concentrated under reduced pressure to give a crude product, which was purified by prep-TLC (DCM: MeOH = 15: 1) to afford (*1S,2R,5R*)-2-allyl-8-benzyl-3-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octane (68 mg, 32.3% for two steps) as a yellow oil.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  7.45 – 7.15 (m, 7H), 6.83 (d,  $J$  = 8.4 Hz, 2H), 5.59-6.56 (m, 1H), 5.10-4.90 (m, 2H), 4.04 (d,  $J$  = 12 Hz, 1H), 3.79 (s, 3H), 3.65-3.35 (m, 2H), 3.25-2.85 (m, 3H), 2.70-2.30 (m, 3H), 2.25 – 2.15 (m, 1H), 2.10-1.60 (m, 5H). LCMS: *m/z* 363.1 ( $M+H^+$ ).

**Intermediate 3 prepared from Intermediate 1 to confirm the stereochemistry**

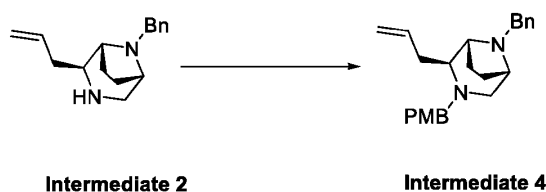


[00208] To a solution of **Intermediate 1**, (*1S,2R,5R*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octane (30 mg, 0.12 mmol, 1.0 eq) in DMF (1.0 mL) was added  $K_2CO_3$  (34 mg, 0.25 mmol, 2.0 eq) and PMBCl (25 mg, 0.16 mmol, 1.3 eq). The mixture was stirred at room temperature for 2 h and quenched with 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 x 2), dried over  $Na_2SO_4$  and evaporated to dryness. The crude product was purified by Prep-TLC (petroleum ether: ethyl acetate 1 = 3 : 1) to give the desired product **Intermediate 3**, (*1S,2R,5R*)-2-allyl-8-benzyl-3-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octane (26 mg, 57.8%) as a colorless oil.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  7.45 – 7.15 (m, 7H), 6.83 (d,  $J$  = 8.6 Hz, 2H), 5.59–6.56 (m, 1H), 5.10–4.90 (m, 2H), 4.04 (d,  $J$  = 13.5 Hz, 1H), 3.79 (s, 3H), 3.65–3.35 (m, 2H), 3.25–2.85 (m, 3H), 2.70–2.30 (m, 3H), 2.25 – 2.15 (m, 1H), 2.10–1.60 (m, 5H). LCMS: 363.2 ( $M+H^+$ ).

#### Intermediate 4

(The enantiomer of Intermediate 3)

(*1R,2R,5S*)-2-allyl-8-benzyl-3-(4-methoxybenzyl)-3,8-diazabicyclo [3.2.1]octane from  
**Intermediate 2**



[00209] To a solution of **Intermediate 2**, (*1R,2R,5S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octane (25 mg, 0.10 mmol, 1.0 eq) in DMF (1.0 mL) was added  $K_2CO_3$  (29 mg, 0.21 mmol, 2.0 eq) and PMBCl (21 mg, 0.13 mmol, 1.3 eq). The mixture was stirred at room temperature for 2 h and 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 Prep-

TLC (petroleum ether: ethyl acetate 1 = 3 : 1) to give the desired product **Intermediate 4**, (*1R,2R,5S*)-2-allyl-8-benzyl-3-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octane (17 mg, 45.9%) as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.45 – 7.15 (m, 7H), 6.83 (d,  $J$  = 8.4 Hz, 2H), 5.59-6.56 (m, 1H), 5.10-4.90 (m, 2H), 4.04 (d,  $J$  = 13.6 Hz, 1H), 3.79 (s, 3H), 3.65-3.35 (m, 2H), 3.25-2.85 (m, 3H), 2.70-2.30 (m, 3H), 2.25 – 2.15 (m, 1H), 2.10-1.60 (m, 5H). LCMS: 363.2 (M+H<sup>+</sup>).

#### Stereochemistry determination

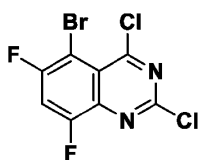
[00210] Chiral HPLC was used to characterize the racemic mixture of **Intermediates 3 and 4**, which were prepared from **Intermediates 1 and 2** respectively. Peak 1 matches the **Intermediate 3** synthesized from the known chiral starting material, tert-butyl (*1S,2S,5R*)-2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and **Intermediate 3** synthesized from **Intermediate 1**. Therefore, we assigned the stereochemistry of **Intermediates 1 and 2** accordingly.

(Chiral HPLC conditions: Mobile phase: A for 0.1%TFA in H<sub>2</sub>O, B for 0.1%TFA in ACN.

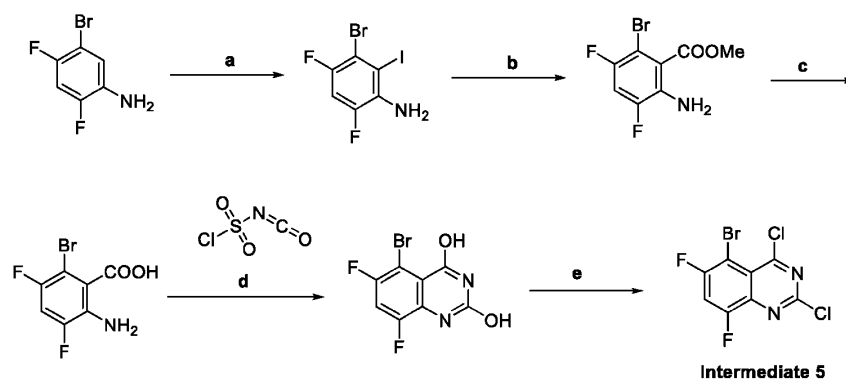
Gradient: A 60%. Column: OD-3R. Flow rate: 0.5 mL/min.)

#### Intermediate 5

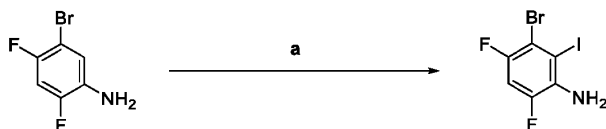
4-((*1R,2R,5S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-2-chloro-6,8-difluoroquinazoline



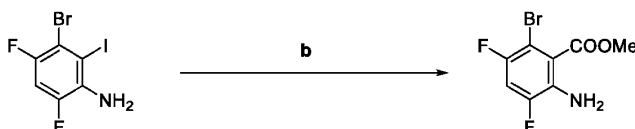
#### Synthetic scheme:



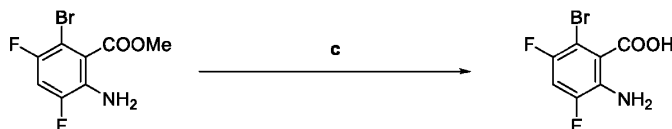


**Step 1: Synthesis of 3-bromo-4,6-difluoro-2-iodoaniline**

[00211] To a solution of 5-bromo-2,4-difluoroaniline (10.0 g, 48.07 mmol, 1.0 eq) in EtOH (200 mL) was added iodine (13.42 g, 52.88 mmol, 1.1 eq), Silver sulfate (14.99 g, 48.07 mmol, 1.0 eq). The mixture was stirred at 25 °C for 1 h. The mixture was filtered, and the filtrate was concentrated to give a crude product, which was purified by silica gel column chromatography (petroleum ether) to afford 3-bromo-4,6-difluoro-2-iodoaniline (7.5 g, 46.5%) as a red solid. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.45 (dd, *J* = 11.1, 8.7 Hz, 1H), 5.33 (s, 2H).

**Step 2: Synthesis of methyl 2-amino-6-bromo-3,5-difluorobenzoate**

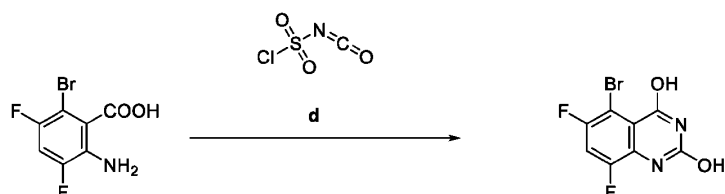
[00212] To a solution of 3-bromo-4,6-difluoro-2-iodoaniline (30.0 g, 89.8 mmol, 1.0 eq) in MeOH (148 mL) was added DMF (209 mL), TEA (27.3 g, 269.5 mmol, 3.0 eq), Pd(OAc)<sub>2</sub> (1 g, 4.5 mmol, 0.05 eq) and dppf (1.25 g, 2.3 mmol, 0.025 eq). The mixture was stirred at 75 °C for 15 h under 0.4 MPa CO. The mixture was concentrated to give a crude product. The mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL x 3). The organic layers were washed with water (100 mL x 2), brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (petroleum ether: EtOAc = 40: 1) to afford methyl 2-amino-6-bromo-3,5-difluorobenzoate (20.0 g, 83.7%) as a red liquid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.45 (dd, *J* = 11.2, 8.8 Hz, 1H), 5.55 (s, 2H), 3.87 (s, 3H).

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

[00213] To a solution of 2-amino-6-bromo-3,5-difluorobenzoate (10 g, 37.6 mmol, 1.0 eq) in MeOH (185 mL) was added NaOH (3.0 g, 75.18 mmol, 2.0 eq) in water (185 mL). The mixture was stirred at 30 °C for 12 h. The reaction mixture was concentrated under reduced pressure to

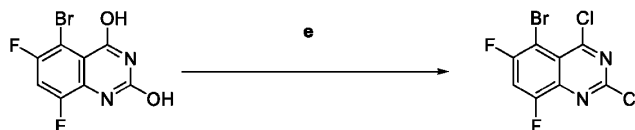
give an intermediate. The solution PH was adjusted to 1 with 1M HCl. Then the mixture was filtered to give 2-amino-6-bromo-3,5-difluorobenzoic acid (5.1 g, 53.8%) as a yellow solid, which was used directly for the next step.

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



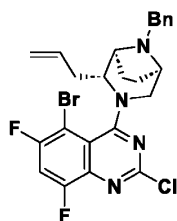
[00214] To a solution of 2-amino-6-bromo-3,5-difluorobenzoic acid (10 g, 39.7 mmol, 1.0 eq) in DCM (100 mL) was added chlorosulfonyl isocyanate (12.9 g, 91.3 mmol, 2.3 eq) at 0 °C under nitrogen atmosphere. The mixture was stirred at room temperature for 7 h. The reaction mixture was concentrated under reduced pressure to give a crude product, which was added 6N HCl (300 mL) and stirred 2 h at 100 °C. The mixture was cooled to room temperature, filtered and dried to give 5-bromo-6,8-difluoroquinazoline-2,4-diol (8.8 g, 80.1%) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 11.43 (d, *J* = 66.4 Hz, 2H), 7.91 (s, 1H).

#### Step 5: Synthesis of 5-bromo-2,4-dichloro-6,8-difluoroquinazoline

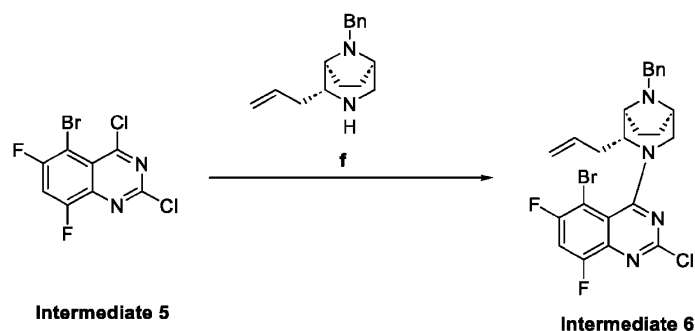


[00215] To a solution of 5-bromo-6,8-difluoroquinazoline-2,4-diol (2.0 g, 7.25 mmol, 1.0 eq) in POCl<sub>3</sub> (20 mL) was added DIEA (2.0 mL). The mixture was stirred at 110 °C for 6 h under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to give the crude product, 5-bromo-2,4-dichloro-6,8-difluoroquinazoline as yellow oil (2.26 g), which was used directly.

#### Intermediate 6



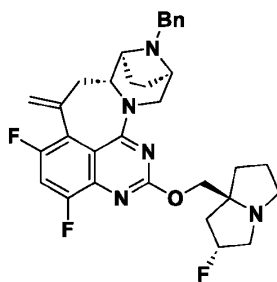
**Synthesis of 4-((1*R*,2*R*,5*S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-2-chloro-6,8-difluoroquinazoline**



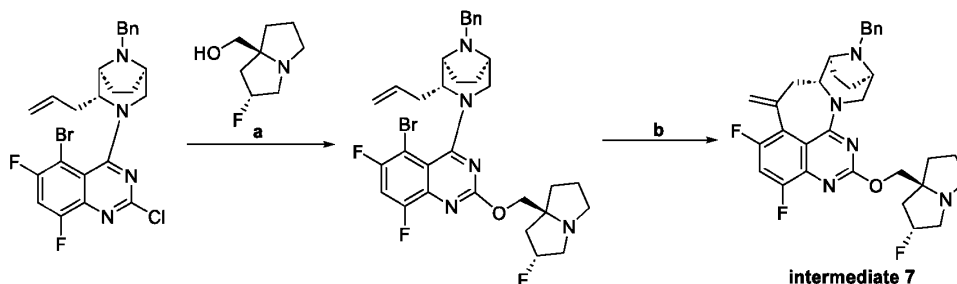
[00216] To a solution of 5-bromo-2,4-dichloro-6,8-difluoroquinazoline (**Intermediate 5**, 2.26 g, 7.26 mmol, 1.0 eq) in DCM (20 mL) was added DIEA (8.2 g, 63.2 mmol, 8.7 eq) and tert-butyl (1*R*, 2*R*, 5*S*)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (**Intermediate 1**, 2.1 g, 8.7 mmol, 1.2 eq) at -40 °C under nitrogen atmosphere. The mixture was stirred at -40 °C for 2 h and added water (30 mL). The solution was extracted with DCM (20 mL x 3). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (petroleum ether: EtOAc = 30: 1) to afford 4-((1*R*,2*R*,5*S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-2-chloro-6,8-difluoroquinazoline (2.6 g, 69.1% for two steps) as a yellow solid. LCMS: *m/z* 518.8, 520.8 (M+H<sup>+</sup>).

**Intermediate 7**

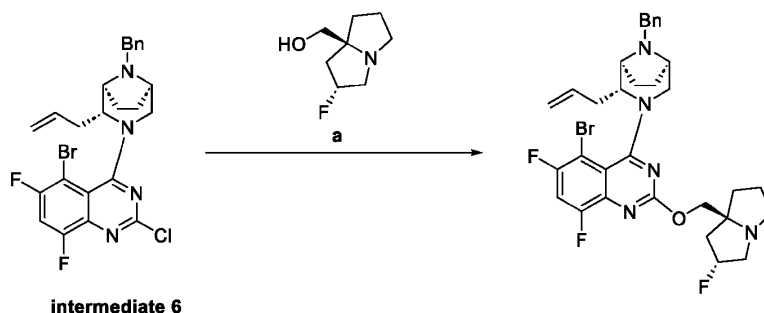
**(1*S*,4*R*,14*aR*)-15-benzyl-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline**



**Synthetic scheme:**

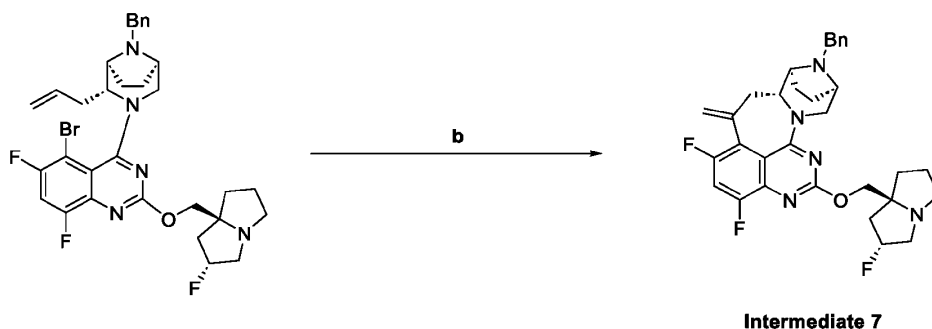


**Step 1: Synthesis of 4-((1*R*,2*R*,5*S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-6,8-difluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)quinazoline**



[00217] To a solution of 4-((1*R*,2*R*,5*S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-2-chloro-6,8-difluoroquinazoline (**Intermediate 6**, 900 mg, 1.74 mmol, 1.0 eq) in DMSO (18 mL) was added ((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methanol (2.2 g, 13.9 mmol, 8.0 eq) and KF (205 mg, 3.53 mmol, 2.03 eq). The mixture was stirred at 100 °C overnight and diluted with H<sub>2</sub>O (55 mL). The solution was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (Petroleum ether: EtOAc = 3: 1) to afford 4-((1*R*,2*R*,5*S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-6,8-difluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)quinazoline (700 mg, 62.7%) as a yellow solid. LCMS: *m/z* 641.9, 643.9 (*M*+*H*<sup>+</sup>).

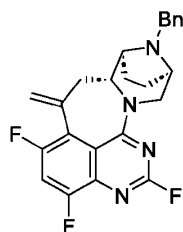
**Step 2: Synthesis of (1*S*,4*R*,14*aR*)-15-benzyl-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline**

**Intermediate 7**

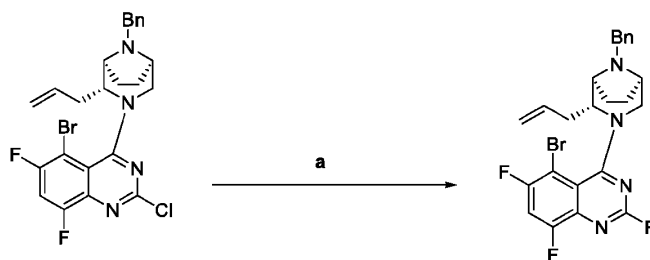
[00218] To a solution of 4-((1*R*,2*R*,5*S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-6,8-difluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)quinazoline (790 mg, 1.23 mmol, 1.0 eq) in DMAc (24 mL) was added KOAc (363 mg, 3.69 mmol, 3.0 eq), Pd(OAc)<sub>2</sub> (28 mg, 0.12 mmol, 0.12 eq) and PPh<sub>3</sub> (65 mg, 0.25 mmol, 0.2 eq) at room temperature under nitrogen atmosphere. The mixture was stirred at 130 °C for 5 h and HPLC showed the reaction was complete. The reaction was diluted with H<sub>2</sub>O (70 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give crude product, which was purified by silica gel column chromatography (DCM: MeOH = 60: 1) to afford (1*S*,4*R*,14*aR*)-15-benzyl-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline (280 mg, 40.6%) as a yellow solid. LCMS: *m/z* 562.0 (M+H<sup>+</sup>).

**Intermediate 8**

(1*S*,4*R*,14*aR*)-15-benzyl-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline

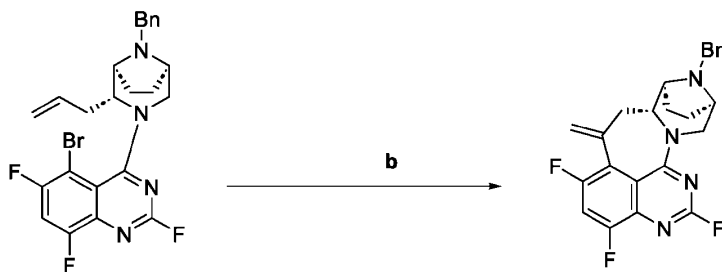


**Step 1: 4-((1*R*,2*R*,5*S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-2,6,8-trifluoroquinazoline**



[00219] To a solution of 4-((1*R*,2*R*,5*S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-2-chloro-6,8-difluoroquinazoline (**Intermediate 6**, 800 mg, 1.5 mmol, 1.0 eq) in DMSO (8 mL) was added KF (179 mg, 3.1 mmol, 2.0 eq). Then the reaction was stirred at 90 °C for 3 h under N<sub>2</sub>. HPLC and TLC show the reaction was completed. The mixture was diluted with water (15 mL) and extracted with EtOAc (15 mL x 3). The combined organic layers was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give a crude product, which was purified by silica gel chromatography (eluted with Petroleum ether : EtOAc = 20:1) to afford 4-((1*R*,2*R*,5*S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-2,6,8-trifluoroquinazoline (620 mg, 80.1%) as a yellow oil. LCMS: *m/z* 503.1 (M+H<sup>+</sup>).

**Step 2: (1*S*,4*R*,14*aR*)-15-benzyl-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline**



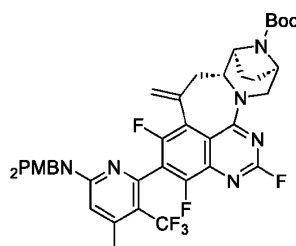
**Intermediate 8**

[00220] To a solution of 4-((1*R*,2*R*,5*S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-2,6,8-trifluoroquinazoline (310 mg, 0.62 mmol, 1.0 eq) in DMAc (9 mL) was added KOAc (181 mg, 1.85 mmol, 3.0 eq), PPh<sub>3</sub> (32 mg, 0.12 mmol, 0.2 eq) and Pd(OAc)<sub>2</sub> (14 mg, 0.06 mmol, 0.1 eq). Then the reaction was stirred at 130 °C for 3 h under N<sub>2</sub>. The mixture was filtered, and the filtrate was diluted with water (15 mL) and extracted with EtOAc (15 mL x 3). The combined organic layers were combined and washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, The residue was purified by silica gel chromatography (eluted with Petroleum ether :

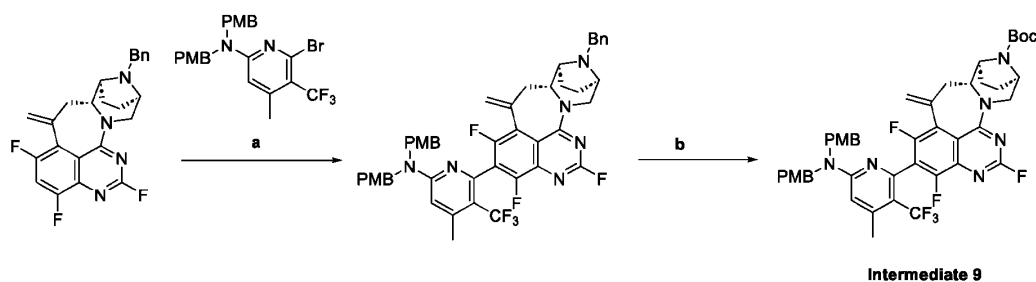
EtOAc = 10:1) to give *(1S,4R,14aR)*-15-benzyl-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline (125 mg, 48.1%) as a yellow solid. LCMS:  $m/z$  423.2 ( $M+H^+$ ).

#### Intermediate 9

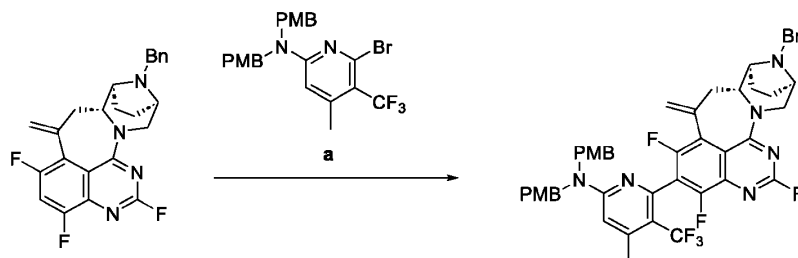
6-((*1S,4R,14aR*)-15-benzyl-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-*N,N*-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine



#### Synthetic scheme:



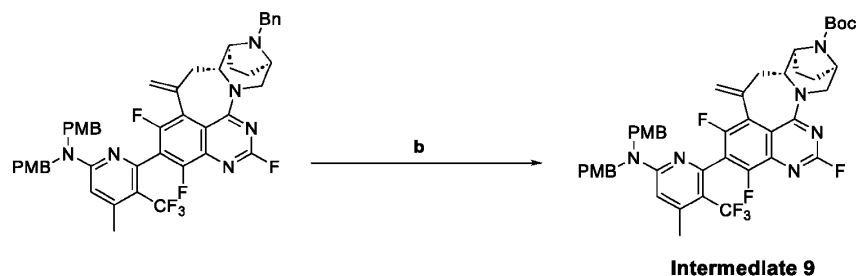
Step 1: 6-((*1S,4R,14aR*)-15-benzyl-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-*N,N*-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine



[00221] To a solution of *(1S,4R,14aR)*-15-benzyl-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline

(**Intermediate 8**, 210 mg, 0.50 mmol, 1.0 eq) in THF (5 mL) was added  $(\text{TMP})_2\text{Zn} \cdot 2\text{MgCl}_2 \cdot 2\text{LiCl}$  in THF (0.4 M, 10 mL, 4 mmol, 8.0 eq) under  $\text{N}_2$ . The mixture was stirred at 50 °C for 1 h. LCMS showed the complete Zn-proton exchange by  $\text{D}_2\text{O}$  quenching of a solution aliquot. Then 6-bromo-*N,N*-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (295 mg, 0.60 mmol, 1.2 eq) and CPhos Pd G<sub>3</sub> (40 mg, 0.05 mmol, 0.1 eq) in 1,4-dioxane (5 mL) was added to the solution. After the reaction was heated at 70 °C for 3 h, the solution was quenched with  $\text{H}_2\text{O}$  (15 mL) and extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure to give a residue, which was purified by silica gel chromatography (eluted with Petroleum ether : EtOAc = 10:1) to afford 6-((1*S*,4*R*,14*aR*)-15-benzyl-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-*N,N*-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (300 mg, 63.1%, with another 40 mg batch) as a yellow solid. LCMS:  $m/z$  837.3 ( $\text{M}+\text{H}^+$ ).

**Step 2: tert-butyl (1*S*,4*R*,14*aR*)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



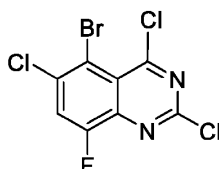
[00222] A solution of 6-((1*S*,4*R*,14*aR*)-15-benzyl-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-*N,N*-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (50 mg, 0.06 mmol, 1.0 eq) in MeOH (5 mL) was added Pd/C (10 mol%, 30 mg) and  $(\text{Boc})_2\text{O}$  (20 mg, 0.09 mmol, 1.5 eq), and hydrogenated with a balloon of hydrogen at room temperature for 12 h. The mixture was filtered, and the filtrate was concentrated to give a crude product, which was purified by Prep TLC (PE: EtOAc = 3:1) to afford tert-butyl (1*S*,4*R*,14*aR*)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-



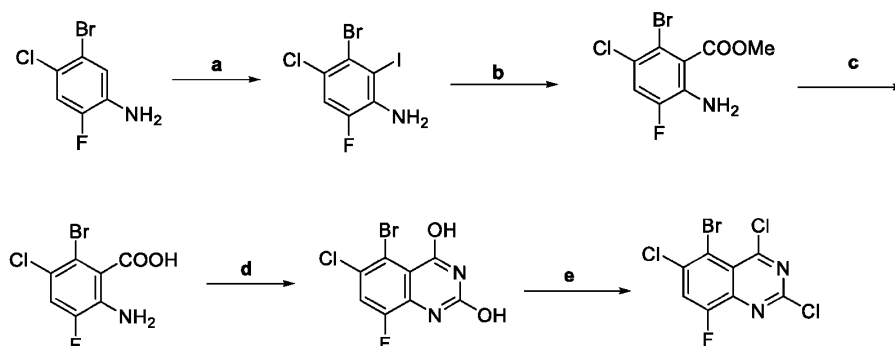
octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (50 mg, crude) as a yellow solid. LCMS:  $m/z$  847.3 ( $M+H^+$ ).

### Intermediate 10

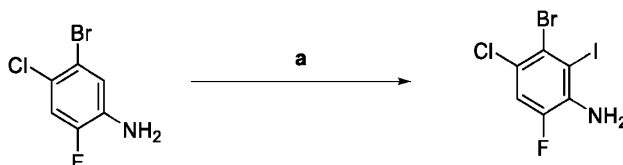
#### 5-bromo-2,4,6-trichloro-8-fluoroquinazoline



#### Synthetic scheme:

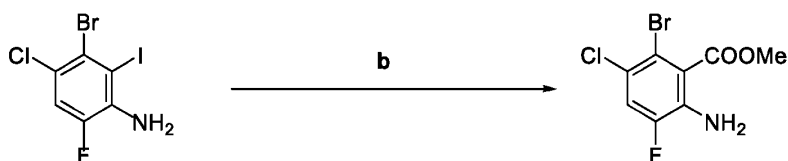


#### Step 1: Synthesis of 3-bromo-4-chloro-6-fluoro-2-iodoaniline



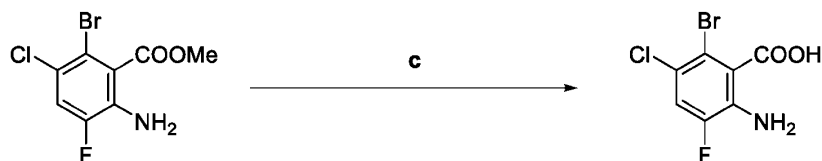
[00223] To a solution of 5-bromo-4-chloro-2-fluoroaniline (24.5 g, 109.15 mmol, 1.0 eq) in EtOH (490 mL) was added iodine (30.47 g, 120.07 mmol, 1.1 eq), silver sulfate (30.03 g, 109.15 mmol, 1.0 eq). The mixture was stirred at 25 °C for 2 h. The mixture was filtered, and the filtrate was concentrated to give a crude product, which was purified by silica gel column chromatography (petroleum ether) to afford 3-bromo-4-chloro-6-fluoro-2-iodoaniline (33 g, 86.3%) as a red solid.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.54 (d,  $J = 10.8$  Hz, 1H), 5.66 (s, 2H).

#### Step 2: Synthesis of methyl 2-amino-6-bromo-5-chloro-3-fluorobenzoate



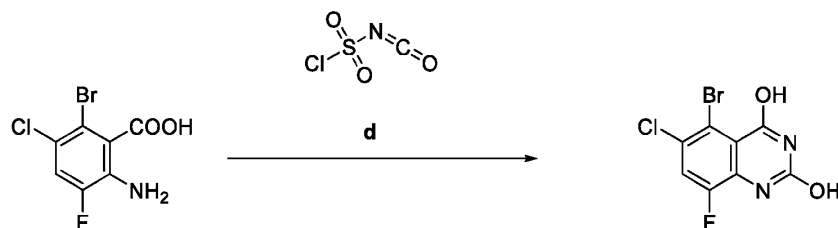
[00224] To a solution of 3-bromo-4-chloro-6-fluoro-2-iodoaniline (20.0 g, 57.09 mmol, 1.0 eq) in MeOH (90 mL) was added DMF (135 mL), TEA (17.33 g, 171.26 mmol, 3.0 eq), Pd(OAc)<sub>2</sub> (641 mg, 2.85 mmol, 0.05 eq) and dppf (791 mg, 1.43 mmol, 0.025 eq). The mixture was stirred at 75 °C for 15 h under 0.4 MPa CO. The mixture was concentrated, diluted with water (50 mL) and extracted with EtOAc (50 mL x 3). The organic layers were washed with water (100 mL x 2), brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (petroleum ether: EtOAc = 80: 1) to afford methyl 2-amino-6-bromo-5-chloro-3-fluorobenzoate (9.0 g, 55.8%) as a red liquid. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.52 (d, *J* = 11.1 Hz, 1H), 5.80 (s, 2H), 3.86 (s, 3H).

### Step 3: Synthesis of 2-amino-6-bromo-5-chloro-3-fluorobenzoic acid



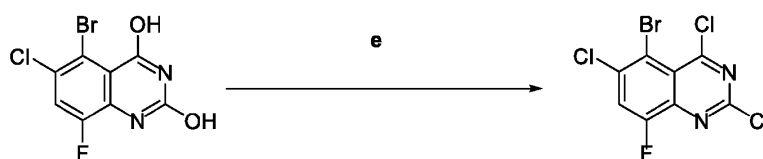
[00225] To a solution of methyl 2-amino-6-bromo-5-chloro-3-fluorobenzoate (8.95 g, 31.68 mmol, 1.0 eq) in MeOH (160 mL) was added NaOH (3.8 g, 95.05 mmol, 3.0 eq) in water (160 mL). The mixture was stirred at 45 °C for 18 h. The reaction mixture was concentrated under reduced pressure to remove MeOH. The resulting mixture was adjusted the pH to ~ 1 with aqueous HCl solution. Then the mixture was filtered, dried to give 2-amino-6-bromo-5-chloro-3-fluorobenzoic acid (7.6 g, 89.4%) as a white solid. LCMS: 265.8 (M-H<sup>-</sup>).

### Step 4: Synthesis of 5-bromo-6-chloro-8-fluoroquinazoline-2,4-diol



[00226] To a solution of 2-amino-6-bromo-5-chloro-3-fluorobenzoic acid (2 g, 7.45 mmol, 1.0 eq) in DCM (10 mL)-was added chlorosulfonyl isocyanate (2.64 g, 18.63 mmol, 2.5 eq) under N<sub>2</sub> at 0 °C. The mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated under reduced pressure to give a crude product, which was added 6N HCl (600 mL) and stirred 2 h at 100 °C. Then the mixture was cooled to room temperature slowly, solid was precipitated, the mixture was filtered, dried to give 5-bromo-6-chloro-8-fluoroquinazoline-2,4-diol (1.56 g, 71.4%) as a yellow solid. LCMS: 290.8 (M-H<sup>-</sup>).

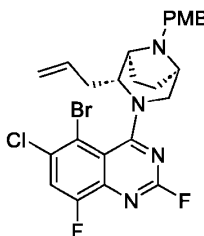
**Step 5: Synthesis of 5-bromo-2,4,6-trichloro-8-fluoroquinazoline**



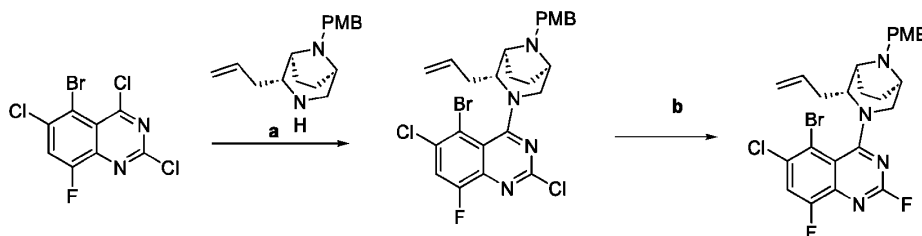
[00227] To a solution of 5-bromo-6-chloro-8-fluoroquinazoline-2,4-diol (3.0 g, 10.22 mmol, 1.0 eq) in POCl<sub>3</sub> (30 mL) was added DIEA (3.0 mL). The mixture was stirred at 110 °C for 5 h under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to give 5-bromo-2,4,6-trichloro-8-fluoroquinazoline (4.2 g, crude) as a brown oil.

**Intermediate 11**

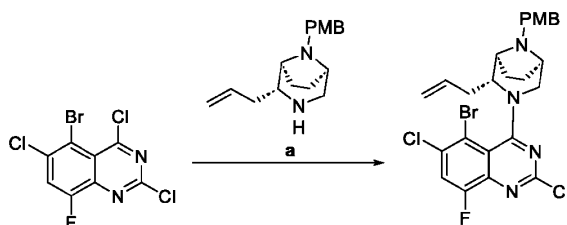
**4-((1S,2R,5R)-2-allyl-8-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-6-chloro-2,8-difluoroquinazoline**



**Synthetic scheme:**

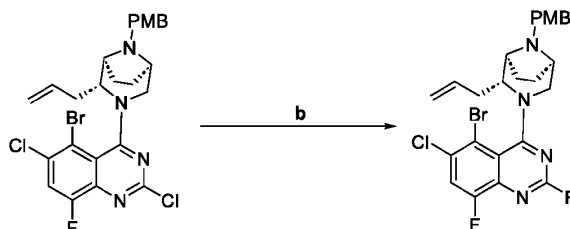


**Step 1: Synthesis of 4-((1S,2R,5R)-2-allyl-8-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-2,6-dichloro-8-fluoroquinazoline**



[00228] To a solution of 5-bromo-2,4,6-trichloro-8-fluoroquinazoline (3.39 g, 10.27 mmol, 1.0 eq) in DCM (40 mL) was added DIEA (11.55 g, 89.38 mmol, 8.7 eq) and (1S,2R,5R)-2-allyl-8-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octane (3.36 g, 12.33 mmol, 1.2 eq) at -40 °C under nitrogen atmosphere. The mixture was stirred at -40 °C for 2 h, diluted with water (30 mL) and extracted with DCM (20 mL x 3). The organic layers were washed with water (20 mL), brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (petroleum ether: EtOAc = 15: 1) to afford 4-((1S,2R,5R)-2-allyl-8-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-2,6-dichloro-8-fluoroquinazoline (4.45 g, 76.5% for two steps) as a yellow solid. LCMS: 564.8 (M+H<sup>+</sup>).

**Step 2: 4-((1S,2R,5R)-2-allyl-8-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-6-chloro-2,8-difluoroquinazoline**

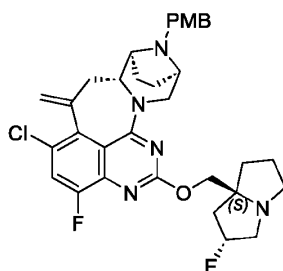


[00229] To a solution of 4-((1S,2R,5R)-2-allyl-8-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-2,6-dichloro-8-fluoroquinazoline (2.2 g, 3.89 mmol, 1.0 eq) in DMSO (20 mL) was added KF (903 mg, 15.54 mmol, 4.0 eq). Then the reaction was stirred at 100 °C for 3 h under N<sub>2</sub>. HPLC and TLC showed the reaction was completed. The mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 3). The organic layers was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a crude product, which was purified by silica gel chromatography (eluted with petroleum ether: EtOAc =

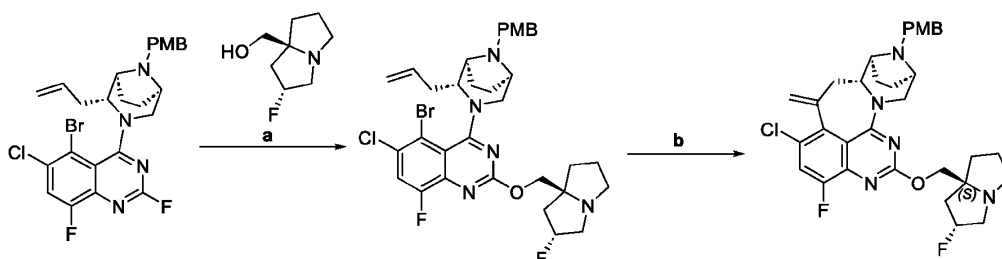
10: 1) to afford 4-((1S,2R,5R)-2-allyl-8-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-6-chloro-2,8-difluoroquinazoline (1.8 g, 84.3%) as a yellow solid. LCMS: 548.8 (M+H<sup>+</sup>).

### Intermediate 12

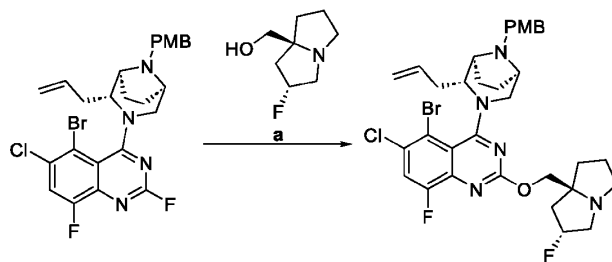
(1S,4R,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline



Synthetic scheme:



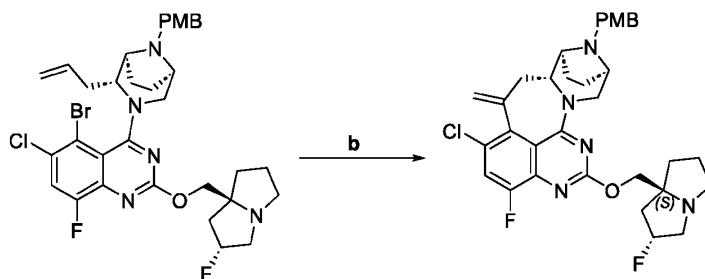
Step 1: 4-((1S,2R,5R)-2-allyl-8-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazoline



[00230] To a solution of (2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (132 mg, 0.83 mmol, 1.2 eq) in THF (6 mL) was added NaH (60% in oil, 83 mg, 2.07 mmol, 3.0 eq)

at 0 °C and then the mixture was stirred for 0.5 h under N<sub>2</sub>. The solution of 4-((1S,2R,5R)-2-allyl-8-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-6-chloro-2,8-difluoroquinazoline (380 mg, 0.69 mmol, 1.0 eq) in THF (2 mL) was added to the mixture and stirred at 25 °C for 3 h. HPLC and TLC showed the reaction was completed. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl solution (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layer was concentrated to give a crude product. The residue was purified by Prep-TLC (DCM: MeOH = 10: 1) to afford 4-((1S,2R,5R)-2-allyl-8-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazoline (400 mg, 84.1%) as a yellow solid. LCMS: 687.8 (M+H<sup>+</sup>).

**Step 2: (1S,4R,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline**

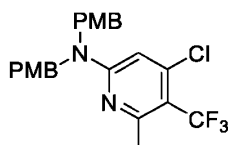


[00231] To a solution of 4-((1S,2R,5R)-2-allyl-8-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazoline (400 mg, 0.58 mmol, 1.0 eq) in DMF (4.8 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (227 mg, 0.70 mmol, 1.2 eq), Pd(OAc)<sub>2</sub> (13 mg, 0.06 mmol, 0.1 eq) and PPh<sub>3</sub> (38 mg, 0.15 mmol, 0.25 eq) at room temperature under nitrogen atmosphere. The mixture was stirred at 80 °C for 7 h under N<sub>2</sub>. HPLC showed the reaction was completed. Then the reaction was added H<sub>2</sub>O (15 mL) and extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give crude product, which was purified by silica gel column chromatography (DCM: MeOH = 80: 1) to afford (1S,4R,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-

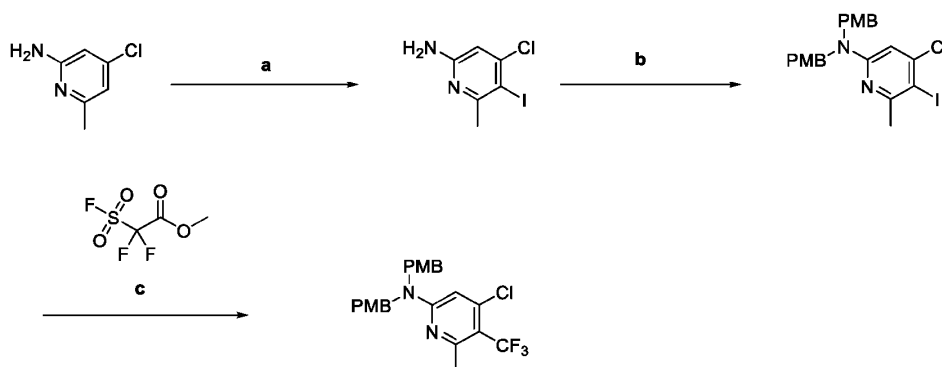
octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline (273 mg, 77.3%) as a yellow solid. LCMS: 608.0 ( $M+H^+$ ).

### Intermediate 13

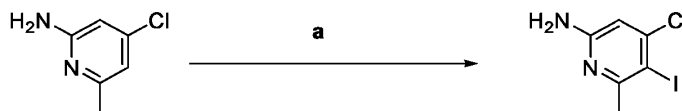
#### 4-Chloro-N,N-bis(4-methoxybenzyl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine



#### Synthetic scheme:

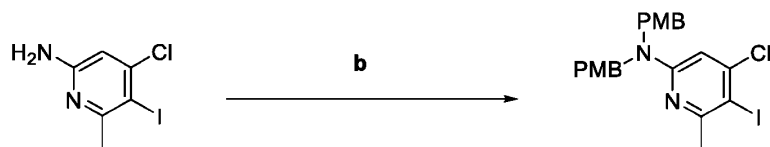


#### Step 1: Synthesis of 4-chloro-5-iodo-6-methylpyridin-2-amine



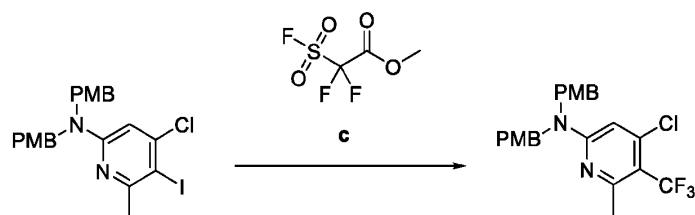
[00232] To a solution of 4-chloro-6-methylpyridin-2-amine (6.0 g, 42.2 mmol, 1.0 eq) in DMF (60 mL) was added NIS (10.0 mg, 44.4 mmol, 1.05 eq). The reaction mixture was stirred at 70 °C for 3 h under  $N_2$  atmosphere. The reaction was quenched with sodium thiosulfate (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over  $Na_2SO_4$ , filtered and concentrated to give a crude. The crude was purified by silica gel column chromatography (Petroleum ether: EtOAc = 4: 1) to give 4-chloro-5-iodo-6-methylpyridin-2-amine (6.9 g, 60.9%) as a yellow solid.  $^1H$  NMR (300 MHz,  $DMSO-d_6$ ):  $\delta$  6.47 (s, 1H), 6.30 (brs, 2H), 2.52 – 2.48 (m, 3H). LCMS:  $m/z$  268.9 ( $M+H^+$ ).

#### Step 2: Synthesis of 4-chloro-5-iodo-N,N-bis(4-methoxybenzyl)-6-methylpyridin-2-amine



[00233] To a solution of 4-chloro-5-iodo-6-methylpyridin-2-amine (8.5 g, 31.7 mmol, 1.0 eq) in DMF (128 mL) was added NaH (60%, 3.8 g, 95.2 mmol, 3.0 eq) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h under N<sub>2</sub> atmosphere. To the reaction mixture was added PMBCl (9.9 g, 63.4 mmol, 2.0 eq). The reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched with H<sub>2</sub>O (637 mL). The mixture was filtered and washed with water (200 mL). The filter cake was diluted with methanol (50 mL) and filtered. The filter cake was evaporated to dryness to give 4-chloro-5-iodo-N,N-bis(4-methoxybenzyl)-6-methylpyridin-2-amine (14.7 g, 91.2%) as a brown solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.18 – 7.08 (m, 4H), 6.89 – 6.79 (m, 4H), 6.42 (s, 1H), 4.64 (s, 4H), 3.79 (s, 6H), 2.70 (s, 3H). LCMS: m/z 509.1 (M+H<sup>+</sup>).

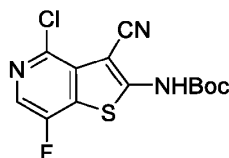
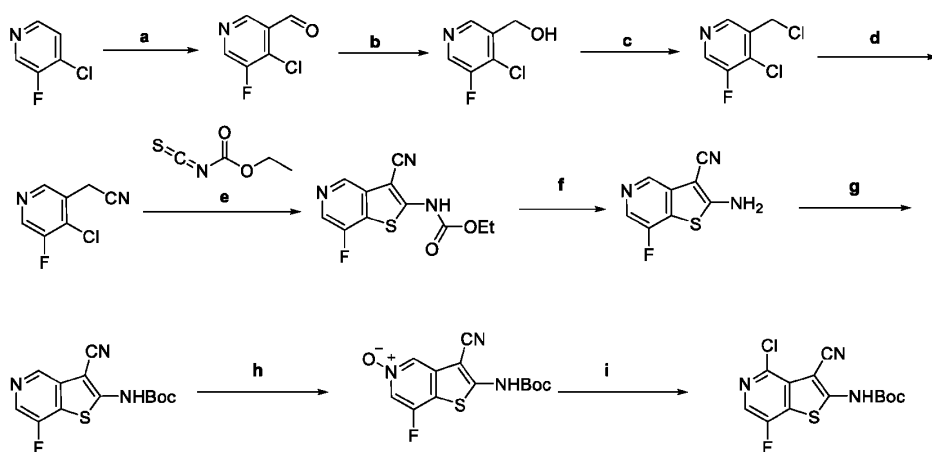
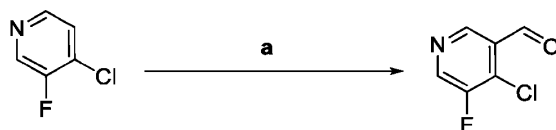
**Step 3: Synthesis of 4-chloro-N,N-bis(4-methoxybenzyl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine**



[00234] To a solution of 4-chloro-5-iodo-N,N-bis(4-methoxybenzyl)-6-methylpyridin-2-amine (34 g, 66.9 mmol, 1.0 eq) in DMF (340 mL) was added methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (32.1 g, 167.3 mmol, 2.5 eq) and CuI (38.2 g, 200.8 mmol, 3.0 eq). The reaction mixture was stirred at 100 °C for 15 h under N<sub>2</sub> atmosphere. The reaction was quenched with H<sub>2</sub>O (150 mL). The mixture was filtered off, washed with EtOAc (200 mL) and separated. The aqueous layer was extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude. The crude was purified by silica gel column chromatography (Petroleum ether: EtOAc = 1: 1) to give 4-chloro-N,N-bis(4-methoxybenzyl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine (18.8 g, 62.4%) as a brown solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.20 – 7.08 (m, 4H), 6.93 – 6.79 (m, 4H), 6.39 (s, 1H), 4.68 (s, 4H), 3.80 (s, 6H), 2.64 – 2.54 (m, 3H). LCMS: m/z 451.1 (M+H<sup>+</sup>).

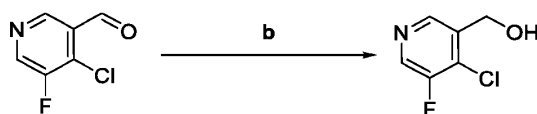
**Intermediate 14**



**tert-butyl (4-chloro-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate****Synthetic scheme:****Step 1: Synthesis of 4-chloro-5-fluoronicotinaldehyde**

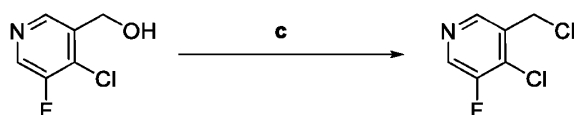
[00235] To a solution of DIPA (120.0 g, 1.2 mol, 1.2 eq) in THF (1.3 L) was added 2.5 M *n*-BuLi in THF (474.4 mL, 1.2 mol, 1.2 eq) at -30 °C. The reaction was stirred at the same temperature for 30 min. To the solution was added 4-chloro-3-fluoropyridine (130.0 g, 988.3 mmol, 1.0 eq) in THF (260 mL) at -78 °C. The reaction was stirred at -78 °C for 8 h. To the mixture was added DMF (86.7 g, 1.2 mol, 1.2 eq). The reaction was stirred at room temperature for 15 min. The reaction was quenched with sat. NH<sub>4</sub>Cl aqueous solution (1 L) at 0 °C. The resulting mixture was extracted by EtOAc (1 L x 2). The combined organic phase was washed with H<sub>2</sub>O (1 L x 2), brine (1 L), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered off and concentrated under reduced pressure to give 4-chloro-5-fluoronicotinaldehyde (180.0 g, crude) as a yellow solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 10.47 (s, 1H), 8.88 (s, 1H), 8.70 (s, 1H).

**Step 2: Synthesis of (4-chloro-5-fluoropyridin-3-yl)methanol**



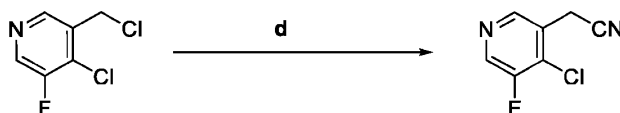
[00236] To a solution of 4-chloro-5-fluoronicotinaldehyde (60.0 g, 376.2 mmol, 1.0 eq) in MeOH (600 mL) was added NaBH<sub>4</sub> (17.1 g, 451.4 mmol, 1.2 eq) at 0 °C. The mixture was stirred at the same temperature for 1 h. The reaction was quenched with sat. NaHCO<sub>3</sub> aqueous solution (500 mL). The resulting mixture was extracted by EtOAc (500 mL x 3). The combined organic phase was washed with brine (500 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a residue. The reaction was carried out for 3 times total 180.0 g 4-chloro-5-fluoronicotinaldehyde. The residue was purified by silica gel column chromatography (Petroleum ether: EtOAc = 3: 1) to give (4-chloro-5-fluoropyridin-3-yl)methanol (70.0 g, 43.8% for 2 steps) as a yellow solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.52 (s, 1H), 8.45 (s, 1H), 4.86 (d, *J* = 3.3 Hz, 1H). LCMS: 162.1 (M+H<sup>+</sup>).

### Step 3: Synthesis of 4-chloro-3-(chloromethyl)-5-fluoropyridine



[00237] To a solution of (4-chloro-5-fluoropyridin-3-yl)methanol (20.0 g, 123.8 mmol, 1.0 eq) in DCM (200 mL) was added SOCl<sub>2</sub> (17.7 g, 14.9 mmol, 1.2 eq) dropwise at 0 °C under N<sub>2</sub> atmosphere. The reaction mixture was stirred at room temperature for 18 h. The reaction was carried out for 2 times total 54.0 g (4-chloro-5-fluoropyridin-3-yl)methanol. The mixture was quenched with H<sub>2</sub>O (300 mL) and separated. The resulting mixture was extracted with EtOAc (300 mL x 3). The combined organic phase was washed with brine (300 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give 4-chloro-3-(chloromethyl)-5-fluoropyridine (65.0 g, crude) as a yellow solid. LCMS: 180.0 (M+H<sup>+</sup>).

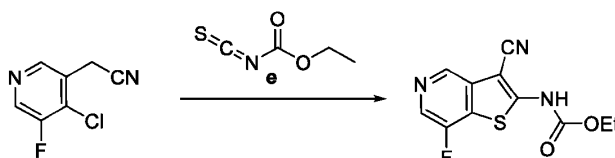
### Step 4: Synthesis of 2-(4-chloro-5-fluoropyridin-3-yl)acetonitrile



[00238] To a solution of 4-chloro-3-(chloromethyl)-5-fluoropyridine (65.0 g, 361.1 mmol, 1.0 eq) and TMSCN (179.1 g, 1.8 mol, 5.0 eq) in ACN (650 mL) was added TBAF (472.1 g, 1.8 mol, 5.0 eq) in THF (650 mL) at 0 °C. The reaction was stirred at room temperature for 1 h under

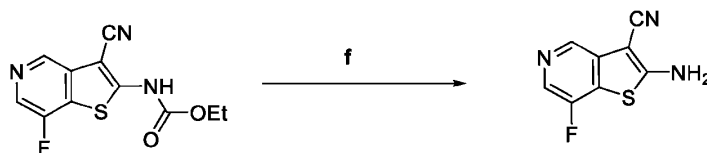
N<sub>2</sub> atmosphere. The reaction mixture was diluted with EtOAc (1 L), washed with H<sub>2</sub>O (1 L x 3), brine (1 L), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a residue. The residue was purified by silica gel column chromatography (Petroleum ether: EtOAc = 3: 1) to give 2-(4-chloro-5-fluoropyridin-3-yl)acetonitrile (31.0 g, 50.2%) as a yellow solid. LCMS: 171.0 (M+H<sup>+</sup>).

**Step 5: Synthesis of ethyl (3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate**



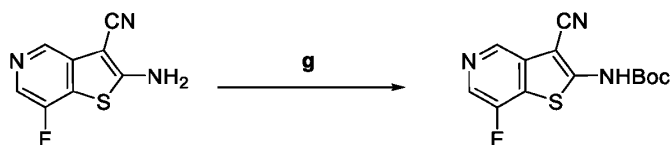
[00239] To a solution of 2-(4-chloro-5-fluoropyridin-3-yl)acetonitrile (15.0 g, 87.9 mmol, 1.0 eq) in DMF (150 mL) was added NaH (60%, 4.2 g, 105.5 mmol, 1.2 eq) at 0 °C. The mixture was stirred at the same temperature for 0.5 h. Compound Ethoxycarbonyl Isothiocyanate (23.1 g, 175.8 mmol, 2.0 eq) was added to the mixture. The mixture was stirred at 100 °C for 1 h. The reaction mixture was quenched with H<sub>2</sub>O (100 mL). The mixture was adjusted pH ~ 6 with 5% aq. citric acid (300 mL). The precipitate formed was filtered off and washed with H<sub>2</sub>O (500 mL), dried in vacuum to give ethyl (3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate (17.0 g, crude) as a yellow solid. LCMS: 266.0 (M+H<sup>+</sup>).

**Step 6: Synthesis of 2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile**



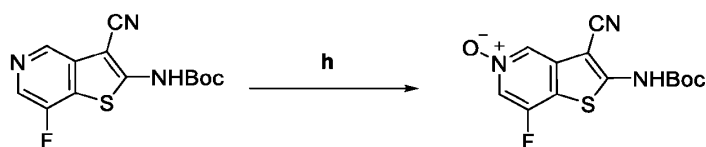
[00240] To a solution of ethyl (3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate (17.0 g, 64.1 mmol, 1.0 eq) in DMSO (170 mL) was added 5 M NaOH aqueous solution (340 mL, 1.7 mol, 26.5 eq). The mixture was stirred at 105 °C for 1.5 h, then cooled to room temperature. The reaction mixture was poured into a mixture of ice/water (700 mL), stirred until all ice had melted, filtered off and washed with H<sub>2</sub>O (300 mL). The solids were dried in a vacuum to give crude 2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile. The aqueous layer was extracted with EtOAc (800 mL x 3). The combined organic layers were washed with brine (800 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness to give compound 2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile (17.0 g, crude) as a yellow solid. LCMS: 194.1 (M+H<sup>+</sup>).

**Step 7: Synthesis of tert-butyl (3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate**



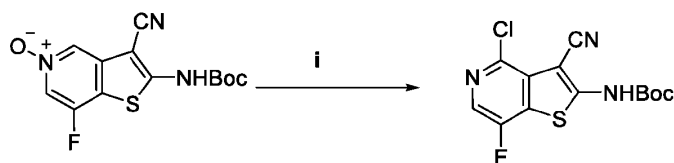
[00241] A mixture of crude 2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile (17.0 g, 88.0 mmol, 1.0 eq), DCM (170 mL), DMF (170 mL) and DIEA (39.1 g, 264.0 mmol, 3.0 eq) was cooled to 0 °C. DMAP (1.1 g, 8.8 mmol, 0.1 eq) and (Boc)<sub>2</sub>O (23.0 g, 105.6 mmol, 1.2 eq) were added. The reaction mixture was stirred at room temperature for 2 h. The reaction was diluted with DCM (400 mL) and 5% aq. citric acid (250 mL). The aqueous phase was washed with DCM (400 mL x 2). The combined organic phases were washed with H<sub>2</sub>O (300 mL x 3), sat. aq. NaHCO<sub>3</sub> (300 mL), brine (300 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude. The crude was purified by silica gel column chromatography (Petroleum ether: EtOAc = 3: 1) to give tert-butyl (3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate (7.0 g, 27.1% for 3 steps) as a yellow solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.83 (s, 1H), 8.36 (s, 1H), 8.00 (brs, 1H), 1.60 (s, 9H). LCMS: 294.2 (M+H<sup>+</sup>).

**Step 8: Synthesis of 2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridine 5-oxide**



[00242] 3-Chloroperoxybenzoic acid (883 mg, 5.1 mmol, 1.5 eq) was added to a solution of tert-butyl (3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate (1.0 g, 3.4 mmol, 1.0 eq) in DCM (20 mL). The reaction mixture was stirred at room temperature overnight. Solids were collected by filtration and dried in a vacuum. The filtrate was concentrated to give a crude. The crude was purified by silica gel column chromatography (DCM: MeOH = 30: 1) to give 2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridine 5-oxide (850 mg, 81.0%) as an off-white solid. LCMS: 310.2 (M+H<sup>+</sup>).

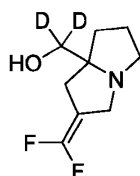
**Step 9: Synthesis of tert-butyl (4-chloro-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate**



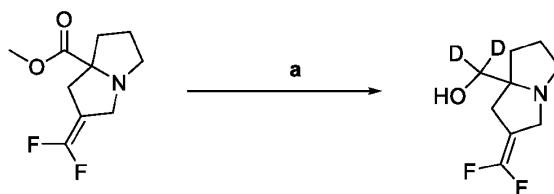
[00243] A suspension of 2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridine 5-oxide (850 mg, 2.7 mmol, 1.0 eq) in 1,2-dichloroethane (5 mL) was cooled to 0 °C. A solution of phosphoryl chloride (8.4 g, 55.0 mmol, 20.0 eq) in 1,2-dichloroethane (5 mL) was added dropwise. The reaction mixture was stirred at room temperature for 30 min, at 45 °C for 2 h and cooled to room temperature. The reaction mixture was concentrated to give a crude. The crude was dissolved in THF (10 mL). To the mixture was added DIEA (1.1 g, 8.2 mmol, 3.0 eq), DMAP (34 mg, 0.27 mmol, 0.1 eq) and (Boc)<sub>2</sub>O (719 mg, 3.3 mmol, 1.2 eq) at 0 °C. The reaction was stirred at room temperature for 2 h. The reaction was quenched with 5% aq. citric acid (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phases were washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude. The crude was purified by silica gel column chromatography (Petroleum ether: EtOAc = 3: 1) to give tert-butyl (4-chloro-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate (414 mg, 46.0%) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 12.24 (brs, 1H), 8.34 (s, 1H), 1.54 (s, 9H). LCMS: 328.3 (M+H<sup>+</sup>).

#### Intermediate 15

(2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methan-d<sub>2</sub>-ol



#### Synthetic Scheme

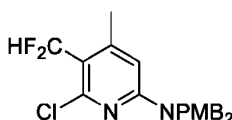


**Step 1: Synthesis of (2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methan-d<sub>2</sub>-ol**

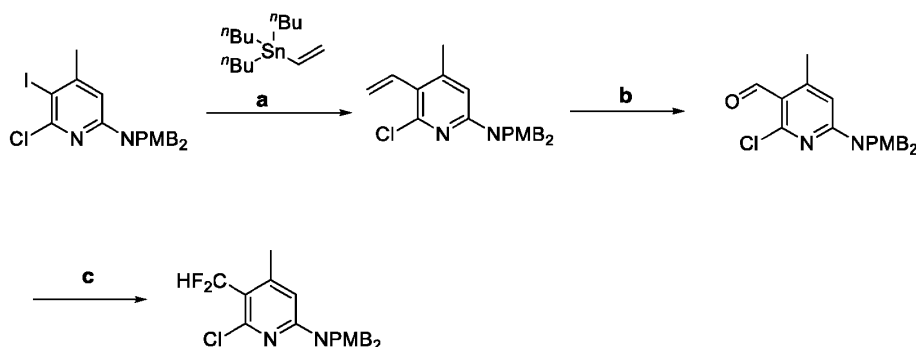
[00244] To a suspension of  $\text{LiAlD}_4$  (155 mg, 3.4 mmol, 1.5 eq) in THF (5 mL) was added methyl 2-(difluoromethylene)tetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (500 mg, 2.3 mmol, 1.0 eq) in THF (5 mL) at 0 °C. The reaction was stirred at 0 °C for 1.5 h. The reaction was quenched with  $\text{H}_2\text{O}$  (0.15 mL), 15% aq. NaOH solution (0.15 mL) and  $\text{H}_2\text{O}$  (0.45 mL) in turns. The mixture was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give a crude. The crude was purified by silica gel column chromatography (DCM: MeOH = 15: 1) to give 2-(difluoromethylene) tetrahydro-1H-pyrrolizin-7a(5H)-yl)methan- $\text{d}_2$ -ol (330 mg, 75.0%) as a colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.65 (d,  $J$  = 14.8 Hz, 1H), 3.35 (d,  $J$  = 14.4 Hz, 1H), 3.26 – 3.14 (m, 1H), 2.95 (brs, 1H), 2.72 – 2.62 (m, 1H), 2.52 – 2.30 (m, 2H), 2.08 – 1.72 (m, 4H).

### Intermediate 16

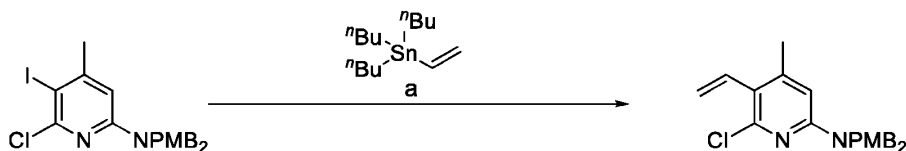
#### 6-chloro-5-(difluoromethyl)-N,N-bis(4-methoxybenzyl)-4-methylpyridin-2-amine



#### Synthetic Scheme



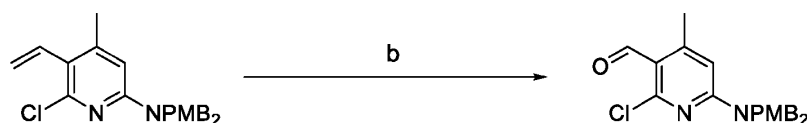
#### Step 1: Synthesis of 6-chloro-N,N-bis(4-methoxybenzyl)-4-methyl-5-vinylpyridin-2-amine



[00245] To a solution of 6-chloro-5-iodo-N,N-bis(4-methoxybenzyl)-4-methylpyridin-2-amine (5.0 g, 9.8 mmol, 1.0 eq) in THF (50.0 mL) was added tributyl(vinyl)stannane (4.7 g, 14.8 mmol, 1.5 eq) and XPhos Pd G3 (833 mg, 0.98 mmol, 0.1 eq) at room temperature. The reaction

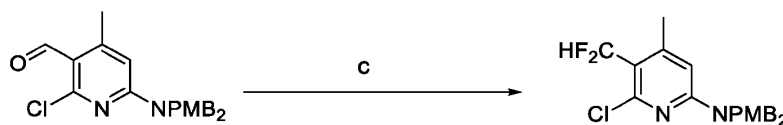
was stirred at 50 °C for 15 h under N<sub>2</sub>. The mixture was partitioned between EtOAc (100 mL) and water (100 mL). The layers were separated. The aqueous layer was extracted with EtOAc (100 mL x 2). The combined organic layers were washed with H<sub>2</sub>O (40 mL), brine (100 mL x 2), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness. The crude product was purified by silica gel column chromatography (petroleum ether: DCM = 2: 1) to give 6-chloro-N,N-bis(4-methoxybenzyl)-4-methyl-5-vinylpyridin-2-amine (6.0 g, crude) as a yellow solid. LCMS: 409.3 (M+H<sup>+</sup>).

**Step 2: Synthesis of 6-(bis(4-methoxybenzyl)amino)-2-chloro-4-methylnicotinaldehyde**



[00246] To a solution of 6-chloro-N,N-bis(4-methoxybenzyl)-4-methyl-5-vinylpyridin-2-amine (6.0 g, 14.7 mmol, 1.0 eq) in THF (180 mL) and H<sub>2</sub>O (18 mL) was added NaIO<sub>4</sub> (19.0 g, 88.2 mmol, 6.0 eq) and K<sub>2</sub>OsO<sub>4</sub>·2H<sub>2</sub>O (458 mg, 1.5 mmol, 0.1 eq). The reaction mixture was stirred at room temperature for 15 h under nitrogen atmosphere. The reaction mixture was quenched with water (100 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness. The crude product was purified by silica gel column chromatography (petroleum ether: DCM = 1: 1) to give 6-(bis(4-methoxybenzyl)amino)-2-chloro-4-methylnicotinaldehyde (1.6 g, 26.5%) as a yellow solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 10.39 (s, 1H), 7.14 (d, *J* = 8.4 Hz, 4H), 6.92 – 6.80 (m, 4H), 6.19 (s, 1H), 4.71 (s, 4H), 3.80 (s, 6H), 2.49 (s, 3H). LCMS: 411.4 (M+H<sup>+</sup>).

**Step 3: Synthesis of 6-chloro-5-(difluoromethyl)-N,N-bis(4-methoxybenzyl)-4-methylpyridin-2-amine**

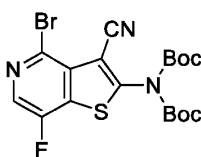


[00247] To a solution of 6-(bis(4-methoxybenzyl)amino)-2-chloro-4-methylnicotinaldehyde (1.2 g, 2.9 mmol, 1.0 eq) in DCE (12.0 mL) was added DAST (943 mg, 5.9 mmol, 2.0 eq). The reaction mixture was stirred at 80 °C for 3 h under nitrogen atmosphere. The reaction mixture was quenched with saturated sodium bicarbonate aqueous solution (40 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with H<sub>2</sub>O (20 mL), brine (20 mL),

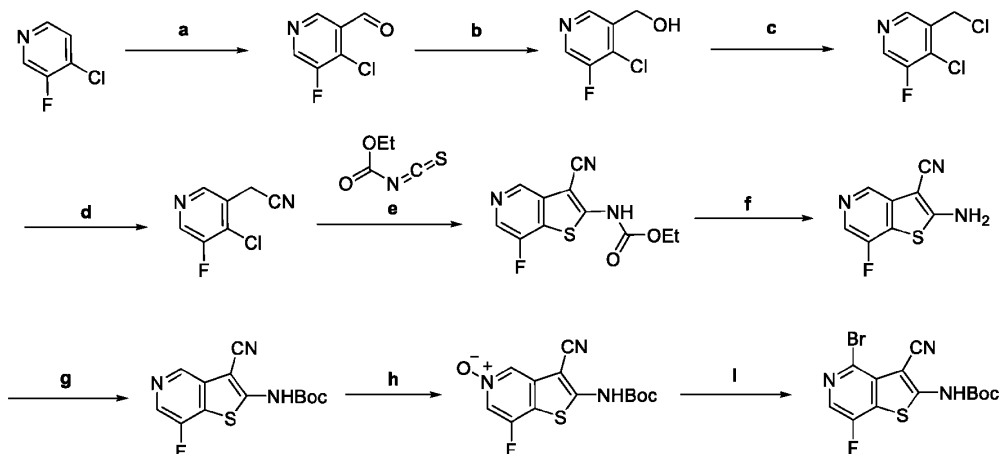
dried over  $\text{Na}_2\text{SO}_4$  and evaporated to dryness. The crude product was purified by silica gel column chromatography (petroleum ether: DCM = 2: 1) to give 6-chloro-5-(difluoromethyl)-N,N-bis(4-methoxybenzyl)-4-methylpyridin-2-amine (533 mg, 42.2%) as a yellow solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.25 – 6.94 (m, 5H), 6.90 – 6.81 (m, 4H), 6.21 (s, 1H), 4.66 (s, 4H), 3.80 (s, 6H), 2.36 (s, 3H).

### Intermediate 17

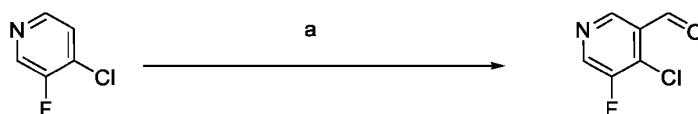
**tert-butyl (4-bromo-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)(tert-butoxycarbonyl)carbamate**



### Synthetic Scheme



### Step 1: Synthesis of 4-chloro-5-fluoronicotinaldehyde

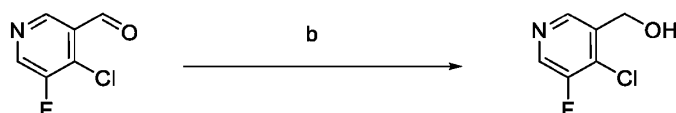


[00248] The solution of diisopropylamine (232.7 g, 2.3 mol, 1.2 eq) in THF (2.5 L) was cooled to  $-30\text{ }^\circ\text{C}$ , added 2.5M n-BuLi in n-hexane (0.92 L, 2.3 mol, 1.2 eq) and stirred at  $-30\text{ }^\circ\text{C}$  for 20 min. Then the mixture cooled at  $-78\text{ }^\circ\text{C}$  was added 4-chloro-3-fluoropyridine (250.0 g, 1.9 mol, 1.0 eq) and stirred at  $-78\text{ }^\circ\text{C}$  for 9 h. Then the reaction was added DMF (168.1 g, 2.3 mol, 1.2 eq) and stirred at room temperature for 15 min. The mixture was quenched with saturated



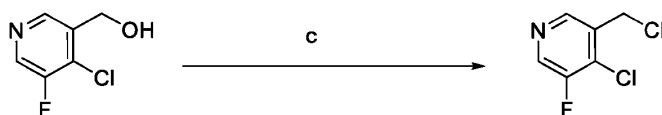
ammonium chloride aqueous solution (2.0 L) and extracted with EtOAc (2.0 L x 3). The combined organic layers were washed with brine (1.0 L), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude 4-chloro-5-fluoronicotinaldehyde (360.0 g, crude) as yellow oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 10.45 (s, 1H), 8.87 (s, 1H), 8.69 (s, 1H)

**Step 2: Synthesis of (4-chloro-5-fluoropyridin-3-yl)methanol**



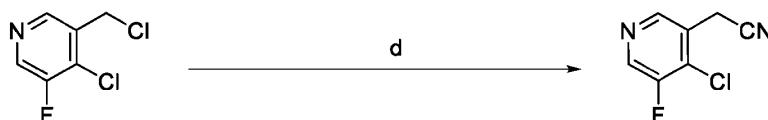
[00249] To a solution of 4-chloro-5-fluoronicotinaldehyde (360.0 g, 2.3 mol, 1.0 eq) in MeOH (3.6 L) cooled at 0 °C was added NaBH<sub>4</sub> (94.6 g, 2.5 mmol, 1.1 eq). The reaction mixture was stirred at 0 °C for 1 h. The mixture was quenched with saturated sodium bicarbonate aqueous solution (2.0 L) and extracted with EtOAc (2.0 L x 3). The combined organic layers were washed with brine (2.0 L), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude. The crude product was purified by silica gel column chromatography (Petroleum ether / EtOAc = 20:1) to give (4-chloro-5-fluoropyridin-3-yl)methanol (130.0 g, 52.3% for two steps) as a white solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.52 (s, 1H), 8.45 (s, 1H), 4.86 (d, *J* = 3.6 Hz, 1H)

**Step 3: Synthesis of 4-chloro-3-(chloromethyl)-5-fluoropyridine**



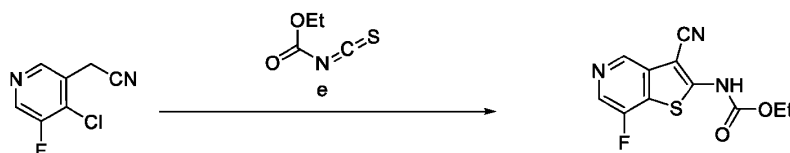
[00250] To a solution of (4-chloro-5-fluoropyridin-3-yl)methanol (130.0 g, 0.8 mol, 1.0 eq) in DCM (1.3 L) cooled at 0 °C was added SOCl<sub>2</sub> (119.0 g, 1.0 mol, 1.2 eq). The reaction mixture was stirred at room temperature for 24 h. The mixture was quenched with water (1.0 L) and extracted with DCM (1.0 L x 3). The combined organic layers were washed with brine (1.0 L), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude. The crude product was purified by silica gel column chromatography (Petroleum ether/ EtOAc = 5:1) to give 4-chloro-3-(chloromethyl)-5-fluoropyridine (120.0 g, 82.9%) as a yellow solid. LCMS: *m/z* 180.1 ([M+H]<sup>+</sup>)

**Step 4: Synthesis of 2-(4-chloro-5-fluoropyridin-3-yl)acetonitrile**



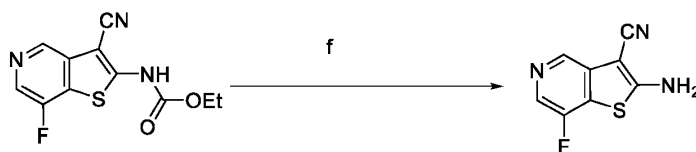
[00251] To a solution of 4-chloro-3-(chloromethyl)-5-fluoropyridine (120.0 g, 0.67 mol, 1.0 eq) and TMSCN (332.3 g, 3.35 mol, 5.0 eq) in ACN (2.4 L) was added TBAF (875.9 g, 3.35 mol, 5.0 eq) in THF (2.4 L) at 0 °C. The reaction mixture was stirred at room temperature for 15 h. The mixture was quenched with water (500 mL) and extracted with EtOAc (1.0 L x 2). The combined organic layers were washed with brine (1.0 L), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude. The crude product was purified by silica gel column chromatography (Petroleum ether/ EtOAc = 5:1) to give 2-(4-chloro-5-fluoropyridin-3-yl)acetonitrile (85.0 g, 74.7%) as a yellow solid. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>Cl<sub>3</sub>): δ 8.69 – 8.50 (m, 2H), 3.85 (s, 2H)

**Step 5: Synthesis of ethyl (3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate**



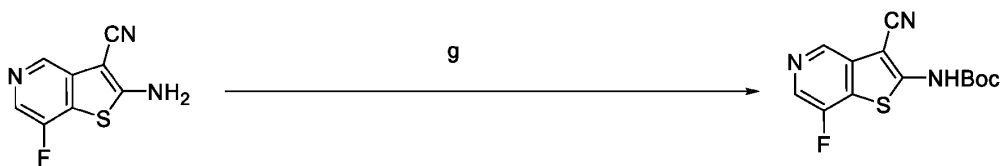
[00252] To a solution of 2-(4-chloro-5-fluoropyridin-3-yl)acetonitrile (85.0 g, 0.50 mol, 1.0 eq) in DMF (850 mL) cooled at 0 °C was added NaH (24.0 g, 0.60 mol, 1.2 eq), the reaction mixture was stirred at 0 °C for 0.5 h. Then the mixture was added O-ethyl carbonisothiocyanatide (65.6 g, 0.60 mol, 1.2 eq), the reaction mixture was stirred at 100 °C for 2 h. The mixture was quenched with water (1.0 L) and filtered to give ethyl (3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate (100.0 g, crude) as a yellow solid. LCMS: m/z 266.0 ([M+H]<sup>+</sup>).

**Step 6: Synthesis of 2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile**



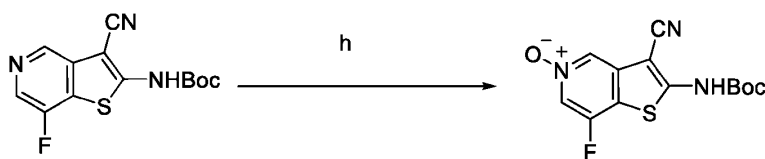
[00253] The solution of ethyl (3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate (100.0 g, 0.38 mol, 1.0 eq) in DMSO (1.0 L) was added 4M NaOH aqueous solution (2.0 L). The reaction mixture was stirred at 105 °C for 2 h. The mixture was poured into ice water (2.0 L) and filtered to give 2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile (60.0 g, crude) as a yellow solid. LCMS: m/z 194.0 ([M+H]<sup>+</sup>)

**Step 7: Synthesis of tert-butyl (3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate**



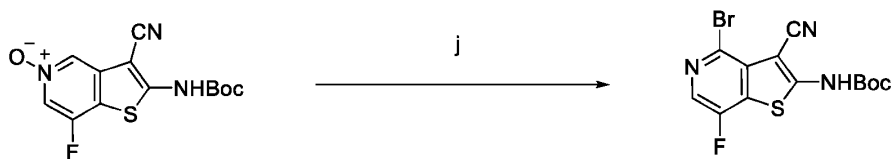
[00254] To a solution of 2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile (60.0 g, 0.31 mol, 1.0 eq) and DIEA (120.0 g, 0.93 mol, 3.0 eq) in DCM (600 mL) cooled at 0 °C was added Boc<sub>2</sub>O (81 g, 0.37 mol, 1.2 eq) and DMAP (1.9 g, 15.5 mmol, 0.05 eq). The reaction mixture was stirred at room temperature for 12 h. The mixture was quenched with 5% citric acid aqueous solution (400 mL) and extracted with EtOAc (400 mL x 3). The combined organic layers were washed with brine (400 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude. The crude product was purified by silica gel column chromatography (Petroleum ether / EtOAc = 1:1) to give tert-butyl (3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate (36.0 g, 41.0% for 3 steps) as a white solid. LCMS: m/z 294.1 ([M+H]<sup>+</sup>)

**Step 8: Synthesis of 2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridine-5-oxide**



[00255] To a solution of tert-butyl (3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate (36.0 g, 0.12 mol, 1.0 eq) in DCM (360 mL) was added m-CPBA (24.2 g, 0.14 mmol, 1.2 eq). The reaction mixture was stirred at room temperature for 15 h. The mixture was concentrated to give a crude. The crude product was purified by silica gel column chromatography (DCM / MeOH = 30:1) to give 2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridine 5-oxide (29.0 g, 76.4%) as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.71 (brs, 1H), 8.47 (s, 1H), 8.12 (d, J = 4.4 Hz, 1H), 1.59 (s, 9H).

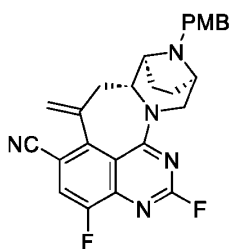
**Step 9: Synthesis of tert-butyl (4-chloro-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate**



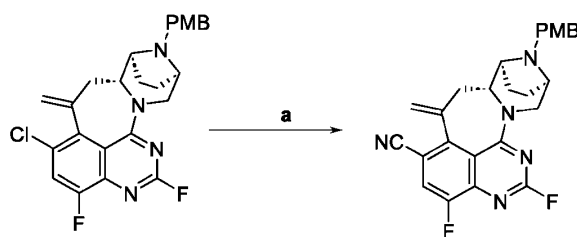
[00256] To a solution of 2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridine 5-oxide (1.0 g, 3.23 mmol, 1.0 eq) in DCE (10 mL) was added POBr<sub>3</sub> (1.4 g, 4.85 mmol, 1.5 eq) and PhNMe<sub>2</sub> (1.2 g, 9.69 mmol, 3.0 eq) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The mixture was concentrated to give a crude. The crude product was purified by flash (DCM / MeOH = 30:1) to give tert-butyl (4-bromo-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate (0.5 g, 41.7%) as a white solid. LCMS: *m/z* 371.9, 374.0 ([M+H]<sup>+</sup>)

#### Intermediate 18

(1*S*,4*R*,14*aR*)-8,10-difluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-12-carbonitrile



#### Synthetic Scheme

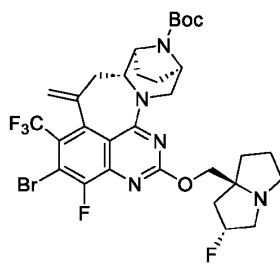


[00257] To solution of (1*S*, 4*R*, 14*aR*)-12-chloro-8, 10-difluoro-15-(4-methoxybenzyl)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline (300.0 mg, 0.64 mmol, 1.0 eq) in NMP (5 mL) was added Zn(CN)<sub>2</sub> (75.0 mg, 5.12 mmol, 8.0 eq), Pd(*t*-Bu<sub>3</sub>P)<sub>2</sub> (164.0 mg, 0.32 mmol, 0.5 eq) at room temperature under N<sub>2</sub>. The sealed vial was irradiated in the microwave at 140 °C for 30 min. The reaction mixture was

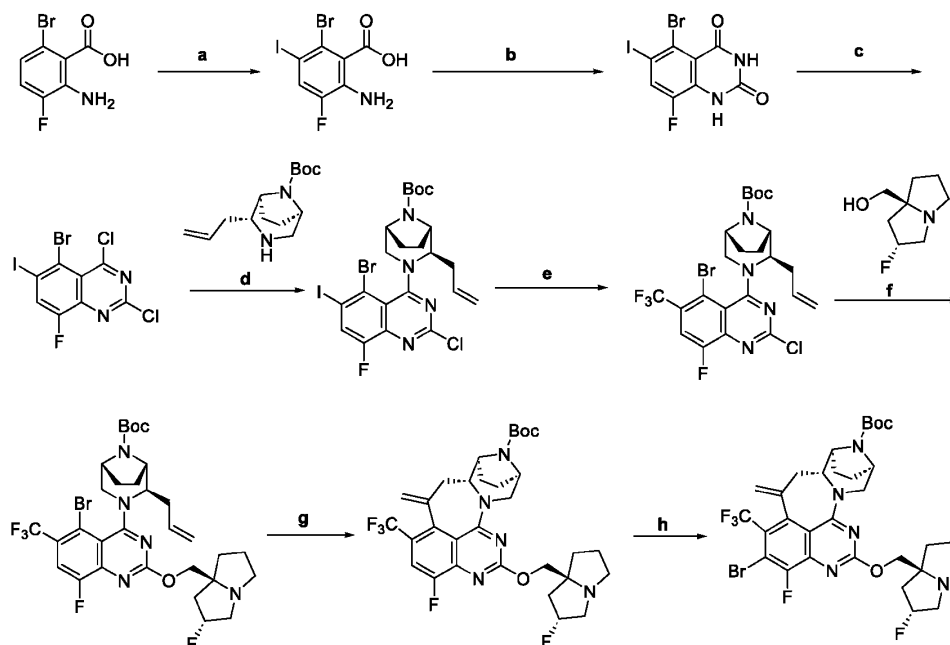
diluted with water (15 mL) and extracted with EtOAc (20 mL x 3). The organic layer was washed with water (10 mL) and brine (10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration, the filtrate was concentrated to afford the residue, which was purified by silica gel column chromatography (Petroleum ether / EtOAc = 6:1) to afford (1*S*, 4*R*, 14*aR*)-8, 10-difluoro-15-(4-methoxybenzyl)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-12-carbonitrile (60.0 mg, 20.3%) as a yellow solid. LCMS: 460.2 (M+H<sup>+</sup>).

#### Intermediate 19

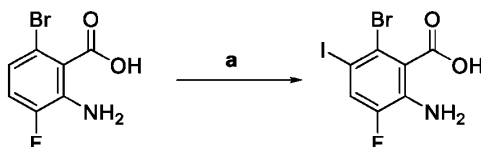
**tert-butyl (1*S*,4*R*,14*aR*)-11-bromo-10-fluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-12-(trifluoromethyl)-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-15-carboxylate**



#### Synthetic Scheme

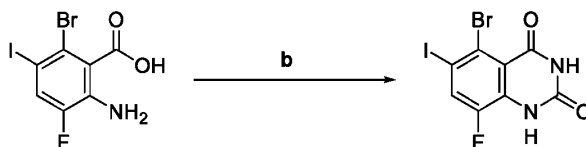


**Step 1: Synthesis of 2-amino-6-bromo-3-fluoro-5-iodobenzoic acid**



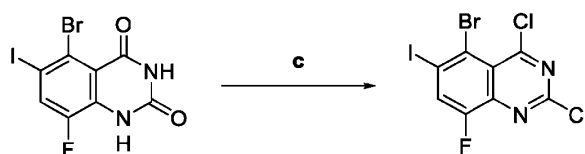
[00258] To a solution of 2-amino-6-bromo-3-fluorobenzoic acid (11 g, 47.0 mmol) in DMF (100 mL) was added N-iodosulfilimine (8.94 g, 51.7 mmol). The reaction mixture was stirred at 80 °C under N<sub>2</sub> for 2h. The cooled reaction mixture was quenched with water, extracted with EtOAc (30 mL x 3), washed by water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by column chromatography on silica gel (MeOH in DCM = 0 ~ 10%) to obtain 2-amino-6-bromo-3-fluoro-5-iodobenzoic acid (11.5 g, 31.9 mmol, 67%) as an orange solid. LC/MS (ESI) m/z: 360.1 [M+H]<sup>+</sup>

**Step 2: Synthesis of 5-bromo-8-fluoro-6-iodoquinazoline-2,4(1H,3H)-dione**



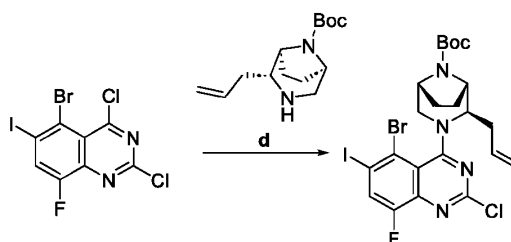
[00259] To a solution of 2-amino-6-bromo-3-fluoro-5-iodobenzoic acid (11.5 g, 31.9 mmol) in DCM (45 mL) was added dropwise chlorosulfonyl isocyanate (10.4 g, 73.4 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 hours and concentrated under reduced pressure. Then HCl (200 mL, 6 mol) was added and stirred at 100 °C for 2 hours. The resulting mixture was cooled to room temperature and filtered, the filter cake was washed by water and dried under reduced pressure to give 5-bromo-8-fluoro-6-iodo-1,2,3,4-tetrahydroquinazoline-2,4-dione (11.5 g, 29.8 mmol, 93%) as a grey solid. LCMS: ESI  $m/z$  385.1  $[M + H]^+$

**Step 3: 5-bromo-2,4-dichloro-8-fluoro-6-iodoquinazoline**



[00260] To a solution of 5-bromo-6,8-difluoroquinazoline-2,4-diol (10 g, 36.1 mmol) in ACN (100 mL) and  $\text{POCl}_3$  (27.8 g, 181 mmol) was added DIEA (11.7 g, 90.9 mmol) and the mixture was stirred at 110 °C overnight. The cooled mixture was concentrated under vacuum to give a crude, which was poured into saturated  $\text{NaHCO}_3$  and extracted with EtOAc. The combined organic phase was washed with brine, dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified by column chromatography on silica gel (EA in PE = 0 ~ 10%) to obtain 5-bromo-2,4-dichloro-8-fluoro-6-iodoquinazoline (6.5 g, 15.409 mmol, 84%) as a yellow solid. LC/MS (ESI)  $m/z$ : 423.1  $[M+H]^+$

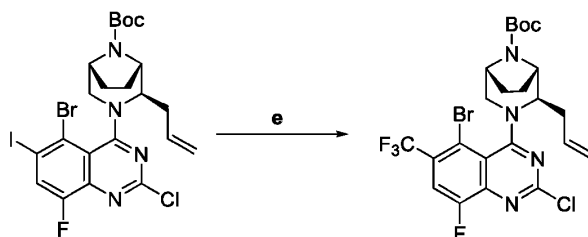
**Step 4: Synthesis of tert-butyl (1S,2R,5R)-2-allyl-3-(5-bromo-2-chloro-8-fluoro-6-iodoquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate**



[00261] To a solution of 5-bromo-2,4-dichloro-8-fluoro-6-iodoquinazoline (7 g, 16.6 mmol) in DCM (5 mL), was added 2-methylpropan-2-yl (1S,2R,5R)-2-(prop-2-enyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (5.03 g, 19.9 mmol) and DIEA (6.43 g, 49.7 mmol).

The reaction mixture was stirred at -50 °C under N<sub>2</sub> for 2h. The cooled reaction mixture was quenched with water, extracted with DCM (100 mL x 3), washed by water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by column chromatography on silica gel (EA in PE = 0 ~ 20%) to obtain 2-methylpropan-2-yl (1S,2R,5R)-3-(5-bromo-2-chloro-8-fluoro-6-iodoquinazolin-4-yl)-2-(prop-2-enyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (6.5 g, 10.2 mmol, 61%) as an yellow solid. LC/MS (ESI) m/z: 639.1 [M+H]<sup>+</sup>

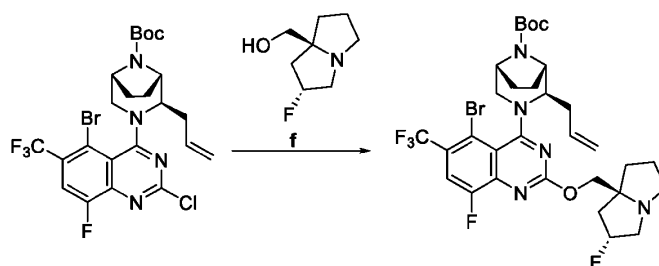
**Step 5: Synthesis of tert-butyl (1S,2R,5R)-2-allyl-3-(5-bromo-2-chloro-8-fluoro-6-(trifluoromethyl) quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate**



[00262] To a solution of 2-methylpropan-2-yl (1S,2R,5R)-3-(5-bromo-2-chloro-8-fluoro-6-iodoquinazolin-4-yl)-2-(prop-2-enyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (6.5 g, 10.193 mmol) in DMA (90 mL), was added CuI (3.88 g, 20.4 mmol) and Methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (11.75 g, 61.2 mmol). The reaction mixture was stirred at 100 °C under N<sub>2</sub> for 3h. The cooled reaction mixture was quenched with water, extracted with EA (30 mL x 3), washed by water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by column chromatography on silica gel (EA in PE = 0 ~ 20%) to obtain 2-methylpropan-2-yl (1S,2R,5R)-3-[5-bromo-2-chloro-8-fluoro-6-(trifluoromethyl)quinazolin-4-yl]-2-(prop-2-enyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (3.8 g, 6.55 mmol, 64%) as an yellow solid. LC/MS (ESI) m/z: 581.1 [M+H]<sup>+</sup>

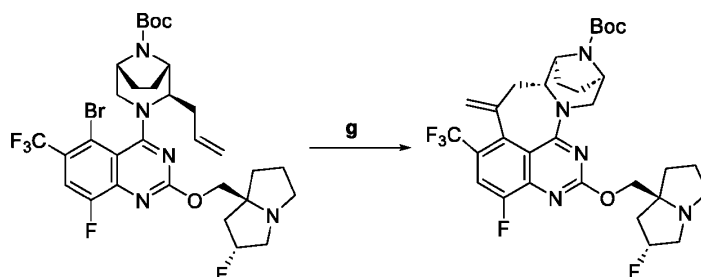
**Step 6: Synthesis of tert-butyl (1S,2R,5R)-2-allyl-3-(5-bromo-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate**





[00263] To a solution of 2-methylpropan-2-yl (1S,2R,5R)-3-[5-bromo-2-chloro-8-fluoro-6-(trifluoromethyl)quinazolin-4-yl]-2-(prop-2-enyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (3.8 g, 6.554 mmol) in dioxane ( 50 mL ). was added [(2R,7aS)-2-fluoro-2,3,5,6,7,7a-hexahydro-1H-pyrrolizin-7a-yl]methanol (8.35 g, 52.4 mmol) and  $\text{Cs}_2\text{CO}_3$  (6.41 g, 19.6 mmol). The reaction mixture was stirred at 80 °C under  $\text{N}_2$  for O/N. The cooled reaction mixture was quenched with water, extracted with EtOAc (20 mL x 3), washed by water and brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified by column chromatography on silica gel (MeOH in DCM = 0 ~ 10%) to obtain 2-methylpropan-2-yl (1S,2R,5R)-3-[5-bromo-8-fluoro-2-({[(2R,7aS)-2-fluoro-2,3,5,6,7,7a-hexahydro-1H-pyrrolizin-7a-yl] methyl} oxy)-6-(trifluoromethyl) quinazolin-4-yl]-2-(prop-2-enyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.6 g, 2.277 mmol, 34%) as an yellow solid. LC/MS (ESI) m/z: 704.1  $[\text{M}+\text{H}]^+$

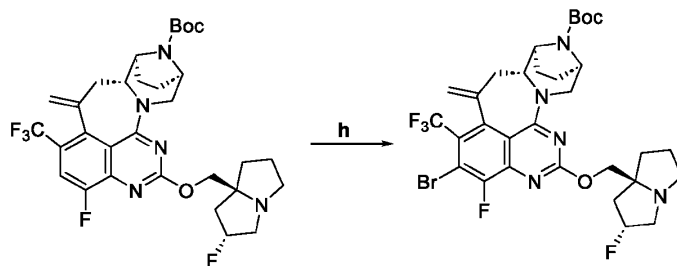
**Step 7: Synthesis of tert-butyl (1S,4R,14aR)-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-12-(trifluoromethyl)-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00264] To a solution of 2-methylpropan-2-yl (1S,2R,5R)-3-[5-bromo-8-fluoro-2-({[(2R,7aS)-2-fluoro-2,3,5,6,7,7a-hexahydro-1H-pyrrolizin-7a-yl] methyl} oxy)-6-(trifluoromethyl) quinazolin-4-yl]-2-(prop-2-enyl)-3,8-diazabicyclo[3.2.1] octane-8-carboxylate (1.6 g, 2.277 mmol) in DMA (5 mL). was added  $\text{PPh}_3$  (0.12 g, 0.455 mmol),  $\text{PPh}_3$  (0.12 g, 0.455

mmol) and Pd(OAc)<sub>2</sub> (0.05 g, 0.228 mmol). The reaction mixture was stirred at 100 °C under N<sub>2</sub> for 2 h. The cooled reaction mixture was quenched with water, extracted with EtOAc (10 mL x 3), washed by water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by column chromatography on silica gel (EA in PE = 0 ~ 10%) to obtain 2-methylpropan-2-yl (4R,7S,8R)-14-fluoro-17-({[(2R,7aS)-2-fluoro-2,3,5,6,7,7a-hexahydro-1H-pyrrolizin-7a-yl]methyl}oxy)-10-methylidene-12-(trifluoromethyl)-2,16,18,20-tetrazapentacyclo[13.3.1.1<sup>4,7</sup>.0<sup>11,19</sup>.0<sup>2,8</sup>]jicosa-1(19),11(12),13,15(16),17-pentaene-20-carboxylate (1.1 g, 1.77 mmol, 77%) as an orange solid. LC/MS (ESI) m/z: 622.1 [M+H]<sup>+</sup>

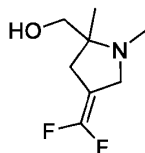
**Step 8: tert-butyl (1S,4R,14aR)-11-bromo-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-12-(trifluoromethyl)-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



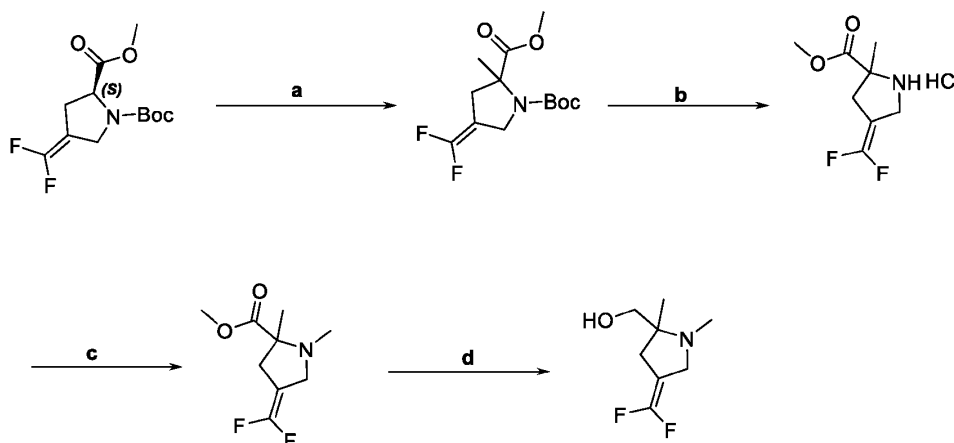
[00265] To a solution of 2-methylpropan-2-yl (4R,7S,8R)-14-fluoro-17-({[(2R,7aS)-2-fluoro-2,3,5,6,7,7a-hexahydro-1H-pyrrolizin-7a-yl]methyl}oxy)-10-methylidene-12-(trifluoromethyl)-2,16,18,20-tetrazapentacyclo[13.3.1.1<sup>4,7</sup>.0<sup>11,19</sup>.0<sup>2,8</sup>]jicosa-1(19),11(12),13,15(16),17-pentaene-20-carboxylate (700 mg, 1.17 mmol) in THF (2 mL) was added LDA (180 mg, 1.689 mmol) at -65 °C. The reaction mixture under N<sub>2</sub> to -15 °C for 10 minutes, then continue to cool to -60 °C, then 1,2-dibromo-1,1,2,2-tetrachloroethane (550 mg, 1.689 mmol) was added at -60 °C. Slowly raise the reaction mixture to room temperature. The reaction mixture was quenched by ice-water, and the mixture was extracted with EtOAc (100 mL\*3). The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue was triturated with (DCM/MeOH=10/1) and filtered to afford 2-methylpropan-2-yl (4R,7S,8R)-13-bromo-14-fluoro-17-({[(2R,7aS)-2-fluoro-2,3,5,6,7,7a-hexahydro-1H-pyrrolizin-7a-yl]methyl}oxy)-10-methylidene-12-(trifluoromethyl)-2,16,18,20-tetrazapentacyclo[13.3.1.1<sup>4,7</sup>.0<sup>11,19</sup>.0<sup>2,8</sup>]jicosa-1(19),11(12),13,15(16),17-pentaene-20-carboxylate (300 mg, 0.428 mmol, 38%) as a yellow solid. LCMS: ESI m/z 700.1 [M + H]<sup>+</sup>.

## Intermediate 20

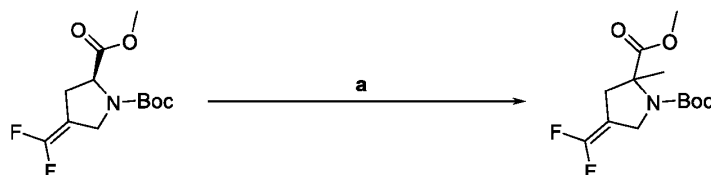
## (4-(difluoromethylene)-1,2-dimethylpyrrolidin-2-yl)methanol



## Synthetic Scheme



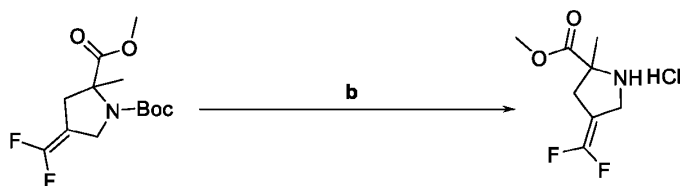
## Step 1: 1-(tert-butyl) 2-methyl 4-(difluoromethylene)-2-methylpyrrolidine-1,2-dicarboxylate



[00266] To a solution of 1-(tert-butyl) 2-methyl (S)-4-(difluoromethylene)pyrrolidine-1,2-dicarboxylate (10.0 g, 36.1 mmol, 1.0 eq) in THF (50 mL) was added LiHMDS (1M in THF) (54.1 mL, 54.1 mmol, 1.5 eq) at -15 °C. The mixture was stirred at -15 °C for 1.5 h under nitrogen atmosphere. Then the mixture was added MeI (10.2 g, 72.2 mmol, 2.0 eq). The mixture was stirred at -15 °C for 2.5 h under nitrogen atmosphere. HPLC showed the reaction was completed. The mixture was added water (100 mL) and extracted with EtOAc (200 mL x 3). The organic layers were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a crude product, which was purified by silica gel column

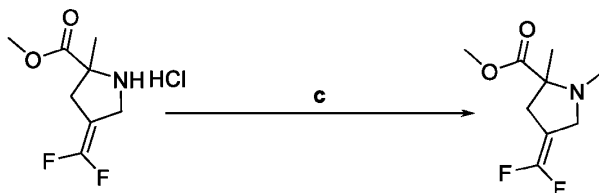
chromatography (petroleum ether: EtOAc = 10: 1) to 1-(tert-butyl) 2-methyl 4-(difluoromethylene)-2-methylpyrrolidine-1,2-dicarboxylate (8.3 g, yield: 79.0%) as a yellow liquid. LCMS: 192.2 (M-Boc + H<sup>+</sup>).

**Step 2: Synthesis of methyl 4-(difluoromethylene)-2-methylpyrrolidine-2-carboxylate hydrochloride**



[00267] To a solution of 1-(tert-butyl) 2-methyl 4-(difluoromethylene)-2-methylpyrrolidine-1,2-dicarboxylate (5.0 g, 17.1 mmol, 1.0 eq) in DCM (25 mL) was added HCl/dioxane (4 M) (25 mL). The mixture was stirred at 25 °C for 12 h. HPLC showed the reaction was complete. The mixture was added saturated sodium carbonate (50 mL) and extracted with DCM: MeOH = (10: 1) (3 mL x 50). The organic layers were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a methyl 4-(difluoromethylene)-2-methylpyrrolidine-2-carboxylate hydrochloride (2.8 g, crude) as a white solid. LCMS: 192.2 (M+H<sup>+</sup>).

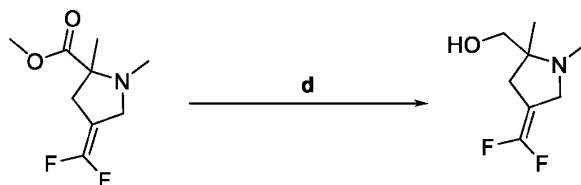
**Step 3: Synthesis of methyl 4-(difluoromethylene)-1,2-dimethylpyrrolidine-2-carboxylate**



[00268] To a solution of methyl 4-(difluoromethylene)-2-methylpyrrolidine-2-carboxylate hydrochloride (2.8 g, 14.7 mmol, 1.0 eq) in MeOH (30 mL) was added Formaldehyde (37% in H<sub>2</sub>O) (3.6 g, 44.1 mmol, 3.0 eq), the mixture was stirred at 25 °C for 0.5 h. Then the mixture was added Sodium cyanoborohydride (1.1 g, 17.6 mmol, 1.2 eq), The mixture was stirred at 25 °C for 2 h. HPLC showed the reaction was completed. Then concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (petroleum ether: EtOAc = 15: 1 and 0.3% Ammonium hydroxide) to afford methyl 4-(difluoromethylene)-1,2-

dimethylpyrrolidine-2-carboxylate (1.2 g, yield: 34.0% for two steps) as a yellow liquid. LCMS: 206.2 ( $M+H^+$ ).

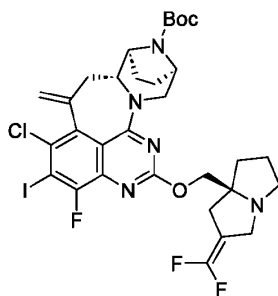
**Step 4: Synthesis of (4-(difluoromethylene)-1,2-dimethylpyrrolidin-2-yl)methanol**



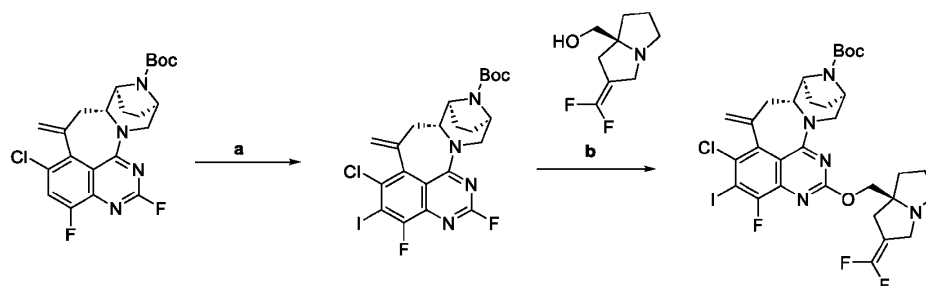
[00269] To a solution of methyl 4-(difluoromethylene)-1,2-dimethylpyrrolidine-2-carboxylate (1.2 g, 5.8 mmol, 1.0 eq) in THF (12 mL) was added LiBH<sub>4</sub>.THF (2M) (4.7 mL, 9.4 mmol, 1.6 eq) at room temperature under nitrogen atmosphere. Then the reaction was stirred at 60 °C for 2 h under N<sub>2</sub>. HPLC showed the reaction was completed. The reaction mixture was quenched by the addition of the 10H<sub>2</sub>O.Na<sub>2</sub>SO<sub>4</sub> (3.8 g). The mixture was filtered, and the filtrate was concentrated to give the (4-(difluoromethylene)-1,2-dimethylpyrrolidin-2-yl)methanol (1.1 g, crude) as a yellow liquid. LCMS: 178.1 ( $M+H^+$ ).

**Intermediate 21**

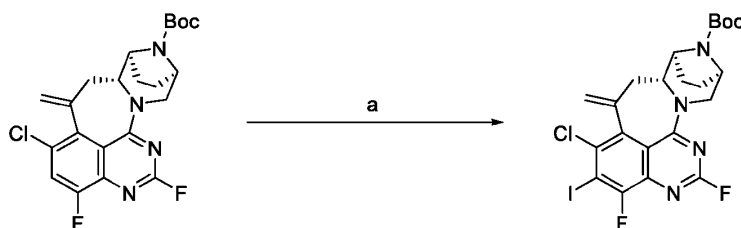
**tert-butyl (1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene) tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-11-iodo-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino [1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



**Synthetic Scheme**

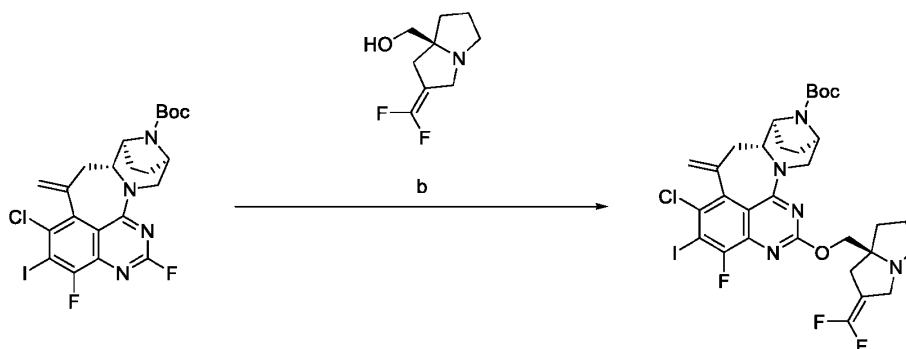


**Step 1: Synthesis of tert-butyl (1S,4R,14aR)-12-chloro-8,10-difluoro-11-iodo-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00270] To a solution of tert-butyl (1S,4R,14aR)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (10.0 g, 22.3 mmol, 1.0 eq) in THF (100 mL) was added LDA (2.0M in THF, 33.4 mL, 3.0 eq) by dropwise at -78°C under N<sub>2</sub>. The mixture was stirred at -78 °C for 1h, then was added I<sub>2</sub> (14.1 g, 55.7 mmol, 2.5 eq) in THF (10.0 mL) by dropwise at -78 °C under N<sub>2</sub>, and the mixture was stirred at -78°C for 1h. The mixture was diluted with water (200 mL) and extracted with EtOAc (200 mL x 2). The organic layers were washed with water (200 mL) and brine (200 mL), then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a residue. The crude product was purified by silica gel chromatography (eluted with petroleum ether: EtOAc = 10: 1) to afford tert-butyl (1S,4R,14aR)-12-chloro-8,10-difluoro-11-iodo-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (12.0 g, purity: 95.0%, yield: 93.6%). LCMS: 575.0 (M+H<sup>+</sup>).

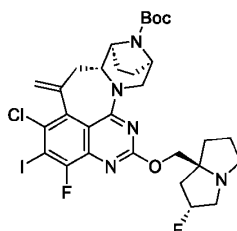
**Step 2: Synthesis of tert-butyl (1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-11-iodo-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



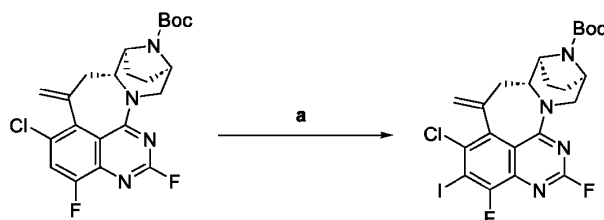
[00271] To a solution of *tert*-butyl (1S,4R,14aR)-12-chloro-8,10-difluoro-11-iodo-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (500.0 mg, 0.87 mmol, 1.0 eq), (S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-ylmethanol (197.0 mg, 1.04 mmol, 1.2 eq) in THF (5 mL) was added *t*-BuONa (167.1 mg, 1.74 mmol, 2.0 eq) at 25 °C. Then DMF (1 mL) was added and stirred at 25 °C for 3 h under N<sub>2</sub>. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The organic layers were washed with water (20 mL x 3) and brine (20 mL), then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a residue. The crude product was purified by silica gel chromatography (eluted with petroleum ether: EtOAc = 3: 1) to afford *tert*-butyl (1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-11-iodo-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (1.2 g, purity: 89%, yield: 77.3%) as a yellow solid. LCMS: 744.1 (M+H<sup>+</sup>).

#### Intermediate 22

***tert*-butyl (1S,4R,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-11-iodo-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epimino azepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**

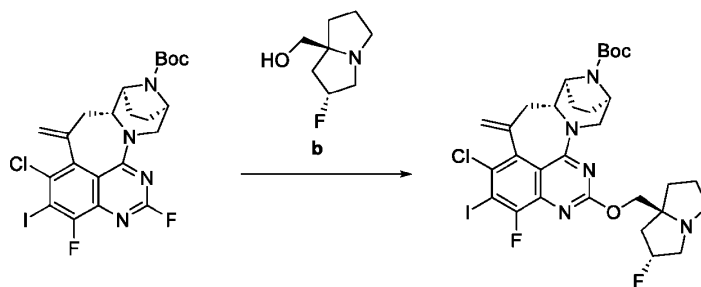


**Step 1: Synthesis of *tert*-butyl (1*S*, 4*R*, 14*aR*)-12-chloro-8, 10-difluoro-11-iodo-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-15-carboxylate**



[00272] To a solution of *tert*-butyl (1*S*, 4*R*, 14*aR*)-12-chloro-8,10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-15-carboxylate (3.0 g, 6.7 mmol, 1.0 eq) in THF (30 mL) was added dropwise LDA (2*M*, 20 mL, 20.1 mmol, 3.0 eq) at -78 °C under N<sub>2</sub>. The mixture was stirred at -78 °C for 1 h under N<sub>2</sub>, added a solution of I<sub>2</sub> (4.26 g, 16.8 mmol, 2.5 eq) in THF (20 mL) at -78 °C under N<sub>2</sub> and stirred at -78 °C for 3 h under N<sub>2</sub>. After completion of the reaction, the reaction mixture was poured into water (30 mL) and extracted with EtOAc (50 mL x 3), the combined organic layers were washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue was purified by silica gel column chromatography (Petroleum ether / EtOAc = 10:1) to afford *tert*-butyl (1*S*, 4*R*, 14*aR*)-12-chloro-8, 10-difluoro-11-iodo-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-15-carboxylate (3.0 g, 77.6%) as a yellow solid. LCMS: 575.1 (M+H<sup>+</sup>).

**Step 2: Synthesis of *tert*-butyl (1*S*, 4*R*, 14*aR*)-12-chloro-10-fluoro-8- (((2*R*, 7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-11-iodo-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-15-carboxylate**

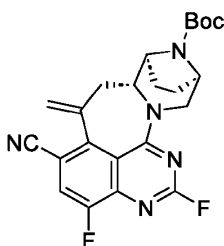




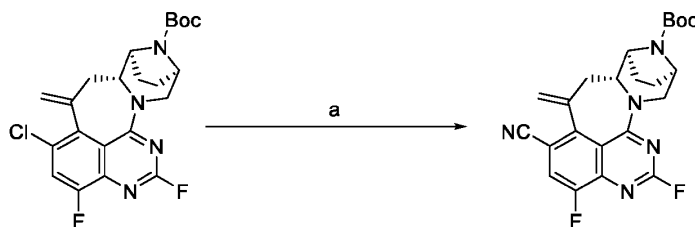
[00273] To a solution of ((2*R*, 7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl) methanol (124.1 mg, 0.78 mmol, 1.5 eq) in THF (1.5 mL) was added NaH (60%) (62.4 mg, 1.56 mmol, 3.0 eq) at 0 °C and then the mixture was stirred for 0.5 h at room temperature under N<sub>2</sub>, added the solution of *tert*-butyl (1*S*, 4*R*, 14*aR*)-12-chloro-8, 10-difluoro-11-iodo-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-15-carboxylate (300.0 mg, 0.52 mmol, 1.0 eq) in THF (3 mL) and stirred at 25 °C for 1.5 h. HPLC and TLC show the reaction was completed. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl aqueous solution (10 mL) and extracted with EtOAc (20 mL x 3). The mixture was concentrated to give a crude product, which was purified by silica gel column chromatography (Petroleum ether / EtOAc = 1:1) to afford *tert*-butyl (1*S*, 4*R*, 14*aR*)-12-chloro-10-fluoro-8-(((2*R*, 7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-11-iodo-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-15-carboxylate (250.0 mg, 67.3%) as a yellow solid. LCMS: 714.1 (M+H<sup>+</sup>).

#### Intermediate 23

***tert*-butyl (1*S*,4*R*,14*aR*)-12-cyano-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino [1',2':1,7]azepino[2,3,4-*de*]quinazoline-15-carboxylate**



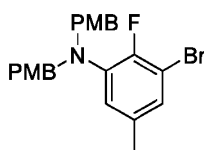
**Step 1: Synthesis of *tert*-butyl (1*S*,4*R*,14*aR*)-12-cyano-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-15-carboxylate**



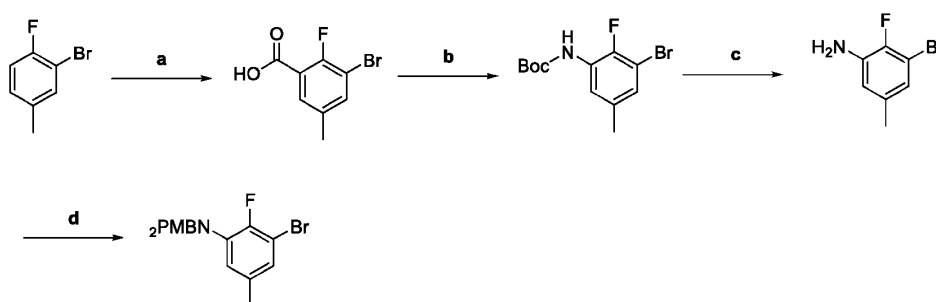
[00274] To solution of *tert*-butyl (1*S*,4*R*,14*aR*)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-15-carboxylate (1.0 g, 2.23 mol, 1.0 eq) in NMP (10 mL) was added Zn(CN)<sub>2</sub> (2.09 g, 17.84 mmol, 8.0 eq), Pd(*t*-Bu<sub>3</sub>P)<sub>2</sub> (574.6 mg, 1.12 mmol, 0.5 eq) at room temperature under N<sub>2</sub>. The sealed vial was irradiated in the microwave at 140 °C for 30 min. The reaction mixture was diluted with water (40 mL), then extracted with EtOAc (20 mL x 3). The organic laver was washed with water (10 mL) and brine (10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration, the filtrate was concentrated to afford crude. The residue was purified by column chromatography on silica gel eluted with (petroleum ether: EtOAc~6: 1) to afford *tert*-butyl (1*S*,4*R*,14*aR*)-12-cyano-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-15-carboxylate (230 mg, 23.3%) as a yellow solid. LCMS: *m/z* 440.2 (M+H<sup>+</sup>).

#### Intermediate 24

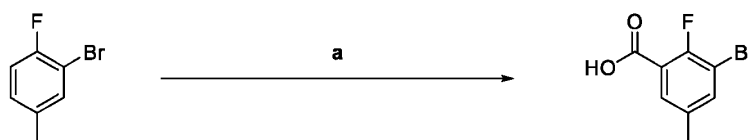
#### 3-bromo-2-fluoro-N,N-bis(4-methoxybenzyl)-5-methylaniline



#### Synthetic Scheme



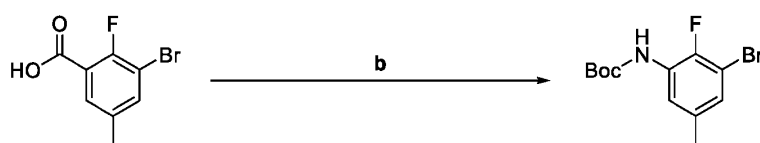
#### Step 1: Synthesis of 3-Bromo-2-fluoro-5-methylbenzoic acid



[00275] To a solution of 2-bromo-1-fluoro-4-methylbenzene (75.0 g, 396.8 mmol, 1.0 eq) and diisopropylamine (44.2 g, 436.4 mmol, 1.1 eq) in anhydrous THF (1.5 L) at -78 °C under N<sub>2</sub> was

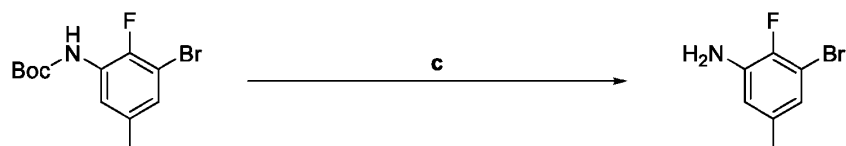
added *n*-BuLi in hexane (2.5M, 190.4 mL, 476.1 mmol, 1.2 eq) dropwise. The mixture was stirred at -78 °C for 1 h, added solid CO<sub>2</sub> (dry ice) and stirred at -78 °C for 3 h. After completion, the mixture was diluted with water (1.0 L), adjusted pH to 2-3 with conc. HCl (37%, 50 mL) and extracted with EtOAc (1.0 L x 2). The organic layer was washed with brine (500 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give 3-bromo-2-fluoro-5-methylbenzoic acid (30.0 g, purity: 94.3%, yield: 30.6 %) as a white solid, which was used in the next step without further purification. LCMS: 233.0, 230.8 (M-H<sup>-</sup>).

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



[00276] To a solution of 3-bromo-2-fluoro-5-methylbenzoic acid (30.0 g, 128.7 mmol, 1.0 eq) in toluene / *t*-BuOH (374 mL / 187 mL) was added DPPA (44.3 g, 160.9 mmol, 1.25 eq) and DIEA (20.0 g, 154.5 mmol, 1.2 eq). The reaction was stirred at reflux for 15 h. The mixture was cooled, diluted with EtOAc (400 mL) and water (100 mL) and then extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness. The crude product was purified by silica gel column chromatography (Petroleum ether / EtOAc = 20:1) to give tert-butyl (3-bromo-2-fluoro-5-methylphenyl)carbamate (24.0 g, purity: 92.0%, yield: 56.4%) as a yellow solid. LCMS: 248.0, 250.0 (M-56+H<sup>+</sup>).

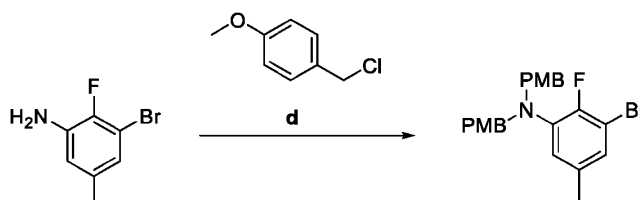
**Step 3: Synthesis of 3-bromo-2-fluoro-5-methylaniline**



[00277] To a solution of tert-butyl (3-bromo-2-fluoro-5-methylphenyl)carbamate (24.1 g, 79.2 mmol, 1.0 eq) in *i*PrOH (240 mL) was added conc. HCl (37%, 67 mL). The reaction was stirred at 60 °C for 2 h. The reaction system was concentrated, added H<sub>2</sub>O (600 mL) and adjusted pH to 7-8 with NaOH aqueous solution (250 mL, 1M). The mixture was added with EtOAc (300 mL) and water (100 mL). The aqueous layer was extracted with EtOAc (100 mL, x 3). The combined organic layers were washed with brine (500 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness.

The crude product was purified by silica gel column chromatography (Petroleum ether / EtOAc = 5:1) to give 3-bromo-2-fluoro-5-methylaniline (16.1 g, purity: 86.0%, yield: 85.6%) as a white solid. LCMS: 204.0, 206.1 ( $M+H^+$ ).

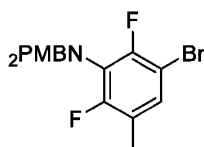
**Step 4: Synthesis of 3-bromo-2-fluoro-*N,N*-bis(4-methoxybenzyl)-5-methylaniline**



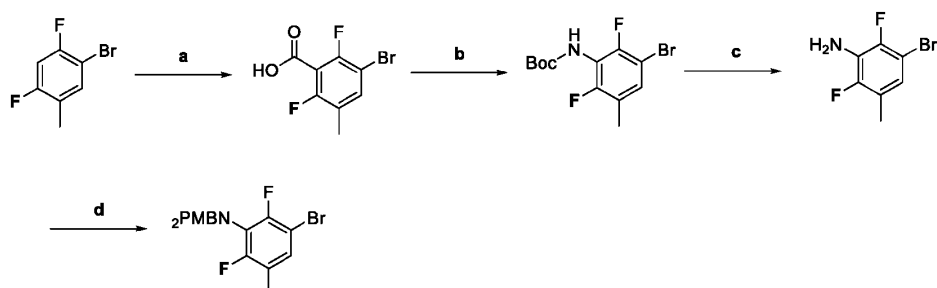
[00278] To a solution of 3-bromo-2-fluoro-5-methylaniline (6.0 g, 29.4 mmol, 1.0 eq) in DMF (90 mL) was added NaH (3.5 g, 60%, 87.5 mmol, 3.0 eq) under  $N_2$  at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, then added 4-methoxybenzylchloride (11.5 g, 73.5 mmol, 2.5 eq) at 0 °C and stirred at room temperature for 18 h. After completion, the mixture was then quenched with saturated  $NH_4Cl$  aqueous solution (200 mL) and extracted with EtOAc (200 mL x 2). The combined organic layers were washed with water (100 mL x 2) and brine (100 mL x 2), dried over  $Na_2SO_4$  and evaporated to dryness. The crude product was purified by silica gel column chromatography (Petroleum ether / EtOAc = 50:1) to give 3-bromo-2-fluoro-*N,N*-bis(4-methoxybenzyl)-5-methylaniline (12.0 g, purity: 83.8%, yield: 91.8%) as a yellow solid. LCMS: 444.0 446.0 ( $M+H^+$ ).

**Intermediate 25**

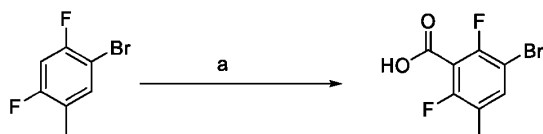
**3-bromo-2,6-difluoro-*N,N*-bis(4-methoxybenzyl)-5-methylaniline**



**Synthetic Scheme**

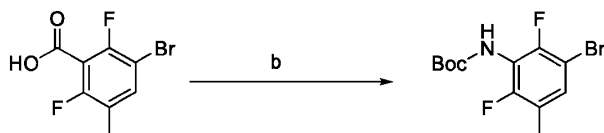


### Step 1: Synthesis of 3-bromo-2,6-difluoro-5-methylbenzoic acid



[00279] To a solution of 1-bromo-2,4-difluoro-5-methylbenzene (5.0 g, 24.1 mmol, 1.0 eq) in THF (50 mL) was added LDA (15.7 mL, 31.4 mmol, 1.3 eq) at -78 °C. The reaction mixture was stirred at the same temperature for 2 h. To the reaction was added large dry ice, the reaction was stirred at room temperature for 1 h. The mixture was quenched with sat.  $\text{NH}_4\text{Cl}$  aqueous solution (50 mL), and the mixture was adjusted pH ~ 1 with 1 N HCl (40 mL). The mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered off and concentrated to give 3-bromo-2,6-difluoro-5-methylbenzoic acid (3.0 g, 49.5%) as a white solid. LCMS:  $m/z$  249/251 ( $[\text{M}-\text{H}]^-$ ).

### Step 2: Synthesis of tert-butyl (3-bromo-2,6-difluoro-5-methylphenyl)carbamate

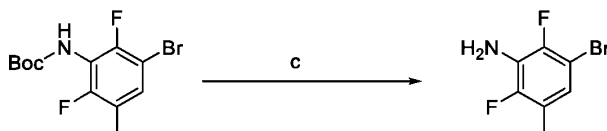


[00280] A solution of 3-bromo-2,6-difluoro-5-methylbenzoic acid (1.0 g, 4.0 mmol, 1.0 eq), TEA (1.2 g, 12.0 mmol, 3.0 eq) and DPPA (2.2 g, 8.0 mmol, 2.0 eq) in t-BuOH (10 mL) was stirred at reflux temperature for 2 h. The mixture was quenched with  $\text{H}_2\text{O}$  (10 mL), and the mixture was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered off and concentrated to a crude product. The crude product was purified by silica gel column chromatography (Petroleum ether/ EtOAc 5/1) to give tert-butyl (3-bromo-2,6-difluoro-5-methylphenyl)carbamate (0.8 g, 80.2%) as a white solid.  $^1\text{H}$

NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.26 – 7.21 (m, 1H), 5.95 (brs, 1H), 2.24 (s, 3H), 1.50 (s, 9H).

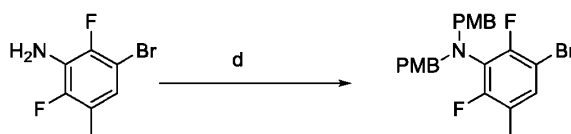
LCMS: m/z 266/268 ([M-56+H]<sup>+</sup>).

### Step 3: Synthesis of 3-bromo-2,6-difluoro-5-methylaniline



[00281] A solution of tert-butyl (3-bromo-2,6-difluoro-5-methylphenyl)carbamate (800 mg, 2.5 mmol, 1.0 eq) in 4 M HCl in dioxane (8 mL) was stirred at 40 °C for 2 h. The precipitate formed was collected by filtration, washed with DCM (5 mL), dried in vacuo under reduced pressure to give 3-bromo-2,6-difluoro-5-methylaniline (0.3 g, 54.4%) as a white solid. LCMS: m/z 222.1/224.0 ([M+H]<sup>+</sup>).

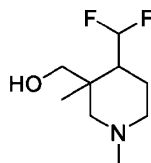
### Step 4: Synthesis of 3-bromo-2,6-difluoro-N,N-bis(4-methoxybenzyl)-5-methylaniline



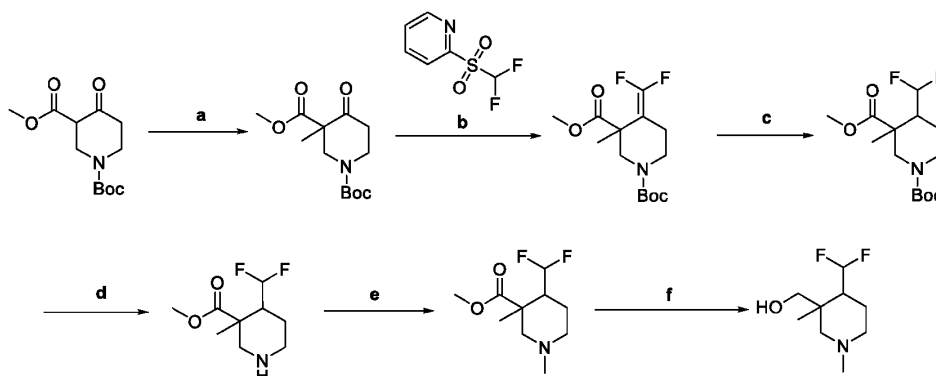
[00282] To a solution of 3-bromo-2,6-difluoro-5-methylaniline (300 mg, 1.4 mmol, 1.0 eq) in DMF (3 mL) was t-BuOK (846 mg, 5.4 mmol, 4.0 eq) and PMBCl (622 mg, 4.1 mmol, 3.0 eq) at 0 °C. The reaction was stirred at the same temperature for 2 h. The mixture was quenched with H<sub>2</sub>O (10 mL), and the mixture was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered off and concentrated to a crude product. The crude product was purified by silica gel column chromatography (Petroleum ether/ EtOAc 10/1) to give tert-butyl (3-bromo-2,6-difluoro-5-methylphenyl)carbamate (400 mg, 64.0%) as a yellow solid. LCMS: m/z 462.0/464.0 ([M+H]<sup>+</sup>).

### Intermediate 26

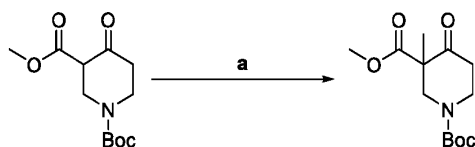
#### (4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methanol



### Synthetic Scheme

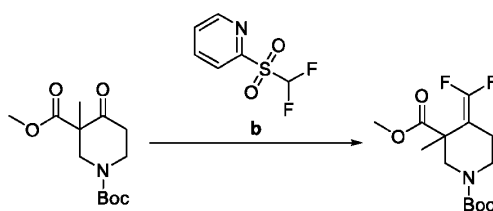


### Step 1: Synthesis of 1-(tert-butyl) 3-methyl 3-methyl-4-oxopiperidine-1,3-dicarboxylate



[00283] To a solution of 1-(tert-butyl) 3-methyl 4-oxopiperidine-1,3-dicarboxylate (30.0 g, 116.60 mmol, 1.0 eq) in Acetonitrile (450 mL) was added  $K_2CO_3$  (56.1 g, 405.78 mmol, 3.5 eq), MeI (30.0 g, 211.05 mmol, 1.8 eq) under  $N_2$ . The mixture was stirred at 40 °C for 8 h under  $N_2$ . HPLC and TLC showed the reaction was completed. The mixture was filtered through a Celite pad, then the filtrate was added water (100 mL) and extracted with DCM (200 mL x 3). The organic layers were washed with brine (100 mL), dried over  $Na_2SO_4$ , filtered and concentrated under reduced pressure to give a 1-(tert-butyl) 3-methyl 3-methyl-4-oxopiperidine-1,3-dicarboxylate (30.0 g, purity: 90%, yield: 94.8%) as a yellow liquid. LCMS: 172.2 (M-100+ $H^+$ ).

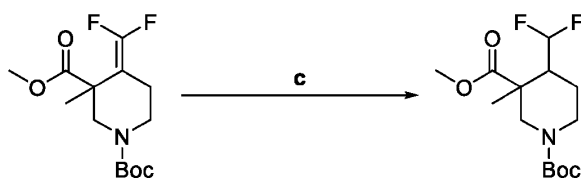
### Step 2: Synthesis of 1-(tert-butyl) 3-methyl 4-(difluoromethylene)-3-methylpiperidine-1,3-dicarboxylate



[00284] To a solution of 1-(tert-butyl) 3-methyl 3-methyl-4-oxopiperidine-1,3-dicarboxylate (10.0 g, 36.86 mmol, 1.0 eq) in DMF (100 mL) was added 2-((difluoromethyl)sulfonyl)pyridine (10.7 g, 55.29 mmol, 1.5 eq) at 0 °C under  $N_2$ . Then the mixture was added t-BuOK (1M in THF) (66.3 mL, 66.34 mmol, 1.8 eq) at 0 °C, stirred at 0 °C for 2 h and stirred at 25 °C for 3 h

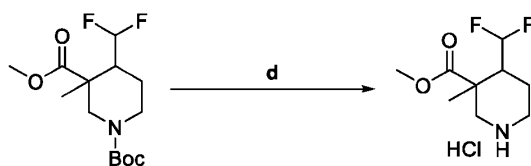
under N<sub>2</sub>. HPLC and TLC showed the reaction was completed. The mixture was added water (100 mL) and extracted with DCM / MeOH (10:1, 200 mL x 3). The organic layers were washed with water (50 mL x 3) and brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (petroleum ether / EtOAc = 30:1) to afford 1-(tert-butyl) 3-methyl 4-(difluoromethylene)-3-methylpiperidine-1,3-dicarboxylate (5.0 g, purity: 93%, yield: 44.4%) as a yellow liquid. LCMS: 250.1 (M-56+H<sup>+</sup>).

**Step 3: Synthesis of 1-(tert-butyl) 3-methyl 4-(difluoromethyl)-3-methylpiperidine-1,3-dicarboxylate**



[00285] To a solution of 1-(tert-butyl) 3-methyl 4-(difluoromethylene)-3-methylpiperidine-1,3-dicarboxylate (5.0 g, 16.38 mmol, 1.0 eq) in MeOH (80 mL) was added Pd/C (2.9 g) under H<sub>2</sub>. The mixture was stirred at 30 °C for 12 h under H<sub>2</sub>. HPLC and TLC showed the reaction was completed. The mixture was filtered through a Celite pad and concentrated under reduced pressure to give 1-(tert-butyl) 3-methyl 4-(difluoromethyl)-3-methylpiperidine-1,3-dicarboxylate (3.7 g, crude, yield: 73.5%) as a yellow liquid. LCMS: 252.0 (M-56+H<sup>+</sup>).

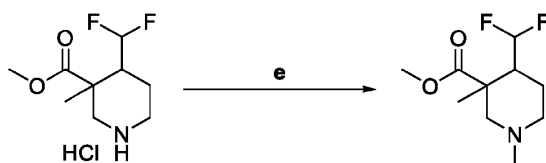
**Step 4: Synthesis of methyl 4-(difluoromethyl)-3-methylpiperidine-3-carboxylate hydrochloride**



[00286] A solution of 1-(tert-butyl) 3-methyl 4-(difluoromethyl)-3-methylpiperidine-1,3-dicarboxylate (3.7 g, 12.05 mmol, 1.0 eq) in HCl/dioxane (40.0 mL, 4N) was stirred at 25 °C for 4 h. HPLC showed the reaction was completed. The mixture concentrated under reduced pressure to give a methyl 4-(difluoromethyl)-3-methylpiperidine-3-carboxylate hydrochloride (3.7, crude) as a white solid. LCMS: 208.3 (M+H<sup>+</sup>).

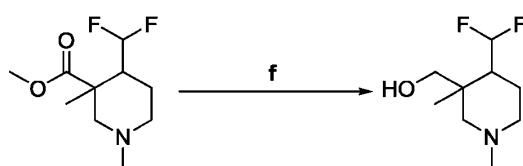
**Step 5: Synthesis of methyl 4-(difluoromethyl)-1,3-dimethylpiperidine-3-carboxylate**





[00287] To a solution of methyl 4-(difluoromethyl)-3-methylpiperidine-3-carboxylate hydrochloride (3.7 g, 15.18 mmol, 1.0 eq) in MeOH (40 mL) was added Formaldehyde (37% in H<sub>2</sub>O) (4.3 g, 52.98 mmol, 3.5 eq). The mixture was stirred at 25 °C for 0.5 h, then added Sodium cyanoborohydride (1.3 g, 21.44 mmol, 1.4 eq) and stirred at 25 °C for 2 h. HPLC showed the reaction was completed. The mixture was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (petroleum ether / EtOAc = 15:1 with 0.3% Ammonium hydroxide) to afford methyl 4-(difluoromethyl)-1,3-dimethylpiperidine-3-carboxylate (1.6 g, yield: 60.8% for two steps) as a yellow liquid. LCMS: 222.1 (M+H<sup>+</sup>).

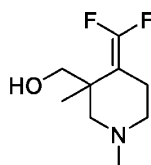
#### Step 6: Synthesis of (4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methanol



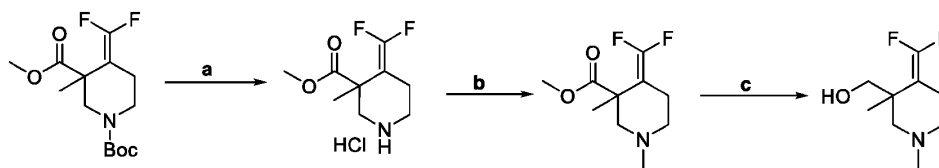
[00288] To a solution of methyl 4-(difluoromethyl)-1,3-dimethylpiperidine-3-carboxylate (1.6 g, 7.23 mmol, 1.0 eq) in THF (16 mL) was added LiAlH<sub>4</sub>•THF (11.6 mL, 1M, 11.65 mmol, 1.6 eq) at room temperature under N<sub>2</sub>. Then the reaction was stirred at 0 °C for 1 h under N<sub>2</sub>. HPLC showed the reaction was completed. The reaction mixture was quenched by the addition of Na<sub>2</sub>SO<sub>4</sub>•10H<sub>2</sub>O (4.6 g) and filtered, the filtrate was concentrated to give (4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methanol (1.6 g, crude) as a yellow liquid. LCMS: 194.2 (M+H<sup>+</sup>).

#### Intermediate 27

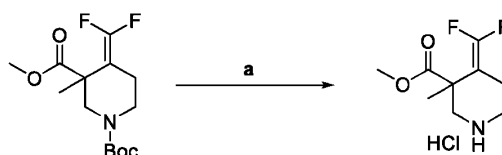
#### (4-(difluoromethylene)-1,3-dimethylpiperidin-3-yl)methanol



#### Synthetic Scheme

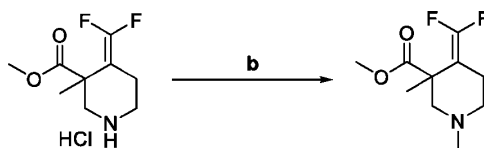


**Step 1: Synthesis of methyl 4-(difluoromethylene)-3-methylpiperidine-3-carboxylate hydrochloride**



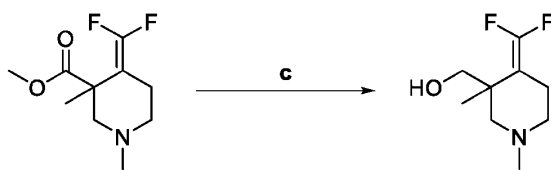
[00289] The solution of 1-(tert-butyl) 3-methyl 4-(difluoromethylene)-3-methylpiperidine-1,3-dicarboxylate (4.0 g, 13.11 mmol, 1.0 eq) in HCl/dioxane (40.0 mL, 4N) was stirred at 25 °C for 4 h. HPLC showed the reaction was completed. The mixture concentrated under reduced pressure to give methyl 4-(difluoromethylene)-3-methylpiperidine-3-carboxylate hydrochloride (4.0 g, crude) as a white solid. LCMS: 206.2 (M+H<sup>+</sup>).

**Step 2: Synthesis of methyl 4-(difluoromethylene)-1,3-dimethylpiperidine-3-carboxylate**



[00290] To a solution of methyl 4-(difluoromethylene)-3-methylpiperidine-3-carboxylate hydrochloride (4.0 g, 13.11 mmol, 1.0 eq) in MeOH (40 mL) was added Formaldehyde (37% in H<sub>2</sub>O) (4.6 g, 56.73 mmol, 4.3 eq). The mixture was stirred at 25 °C for 0.5 h, added Sodium cyanoborohydride (1.4 g, 23.18 mmol, 1.8 eq) and stirred at 25 °C for 2 h. HPLC showed the reaction was completed. Then the mixture was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (petroleum ether / EtOAc = 15:1 with 0.3% Ammonium hydroxide) to afford methyl 4-(difluoromethylene)-1,3-dimethylpiperidine-3-carboxylate (1.7 g, purity: 92%, yield: 59.2% for two steps) as a yellow liquid. LCMS: 220.2 (M+H<sup>+</sup>).

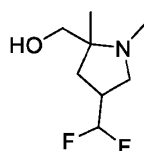
**Step 3: Synthesis of (4-(difluoromethylene)-1,3-dimethylpiperidin-3-yl)methanol**



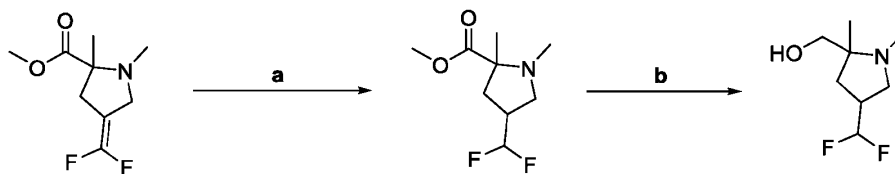
[00291] To a solution of methyl 4-(difluoromethylene)-1,3-dimethylpiperidine-3-carboxylate (1.7 g, 8.25 mmol, 1.0 eq) in THF (17 mL) was added  $\text{LiBH}_4$  in THF (6.2 mL, 2M, 12.38 mmol, 1.5 eq) at room temperature under  $\text{N}_2$ . Then the reaction was stirred at 50 °C for 1 h under  $\text{N}_2$ . HPLC showed the reaction was completed. The reaction mixture was quenched by the addition of the  $10\text{H}_2\text{O} \cdot \text{Na}_2\text{SO}_4$  (4.8 g). The mixture was filtered and the filtrate was concentrated to give (4-(difluoromethylene)-1,3-dimethylpiperidin-3-yl)methanol (1.7 g, crude) as a yellow liquid. LCMS: 192.0 ( $\text{M}+\text{H}^+$ ).

#### Intermediate 28

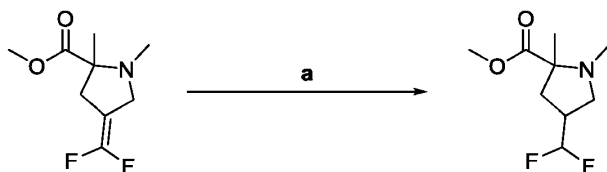
(4-(difluoromethyl)-1,2-dimethylpyrrolidin-2-yl)methanol



#### Synthetic Scheme



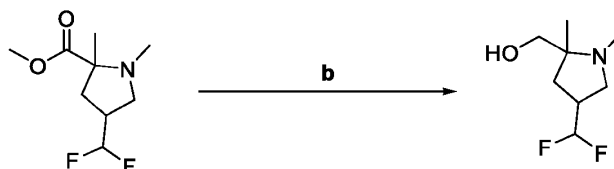
#### Step 1: Synthesis of methyl 4-(difluoromethyl)-1,2-dimethylpyrrolidine-2-carboxylate



[00292] To a solution of methyl 4-(difluoromethylene)-1,2-dimethylpyrrolidine-2-carboxylate (2.0 g, 9.75 mmol, 1.0 eq) in MeOH (50 mL) was added Pd/C (1.7 g) under  $\text{H}_2$ . The mixture was stirred at 30 °C for 12 h under  $\text{H}_2$ . HPLC and TLC showed the reaction was completed. The mixture was filtered through a Celite pad and concentrated under reduced pressure to give

methyl 4-(difluoromethyl)-1,2-dimethylpyrrolidine-2-carboxylate (1.2 g, crude) as a yellow liquid. LCMS: 208.2 ( $M+H^+$ ).

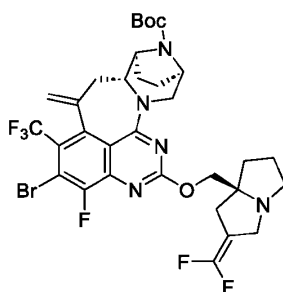
**Step 2: Synthesis of (4-(difluoromethyl)-1,2-dimethylpyrrolidin-2-yl)methanol**



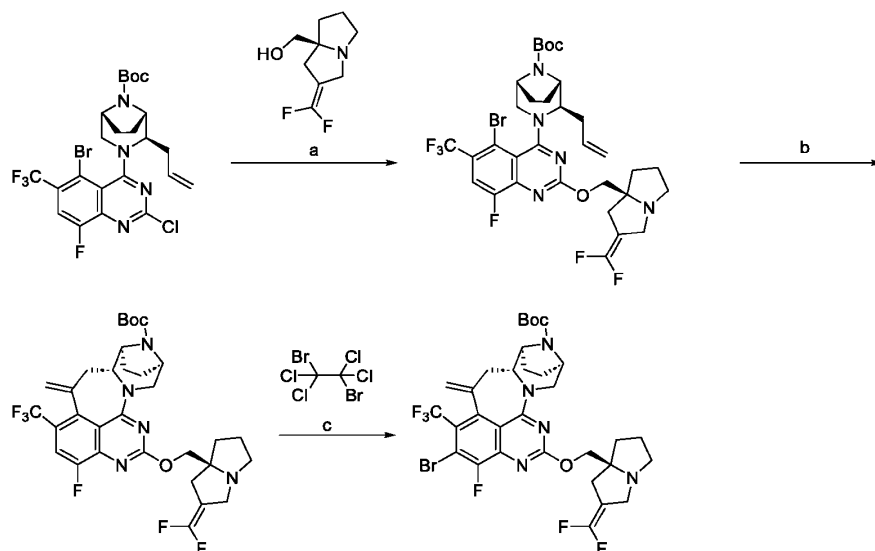
[00293] To a solution of methyl 4-(difluoromethyl)-1,2-dimethylpyrrolidine-2-carboxylate (1.2 g, 6.32 mmol, 1.0 eq) in THF (12 mL) was added  $LiAlH_4 \cdot THF$  (9.5 mL, 1M, 9.48 mmol, 1.5 eq) at room temperature under nitrogen atmosphere. Then the reaction was stirred at 60 °C for 2 h under  $N_2$ . HPLC showed the reaction was completed. The reaction mixture was quenched by the addition of the  $10H_2O \cdot Na_2SO_4$  (3.8 g). The mixture was filtered, and the filtrate was concentrated to give (4-(difluoromethyl)-1,2-dimethylpyrrolidin-2-yl)methanol (1.1 g, crude) as a yellow liquid. LCMS: 180.2 ( $M+3H^+$ ).

**Intermediate 29**

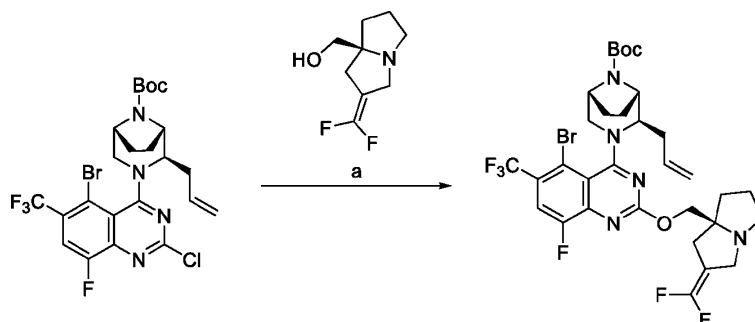
**tert-butyl (1S,4R,14aR)-11-bromo-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-12-(trifluoromethyl)-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



**Synthetic Scheme**

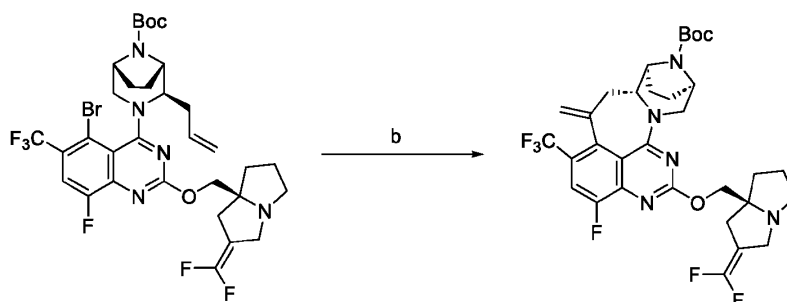


**Step 1: Synthesis of tert-butyl (1S,2R,5R)-2-allyl-3-(5-bromo-2-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8-fluoro-6-(trifluoromethyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate**



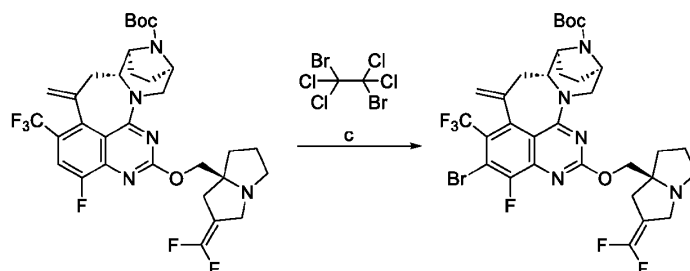
[00294] To a solution of 2-methylpropan-2-yl (1S,2R,5R)-3-[5-bromo-2-chloro-8-fluoro-6-(trifluoromethyl)quinazolin-4-yl]-2-(prop-2-enyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (3.2 g, 5.52 mmol) in dioxane (30 mL) were added [(7aS)-2-(difluoromethylidene)-2,3,5,6,7,7a-hexahydro-1H-pyrrolizin-7a-yl]methanol (3.13 g, 16.6 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (5.39 g, 16.6 mmol). The mixture was stirred at 85 °C under N<sub>2</sub> for ON. The cooled reaction mixture was diluted water, extracted with EA. The organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 0-30%) to afford (2.1 g, 2.87 mmol, 52%) as a yellow solid. LCMS: ESI m/z 734.4 [M + H]<sup>+</sup>.

**Step 2: Synthesis of tert-butyl (1S,4R,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-12-(trifluoromethyl)-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00295] To a solution of 2-methylpropan-2-yl (1S,2R,5R)-3-[2-({[(7aS)-2-(difluoromethylidene)-2,3,5,6,7,7a-hexahydro-1H-pyrrolizin-7a-yl]methyl}oxy)-5-bromo-8-fluoro-6-(trifluoromethyl)quinazolin-4-yl]-2-(prop-2-enyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2 g, 2.73 mmol) in DMA (20 mL) were added Pd(OAc)<sub>2</sub> (0.07 g, 0.328 mmol), PPh<sub>3</sub> (0.14 g, 0.546 mmol) and KOAc (0.54 g, 5.46 mmol). The mixture was stirred at 130 °C under N<sub>2</sub> for 2h. The reaction mixture was diluted water, extracted with EA. The organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue was purified using silica gel column chromatography eluted with methanol in dichloromethane (gradient: 0-10%) to afford tert-butyl (1S,4R,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-12-(trifluoromethyl)-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (1 g, 1.54 mmol, 56%) as a yellow solid. LCMS: ESI m/z 652.4 [M + H]<sup>+</sup>.

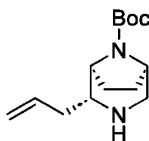
**Step 3: Synthesis of tert-butyl (1S,4R,14aR)-11-bromo-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-12-(trifluoromethyl)-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



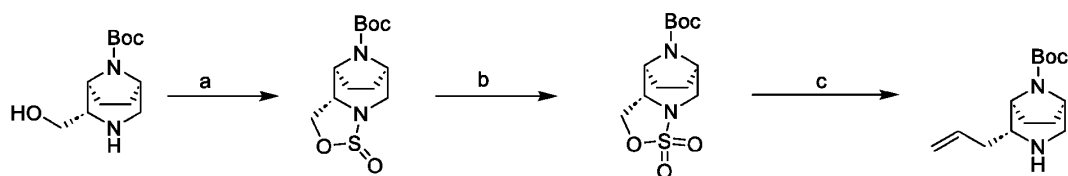
[00296] To a solution of di(prop-2-yl)amine (0.398 mL, 2.824 mmol) in THF (5 mL) was added N-BULI (1.13 mL, 2.82 mmol) at  $-78^{\circ}\text{C}$  for 15 minutes. Then added 2-methylpropan-2-yl (4R,7S,8R)-17-({[(7aS)-2-(difluoromethylidene)-2,3,5,6,7,7a-hexahydro-1H-pyrrolizin-7a-yl]methyl}oxy)-14-fluoro-10-methylidene-12-(trifluoromethyl)-2,16,18,20-tetrazapentacyclo[13.3.1.1<sup>4,7</sup>.0<sup>11,19</sup>.0<sup>2,8</sup>]jcosa-1(19),11(12),13,15(16),17-pentaene-20-carboxylate (920 mg, 1.41 mmol). The reaction was stirred at  $-15^{\circ}\text{C}$  for 15 minutes and then cooled to  $-78^{\circ}\text{C}$ . 1,2-dibromo-1,1,2,2-tetrachloroethane (690 mg, 2.12 mmol) was added. The reaction was stirred at  $-15^{\circ}\text{C}$  for 15 minutes. The reaction mixture was diluted water, extracted with EA. The organic phase was washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated. The residue was purified using silica gel column chromatography eluted with methanol in dichloromethane (gradient: 0-10%) to afford 2-methylpropan-2-yl (4R,7S,8R)-17-({[(7aS)-2-(difluoromethylidene)-2,3,5,6,7,7a-hexahydro-1H-pyrrolizin-7a-yl]methyl}oxy)-13-bromo-14-fluoro-10-methylidene-12-(trifluoromethyl)-2,16,18,20-tetrazapentacyclo[13.3.1.1<sup>4,7</sup>.0<sup>11,19</sup>.0<sup>2,8</sup>]jcosa-1(19),11(12),13,15(16),17-pentaene-20-carboxylate (250 mg, 0.342 mmol, 24%) as a yellow solid. LCMS: ESI  $m/z$  732.3  $[\text{M} + \text{H}]^+$ .

#### Intermediate 30

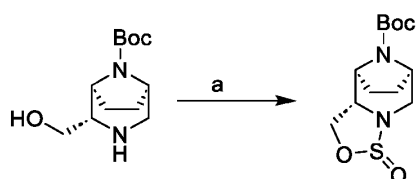
**tert-butyl (1R,2R,5S)-2-allyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate**



#### Synthetic Scheme

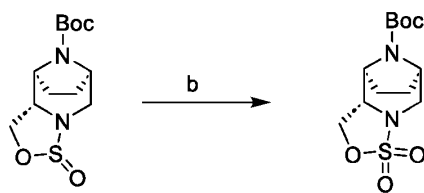


**Step 1: Synthesis of tert-butyl (3aS,4R,7S)-hexahydro-3H-4,7-epimino[1,2,3]oxathiazolo [3,4-a]azepine-10-carboxylate 1-oxide**



[00297] To the reactor was added imidazole (6.32 g, 92.9 mmol, 4.5 eq) and DCM (50 mL) under N<sub>2</sub> and the solution was cooled down to -10~0 °C; SOCl<sub>2</sub> (2.25 mL, 31 mmol, 1.5 eq) was added dropwise and stirred for 1h while maintaining the temperature at -10~0 °C, followed by the addition of a solution of tert-butyl (1R,2S,5S)-2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (5.0 g, 20.65 mmol, 1.00 eq) in DCM (10 mL); The mixture was warmed to room temperature and stirred for 12 hours. TLC showed the reaction was completed. The reaction was quenched with saturated NH<sub>4</sub>Cl (20 mL) and separated; The aqueous phase was extracted with DCM (10 mL). The organic phase was concentrated to afford the crude product (5.95 g, 100% crude yield) which was used directly for the next step.

**Step 2: Synthesis of tert-butyl (3aS,4R,7S)-hexahydro-3H-4,7-epimino[1,2,3]oxathiazolo [3,4-a]azepine-10-carboxylate 1,1-dioxide**

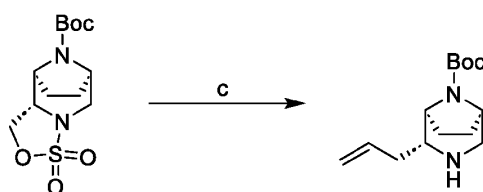


[00298] The mixture of tert-butyl (3aS,4R,7S)-hexahydro-3H-4,7-epimino[1,2,3]oxathiazolo [3,4-a]azepine-10-carboxylate 1-oxide (5.95 g, 20.65mmol, 1.00 eq), RuCl<sub>3</sub>·H<sub>2</sub>O (54.9 mg, 0.21 mmol, 0.01 eq), ACN (32mL ) and H<sub>2</sub>O (10 mL) was cooled down to 0-10 °C. NaIO<sub>4</sub> (5.3 g, 24.8 mmol, 1.20 eq) was added in portions, then warmed to room temperature and stirred for 4 hr. LC showed the reaction was completed. A solution of Na<sub>2</sub>SO<sub>3</sub> (7.82g, 3.00 eq) in H<sub>2</sub>O (20 mL) was



added dropwise while controlling the temperature at 0~10 °C. The mixture was extracted with EtOAc (10 mL x 2); The combined organic layer was washed with saturated Na<sub>2</sub>SO<sub>3</sub> solution, then concentrated to afford the crude product, which was triturated with n-heptane (10 mL) at 25 °C for 1 hr. The solid was filtered and filter cake was dried at 50 °C to afford the desired product (3.5 g, 11.5 mmol, 55.7% yield) .

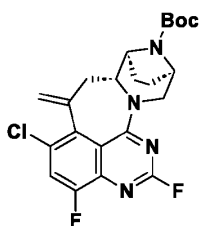
**Step 3: Synthesis of tert-butyl (1R,2R,5S)-2-allyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate**



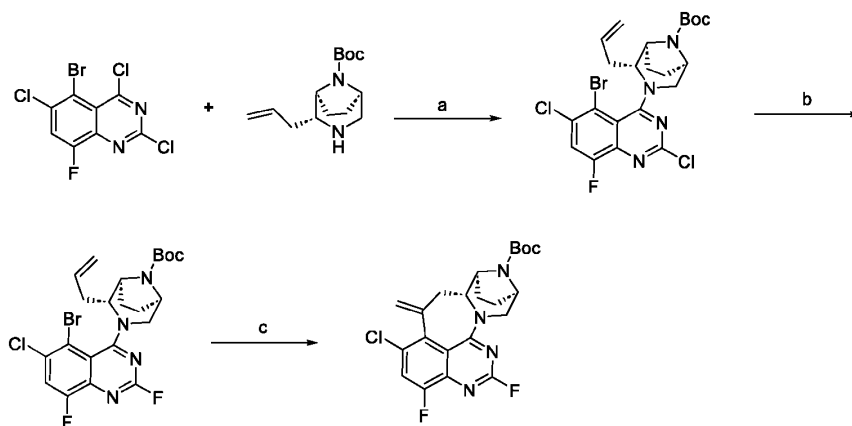
[00299] The solution of tert-butyl (3aS,4R,7S)-hexahydro-3H-4,7-epimino[1,2,3]oxathiazolo[3,4-a]azepine-10-carboxylate 1,1-dioxid (0.5 g, 1.64 mmol, 1 eq), CuI (32 mg, 0.10 eq) in THF (5 mL) under N<sub>2</sub> was cooled down to -45~-35 °C; Vinyl Grignard solution (3.3 mmol, 2.00 eq) was added dropwise at -50~-40 °C. The solution was warmed to room temperature slowly and stirred for 16 hrs, then quenched slowly with 2 N HCl (1.65 mL, 3.3 mmol, 2.00 eq) at 0-10 °C. The reaction mixture was stirred at 25 °C for 4 hrs and adjusted pH=9-10 with 25% NH<sub>3</sub>.H<sub>2</sub>O (5 mmol, 3.00 eq); The solution was extracted with 2-Me-THF (10 mL x2);The organic phase was concentrated to afford the crude, which was purified by silica gel chromatograph to afford the desired product, tert-butyl (1R,2R,5S)-2-allyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (0.15g, 0.6 mmol, 36.2% yield).

**Intermediate 31**

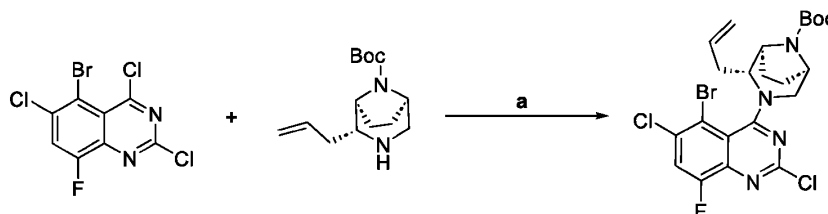
**tert-butyl (1S,4R,14aR)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



**Synthetic Scheme**

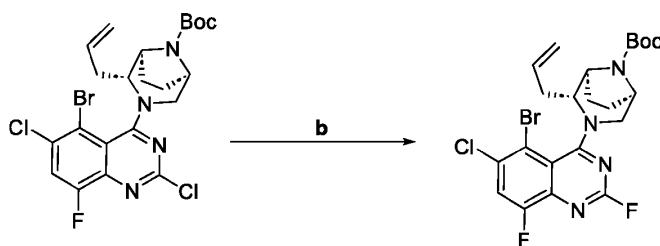


**Step 1: Synthesis of *tert*-butyl (1S,2R,5R)-2-allyl-3-(5-bromo-2,6-dichloro-8-fluoroquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate**



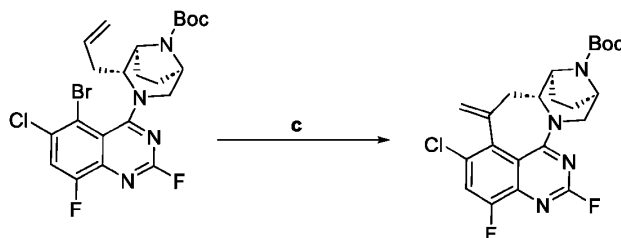
[00300] To a solution of 5-bromo-2,4,6-trichloro-8-fluoroquinazoline (73.0 g, 221.21 mmol, 1.0 eq) in DCM (730 mL) was added *tert*-butyl (1S,2R,5R)-2-allyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (61.4 g, 243.33 mmol, 1.1 eq) at -40 °C under N<sub>2</sub>, then was added DIEA (228.7 g, 1769.68 mmol, 8.0 eq) under N<sub>2</sub>. The mixture was stirred at -40 °C for 2 h. Then LCMS showed the reaction was completed. The reaction mixture was diluted with water (500 mL) and extracted with DCM (500 mL x 3). The organic layers were washed with brine (150 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (petroleum ether / EtOAc = 20:1) to afford *tert*-butyl (1S,2R,5R)-2-allyl-3-(5-bromo-2,6-dichloro-8-fluoroquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (87 g, purity: 93%, yield: 72.2%) as a yellow solid. LCMS: 545.0 (M+H<sup>+</sup>).

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



[00301] To a solution of *tert*-butyl (1S,2R,5R)-2-allyl-3-(5-bromo-2,6-dichloro-8-fluoroquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (87.0 g, 158.50 mmol, 1.0 eq) in DMSO (870 mL) was added KF (36.8 g, 633.88 mmol, 4.0 eq) under N<sub>2</sub>. The mixture was stirred at 90 °C for 3 h. Then LCMS showed the reaction was completed. The reaction mixture was diluted with water (500 mL) and extracted with EtOAc (500 mL x 3). The organic layer was washed with water (200 mL x 3) and brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (petroleum ether / EtOAc = 20:1) to afford *tert*-butyl (1S,2R,5R)-2-allyl-3-(5-bromo-6-chloro-2,8-difluoroquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (70.0 g, purity: 93%, yield: 83.6%) as a yellow solid. LCMS: 529.0 (M+H<sup>+</sup>).

**Step 3: Synthesis of *tert*-butyl (1S,4R,14aR)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**

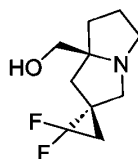


[00302] To a solution of *tert*-butyl (1S,2R,5R)-2-allyl-3-(5-bromo-6-chloro-2,8-difluoroquinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (70.0 g, 132.51 mmol, 1.0 eq) in 1,4-dioxane (700 mL) was added PPh<sub>3</sub> (10.4 g, 39.75 mmol, 0.3 eq), Pd(OAc)<sub>2</sub> (4.5 g, 19.88 mmol, 0.15 eq), DIEA (51.7 g, 397.53 mmol, 3.0 eq) under N<sub>2</sub>. The mixture was stirred at 110 °C for 3 h. Then LCMS showed the reaction was completed. The reaction mixture was diluted with water (500 mL) and extracted with EtOAc (500 mL x 3). The organic layer was washed with brine (200 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced

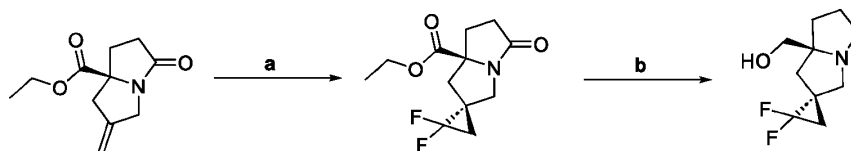
pressure to give a residue, which was purified by silica gel column chromatography (petroleum ether / EtOAc = 20:1) to afford *tert*-butyl (1S,4R,14aR)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (51.5 g, purity: 89%, yield: 86.6%) as a yellow solid. LCMS: 449.1 (M+H<sup>+</sup>).

#### Intermediate 32

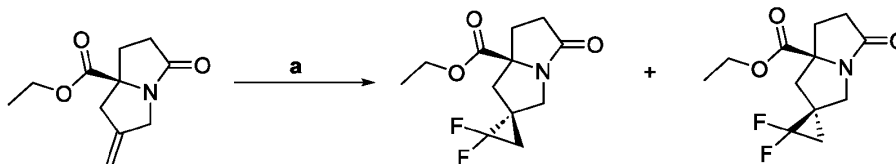
((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methanol



#### Synthetic Scheme



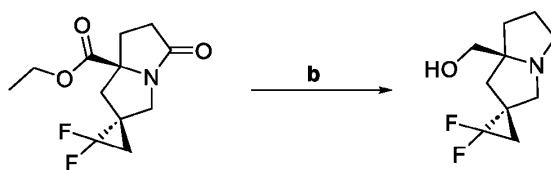
**Step 1: Synthesis of ethyl (1S, 7a'S)-2, 2-difluoro-5'-oxodihydro-1'H, 3'H-spiro[cyclopropane-1, 2'-pyrrolizine]-7a'(5'H)-carboxylate (assumed) and ethyl (1R, 7a'S)-2, 2-difluoro-5'-oxodihydro-1'H, 3'H-spiro[cyclopropane-1, 2'-pyrrolizine]-7a'(5'H)-carboxylate**



[00303] To a solution of ethyl (S)-2-methylene-5-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (900 mg, 4.30 mmol, 1.0 eq) in THF (4.5 mL) was added TMSCF<sub>3</sub> (2.1 g, 15.05 mmol, 3.5 eq) and NaI (322 mg, 2.15 mmol, 0.5 eq) at room temperature in sealed tube. The mixture was stirred at 80 °C for 16 h under nitrogen atmosphere. After completion, the mixture was filtered and the filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (Petroleum ether / EtOAc = 3:2) to give ethyl (1S,7a'S)-2,2-difluoro-5'-oxodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizine]-7a'(5'H)-carboxylate (assumed) (210 mg, the faster spot, yield: 19.1%) as a yellow oil and

purified by silica gel column chromatography (Petroleum ether / EtOAc = 1:5) to give ethyl ((1R,7a'S)-2,2-difluoro-5'-oxodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizine]-7a'(5'H)-carboxylate (assumed) (200 mg, the slower spot, yield: 18.2%) as a yellow oil. LCMS: 260.2 (M+H<sup>+</sup>).

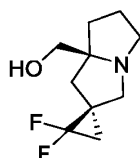
**Step 2: Synthesis of ((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methanol**



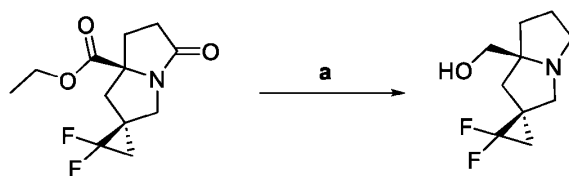
[00304] To a solution of ethyl ((1S, 7a'S)-2, 2-difluoro-5'-oxodihydro-1'H, 3'H-spiro[cyclopropane-1, 2'-pyrrolizine]-7a'(5'H)-carboxylate (270 mg, 1.04 mmol, 1.0 eq) in THF (3 mL) was added dropwise LiAlH<sub>4</sub> in THF (3.6 mL, 1M, 3.65 mmol, 3.5 eq) at room temperature. The mixture was stirred at 65 °C for 1 h. HPLC and TLC showed the reaction was completed. The mixture was cooled, quenched with Na<sub>2</sub>SO<sub>4</sub>•10H<sub>2</sub>O (1.4 g) and filtered, the filtrate was concentrated under reduced pressure to give ((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methanol (200 mg, crude) as a colorless oil. LCMS: 204.2 (M+H<sup>+</sup>).

**Intermediate 33**

**((1R,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methanol**



**Synthetic Scheme**

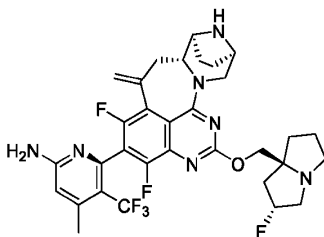


**Step 1: Synthesis of ((1R,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methanol**

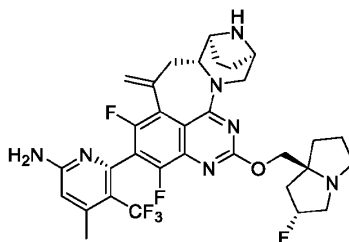
[00305] To a solution of ethyl (1R,7a'S)-2,2-difluoro-5'-oxodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizine]-7a'(5'H)-carboxylate (250 mg, 0.96 mmol, 1.0 eq) in THF (3 mL) was added dropwise LiAlH<sub>4</sub> in THF (3.4 mL, 1M, 3.40 mmol, 3.5 eq) at room temperature. The mixture was stirred at 65 °C for 1 h. HPLC and TLC showed the reaction was completed. The mixture was cooled, then quenched with Na<sub>2</sub>SO<sub>4</sub>•10H<sub>2</sub>O (1.3 g) and filtered, the filtrate was concentrated under reduced pressure to give ((1R,7a'S)-2, 2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methanol (190 mg, crude) as a colorless oil. LCMS: 204.2 (M+H<sup>+</sup>).

**Examples 1 & 2**

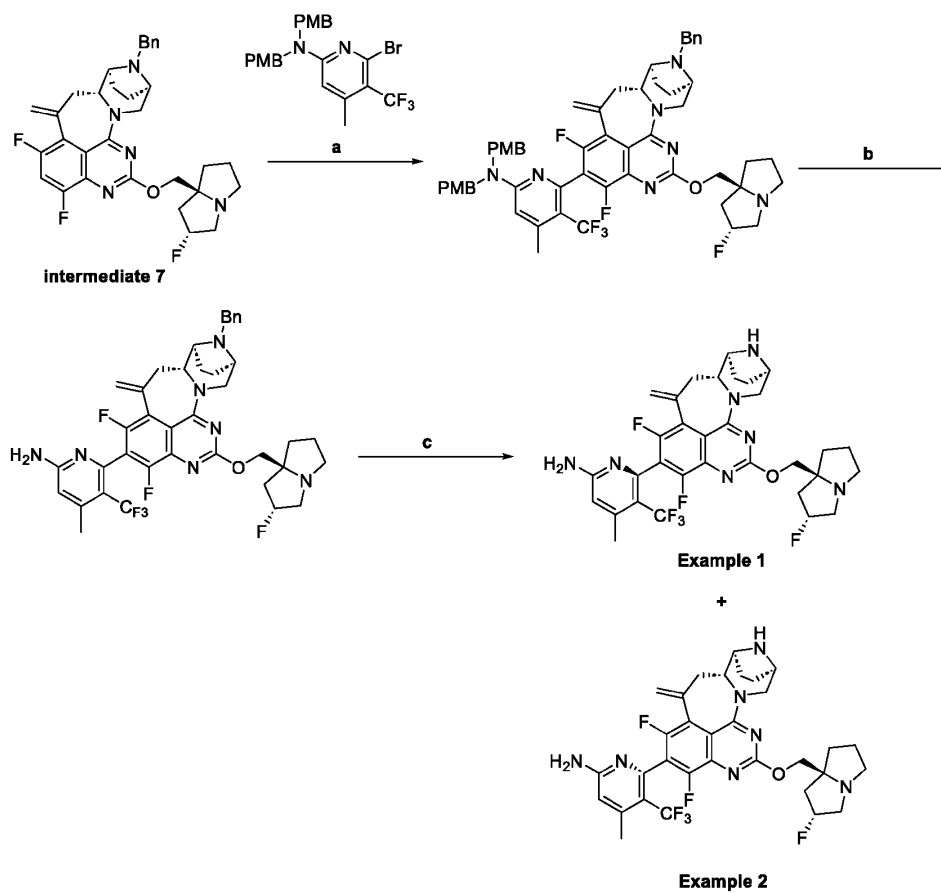
**6-((1S,4R,11S,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (Example 1)**



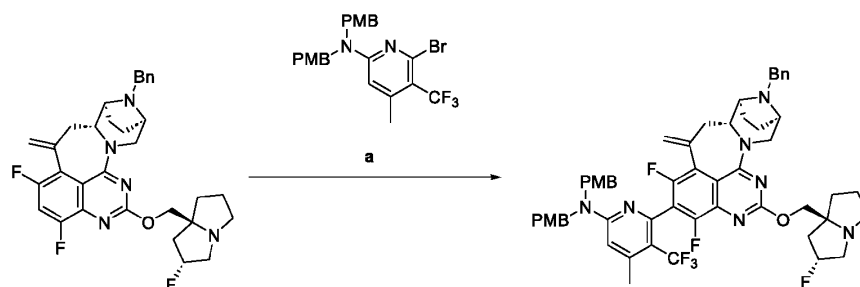
**6-((1S,4R,11R,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (Example 2)**



**Synthetic scheme**

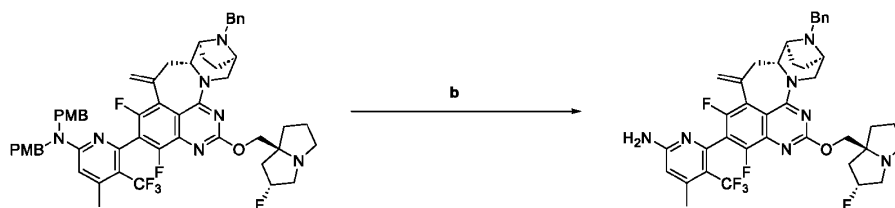


**Step 1: Synthesis of 6-((1*S*,4*R*,14*aR*)-15-benzyl-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazolin-11-yl)-*N,N*-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine**



[00306] To a solution of ((*1S,4R,14aR*)-15-benzyl-10,12-difluoro-8-(((*2R,7aS*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline (**Intermediate 7**, 270 mg, 0.48 mmol, 1.0 eq) in THF (3 mL) was added (TMP)<sub>2</sub>Zn·2MgCl<sub>2</sub>·2LiCl (0.4 M, 7.2 mL, 2.9 mmol, 6.0 eq) under N<sub>2</sub>. The mixture was stirred at 50 °C for 2 h. LCMS showed the deprotonation was completed by D<sub>2</sub>O quenching. A mixture of 6-bromo-*N,N*-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (285 mg, 0.58 mmol, 1.2 eq) and CPhos Pd G<sub>3</sub> (40 mg, 0.05 mmol, 0.1 eq) in 1,4-dioxane (3 mL) was added to the mixture. The solution was stirred at 70 °C for 3 h. The reaction mixture was quenched with H<sub>2</sub>O (15 mL) and extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give a residue, which was purified by Pre-TLC (DCM: MeOH = 10: 1) to afford 6-(((*1S,4R,14aR*)-15-benzyl-10,12-difluoro-8-(((*2R,7aS*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-*N,N*-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (280 mg, 59.8%) as a yellow solid. LCMS: *m/z* 975.9 (M+H<sup>+</sup>).

**Step 2: Synthesis of 6-(((*1S,4R,14aR*)-15-benzyl-10,12-difluoro-8-(((*2R,7aS*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-*N,N*-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine**

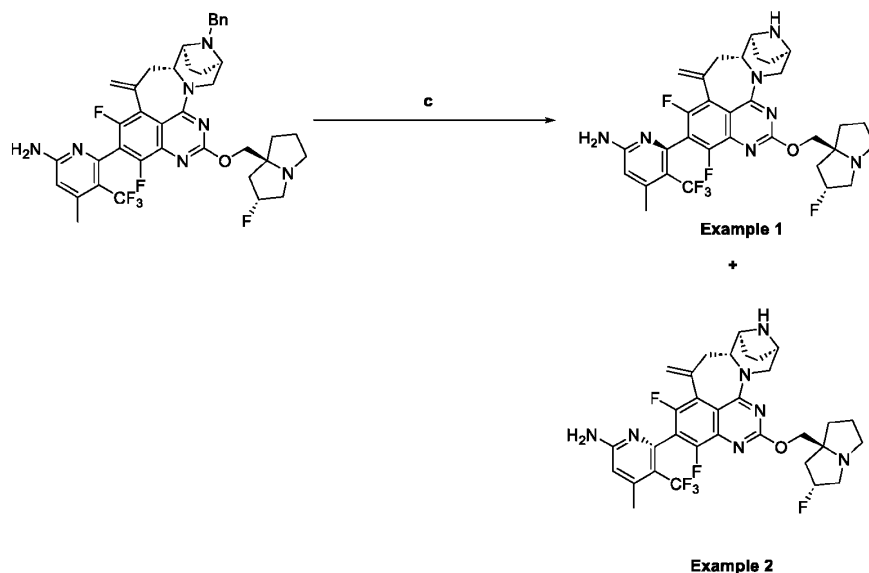


[00307] A solution of 6-(((*1S,4R,14aR*)-15-benzyl-10,12-difluoro-8-(((*2R,7aS*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-*N,N*-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (280 mg, 0.29 mmol, 1.0 eq) in TFA (15 mL) was stirred at 40 °C for 3 h. The mixture was concentrated to give 6-(((*1S,4R,14aR*)-15-benzyl-10,12-difluoro-8-(((*2R,7aS*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-



yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (crude) as a brown solid, which was used for next step without further purification. LCMS:  $m/z$  735.9 ( $M+H^+$ ).

**Step 3: Synthesis of 6-((1*S*,4*R*,11*S*,14*aR*)-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (Example 1) and 6-((1*S*,4*R*,11*R*,14*aR*)-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (Example 2)**



[00308] A mixture of 6-((1*S*,4*R*,14*aR*)-15-benzyl-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (387 mg crude, 0.29 mmol) and Pd/C (30%, 116 mg) in MeOH (10 mL) was hydrogenated with a H<sub>2</sub> balloon at room temperature for 1.5 h. LCMS showed the reaction was completed. The mixture was filtered and concentrated to give a crude product, which was purified by prep-HPLC, followed by the SFC separation to give two single diastereomers:

[00309] 6-((1*S*,4*R*,11*S*,14*aR*)-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino [2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (14.5 mg, 7.7% for two steps) as a white solid (SFC peak 1,

**Example 1),**

[00310] <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN): δ 6.57 (s, 1H), 5.66 (s, 1H), 5.48 (s, 2H), 5.44 (d, *J* = 4.0 Hz, 1H), 5.29 (d, *J* = 53.6 Hz, 1H), 5.10 (d, *J* = 11.6 Hz, 1H), 4.22 (d, *J* = 10.8 Hz, 1H), 4.12 (d, *J* = 10.8 Hz, 1H), 3.99 (dd, *J* = 11.8, 4.4 Hz, 1H), 3.65 (s, 1H), 3.48 (s, 1H), 3.24 – 3.20 (m, 2H), 3.15 – 3.12 (m, 2H), 2.98 – 2.92 (m, 1H), 2.82 (dd, *J* = 13.2, 4.4 Hz, 1H), 2.60-2.07 (m, 8H), 1.88 – 1.82 (m, 2H), 1.72 – 1.62 (m, 3H). LCMS: *m/z* 645.9 (M+H<sup>+</sup>); and

[00311] 6-((1*S*,4*R*,11*R*,14*aR*)-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (16.2 mg, 8.6% for two steps) as a white solid (SFC peak 2, **Example 2),**

[00312] <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN): δ 6.56 (s, 1H), 5.65 (s, 1H), 5.46 (s, 2H), 5.40 (d, *J* = 4.0 Hz, 1H), 5.26 (d, *J* = 53.2 Hz, 1H), 5.14 (d, *J* = 12.4 Hz, 1H), 4.11 (dd, *J* = 22.8, 10.4 Hz, 2H), 3.89 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.56 (s, 1H), 3.38 (s, 1H), 3.25-3.12 (m, 3H), 3.09 (s, 1H), 3.01 (d, *J* = 12.8 Hz, 1H), 2.94 – 2.88 (m, 1H), 2.79 (dd, *J* = 13.2, 4.0 Hz, 1H), 2.46-2.40 (m, 4H), 2.14 – 2.05 (m, 4H), 1.90 – 1.81 (m, 2H), 1.61 – 1.52 (m, 3H). LCMS: *m/z* 645.9 (M+H<sup>+</sup>).

**SFC separation conditions:**

**Analytical method:**

[00313] Instrument: Waters UPC2 analytical SFC (SFC-H). Column: ChiralCel OX, 150×4.6mm I.D., 3μm

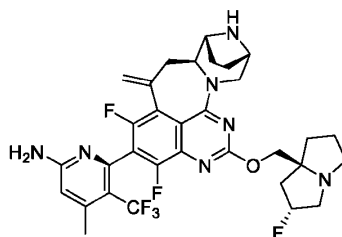
Mobile phase: A for CO<sub>2</sub> and B for Ethanol (0.05%DEA). Gradient: B 40%. Flow rate: 2.5 mL/min. Back pressure: 100 bar. Column temperature: 35°C. Wavelength: 220nm.

**Preparative method:**

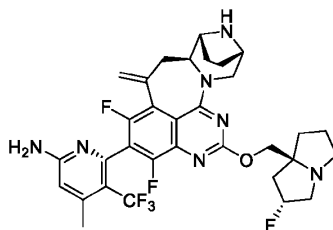
[00314] Instrument: WATERS 150 preparative SFC(SFC-26). Column: ChiralCel OX, 250×30mm I.D., 10μm. Mobile phase: A for CO<sub>2</sub> and B for Ethanol (0.1%NH<sub>3</sub>H<sub>2</sub>O). Gradient: B 45%. Flow rate: 150 mL /min. Back pressure: 100 bar. Column temperature: 38°C. Wavelength: 220nm. Cycle time: ~9.5 min.

**Examples 3 & 4**

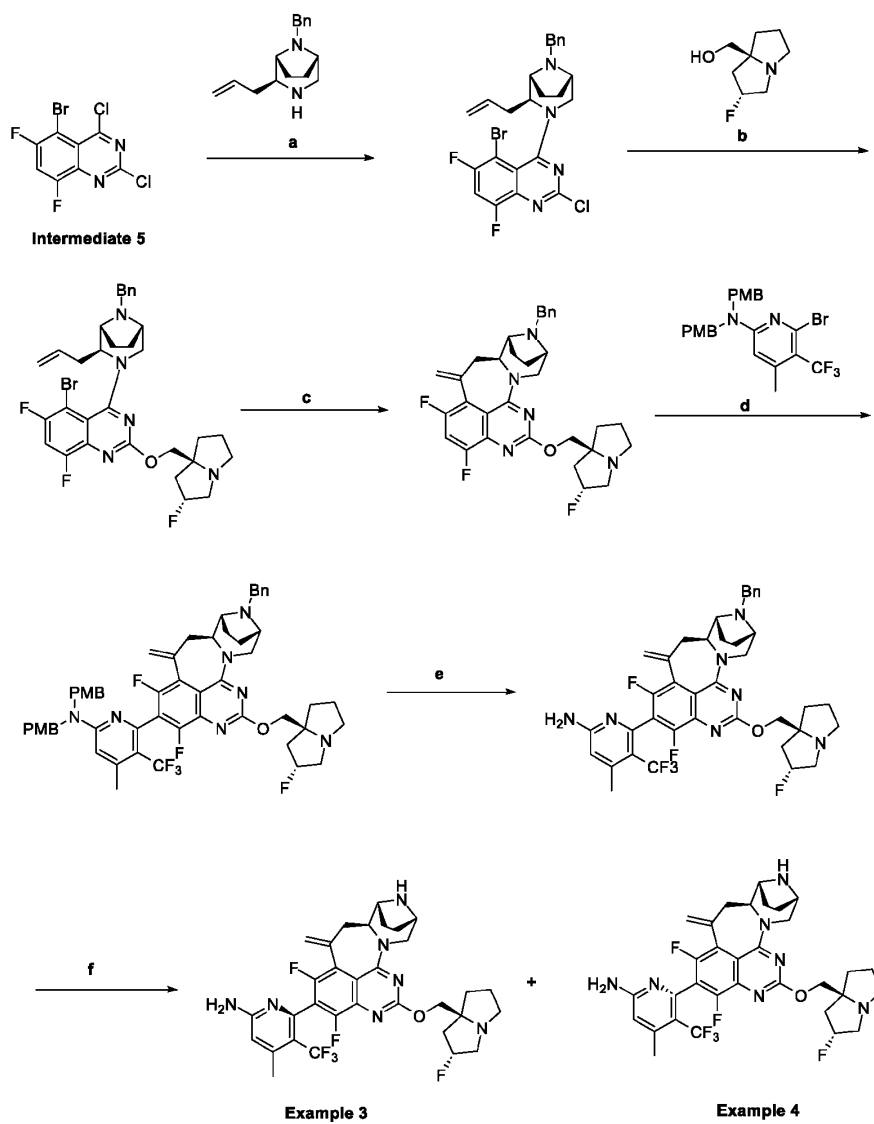
6-((1*R*,4*S*,11*S*,14*aS*)-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (Example 3)



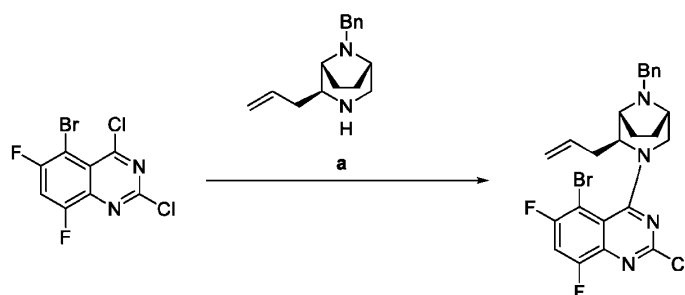
6-((1*R*,4*S*,11*R*,14*aS*)-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (Example 4)



Synthetic scheme

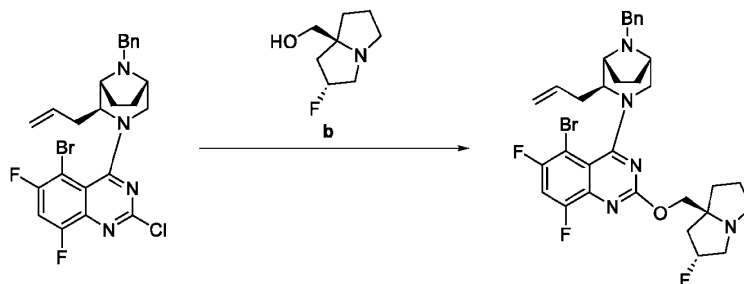


Step 1: Synthesis of 4-((1*R*,2*S*,5*S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-2-chloro-6,8-difluoroquinazoline



[00315] To a solution of 5-bromo-2,4-dichloro-6,8-difluoroquinazoline (**Intermediate 5**, 587 mg, 1.44 mmol, 1.0 eq) in DCM (10 mL) was added DIEA (1.6 g, 12.53 mmol, 8.7 eq) and (*1R,2S,5S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octane (**Intermediate 2**, 419 mg, 1.73 mmol, 1.2 eq) at  $-40^{\circ}\text{C}$  under nitrogen atmosphere. The mixture was stirred at  $-40^{\circ}\text{C}$  for 2 h and added water (20 mL). The mixture was extracted with DCM (20 mL x 3). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (petroleum ether: EtOAc = 30: 1) to afford 4-((*1R,2S,5S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-2-chloro-6,8-difluoroquinazoline (0.35 g, 46.8 % for two steps) as a yellow solid. LCMS:  $m/z$  518.8, 520.8 ( $\text{M}+\text{H}^+$ ).

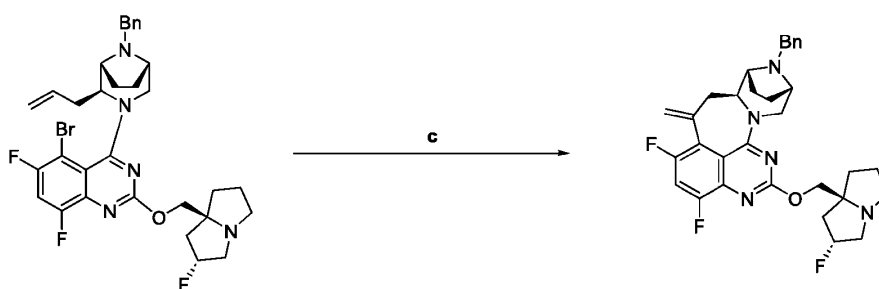
**Step 2: 4-((*1R,2S,5S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-6,8-difluoro-2-(((*2R,7aS*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazoline**



[00316] To a solution of 4-((*1R,2S,5S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-2-chloro-6,8-difluoroquinazoline (290 mg, 0.56 mmol, 1.0 eq) in DMSO (3 mL) was added ((*2R,7aS*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (711 mg, 4.46 mmol, 8.0 eq) and KF (66 mg, 1.13 mmol, 2.03 eq). The solution was heated at  $100^{\circ}\text{C}$  overnight. The reaction mixture was diluted with  $\text{H}_2\text{O}$  (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and

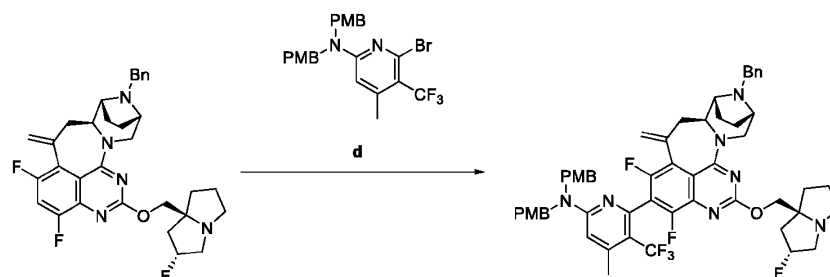
concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (petroleum ether: EtOAc = 3: 1) to afford 4-((1*R*,2*S*,5*S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-6,8-difluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)quinazoline (260 mg, 77.9%) as a yellow solid. LCMS: *m/z* 641.9, 643.9 (*M*+*H*<sup>+</sup>).

**Step 3: (1*R*,4*S*,14*aS*)-15-benzyl-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline**



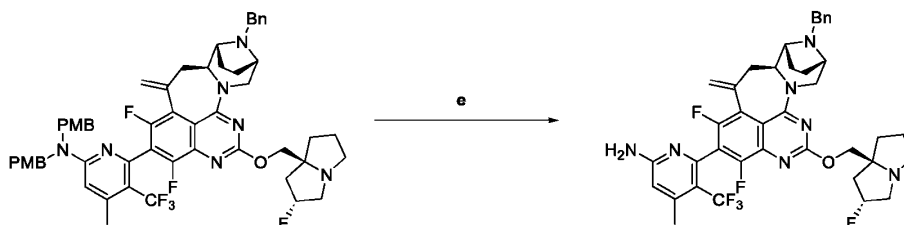
[00317] To a solution of 4-((1*R*,2*S*,5*S*)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-6,8-difluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)quinazoline (400 mg, 0.62 mmol, 1.0 eq) in DMAc (12 mL) was added KOAc (183 mg, 1.87 mmol, 3.0 eq), Pd(OAc)<sub>2</sub> (14 mg, 0.06 mmol, 0.1 eq) and PPh<sub>3</sub> (33 mg, 0.13 mmol, 0.2 eq) at room temperature under nitrogen atmosphere. The mixture was heated at 130 °C for 5 h and HPLC showed the reaction was completed. The reaction was diluted H<sub>2</sub>O (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give crude product, which was purified by silica gel column chromatography (DCM: MeOH = 60: 1) to afford (1*R*,4*S*,14*aS*)-15-benzyl-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline (123 mg, 35.2%) as a yellow solid. LCMS: *m/z* 562.0 (*M*+*H*<sup>+</sup>).

**Step 4: 6-((1*R*,4*S*,14*aS*)-15-benzyl-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-*N,N*-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine**



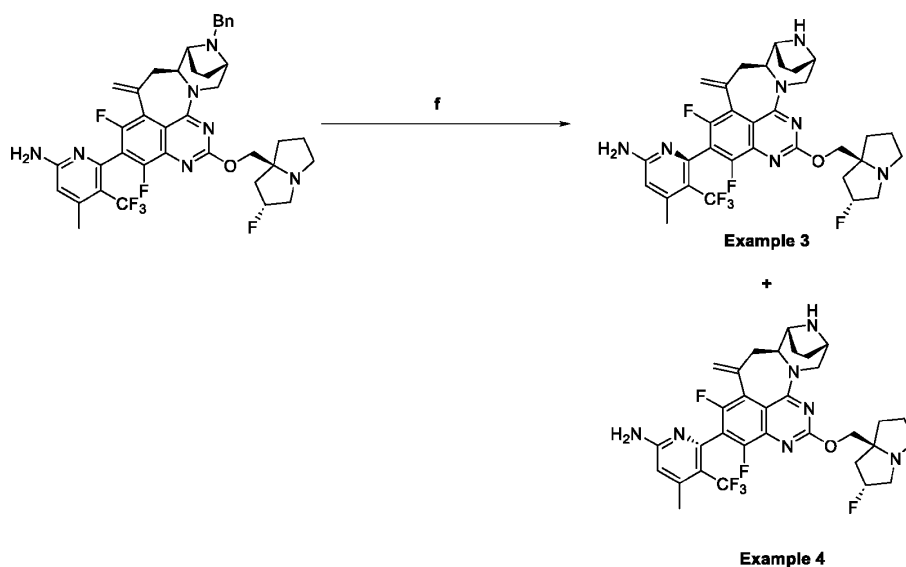
[00318] To a solution of *(1R,4S,14aS)*-15-benzyl-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline (140 mg, 0.25 mmol, 1.0 eq) in THF (6 mL) was added (TMP)<sub>2</sub>Zn·2MgCl<sub>2</sub>·2LiCl (0.4 M, 3.75 mL, 1.5 mmol, 6.0 eq) under N<sub>2</sub>. The mixture was stirred at 50 °C for 2 h. LCMS showed the reaction was completed by D<sub>2</sub>O (0.1 mL) quenching. Then a mixture of 6-bromo-*N,N*-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (148 mg, 0.3 mmol, 1.2 eq) and CPhos Pd G3 (20 mg, 0.03 mmol, 0.1 eq) in 1,4-dioxane (6 mL) was added. The mixture was heated at 70 °C for 3 h and cooled down to RT. H<sub>2</sub>O (15 mL) was added and the mixture was extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give a residue, which was purified by Prep-TLC (DCM: MeOH = 10: 1) to afford 6-(((*1R,4S,14aS*)-15-benzyl-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazolin-11-yl)-*N,N*-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (87 mg, 35.7%) as a yellow solid. LCMS: *m/z* 975.9 (M+H<sup>+</sup>).

**Step 5: 6-(((*1R,4S,14aS*)-15-benzyl-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine**



[00319] A solution of 6-((1*R*,4*S*,14*aS*)-15-benzyl-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino [1',2':1,7]azepino[2,3,4-*de*]quinazolin-11-yl)-*N,N*-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (85 mg, 0.09 mmol, 1.0 eq) in TFA (5 mL) was stirred at 50 °C for 3 h, and concentrated to give a crude product, 6-((1*R*,4*S*,14*aS*)-15-benzyl-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (102 mg,) as a brown solid, which was used for next step without further purification. LCMS: *m/z* 735.9 (*M*+*H*<sup>+</sup>).

**Step 6: Synthesis of 6-((1*R*,4*S*,11*S*,14*aS*)-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (Example 3) and 6-((1*R*,4*S*,11*R*,14*aS*)-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (Example 4)**





[00320] A mixture of 6-((1*R*,4*S*,14*aS*)-15-benzyl-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (130 mg crude, 0.18 mmol) and Pd/C (30%, 35 mg) in MeOH (4 mL) was hydrogenated with a balloon of hydrogen at room temperature for 1.5 h. HPLC showed the reaction was completed. The mixture was filtered and concentrated to give a crude product, which was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 25% to 40%) followed by SFC to give the two diastereomers:

[00321] 6-((1*R*,4*S*,11*S*,14*aS*)-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (4.2mg, ee > 95%, 7.4% for two steps) as a white solid (SFC Peak 1, **Example 3**). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN): δ 6.58 (s, 1H), 5.67 (s, 1H), 5.48 (s, 2H), 5.42 (d, *J* = 4.0 Hz, 1H), 5.40-5.10 (m, 2H), 4.18 (d, *J* = 10.4 Hz, 1H), 4.06 (d, *J* = 10.4 Hz, 1H), 3.91 (dd, *J* = 12.2, 4.4 Hz, 1H), 3.57 (s, 1H), 3.39 (d, *J* = 5.6 Hz, 1H), 3.25-2.75 (m, 6H), 2.50-2.40 (m, 4H), 2.15-2.05 (m, 4H), 1.95-1.80 (m, 2H), 1.67-1.53 (m, 3H). LCMS: *m/z* 645.9 (M+H<sup>+</sup>); and

[00322] 6-((1*R*,4*S*,11*R*,14*aS*)-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (4.16 mg, ee > 95%, 7.4% for two steps, with another 20 mg batch) as a white solid (SFC Peak 2, **Example 4**). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN): δ 6.58 (s, 1H), 5.68 (s, 1H), 5.49 (s, 2H), 5.46 (d, *J* = 4.0 Hz, 1H), 5.30 (d, *J* = 53.2 Hz, 1H), 5.15-5.02 (m, 1H), 4.25-4.12 (m, 2H), 3.97 (dd, *J* = 11.6, 4.4 Hz, 1H), 3.64 (s, 1H), 3.46 (d, *J* = 5.2 Hz, 1H), 3.30-3.05 (m, 4H), 3.02-2.90 (m, 1H), 2.88-2.78 (m, 1H), 2.50-2.40 (m, 4H), 2.18-2.12 (m, 4H), 1.90-1.80 (m, 2H), 1.75-1.60 (m, 3H). LCMS: *m/z* 645.9 (M+H<sup>+</sup>).

**SFC conditions:**

**Analytical separation method:**

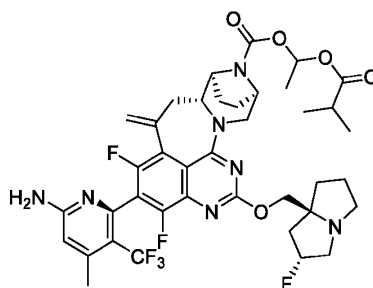
[00323] Instrument: Waters UPC2 analytical SFC (SFC-H). Column: ChiralPak IC, 150×4.6mm I.D., 3μm. Mobile phase: A for CO<sub>2</sub> and B for Ethanol (0.05%DEA). Gradient: B 50%. Flow rate: 2.5 mL/min. Back pressure: 100 bar. Column temperature: 35°C. Wavelength: 220nm

**Preparative separation method**

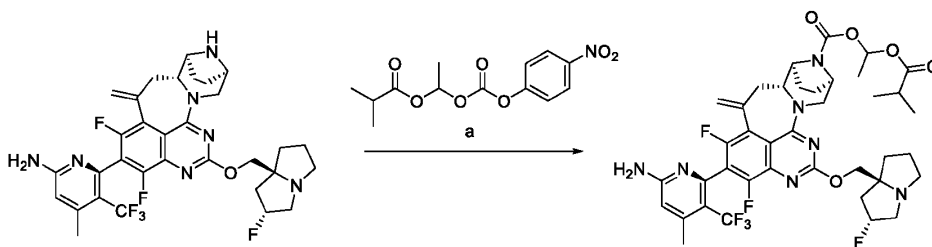
[00324] Instrument: WATERS 150 preparative SFC(SFC-26). Column: ChiralPak IC, 250×30mm I.D., 10μm. Mobile phase: A for CO<sub>2</sub> and B for Ethanol (0.1%NH<sub>3</sub>H<sub>2</sub>O). Gradient: B 40%. Flow rate:150 mL /min. Back pressure: 100 bar. Column temperature: 38°C. Wavelength: 220nm. Cycle time: ~13min.

**Example 5**

**1-(Isobutyryloxy)ethyl (1*S*,4*R*,11*S*,14*aR*)-11-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



**Synthesis of 1-(isobutyryloxy)ethyl (1*S*,4*R*,11*S*,14*aR*)-11-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**

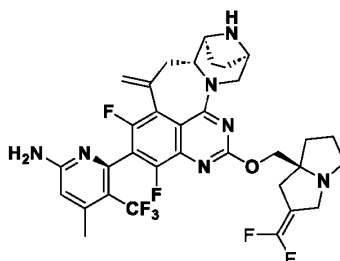


[00325] To a solution of 6-(((1*S*,4*R*,11*S*,14*aR*)-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridine-2-amine (10 mg, 0.015 mmol, 1.0 eq) in DCM (1 mL) was added DIEA (5.8 mg, 0.045 mmol, 3.0 eq), followed by the addition of 1-(((4-nitrophenoxy)carbonyl)oxy)ethyl isobutyrate

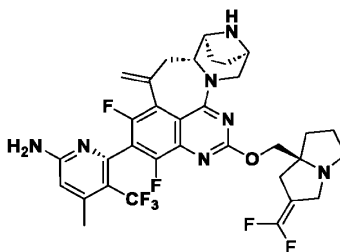
(5.5 mg, 0.018 mmol, 1.2 eq). The reaction was stirred at room temperature for 36 h under N<sub>2</sub>. HPLC and TLC showed the reaction was completed. The mixture was concentrated under reduced pressure to give a residue, which was purified by Prep-TLC (DCM: MeOH = 10: 1) to afford 1-(isobutyryloxy)ethyl (1*S*,4*R*,11*S*,14*aR*)-11-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-10,12-difluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (6.23 mg, 50.1% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, CH<sub>3</sub>CN):  $\delta$  6.90-6.70 (m, 1H), 6.60 (s, 1H), 5.72 (s, 1H), 5.60-5.30 (m, 4H), 5.20 (d, *J* = 13.2 Hz, 1H), 4.53 (s, 2H), 4.42 (s, 1H), 4.23 (s, 1H), 410-3.90 (m, 1H), 3.80-3.40 (m, 3H), 3.25-3.05 (m, 2H), 3.00-2.85 (m, 1H), 2.60-2.50 (m, 1H), 2.48-2.38 (m, 4H), 1.88-1.75 (m, 2H), 1.55-1.25 (m, 11H), 1.15 (s, 6H). LCMS: *m/z* 803.9 (M+H<sup>+</sup>).

#### Examples 6 & 7

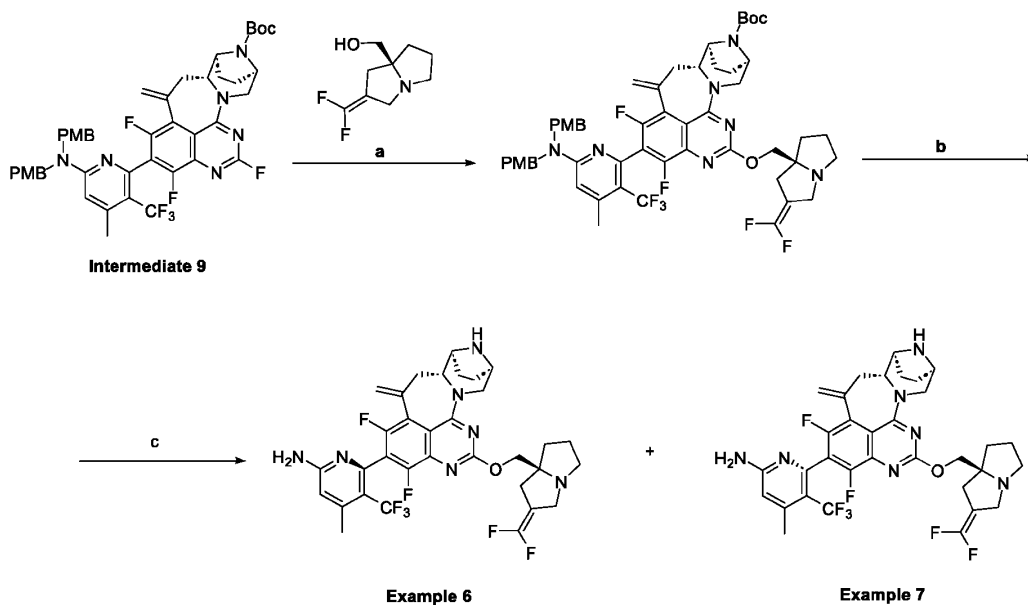
**6-((1*S*,4*R*,11*S*,14*aR*)-8-(((*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (Example 6)**



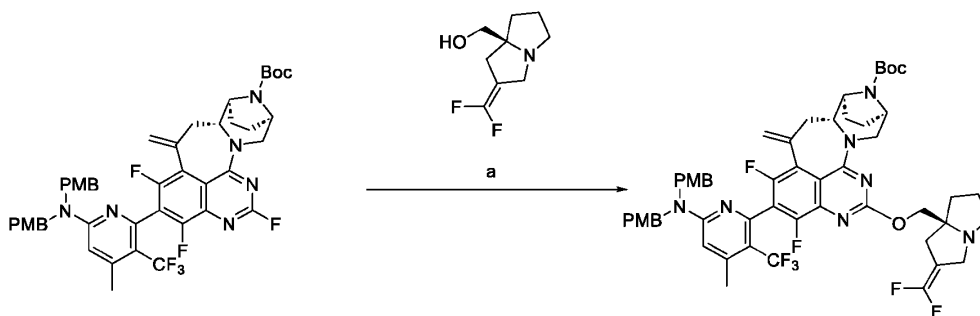
**6-((1*S*,4*R*,11*R*,14*aR*)-8-(((*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (Example 7)**



## Synthetic scheme



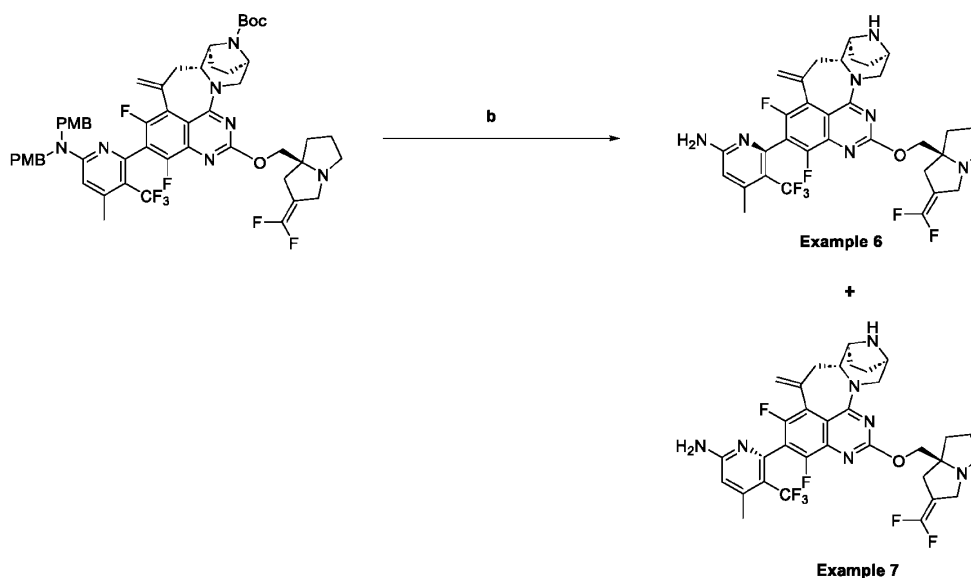
**Step 1: tert-butyl (1*S*,4*R*,14*aR*)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8-(((*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-15-carboxylate**



[00326] To a solution of (*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methanol (**Intermediate 9**, 17 mg, 0.09mmol, 1.5 eq) in THF (0.5 ml) was added NaH (60%) (7 mg, 0.177mmol, 3.0 eq) at 0 °C and then the mixture was stirred for 0.5 h under N<sub>2</sub>. The solution of tert-butyl (1*S*,4*R*,14*aR*)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl) pyridin-2-yl)-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino [1',2':1,7]azepino[2,3,4-*de*]quinazoline-15-carboxylate (50 mg, 0.06 mmol,

1.0 eq) in THF (0.5 mL) was added to the mixture and stirred at 35 °C for 1 h. HPLC and TLC show the reaction was completed. The reaction was quenched with saturated NH<sub>4</sub>Cl solution (5 mL) and extracted with EtOAc (5 mL x 3). The combined organic layers were concentrated to give a crude product, which was purified by Pre-TLC (PE: EtOAc = 1:1) to afford tert-butyl ((*S*,4*R*,14*aR*)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8-(((*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (20 mg, 33%). LCMS: *m/z* 1016.2 (M+H<sup>+</sup>).

**Step 2: 6-((*S*,4*R*,14*aR*)-8-(((*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine**



[00327] A mixture of tert-butyl ((*S*,4*R*,14*aR*)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8-(((*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (60 mg, 0.06 mmol) in TFA (3 mL) was stirred at 50 °C for 3 h. HPLC showed the reaction was completed. The mixture was concentrated to give a residue, which was dissolved in DCM/MeOH (10/1) and washed with saturated aqueous NaHCO<sub>3</sub> (10 mL) and brine (10 mL). The organic layer was dried over

Na<sub>2</sub>SO<sub>4</sub>, concentrated to afford a residue, which was purified by prep-TLC (DCM/MeOH~10/1) to afford the product with two diastereomers. LCMS: m/z 676.2 (M+H<sup>+</sup>).

The product was further separated by SFC and purified by HPLC to give:

[00328] 6-((1S,4R,11S,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (SFC Peak 1, **Example 6**, free base). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN): δ 6.56 (s, 1H), 5.65 (s, 1H), 5.48 (s, 2H), 5.43 (d, *J* = 4.0 Hz, 1H), 5.15-5.00 (m, 1H), 4.20-4.10 (m, 2H), 3.95-3.85 (m, 1H), 3.75-3.62 (m, 1H), 3.61-3.53 (br, 1H), 3.45-3.30 (m, 2H), 3.10-3.00 (m, 2H), 2.85-2.55 (m, 3H), 2.45-2.35 (m, 4H), 2.12-2.00 (m, 3H), 1.90-1.75 (m, 4H), 1.70-1.50 (m, 3H). LCMS: m/z 675.9 (M+H<sup>+</sup>);

[00329] 6-((1S,4R,11S,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridine-2-amine formic acid salt (0.4 FA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN): δ 8.16 (s, 0.4 H), 6.56 (s, 1H), 5.65 (s, 1H), 5.46 (s, 2H), 5.43 (d, *J* = 4.0 Hz, 1H), 5.15-5.00 (m, 1H), 4.20-4.10 (m, 2H), 3.95-3.85 (m, 1H), 3.75-3.62 (m, 1H), 3.61-3.53 (br, 1H), 3.45-3.30 (m, 2H), 3.10-3.00 (m, 2H), 2.85-2.55 (m, 3H), 2.45-2.35 (m, 5H), 2.20-2.00 (m, 2H), 1.90-1.75 (m, 4H), 1.70-1.50 (m, 3H). LCMS: m/z 675.9 (M+H<sup>+</sup>); and

[00330] 6-((1S,4R,11R,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (SFC Peak 2, **Example 7**, free base). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN): δ 6.56 (s, 1H), 5.65 (s, 1H), 5.48 (s, 2H), 5.45-5.38 (br, 1H), 5.20-5.05 (m, 1H), 4.20-4.10 (m, 2H), 4.00-3.87 (m, 1H), 3.75-3.65 (m, 1H), 3.64-3.53 (br, 1H), 3.45-3.30 (m, 2H), 3.15-3.00 (m, 2H), 2.87-2.52 (m, 3H), 2.46-2.33 (m, 4H), 2.12-2.02 (m, 3H), 1.90-1.70 (m, 4H), 1.70-1.50 (m, 3H). LCMS: m/z 675.9 (M+H<sup>+</sup>).

[00331] 6-((1S,4R,11R,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine formic acid salt (0.6 FA). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN): δ 8.14 (s, 0.6 H), 6.56 (s, 1H), 5.65 (s,

1H), 5.48 (s, 2H), 5.45-5.38 (br, 1H), 5.20-5.05 (m, 1H), 4.20-4.10 (m, 2H), 4.00-3.87 (m, 1H), 3.75-3.65 (m, 1H), 3.64-3.53 (br, 1H), 3.45-3.30 (m, 2H), 3.15-3.00 (m, 2H), 2.87-2.52 (m, 3H), 2.46-2.33 (m, 5H), 2.20-2.02 (m, 2H), 1.90-1.70 (m, 4H), 1.70-1.50 (m, 3H). LCMS: m/z 675.9 (M+H<sup>+</sup>).

**SFC separation conditions:**

**Analytical method:**

[00332] Instrument: Waters UPC2 analytical SFC (SFC-H). Column: ChiralCel OX, 150×4.6mm I.D., 3μm

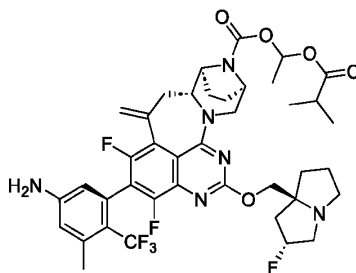
[00333] Mobile phase: A for CO<sub>2</sub> and B for Ethanol (0.05%DEA). Gradient: B 40%. Flow rate: 2.5 mL/min. Back pressure: 100 bar. Column temperature: 35°C. Wavelength: 220nm.

**Preparative method:**

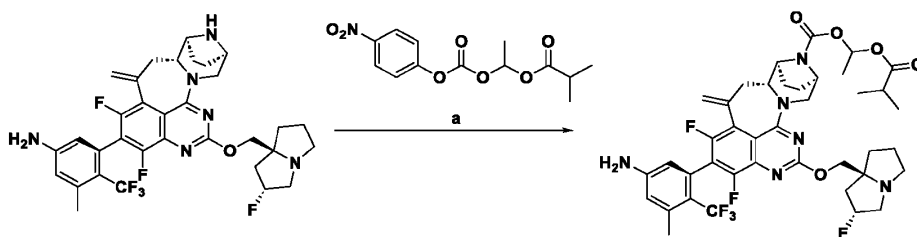
[00334] Instrument: WATERS 150 preparative SFC(SFC-26). Column: ChiralCel OX, 250×30mm I.D., 10μm. Mobile phase: A for CO<sub>2</sub> and B for Ethanol (0.1%NH<sub>3</sub>H<sub>2</sub>O). Gradient: B 45%. Flow rate: 150 mL /min. Back pressure: 100 bar. Column temperature: 38°C. Wavelength: 220nm. Cycle time: ~ 7 min.

**Example 8**

**1-(Isobutyryloxy)ethyl (1S,4R,11R,14aR)-11-(5-amino-3-methyl-2-(trifluoromethyl)phenyl)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



**Synthetic scheme**

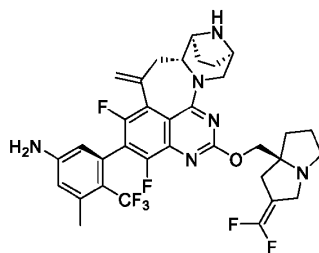


[00335] To a solution of 3-((1S,4R,11R,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-methyl-4-(trifluoromethyl)aniline (10 mg, 0.016 mmol, 1.0 eq) in DCM (1 mL) was added DIEA (6.2 mg, 0.048 mmol, 3.0 eq) and 1-(((4-nitrophenoxy)carbonyl)oxy)ethyl isobutyrate (5.6 mg, 0.019 mmol, 1.2 eq). Then the reaction was stirred at room temperature for 36 h under N<sub>2</sub>. HPLC and TLC showed the reaction was completed. The mixture was concentrated under reduced pressure to give a crude, which was purified by Prep-TLC (DCM: MeOH = 10: 1) to afford 1-((isobutyryloxy)ethyl (1S,4R,11R,14aR)-11-(5-amino-3-methyl-2-(trifluoromethyl)phenyl)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (8 mg, 64.2%) as a white solid. LCMS: *m/z* 803.2 (M+H<sup>+</sup>). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 6.77 – 6.71 (m, 1H), 6.62 (s, 1H), 6.30 (s, 1H), 5.92 (brs, 2H), 5.73 (s, 1H), 5.45 (d, *J* = 3.0 Hz, 1H), 5.30 (d, *J* = 54.0, 1H), 5.05 – 4.85 (m, 1H), 4.38 (s, 1H), 4.00 – 4.25 (m, 3H), 3.92 – 3.70 (m, 1H), 3.19 – 2.72 (m, 8H), 2.36 (d, *J* = 2.1 Hz, 3H), 2.14 – 2.01 (m, 4H), 1.85–1.75 (m, 3H), 1.48 (d, *J* = 5.4 Hz, 3H), 1.41 – 1.24 (m, 3H), 1.09 – 1.05 (m, 6H). LCMS: *m/z* 803.2 (M+H<sup>+</sup>).

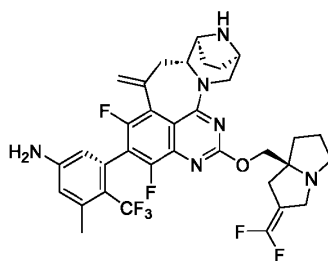
### Examples 9 & 10

**Example 9: 3-((1S,4R,11R,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7] azepino[2,3,4-de]quinazolin-11-yl)-5-methyl-4-(trifluoromethyl)aniline**

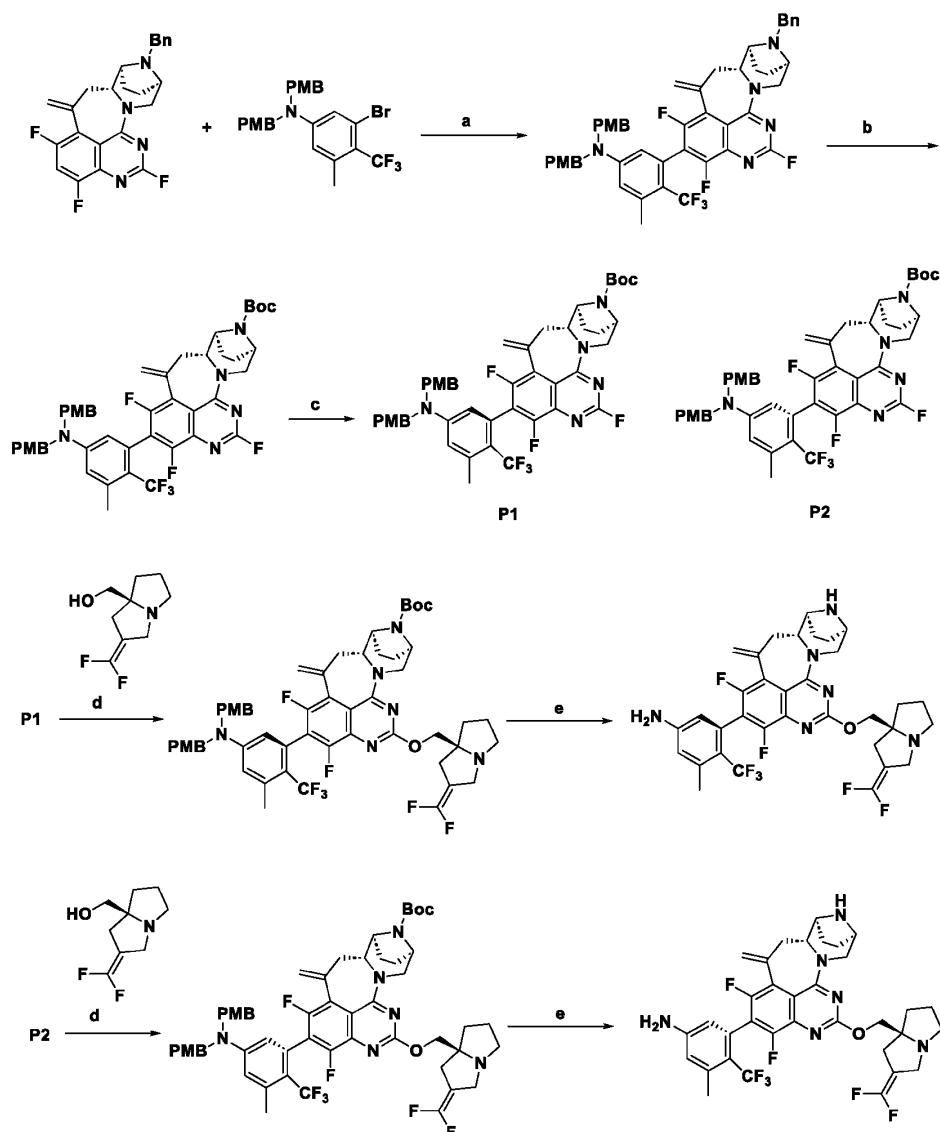




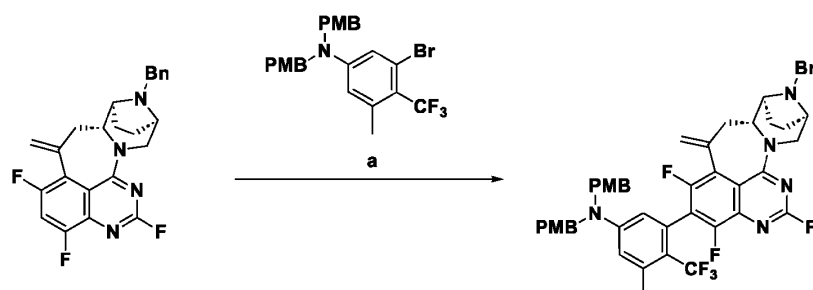
**Example 10: 3-((1S,4R,11S,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7] azepino[2,3,4-de]quinazolin-11-yl)-5-methyl-4-(trifluoromethyl)aniline**



**Synthetic scheme**

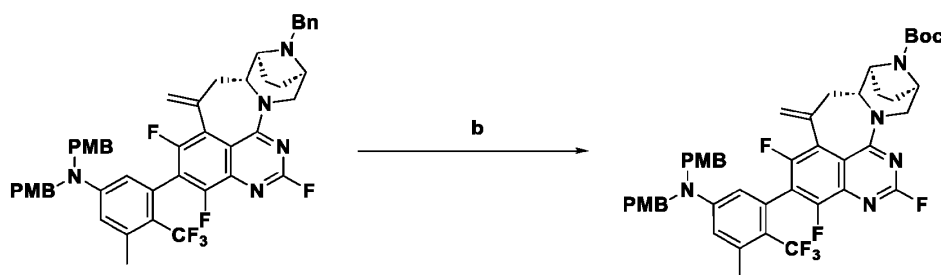


**Step 1: Synthesis of 3-((1S,4R,14aR)-15-benzyl-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-N,N-bis(4-methoxybenzyl)-5-methyl-4-(trifluoromethyl)aniline**



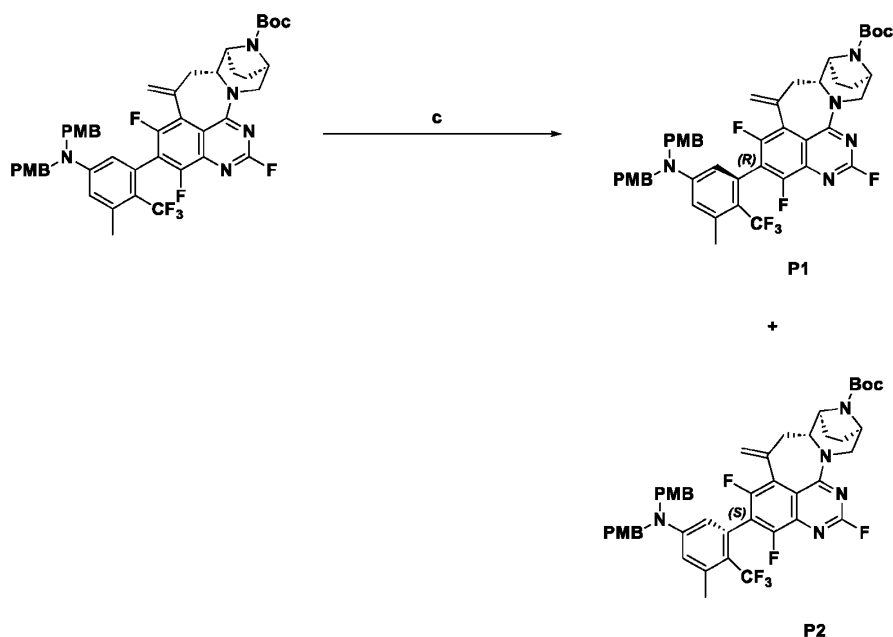
[00336] To a solution of (1S,4R,14aR)-15-benzyl-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline (2.4 g, 5.7 mmol, 1.0 eq) in THF (24 mL) was added (TMP)<sub>2</sub>Zn·2MgCl<sub>2</sub>·2LiCl (0.4 M, 85.3 mL, 34.1 mmol, 6.0 eq) under N<sub>2</sub>. The mixture was stirred at 50 °C for 2 h. Then LCMS showed the reaction was completed. Then a mixture of 3-bromo-N,N-bis(4-methoxybenzyl)-5-methyl-4-(trifluoromethyl)aniline (3.4 g, 6.8 mmol, 1.2 eq) and CPhos Pd G3 (460 mg, 0.57 mmol, 0.1 eq) in 1,4-dioxane (24 mL) was added to the mixture. The mixture was stirred at 70 °C for 3 h. The reaction mixture was quenched with H<sub>2</sub>O (50 mL) and extracted with EtOAc (100 mL x 3). The organic layers were washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (PE: EtOAc = 6: 1) to afford 3-((1S,4R,14aR)-15-benzyl-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-N,N-bis(4-methoxybenzyl)-5-methyl-4-(trifluoromethyl)aniline (3.5 g, 73.5%) as a yellow solid. LCMS: m/z 836.2 (M+H<sup>+</sup>).

**Step 2: Synthesis of tert-butyl (1S,4R,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00337] A solution of 3-((1S,4R,14aR)-15-benzyl-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-N,N-bis(4-methoxybenzyl)-5-methyl-4-(trifluoromethyl)aniline (500 mg, 0.6 mmol, 1.0 eq) in MeOH (30 mL) was added Pd/C (30%, 150 mg) and Boc<sub>2</sub>O (196 mg, 0.9 mmol, 1.5 eq). The mixture was hydrogenated at room temperature for 12 h. HPLC showed the reaction was completed. The mixture was filtered and concentrated to give a crude product. The residue was purified by Prep-TLC (DCM) to afford tert-butyl (1S,4R,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (225 mg, 45%) as a yellow solid. LCMS: m/z 846.3 (M+H<sup>+</sup>).

**Step 3: Synthesis of tert-butyl (1S,4R,11R,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate and tert-butyl (1S,4R,11S,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00338] The compound tert-butyl (1S,4R,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (550 mg, 0.65 mmol) was separated by twice SFC to afford tert-butyl (1S,4R,11R,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (**P1**, retention time = 1.862, 110 mg, 20.0%) and tert-butyl (1S,4R,11S,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (**P2**, retention time = 2.195, 140 mg, 25.5%).

**First SFC conditions:**

**Analytical separation method:**

[00339] Instrument: Waters UPC2 analytical SFC (SFC-H). Column: ChiralPak IG, 150×4.6mm I.D., 3µm. Mobile phase: A for CO<sub>2</sub> and B for Ethanol (0.05%DEA). Gradient: B 40%. Flow rate: 2.5 mL/min. Back pressure: 100 bar. Column temperature: 35°C. Wavelength: 220nm

**Preparative separation method**

[00340] Instrument: WATERS 150 preparative SFC(SFC-26). Column: ChiralPak IG, 250×30mm I.D., 10µm. Mobile phase: A for CO<sub>2</sub> and B for Ethanol. Gradient: B 30%. Flow rate: 150 mL /min. Back pressure: 100 bar. Column temperature: 38°C. Wavelength: 220nm. Cycle time: ~ 6 min.

**Second SFC conditions:**

**Analytical separation method:**

[00341] Instrument: Waters UPC2 analytical SFC (SFC-H). Column: Cellulose-2, 150×4.6mm I.D., 3µm

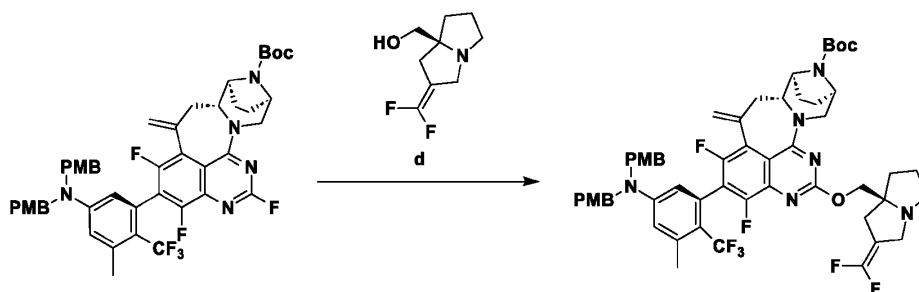
[00342] Mobile phase: A for CO<sub>2</sub> and B for Methanol (0.05%DEA). Gradient: B 5-40%. Flow rate: 2.5 mL/min. Back pressure: 100 bar. Column temperature: 35°C. Wavelength: 220nm.

**Preparative separation method**

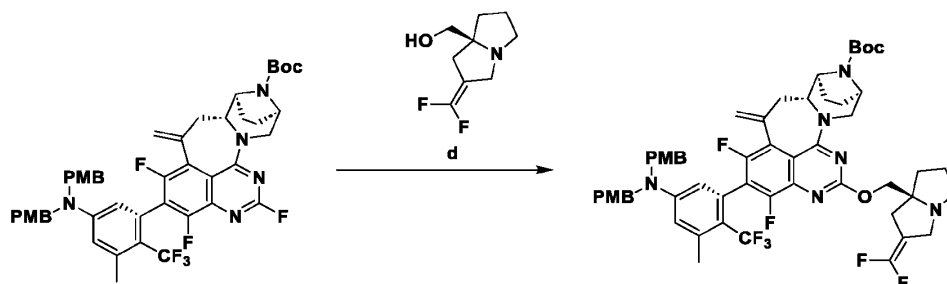
[00343] Instrument: WATERS 150 preparative SFC(SFC-26). Column: Cellulose-2, 250×30mm I.D., 10µm. Mobile phase: A for CO<sub>2</sub> and B for Methanol. Gradient: B 45%. Flow

rate: 130 mL /min. Back pressure: 100 bar. Column temperature: 38°C. Wavelength: 220nm.  
Cycle time: ~ 6 min.

**Step 4: Synthesis of tert-butyl (1S,4R,11R,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate and tert-butyl (1S,4R,11S,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**

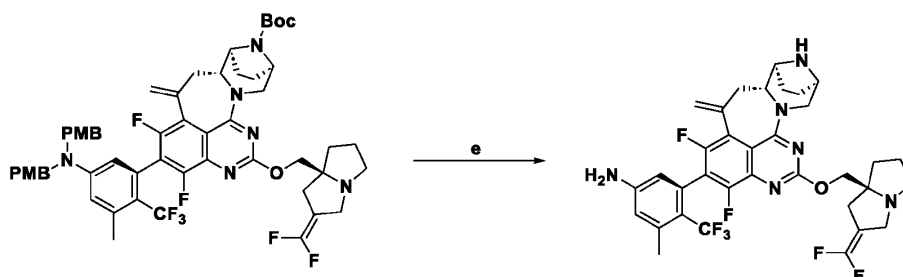


[00344] To a solution of (S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (38.7 mg, 0.20 mmol, 1.5 eq) in THF (0.5 mL) was added NaH (60%) (16.0 mg, 0.39 mmol, 3.0 eq) at 0 °C and then the mixture was stirred for 0.5 h at room temperature under N<sub>2</sub>. The solution of tert-butyl (1S,4R,11R,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl) phenyl)-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (110 mg, 0.13 mmol, 1.0 eq) in THF (1.5 mL) was added to the mixture and stirred at 25 °C for 1.5 h. HPLC and TLC show the reaction was completed. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl solution (10 mL) and extracted with EtOAc (10 mL x 3). The organic layer was concentrated to give a crude product. The residue was purified by Prep-TLC (DCM: MeOH = 10:1) to afford tert-butyl (1S,4R,11R,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (70 mg, 51.7%) as a yellow solid. LCMS: 1015.2 (M+H<sup>+</sup>).

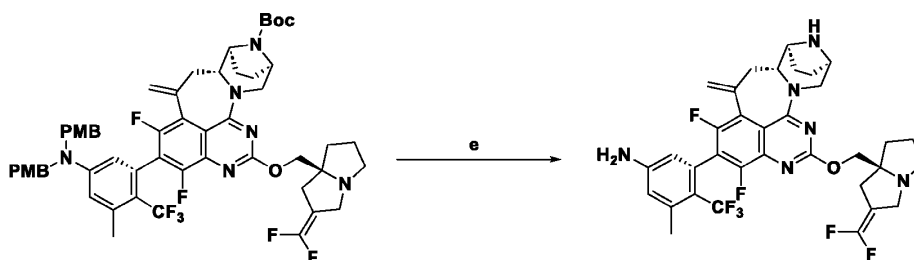


[00345] To a solution of (S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-ylmethanol (47.2 mg, 0.25 mmol, 1.5 eq) in THF (1 mL) was added NaH (60%) (20.0 mg, 0.50 mmol, 3.0 eq) at 0 °C and then the mixture was stirred for 0.5 h at room temperature under N<sub>2</sub>. The solution of tert-butyl (1S,4R,11S,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino [1',2':1,7] azepino[2,3,4-de]quinazoline-15-carboxylate (140 mg, 0.17 mmol, 1.0 eq) in THF (2 mL) was added to the mixture and the reaction mixture was stirred at 25 °C for 1.5 h. HPLC and TLC showed the reaction was completed. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl solution (10 mL) and extracted with EtOAc (10 mL x 3). The organic layer was concentrated to give a crude product. The residue was purified by Prep-TLC (DCM: MeOH = 10:1) to afford tert-butyl (1S,4R,11S,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino [1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (100 mg, 65.7%) as a yellow solid. LCMS: 1015.2 (M+H<sup>+</sup>).

**Step 5: Synthesis of 3-((1S,4R,11R,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-methyl-4-(trifluoromethyl)aniline and 3-((1S,4R,11S,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-methyl-4-(trifluoromethyl)aniline**



[00346] A mixture of tert-butyl tert-butyl (1S,4R,11R,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (70 mg, 0.069mmol) in TFA (1.5 mL) was stirred at 50 °C for 3 h under N<sub>2</sub>. The mixture was concentrated to give a crude. Then the crude was added saturated sodium bicarbonate aqueous solution (10 mL) to adjusted pH = (7 ~ 8) and extracted with DCM / MeOH = 10 / 1 (10 mL x 3). The combined organic layers were washed with brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give crude product. The crude was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 5% to 50%) to afford 3-(((1S,4R,11R,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-methyl-4-(trifluoromethyl)aniline (8 mg, 17.4%) as a white solid. LCMS: m/z 675.3 (M+H<sup>+</sup>). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 6.64 (s, 1H), 6.38 (s, 1H), 5.72 (s, 1H), 5.58 (d, J = 3.3 Hz, 1H), 5.34-5.29 (m, 1H), 4.57-4.52 (m, 3H), 4.29-4.23 (m, 2H), 4.00-3.96 (m, 3H), 3.75-3.60 (m, 3H), 3.03-2.98 (m, 1H), 2.94-2.82 (m, 2H), 2.64-2.55 (m, 1H), 2.50-2.47 (m, 4H), 2.40-2.33 (m, 2H), 2.25-2.12 (m, 4H), 2.04-1.97 (m, 3H).



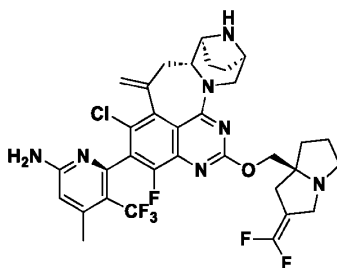


[00347] A mixture of tert-butyl (1S,4R,11S,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (100 mg, 0.099mmol) in TFA (2 mL) was stirred at 50 °C for 3 h under N<sub>2</sub>. The mixture was concentrated to give a crude. Then the crude was added saturated sodium bicarbonate aqueous solution (10 mL) to adjusted pH = (7 ~ 8) and extracted with DCM / MeOH = 10 / 1 (10 mL x 3). The combined organic layers were washed with brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give a residue. The crude was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 5% to 50%) to afford 3-((1S,4R,11S,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-methyl-4-(trifluoromethyl)aniline (20.9 mg, 31.3%) as a white solid. LCMS: m/z 675.2 (M+H<sup>+</sup>).

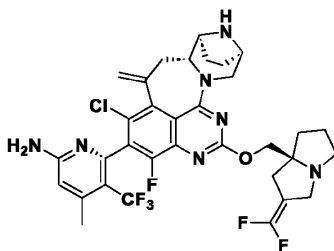
[00348] <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 6.61 (s, 1H), 6.28 (s, 1H), 5.91 (brs, 2H), 5.67 (s, 1H), 5.34 (s, 1H), 5.00 (d, *J* = 12.0 Hz, 1H), 4.12-4.05 (m, 2H), 3.87 (d, *J* = 12.0 Hz, 1H), 3.64 (d, *J* = 14.8 Hz, 1H), 3.54 (s, 1H), 3.86 (m, 1H), 3.32-3.29 (m, 1H), 3.05 – 2.98 (m, 2H), 2.84-2.81 (m, 1H), 2.65-2.55 (m, 3H), 2.42-2.36 (m, 5H), 2.01-1.92 (m, 2H), 1.85-1.73 (m, 3H), 1.57-1.55 (m, 3H).

### Examples 11 & 12

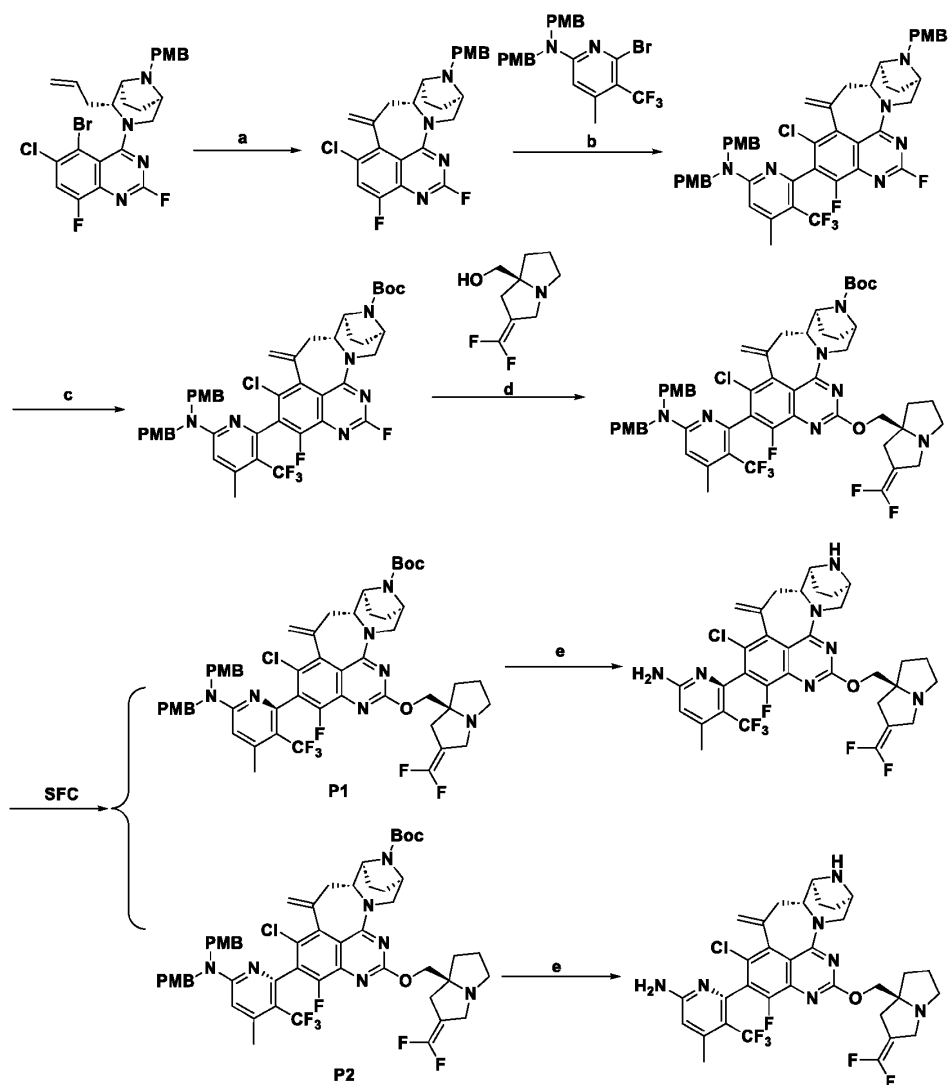
**Example 11: 6-((1S,4R,11R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene) tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino [1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine**



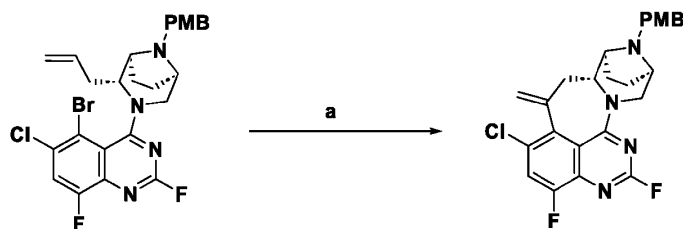
**Example 12: 6-((1S,4R,11S,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine**



**Synthetic scheme**

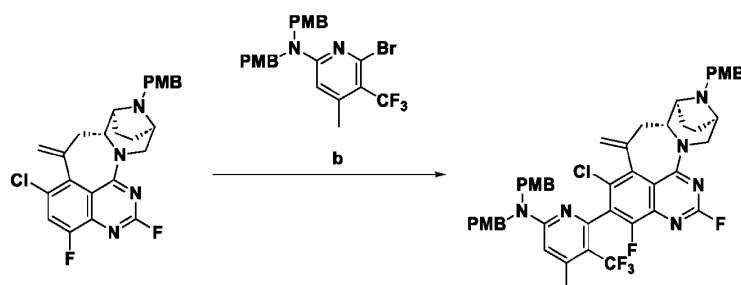


Step 1: Synthesis of (1S,4R,14aR)-12-chloro-8,10-difluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline



[00349] To a solution of 4-((1S,2R,5R)-2-allyl-8-(4-methoxybenzyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-bromo-6-chloro-2,8-difluoroquinazoline (1.4 g, 2.6 mmol, 1.0 eq) in Dioxane (14 mL) was added DIEA (1.0 g, 7.8 mmol, 3 eq), Pd(OAc)<sub>2</sub> (88 mg, 0.39 mmol, 0.15 eq) and PPh<sub>3</sub> (205 mg, 0.78 mmol, 0.3 eq) at room temperature under nitrogen atmosphere. The mixture was stirred at 110 °C for 6 h under N<sub>2</sub>. HPLC showed the reaction was completed. Then the reaction was added H<sub>2</sub>O (20 mL) and extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give crude product, which was purified by silica gel column chromatography (petroleum ether: EtOAc = 10: 1) to afford (1S,4R,14aR)-12-chloro-8,10-difluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline (800 mg, 65.7%) as a yellow solid. LCMS: m/z 468.9 (M+H<sup>+</sup>).

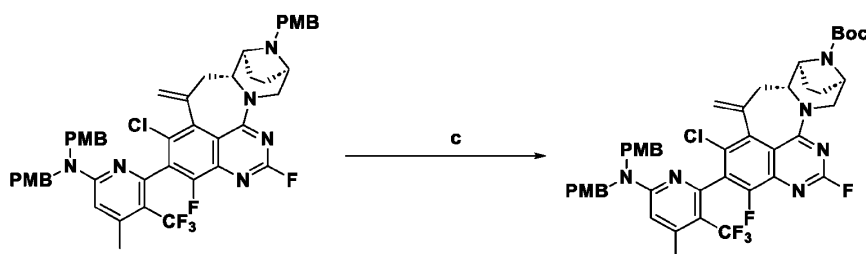
**Step 2: Synthesis of 6-((1S,4R,14aR)-12-chloro-8,10-difluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-N,N-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine**



[00350] To a solution of (1S,4R,14aR)-12-chloro-8,10-difluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline (850 mg, 1.8 mmol, 1.0 eq) in THF (9 mL) was added (TMP)<sub>2</sub>Zn·2MgCl<sub>2</sub>·2LiCl (0.4 M, 27.2 mL, 10.9 mmol, 6.0 eq) under N<sub>2</sub>. The mixture was stirred at 50 °C for 2 h. Then LCMS showed the reaction was completed by quenching using D<sub>2</sub>O. A mixture of 6-bromo-N,N-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (1.1 g, 2.2 mmol, 1.2 eq) and CPhos Pd G3 (145 mg, 0.18 mmol, 0.1 eq) in 1,4-dioxane (9 mL) was added to the mixture. The mixture was stirred at 70 °C for 3 h. The reaction mixture was quenched with H<sub>2</sub>O (15 mL) and extracted with EtOAc (20 mL x 3). The organic layers were washed with brine (15

mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether: EtOAc = 6: 1) to afford 6-((1S,4R,14aR)-12-chloro-8,10-difluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-N,N-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (1.0 g, 61.1%) as a yellow solid. LCMS: m/z 882.8 (M+H<sup>+</sup>).

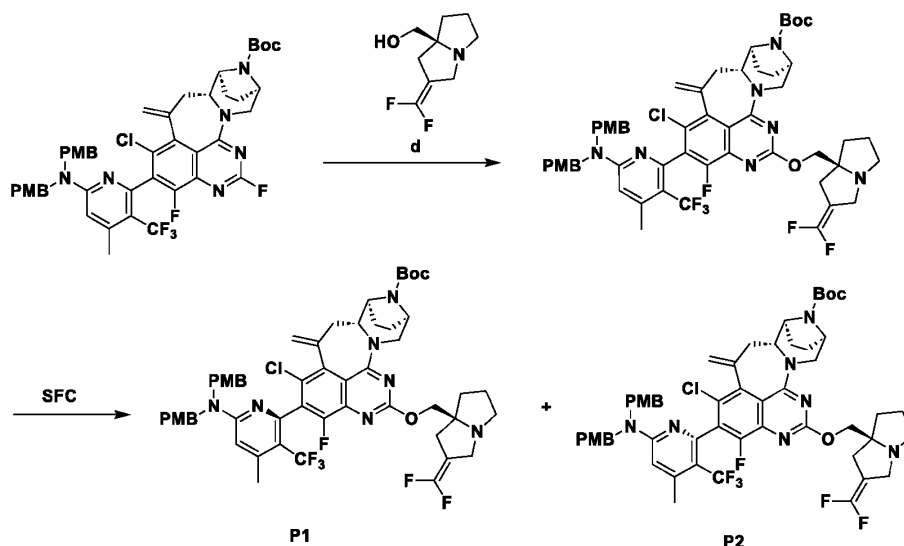
**Step 3: Synthesis of tert-butyl (1S,4R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00351] A solution of 6-((1S,4R,14aR)-12-chloro-8,10-difluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-N,N-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (1.0 g, 1.1 mmol, 1.0 eq) and Lindlar catalyst (Pd/BaSO<sub>4</sub>) (50%, 500 mg) in THF (15 mL) was hydrogenated with a balloon of hydrogen at 65 °C for 20 h. HPLC showed the reaction was completed. The mixture was filtered and concentrated to give a crude product. The residue was purified by Prep-TLC (petroleum ether: EtOAc = 3:1) to afford tert-butyl (1S,4R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (510 mg, 53.5%) as a yellow solid. LCMS: m/z 863.2 (M+H<sup>+</sup>).

**Step 4: Synthesis of tert-butyl (1S,4R,11R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate and tert-butyl (1S,4R,11S,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-**

2-yl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate



[00352] To a solution of (S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (118 mg, 0.63 mmol, 1.5 eq) in THF (1.5 mL) was added NaH (60%) (50.4 mg, 1.26 mmol, 3.0 eq) at 0 °C and then the mixture was stirred for 0.5 h at room temperature under N<sub>2</sub>. The solution of tert-butyl (1S,4R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (360 mg, 0.42 mmol, 1.0 eq) in THF (4 mL) was added to the mixture and stirred at 25 °C for 1.5 h. HPLC and TLC show the reaction was completed. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl solution (10 mL) and extracted with EtOAc (10 mL x 3). The mixture was concentrated to give a crude product. The residue was purified by Prep-TLC (DCM: MeOH = 10:1) to afford tert-butyl (1S,4R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (300 mg, 69.0%) as a yellow solid. LCMS: 1032.4 (M+H<sup>+</sup>).

[00353] The diastereomers were separated by SFC to afford tert-butyl (1S,4R,11R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (**P1**, retention time = 1.518 minutes, 150 mg, with another ~200 mg batch) and tert-butyl (1S,4R,11S,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (**P2**, retention time = 2.164 minutes, 87 mg, with another ~ 200 mg batch).

**SFC conditions:**

**Analytical separation method:**

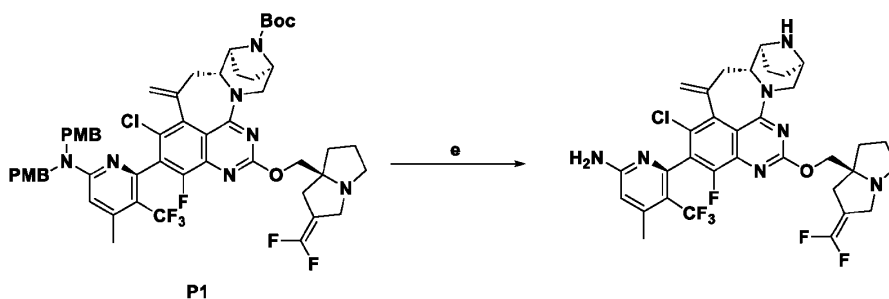
[00354] Instrument: Waters UPC2 analytical SFC (SFC-H). Column: ChiralPak IG, 150×4.6mm I.D., 3µm.

[00355] Mobile phase: A for CO<sub>2</sub> and B for Ethanol (0.05%DEA). Gradient: B 50%. Flow rate: 2.5 mL/min. Back pressure: 100 bar. Column temperature: 35°C. Wavelength: 220nm.

**Preparative separation method**

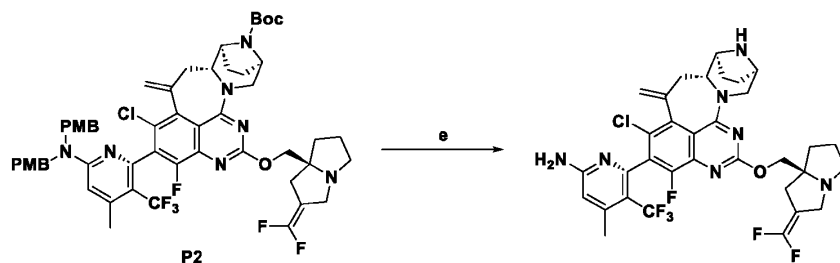
[00356] Instrument: WATERS 150 preparative SFC(SFC-26). Column: ChiralPak IG, 250×30mm I.D., 10µm. Mobile phase: A for CO<sub>2</sub> and B for Ethanol (0.1%NH<sub>3</sub>H<sub>2</sub>O). Gradient: B 45%. Flow rate: 120 mL/min. Back pressure: 100 bar. Column temperature: 38°C. Wavelength: 254nm. Cycle time: ~ 4 min.

**Step 5: Synthesis of 6-((1S,4R,11R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine and 6-((1S,4R,11S,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-**



[00357] A mixture of tert-butyl (1S,4R,11R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (150 mg, 0.15 mmol) in TFA (3 mL) was stirred at 50 °C for 3 h under N<sub>2</sub>. The mixture was concentrated to give a crude, which was added saturated sodium bicarbonate aqueous solution (15 mL) to adjusted pH = (7 ~ 8) and extracted with DCM / MeOH = 10 / 1 (15 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give crude product, which was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 20% to 46%) to afford 6-((1S,4R,11R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (25 mg, with 0.4 FA, 24%) as a white solid. LCMS: m/z 691.9 (M+H<sup>+</sup>).

[00358] <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 6.86 (brs, 2H), 6.47 (s, 1H), 5.75 (s, 1H), 5.30 (s, 1H), 5.02 (d, *J* = 11.7 Hz, 1H), 4.14 - 4.03 (m, 2H), 4.00-3.85 (m, 1H), 3.66-3.60 (m, 3H), 3.45-3.05 (m, 3H), 3.02-2.85 (m, 2H), 2.75-2.51 (m, 2H), 2.45-2.39 (m, 1H), 2.36 (d, *J* = 1.2, 3H), 2.29-2.21 (m, 1H), 2.00-1.71 (m, 5H), 1.61-1.55 (m, 3H).

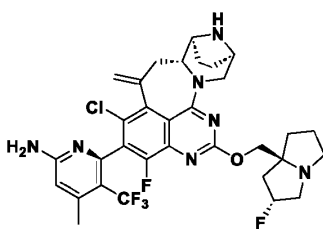




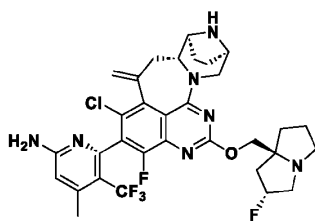
[00359] A mixture of tert-butyl (1S,4R,11S,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (87 mg, 0.08 mmol) in TFA (2.0 mL) was stirred at 50 °C for 3 h under N<sub>2</sub>. The mixture was concentrated to give a crude, which was added saturated sodium bicarbonate aqueous solution (15 mL) to adjusted pH = (7 ~ 8) and extracted with DCM / MeOH = 10 / 1 (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give crude product, which was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 10% to 65%) to afford 6-((1S,4R,11S,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (13 mg, with 0.8 FA, 23.5%) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 6.82 (brs, 2H), 6.47 (s, 1H), 5.76 (s, 1H), 5.33 (s, 1H), 5.09 (d, *J* = 12.0 Hz, 1H), 4.15-4.01 (m, 2H), 4.00-3.90 (m, 1H), 3.69-3.55 (m, 2H), 3.50-3.05 (m, 3H), 3.02-2.89 (m, 2H), 2.70-2.60 (m, 1H), 2.42-2.21 (m, 7H), 1.96-1.77(m, 5H), 1.60-1.54 (m, 3H); LCMS: *m/z* 691.9 (M+H<sup>+</sup>).

### Examples 13 & 14

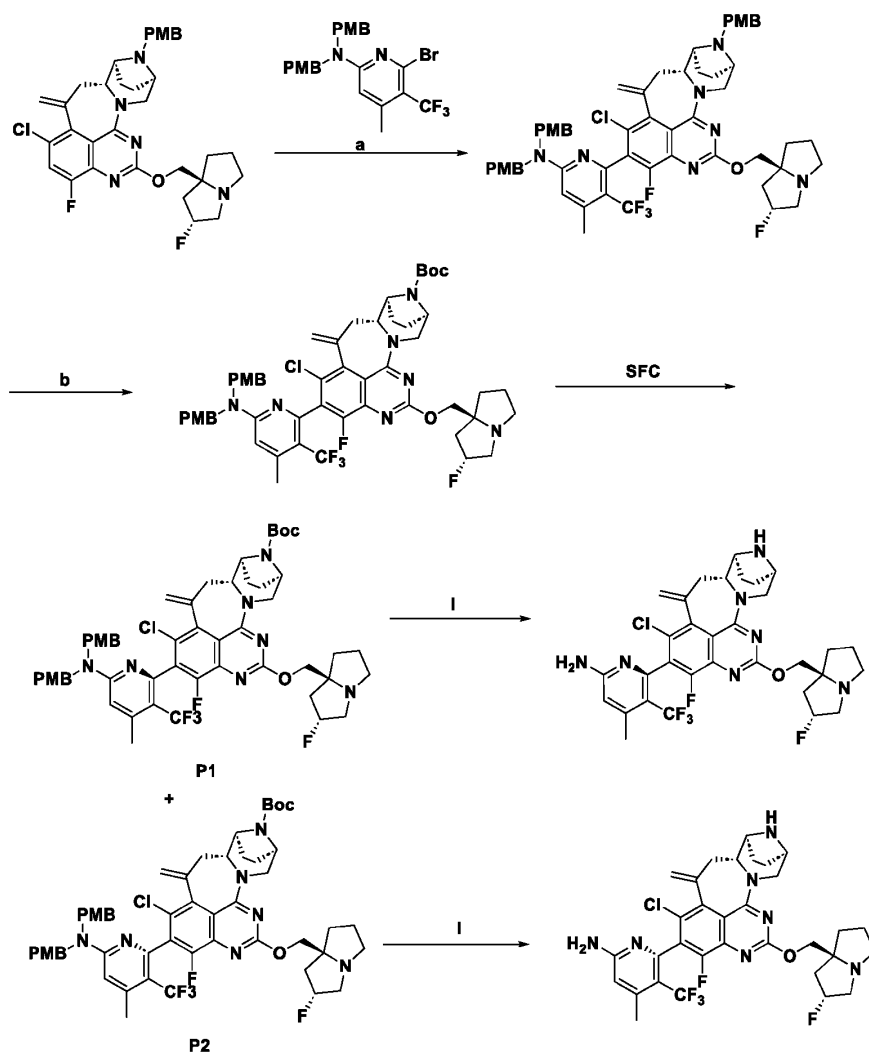
**Example 13:** 6-((1S,4R,11R,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino [2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine



**Example 14:** 6-((1S,4R,11S,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino [1',2':1,7]azepino [2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine

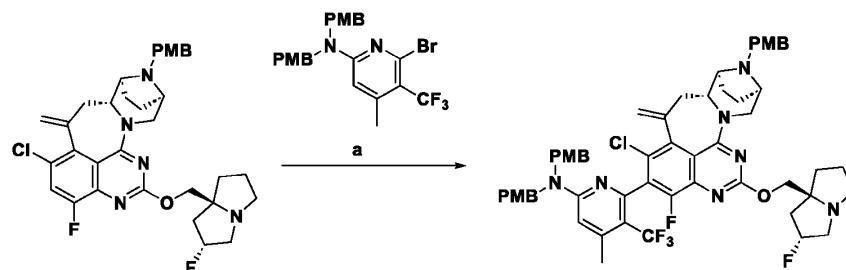


## Synthetic scheme



Step 1: 6-((1S,4R,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-

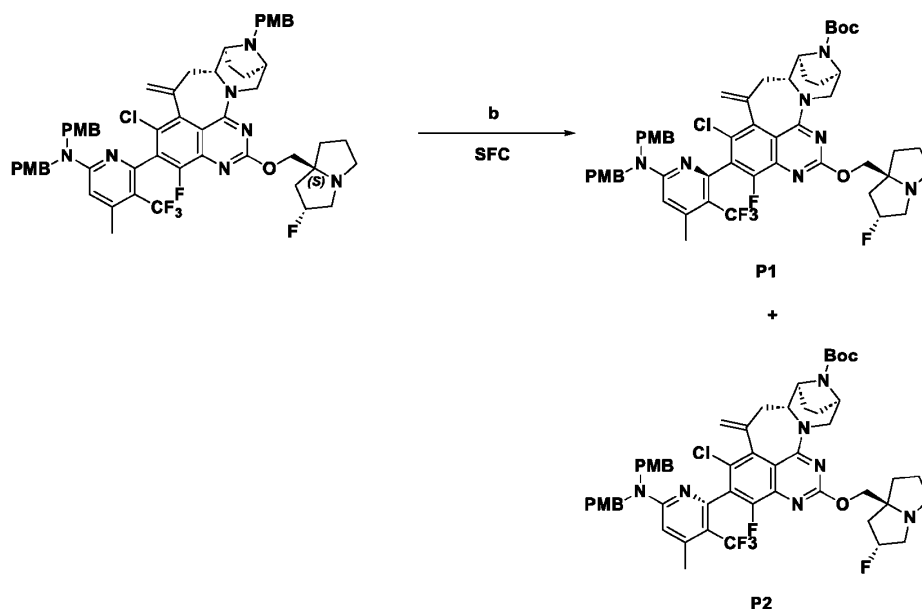
octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-N,N-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine



[00360] To a solution of (1S,4R,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline (330 mg, 0.54 mmol, 1.0 eq) in THF (7 mL) was added (TMP)<sub>2</sub>Zn·2MgCl<sub>2</sub>·2LiCl (0.4 M, 9.5 mL, 3.80 mmol, 7.0 eq) under N<sub>2</sub>. The mixture was stirred at 50 °C for 2 h. Then LCMS showed the reaction was completed by quenching with D<sub>2</sub>O (0.4 mL). Then a mixture of 6-bromo-N,N-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (323 mg, 0.65 mmol, 1.2 eq) and CPhos Pd G3 (44 mg, 0.05 mmol, 0.1 eq) in 1,4-dioxane (7 mL) was added to the mixture. The mixture was stirred at 70 °C for 3 h. The reaction mixture was quenched with H<sub>2</sub>O (15 mL) and extracted with EtOAc (15 mL x 3). The organic layers were washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (DCM: MeOH = 70: 1) to afford 6-(((1S,4R,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-N,N-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (300 mg, 54.0%) as a yellow solid. LCMS: 1022.2 (M+H<sup>+</sup>).

**Step 2: tert-butyl (1S,4R,11R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate and tert-butyl (1S,4R,11S,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-**

yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate



[00361] A solution of 6-((1S,4R,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-N,N-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (100 mg, 0.09 mmol, 1.0 eq) and Pd/C (30%, 33 mg) in MeOH (7 mL) was hydrogenated with a balloon of hydrogen at 55 °C for 40 h. HPLC showed the reaction was completed. The mixture was filtered and concentrated to give a crude residue, which was purified by Prep-TLC (DCM: MeOH = 10: 1) to afford tert-butyl (1S,4R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (66 mg, 67.3%, diastereomers) as a yellow solid. LCMS: 1002.2 (M+H<sup>+</sup>).

[00362] The diastereomers were separated by SFC to afford tert-butyl (1S,4R,11R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-

carboxylate (**P1**, retention time = 1.910 minutes, 75 mg, with another ~150mg batch) as a yellow solid and tert-butyl (1S,4R,11S,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (**P2**, retention time = 3.024 minutes, 55 mg, with another ~150mg batch) as a yellow solid.

#### SFC conditions:

##### Analytical separation method:

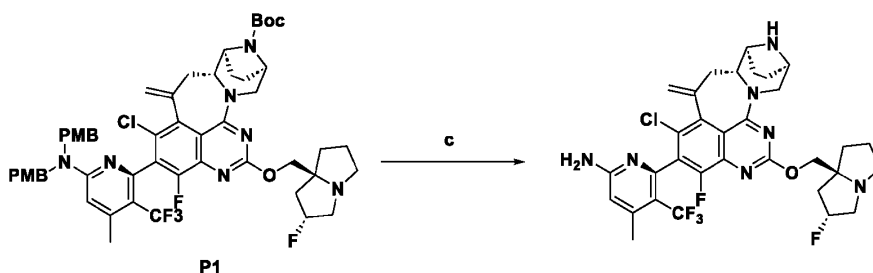
[00363] Instrument: Waters UPC2 analytical SFC (SFC-H). Column: ChiralPak IG, 150×4.6mm I.D., 3μm.

[00364] Mobile phase: A for CO<sub>2</sub> and B for Isopropanol (0.05%DEA). Gradient: B 40%. Flow rate: 2.5 mL/min. Back pressure: 100 bar. Column temperature: 35°C. Wavelength: 220nm.

##### Preparative separation method

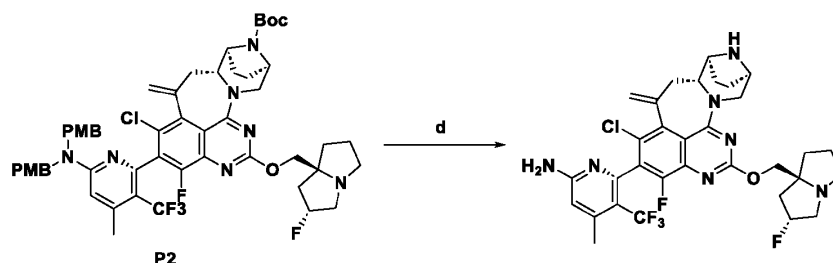
[00365] Instrument: WATERS 150 preparative SFC(SFC-26). Column: ChiralPak IG, 250×30mm I.D., 10μm. Mobile phase: A for CO<sub>2</sub> and B for Isopropanol (0.1%NH<sub>3</sub>H<sub>2</sub>O). Gradient: B 40%. Flow rate: 120 mL /min. Back pressure: 100 bar. Column temperature: 38°C. Wavelength: 220nm. Cycle time: ~ 4 min.

**Step 3:** 6-(((1S,4R,11R,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine and 6-(((1S,4R,11S,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine



[00366] A mixture of tert-butyl (1S,4R,11R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (75 mg, 0.07mmol) in TFA (2.5 mL) was stirred at 50 °C for 3 h. The mixture was concentrated to give a residue, which was added saturated NaHCO<sub>3</sub> solution (15 mL) to adjusted pH = (7 ~ 8) and extracted with DCM: MeOH = 10: 1 (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give crude product, which was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 10% to 65%) to afford 6-((1S,4R,11R,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (18 mg, with 0.87 FA, 35%) as a white solid.

[00367] <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 6.85 (s, 2H), 6.47 (s, 1H), 5.75 (s, 1H), 5.30 (s, 1H), 5.27 (d, *J* = 54.3 Hz, 1H), 5.03 (d, *J* = 12.0 Hz, 1H), 4.03 (dd, *J* = 35.1 Hz, 10.2 Hz, 2H), 3.95-3.88 (m, 1H), 3.59 (s, 2H), 3.42 (s, 2H), 3.15-3.08 (m, 3H), 2.99-2.90 (m, 2H), 2.86-2.71 (m, 1H), 2.36 (d, *J* = 1.5 Hz, 3H), 2.29-2.25 (m, 1H), 2.20 -2.12 (m, 1H), 2.05-1.92 (m, 3H), 1.85-1.75 (m, 3H), 1.54 (s, 2H). LCMS: *m/z* 661.9 (M+H<sup>+</sup>).



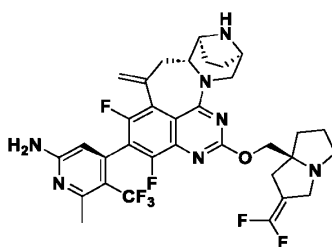
[00368] A mixture of tert-butyl (1S,4R,11S,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (55 mg, 0.05mmol) in TFA (2.0 mL) was stirred at 50 °C for 3 h. The mixture was concentrated to give residue, which was added saturated NaHCO<sub>3</sub> solution (15 mL) to adjusted pH = (7 ~ 8) and extracted with DCM: MeOH = 10: 1 (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried

over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give crude product, which was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 10% to 65%) to afford 6-((1S,4R,11S,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (21 mg, with 0.6 FA, 57%) as a white solid.

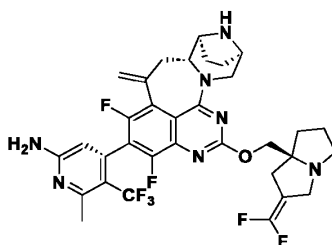
[00369] <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 6.82 (s, 2H), 6.47 (s, 1H), 5.76 (s, 1H), 5.31 (s, 1H), 5.27 (d, *J* = 54.3 Hz, 1H), 5.08 (d, *J* = 12.0 Hz, 1H), 4.11-3.89 (m, 3H), 3.59 (s, 2H), 3.41 (s, 2H), 3.13-3.08 (m, 3H), 2.99-2.89 (m, 2H), 2.86-2.71 (m, 1H), 2.36 (d, *J* = 1.2 Hz, 3H), 2.28-2.23 (m, 1H), 2.19-2.01 (m, 2H), 2.00-1.94 (m, 2H), 1.85-1.75 (m, 3H), 1.51-1.50 (m, 2H). LCMS: *m/z* 661.9 (M+H<sup>+</sup>).

### Examples 15 & 16

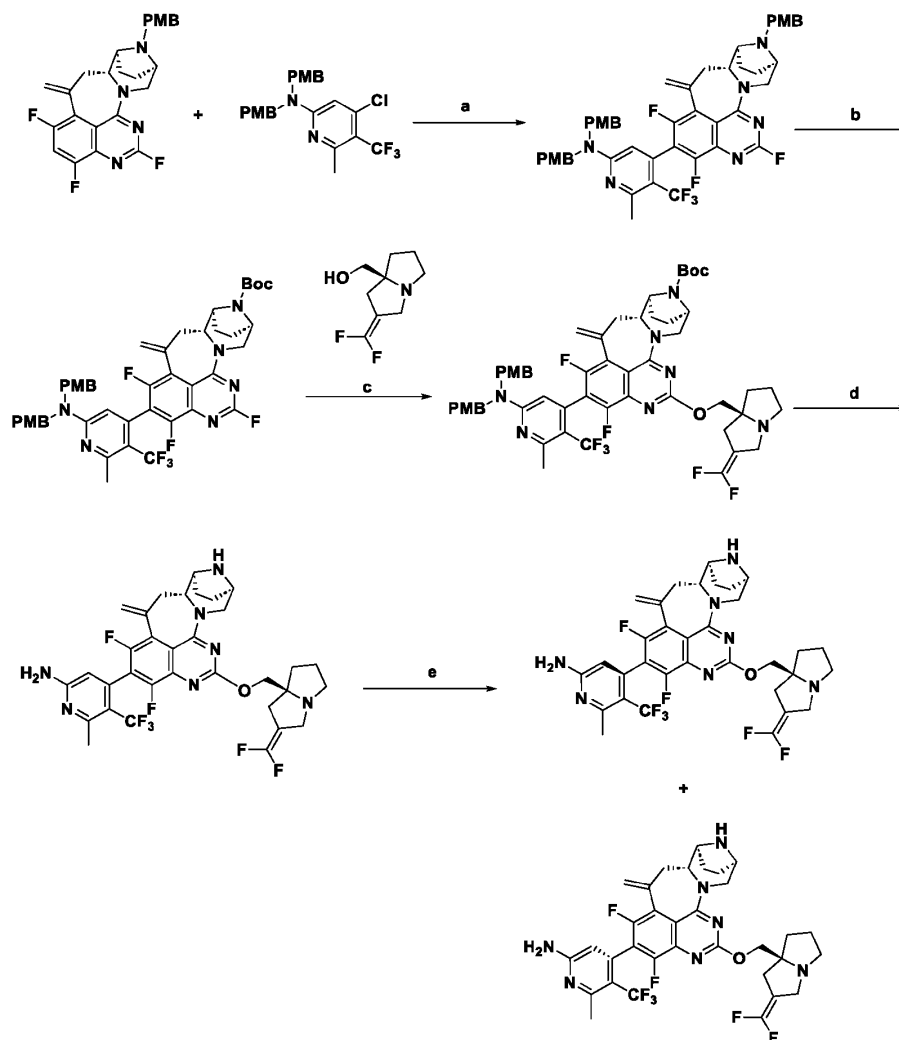
**Example 15:** 4-((1S,4R,11R,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino [1',2':1,7] azepino[2,3,4-de]quinazolin-11-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine 2,2,2-trifluoroacetate



**Example 16:** 4-((1S,4R,11S,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino [2,3,4-de]quinazolin-11-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

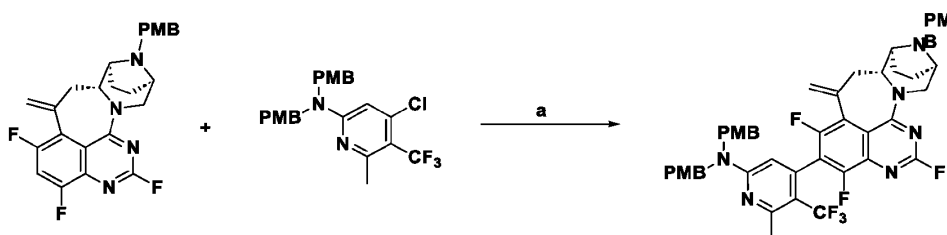


## Synthesis scheme



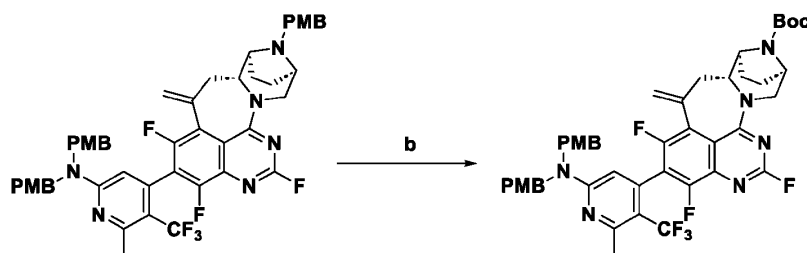
Step 1: Synthesis of N,N-bis(4-methoxybenzyl)-6-methyl-4-((1S,4R,14aR)-8,10,12-trifluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-(trifluoromethyl)pyridin-2-amine





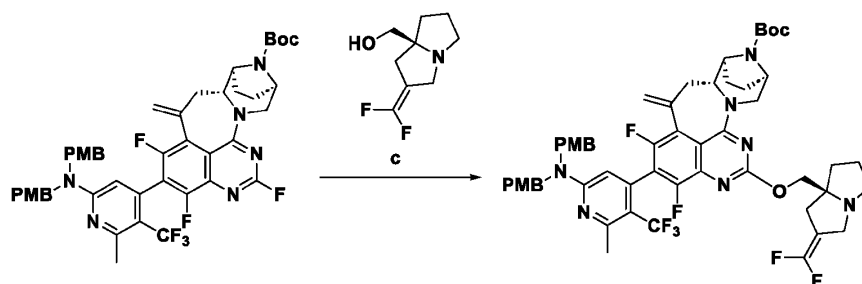
[00370] To a solution of (1S,4R,14aR)-8,10,12-trifluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline (4.0 g, 8.8 mmol, 1.0 eq) in THF (20 mL) was added 0.4 M (TMP)<sub>2</sub>Zn·MgCl<sub>2</sub>·LiCl in THF (132.7 mL, 53.1 mmol, 6.0 eq) dropwise with double-ended syringe. The reaction mixture was stirred at 50 °C for 2 h under N<sub>2</sub> atmosphere. To the reaction mixture was added a solution of 4-chloro-N,N-bis(4-methoxybenzyl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine (4.78 g, 10.6 mmol, 1.2 eq) and CPhos Pd G3 (713 mg, 0.88 mmol, 0.1 eq) in dioxane (40 mL). The reaction mixture was stirred at 70 °C for 2 h. The reaction was quenched with H<sub>2</sub>O (150 mL). The mixture was filtered off, washed with EtOAc (200 mL) and separated. The aqueous layer was extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude. The crude was purified by silica gel column chromatography (Petroleum ether: EtOAc = 1: 1) to give N,N-bis(4-methoxybenzyl)-6-methyl-4-((1S,4R,14aR)-8,10,12-trifluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-(trifluoromethyl)pyridin-2-amine (4.0 g, 51.9%) as a brown solid. LCMS: m/z 867.2 (M+H<sup>+</sup>).

**Step 2: Synthesis of tert-butyl (1S,4R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00371] A solution of N,N-bis(4-methoxybenzyl)-6-methyl-4-((1S,4R,14aR)-8,10,12-trifluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-(trifluoromethyl)pyridin-2-amine (4.0 g, 4.6 mmol, 1.0 eq), Boc<sub>2</sub>O (1.5 g, 6.9 mmol, 1.5 eq) and Pd/BaSO<sub>4</sub> (2.0 g, 50% w/w) in THF (40 mL) was stirred at 65 °C for 20 h. The mixture was filtered through a Celite pad, and the filtrate was concentrated to give a residue. The residue was purified by silica gel column chromatography (Petroleum ether: EtOAc = 1: 1) to give tert-butyl (1S,4R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (3.0 g, 75.4%) as a yellow solid. LCMS: m/z 847.5 (M+H<sup>+</sup>).

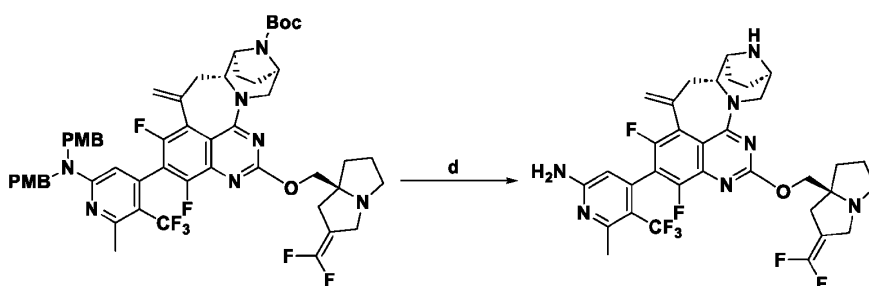
**Step 3: Synthesis of tert-butyl (1S,4R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00372] To a solution of compound (S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (168 mg, 0.89 mmol, 1.5 eq) in THF (6 mL) was added NaH (60%, 71 mg, 1.77 mmol, 3.0 eq). The mixture was stirred at room temperature for 0.5 h. Compound tert-butyl (1S,4R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (500 mg, 0.59 mmol, 1.0 eq) was added. The mixture was stirred at 40 °C for 1 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 H<sub>2</sub>O (20 mL), brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness. The crude product was purified by silica gel column chromatography (Dichloromethane: Methanol = 40: 1) to give compound tert-butyl (1S,4R,14aR)-11-(6-(bis(4-

methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (400 mg, 66.7%) as a yellow solid. LCMS:  $m/z$  509.0 ( $M/2+H^+$ ).

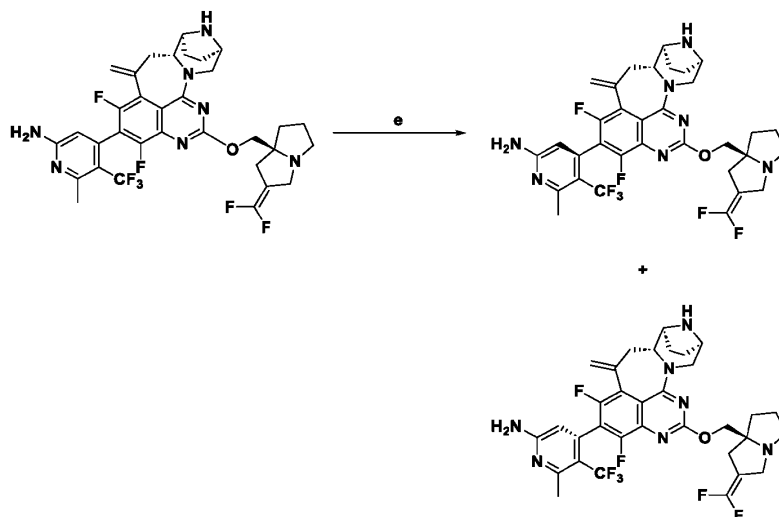
**Step 4: Synthesis of 4-((1S,4R,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine**



[00373] A solution of tert-butyl (1S,4R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (400 mg, 0.39 mmol, 1.0 eq) in TFA (8 mL) was stirred at 50 °C for 4 h. The mixture was concentrated to give a residue. The residue was purified by prep-TLC (Dichloromethane: Methanol = 5: 1, acetonitrile with 0.1%  $\text{NH}_4\text{OH}$  in MeOH) to give compound 4-((1S,4R,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine (108 mg, 40.6%) as a yellow solid.

**Step 5: Synthesis of 4-((1S,4R,11R,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine 2,2,2-trifluoroacetate formate (1 : 0.2 : 0.6) and 4-((1S,4R,11S,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-**

epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine formate (1 : 0.5)



[00374] Compound 4-((1S,4R,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine (130 mg) was purified by Chiral HPLC (Column: CHIRALPAK IE, 2 cm x 25cm, 5 $\mu$ m, Mobile phase: A for Hexane (0.5% 2mM NH<sub>3</sub>-MeOH) and B for EtOH, Flow rate: 20 mL/min, Column temperature: 25 °C) to afford 4-((1S,4R,11R,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine 2,2,2-trifluoroacetate formate (1 : 0.2 : 0.6) (32 mg, 24.6%) and 4-((1S,4R,11S,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine formate (1 : 0.5) (24 mg, 18.5%).

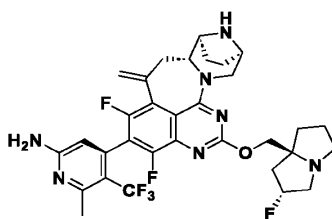
[00375] **P1:** 4-((1S,4R,11R,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine 2,2,2-trifluoroacetate formate (1 : 0.2 : 0.6): Chiral purity:

98.55% de, retention time: 6.523 min; Chiral HPLC method: Column: CHIRALPAK IB N-3, 4.6 x 100 mm, 3  $\mu$ m, Mobile phase: A for Hex and B for EtOH (0.1% TFA), Gradient: B 10%, Flow rate: 0.8 mL/min, Column temperature: 25 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  8.49 (brs, 1H), 6.33 (s, 1H), 5.77 (s, 1H), 5.56 (d,  $J$  = 3.9 Hz, 1H), 5.30 (dd,  $J$  = 14.4, 2.8 Hz, 1H), 4.41 – 4.25 (m, 2H), 4.12 (dd,  $J$  = 11.4, 4.5 Hz, 1H), 4.03 (s, 1H), 3.94 – 3.79 (m, 2H), 3.52 (d,  $J$  = 14.1 Hz, 1H), 3.37 – 3.32 (m, 1H), 3.27 – 3.18 (m, 1H), 2.99 – 2.74 (m, 3H), 2.63 – 2.38 (m, 6H), 2.22 – 1.83 (m, 7H). LCMS:  $m/z$  676.5 ( $\text{M}+\text{H}^+$ ).

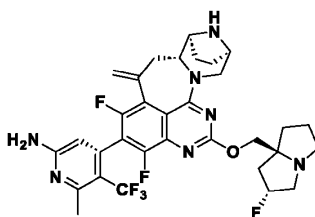
[00376] **P2**: 4-((1S,4R,11S,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine formate (1 : 0.5): Chiral purity: 97.57% de, retention time: 5.447 min; Chiral HPLC method: Column: CHIRALPAK IB N-3, 4.6 x 100 mm, 3  $\mu$ m, Mobile phase: A for Hex and B for EtOH (0.1% TFA), Gradient: B 10%, Flow rate: 0.8 mL/min, Column temperature: 25 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  8.49 (brs, 1H), 6.30 (s, 1H), 5.76 (s, 1H), 5.52 (d,  $J$  = 3.9 Hz, 1H), 5.32 (d,  $J$  = 13.5 Hz, 1H), 4.42 – 4.27 (m, 2H), 4.16 – 4.04 (m, 1H), 4.02 – 3.77 (m, 3H), 3.56 – 3.43 (m, 1H), 3.28 – 3.13 (m, 2H), 2.97 – 2.71 (m, 3H), 2.65 – 2.32 (m, 6H), 2.23 – 1.79 (m, 7H). LCMS:  $m/z$  676.4 ( $\text{M}+\text{H}^+$ ).

### Examples 17 & 18

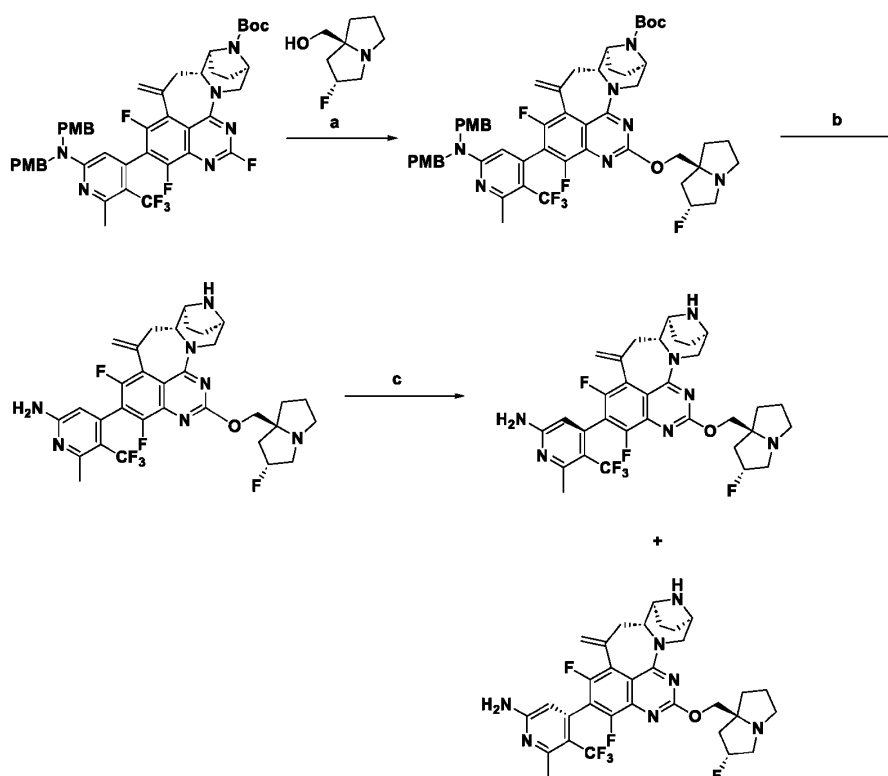
**Example 17: 4-((1S,4R,11R,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino [2,3,4-de]quinazolin-11-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine**



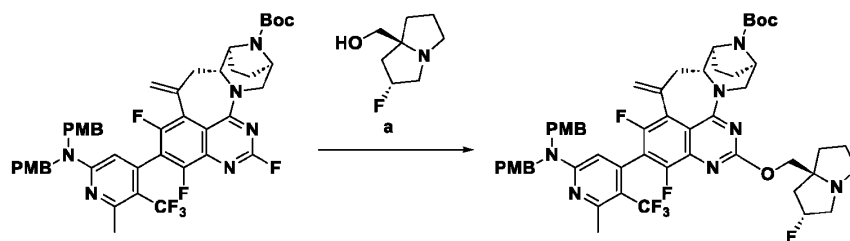
**Example 18: 4-((1S,4R,11S,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino [2,3,4-de]quinazolin-11-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine**



### Synthesis scheme

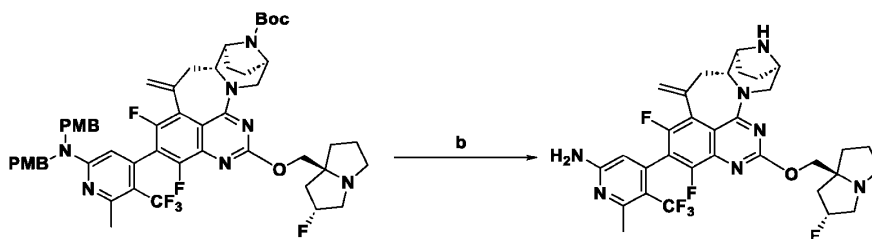


Step 1: Synthesis of tert-butyl (1S,4R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate



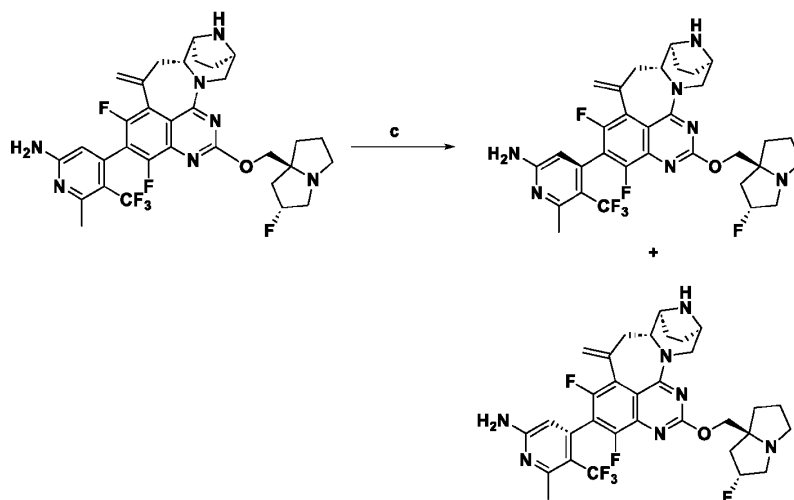
[00377] To a solution of compound ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (113 mg, 0.71 mmol, 1.5 eq) in THF (6 mL) was added NaH (60%, 57 mg, 1.42 mmol, 3.0 eq). The mixture was stirred at room temperature for 0.5 h. Compound tert-butyl (1S,4R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (400 mg, 0.47 mmol, 1.0 eq) was added. The mixture was stirred at 40 °C for 1 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 H<sub>2</sub>O (20 mL), brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness. The crude product was purified by silica gel column chromatography (Dichloromethane: Methanol = 40: 1) to give compound tert-butyl (1S,4R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (300 mg, 64.4%) as a yellow solid. LCMS: m/z 986.5 (M+H<sup>+</sup>).

**Step 2: Synthesis of 4-(((1S,4R,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine**



[00378] A solution of tert-butyl (1S,4R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (400 mg, 0.41 mmol, 1.0 eq) in TFA (8.0 mL) was stirred at 50 °C for 4 h. The mixture was concentrated to give a residue. The residue was purified by prep-TLC (Dichloromethane: Methanol = 5: 1, acetonitrile with 0.1% NH<sub>4</sub>OH in MeOH) to give compound 4-((1S,4R,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine (120 mg, 45.8%) as a yellow solid. LCMS: m/z 646.4 (M+H<sup>+</sup>).

**Step 3: Synthesis of 4-((1S,4R,11R,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine formate (1 : 1) and 4-((1S,4R,11S,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine formate (1 : 0.9)**



[00379] Compound 4-((1S,4R,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-6-methyl-5-



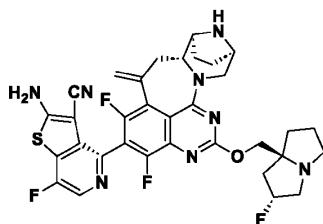
(trifluoromethyl)pyridin-2-amine (150 mg) was purified by Chiral HPLC (Column: CHIRALPAK IE, 2 cm x 25cm, 5 $\mu$ m, Mobile phase: A for Hexane (0.5% 2mM NH<sub>3</sub>-MeOH) and B for EtOH, Flow rate: 20 mL/min, Column temperature: 25 °C) to afford 4-((1S,4R,11R,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine formate (1 : 1) (53 mg, 35.3%) and 4-((1S,4R,11S,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine formate (1 : 0.9) (24 mg, 16.0%).

[00380] **P1:** 4-((1S,4R,11R,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine formate (1 : 1): Chiral purity: 97.45% ee; retention time: 7.337 min; Chiral HPLC method: Column: CHIRALPAK IB N-3, 4.6 x 100 mm, 3  $\mu$ m, Mobile phase: A for Hex and B for EtOH (0.1% TFA), Gradient: B 10%, Flow rate: 0.8 mL/min, Column temperature: 25 °C. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD):  $\delta$  8.49 (brs, 1H), 6.32 (s, 1H), 5.77 (s, 1H), 5.60 – 5.24 (m, 3H), 4.51 – 4.35 (m, 2H), 4.20 – 4.07 (m, 1H), 3.98 (s, 1H), 3.91 – 3.77 (m, 1H), 3.74 – 3.47 (m, 3H), 3.25 – 3.18 (m, 1H), 3.01 – 2.86 (m, 1H), 2.65 – 2.49 (m, 5H), 2.49 – 2.09 (m, 6H), 2.08 – 1.79 (m, 4H). LCMS: m/z 646.4 (M+H<sup>+</sup>).

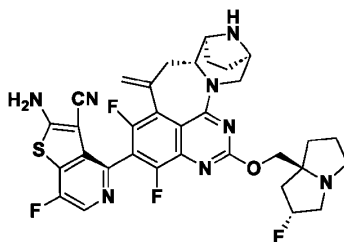
[00381] **P2:** 4-((1S,4R,11S,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine formate (1 : 0.9): Chiral purity: 98.24% ee; retention time: 6.063 min; Chiral HPLC method: Column: CHIRALPAK IB N-3, 4.6 x 100 mm, 3  $\mu$ m, Mobile phase: A for Hex and B for EtOH (0.1% TFA), Gradient: B 10%, Flow rate: 0.8 mL/min, Column temperature: 25 °C. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD):  $\delta$  8.51 (brs, 1H), 6.30 (s, 1H), 5.76 (s, 1H), 5.58 – 5.25 (m, 3H), 4.49 – 4.30 (m, 2H), 4.11 (dd, *J* = 11.6, 4.4 Hz, 1H), 3.92 (s, 1H), 3.77 (s, 1H), 3.66 – 3.41 (m, 3H), 3.28 – 3.12 (m, 2H), 2.92 (dd, *J* = 13.6, 4.4 Hz, 1H), 2.61 – 2.47 (m, 4H), 2.45 – 2.08 (m, 6H), 2.06 – 1.79 (m, 4H). LCMS: m/z 646.3 (M+H<sup>+</sup>).

## Examples 19 &amp; 20

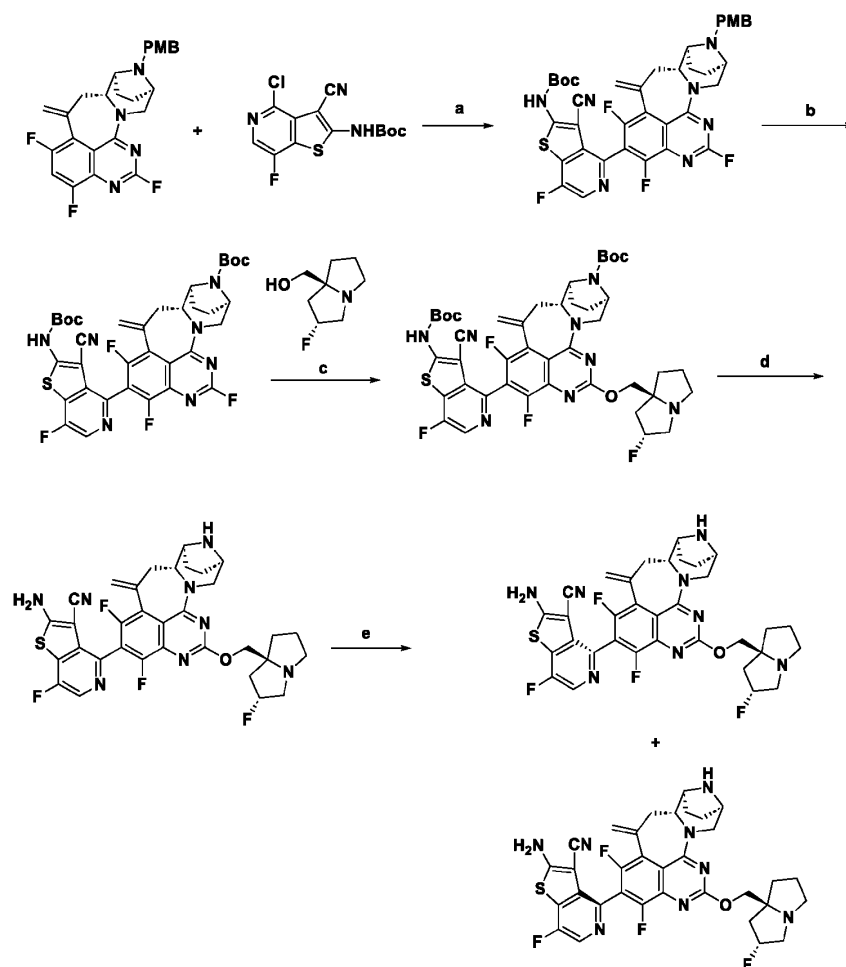
**Example 19:** 2-amino-4-((1S,4R,11S,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino [2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile



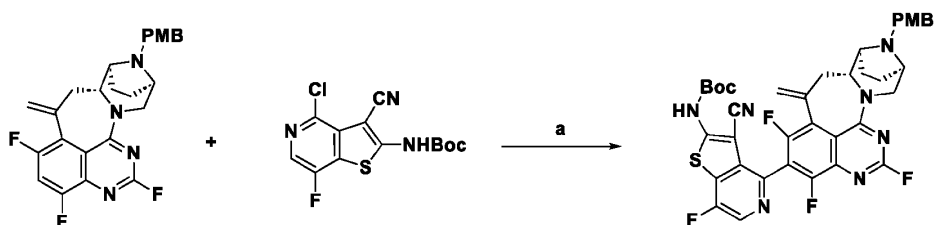
**Example 20:** 2-amino-4-((1S,4R,11R,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino [2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile



Synthesis scheme

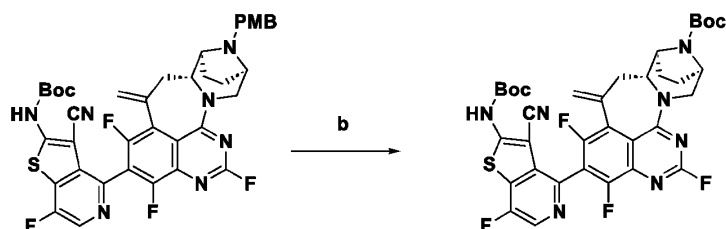


**Step 1: Synthesis of tert-butyl (3-cyano-7-fluoro-4-((1S,4R,14aR)-8,10,12-trifluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)thieno[3,2-c]pyridin-2-yl)carbamate**



[00382] To a solution of (1S,4R,14aR)-8,10,12-trifluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline (400 mg, 0.88 mmol, 1.0 eq) in THF (4 mL) was added 0.4 M (TMP)<sub>2</sub>Zn·MgCl<sub>2</sub>·LiCl in THF (13.3 mL, 5.3 mmol, 6.0 eq) dropwise with double-ended syringe. The reaction mixture was stirred at 50 °C for 2 h under N<sub>2</sub>. To the reaction mixture was added a solution of tert-butyl (4-chloro-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate (319 mg, 0.97 mmol, 1.1 eq) and CPhos Pd G3 (71 mg, 0.09 mmol, 0.1 eq) in dioxane (4 mL). The reaction mixture was stirred at 70 °C for 2 h. The reaction was quenched with H<sub>2</sub>O (5 mL). The mixture was filtered off, washed with EtOAc (200 mL) and separated. The aqueous layer was extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude. The crude was purified by silica gel column chromatography (Petroleum ether: EtOAc = 2: 1) to give tert-butyl (3-cyano-7-fluoro-4-((1S,4R,14aR)-8,10,12-trifluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)thieno[3,2-c]pyridin-2-yl)carbamate (400 mg, 60.9%) as a brown solid. LCMS: m/z 744.4 (M+H<sup>+</sup>).

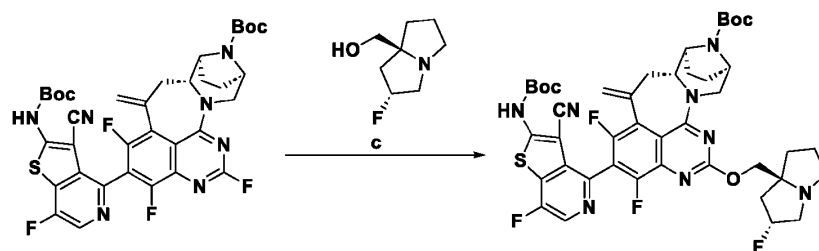
**Step 2: Synthesis of tert-butyl (1S,4R,14aR)-11-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00383] A solution of tert-butyl (3-cyano-7-fluoro-4-((1S,4R,14aR)-8,10,12-trifluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)thieno[3,2-c]pyridin-2-yl)carbamate (140 mg, 0.19 mmol, 1.0 eq), Boc<sub>2</sub>O (123 mg, 0.57 mmol, 3.0 eq) and Pd/BaSO<sub>4</sub> (70 mg, 50% w/w) in THF (3 mL) was stirred at 65 °C for 20 h. The mixture was filtered through a Celite pad, the filtrate was concentrated to give a residue. The residue was purified by silica gel column chromatography (Petroleum ether: EtOAc = 3: 1) to give tert-butyl (1S,4R,14aR)-11-(2-((tert-

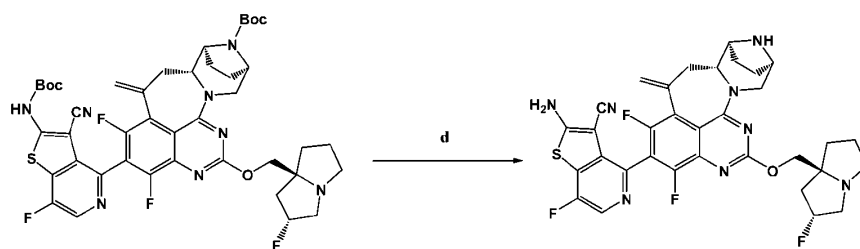
butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (100 mg, 73.5%) as a yellow solid. LCMS:  $m/z$  724.8 ( $M+H^+$ ).

**Step 3: Synthesis of tert-butyl (1S,4R,14aR)-11-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



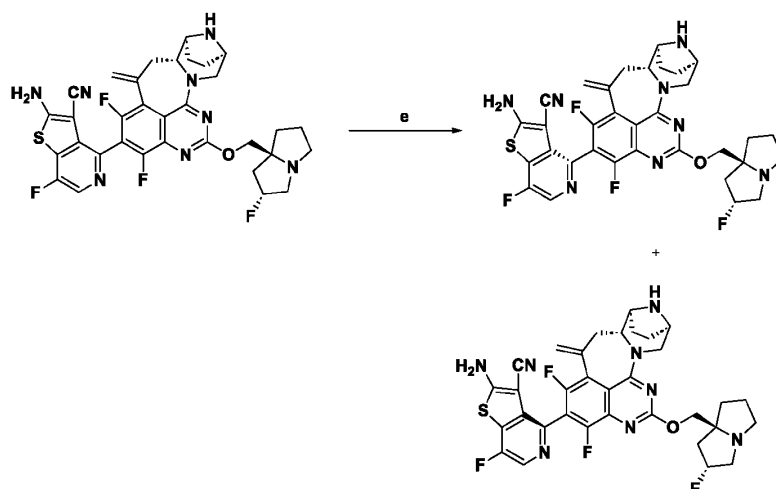
[00384] To a solution of ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (66 mg, 0.41 mmol, 1.5 eq) in THF (2 mL) was added NaH (60%, 33 mg, 0.83 mmol, 3.0 eq). The mixture was stirred at room temperature for 0.5 h. Compound tert-butyl (1S,4R,14aR)-11-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (200 mg, 0.28 mmol, 1.0 eq) was added. The mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with water (5 mL). The aqueous layer was extracted with ethyl acetate (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 (Dichloromethane: Methanol = 15: 1) to give compound tert-butyl (1S,4R,14aR)-11-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (200 mg, 83.9%) as a yellow solid. LCMS: 863.3 ( $M+H^+$ ).

**Step 4: Synthesis of 2-amino-4-((1S,4R,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile 2,2,2-trifluoroacetate (1 : 1)**



[00385] To a solution of tert-butyl (1S,4R,14aR)-11-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (200 mg, 0.23 mmol, 1.0 eq) in DCM (3 mL) was added TFA (1.0 mL). The reaction was stirred at 25 °C for 2 h. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC (acetonitrile with 0.1% TFA in water, 15% to 50%) to give compound 2-amino-4-((1S,4R,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile 2,2,2-trifluoroacetate (1 : 1) (110 mg, 62.4%) as a yellow solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 8.35 (s, 1H), 5.83 (d, *J* = 5.6 Hz, 1H), 5.74 – 5.38 (m, 3H), 4.80 – 4.59 (m, 2H), 4.39 – 4.21 (m, 2H), 4.18 – 4.12 (m, 1H), 4.09 – 3.89 (m, 3H), 3.53 – 3.42 (m, 2H), 3.08 – 2.95 (m, 1H), 2.76 – 2.30 (m, 7H), 2.20 – 2.00 (m, 4H). LCMS: 663.3 (M-TFA+H<sup>+</sup>).

**Step 5: Synthesis of 2-amino-4-((1S,4R,11S,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile 2,2,2-trifluoroacetate (1 : 0.54) and 2-amino-4-((1S,4R,11R,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile 2,2,2-trifluoroacetate (1 : 0.05)**



[00386] Compound 2-amino-4-((1S,4R,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile 2,2,2-trifluoroacetate (140 mg) was purified by Chiral HPLC (Column: CHIRALPAK IK, 2 cm x 25cm, 5 $\mu$ m, Mobile phase: A for MTBE (0.5% 2mM NH<sub>3</sub>-MeOH) and B for EtOH: DCM, Gradient: B 20%, Flow rate: 20 mL/min, Back pressure: 100 bar, Column temperature: 25 °C) to afford 2-amino-4-((1S,4R,11S,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile 2,2,2-trifluoroacetate (1 : 0.54) (38 mg, 27.1%) as a white solid and 2-amino-4-((1S,4R,11R,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile 2,2,2-trifluoroacetate (1 : 0.05) (50 mg, 35.7%) as a white solid.

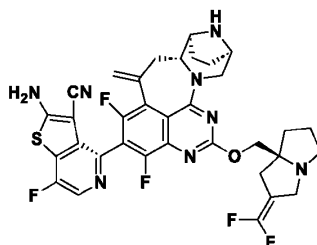
[00387] **P1**: 2-amino-4-((1S,4R,11S,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile 2,2,2-trifluoroacetate (1 : 0.54): Chiral purity: 98.08% ee; retention time: 1.521 min; Chiral SFC method: Column: CHIRALPAK IK-3, 4.6 x 50 mm, 3  $\mu$ m, Mobile phase: A for MTBE (0.1% DEA) and B for EtOH: DCM = 1 : 1, Gradient: B 20%, Flow rate: 1.0 mL/min,

Back pressure: 100 bar, Column temperature: 25 °C. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 8.32 (s, 1H), 5.73 (s, 1H), 5.56 – 5.31 (m, 3H), 4.51 – 4.30 (m, 2H), 4.18 – 4.06 (m, 1H), 3.92 – 3.82 (m, 1H), 3.80 – 3.69 (m, 1H), 3.61 – 3.43 (m, 3H), 3.29 – 3.16 (m, 2H), 2.99 – 2.76 (m, 1H), 2.61 – 1.81 (m, 11H). LCMS: 663.2 (M-0.54TFA+H<sup>+</sup>).

[00388] **P2**: 2-amino-4-((1S,4R,11R,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile 2,2,2-trifluoroacetate (1 : 0.05): Chiral purity: 98.88% ee; retention time: 1.521 min; Chiral SFC method: Column: CHIRALPAK IK-3, 4.6 x 50 mm, 3 μm, Mobile phase: A for MTBE (0.1% DEA) and B for EtOH: DCM = 1 : 1, Gradient: B 20%, Flow rate: 1.0 mL/min, Back pressure: 100 bar, Column temperature: 25 °C. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 8.31 (s, 1H), 5.71 (s, 1H), 5.57 (d, *J* = 3.6 Hz, 1H), 5.35 – 5.21 (m, 2H), 4.38 – 4.18 (m, 2H), 4.10 – 3.95 (m, 1H), 3.70 – 3.65 (m, 1H), 3.51 – 3.43 (m, 1H), 3.31 – 2.88 (m, 6H), 2.56 – 2.16 (m, 5H), 2.08 – 1.65 (m, 6H). LCMS: 663.2 (M-0.05TFA+H<sup>+</sup>).

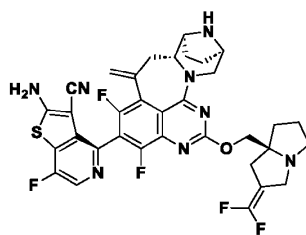
### Examples 21 & 22

**Example 21: 2-amino-4-((1S,4R,11S,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile**

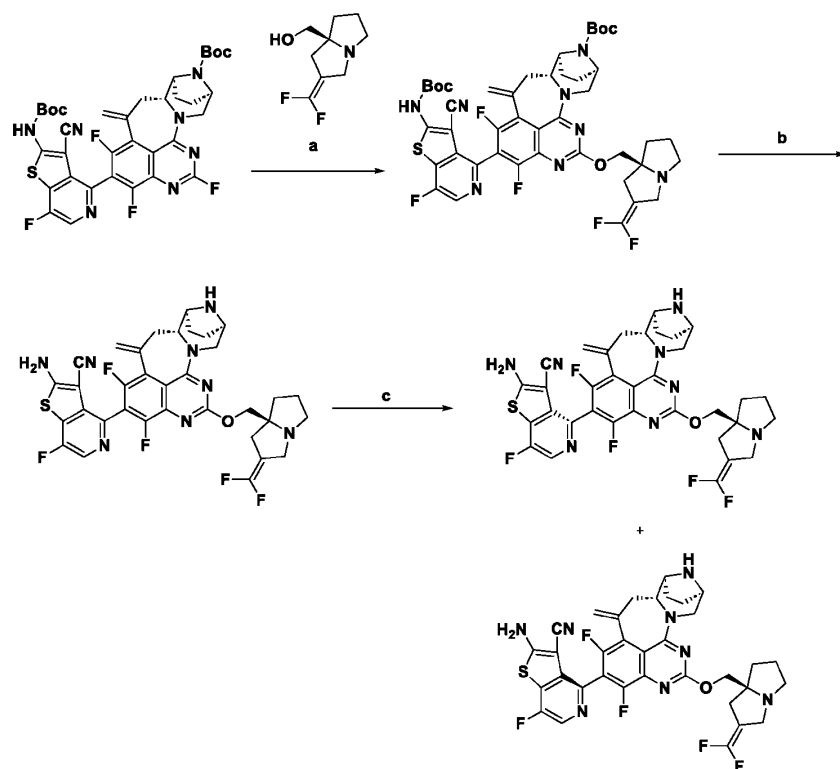


**Example 22: 2-amino-4-((1S,4R,11R,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14 a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile**

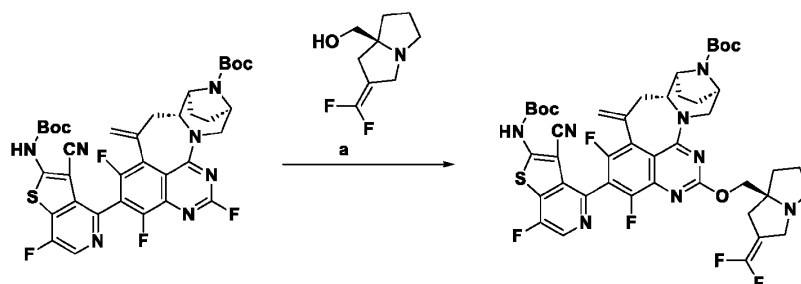




### Synthesis scheme

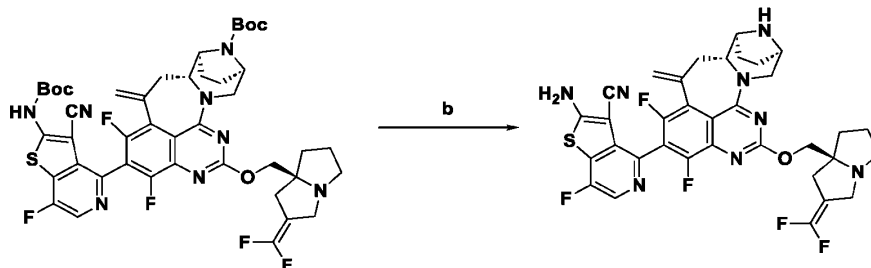


Step 1: Synthesis of tert-butyl (1S,4R,14aR)-11-(2-(((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate



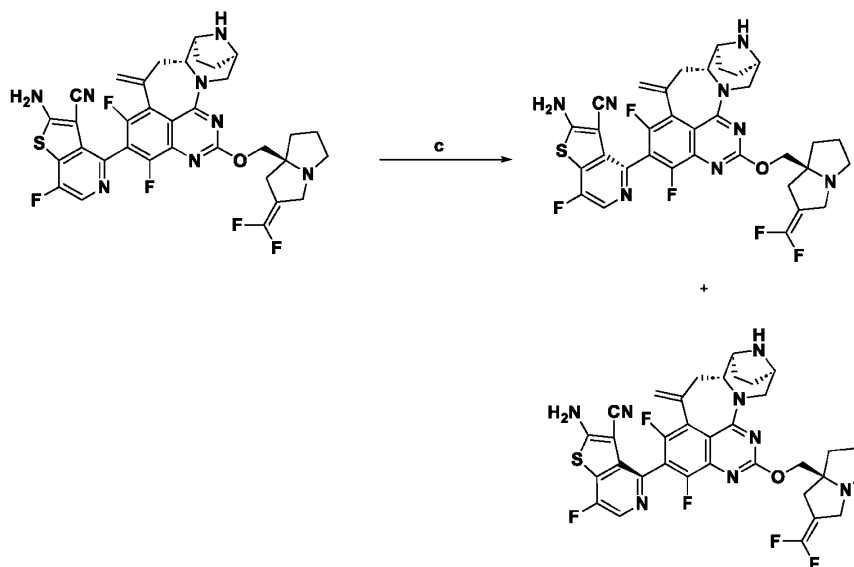
[00389] To a solution of (S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-ylmethanol (71 mg, 0.37 mmol, 1.5 eq) in THF (2 mL) was added NaH (60%, 30 mg, 0.75 mmol, 3.0 eq). The mixture was stirred at room temperature for 0.5 h. Compound tert-butyl (1S,4R,14aR)-11-(2-(((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (180 mg, 0.25 mmol, 1.0 eq) was added. The mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with water (5 mL). The aqueous layer was extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness. The crude product was purified by prep-TLC (Dichloromethane: Methanol = 15: 1) to give compound tert-butyl (1S,4R,14aR)-11-(2-(((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (100 mg, 45.0%) as a yellow solid. LCMS: 893.2 (M+H<sup>+</sup>).

**Step 2: Synthesis of 2-amino-4-((1S,4R,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile 2,2,2-trifluoroacetate (1: 1)**



[00390] To a solution of tert-butyl (1S,4R,14aR)-11-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (100 mg, 0.11 mmol, 1.0 eq) in DCM (3 mL) was added TFA (1.0 mL). The reaction was stirred at 25 °C for 2 h. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC (acetonitrile with 0.1% TFA in water, 15% to 50%) to give compound 2-amino-4-((1S,4R,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile 2,2,2-trifluoroacetate (1 : 1) (74 mg, 83.6%) as a yellow solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 8.35 (s, 1H), 5.91 – 5.33 (m, 3H), 4.80 – 4.66 (m, 2H), 4.56 – 4.41 (m, 1H), 4.32 – 4.08 (m, 4H), 3.87 – 3.74 (m, 1H), 3.49 – 3.35 (m, 2H), 3.12 – 2.85 (m, 3H), 2.74 – 1.92 (m, 10H). LCMS: 693.3 (M-TFA+H<sup>+</sup>).

**Step 3: Synthesis of 2-amino-4-((1S,4R,11S,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile 2,2,2-trifluoroacetate (1 : 0.36) and 2-amino-4-((1S,4R,11R,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile 2,2,2-trifluoroacetate (1 : 0.44)**



[00391] Compound 2-amino-4-((1S,4R,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile 2,2,2-trifluoroacetate (1 : 1) (74 mg) was separated by preparative Chiral HPLC (Column: CHIRALPAK IF, 2 cm x 25cm, 5 $\mu$ m, Mobile phase: A for MTBE (0.5% 2mM NH<sub>3</sub>-MeOH) and B for MeOH : DCM, Gradient: B 20%, Flow rate: 20 mL/min, Column temperature: 25 °C) to afford 2-amino-4-((1S,4R,11S,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile 2,2,2-trifluoroacetate (1 : 0.36) (13.6 mg, 18.4%) as a white solid and 2-amino-4-((1S,4R,11R,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile 2,2,2-trifluoroacetate (1 : 0.44) (14.2 mg, 19.2%) as a white solid.

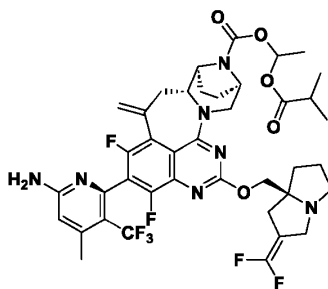
[00392] **P1**: 2-amino-4-((1S,4R,11S,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile 2,2,2-trifluoroacetate (1 : 0.36): Chiral purity: 97% de; retention time: 7.777 min; UPCC method: Column: CHIRALPAK OD-3 4.6mm\*250mm, 3 $\mu$ m, Mobile phase: A CO<sub>2</sub>; B

0.1%DEA IN MeOH, Flow rate: 2.0 mL/min, 210nm, Column temperature: 35 °C. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 8.32 (s, 1H), 5.75 (s, 1H), 5.56 (d, *J* = 3.9 Hz, 1H), 5.37 (dd, *J* = 13.8, 2.7 Hz, 1H), 4.46 – 4.31 (m, 2H), 4.20 – 4.09 (m, 1H), 4.08 – 3.99 (m, 1H), 3.98 – 3.80 (m, 2H), 3.60 – 3.50 (m, 1H), 3.31 – 3.21 (m, 2H), 2.98 – 2.80 (m, 3H), 2.60 – 2.42 (m, 3H), 2.21 – 1.89 (m, 7H). LCMS: 693.4 (M-0.36TFA+H<sup>+</sup>).

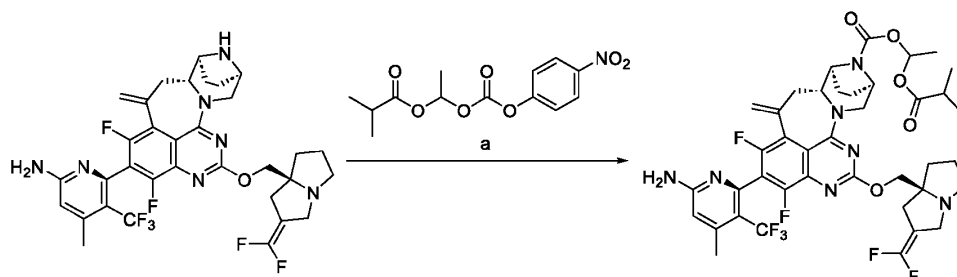
[00393] **P2**: 2-amino-4-((1S,4R,11R,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile 2,2,2-trifluoroacetate (1 : 0.44) : Chiral purity: 97.8% de; retention time: 11.217 min; UPCC method: Column: CHIRALPAK OD-3 4.6mm\*250mm, 3μm, Mobile phase: A CO<sub>2</sub>; B 0.1%DEA IN MeOH, Flow rate: 2.0 mL/min, 210nm, Column temperature: 35 °C. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 8.32 (s, 1H), 5.76 (s, 1H), 5.63 (d, *J* = 3.6 Hz, 1H), 5.32 (dd, *J* = 14.0, 3.2 Hz, 1H), 4.42 – 4.29 (m, 2H), 4.20 – 4.09 (m, 1H), 4.00 – 3.82 (m, 3H), 3.59 – 3.48 (m, 1H), 3.31 – 3.16 (m, 2H), 2.99 – 2.68 (m, 3H), 2.65 – 2.39 (m, 3H), 2.21 – 1.89 (m, 7H). LCMS: 693.4 (M-0.44TFA+H<sup>+</sup>).

### Example 23

**1-(Isobutyryloxy)ethyl (1S,4R,11S,14aR)-11-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8-(((S)-2-(difluoromethylene) tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino [1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



Synthetic scheme



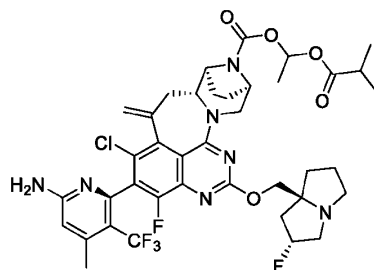
**Step 1: Synthesis of 1-(isobutyryloxy)ethyl (1S, 4R, 11S, 14aR)-11-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10, 12-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1, 4-epiminoazepino[1', 2': 1, 7]azepino[2, 3, 4-de]quinazoline-15-carboxylate**

[00394] To a solution of 6-((1S,4R,11S,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (27 mg, 0.04 mmol, 1.0 eq) in DCM (3 mL) was added DIEA (16 mg, 0.12 mmol, 3.0 eq) and 1-(((4-nitrophenoxy)carbonyl)oxy)ethyl isobutyrate (15 mg, 0.05 mmol, 1.3 eq) under nitrogen atmosphere. The reaction was stirred at room temperature for 2 days. The mixture was concentrated under reduced pressure to give a crude product, which was purified by prep-TLC (DCM: MeOH = 10: 1) to give an impure crude, which was further purified by prep-HPLC (acetonitrile in water) to give 1-(isobutyryloxy)ethyl (1S, 4R, 11S, 14aR)-11-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10, 12-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1, 4-epiminoazepino[1', 2': 1, 7]azepino[2, 3, 4-de]quinazoline-15-carboxylate (10 mg, purity: 95.4%, yield: 30.0%) as a white solid. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>CN): δ 6.85-6.75 (m, 1H), 6.56 (s, 1H), 5.69 (brs, 1H), 5.52-5.45 (m, 3H), 5.15 – 5.05 (m, 1H), 4.44 – 4.36 (m, 1H), 4.22 – 4.16 (m, 3H), 3.98 – 3.85 (m, 1H), 3.75 – 3.62 (m, 1H), 3.38 – 3.29 (m, 1H), 3.15-3.00 (m, 2H), 2.95-2.80 (m, 1H), 2.72-2.50 (m, 4H), 2.48-2.30 (m, 5H), 2.05-1.99 (m, 2H), 1.89-1.75 (m, 5H), 1.49 (d, *J* = 5.4 Hz, 3H), 1.12 (d, *J* = 6.9 Hz, 6H); LCMS: 834.2 (M+H<sup>+</sup>).

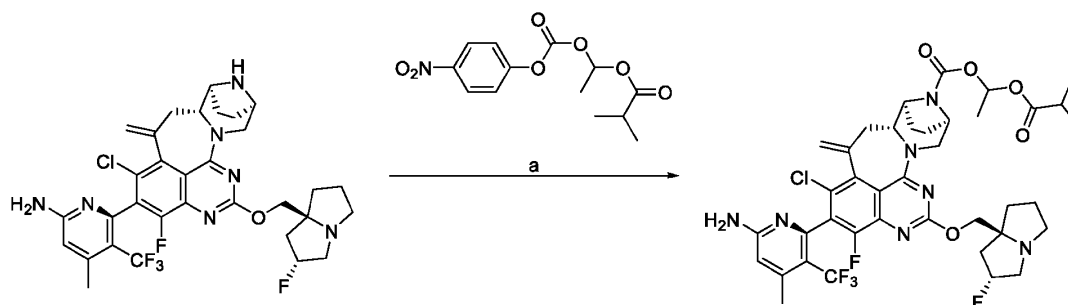
**Example 24**

**1-(Isobutyryloxy) ethyl (1S, 4R, 11R, 14aR)-11-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-10-fluoro-8- (((2R, 7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-**

yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-15-carboxylate



### Synthetic scheme



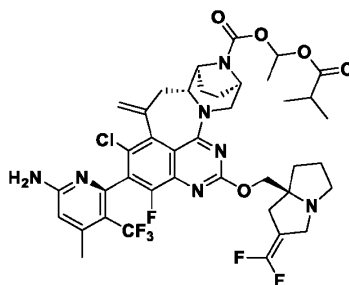
**Step 1: Synthesis of 1-(isobutyryloxy) ethyl (1S, 4R, 11R, 14aR)-11-(6-amino-4-methyl-3-(trifluoromethyl) pyridin-2-yl)-12-chloro-10-fluoro-8-(((2R, 7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-15-carboxylate**

[00395] To a solution of 6-((1S, 4R, 11R, 14aR)-12-chloro-10-fluoro-8-(((2R, 7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazolin-11-yl)-4-methyl-5-(trifluoromethyl) pyridin-2-amine (450.0 mg, 0.68 mmol, 1.0 eq) in DCM (5 mL) was added DIEA (263.6 mg, 2.04 mmol, 3.0 eq) and 1-(((4-nitrophenoxy) carbonyl) oxy) ethyl isobutyrate (243.6 mg, 0.82 mmol, 1.2 eq). Then the reaction was stirred at room temperature for 36 h under N<sub>2</sub>. HPLC and TLC showed the reaction was completed. The reaction mixture was diluted with water (15 mL) and extracted with DCM (15 mL x 3). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and was concentrated to afford the crude product, which was purified by silica gel column chromatography (DCM / MeOH = 30:1) to afford 1-(isobutyryloxy) ethyl (1S, 4R, 11R, 14aR)-11-(6-amino-4-methyl-3-(trifluoromethyl) pyridin-2-yl)-12-chloro-10-fluoro-8-(((2R, 7aS)-2-

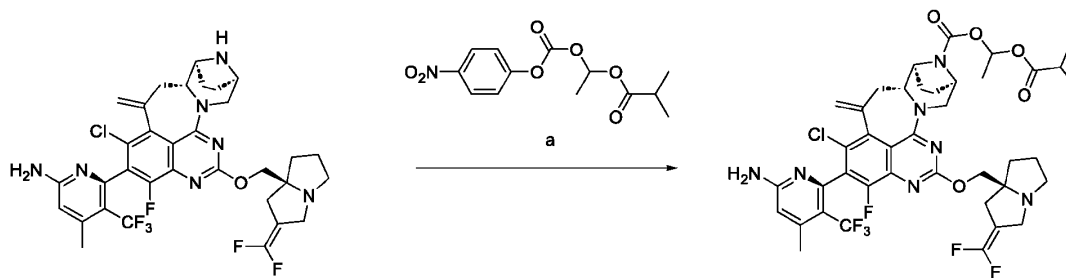
fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-15-carboxylate (375.6 mg, 67.6%) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 6.86 (brs, 2H), 6.78 – 6.61 (m, 1H), 6.48 (s, 1H), 5.90 – 5.70 (m, 1H), 5.48 – 5.00 (m, 3H), 4.47 – 4.30 (m, 1H), 4.28 – 3.81 (m, 4H), 3.25 – 2.97 (m, 4H), 2.90 – 2.77 (m, 1H), 2.63 – 2.53 (m, 1H), 2.44 – 2.28 (m, 4H), 2.22 – 1.95 (m, 4H), 1.94 – 1.60 (m, 6H), 1.47 (s, 3H), 1.30 – 1.00 (m, 7H); LCMS: *m/z* 820.2 (M+H<sup>+</sup>).

### Example 25

1-(Isobutyryloxy)ethyl (1*S*,4*R*,11*R*,14*aR*)-11-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-(((*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-15-carboxylate



### Synthetic scheme



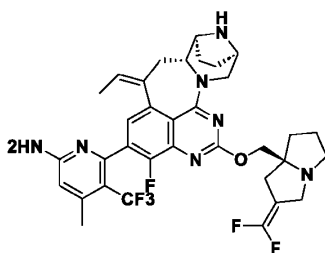
Step 1: 1-(isobutyryloxy)ethyl (1*S*,4*R*,11*R*,14*aR*)-11-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-(((*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-15-carboxylate



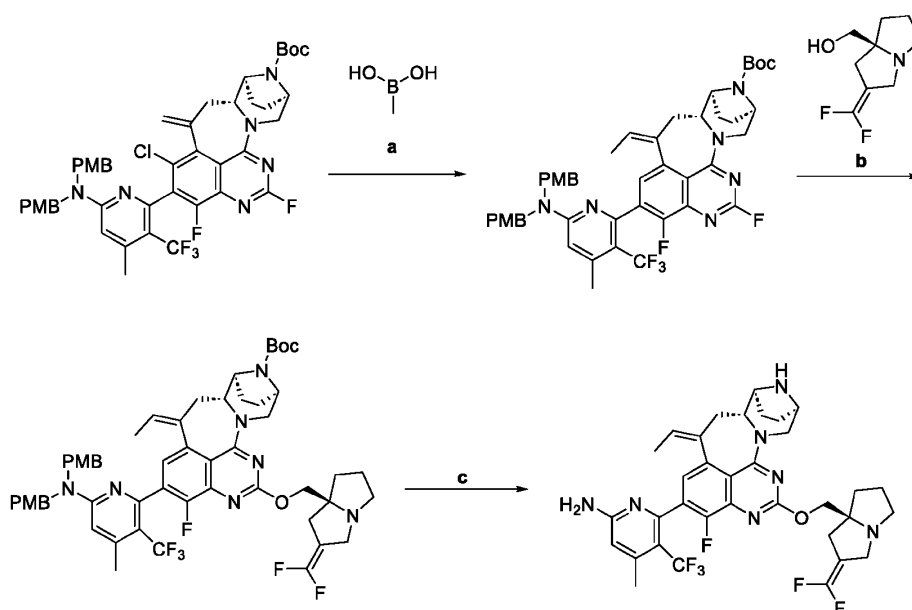
[00396] To a solution of 6-((1S,4R,11R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (500.0 mg, 0.72 mmol, 1.0 eq) in DCM (5.0 mL) was added 1-(((4-nitrophenoxy)carbonyl)oxy)ethyl isobutyrate (256.0 mg, 0.86 mmol, 1.2 eq), DIEA (280.0 mg, 2.16 mmol, 3.0 eq). Then the reaction was stirred at room temperature for 2 h under N<sub>2</sub>. HPLC and TLC showed the reaction was completed. The mixture was added water (10 mL) and extracted with EtOAc (10 mL x 3). The organic layers were washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give crude product, the residue was purified by column chromatography on silica gel eluted with (DCM: MeOH = 20: 1) to afford 1-(isobutyryloxy)ethyl (1S,4R,11R,14aR)-11-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (390 mg, yield: 63.6 %) as a white solid. LCMS: m/z 850.2 (M+H<sup>+</sup>). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 6.87 (s, 2H), 6.75-6.70 (m, 1H), 6.48 (s, 1H), 5.82 (s, 1H), 5.38 (s, 1H), 5.20-5.00 (m, 1H), 4.40-4.30 (m, 1H), 4.19 - 4.00 (m, 3H), 3.92 - 3.82 (m, 1H), 3.70-3.55 (m, 1H), 3.25-2.90 (m, 4H), 2.66-2.49 (m, 3H), 2.45-2.30 (m, 5H), 2.10-2.00 (m, 1H), 1.96-1.85 (m, 1H), 1.85 - 1.61 (m, 6H), 1.47 (d, *J* = 3.9 Hz, 3H), 1.23 (s, 1H), 1.06 (d, *J* = 4.5 Hz, 6H).

#### Example 26

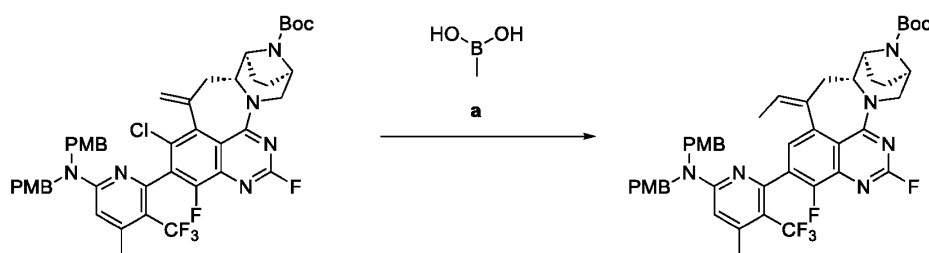
**6-((1S,4R,14aR,Z)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-ethylidene-10-fluoro-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine formate (1: 0.46)**



**Synthetic scheme**



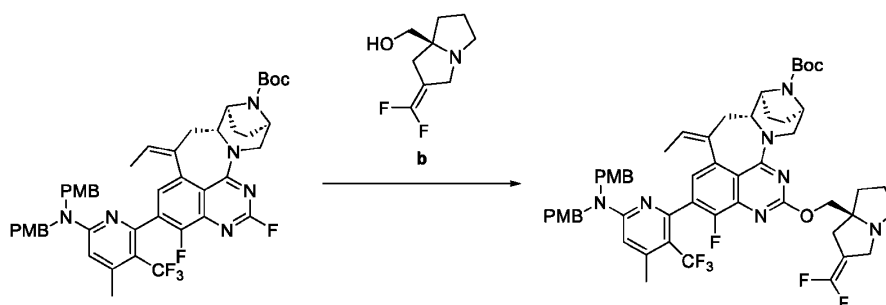
**Step 1: Synthesis of tert-butyl (1S,4R,14aR,Z)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-13-ethylidene-8,10-difluoro-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00397] To a solution of tert-butyl (1S,4R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (170 mg, 0.2 mmol, 1.0 eq) in dioxane/H<sub>2</sub>O (2.1 mL/0.7 mL) was added methylboronic acid (18 mg, 0.3 mmol, 1.5 eq), S-Phos Pd G3 (23.4 mg, 0.03 mmol, 0.15 eq) and K<sub>2</sub>CO<sub>3</sub> (82.9 mg, 0.6 mmol, 3.0 eq) at room temperature under N<sub>2</sub>. The mixture was irradiated in the microwave at 120 °C for 3 h. HPLC and TLC showed the reaction was completed. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (10 mL x 3). The organic phase was washed with water (10 mL) and brine (10 mL). The organic layer was

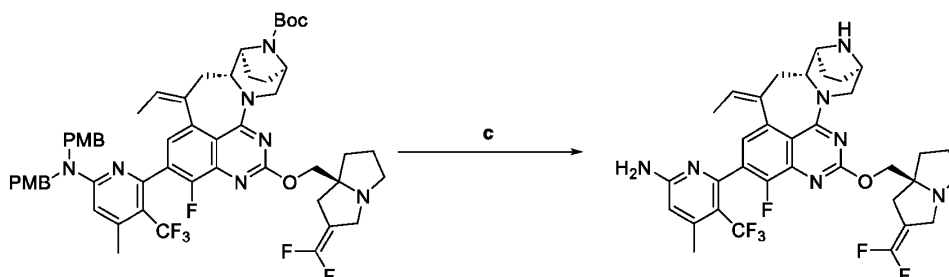
dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to give a crude product. The residue was purified by Prep-TLC (petroleum ether: EtOAc = 3: 1) to afford tert-butyl (1S,4R,14aR,Z)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-13-ethylidene-8,10-difluoro-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (40 mg, HPLC~50%, 12.0%) as a yellow solid. LCMS: 843.4 (M+H<sup>+</sup>).

**Step 2: Synthesis of tert-butyl (1S,4R,14aR,Z)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-ethylidene-10-fluoro-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00398] To a solution of (S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (6.8 mg, 0.036 mmol, 1.5 eq) in THF (0.5 mL) was added NaH (60%) (2.9 mg, 0.072 mmol, 3.0 eq) at 0 °C and the mixture was stirred for 0.5 h at room temperature under N<sub>2</sub>. The solution of tert-butyl (1S,4R,14aR,Z)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-13-ethylidene-8,10-difluoro-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (40 mg, HPLC~50%, 0.024 mmol, 1.0 eq) in THF (0.5 mL) was added to the mixture and the reaction mixture was stirred at 25 °C for 1.5 h. HPLC and TLC showed the reaction was completed. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl solution (5 mL) and extracted with EtOAc (5 mL x 3). The organic layer was concentrated to give a crude product. The residue was purified by Prep-TLC (DCM: MeOH = 10: 1) to afford tert-butyl (1S,4R,14aR,Z)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-ethylidene-10-fluoro-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (15 mg, HPLC~70%, 43.8%) as a yellow solid. LCMS: 1012.4 (M+H<sup>+</sup>).

**Step 3: Synthesis of 6-((1S,4R,14aR,Z)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-ethylidene-10-fluoro-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine formate (1: 0.46)**

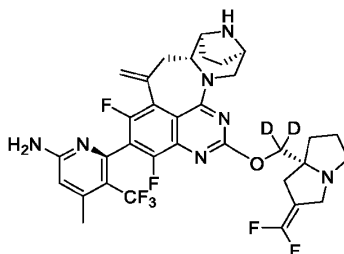


[00399] A mixture of tert-butyl (1S,4R,14aR,Z)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-ethylidene-10-fluoro-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (15 mg, 0.015 mmol, 1.0 eq) in TFA (1 mL) was stirred at 50 °C for 2 h under N<sub>2</sub>. The mixture was concentrated to give a crude. Then the crude was added saturated sodium bicarbonate aqueous solution (15 mL) to adjusted PH = (7 ~ 8) and extracted with DCM: MeOH = 10: 1 (10 mL x 3). The combined organic layers were washed with brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give crude product. The crude was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 5% to 40%) to give 6-((1S,4R,14aR,Z)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-ethylidene-10-fluoro-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine formate (1: 0.46) (1.5 mg, 14.7%) as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN): δ 7.00 – 6.87 (m, 1H), 6.51 (s, 1H), 5.91 – 5.78 (m, 1H), 5.39 (brs, 2H), 5.31 – 5.11 (m, 1H), 4.20 – 4.13 (m, 2H), 3.87 – 3.84 (m, 1H), 3.71 (d, *J* = 16.0 Hz, 1H), 3.56 (s, 1H), 3.37 – 3.34 (m, 2H), 3.09 – 2.96 (m, 2H), 2.72 – 2.61 (m, 3H), 2.43 – 2.33 (m, 5H), 2.12 – 2.05 (m, 5H), 1.80 – 1.73 (m, 4H), 1.67 – 1.56 (m, 3H). LCMS: *m/z* 671.9 (M-0.46FA+H<sup>+</sup>).

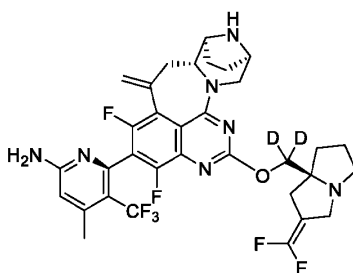
#### Examples 27, 28, 29 & 30

**Example 27: 6-((1S,4R,11S,14aR)-8-(((R)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy-d<sub>2</sub>)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-**

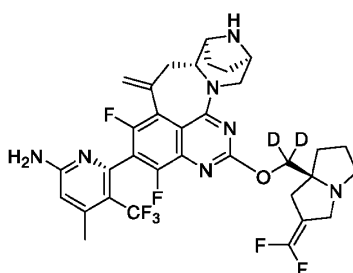
epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine



Example 28: 6-((1S,4R,11S,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy-d<sub>2</sub>)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine

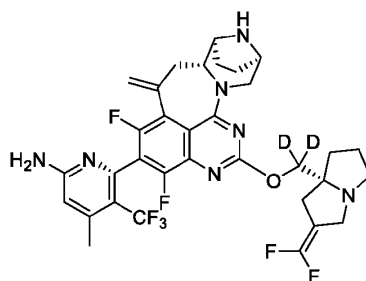


Example 29: 6-((1S,4R,11R,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy-d<sub>2</sub>)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine

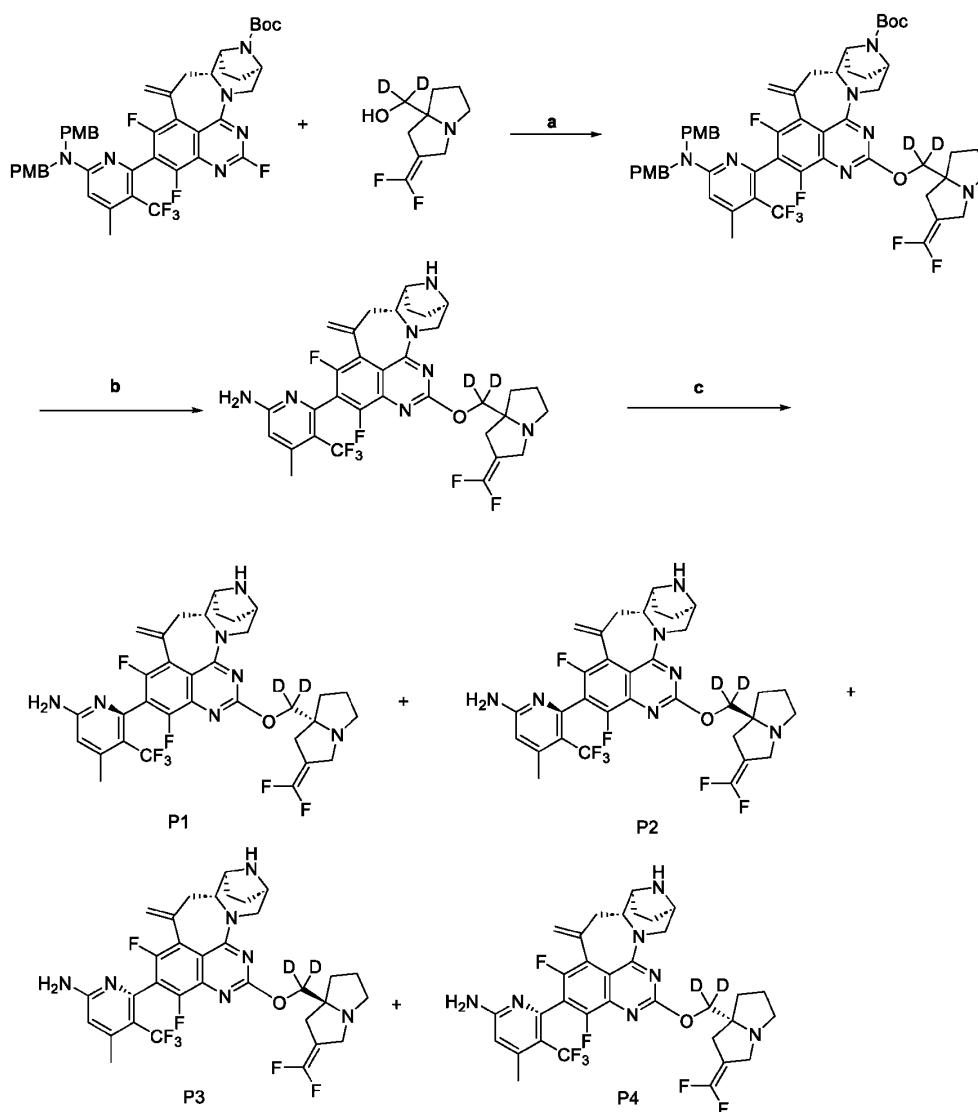


Example 30: 6-((1S,4R,11R,14aR)-8-(((R)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy-d<sub>2</sub>)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-

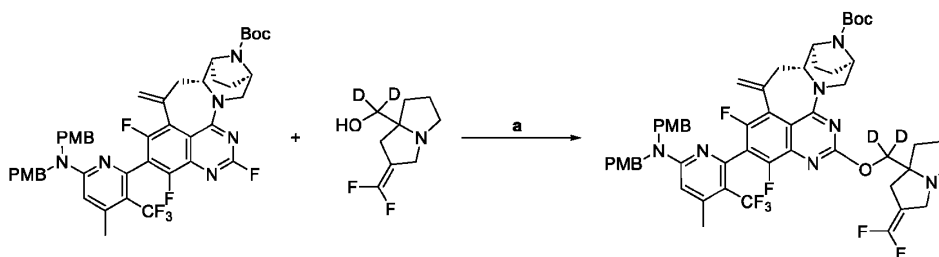
**epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine**



**Synthetic scheme**

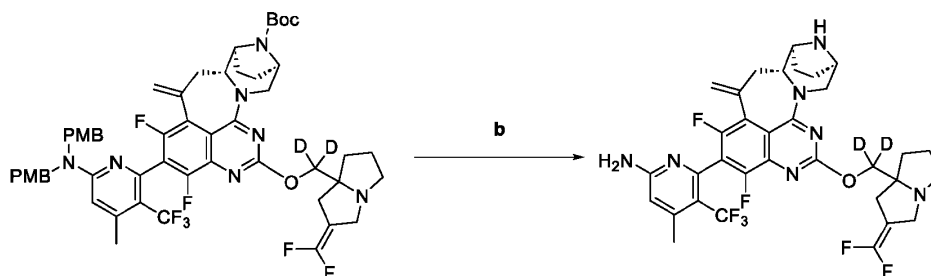


**Step 1: Synthesis of tert-butyl (1S,4R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8-((2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy-d<sub>2</sub>)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00400] To a solution of (2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy-d<sub>2</sub>-ol (51 mg, 0.27 mmol, 1.5 eq) in THF (2 mL) was added NaH (60%) (42 mg, 1.06 mmol, 6.0 eq) at 0 °C. The reaction mixture was stirred at 27 °C for 2 h under N<sub>2</sub>. To the reaction mixture was added tert-butyl (1S,4R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (150 mg, 0.18 mmol, 1.0 eq) in THF (2 mL). The reaction was stirred at 32 °C for 15 h. The reaction was quenched with H<sub>2</sub>O (2 mL) at 0 °C. The resulting mixture was extracted with EtOAc (5 mL x 2). The combined organic layers were washed with brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude. The crude was purified by silica gel column chromatography (Petroleum ether: EtOAc = 1: 1) to give tert-butyl (1S,4R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8-((2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy-d<sub>2</sub>)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (120 mg, 66.6%) as a yellow solid. LCMS: m/z 509.9 (M/2+H<sup>+</sup>).

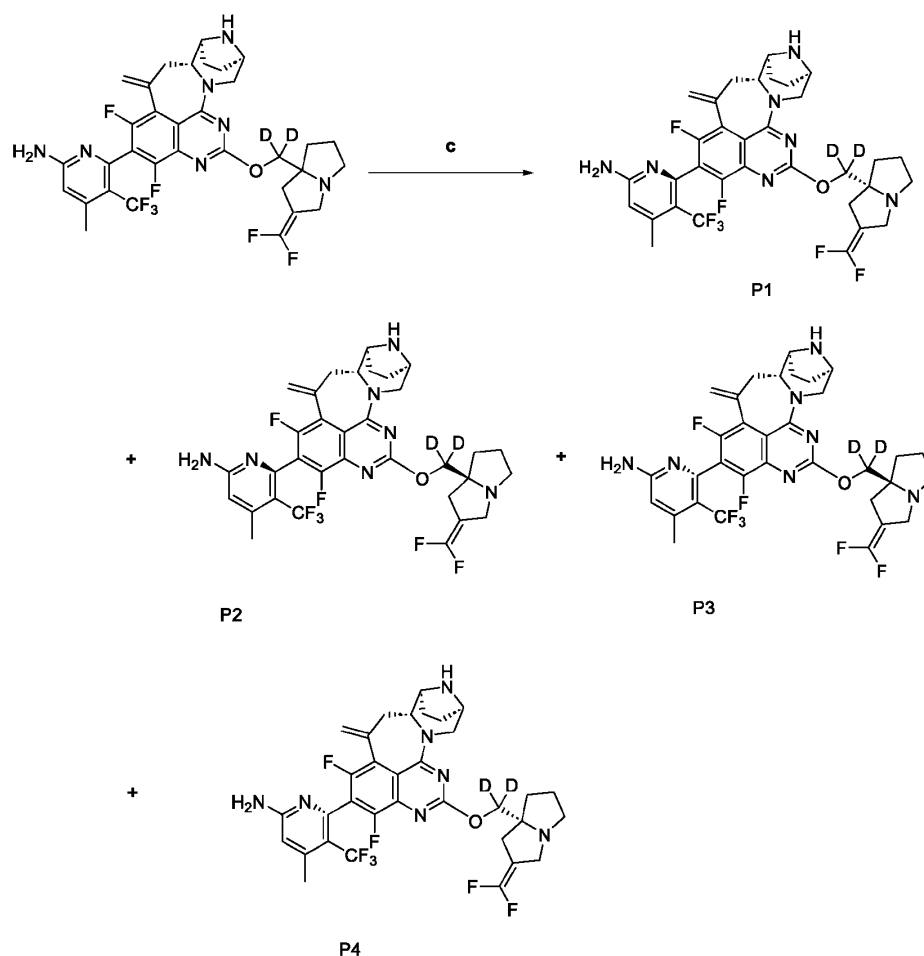
**Step 2: Synthesis of 6-((1S,4R,14aR)-8-((2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy-d<sub>2</sub>)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine**





[00401] A solution of tert-butyl (1S,4R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8-((2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy-d<sub>2</sub>)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (120 mg, 0.12 mmol, 1.0 eq) in TFA (2 mL) was stirred at 50 °C for 2 h under N<sub>2</sub>. The reaction was concentrated at 35 °C to give a residue. The residue was dissolved in MeOH (4 mL) and filtered off. The filtrate was concentrated to give a crude. The crude was triturated with MTBE/EtOAc (20/1, 5 mL) and filtered to afford a solid. The solid was adjusted pH ~ 8 with sat. NaHCO<sub>3</sub> aqueous solution (10 mL) and extracted with EtOAc (10 mL x 2). The combined organic layers were washed with sat. NaHCO<sub>3</sub> aqueous solution (10 mL), brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give 6-((1S,4R,14aR)-8-((2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy-d<sub>2</sub>)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (45 mg, 56.3%) as a yellow solid. LCMS: m/z 678.6 (M+H<sup>+</sup>).

**Step 3: Chiral separation to prepare 6-((1S,4R,11S,14aR)-8-(((R)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy-d<sub>2</sub>)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine, 6-((1S,4R,11S,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy-d<sub>2</sub>)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine, 6-((1S,4R,11R,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy-d<sub>2</sub>)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine and 6-((1S,4R,11R,14aR)-8-(((R)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy-d<sub>2</sub>)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine**



[00402] Compound 6-((1S,4R,14aR)-8-((2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy-d<sub>2</sub>)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (45 mg) was separated by preparative Chiral HPLC (Column: CHIRAL ART Cellulose-SC, 2 cm x 25cm, 5 $\mu$ m, Mobile phase: A for Hex (0.5% 2mM NH<sub>3</sub>-MeOH) and B for EtOH, Flow rate: 20 mL/min, Column temperature: 25 °C, UV 220 nm) to afford part A (P1+P2) and part B (P3+P4).

[00403] Part A (P1+P2) was further separated by preparative Chiral HPLC (Column: CHIRAL ART Cellulose-SC, 2 cm x 25cm, 5 $\mu$ m, Mobile phase: A for Hex (0.5% 2mM NH<sub>3</sub>-MeOH) and B for EtOH, Flow rate: 20 mL/min, Column temperature: 25 °C, UV 220 nm) to afford 6-((1S,4R,11S,14aR)-8-(((R)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-

yl)methoxy-d<sub>2</sub>)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (P1: 1.9 mg, 4.2%) and 6-((1S,4R,11S,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy-d<sub>2</sub>)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (P2: 2.1 mg, 4.6%).

[00404] Part B (P3+P4) was further separated by preparative Chiral HPLC (Column: CHIRALPAK IE, 2 cm x 25cm, 5µm, Mobile phase: A for Hex (0.5% 2mM NH<sub>3</sub>-MeOH) and B for MeOH:DCM (1:1), Flow rate: 20 mL/min, Column temperature: 25 °C, UV 220 nm) to afford 6-((1S,4R,11R,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy-d<sub>2</sub>)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (P3: 2.1 mg, 4.6%) and 6-((1S,4R,11R,14aR)-8-(((R)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy-d<sub>2</sub>)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (P4: 2.0 mg, 4.4%).

[00405] **Peak 1:** 6-((1S,4R,11S,14aR)-8-(((R)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy-d<sub>2</sub>)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine: Chiral purity: 99.09% ee; retention time: 4.604 min; Chiral HPLC method: Column: CHIRALPAK IE-3, 4.6\*50 mm, 3 µm, Mobile phase: Hex(0.1%DEA):(MeOH:DCM=1:1)=70:30, Flow rate: 1.0 mL/min, Column temperature: 25 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 6.46 (s, 1H), 5.65 (s, 1H), 5.58 (s, 1H), 5.25 – 5.16 (m, 1H), 4.79 – 4.71 (m, 2H), 4.08 – 4.02 (m, 1H), 3.87 – 3.62 (m, 3H), 3.52 – 3.21 (m, 3H), 2.88 – 2.79 (m, 2H), 2.74 – 2.62 (m, 1H), 2.52 – 2.35 (m, 6H), 2.18 – 1.96 (m, 5H), 2.86 – 1.71 (m, 3H). LCMS: m/z 678.2 (M+H<sup>+</sup>).

[00406] **Peak 2:** 6-((1S,4R,11S,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy-d<sub>2</sub>)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine: Chiral purity: 98.24% ee; retention time: 5.243 min; Chiral HPLC method: Column: CHIRALPAK IE-3, 4.6\*50 mm, 3 µm, Mobile phase:

Hex(0.1%DEA):(MeOH:DCM=1:1)=70:30, Flow rate: 1.0 mL/min, Column temperature: 25 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 6.46 (s, 1H), 5.63–5.42 (m, 2H), 5.21–5.08 (m, 1H), 4.82–4.65 (m, 2H), 4.06–3.94 (m, 1H), 3.75–3.52 (m, 3H), 3.37–3.11 (m, 3H), 2.83–2.61 (m, 3H), 2.26–2.12 (m, 6H), 2.25–2.12 (m, 2H), 1.94–1.75 (m, 6H). LCMS: m/z 678.2 (M+H<sup>+</sup>).

[00407] **Peak 3:** 6-((1S,4R,11R,14aR)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy-d<sub>2</sub>)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine: Chiral purity: 98.24% ee; retention time: 2.877 min; Chiral HPLC method: Column: CHIRALPAK IE-3, 4.6\*50 mm, 3 μm, Mobile phase:

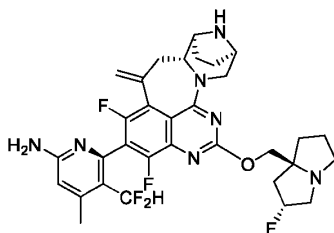
HEX(0.1%DEA):EtOH=70:30, Flow rate: 1.0 mL/min, Column temperature: 25 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 6.46 (s, 1H), 5.68–5.47 (m, 2H), 5.36–5.19 (m, 1H), 4.86–4.59 (m, 2H), 4.21–4.05 (m, 1H), 3.85–3.62 (m, 3H), 3.41–3.15 (m, 3H), 2.84–2.61 (m, 3H), 2.22–2.13 (m, 6H), 2.25–2.12 (m, 1H), 1.95–1.66 (m, 7H). LCMS: m/z 678.3 (M+H<sup>+</sup>).

[00408] **Peak 4:** 6-((1S,4R,11R,14aR)-8-(((R)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy-d<sub>2</sub>)-10,12-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine: Chiral purity: 98.24% ee; retention time: 2.989 min; Chiral HPLC method: Column: CHIRALPAK IE-3, 4.6\*50 mm, 3 μm, Mobile phase:

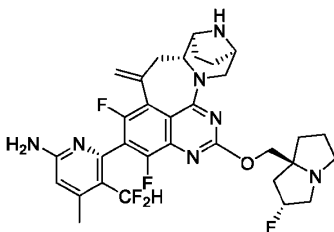
HEX(0.1%DEA):EtOH=70:30, Flow rate: 1.0 mL/min, Column temperature: 25 °C. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 6.59 (s, 1H), 5.75–5.62 (m, 1H), 5.51–5.39 (m, 1H), 5.23–5.19 (m, 1H), 4.08–3.96 (m, 1H), 3.87–3.76 (m, 1H), 3.74–3.67 (m, 1H), 3.57–3.49 (m, 1H), 3.47–3.38 (m, 1H), 3.21–3.09 (m, 2H), 2.92–2.65 (m, 3H), 2.56–2.41 (m, 5H), 2.33–2.21 (m, 1H), 2.18–2.07 (m, 1H), 2.02–1.71 (m, 6H). LCMS: m/z 678.4 (M+H<sup>+</sup>).

### Examples 31 & 32

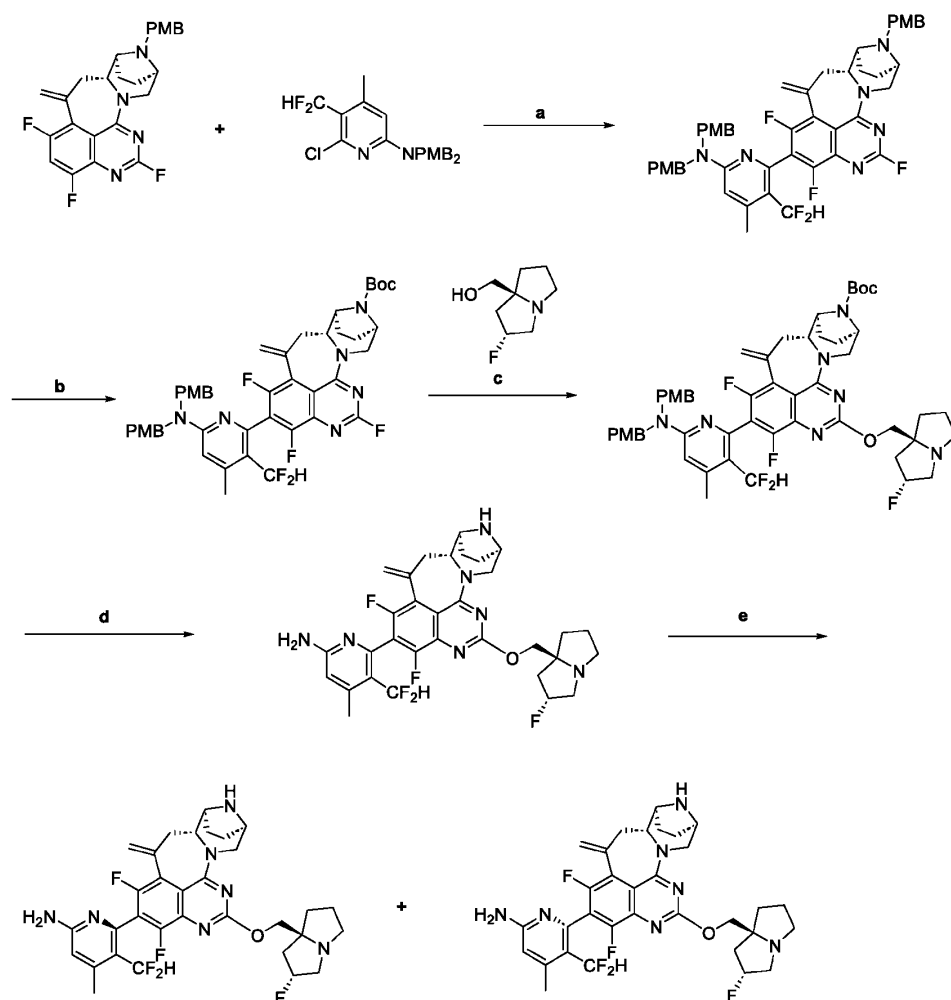
**Example 31:** 6-((1S,4R,11S,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino [2,3,4-de]quinazolin-11-yl)-5-(difluoromethyl)-4-methylpyridin-2-amine



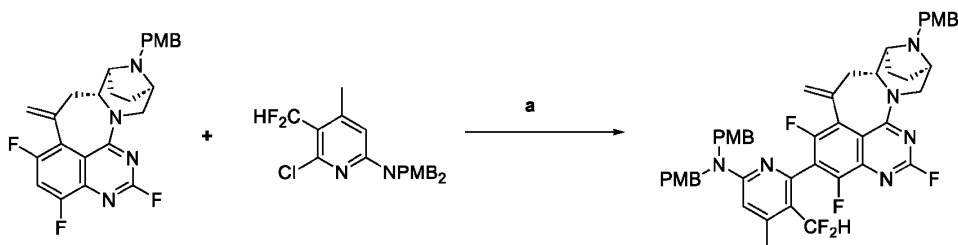
**Example 32: 6-((1S,4R,11R,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino [2,3,4-de]quinazolin-11-yl)-5-(difluoromethyl)-4-methylpyridin-2-amine**



**Synthetic scheme**

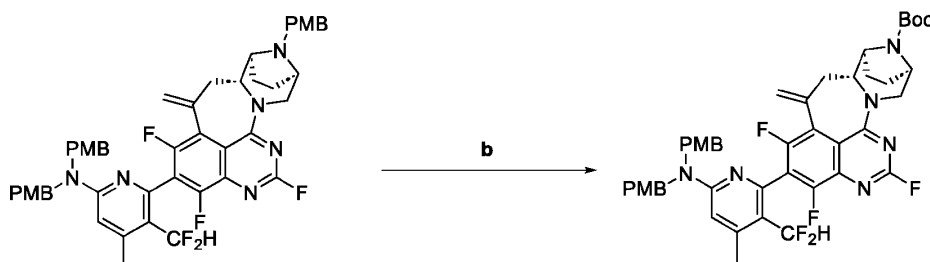


**Step 1: Synthesis of 5-(difluoromethyl)-N,N-bis(4-methoxybenzyl)-4-methyl-6-((1S,4R,14aR)-8,10,12-trifluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)pyridin-2-amine**



[00409] To a solution of (1S,4R,14aR)-8,10,12-trifluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline (180 mg, 0.4 mmol, 1.0 eq) in THF (2.0 mL) was added 0.4 M (TMP)<sub>2</sub>Zn·MgCl<sub>2</sub>·LiCl in THF (6.0 mL, 2.4 mmol, 6.0 eq) dropwise with double-ended syringe. The reaction mixture was stirred at 50 °C for 2 h under N<sub>2</sub> atmosphere. To the reaction mixture was added a solution of 6-chloro-5-(difluoromethyl)-N,N-bis(4-methoxybenzyl)-4-methylpyridin-2-amine (172 mg, 0.4 mmol, 1.0 eq) and CPhos Pd G3 (32 mg, 0.04 mmol, 0.1 eq) in dioxane (4.0 mL). The reaction mixture was stirred at 100 °C for 2 h. The reaction was quenched with H<sub>2</sub>O (40 mL). The mixture was filtered off, washed with EtOAc (200 mL) and separated. The aqueous layer was extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude. The crude was purified by silica gel column chromatography (Petroleum ether: EtOAc = 1: 1) to give 5-(difluoromethyl)-N,N-bis(4-methoxybenzyl)-4-methyl-6-((1S,4R,14aR)-8,10,12-trifluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)pyridin-2-amine (166 mg, 49.2%) as a brown solid. LCMS: m/z 849.3 (M+H<sup>+</sup>).

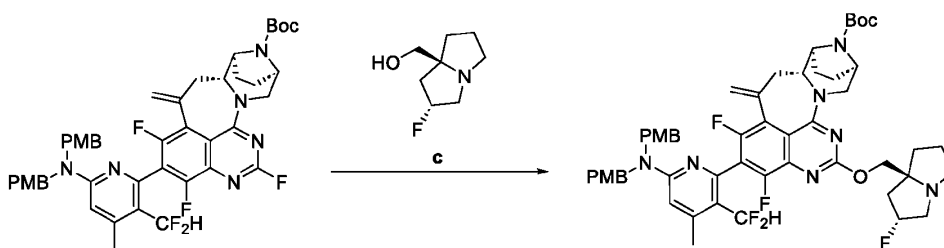
**Step 2: Synthesis of tert-butyl (1S,4R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-3-(difluoromethyl)-4-methylpyridin-2-yl)-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00410] A solution of 5-(difluoromethyl)-N,N-bis(4-methoxybenzyl)-4-methyl-6-((1S,4R,14aR)-8,10,12-trifluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)pyridin-2-amine (300 mg, 0.35 mmol, 1.0 eq), Boc<sub>2</sub>O (116 mg, 0.53 mmol, 1.5 eq) and Pd/BaSO<sub>4</sub> (150 mg, 50% w/w) in THF (6.0 mL) was stirred at 65 °C for 20 h. The mixture was filtered through a Celite pad, the filtrate was concentrated to give a residue. The residue was purified by silica gel column

chromatography (Petroleum ether: EtOAc = 1: 1) to give tert-butyl (1S,4R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-3-(difluoromethyl)-4-methylpyridin-2-yl)-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (163 mg, 55.6%) as a yellow solid. LCMS:  $m/z$  829.3 ( $M+H^+$ ).

**Step 3: Synthesis of tert-butyl (1S,4R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-3-(difluoromethyl)-4-methylpyridin-2-yl)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**

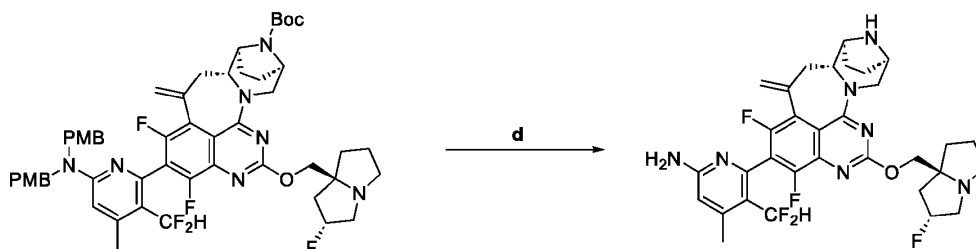


[00411] To a solution of compound (2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (29 mg, 0.18 mmol, 1.5 eq) in THF (6 mL) was added NaH (60%, 14 mg, 0.36 mmol, 3.0 eq). The mixture was stirred at room temperature for 0.5 h. Compound tert-butyl (1S,4R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-3-(difluoromethyl)-4-methylpyridin-2-yl)-8,10,12-trifluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (100 mg, 0.12 mmol, 1.0 eq) was added. The mixture was stirred at 30 °C for 1 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 H<sub>2</sub>O (20 mL), brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness. The crude product was purified by silica gel column chromatography (Dichloromethane: Methanol = 40: 1) to give tert-butyl (1S,4R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-3-(difluoromethyl)-4-methylpyridin-2-yl)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (79 mg, 67.6%) as a yellow solid. LCMS:  $m/z$  485.1 ( $M/2+H^+$ ).

**Step 4: Synthesis of 6-((1S,4R,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-**

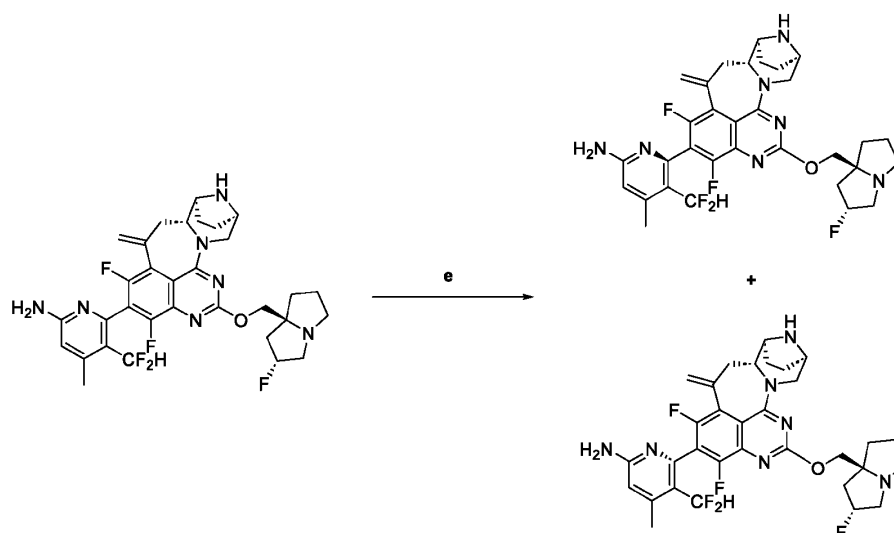


epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-(difluoromethyl)-4-methylpyridin-2-amine



[00412] A solution of tert-butyl (1S,4R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-3-(difluoromethyl)-4-methylpyridin-2-yl)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (130 mg, 0.13 mmol, 1.0 eq) in TFA (2 mL) was stirred at 50 °C for 4 h. The mixture was concentrated to give a residue. The residue was purified by prep-TLC (Dichloromethane: Methanol = 5: 1, acetonitrile with 0.1% NH<sub>4</sub>OH in MeOH) to give compound 6-((1S,4R,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-(difluoromethyl)-4-methylpyridin-2-amine (56 mg, 66.8%) as a yellow solid. LCMS: m/z 628.3 (M+H<sup>+</sup>).

**Step 5: Chiral Separation to prepare of 6-((1S,4R,11S,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-(difluoromethyl)-4-methylpyridin-2-amine and 6-((1S,4R,11R,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluoro tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-(difluoromethyl)-4-methylpyridin-2-amine;**



[00413] Compound 6-((1S,4R,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino [1',2':1,7] azepino[2,3,4-de]quinazolin-11-yl)-5-(difluoromethyl)-4-methylpyridin-2-amine (65 mg) was separated by Chiral HPLC (Column: CHIRALPAK IE, 2 cm x 25cm, 5 $\mu$ m, Mobile phase: A for MTBE (0.1% TEA):(EtOH : DCM = 1:1)=70:30, Flow rate: 20 mL/min, Column temperature: 25 °C) to afford 6-((1S,4R,11S,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino [1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-(difluoromethyl)-4-methylpyridin-2-amine (13.9 mg, 21.4%) and 6-((1S,4R,11R,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-(difluoromethyl)-4-methylpyridin-2-amine (9.6 mg, 14.8%).

[00414] **Peak 1:** 6-((1S,4R,11S,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-(difluoromethyl)-4-methylpyridin-2-amine: Chiral purity: 70.30% ee; retention time: 8.957 min; Chiral HPLC method: Column: CHIRALPAK IB N-3, 4.6 x 100 mm, 3  $\mu$ m, Mobile phase: A for Hex and B for EtOH (0.1% TFA), Gradient: B 10%, Flow rate: 0.8 mL/min, Column temperature: 25 °C. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD):  $\delta$  6.70 – 6.25 (m, 2H), 5.71 (s, 1H), 5.53 – 5.18 (m, 3H), 4.23 (q, *J* =

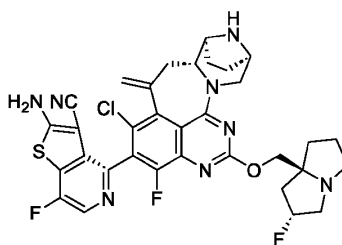
10.5 Hz, 2H), 4.01 (dd,  $J = 12.0, 4.5$  Hz, 1H), 3.70 – 3.58 (m, 1H), 3.54 – 3.44 (m, 1H), 3.28 – 2.96 (m, 5H), 2.95 – 2.81 (m, 1H), 2.47 (s, 3H), 2.43 – 2.32 (m, 1H), 2.31 – 1.64 (m, 10H).

LCMS:  $m/z$  628.3 ( $M+H^+$ ).

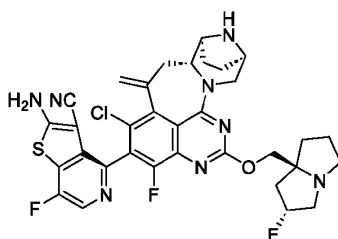
[00415] **Peak 2:** 6-((1S,4R,11R,14aR)-10,12-difluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-(difluoromethyl)-4-methylpyridin-2-amine: Chiral purity: 66.12% ee; retention time: 5.385 min; Chiral HPLC method: Column: CHIRALPAK IB N-3, 4.6 x 100 mm, 3  $\mu$ m, Mobile phase: A for Hex and B for EtOH (0.1% TFA), Gradient: B 10%, Flow rate: 0.8 mL/min, Column temperature: 25 °C.  $^1H$  NMR (300 MHz,  $CD_3OD$ ):  $\delta$  6.67 – 6.24 (m, 2H), 5.71 (s, 1H), 5.55 – 5.16 (m, 3H), 4.23 (q,  $J = 10.5$  Hz, 2H), 4.01 (dd,  $J = 12.3, 4.5$  Hz, 1H), 3.70 – 3.60 (m, 1H), 3.55 – 3.45 (m, 1H), 3.28 – 3.23 (m, 1H), 3.22 – 3.11 (m, 2H), 3.09 – 2.97 (m, 1H), 2.94 – 2.81 (m, 1H), 2.62 – 2.51 (m, 1H), 2.47 (s, 3H), 2.40 – 1.65 (m, 11H). LCMS:  $m/z$  628.3 ( $M+H^+$ ).

#### Examples 33 & 34

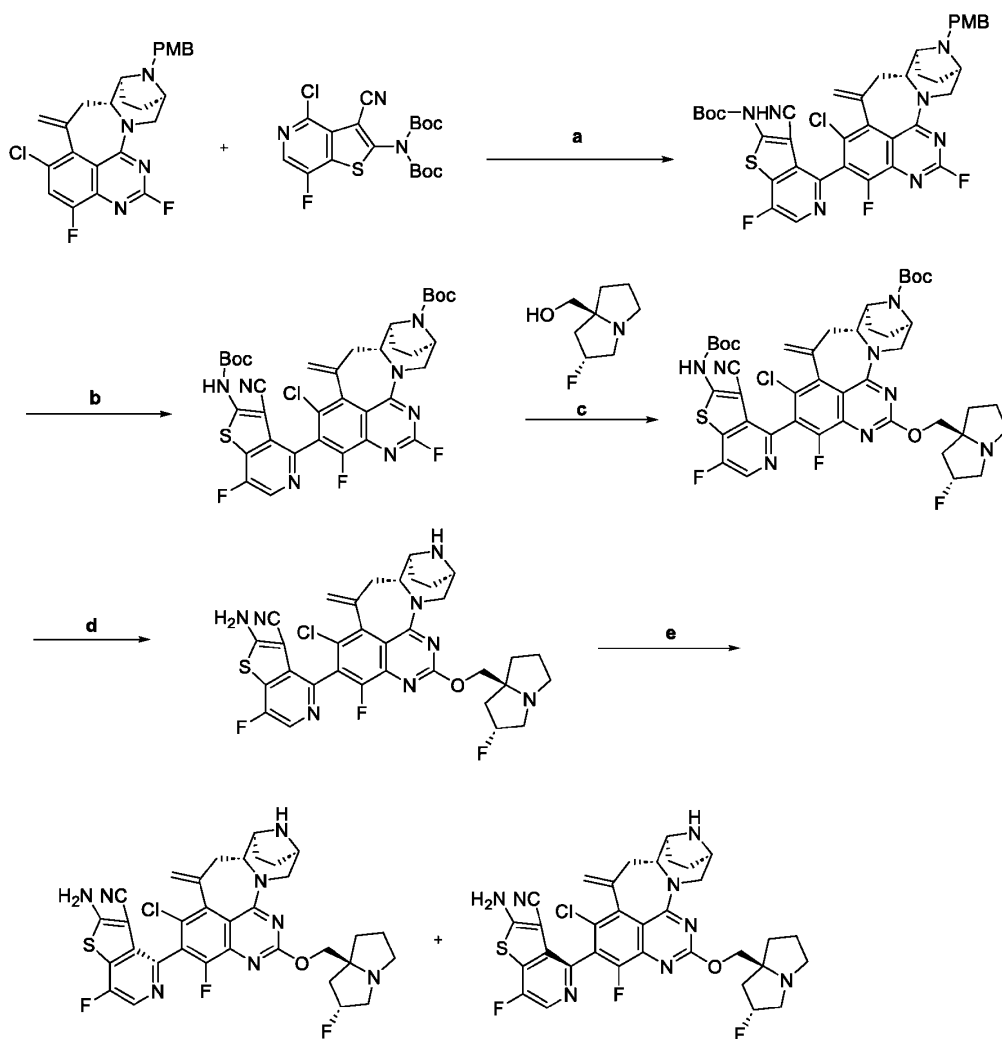
**Example 33:** 2-amino-4-((1S,4R,11R,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino [1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile



**Example 34:** 2-amino-4-((1S,4R,11S,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino [1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile

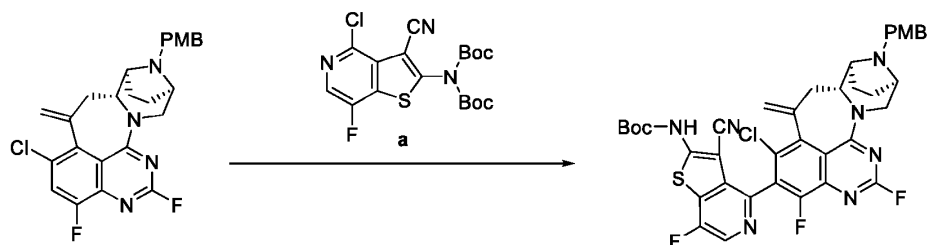


### Synthetic scheme



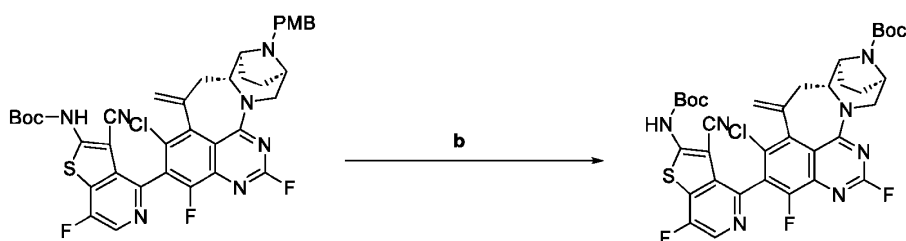
**Step 1: Synthesis of tert-butyl (4-((1S,4R,14aR)-12-chloro-8,10-difluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino**

**[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate**



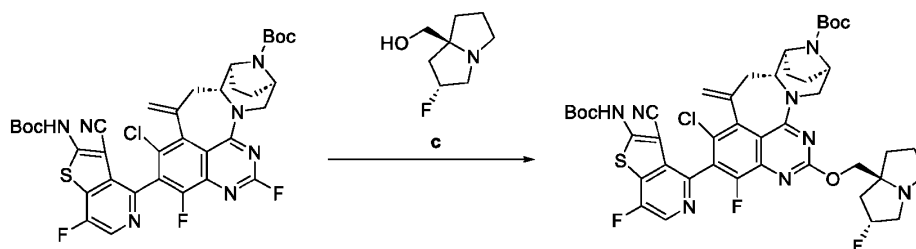
[00416] To a solution of (1S,4R,14aR)-12-chloro-8,10-difluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline (1.0 g, 2.13 mmol, 1.0 eq) in THF (10 mL) was added (TMP)<sub>2</sub>Zn·MgCl<sub>2</sub>·LiCl (0.4 M, 32 mL, 12.8 mmol, 6.0 eq) under N<sub>2</sub>, the mixture was stirred at 50 °C for 2 h. Then a mixture of tert-butyl (tert-butoxycarbonyl)(4-bromo-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate (906 mg, 2.12 mmol, 1.3 eq) and C Phos Pd G4 (263 mg, 0.32 mmol, 0.15 eq) in 1,4-dioxane (3 mL) was added to the mixture. The mixture was stirred at 100 °C for 15 h under N<sub>2</sub>. The reaction was quenched with H<sub>2</sub>O (10 mL). The mixture was filtered, the filter cake was washed with large EtOAc and separated. The aqueous layer was extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude. The crude was purified by silica gel column chromatography (Petroleum ether: EtOAc = 1: 1) to give tert-butyl (4-((1S,4R,14aR)-12-chloro-8,10-difluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate (530 mg, 32.7%) as a brown solid. LCMS: m/z 760.2 (M+H<sup>+</sup>).

**Step 2: Synthesis of tert-butyl (1S,4R,14aR)-11-(2-(((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00417] A solution of tert-butyl (4-((1S,4R,14aR)-12-chloro-8,10-difluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate (285 mg, 0.38 mmol, 1.0 eq), Boc<sub>2</sub>O (246 mg, 1.13 mmol, 3.0 eq) and Pd/BaSO<sub>4</sub> (285 mg, 100% w/w) in THF (5 mL) was stirred at 65 °C for 20 h. The mixture was filtered through a Celite pad, the filtrate was concentrated to give a residue. The residue was purified by silica gel column chromatography (Petroleum ether: EtOAc = 1: 1) to give tert-butyl (1S,4R,14aR)-11-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (125 mg, 45.0%) as a yellow solid. LCMS: m/z 740.2 (M+H<sup>+</sup>).

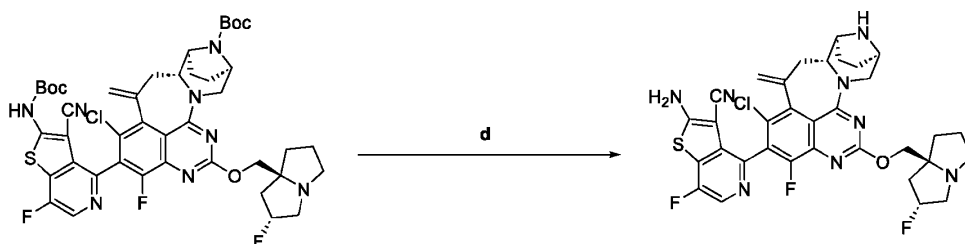
**Step 3: Synthesis of tert-butyl (1S,4R,14aR)-11-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00418] To a solution of ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (36 mg, 0.22 mmol, 1.5 eq) in THF (2 mL) was added NaH (18 mg, 0.45 mmol, 3.0 eq), the reaction mixture was stirred at 25 °C for 0.5 h under N<sub>2</sub>. To the reaction mixture was added tert-butyl (1S,4R,14aR)-11-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (110 mg, 0.15 mmol, 1.0 eq) in THF (2 mL), the reaction was stirred at 25 °C for 2 h. The reaction was quenched with H<sub>2</sub>O (2 mL) at 0 °C. The resulting mixture was extracted with EtOAc (5 mL x 2). The combined organic layers were washed with brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude. The crude was purified by Prep-TLC (DCM: MeOH = 15: 1) to give tert-butyl (1S,4R,14aR)-11-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-

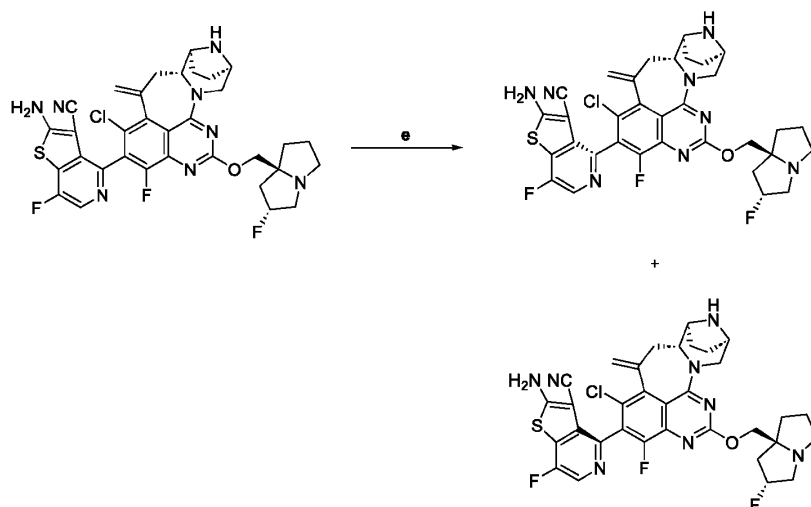
12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (100 mg, 76.5%) as a yellow solid. LCMS:  $m/z$  879.2 ( $M+H^+$ ).

**Step 4: Synthesis of 2-amino-4-((1S,4R,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile**



[00419] To a solution of tert-butyl (1S,4R,14aR)-11-(2-(((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (100 mg, 0.11 mmol, 1.0 eq) in DCM (2 mL) was added TFA (1 mL, 13.0 mmol, 118.2 eq). The reaction mixture was stirred at 25 °C for 2 h. The reaction was concentrated to give a crude. The crude was purified by Prep-HPLC (10% ~ 55% ACN in water with 0.1% FA) to give 2-amino-4-((1S,4R,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile (55 mg, 71.1%) as a yellow solid. LCMS:  $m/z$  679.2 ( $M+H^+$ ).

**Step 5: Chiral separation to prepare 2-amino-4-((1S,4R,11R,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile formate (1:0.15) and 2-amino-4-((1S,4R,11S,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile formate (1:0.25)**



[00420] Compound 2-amino-4-((1S,4R,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile (55 mg) was separated by preparative Chiral HPLC (Column: CHIRALPAK IK, 2 cm x 25 cm, 5  $\mu$ m, Mobile phase: A for MTBE (0.5% 2mM  $\text{NH}_3$ -MeOH) : B for (MeOH: DCM = 1: 1) = 80:20, Flow rate: 20 mL/min, Column temperature: 25  $^\circ\text{C}$ , UV 220 nm) to afford 2-amino-4-((1S,4R,11R,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile formate (1:0.15) (**Peak 1**: 18.3 mg, 33.3%) and 2-amino-4-((1S,4R,11S,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile formate (1:0.25) (**P2**: 15.9 mg, 28.9%) respectively.

[00421] **Peak 1**: 2-amino-4-((1S,4R,11R,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile formate (1:0.15): Chiral purity: 99.72% ; retention time: 8.187 min; UPCC method: Column: CHIRALPAK OD-3, 4.6mm\*250mm, 3  $\mu$ m, Mobile phase:  $\text{CO}_2$ : 0.1% DEA in MeOH = 70: 30, Flow rate: 2.0 mL/min, Column temperature: 35  $^\circ\text{C}$ .



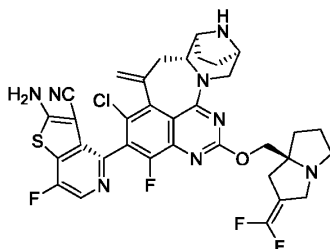
[00422]  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  8.30 (s, 1H), 5.79 (s, 1H), 5.56 – 5.28 (m, 3H), 4.42 – 4.25 (m, 2H), 4.18 – 4.09 (m, 1H), 3.80 – 3.62 (m, 2H), 3.55 – 3.39 (m, 2H), 3.30 – 3.12 (m, 2H), 3.11 – 2.89 (m, 2H), 2.49 – 1.65 (m, 11H). LCMS:  $m/z$  678.9 ( $\text{M}-0.15\text{FA}+\text{H}^+$ ).

[00423] **Peak 2:** 2-amino-4-((1S,4R,11S,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile formate (1:0.25): Chiral purity: 99.18% de; retention time: 16.066 min; UPCC method: Column: CHIRALPAK OD-3, 4.6mm\*250mm, 3  $\mu\text{m}$ , Mobile phase:  $\text{CO}_2$ : 0.1% DEA in MeOH = 70: 30, Flow rate: 2.0 mL/min, Column temperature: 35  $^\circ\text{C}$ .

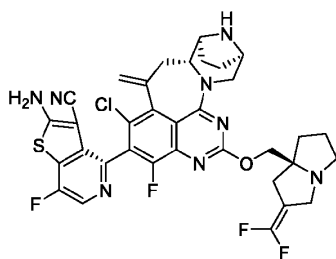
$^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  8.30 (s, 1H), 5.82 (s, 1H), 5.60 – 5.30 (m, 3H), 4.45 – 4.29 (m, 2H), 4.18 – 4.06 (m, 1H), 3.82 – 3.52 (m, 2H), 3.50 – 3.38 (m, 2H), 3.30 – 2.95 (m, 4H), 2.50 – 1.70 (m, 11H). LCMS:  $m/z$  678.8 ( $\text{M}-0.25\text{FA}+\text{H}^+$ ).

### Examples 35 & 36

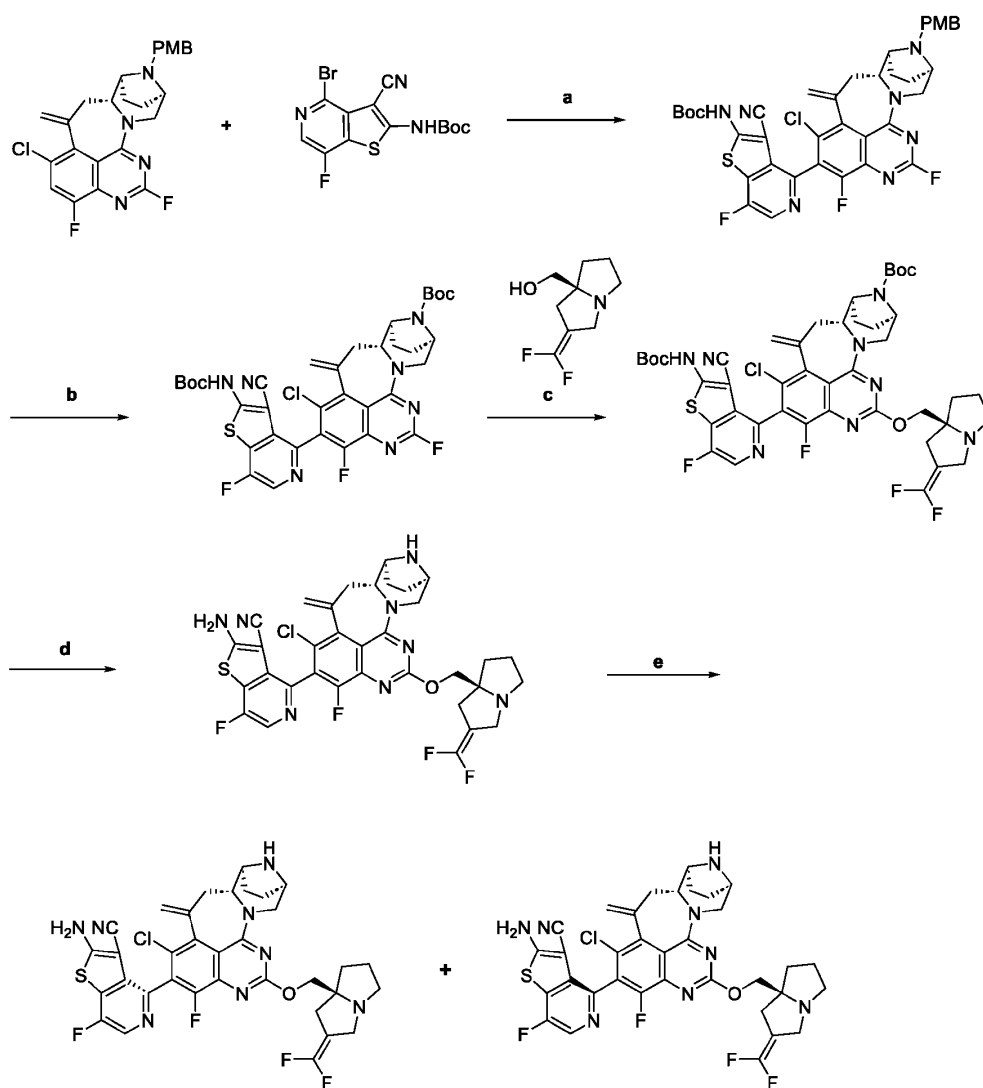
**Example 35:** 2-amino-4-((1S,4R,11R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene) tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epimino azepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile



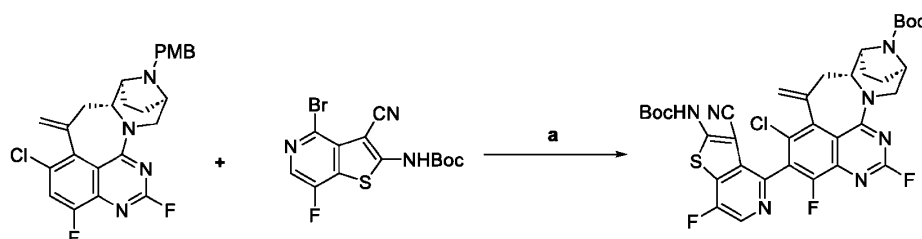
**Example 36:** 2-amino-4-((1S,4R,11S,14aR)-12-chloro-8-(((S)-2-(difluoromethylene) tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile



## Synthetic scheme

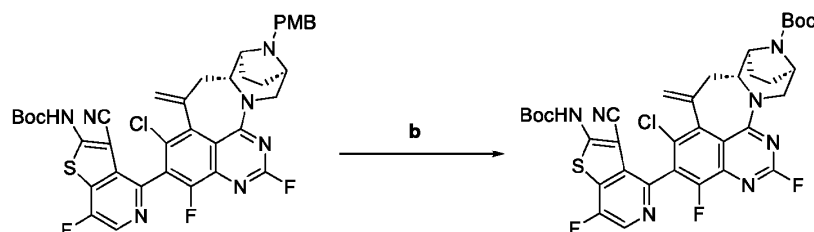


**Step 1: Synthesis of tert-butyl (4-((1S,4R,14aR)-12-chloro-8,10-difluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate**



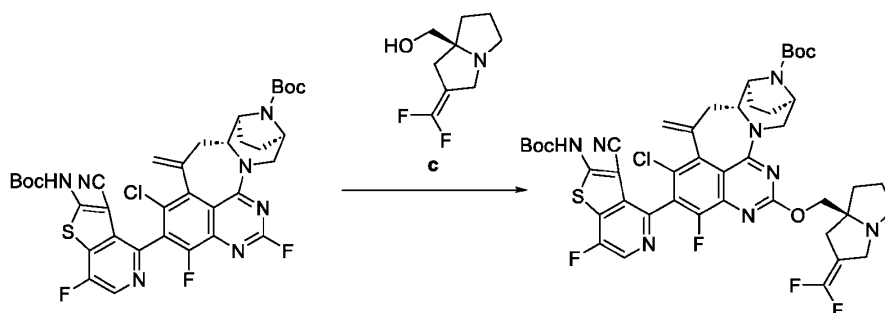
[00424] To a solution of (1S,4R,14aR)-12-chloro-8,10-difluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline (1.0 g, 2.13 mmol, 1.0 eq) in THF (10 mL) was added (TMP)<sub>2</sub>Zn·MgCl<sub>2</sub>·LiCl (0.4 M, 32 mL, 12.8 mmol, 6.0 eq) under N<sub>2</sub>, the mixture was stirred at 50 °C for 2 h. Then a mixture of tert-butyl (4-chloro-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate (1.0 g, 2.78 mmol, 1.3 eq) and C Phos Pd G4 (263 mg, 0.32 mmol, 0.15 eq) in 1,4-dioxane (3 mL) was added to the mixture. The mixture was stirred at 100 °C for 15 h under N<sub>2</sub>. The reaction was quenched with H<sub>2</sub>O (10 mL). The mixture was filtered, the filter cake was washed with large EtOAc and separated. The aqueous layer was extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude. The crude product was purified by silica gel column chromatography (Petroleum ether: EtOAc = 1: 1) to give tert-butyl (4-((1S,4R,14aR)-12-chloro-8,10-difluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate (530 mg, 32.7%) as a brown solid. LCMS: m/z 760.2 (M+H<sup>+</sup>).

**Step 2: Synthesis of tert-butyl (1S,4R,14aR)-11-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00425] A solution of tert-butyl (4-((1S,4R,14aR)-12-chloro-8,10-difluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate (285 mg, 0.38 mmol, 1.0 eq),  $\text{Boc}_2\text{O}$  (246 mg, 1.13 mmol, 3.0 eq) and  $\text{Pd}/\text{BaSO}_4$  (285 mg, 100% w/w) in THF (5 mL) was stirred at 65 °C for 20 h. The mixture was filtered through a Celite pad, the filtrate was concentrated to give a residue. The residue was purified by silica gel column chromatography (Petroleum ether: EtOAc = 1: 1) to give tert-butyl (1S,4R,14aR)-11-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (125 mg, 45.0%) as a yellow solid. LCMS:  $m/z$  740.2 ( $\text{M}+\text{H}^+$ ).

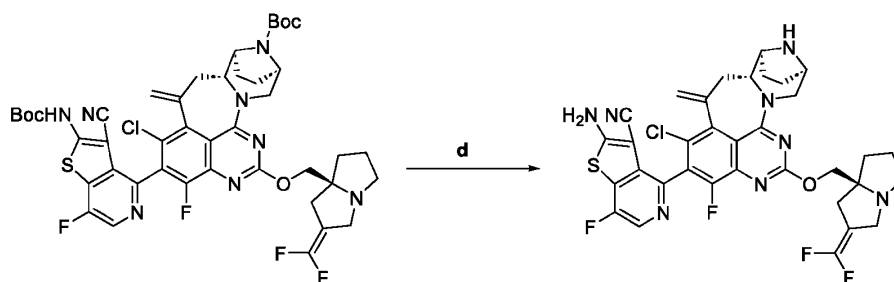
**Step 3: Synthesis of tert-butyl (1S,4R,14aR)-11-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00426] To a solution of (S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (46 mg, 0.24 mmol, 1.5 eq) in THF (2 mL) was added NaH (19 mg, 0.49 mmol, 3.0 eq), the reaction mixture was stirred at 25 °C for 0.5 h under  $\text{N}_2$ . To the reaction mixture was added tert-butyl (1S,4R,14aR)-11-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-

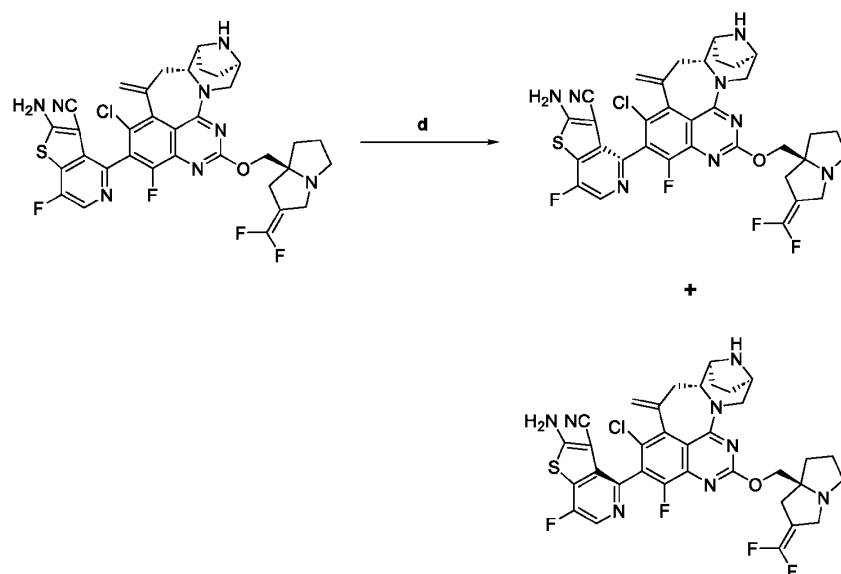
c]pyridin-4-yl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (120 mg, 0.16 mmol, 1.0 eq) in THF (2 mL), the reaction was stirred at 32 °C for 2 h. The reaction was quenched with H<sub>2</sub>O (2 mL) at 0 °C. The resulting mixture was extracted with EtOAc (5 mL x 2). The combined organic layers were washed with brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude. The crude was purified by Prep-TLC (DCM: MeOH = 15: 1) to give tert-butyl (1S,4R,14aR)-11-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (50 mg, 33.9%) as a yellow solid. LCMS: m/z 909.3 (M+H<sup>+</sup>).

**Step 4: Synthesis of 2-amino-4-((1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile**



[00427] To a solution of tert-butyl (1S,4R,14aR)-11-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (77 mg, 0.085 mmol, 1.0 eq) in DCM (2 mL) was added TFA (1 mL, 13.1 mmol, 153.7 eq), the reaction mixture was stirred at 25 °C for 2 h. The reaction was concentrated to give a crude. The crude was purified by Prep-HPLC (10% ~ 55% ACN in water with 0.1% FA) to give 2-amino-4-((1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile (50 mg, 83.5%) as a yellow solid. LCMS: m/z 709.1 (M+H<sup>+</sup>).

**Step 5: Chiral separation to prepare 2-amino-4-((1S,4R,11R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile and 2-amino-4-((1S,4R,11S,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile**



[00428] 2-amino-4-((1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile (50 mg) was separated by preparative Chiral HPLC (Column: CHIRAL Cellulose SB, 2 cm x 25 cm, 5  $\mu$ m, Mobile phase: A for MTBE (0.5% 2mM  $\text{NH}_3$ -MeOH) and B for (MeOH: DCM = 1: 1) = 80:20, Flow rate: 20 mL/min, Column temperature: 25  $^\circ\text{C}$ , UV 220 nm) to afford 2-amino-4-((1S,4R,11R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile (6.4 mg, 12.8%) and 2-amino-4-((1S,4R,11S,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-

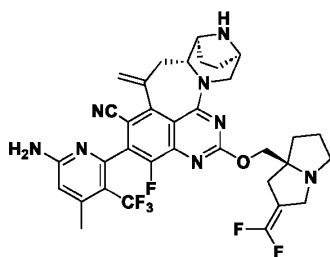
1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile (8.0 mg, 16.0%) respectively.

[00429] **Peak 1:** 2-amino-4-((1S,4R,11R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile: Chiral purity: 98.96% de; retention time: 7.806 min; UPCC method: Column: CHIRALPAK OD-3, 4.6mm\*250mm, 3  $\mu$ m, Mobile phase: CO<sub>2</sub>: 0.1% DEA in MeOH = 70: 30, Flow rate: 2.0 mL/min, Column temperature: 35 °C. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD):  $\delta$  8.29 (s, 1H), 5.89 – 5.79 (m, 1H), 5.60 – 5.35 (m, 2H), 4.32 – 4.20 (m, 2H), 4.11 – 4.01 (m, 1H), 3.84 – 3.72 (m, 1H), 3.70 – 3.65 (m, 1H), 3.58 – 3.50 (m, 1H), 3.48 – 3.40 (m, 1H), 3.22 – 3.10 (m, 2H), 3.01 – 2.89 (m, 1H), 2.88 – 2.79 (m, 1H), 2.78 – 2.70 (m, 1H), 2.59 – 2.41 (m, 2H), 2.20 – 1.66 (m, 8H). LCMS: m/z 709.1 (M+H<sup>+</sup>).

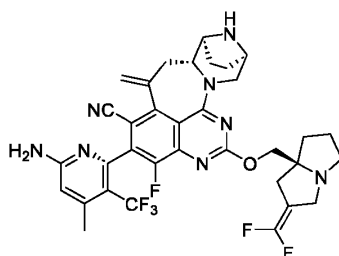
[00430] **Peak 2:** 2-amino-4-((1S,4R,11S,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile: Chiral purity: 99.36% de; retention time: 15.847 min; UPCC method: Column: CHIRALPAK OD-3, 4.6mm\*250mm, 3  $\mu$ m, Mobile phase: CO<sub>2</sub>: 0.1% DEA in MeOH = 70: 30, Flow rate: 2.0 mL/min, Column temperature: 35 °C. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD):  $\delta$  8.29 (s, 1H), 5.89 – 5.79 (m, 1H), 5.54 – 5.51 (m, 1H), 5.41 – 5.28 (m, 1H), 4.32 – 4.20 (m, 2H), 4.11 – 4.01 (m, 1H), 3.84 – 3.72 (m, 1H), 3.71 – 3.67 (m, 1H), 3.56 – 3.51 (m, 1H), 3.48 – 3.41 (m, 1H), 3.22 – 3.10 (m, 2H), 3.05 – 2.91 (m, 1H), 2.85 – 2.63 (m, 2H), 2.53 – 2.35 (m, 2H), 2.17 – 1.89 (m, 5H), 1.81 – 1.62 (m, 3H). LCMS: m/z 709.2 (M+H<sup>+</sup>).

#### Examples 37, 38 & 39

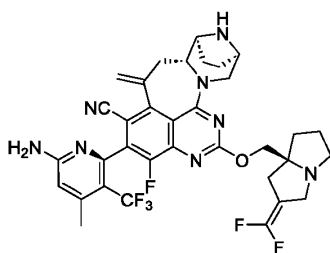
**Example 37: (1S, 4R, 14aR)-11-(6-amino-4-methyl-3-(trifluoromethyl) pyridin-2-yl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a (5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-de] quinazoline-12-carbonitrile**



**Example 38:** (1S,4R,11R,14aR)-11-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-12-carbonitrile

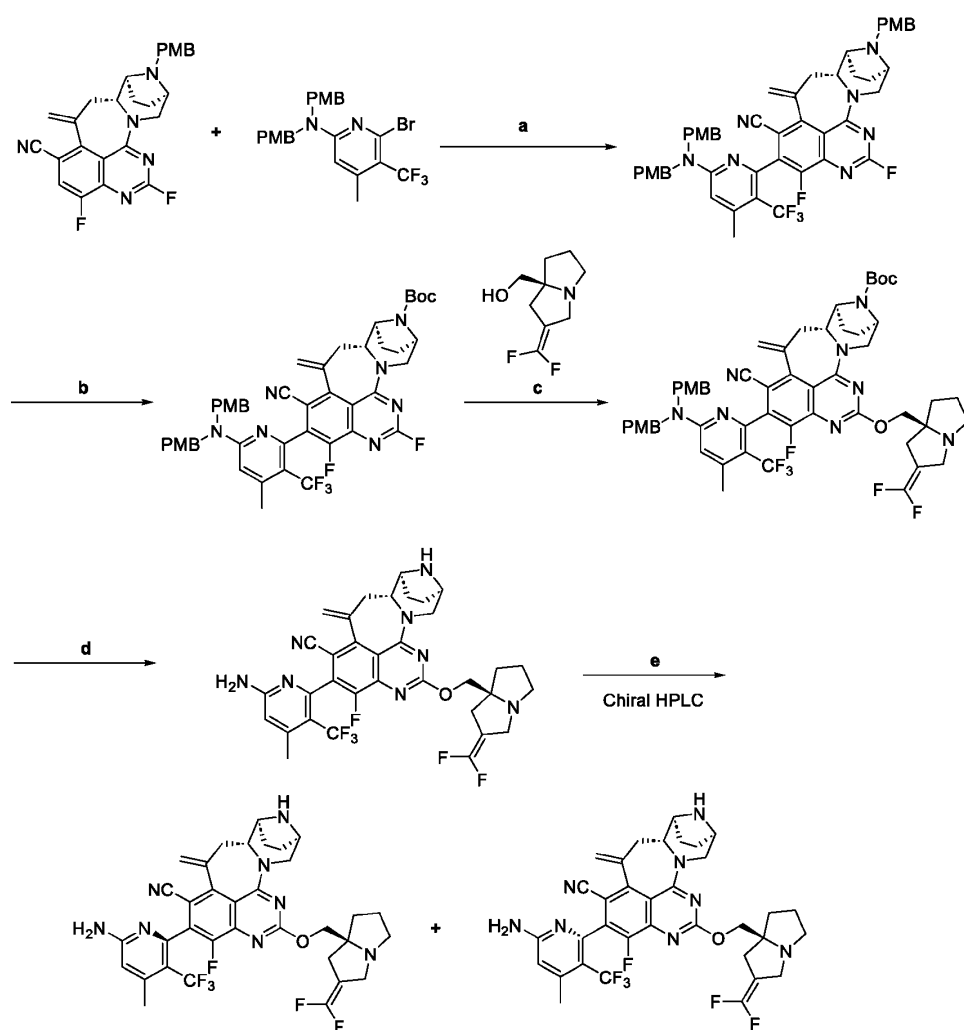


**Example 39:** (1S,4R,11S,14aR)-11-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-12-carbonitrile

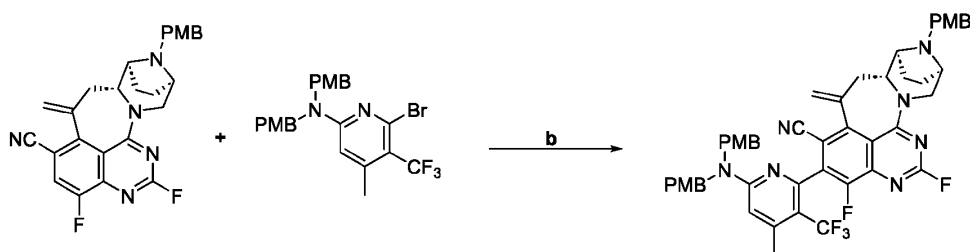


**Synthetic scheme**



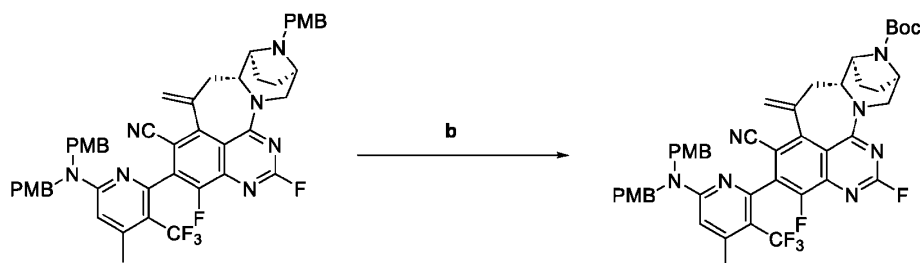


**Step 1: Synthesis of (1*S*, 4*R*, 14*aR*)-11-(6-(bis(4-methoxybenzyl) amino)-4-methyl-3-(trifluoromethyl) pyridin-2-yl)-8, 10-difluoro-15-(4-methoxybenzyl)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1,4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-12-carbonitrile**



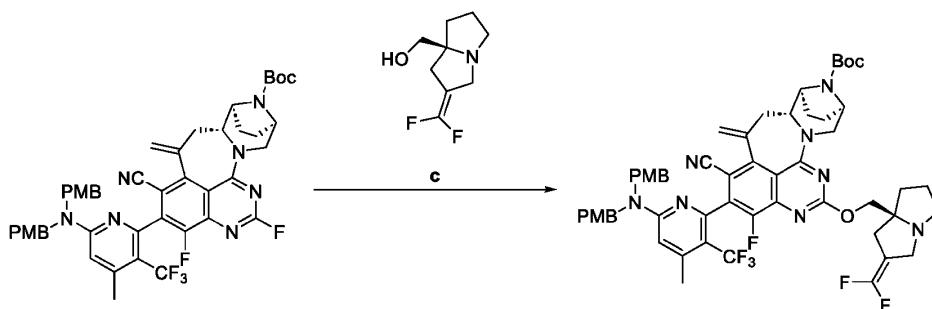
[00431] To a solution of (1*S*, 4*R*, 14*aR*)-8, 10-difluoro-15-(4-methoxybenzyl)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-12-carbonitrile (210.0 mg, 0.46 mmol, 1.0 eq) in THF (3 mL) was added (TMP)<sub>2</sub>Zn·2MgCl<sub>2</sub>·2LiCl (0.4 M, 6.9 mL, 2.76 mmol, 6.0 eq) under N<sub>2</sub>. The mixture was stirred at 50 °C for 2 h. Then LCMS showed the reaction was completed by D<sub>2</sub>O (2 drops) quenching. Then the mixture was added a mixture of 6-bromo-*N,N*-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (273.0 mg, 0.55 mmol, 1.2 eq) and CPhos Pd G3 (40.0 mg, 0.05 mmol, 0.1 eq) in 1,4-dioxane (3 mL). The mixture was stirred at 70 °C for 3 h. The reaction mixture was quenched with H<sub>2</sub>O (10 mL) and extracted with EtOAc (20 mL x 3). The organic layers were washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (Petroleum ether / EtOAc = 4:1) to afford (1*S*, 4*R*, 14*aR*)-11-(6-(bis(4-methoxybenzyl) amino)-4-methyl-3-(trifluoromethyl) pyridin-2-yl)-8, 10-difluoro-15-(4-methoxybenzyl)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-12-carbonitrile (220.0 mg, 54.3%) as a yellow solid. LCMS: 874.3 (M+H<sup>+</sup>).

**Step 2: Synthesis of *tert*-butyl (1*S*, 4*R*, 14*aR*)-11-(6-(bis(4-methoxybenzyl) amino)-4-methyl-3-(trifluoromethyl) pyridin-2-yl)-12-cyano-8, 10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino[1', 2':1, 7]azepino[2, 3, 4-*de*] quinazoline-15-carboxylate**



[00432] To a solution of (1*S*, 4*R*, 14*aR*)-11-(6-(bis (4-methoxybenzyl) amino)-4-methyl-3-(trifluoromethyl) pyridin-2-yl)-8, 10-difluoro-15-(4-methoxybenzyl)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-12-carbonitrile (170.0 mg, 0.19 mmol, 1.0 eq) in THF (2 mL) was added Boc<sub>2</sub>O (62.0 mg, 0.29 mmol, 1.5 eq) and Pd/BaSO<sub>4</sub> (85.0 mg, 50% w/w) at room temperature. The mixture was stirred at 65 °C for 24 h under hydrogen atmosphere. The reaction mixture was filtered and concentrated to give a crude. The crude product was purified by Prep-TLC (Petroleum ether / EtOAc = 2:1) to give *tert*-butyl (1*S*, 4*R*, 14*aR*)-11-(6-(bis (4-methoxybenzyl) amino)-4-methyl-3-(trifluoromethyl) pyridin-2-yl)-12-cyano-8,10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-15-carboxylate (90.0 mg, 57.9%) as a yellow solid. LCMS: 854.3 (M+H<sup>+</sup>).

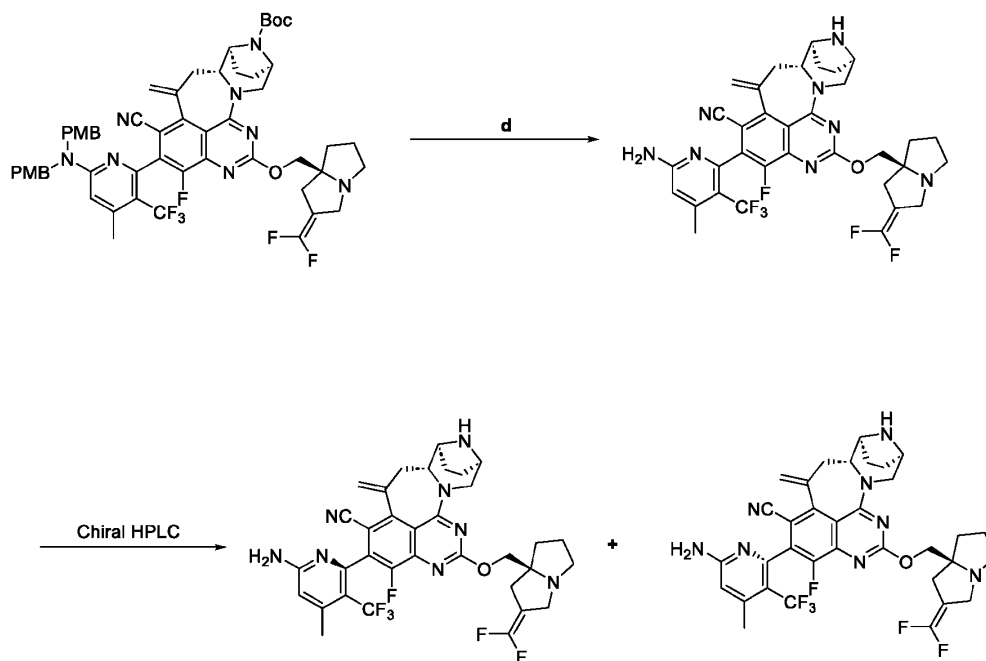
**Step 3: Synthesis of *tert*-butyl (1*S*, 4*R*, 14*aR*)-11-(6-(bis(4-methoxybenzyl) amino)-4-methyl-3-(trifluoromethyl) pyridin-2-yl)-12-cyano-8-(((*S*)-2-(difluoromethylene) tetrahydro-1*H*-pyrrolizin-7*a* (5*H*)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-15-carboxylate**



[00433] To a solution of (*S*)-2-(difluoromethylene) tetrahydro-1*H*-pyrrolizin-7*a* (5*H*)-yl methanol (30.0 mg, 0.16 mmol, 1.5 eq) in THF (0.5 mL) was added NaH (60%) (13.0 mg, 0.33 mmol, 3.0 eq) at 0 °C and then the mixture was stirred for 0.5 h at room temperature under N<sub>2</sub>. The solution of *tert*-butyl (1*S*, 4*R*, 14*aR*)-11-(6-(bis (4-methoxybenzyl) amino)-4-methyl-3-(trifluoromethyl) pyridin-2-yl)-12-cyano-8, 10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-15-carboxylate (90.0 mg, 0.11 mmol, 1.0 eq) in THF (1 mL) was added to the mixture and stirred at 25 °C for 1.5 h. HPLC and TLC show the reaction was completed. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl solution (5 mL) and extracted with EtOAc (10 mL x 3). The mixture was

concentrated to give a crude product, which was purified by Prep-TLC (DCM / MeOH = 20:1) to afford *tert*-butyl (1*S*, 4*R*, 14*aR*)-11-(6-(bis (4-methoxybenzyl) amino)-4-methyl-3-(trifluoromethyl) pyridin-2-yl)-12-cyano-8-(((*S*)-2-(difluoromethylene) tetrahydro-1*H*-pyrrolizin-7*a* (5*H*)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-15-carboxylate (80.0 mg, 70.9%) as a yellow solid. LCMS: 1023.4 (M+H<sup>+</sup>).

**Step 4: Synthesis of (1*S*, 4*R*, 14*aR*)-11-(6-amino-4-methyl-3-(trifluoromethyl) pyridin-2-yl)-8-(((*S*)-2-(difluoromethylene) tetrahydro-1*H*-pyrrolizin-7*a* (5*H*)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-12-carbonitrile formate (1:1), (1*S*,4*R*,11*R*,14*aR*)-11-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8-(((*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-12-carbonitrile and (1*S*,4*R*,11*S*,14*aR*)-11-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8-(((*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-12-carbonitrile**



[00434] The mixture of *tert*-butyl (1*S*, 4*R*, 14*aR*)-11-(6-(bis (4-methoxybenzyl) amino)-4-methyl-3-(trifluoromethyl) pyridin-2-yl)-12-cyano-8-(((*S*)-2-(difluoromethylene) tetrahydro-1*H*-pyrrolizin-7*a* (5*H*)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1,4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-15-carboxylate (25.0 mg, 0.02 mmol, 1.0 eq) in TFA (1 mL) was stirred at 50 °C for 3 h under N<sub>2</sub>. After completion, the mixture was cooled to room temperature and concentrated to give a crude. The crude was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 30% to 75%) to afford (1*S*, 4*R*, 14*aR*)-11-(6-amino-4-methyl-3-(trifluoromethyl) pyridin-2-yl)-8-(((*S*)-2-(difluoromethylene) tetrahydro-1*H*-pyrrolizin-7*a* (5*H*)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-12-carbonitrile formate (1:1) (2.3 mg, 15.0%) as a white solid.

[00435] <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 6.92 (d, *J* = 16.0 Hz, 2H), 6.52 (s, 1H), 5.75 (s, 1H), 5.51 (d, *J* = 3.6 Hz, 1H), 5.15 – 5.10 (m, 1H), 4.17 – 4.07 (m, 2H), 3.96 – 3.93 (m, 1H), 3.65 – 3.58 (m, 3H), 3.10 – 2.98 (m, 3H), 2.67 – 2.57 (m, 2H), 2.45 – 2.32 (m, 6H), 1.96 – 1.75 (m, 6H), 1.59 – 1.44 (m, 3H). LCMS: *m/z* 683.2 (M-FA+H<sup>+</sup>).

[00436] 35 mg of the diastereomers were purified by chiral HPLC to give the following 2 isomers:

[00437] **Peak 1:** (1*S*,4*R*,11*R*,14*aR*)-11-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8-(((*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-12-carbonitrile (2.0 mg, peak 1, de ~ 84.4%, retention time = 2.281 under the Analytical separation method)

[00438] <sup>1</sup>H NMR (400 MHz, MeOD): δ 6.62 (s, 1H), 5.77 (s, 1H), 5.62 (s, 1H), 5.42 – 5.38 (m, 1H), 4.40-2.20 (qm, 2H), 4.09 – 4.05 (m, 1H), 3.85 – 3.70 (m, 1H), 3.70-3.60 (m, 1H), 3.60 – 3.50 (m, 1H), 3.45 – 3.35 (m, 1H), 3.19 – 3.11 (m, 2H), 3.03 – 2.99 (m, 1H), 2.82 – 2.60 (m, 2H), 2.52 – 2.45 (m, 5H), 2.15 – 2.10 (m, 2H), 2.00 – 1.86 (m, 3H), 1.79 – 1.62 (m, 3H). LCMS: *m/z* 683.2 (M +H<sup>+</sup>).

**Peak 2:**

[00439] (1*S*,4*R*,11*S*,14*aR*)-11-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8-(((*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-fluoro-13-methylene-

1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-12-carbonitrile (2.2 mg, peak 2, de ~ 78.7%, retention time = 3.827 under the Analytical separation method)

[00440] <sup>1</sup>H NMR (400 MHz, MeOD):  $\delta$  6.62 (s, 1H), 5.78 (s, 1H), 5.67 (s, 1H), 5.43 – 5.39 (m, 1H), 4.35–4.20 (m, 2H), 4.09 – 4.00 (m, 1H), 3.82 – 3.72 (m, 1H), 3.70–3.60 (m, 1H), 3.60 – 3.51 (m, 1H), 3.45 – 3.35 (m, 1H), 3.19 – 3.12 (m, 2H), 3.09 – 3.00 (m, 1H), 2.81 – 2.61 (m, 2H), 2.61 – 2.45 (m, 5H), 2.18 – 2.08 (m, 2H), 2.01 – 1.86 (m, 3H), 1.81 – 1.70 (m, 3H). LCMS: m/z 683.2 (M + H<sup>+</sup>).

#### Chiral separation conditions:

##### Analytical separation method

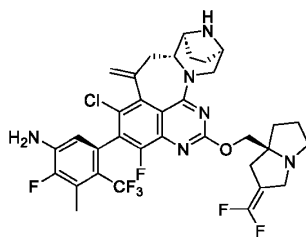
[00441] Instrument: SHIMADZU LC-20A. Column: CHIRALPAK IE-3, 4.6cm × 50cm, 3 $\mu$ m. Mobile phase: MTBE (0.1%DEA) : (MeOH : DCM = 1 : 1) = 95:5. Flow rate: 1 mL /min. Column temperature: 25°C. Wavelength: 254 nm.

##### Preparative separation method

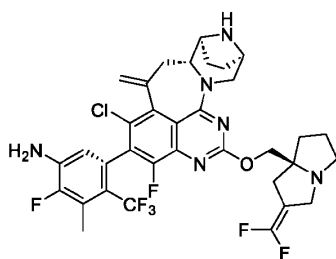
[00442] Instrument: Prep-HPLC-Gilson. Column: CHIRALPAK IK, 2cm × 25cm, 5 $\mu$ m. Mobile phase: MTBE : (MeOH : DCM = 1 : 1) = 95:5. Flow rate: 20 mL /min. Column temperature: 25°C. Wavelength: 220 nm

#### Examples 40 & 41

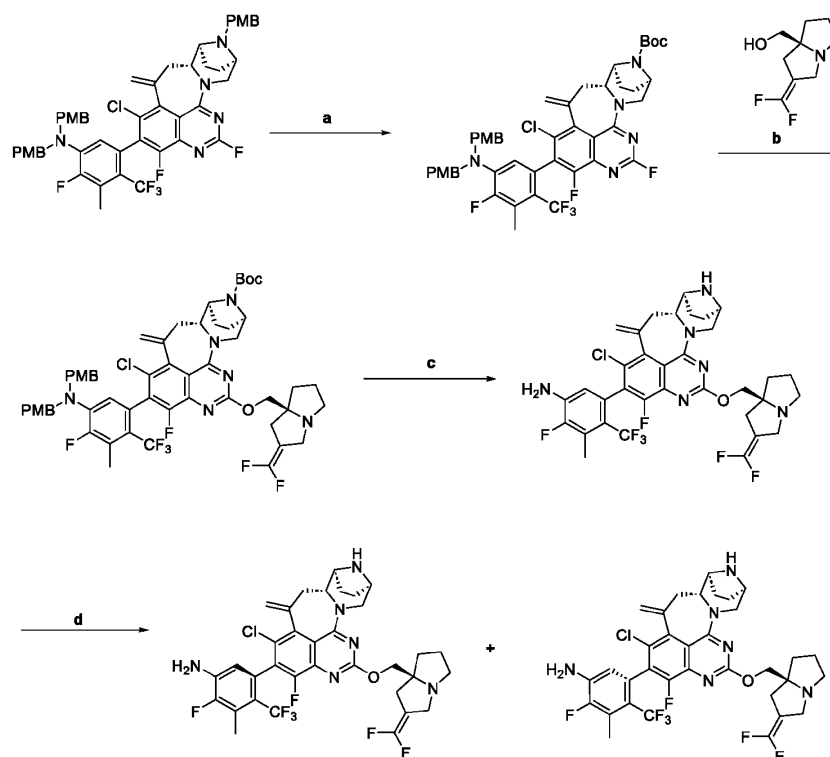
**Example 40:** 5-((1S,4R,11S,14aR)-12-chloro-8-(((S)-2-(difluoro-methylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino [1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline



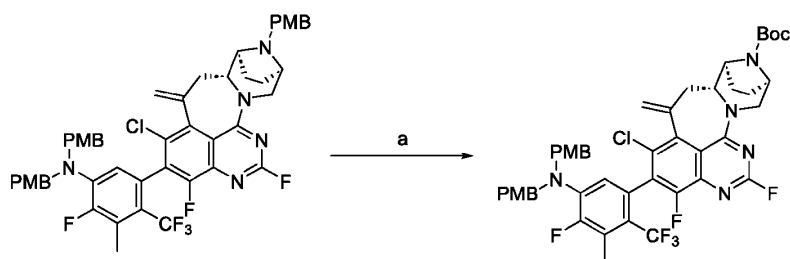
**Example 41:** 5-((1S,4R,11R,14aR)-12-chloro-8-(((S)-2-(difluoro-methylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino [1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline



### Synthetic scheme

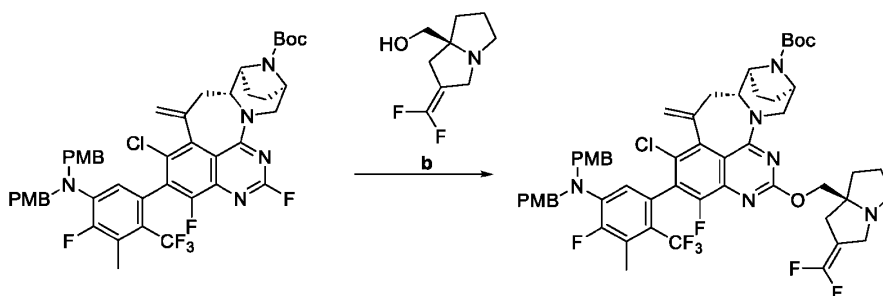


**Step 1: Synthesis of tert-butyl (1S,4R,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00443] To a solution of 5-((1S,4R,14aR)-12-chloro-8,10-difluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-2-fluoro-N,N-bis(4-methoxybenzyl)-3-methyl-4-(trifluoromethyl)aniline (450 mg, 0.5 mmol, 1.0 eq) in THF (5 mL) was added  $\text{Boc}_2\text{O}$  (327 mg, 1.5 mmol, 3.0 eq) and  $\text{Pd/BaSO}_4$  (450 mg). The reaction mixture was stirred at 65 °C for 15 h. The mixture was filtered and concentrated to yield a crude product. The crude product was purified by Prep-TLC (DCM: MeOH = 15: 1) to give tert-butyl (1S,4R,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (300 mg, 68.2%) as a yellow solid. LCMS:  $m/z$  880.2 ( $[\text{M}+\text{H}]^+$ ).

**Step 2: Synthesis of tert-butyl (1S,4R,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**

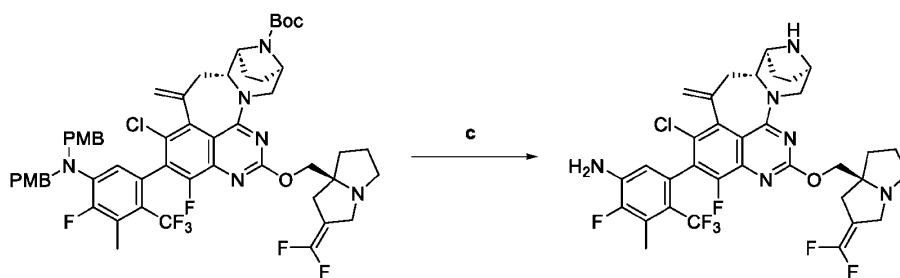


[00444] To a solution of (S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (90.8 mg, 0.48 mmol, 1.5 eq) in THF (2 mL) was added NaH (38.4 mg, 0.96 mmol, 3.0 eq). The reaction mixture was stirred at room temperature for 1 h. The mixture was added tert-butyl (1S,4R,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-



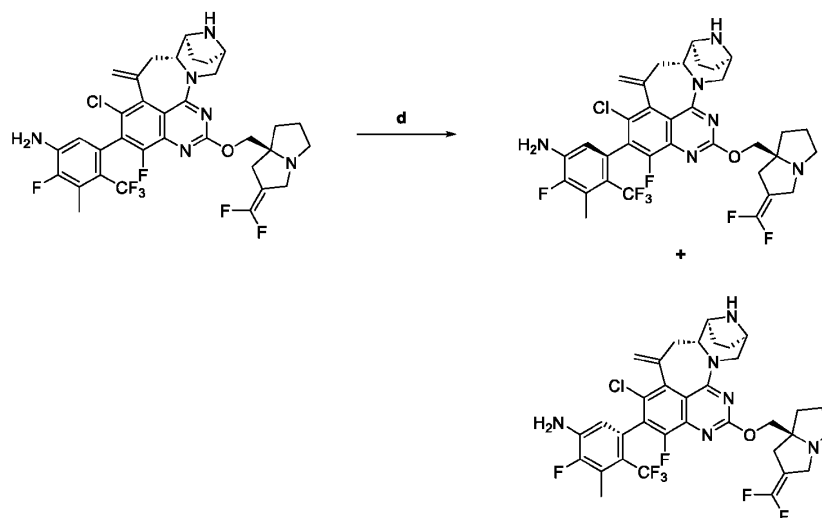
1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (279.0 mg, 0.32 mmol, 1.0 eq). The mixture was quenched with water (5 mL), extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude product. The crude product was purified by prep-TLC (DCM: MeOH = 15: 1) to give tert-butyl (1S,4R,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (170 mg, 51.1%) as a colorless oil. LCMS: m/z 1049.4 ([M+H]<sup>+</sup>).

**Step 3: Synthesis of 5-((1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline**



[00445] To a solution of (1S,4R,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (140 mg, 0.13 mmol, 1.0 eq) was added TFA (1 mL). The reaction mixture was stirred at 50 °C for 2 h. The mixture was concentrated to give a crude product. The crude product was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 30% to 40%) to give 5-((1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline (50.0 mg, 52.9%) as a white solid. LCMS: m/z 709.2 ([M+H]<sup>+</sup>).

**Step 4: Synthesis of 5-((1S,4R,11S,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline and 5-((1S,4R,11R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline**



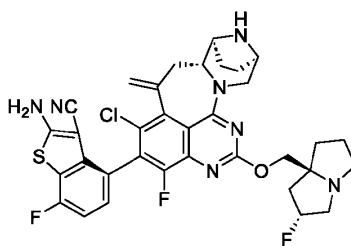
[00446] Compound 5-((1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline (50 mg) was separated by Prep-Chiral HPLC (Column: Enantiocel C9, 2 cm x 25 cm, 5  $\mu$ m, Mobile phase: Hex (0.5% 2mM  $\text{NH}_3$ -MeOH): IPA=60:40, Flow rate: 20 mL/min, Column temperature: 25  $^\circ\text{C}$ , UV 220 nm) to afford 5-((1S,4R,11S,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline (12 mg, 24.0%) and 5-((1S,4R,11R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline (3 mg, 6.0%).

[00447] **P1:** 5-((1S,4R,11S,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline: Chiral purity: 100.0% de; retention time: 1.20 min; Chiral HPLC method: Column: Enantiocel C9-3, 4.6mm\*50mm, 3  $\mu$ m, Mobile phase: Hex(0.1%DEA):IPA=60:40, Flow rate: 1.0 mL/min, Column temperature: 25  $^{\circ}$ C.  $^1$ H NMR (400 MHz, DMSO- $d_6$ )  $\delta$  6.44 (d,  $J$  = 8.4 Hz, 1H), 5.99 (brs, 2H), 5.74 (s, 1H), 5.31 (s, 1H), 5.01 (d,  $J$  = 11.6 Hz, 1H), 4.14 – 4.04 (m, 2H), 3.97 – 3.86 (m, 1H), 3.69 – 3.59 (m, 1H), 3.56 – 3.48 (m, 1H), 3.38 – 3.34 (m, 1H), 3.30 – 3.26 (m, 1H), 3.10 (d,  $J$  = 12.4 Hz, 1H), 3.01 – 2.91 (m, 2H), 2.70 – 2.55 (m, 2H), 2.45 – 2.34 (m, 2H), 2.32 (s, 3H), 2.27 – 2.19 (m, 1H), 1.96 – 1.74 (m, 5H), 1.60 – 1.45 (m, 3H).

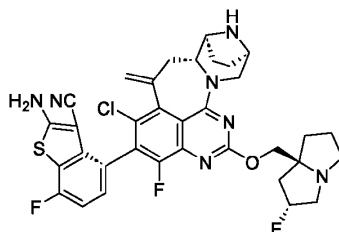
[00448] **P2:** 5-((1S,4R,11S,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline: Chiral purity: 99.5% de; retention time: 1.61 min; Chiral HPLC method: Column: Enantiocel C9-3, 4.6mm\*50mm, 3  $\mu$ m, Mobile phase: Hex(0.1%DEA):IPA=60:40, Flow rate: 1.0 mL/min, Column temperature: 25  $^{\circ}$ C.  $^1$ H NMR (400 MHz, DMSO- $d_6$ )  $\delta$  6.41 (d,  $J$  = 8.4 Hz, 1H), 6.00 (brs, 2H), 5.74 (s, 1H), 5.29 (s, 1H), 5.04 (d,  $J$  = 11.6 Hz, 1H), 4.19 – 4.03 (m, 2H), 3.97 – 3.86 (m, 1H), 3.69 – 3.60 (m, 1H), 3.56 – 3.48 (m, 1H), 3.40 – 3.34 (m, 1H), 3.30 – 3.26 (m, 1H), 3.10 (d,  $J$  = 12.4 Hz, 1H), 3.02 – 2.95 (m, 1H), 2.94 – 2.86 (m, 1H), 2.70 – 2.54 (m, 2H), 2.44 – 2.34 (m, 2H), 2.33 (s, 3H), 2.32 – 2.27 (m, 1H), 1.97 – 1.75 (m, 5H), 1.61 – 1.46 (m, 3H).

#### Examples 42 & 43

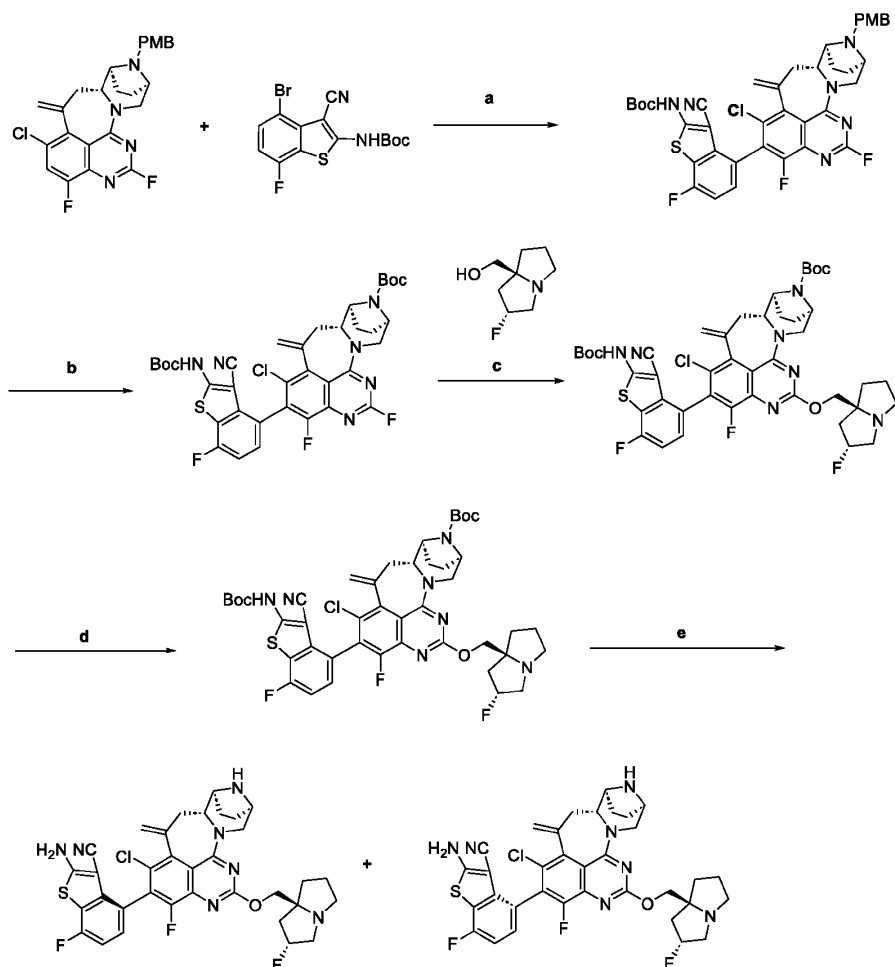
**Example 42:** 2-amino-4-((1S,4R,11R,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile



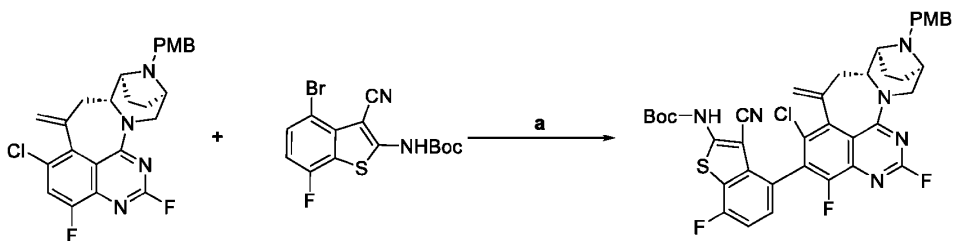
**Example 43: 2-amino-4-(((1S, 4R, 11S, 14aR)-12-chloro-10-fluoro-8-(((2R, 7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1', 2':1, 7]azepino[2, 3, 4-de]quinazolin-11-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile**



**Synthetic scheme**

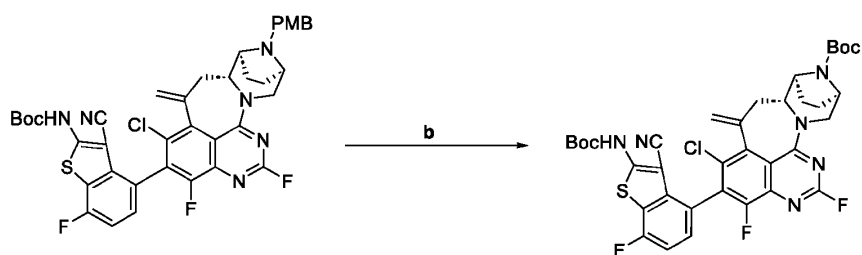


**Step 1: Synthesis of tert-butyl (4-((1S,4R,14aR)-12-chloro-8,10-difluoro-15-(4-methoxybenzyl)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1',2':1,7] azepino[2,3,4-de] quinazolin-11-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate**



[00449] To a solution of (1S, 4R, 14aR)-12-chloro-8,10-difluoro-15-(4-methoxybenzyl)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline (300 mg, 0.64 mmol, 1.0 eq) in THF (5 mL) was added (TMP)<sub>2</sub>Zn·2MgCl<sub>2</sub>·2LiCl (0.4 M, 9.6 mL, 3.84 mmol, 6.0 eq) under N<sub>2</sub>. The mixture was stirred at 50 °C for 1 h. Then LCMS showed the reaction was completed by D<sub>2</sub>O quenching. Then the mixture was added a mixture of *tert*-butyl (4-bromo-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate (285 mg, 0.77 mmol, 1.2 eq) and Cphos Pd G3 (52 mg, 0.06 mmol, 0.1 eq) in 1,4-dioxane (5 mL). The mixture was stirred at 70 °C for 3 h. LCMS and HPLC showed the reaction was completed, the mixture was cooled to 0 °C~10 °C, quenched with water (5 mL) and filtered to give filter cake 1 and filtrate 1. The filter cake 1 was triturated with EtOAc (50 mL) to obtain filtrate 2. Merge the filtrate 1 and filtrate 2, then the organic layer was washed with brine (20 mL) and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (petroleum ether / EtOAc = 4:1) to afford *tert*-butyl (4-((1S,4R,14aR)-12-chloro-8,10-difluoro-15-(4-methoxybenzyl)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate (298 mg, purity: 90%, yield: 61.3%). LCMS: 759.2 (M+H<sup>+</sup>).

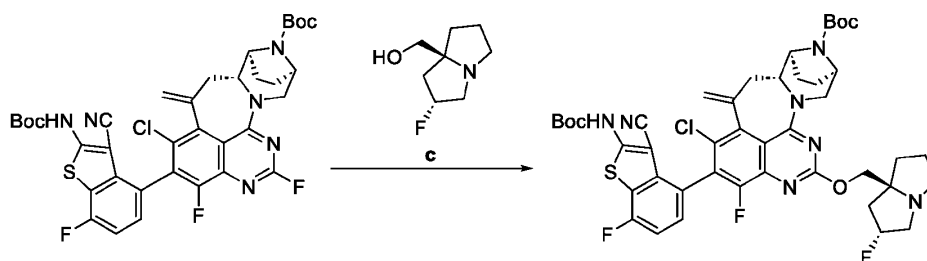
**Step 2: Synthesis of *tert*-butyl (1S,4R,14aR)-11-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-12-chloro-8,10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00450] To a solution of *tert*-butyl (4-((1S,4R,14aR)-12-chloro-8,10-difluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate (200 mg, 0.26 mmol, 1.0 eq) in THF (4 mL) was added Boc<sub>2</sub>O (118 mg, 0.54 mmol, 1.5 eq) and Pd/BaSO<sub>4</sub> (100 mg, 50% w/w) at room temperature. The mixture was stirred

at 65 °C for 40 h under hydrogen atmosphere. The reaction mixture was filtered and concentrated to give a crude. The crude product was purified by Prep-TLC (Petroleum ether / EtOAc = 2:1) to give tert-butyl (1S, 4R, 14aR)-11-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-12-chloro-8,10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (110 mg, purity: 70%, yield: 56.7%) as a yellow solid. LCMS: 739.2 (M+H<sup>+</sup>).

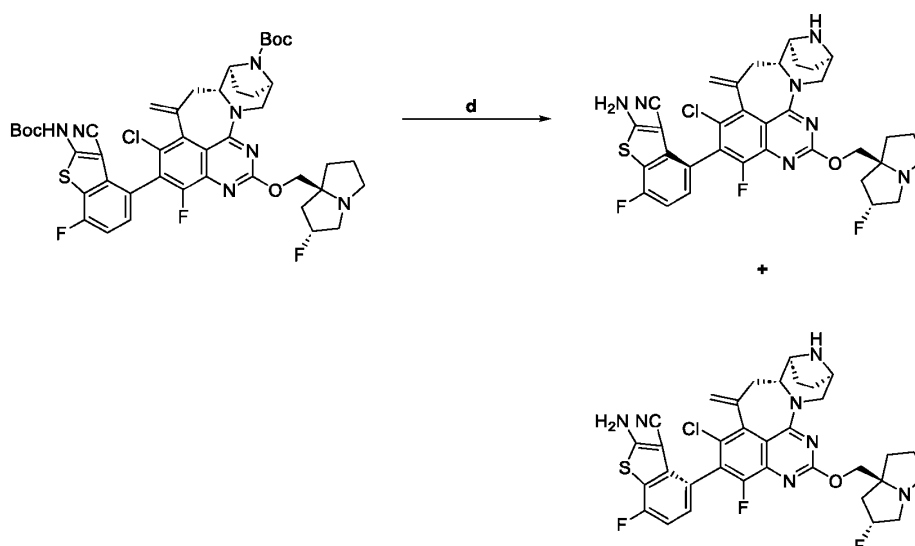
**Step 3: Synthesis of tert-butyl (1S,4R,14aR)-11-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00451] To a solution of ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl) methanol (30 mg, 0.19 mmol, 1.2 eq) in THF (0.5 mL) was added NaH (60%) (19 mg, 0.47 mmol, 3.0 eq) at 0 °C and then the mixture was stirred for 0.5 h at room temperature under N<sub>2</sub>. The mixture was added the solution of tert-butyl (1S, 4R, 14aR)-11-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-12-chloro-8,10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (117 mg, 0.16 mmol, 1.0 eq) in THF (1.0 mL) and stirred at 25 °C for 1.5 h. HPLC and TLC show the reaction was completed. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl aqueous solution (5 mL) and extracted with EtOAc (10 mL x 3). The organic layers were washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give a residue, which was purified by Prep-TLC (DCM / MeOH = 10:1) to afford tert-butyl (1S,4R,14aR)-11-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-

de]quinazoline-15-carboxylate (54 mg, purity: 90%, yield: 38.6%) as a yellow solid. LCMS: 878.2 ( $M+H^+$ ).

**Step 4: Chiral separation to prepare 2-amino-4-((1S,4R,11R,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1', 2':1, 7]azepino[2, 3, 4-de]quinazolin-11-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile and 2-amino-4-((1S, 4R, 11S, 14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile**



[00452] The mixture of tert-butyl (1S, 4R, 14aR)-11-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (95 mg, 0.11 mmol, 1.0 eq) in TFA (1 mL)/DCM (1 mL) was stirred at room temperature for 2 h under  $N_2$ . After completion, the mixture was concentrated to give a crude. The crude was dissolved in DCM/MeOH (10:1, 15 mL) and washed with saturated  $Na_2CO_3$  aqueous solution (10 mL x 3). The organic layer was washed with brine (10 mL), dried over  $Na_2SO_4$ , filtered and concentrated under reduced pressure to give a residue, which was purified by prep-TLC (DCM / MeOH = 10:1) to afford 2-amino-4-((1S, 4R, 14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-



1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (40 mg, purity: 90%, yield: 54.5%) as a yellow solid. Further chiral separation by chiral HPLC gave these two compounds:

[00453] **Peak 1:** 2-amino-4-((1S,4R,11R,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1', 2':1, 7]azepino[2, 3, 4-de]quinazolin-11-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (12.8 mg, purity: 94.8%, yield: 17.4%, retention time = 13.586 under the analytical chiral separation condition) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.09 (brs, 2H), 7.24 (dd, *J* = 8.4, 5.2 Hz, 1H), 7.15-7.05 (m, 1H), 5.75 (s, 1H), 5.37 (s, 1H), 5.36 – 5.15 (m, 2H), 5.15 – 5.00 (m, 1H), 4.14 – 3.90 (m, 3H), 3.65 – 3.52 (m, 1H), 3.16 – 3.04 (m, 3H), 3.03 – 2.98 (m, 1H), 2.97 – 2.90 (m, 1H), 2.89 – 2.75 (m, 1H), 2.38 – 2.23 (m, 1H), 2.20 – 2.10 (m, 1H), 2.09 – 1.91 (m, 3H), 1.89 – 1.69 (m, 3H), 1.66 – 1.40 (m, 3H), 1.28 – 1.10 (m, 2H). LCMS: *m/z* 678.2 (M+H<sup>+</sup>).

[00454] **Peak 2:** 2-amino-4-((1S, 4R, 11S, 14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (2.5 mg, purity: 92.9%, yield: 3.4%, retention time = 21.400 under the analytical chiral separation condition) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.06 (brs, 2H), 7.35-7.20 (m, 1H), 7.18-7.05 (m, 1H), 5.70 (s, 1H), 5.40 – 5.00 (m, 3H), 4.13 – 4.03 (m, 1H), 4.02 – 3.87 (m, 2H), 3.60 – 3.50 (m, 1H), 3.20 – 3.03 (m, 3H), 3.02 – 2.98 (m, 1H), 2.97 – 2.77 (m, 2H), 2.37 – 2.22 (m, 1H), 2.20 – 1.91 (m, 4H), 1.90 – 1.68 (m, 3H), 1.65 – 1.40 (m, 3H), 1.38 – 1.25 (m, 2H). LCMS: *m/z* 678.2 (M+H<sup>+</sup>).

**The analytical chiral separation condition:**

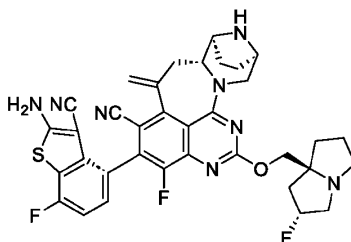
[00455] Instrument: Waters UPCC. Column: CHIRALPAK AS-3, 150×4.6 mm, 3 μm. Mobile phase: A for CO<sub>2</sub> and B for 0.1%DEA in MeOH. Gradient: B 20%. Flow rate: 2.0 mL/min. Column temperature: 35°C. Injection volume: 3.0 μl, Wavelength: 210nm.

**The preparative chiral separation method:**

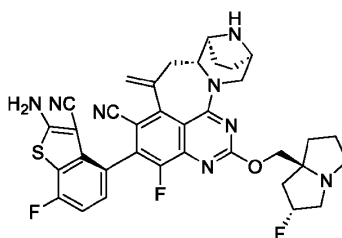
[00456] Instrument: Prep-HPLC-Gilson. Column: CHIRALPAK IK, 2 cm x 25 cm, 5 μm. Mobile phase: A for Hex (0.5% 2mM NH<sub>3</sub>-MeOH) and B for EtOH. Flow rate: 20 mL /min. Column temperature: 25°C. Wavelength: 220nm.

## Examples 44 &amp; 45

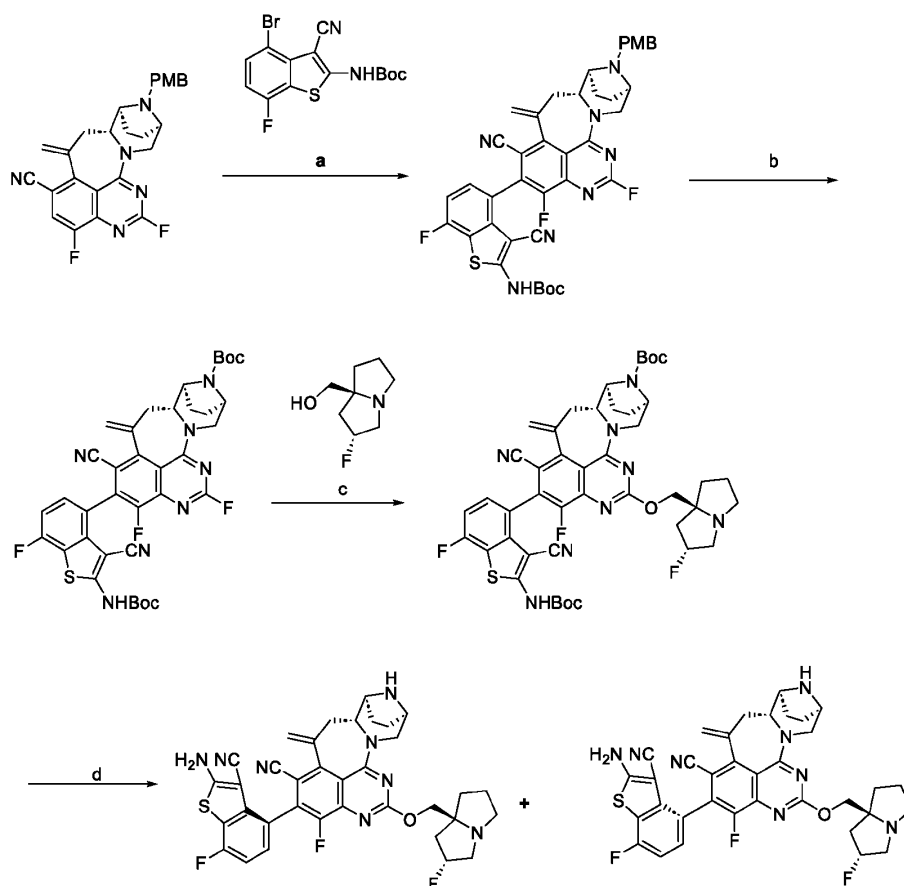
**Example 44: (1S,4R,11R,14aR)-11-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-12-carbonitrile**



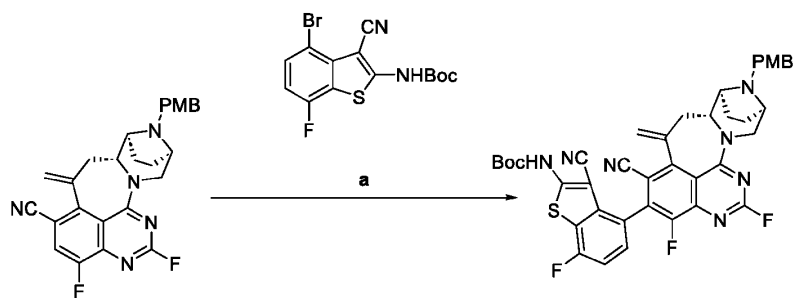
**Example 45: (1S,4R,11S,14aR)-11-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-12-carbonitrile**



Synthetic scheme

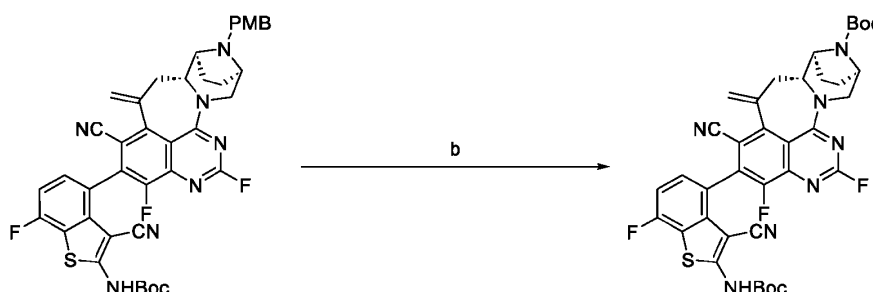


**Step 1: Synthesis of tert-butyl (3-cyano-4-((1S,4R,14aR)-12-cyano-8,10-difluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate**



[00457] To a solution of (1*S*,4*R*,14*aR*)-8,10-difluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-12-carbonitrile (250 mg, 0.54 mmol, 1.0 eq) in THF (3 mL) was added (TMP)<sub>2</sub>Zn·2MgCl<sub>2</sub>·2LiCl (0.4 M, 8.1 mL, 3.24 mmol, 6.0 eq) under N<sub>2</sub>. The mixture was stirred at 50 °C for 2 h. Then LCMS showed the reaction was completed by D<sub>2</sub>O (2 drops) quenching. Then the mixture was added a mixture of *tert*-butyl (4-bromo-3-cyano-7-fluorobenzo[*b*]thiophen-2-yl)carbamate (241 mg, 0.65 mmol, 1.2 eq) and Cphos Pd G3 (44 mg, 0.054 mmol, 0.1 eq) in 1,4-dioxane (3 mL). The mixture was stirred at 70 °C for 3 h. The reaction mixture was quenched with H<sub>2</sub>O (10 mL) and extracted with EtOAc (20 mL x 3). The organic layers were washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by Prep-TLC (Petroleum ether / EtOAc = 2:1) to afford *tert*-butyl (3-cyano-4-((1*S*,4*R*,14*aR*)-12-cyano-8,10-difluoro-15-(4-methoxybenzyl)-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazolin-11-yl)-7-fluorobenzo[*b*]thiophen-2-yl)carbamate (200 mg, 50%) as a yellow solid. LCMS: 750.2 (M+H<sup>+</sup>).

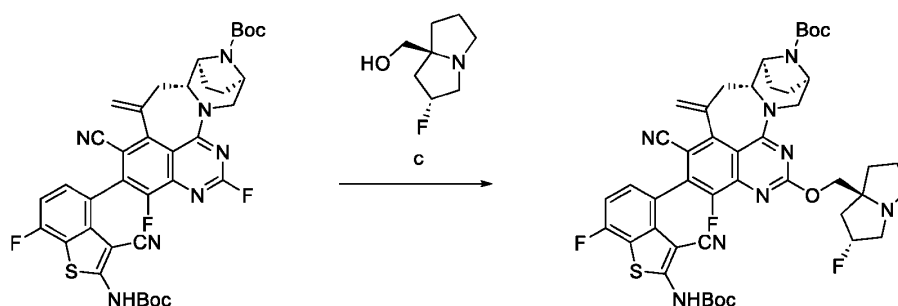
**Step 2: Synthesis of *tert*-butyl (1*S*, 4*R*, 14*aR*)-11-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[*b*]thiophen-4-yl)-12-cyano-8,10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino[1', 2':1, 7]azepino [2, 3, 4-*de*]quinazoline-15-carboxylate**



[00458] To a solution of *tert*-butyl (3-cyano-4-((1*S*, 4*R*, 14*aR*)-12-cyano-8,10-difluoro-15-(4-methoxybenzyl)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino[1', 2':1, 7]azepino[2, 3, 4-*de*]quinazolin-11-yl)-7-fluorobenzo[*b*]thiophen-2-yl)carbamate (270 mg, 0.36 mmol, 1.0 eq) in THF (3 mL) was added Boc<sub>2</sub>O (118 mg, 0.54 mmol, 1.5 eq) and Pd/BaSO<sub>4</sub> (135 mg, 50% w/w) at room temperature. The mixture was stirred at 65 °C for 40 h under hydrogen atmosphere. The reaction mixture was filtered and concentrated to give a crude. The crude product was purified by Prep-TLC (Petroleum ether / EtOAc = 2:1) to give *tert*-butyl (1*S*, 4*R*,

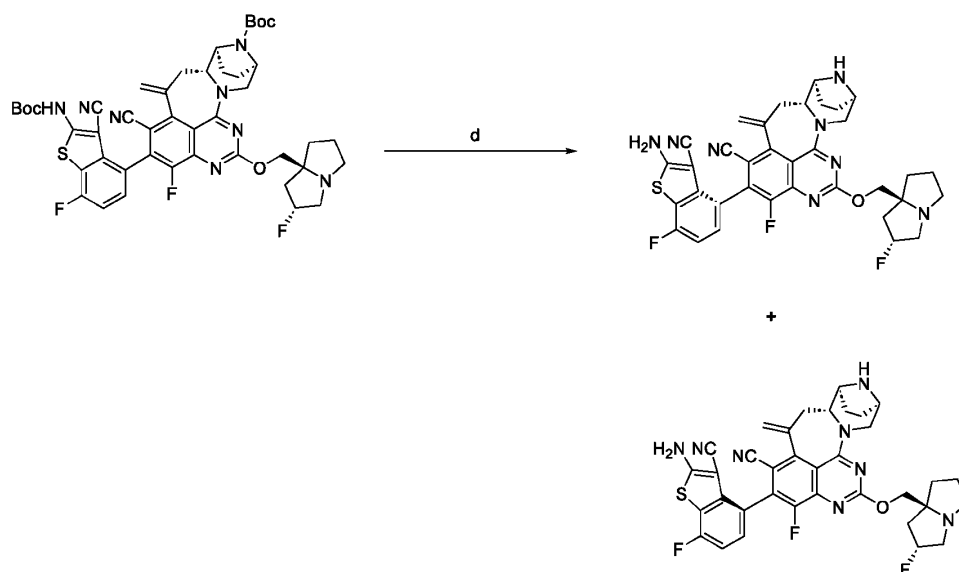
14*aR*)-11-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-12-cyano-8, 10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino[1', 2':1, 7] azepino[2, 3, 4-*de*]quinazoline-15-carboxylate (130 mg, 50%) as a yellow solid. LCMS: 730.2 ( $M+H^+$ ).

**Step 3: Synthesis of *tert*-butyl (1*S*, 4*R*, 14*aR*)-11-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-12-cyano-10-fluoro-8-(((2*R*, 7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino[1', 2':1, 7]azepino[2, 3, 4-*de*]quinazoline-15-carboxylate**



[00459] To a solution of ((2*R*, 7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl) methanol (43 mg, 0.27 mmol, 1.5 eq) in THF (0.5 mL) was added NaH (60%) (22 mg, 0.54 mmol, 3.0 eq) at 0 °C and then the mixture was stirred for 0.5 h at room temperature under N<sub>2</sub>. The mixture was added the solution of *tert*-butyl (1*S*, 4*R*, 14*aR*)-11-(2-((*tert*-butoxycarbonyl) amino)-3-cyano-7-fluorobenzo [b] thiophen-4-yl)-12-cyano-8, 10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-15-carboxylate (130 mg, 0.18 mmol, 1.0 eq) in THF (1.5 mL) and stirred at 25 °C for 1.5 h. HPLC and TLC show the reaction was completed. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl aqueous solution (5 mL) and extracted with EtOAc (10 mL x 3). The organic layers were washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give a residue, which was purified by Pre-TLC (DCM / MeOH = 20:1) to afford *tert*-butyl (1*S*, 4*R*, 14*aR*)-11-(2-((*tert*-butoxycarbonyl) amino)-3-cyano-7-fluorobenzo [b] thiophen-4-yl)-12-cyano-10-fluoro-8-(((2*R*, 7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-15-carboxylate (60 mg, 38.3%) as a yellow solid. LCMS: 869.4 ( $M+H^+$ ).

**Step 4: Synthesis of (1S,4R,11R,14aR)-11-(2-amino-3-cyano-7-fluorobenzo [b] thiophen-4-yl)-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-de] quinazoline-12-carbonitrile and (1S,4R,11S,14aR)-11-(2-amino-3-cyano-7-fluorobenzo [b] thiophen-4-yl)-10-fluoro-8-(((2R, 7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-de] quinazoline-12-carbonitrile**



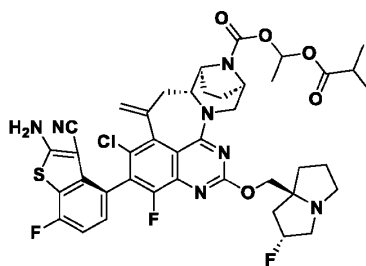
[00460] The mixture of *tert*-butyl (1S, 4R, 14aR)-11-(2-((*tert*-butoxycarbonyl) amino)-3-cyano-7-fluorobenzo [b] thiophen-4-yl)-12-cyano-10-fluoro-8-(((2R, 7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-de] quinazoline-15-carboxylate (60 mg, 0.069 mmol, 1.0 eq) in TFA (1 mL)/DCM (1 mL) was stirred at room temperature for 2 h under N<sub>2</sub>. After completion, the mixture was concentrated to give a crude. The crude was dissolved in DCM/MeOH (10:1, 15 mL) and washed with saturated Na<sub>2</sub>CO<sub>3</sub> aqueous solution (10 mL x 3). The organic layer was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-TLC (DCM / NH<sub>3</sub>-MeOH = 20:1) to afford (1S,4R,11R,14aR)-11-(2-amino-3-cyano-7-fluorobenzo [b] thiophen-4-yl)-10-fluoro-8-(((2R, 7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-de] quinazoline-12-

carbonitrile (9 mg, 18.8%, retention time = 9.170 under the analytical chiral separation condition) as a yellow solid.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  8.16 (brs, 2H), 7.41 (dd,  $J = 8.4$ , 5.2 Hz, 1H), 7.18 (t,  $J = 8.4$  Hz, 1H), 5.73 (s, 1H), 5.55 (s, 1H), 5.40 – 5.10 (m, 2H), 4.20 – 3.92 (m, 3H), 3.70 – 3.55 (m, 1H), 3.50 – 3.35 (m, 1H), 3.20 – 2.92 (m, 5H), 2.90 – 2.77 (m, 1H), 2.40–2.20 (m, 1H), 2.21 – 1.93 (m, 3H), 1.92 – 1.69 (m, 4H), 1.66 – 1.30 (m, 4H). LCMS:  $m/z$  669.2 ( $\text{M}+\text{H}^+$ ).

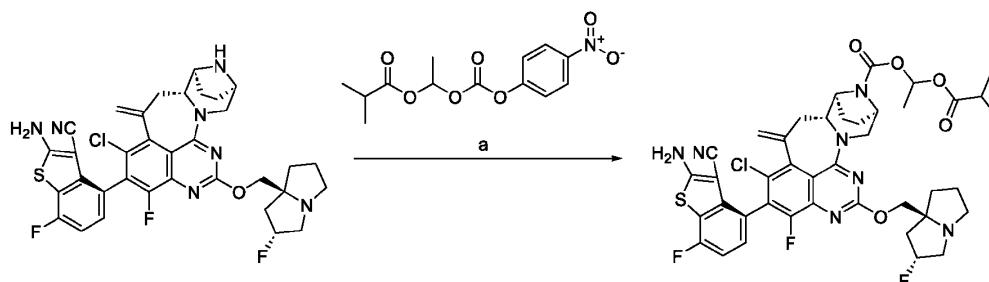
[00461] (1S,4R,11S,14aR)-11-(2-amino-3-cyano-7-fluorobenzo [b] thiophen-4-yl)-10-fluoro-8-(((2*R*, 7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-12-carbonitrile (11 mg, 23.2%, retention time = 12.000 under the analytical chiral separation condition) was obtained as a yellow solid. (The analytical chiral separation condition: Instrument: Waters UPCC. Column: CHIRALPAK OD-3, 250×4.6 mm, 3  $\mu\text{m}$ . Mobile phase: A for  $\text{CO}_2$  and B for 0.1%DEA in EtOH. Gradient: B 30%. Flow rate: 2.0 mL/min. Column temperature: 35°C. Injection volume: 5.0  $\mu\text{l}$ , Wavelength: 210nm.).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  8.19 (brs, 2H), 7.34 (dd,  $J = 8.4$ , 5.2 Hz, 1H), 7.17 (t,  $J = 8.8$  Hz, 1H), 5.76 (s, 1H), 5.58 (s, 1H), 5.42 – 5.10 (m, 2H), 4.18 – 3.90 (m, 3H), 3.70 – 3.40 (m, 2H), 3.20 – 2.91 (m, 5H), 2.90 – 2.75 (m, 1H), 2.50 – 2.40 (m, 1H), 2.20 – 1.70 (m, 7H), 1.69 – 1.40 (m, 4H). LCMS:  $m/z$  669.2 ( $\text{M}+\text{H}^+$ ).

### Example 46

**Example 46: 1-(isobutyryloxy)ethyl (1S, 4R, 11R, 14aR)-11-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-12-chloro-10-fluoro-8-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-15-carboxylate**



Synthetic scheme



**Step 1: Synthesis of 1-(isobutyryloxy)ethyl (1S, 4R, 11R, 14aR)-11-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1',2':1,7] azepino[2,3,4-de]quinazoline-15-carboxylate**

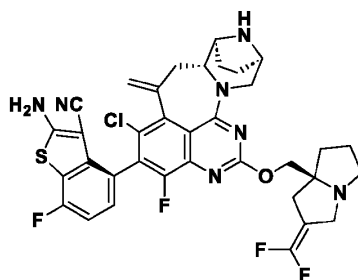
[00462] To a solution of 2-amino-4-((1S,4R,11R,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino [1',2':1,7] azepino[2,3,4-de]quinazolin-11-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (70.0 mg, 0.10 mmol, 1.0 eq) in THF (1.5 mL) was added  $\text{NaHCO}_3$  (86.7 mg, 1.0 mmol, 10.0 eq), 1-(((4-nitrophenoxy)carbonyl)oxy)ethyl isobutyrate (32.0 mg, 0.11 mmol, 1.1 eq) and water (0.3 mL). Then the reaction was stirred at room temperature for 16 h under  $\text{N}_2$ . HPLC and TLC showed the reaction was completed. The mixture was added water (10 mL) and extracted with EtOAc (10 mL x 3). The organic layers were washed with brine (20 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to give a crude product, which was purified by Prep-HPLC (acetonitrile with 0.04%  $\text{NH}_4\text{HCO}_3$  in water, 45% to 90%) to afford 1-(isobutyryloxy)ethyl (1S,4R,11R,14aR)-11-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (25.1 mg, purity: 98.4%, yield: 29.1%) as a white solid.

[00463]  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.09 (brs, 2H), 7.30-7.17 (m, 1H), 7.16-7.05 (m, 1H), 6.80 – 6.62 (m, 1H), 5.90 – 5.75 (m, 1H), 5.44 (s, 1H), 5.40 – 5.13 (m, 2H), 4.50 – 4.34 (m, 1H), 4.28 – 4.15 (m, 1H), 4.15 – 4.01 (m, 2H), 4.00 – 3.81 (m, 1H), 3.23 – 3.06 (m, 3H), 3.05 – 2.90 (m, 2H), 2.87 – 2.76 (m, 1H), 2.65 – 2.52 (m, 1H), 2.45 – 2.30 (m, 1H), 2.23 – 1.93 (m, 4H), 1.92 – 1.57 (m, 6H), 1.48 (d,  $J$  = 5.2 Hz, 3H), 1.08 (d,  $J$  = 6.8 Hz, 6H). LCMS:  $m/z$  836.2 ( $\text{M}+\text{H}^+$ ).

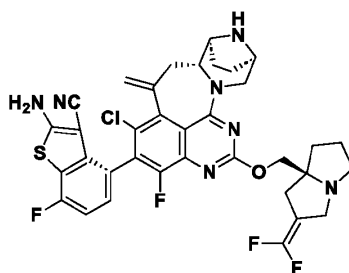


## Examples 47 &amp; 48

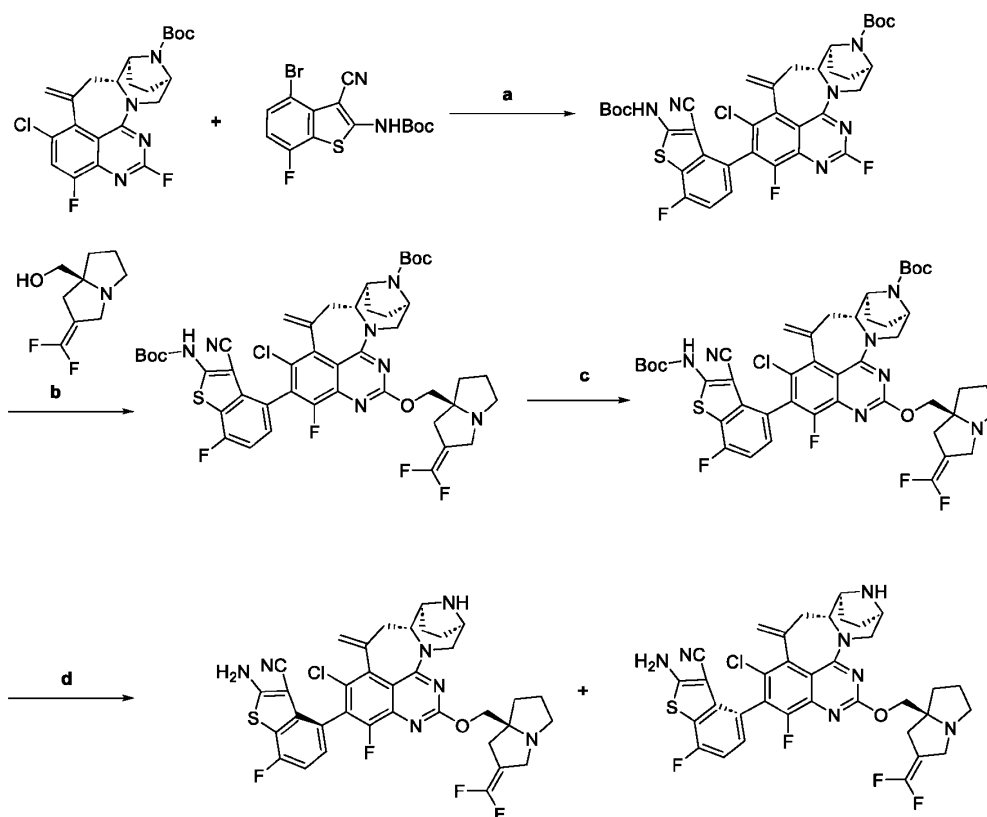
**Example 47:** 2-amino-4-((1S, 4R, 11R, 14aR)-12-methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile



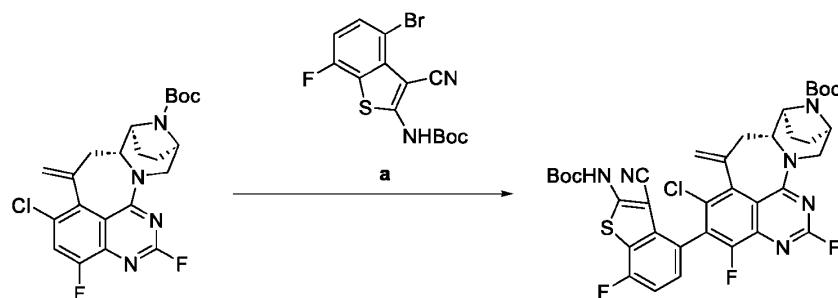
**Example 48:** 2-amino-4-((1S, 4R, 11S, 14aR)-12-chloro-8-(((S)-2-(difluoromethylene) tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile



Synthetic scheme



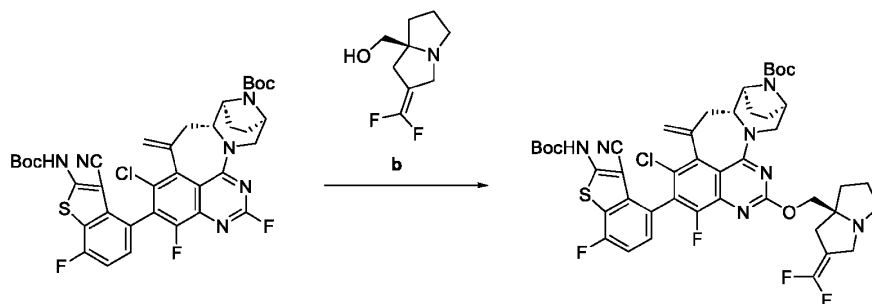
**Step 1: Synthesis of *tert*-butyl (1S,4R,14aR)-11-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[*b*]thiophen-4-yl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00464] To a solution of *tert*-butyl (1S,4R,14aR)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (5.0 g, 11.14 mmol, 1.0 eq) in THF (50 mL) was added (TMP)<sub>2</sub>Zn·2MgCl<sub>2</sub>·2LiCl (0.4 M, 83.5 mL, 33.42 mmol, 3.0 eq) under N<sub>2</sub>. The mixture was stirred at 50 °C for 1 h. Then

LCMS showed the reaction was completed by D<sub>2</sub>O (2 drops) quenching. Then the mixture was added a mixture of *tert*-butyl (4-bromo-3-cyano-7-fluorobenzo[*b*]thiophen-2-yl)carbamate (5.0 g, 13.37 mmol, 1.2 eq) and Cphos Pd G<sub>3</sub> (898 mg, 1.11 mmol, 0.1 eq) in 1,4-dioxane (50 mL). The mixture was stirred at 70 °C for 3 h. LCMS and HPLC showed the reaction was completed. The mixture was cooled to 0 °C~10 °C, quenched with water (5 mL) and filtered to give a filter cake and the filtrate 1. The filter cake was triturated with EtOAc (500 mL) to give filtrate 2. The combined solution of the filtrate of 1 and filtrate 2 was washed with brine (100 mL) and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (petroleum ether / EtOAc = 8:1) to afford *tert*-butyl (1*S*,4*R*,14*aR*)-11-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[*b*]thiophen-4-yl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-15-carboxylate (6.9 g, purity: 88%, yield: 83.8%). LCMS: 739.2 (M+H<sup>+</sup>).

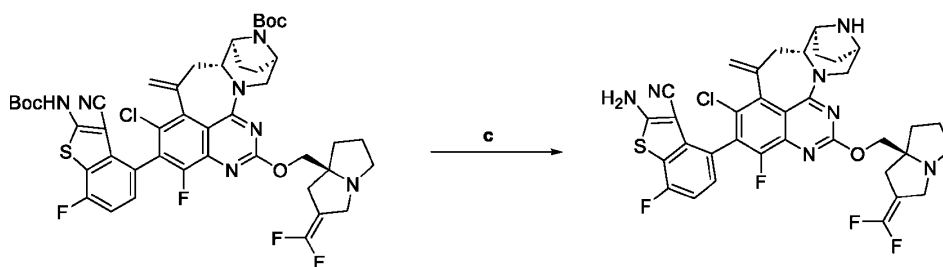
**Step 2: Synthesis of *tert*-butyl (1*S*,4*R*,14*aR*)-11-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[*b*]thiophen-4-yl)-12-chloro-8-(((*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-15-carboxylate**



[00465] To a solution of (*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methanol (715 mg, 3.78 mmol, 1.2 eq) in THF (10 mL) was added NaH (60%) (378 mg, 9.44 mmol, 3.0 eq) at 0 °C and then the mixture was stirred for 0.5 h at room temperature under N<sub>2</sub>. The mixture was added the solution of *tert*-butyl (1*S*, 4*R*, 14*aR*)-11-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[*b*]thiophen-4-yl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-15-carboxylate (1.7 g, 3.15 mmol, 1.0 eq) in THF (7 mL) and stirred at 25 °C for

1.5 h. HPLC and TLC showed the reaction was completed. The reaction mixture was quenched with saturated  $\text{NH}_4\text{Cl}$  aqueous solution (20 mL) and extracted with EtOAc (20 mL x 3). The organic layers were washed with brine (15 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (petroleum ether / EtOAc = 2:1) to afford *tert*-butyl (1S, 4R, 14aR)-11-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[*b*]thiophen-4-yl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (1.7 g, purity: 90%, yield: 81.4%) as a yellow solid. LCMS: 908.2 ( $\text{M}+\text{H}^+$ ).

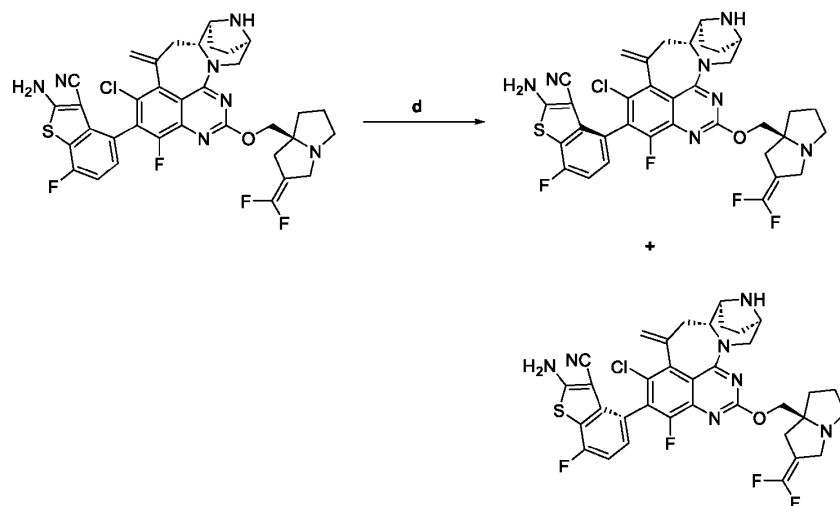
**Step 3: Synthesis of 2-amino-4-((1S, 4R, 4aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1',2':1,7] azepino [2,3,4-de] quinazolin-11-yl)-7-fluorobenzo[*b*]thiophene-3-carbonitrile**



[00466] To a solution of *tert*-butyl (1S,4R,14aR)-11-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[*b*]thiophen-4-yl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1',2':1,7] azepino [2,3,4-de] quinazoline-15-carboxylate (2.0 g, 2.20 mmol, 1.0 eq) in TFA (20 mL) and DCM (20 mL) was stirred at room temperature for 2 h under  $\text{N}_2$ . After completion, the mixture was concentrated to give a crude. The crude was dissolved in DCM/MeOH (10:1, 30 mL) and washed with saturated  $\text{Na}_2\text{CO}_3$  aqueous solution (15 mL x 3). The organic layer was washed with brine (15 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (DCM /  $\text{NH}_3$ -MeOH = 60:1) to afford 2-amino-4-((1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-

de] quinazolin-11-yl)-7-fluorobenzo [b] thiophene-3-carbonitrile (1.2 g, purity: 97%, yield: 76.9%) as a yellow solid.

**Step 4: Chiral Separation to prepare two pure diastereomers**



[00467] Chiral separation by chiral HPLC gave these two compounds:

[00468] 2-amino-4-((1S, 4R, 11R, 14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-de] quinazolin-11-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (350 mg, purity: 97.1%, yield: 22.4%, retention time = 12.957 under the analytical chiral separation condition) as a yellow solid.

[00469] <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  8.09 (brs, 2H), 7.24 (dd, *J* = 8.4, 5.2 Hz, 1H), 7.20-7.05 (m, 1H), 5.75 (s, 1H), 5.36 (s, 1H), 5.15-5.00 (m, 1H), 4.18 – 4.00 (m, 2H), 3.99 – 3.88 (m, 1H), 3.70 – 3.59 (m, 1H), 3.58 – 3.48 (m, 1H), 3.44 – 3.20 (m, 2H), 3.10 (d, *J* = 12.8 Hz, 1H), 3.04 – 2.90 (m, 2H), 2.89 – 2.70 (m, 1H), 2.69 – 2.51 (m, 2H), 2.46 – 2.20 (m, 2H), 2.03 – 1.70 (m, 5H), 1.62 – 1.40 (m, 3H). LCMS: *m/z* 708.2 (M+H<sup>+</sup>).

[00470] 2-amino-4-((1S, 4R, 11S, 14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1',2':1,7] azepino [2,3,4-de] quinazolin-11-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (294 mg, purity: 99.3%, yield: 18.8%, retention time = 5.084 under the analytical chiral separation condition) as a yellow solid.

[00471]  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.06 (brs, 2H), 7.30 (dd,  $J = 8.0, 5.2$  Hz, 1H), 7.14 (t,  $J = 9.2$  Hz, 1H), 5.70 (s, 1H), 5.28 (s, 1H), 5.15-5.05 (m, 1H), 4.18 – 4.01 (m, 2H), 3.99 – 3.89 (m, 1H), 3.70 – 3.59 (m, 1H), 3.58 – 3.48 (m, 1H), 3.44 – 3.20 (m, 2H), 3.12 (d,  $J = 12.4$  Hz, 1H), 3.06 – 2.71 (m, 3H), 2.69 – 2.51 (m, 2H), 2.46 – 2.35 (m, 1H), 2.35 – 2.20 (m, 1H), 2.03 – 1.91 (m, 1H), 1.90 – 1.70 (m, 4H), 1.62 – 1.40 (m, 2H), 1.39 – 1.28 (m, 1H). LCMS:  $m/z$  708.2 ( $\text{M}+\text{H}^+$ ).

**The analytical chiral separation condition:**

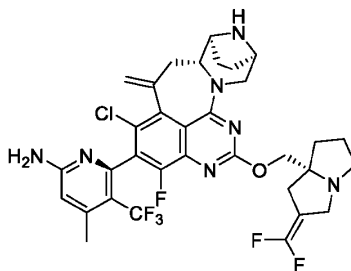
[00472] Instrument: Waters UPCC. Column: CHIRALPAK IG-3, 250×4.6 mm, 3  $\mu\text{m}$ . Mobile phase: A for  $\text{CO}_2$  and B for 0.1%DEA in MeOH. Gradient: B 40%. Flow rate: 2.0 mL/min. Column temperature: 35°C. Injection volume: 10.0  $\mu\text{l}$ , Wavelength: 210nm.

**The Preparative chiral separation condition:**

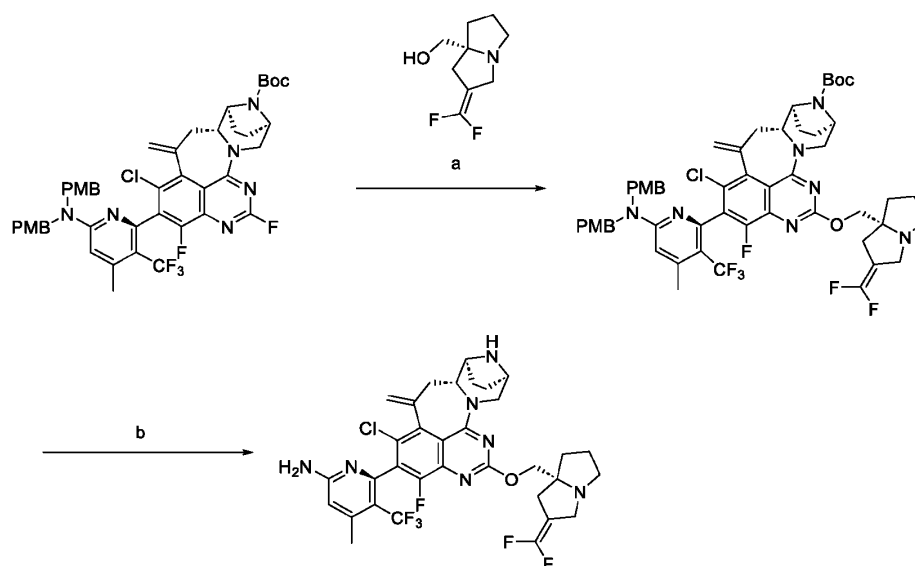
[00473] Instrument: Prep-HPLC-Gilson. Column: CHIRALPAK IK, 2 cm x 25 cm, 5 $\mu\text{m}$ . Mobile phase: A for Hex (0.5% 2mM  $\text{NH}_3$ -MeOH) and B for EtOH. Flow rate: 20 mL /min. Column temperature: 25°C. Wavelength: 220nm.

**Example 49**

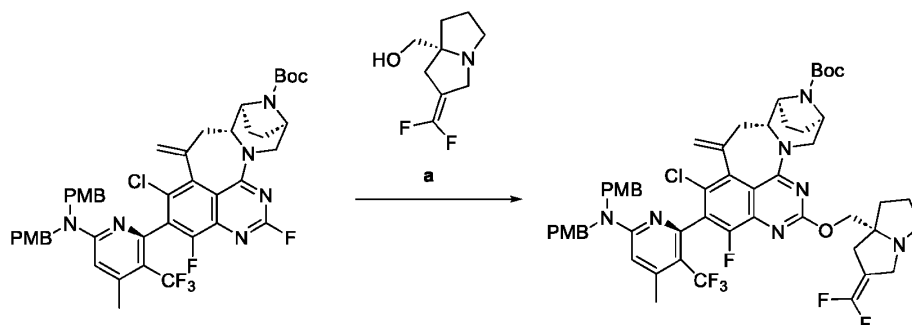
**6-((1S, 4R, 11R, 14aR)-12-chloro-8-(((R)-2-(difluoromethylene) tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-de] quinazolin-11-yl)-4-methyl-5-(trifluoromethyl) pyridin-2-amine**



**Synthetic scheme**



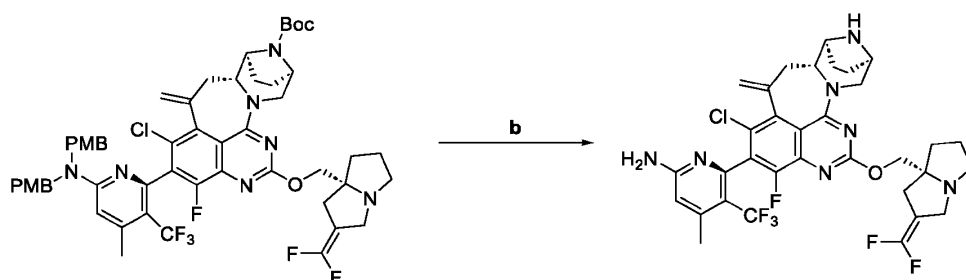
**Step 1: Synthesis of *tert*-butyl (1*S*, 4*R*, 11*R*, 14*aR*)-11-(6-(bis (4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl) pyridin-2-yl)-12-chloro-8- (((*R*)-2-(difluoromethylene) tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-15-carboxylate**



[00474] To a solution of (*R*)-2-(difluoromethylene) tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl) methanol (107.8 mg, 0.57 mmol, 1.5 eq) in THF (1.5 mL) was added NaH (60%) (45.6 mg, 1.14 mmol, 3.0 eq) at 0 °C and then the mixture was stirred for 0.5 h at room temperature under N<sub>2</sub>, added the solution of *tert*-butyl (1*S*, 4*R*, 14*aR*)-11-(6-(bis (4-methoxybenzyl) amino)-4-methyl-3-(trifluoromethyl) pyridin-2-yl)-12-chloro-8, 10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-15-carboxylate (330.0 mg, 0.38 mmol, 1.0 eq) in THF (4 mL) and stirred at 25 °C for 1.5 h. HPLC and TLC

show the reaction was completed. The reaction mixture was quenched with saturated  $\text{NH}_4\text{Cl}$  aqueous solution (10 mL) and extracted with EtOAc (20 mL x 3). The combined organic phase was concentrated to give a crude product, which was purified by silica gel column chromatography (DCM / MeOH = 80:1) to afford *tert*-butyl (1*S*, 4*R*, 11*R*, 14*aR*)-11-(6-(bis (4-methoxybenzyl) amino)-4-methyl-3-(trifluoromethyl) pyridin-2-yl)-12-chloro-8-(((*R*)-2-(difluoromethylene) tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-15-carboxylate (240.0 mg, 60.8%) as a yellow solid. LCMS: 516.7 (1/2M+ $\text{H}^+$ ).

**Step 2: Synthesis of 6-((1*S*, 4*R*, 11*R*, 14*aR*)-12-chloro-8-(((*R*)-2-(difluoromethylene) tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazolin-11-yl)-4-methyl-5-(trifluoromethyl) pyridin-2-amine**



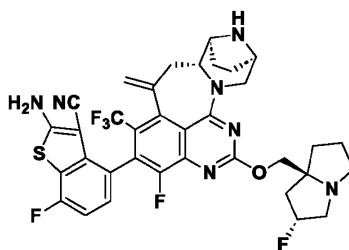
[00475] A mixture of *tert*-butyl (1*S*, 4*R*, 11*R*, 14*aR*)-11-(6-(bis (4-methoxybenzyl) amino)-4-methyl-3-(trifluoromethyl) pyridin-2-yl)-12-chloro-8-(((*R*)-2-(difluoromethylene) tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-15-carboxylate (240.0 mg, 0.23 mmol, 1.0 eq) in TFA (3 mL) was stirred at 50 °C for 3 h under  $\text{N}_2$ . After completion, the mixture was concentrated to give a crude, which was adjusted pH to 7 ~ 8 with saturated  $\text{Na}_2\text{CO}_3$  aqueous solution (30 mL) and extracted with DCM / MeOH (10:1, 20 mL x 3). The combined organic layers were washed with brine (10 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (acetonitrile with 0.1%  $\text{NH}_4\text{HCO}_3$  in water, 20% to 90%) to afford 6-((1*S*, 4*R*, 11*R*, 14*aR*)-12-chloro-8-(((*R*)-2-(difluoromethylene) tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazolin-11-yl)-4-methyl-5-(trifluoromethyl) pyridin-2-amine (36.0 mg, 22.6%) as a white solid.



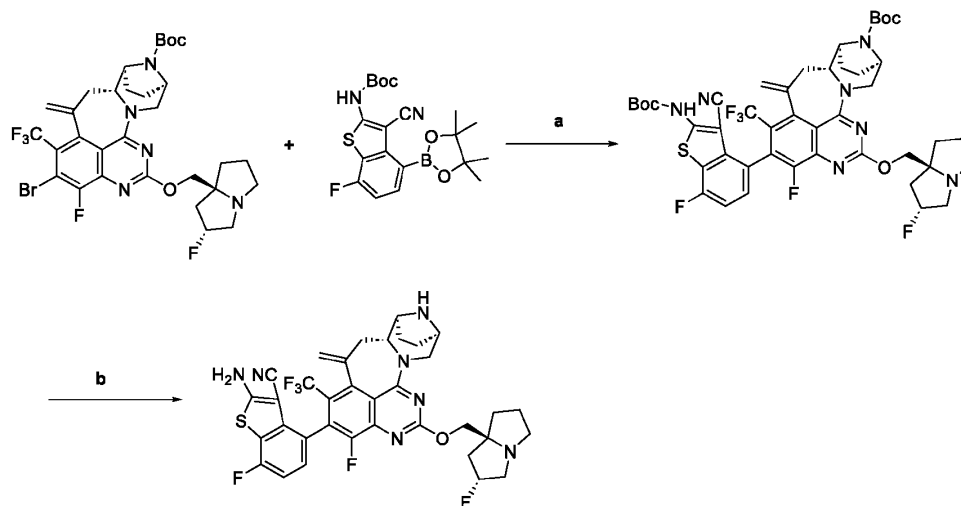
$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  6.84 (brs, 2H), 6.47 (s, 1H), 5.74 (s, 1H), 5.28 (s, 1H), 5.10–4.90 (m, 1H), 4.18–4.02 (m, 2H), 3.98–3.84 (m, 1H), 3.70–3.61 (m, 1H), 3.58–3.49 (m, 1H), 3.40–3.20 (m, 2H), 3.10 (d,  $J$  = 12.4 Hz, 1H), 3.03–2.88 (m, 2H), 2.83–2.53 (m, 3H), 2.45–2.31 (m, 4H), 2.30–2.15 (m, 1H), 2.03–1.70 (m, 5H), 1.63–1.40 (m, 3H). LCMS:  $m/z$  692.2 ( $M+H^+$ ).

### Example 50

(5aR,6S,9R)-12-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-1-fluoro-N-methyl-4-methylene-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxamide



### Synthetic scheme



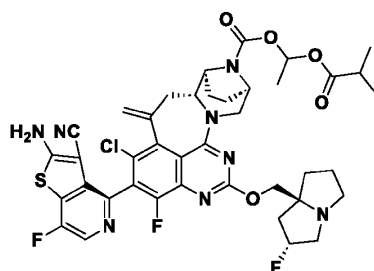
[00476] **Step 1:** To a solution of 2-methylpropan-2-yl (4R,7S,8R)-13-bromo-14-fluoro-17-(([(2R,7aS)-2-fluoro-2,3,5,6,7,7a-hexahydro-1H-pyrrolizin-7a-yl]methyl}oxy)-10-methylidene-12-(trifluoromethyl)-2,16,18,20-tetrazapentacyclo[13.3.1.1<sup>4,7</sup>.0<sup>11,19</sup>.0<sup>2,8</sup>]jicosa-

1(19),11(12),13,15(16),17-pentaene-20-carboxylate (200 mg, 0.285 mmol) in dioxane (5 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (279 mg, 0.856 mmol) and Pd(DPEphos)Cl<sub>2</sub> (61.3 mg, 0.086 mmol), the mixture was degassed and purged with nitrogen for several times, then stirred at 100 °C for 16 hours under nitrogen atmosphere. The mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-10%, DCM in MeOH) to afford 2-methylpropan-2-yl (4R,7S,8R)-13-[3-cyano-7-fluoro-2-({[(2-methylprop-2-yl)oxy]carbonyl}amino)benzothiophen-4-yl]-14-fluoro-17-({[(2R,7aS)-2-fluoro-2,3,5,6,7,7a-hexahydro-1H-pyrrolizin-7a-yl]methyl}oxy)-10-methylidene-12-(trifluoromethyl)-2,16,18,20-tetrazapentacyclo[13.3.1.14,7.011,19.02,8]jicosa-1(19),11(12),13,15(16),17-pentaene-20-carboxylate (60 mg, 0.066 mmol, 23%) as a yellow oil. LCMS: ESI m/z 912.0 [M + H]<sup>+</sup>.

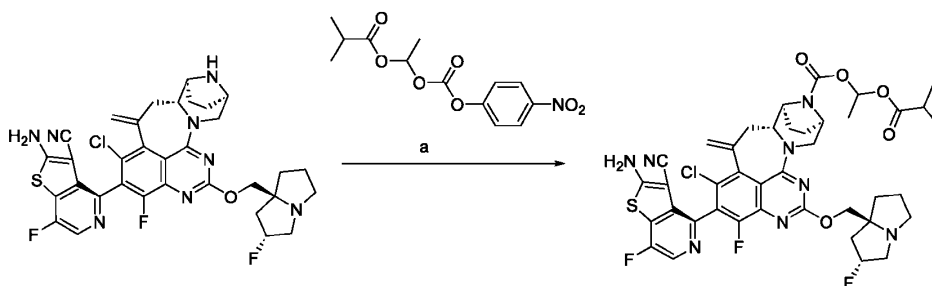
[00477] **Step 2:** To a solution of 2-methylpropan-2-yl (4R,7S,8R)-13-[3-cyano-7-fluoro-2-({[(2-methylprop-2-yl)oxy]carbonyl}amino)benzo[b]thiophen-4-yl]-14-fluoro-17-({[(2R,7aS)-2-fluoro-2,3,5,6,7,7a-hexahydro-1H-pyrrolizin-7a-yl]methyl}oxy)-10-methylidene-12-(trifluoromethyl)-2,16,18,20-tetrazapentacyclo[13.3.1.14,7.011,19.02,8]jicosa-1(19),11(12),13,15(16),17-pentaene-20-carboxylate (40 mg, 0.044 mmol) in DCM (3 mL) was added dropwise TFA (1 mL, 13.0 mmol) with mixing at rt. The resulting mixture was allowed to be warmed to room temperature for 30 min. The reaction was complete detected by LCMS. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to afford 2-amino-7-fluoro-4-[(4R,7S,8R)-14-fluoro-17-({[(2R,7aS)-2-fluoro-2,3,5,6,7,7a-hexahydro-1H-pyrrolizin-7a-yl]methyl}oxy)-10-methylidene-12-(trifluoromethyl)-2,16,18,20-tetrazapentacyclo[13.3.1.14,7.011,19.02,8]jicosa-1(19),11(12),13,15(16),17-pentaen-13-yl]benzo[b]thiophene-3-carbonitrile (6.3 mg, 0.009 mmol, 20%) as a white solid. LCMS: ESI m/z 712.2 [M + H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) δ 7.29 – 7.12 (m, 1H), 7.06 – 6.98 (m, 1H), 6.05 – 5.11 (m, 4H), 4.75 – 4.61 (m, 2H), 4.46 – 4.37 (m, 1H), 4.36 – 4.16 (m, 2H), 4.07 – 3.84 (m, 3H), 3.51 – 3.41 (m, 1H), 3.29 – 3.03 (m, 2H), 2.75 – 1.93 (m, 11H).

### Example 51

**1-(isobutyryloxy)ethyl (1S,4R,11S,14aR)-11-(2-amino-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino [2,3,4-de]quinazoline-15-carboxylate**



### Synthesis scheme



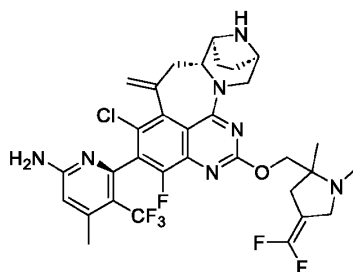
### Step 1: Synthesis of 1-(isobutyryloxy)ethyl (1S,4R,11S,14aR)-11-(2-amino-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate

[00478] To a solution of compound 2-amino-4-(((1S,4R,11S,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile (70 mg, 0.10 mmol, 1.0 eq) in THF (1.0 mL) and H<sub>2</sub>O (0.2 mL) was added compound 1-(((4-nitrophenoxy)carbonyl)oxy)ethyl isobutyrate (25 mg, 0.08 mmol, 0.8 eq) and NaHCO<sub>3</sub> (87 mg, 1.03 mmol, 10.0 eq). The mixture was stirred at room temperature for 5 h. The mixture was partitioned between EtOAc (10 mL) and water (10 mL). The layers were separated. The aqueous layer was extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness. The crude product was purified by Prep-HPLC (acetonitrile with 0.1% FA in water, 30% to 80%) to give compound 1-(isobutyryloxy)ethyl (1S,4R,11S,14aR)-11-(2-amino-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate formate (1:0.19) (12.8

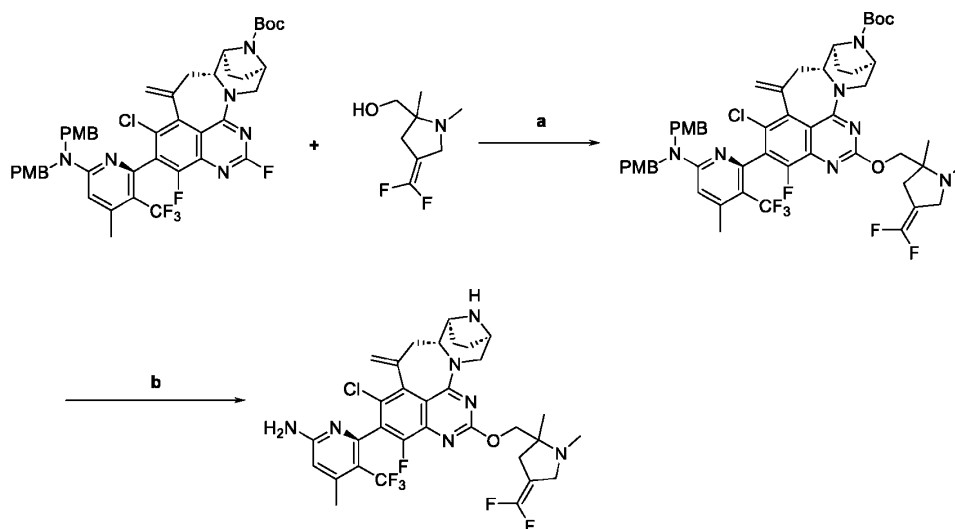
mg, 14.7%) as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  8.51 (s, 0.19H), 8.30 (s, 1H), 6.91 – 6.69 (m, 1H), 5.84 (s, 1H), 5.57 (s, 1H), 5.50 – 5.28 (m, 2H), 4.58 – 4.41 (m, 1H), 4.37 – 4.21 (m, 3H), 4.18 – 3.99 (m, 1H), 3.52 – 3.36 (m, 1H), 3.31 – 3.02 (m, 5H), 2.71 – 2.51 (m, 1H), 2.49 – 2.15 (m, 5H), 2.11 – 1.99 (m, 2H), 1.97 – 1.81 (m, 3H), 1.78 – 1.63 (m, 1H), 1.54 (d,  $J$  = 5.2 Hz, 3H), 1.28 – 1.11 (m, 6H). LCMS: 837.2 (M-0.19 FA+ $\text{H}^+$ ).

### Example 52

**6-((1S,4R,11R,14aR)-12-chloro-8-((4-(difluoromethylene)-1,2-dimethylpyrrolidin-2-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine**

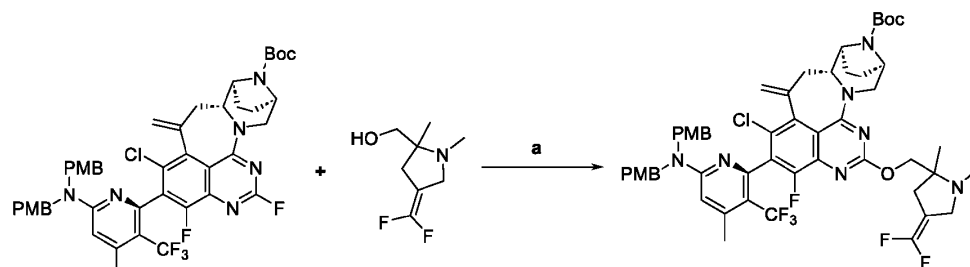


### Synthetic scheme



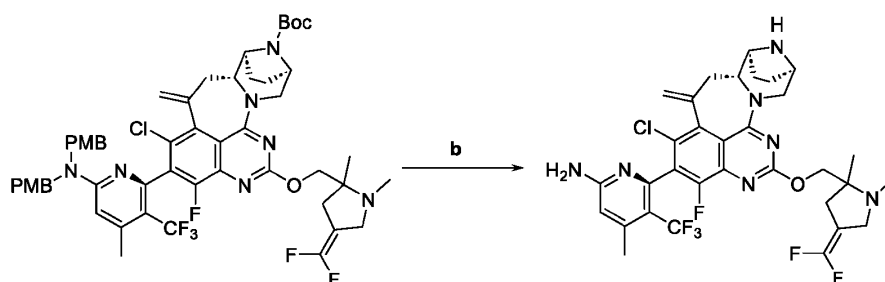
**Step 1: tert-butyl (1RS,4SR,11S,14aSR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-((4-(difluoromethylene)-1,2-dimethylpyrrolidin-**

**2-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00479] To a solution of (4-(difluoromethylene)-1,2-dimethylpyrrolidin-2-yl)methanol (60 %) (200.0 mg, 0.68 mmol, 1.5 eq) in THF (2 mL) was added NaH (60%) (55.0 mg, 1.4 mmol, 3.0 eq) at 0 °C under nitrogen atmosphere. The mixture was stirred at room temperature for 0.5 h under N<sub>2</sub>. Then was added tert-butyl (1*RS*,4*SR*,11*S*,14*aSR*)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (390.0 mg, 0.45 mmol, 1.0 eq) in THF (4 mL) at room temperature under nitrogen atmosphere. The mixture was stirred at room temperature for 2 h under N<sub>2</sub>. HPLC showed the reaction was completed. The reaction mixture was quenched by the addition of the saturated aqueous NH<sub>4</sub>Cl (5 mL). Then the reaction was filtered and the filtrate was diluted extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give crude product, which was purified by silica gel column chromatography (eluted with petroleum ether: EtOAc = 2: 1) to afford tert-butyl (1*RS*,4*SR*,11*S*,14*aSR*)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-((4-(difluoromethylene)-1,2-dimethylpyrrolidin-2-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (390.0 mg, purity: 95%, yield: 82.5%) as a yellow solid. LCMS: 1020.2 (M+H<sup>+</sup>).

**Step 2: 6-((1*RS*,4*SR*,11*S*,14*aSR*)-12-chloro-8-((4-(difluoromethylene)-1,2-dimethylpyrrolidin-2-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine**

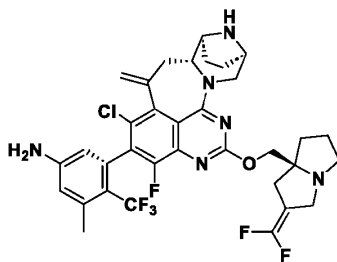


[00480] To a solution of tert-butyl (1*RS*,4*SR*,11*S*,14*aSR*)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-((4-(difluoromethylene)-1,2-dimethylpyrrolidin-2-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-15-carboxylate (100.0 mg, 0.1 mmol, 1.0 eq) in TFA (3 mL). The mixture was stirred at 50 °C for 3 h. HPLC showed the reaction was completed. The mixture was adjusted to pH ~ 7 with saturated aqueous Na<sub>2</sub>CO<sub>3</sub> (5 mL). Then the reaction was filtered, and the filtrate was diluted extracted with DCM: MeOH = (10: 1) (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give crude product, which was purified by silica gel column chromatography (DCM: 7.0 M NH<sub>3</sub> In MeOH = 20: 1) to afford 6-((1*RS*,4*SR*,11*S*,14*aSR*)-12-chloro-8-((4-(difluoromethylene)-1,2-dimethylpyrrolidin-2-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (50.0 mg, purity: 96%, yield: 73.5%).

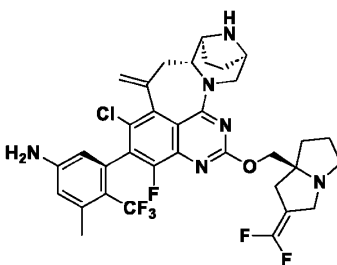
[00481] <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 6.85 (s, 2H), 6.47 (s, 1H), 5.74 (s, 1H), 5.29 (s, 1H), 5.10-4.90 (m, 1H), 4.40-4.15 (m, 2H), 4.00-3.80 (m, 1H), 3.60-3.40 (m, 2H), 3.20-3.00 (m, 2H), 2.96-2.85 (m, 2H), 2.40-2.20 (m, 6H), 1.60-1.40 (m, 3H), 1.35-1.15 (m, 4H), 1.06 (s, 3H). LCMS: 680.3 (M+H<sup>+</sup>).

### Examples 53 & 54

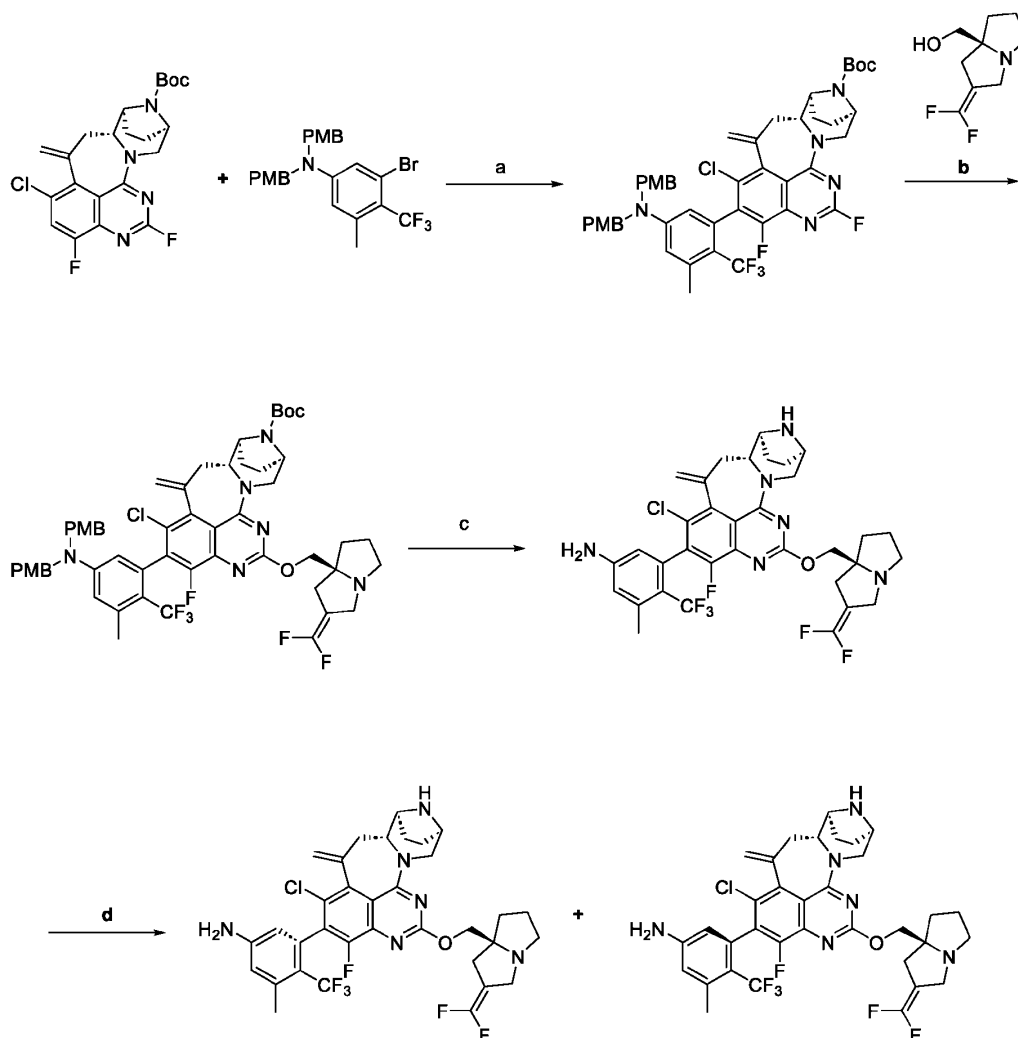
**Example 53: 3-((1*S*,4*R*,11*R*,14*aR*)-12-chloro-8-(((*S*)-2-(difluoromethylene) tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino [1',2':1,7]azepino[2,3,4-*de*]quinazolin-11-yl)-5-methyl-4-(trifluoromethyl)aniline**



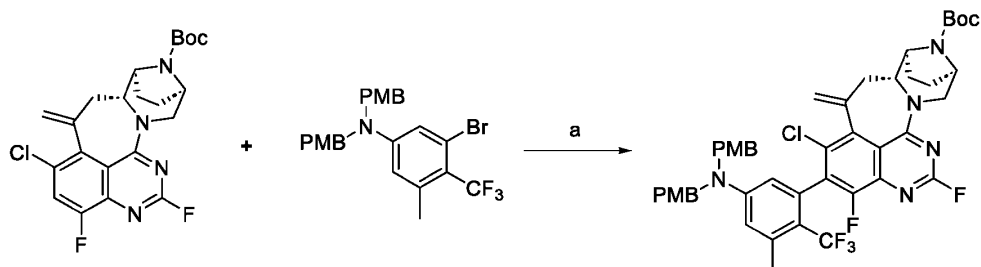
**Example 54:** 3-((1S,4R,11S,14aR)-12-chloro-8-(((S)-2-(difluoromethylene) tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino [1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-methyl-4-(trifluoromethyl)aniline



Synthesis scheme



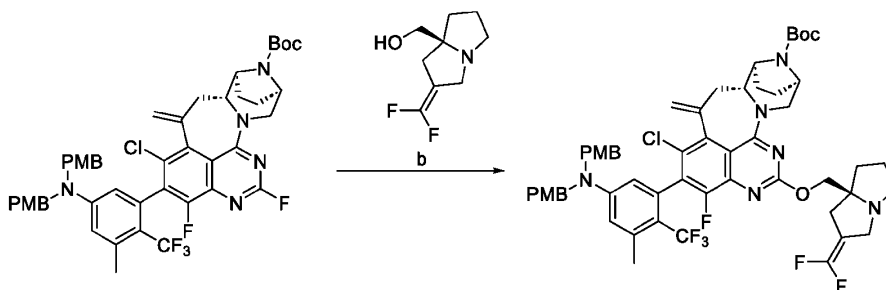
**Step 1: Synthesis of tert-butyl (1S,4R,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**





[00482] To a solution of tert-butyl (1S,4R,14aR)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (1.0 g, 2.23 mmol, 1.0 eq) in THF (10 mL) was added (TMP)<sub>2</sub>Zn·MgCl<sub>2</sub>·LiCl (0.4 M, 33 mL, 13.4 mmol, 6.0 eq) under N<sub>2</sub>, the mixture was stirred at 50 °C for 2 h. Then a mixture of 3-bromo-N,N-bis(4-methoxybenzyl)-5-methyl-4-(trifluoromethyl)aniline (1.3 g, 2.68 mmol, 1.2 eq) and RuPhos Pd G2 (260 mg, 0.33 mmol, 0.15 eq) in 1,4-dioxane (3 mL) was added to the mixture. The mixture was stirred at 70 °C for 2 h under N<sub>2</sub>. The reaction was quenched with H<sub>2</sub>O (10 mL). The mixture was filtered, the filter cake was washed with large EtOAc and separated. The aqueous layer was extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude product. The crude product was purified by silica gel column chromatography (Petroleum ether: EtOAc = 1: 1) to give tert-butyl (1S,4R,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (957 mg, 49.8%) as a brown solid. LCMS: m/z 862.2 (M+H<sup>+</sup>).

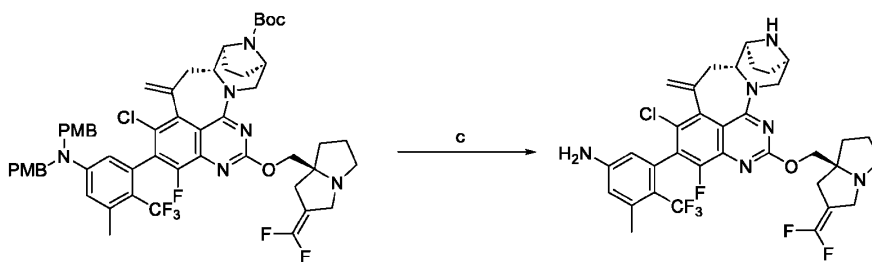
**Step 2: Synthesis of tert-butyl (1S,4R,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00483] To a solution of (S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-ylmethanol (329 mg, 1.74 mmol, 1.5 eq) in THF (10 mL) was added NaH (139 mg, 3.48 mmol, 3.0 eq), the reaction mixture was stirred at room temperature for 0.5 h under N<sub>2</sub>. To the reaction mixture was added tert-butyl (1S,4R,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (1.0 g, 1.16 mmol,

1.0 eq) in THF (2 mL), the reaction was stirred at room temperature for 2 h. The reaction was quenched with H<sub>2</sub>O (20 mL) at 0 °C. The resulting mixture was extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude product. The crude product was purified by silica gel column chromatography (DCM: MeOH = 60: 1) to give tert-butyl (1S,4R,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (773 mg, 64.6%) as a yellow solid. LCMS: m/z 1031.3 (M+H<sup>+</sup>).

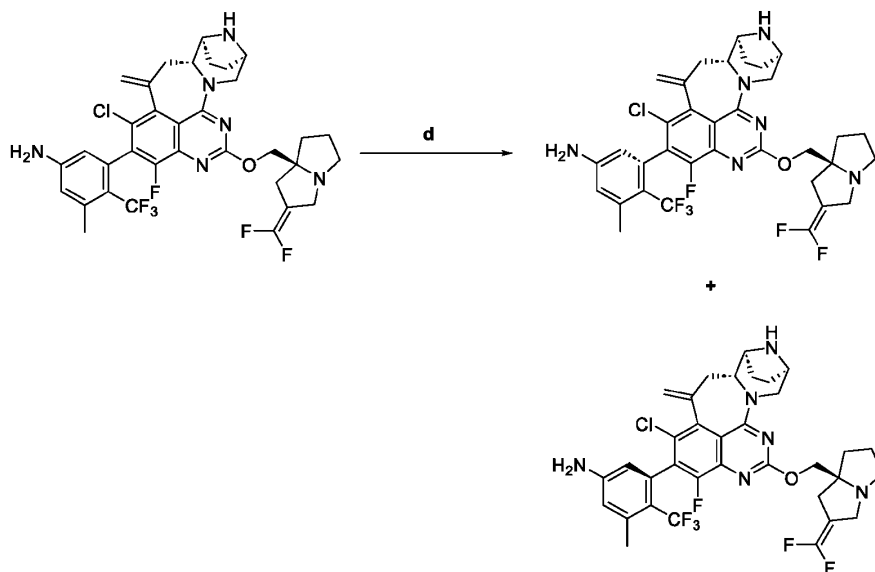
**Step 3: Synthesis of 3-((1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-methyl-4-(trifluoromethyl)aniline**



[00484] A solution of tert-butyl (1S,4R,14aR)-11-(5-(bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (800 mg, 0.78 mmol, 1.0 eq) in TFA (8 mL) was stirred at 50 °C for 3 h. The reaction was concentrated to give a crude product. The crude product was purified by Prep-HPLC (10% ~ 55% ACN in water with 0.1% FA) to give 3-((1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-methyl-4-(trifluoromethyl)aniline (376 mg, 70.2%) as a yellow solid. LCMS: m/z 691.3 (M+H<sup>+</sup>).

**Step 4: Synthesis of 3-((1S,4R,11R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-**

octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-methyl-4-(trifluoromethyl)aniline formate 2,2,2-trifluoroacetate (1:0.15:1.88) and 3-((1S,4R,11S,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-methyl-4-(trifluoromethyl)aniline



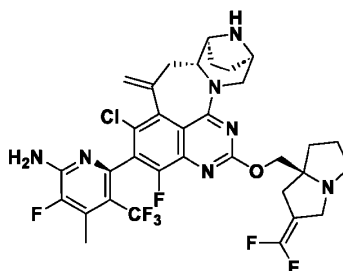
[00485] 2-amino-4-((1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile (400 mg) was separated by chiral preparative HPLC (Column: Lux Cellulose-3, 2 cm x 25 cm, 5  $\mu$ m, Mobile phase: A for Hex (0.5% 2mM  $\text{NH}_3$ -MeOH) : B for EtOH = 50 : 50, Flow rate: 20 mL/min, Column temperature: 25  $^\circ\text{C}$ , UV 220 nm) to afford 3-((1S,4R,11R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-methyl-4-(trifluoromethyl)aniline formate 2,2,2-trifluoroacetate (1:0.15:1.88) (60 mg, 11.3%) and 3-((1S,4R,11S,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-methyl-4-(trifluoromethyl)aniline formate 2,2,2-trifluoroacetate (1:0.62:1.59) (100 mg, 18.8%) respectively.

[00486] **Peak 1:** 3-((1S,4R,11R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-methyl-4-(trifluoromethyl)aniline formate 2,2,2-trifluoroacetate (1:0.15:1.88): Chiral purity: 98.00% de; retention time: 18.249 min; UPCC method: Column: CHIRALPAK OD-3, 4.6mm\*250mm, 3  $\mu$ m, Mobile phase: A for CO<sub>2</sub>: B for 0.1% DEA in MeOH = 75: 25, Flow rate: 2.0 mL/min, Column temperature: 35 °C. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD):  $\delta$  8.18 (s, 0.15H), 6.70 (s, 1H), 6.25 (d,  $J$  = 2.4 Hz, 1H), 5.90 (s, 1H), 5.61 – 5.55 (m, 2H), 4.66 – 4.56 (m, 2H), 4.35 – 4.23 (m, 3H), 4.09 (d,  $J$  = 5.2 Hz, 1H), 3.96 (d,  $J$  = 14.4 Hz, 1H), 3.69 – 3.59 (m, 1H), 3.45 – 3.39 (m, 1H), 3.27 – 3.16 (m, 1H), 3.07 – 2.99 (m, 2H), 2.80 (d,  $J$  = 16.0 Hz, 1H), 2.52 – 2.42 (m, 5H), 2.36 – 1.93 (m, 7H). LCMS: m/z 691.2 (M-0.15 FA-1.88 TFA+H<sup>+</sup>).

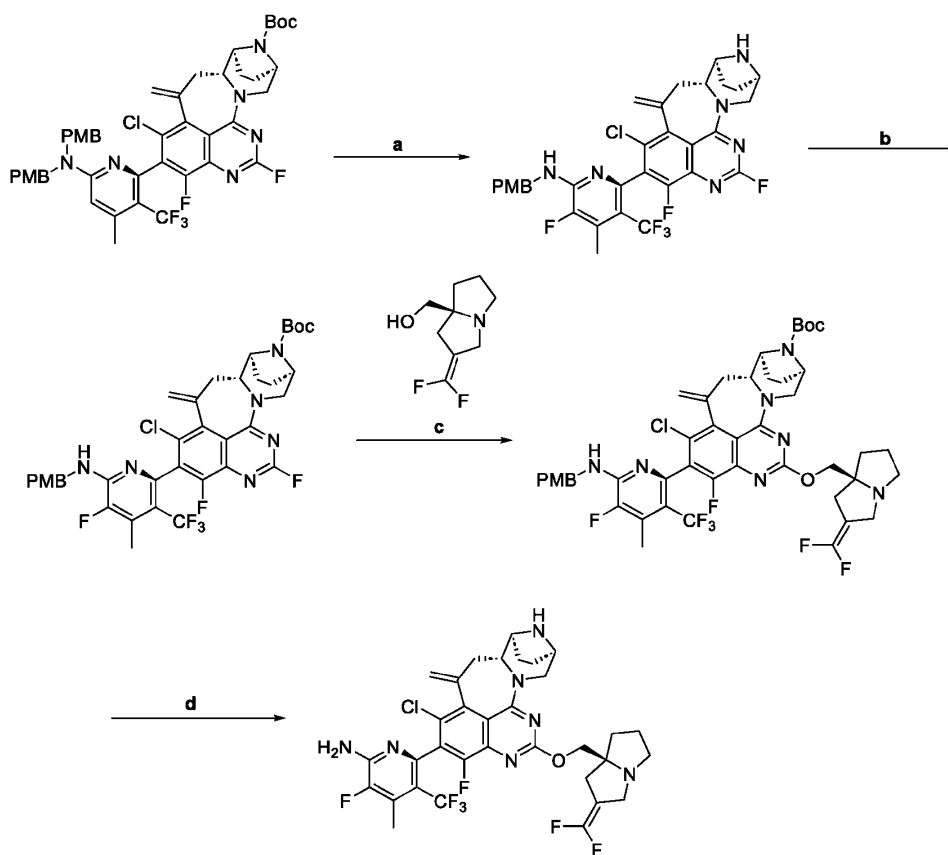
[00487] **Peak 2:** 3-((1S,4R,11S,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-methyl-4-(trifluoromethyl)aniline formate 2,2,2-trifluoroacetate (1:0.62:1.59): Chiral purity: 95.60% de; retention time: 21.760 min; UPCC method: Column: CHIRALPAK OD-3, 4.6mm\*250mm, 3  $\mu$ m, Mobile phase: A for CO<sub>2</sub>: B for 0.1% DEA in MeOH = 75: 25, Flow rate: 2.0 mL/min, Column temperature: 35 °C. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD):  $\delta$  8.27 (s, 0.62H), 6.70 (s, 1H), 6.28 (d,  $J$  = 2.4 Hz, 1H), 5.89 (s, 1H), 5.61 – 5.52 (m, 2H), 4.59 – 4.52 (m, 2H), 4.30 – 4.20 (m, 3H), 4.10 – 4.02 (m, 1H), 3.88 (d,  $J$  = 14.4 Hz, 1H), 3.60 – 3.54 (m, 1H), 3.41 (d,  $J$  = 14.4 Hz, 1H), 3.16 – 3.09 (m, 1H), 3.07 – 2.95 (m, 2H), 2.75 (d,  $J$  = 16.0 Hz, 1H), 2.52 – 2.42 (m, 5H), 2.32 – 1.95 (m, 7H). LCMS: m/z 691.2 (M-0.62 FA-1.59 TFA+H<sup>+</sup>).

### Example 55

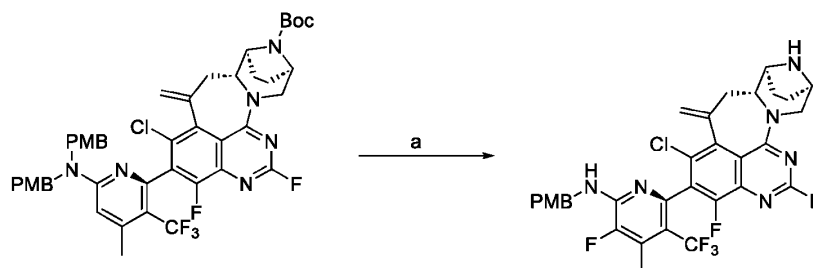
**6-((1S, 4R, 11R, 14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-de] quinazolin-11-yl)-3-fluoro-4-methyl-5-(trifluoromethyl)pyridin-2-amine**



### Synthetic scheme

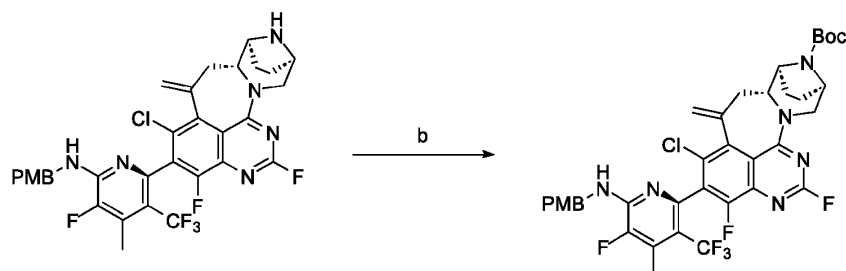


**Step 1: Synthesis of 6-((1S, 4R, 11R, 14aR)-12-chloro-8,10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-de] quinazolin-11-yl)-3-fluoro-N-(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine**



[00488] To a solution of *tert*-butyl (1S, 4R, 11R, 14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8,10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (500.0 mg, 0.58 mmol, 1.0 eq), in ACN (5.0 mL) was added Selectfluor (410.5 mg, 1.16 mmol, 2.0 eq) at 25 °C. Then the mixture was stirred at 50 °C for 16 h under N<sub>2</sub>. The mixture was diluted with water (15 mL) and extracted with EtOAc (15 mL x 3). The organic layers were washed with brine (20 mL), then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a residue, which was purified by silica gel chromatography (DCM / MeOH = 10:1) to afford 6-((1S, 4R, 11R, 14aR)-12-chloro-8,10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-3-fluoro-N-(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (230 mg, purity: 65%, yield: 39.0%). LCMS: 661.2 (M+H<sup>+</sup>).

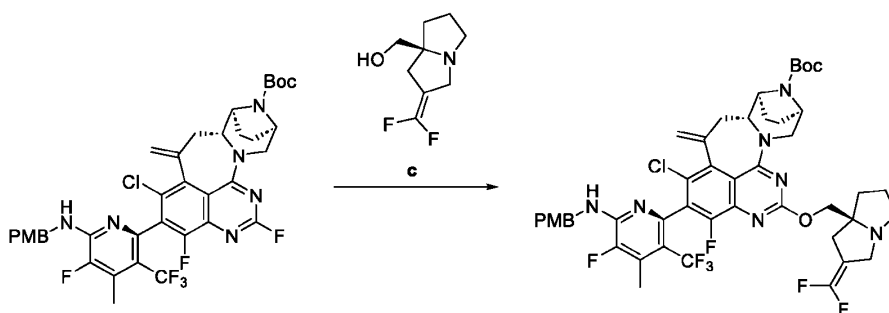
**Step 2: Synthesis of *tert*-butyl (1S, 4R, 11R, 14aR)-12-chloro-8,10-difluoro-11-(5-fluoro-6-((4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00489] To a solution of 6-((1S, 4R, 11R, 14aR)-12-chloro-8,10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-3-fluoro-N-(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (230.0 mg, 0.35

mmol, 1.0 eq), DIEA (134.8 mg, 1.04 mmol, 3.0 eq) in DCM (3 mL) was added (Boc)<sub>2</sub>O (151.9 mg, 0.70 mmol, 2.0 eq). The mixture was stirred at room temperature for 2 h under N<sub>2</sub>. Upon completion, the mixture was diluted with water (20 mL) and extracted with DCM (20 mL x 3). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to give a residue, which was purified by prep-TLC (petroleum ether / EtOAc = 2:1) to afford *tert*-butyl (1S, 4R, 11R, 14aR)-12-chloro-8,10-difluoro-11-(5-fluoro-6-((4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (48.0 mg, purity: 78%, yield: 21.7%) as a yellow solid. LCMS: 761.2 (M+H<sup>+</sup>).

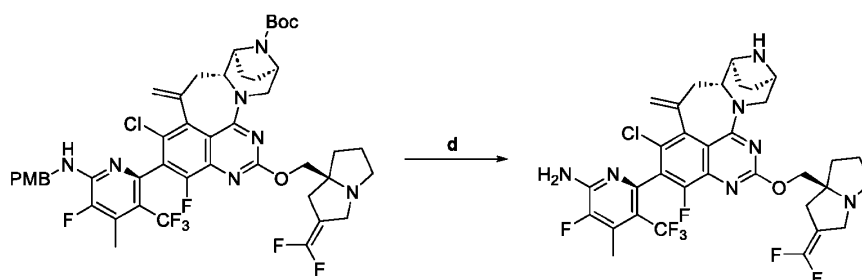
**Step 3: Synthesis of *tert*-butyl (1S, 4R, 11R, 14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-11-(5-fluoro-6-((4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00490] To a solution of *tert*-butyl (1S, 4R, 11R, 14aR)-12-chloro-8,10-difluoro-11-(5-fluoro-6-((4-methoxybenzyl) amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (48.0 mg, 0.06 mmol, 1.0 eq), (S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (14.3 mg, 0.08 mmol, 1.2 eq) in THF (1.0 mL) was added *t*-BuONa (12.0 mg, 0.12 mmol, 2.0 eq) at 15 °C. Then the mixture was added DMF (0.2 mL) and stirred at 25 °C for 2 h under N<sub>2</sub>. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The organic layers were washed with water (20 mL x 3) and brine (20 mL), then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a residue, which was purified by prep-TLC (DCM / MeOH = 10:1) to afford *tert*-butyl (1S, 4R, 11R, 14aR)-12-chloro-8-(((S)-2-

(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-11-(5-fluoro-6-((4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1',2':1,7] azepino[2,3,4-de]quinazoline-15-carboxylate (34.0 mg, purity: 90%, yield: 66.8%). LCMS: 930.2 (M+H<sup>+</sup>).

**Step 4: Synthesis of 6-((1S, 4R, 11R, 14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-de] quinazolin-11-yl)-3-fluoro-4-methyl-5-(trifluoromethyl) pyridin-2-amine formate (1:0.58)**



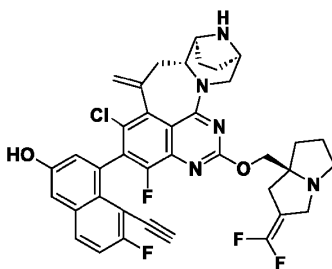
[00491] The solution of tert-butyl (1S, 4R, 11R, 14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-11-(5-fluoro-6-((4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1',2':1,7] azepino [2,3,4-de] quinazoline-15-carboxylate (34.0 mg, 0.04 mmol, 1.0 eq) in TFA (0.6 mL) was stirred at 50 °C for 2 h under N<sub>2</sub>. Then the mixture was concentrated under reduced pressure to give a crude product, which was adjusted pH to 7~8 with saturated sodium bicarbonate aqueous solution and extracted with DCM / MeOH (10:1, 10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a crude. The crude was purified by Prep-HPLC (acetonitrile with 0.1% FA in water, 50% to 80%) to afford 6-((1S, 4R, 11R, 14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-3-fluoro-4-methyl-5-(trifluoromethyl)pyridin-2-amine formate (1:0.58) (9.3 mg, purity: 97.0%, yield: 37.2%) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.20 (brs, 0.58H), 7.22 (brs, 2H), 5.75 (s, 1H), 5.29 (s, 1H), 5.10-4.90 (m, 1H), 4.18 – 4.00 (m, 2H), 3.99 – 3.87 (m, 1H), 3.70 – 3.60 (m, 2H), 3.59 – 3.50 (m, 2H), 3.18 – 3.06 (m, 2H), 3.05 – 2.84 (m, 2H), 2.70 – 2.51 (m, 2H), 2.44 – 2.38



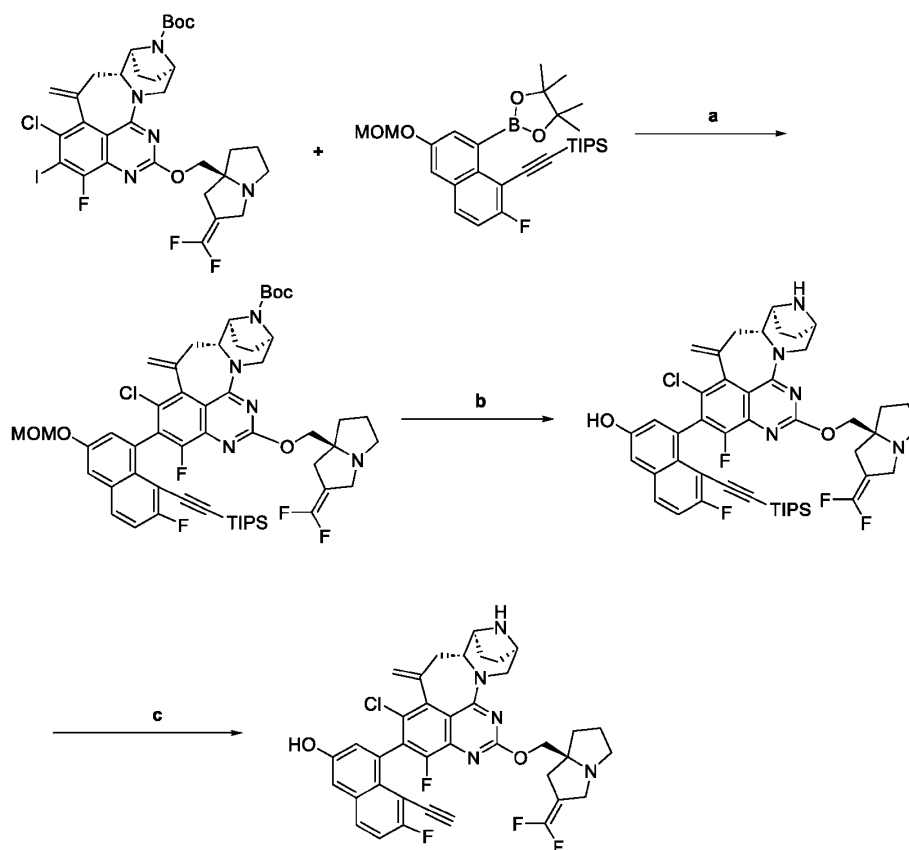
(m, 1H), 2.34 (s, 3H), 2.30-2.20 (m, 1H), 1.99 – 1.83 (m, 3H), 1.83 – 1.70 (m, 2H), 1.63 – 1.40 (m, 3H). LCMS:  $m/z$  710.2 ( $M+H^+$ ).

#### Example 56

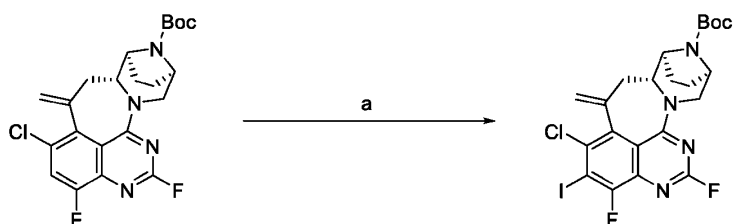
**4-((1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-ethynyl-6-fluoronaphthalen-2-ol**



**Synthetic scheme**



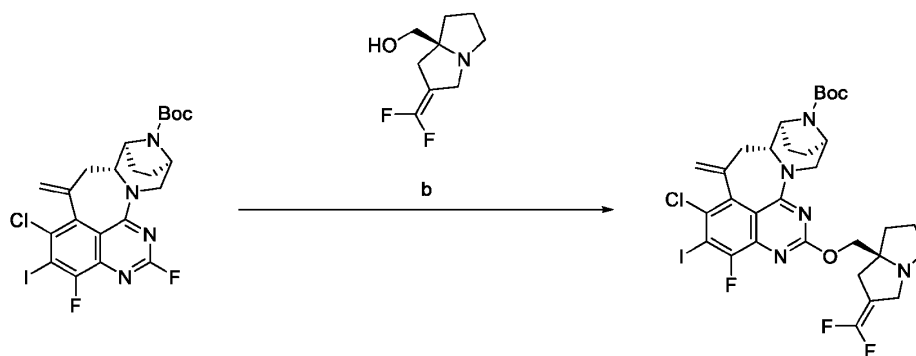
**Step 1: Synthesis of tert-butyl (1S,4R,14aR)-12-chloro-8,10-difluoro-11-iodo-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00492] To a solution of tert-butyl (1S,4R,14aR)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (10.0 g, 22.3 mmol, 1.0 eq) in THF (100 mL) was added LDA (2.0M in THF, 33.4 mL, 3.0 eq) by dropwise at -78°C under N<sub>2</sub>. The mixture was stirred at -78 °C for 1h, then was added I<sub>2</sub> (14.1 g, 55.7 mmol, 2.5 eq) in THF (10.0 mL) by dropwise at -78 °C under N<sub>2</sub>, and the

mixture was stirred at -78°C for 1h. The mixture was diluted with water (200 mL) and extracted with EtOAc (200 mL x 2). The organic layers were washed with water (200 mL) and brine (200 mL), then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a residue. The crude product was purified by silica gel chromatography (eluted with petroleum ether: EtOAc = 10: 1) to afford tert-butyl (1S,4R,14aR)-12-chloro-8,10-difluoro-11-iodo-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (12.0 g, purity: 95.0%, yield: 93.6%). LCMS: 575.0 (M+H<sup>+</sup>).

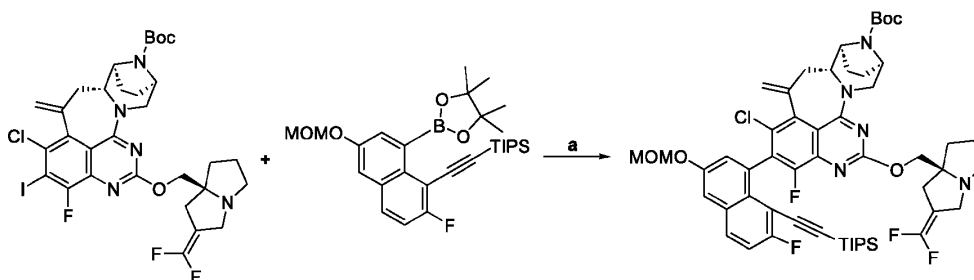
**Step 2: Synthesis of tert-butyl (1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-11-iodo-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00493] To a solution of tert-butyl (1S,4R,14aR)-12-chloro-8,10-difluoro-11-iodo-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (500.0 mg, 0.87 mmol, 1.0 eq), (S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-ylmethanol (197.0 mg, 1.04 mmol, 1.2 eq) in THF (5 mL) was added *t*-BuONa (167.1 mg, 1.74 mmol, 2.0 eq) at 25 °C. Then DMF (1 mL) was added and stirred at 25 °C for 3 h under N<sub>2</sub>. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The organic layers were washed with water (20 mL x 3) and brine (20 mL), then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a residue. The crude product was purified by silica gel chromatography (eluted with petroleum ether: EtOAc = 3: 1) to afford tert-butyl (1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-11-iodo-13-methylene-1,2,3,4,5,13,14,14a-octahydro-

1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (1.2 g, purity: 89%, yield: 77.3%) as a yellow solid. LCMS: 744.1 (M+H<sup>+</sup>).

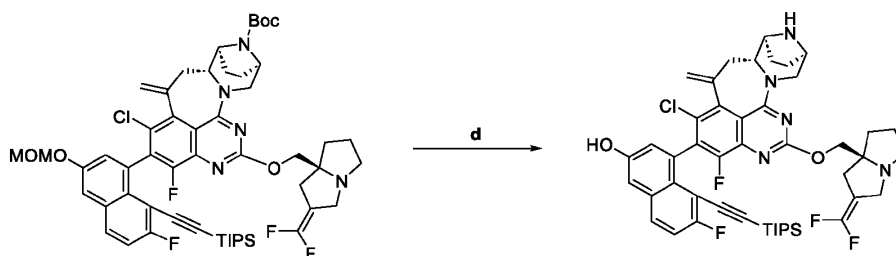
**Step 3: Synthesis of tert-butyl (1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-11-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00494] To a solution of tert-butyl (1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-11-iodo-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (500.0 mg, 0.67 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 (413.7 mg, 0.81 mmol, 1.2 eq), Cs<sub>2</sub>CO<sub>3</sub> (655.8 mg, 2.02 mmol, 3.0 eq) and cataCXium A Pd G3 (97.8 mg, 0.13 mmol, 0.2 eq) in the microwave tube, Toluene (5 mL) and water (1 mL) was added. The tube was irradiated under microwave at 120 °C for 1.5 h under N<sub>2</sub>. Upon completion, the mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to give a residue. The crude product was purified by prep-TLC (petroleum ether/ EtOAc = 1: 1) to afford tert-butyl (1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-11-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (450 mg, purity: 85%, yield: 66.8%) as a yellow solid. LCMS: 501.8 (1/2M+H<sup>+</sup>).

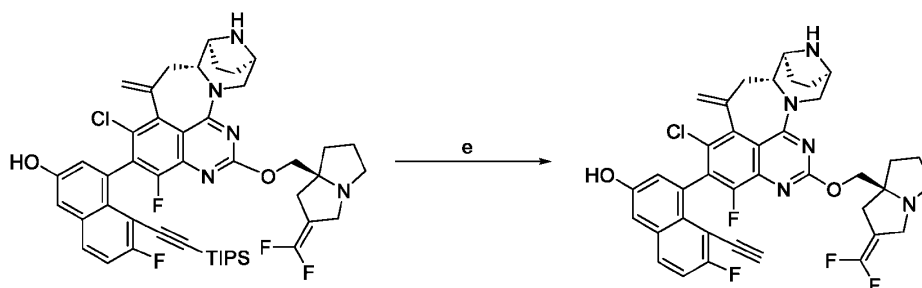
**Step 4: Synthesis of 4-((1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-**

**1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol**



To a solution of tert-butyl (1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-11-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-15-carboxylate (50.0 mg, 0.05 mmol, 1.0 eq) in ACN (1 mL) was added HCl/dioxane(4M) (0.5 mL, 2.00 mmol, 40.0 eq) at 25 °C under N<sub>2</sub> atmosphere. Then the reaction was stirred at 25 °C for 1.5 h. Then the mixture was concentrated to give a residue to afford 4-((1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (60 mg, purity: crude) as a brown solid. LCMS: 858.3 (M+H<sup>+</sup>).

**Step 5: Synthesis of 4-((1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate (1:0.77)**

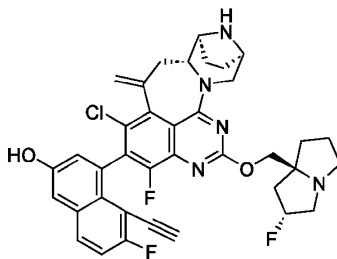


[00495] To a solution of 4-((1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-

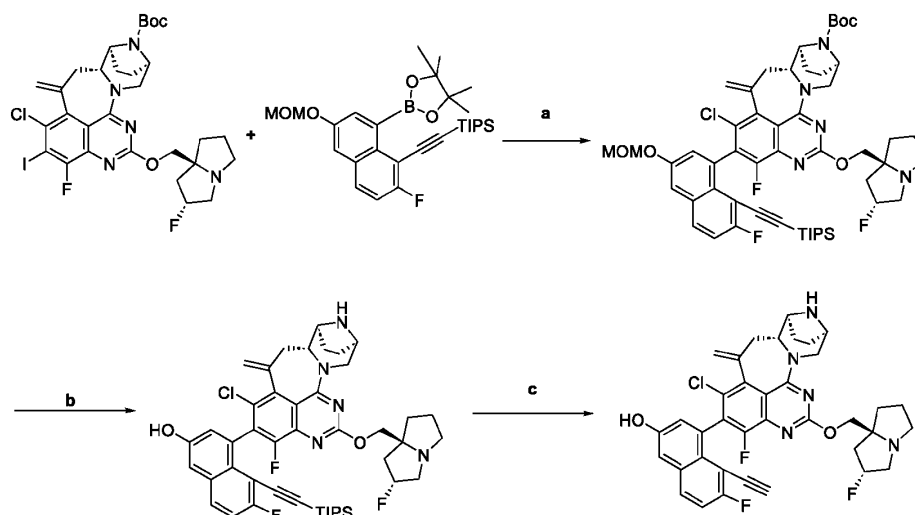
epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (60.0 mg, 0.07 mmol, 1.0 eq) in DMF (0.6 mL) was added CsF (159.4 mg, 1.05 mmol, 15.0 eq) and stirred at 50 °C for 2 h. The product was filtered to give a crude. The crude was purified by Prep-HPLC (acetonitrile with 0.1% FA in water, 40% to 80%) to afford 4-((1*S*,4*R*,14*aR*)-12-chloro-8-(((*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate (1:0.77) (6 mg, purity: 97%, yield: 17.1% with two steps) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 10.14 (brs, 1H), 8.17 (s, 0.77H), 7.98 – 7.95 (m, 1H), 7.50–7.40 (m, 1H), 7.41 – 7.33 (m, 1H), 7.10 – 6.98 (m, 1H), 5.74 (s, 1H), 5.35 (d, *J* = 21.2 Hz, 1H), 5.15 – 4.94 (m, 1H), 4.15 – 4.02 (m, 3H), 4.01 – 3.92 (m, 2H), 3.69 – 3.64 (m, 2H), 3.64 – 3.60 (m, 2H), 3.02 – 2.94 (m, 2H), 2.70 – 2.55 (m, 2H), 2.44 – 2.38 (m, 2H), 2.34 – 2.26 (m, 1H), 2.06 – 1.73 (m, 6H), 1.70 – 1.55 (m, 3H). LCMS: *m/z* 702.2 (*M*+*H*<sup>+</sup>).

#### Example 57

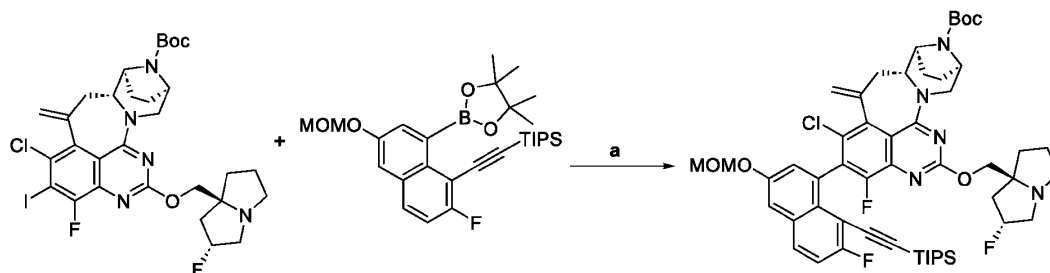
**4-((1*S*, 4*R*, 14*aR*)-12-chloro-10-fluoro-8- (((2*R*, 7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1,4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazolin-11-yl)-5-ethynyl-6-fluoronaphthalen-2-ol**



Synthetic scheme



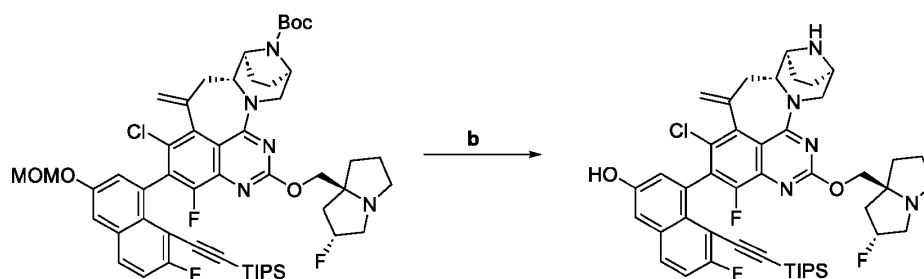
**Step 1: Synthesis of *tert*-butyl (1*S*, 4*R*, 14*aR*)-12-chloro-10-fluoro-11-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl) ethynyl) naphthalen-1-yl)-8-(((2*R*, 7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-15-carboxylate**



[00496] A sealed vial was charged with *tert*-butyl (1*S*, 4*R*, 14*aR*)-12-chloro-10-fluoro-8-(((2*R*, 7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-11-iodo-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-15-carboxylate (250.0 mg, 0.35 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 (215.2 mg, 0.42 mmol, 1.2 eq), Cs<sub>2</sub>CO<sub>3</sub> (342.1 mg, 1.05 mmol, 3.0 eq), CataCXium A Pd G3 (51.0 mg, 0.07 mmol, 0.2 eq) and Toluene / H<sub>2</sub>O (3 mL / 0.6 mL). The sealed vial was irradiated in the microwave at 120 °C for 1.5 h. After completion of the reaction, the reaction mixture was poured into water (10 mL) and extracted with EtOAc (15 mL x 3), the combined organic layers were washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue was purified by

silica gel column chromatography (Petroleum ether / EtOAc = 2:1) to afford *tert*-butyl (1*S*, 4*R*, 14*aR*)-12-chloro-10-fluoro-11-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl) ethynyl) naphthalen-1-yl)-8-(((2*R*, 7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-15-carboxylate (240.0 mg, 81.8%) as a yellow solid. LCMS: 972.4 (M+H<sup>+</sup>).

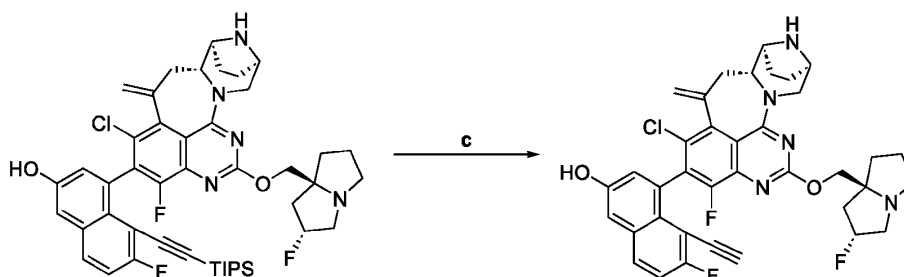
**Step 2: Synthesis of 4-((1*S*, 4*R*, 14*aR*)-12-chloro-10-fluoro-8-(((2*R*, 7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazolin-11-yl)-6-fluoro-5-((triisopropylsilyl) ethynyl) naphthalen-2-ol**



[00497] A mixture of *tert*-butyl (1*S*, 4*R*, 14*aR*)-12-chloro-10-fluoro-11-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl) ethynyl) naphthalen-1-yl)-8-(((2*R*, 7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazoline-15-carboxylate (40.0 mg, 0.041 mmol, 1.0 eq) in CCl<sub>4</sub> (1 mL) / HCl-dioxane (1 mL, 4N) was stirred at room temperature for 2 h. The mixture was concentrated to give 4-((1*S*, 4*R*, 14*aR*)-12-chloro-10-fluoro-8-(((2*R*, 7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazolin-11-yl)-6-fluoro-5-((triisopropylsilyl) ethynyl) naphthalen-2-ol (50 mg crude) as a brown solid, which was used for next step directly without further purification. LCMS: 828.3 (M+H<sup>+</sup>).

**Step 3: Synthesis of 4-((1*S*, 4*R*, 14*aR*)-12-chloro-10-fluoro-8-(((2*R*, 7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazolin-11-yl)-5-ethynyl-6-fluoronaphthalen-2-ol**

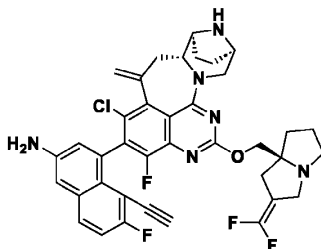




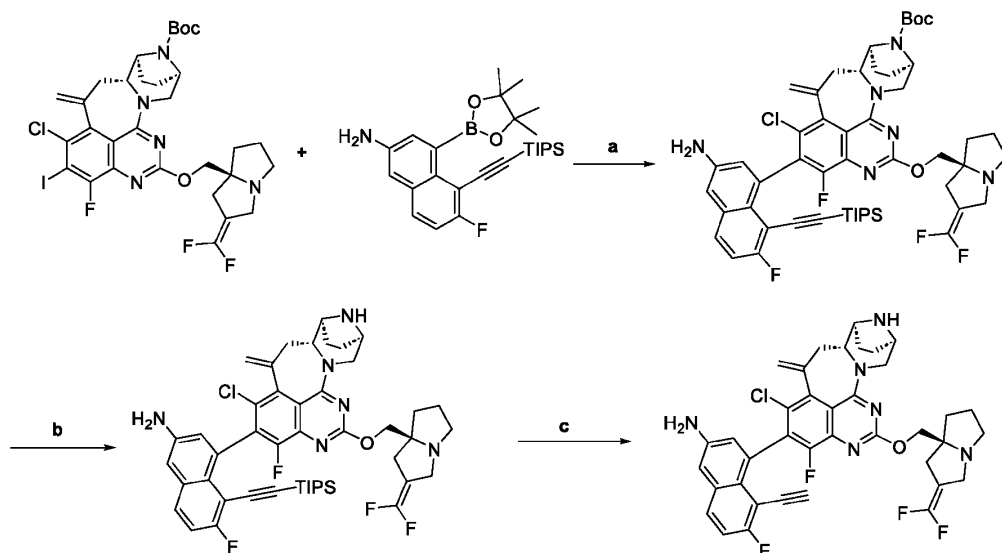
[00498] To solution of 4-((1*S*, 4*R*, 14*aR*)-12-chloro-10-fluoro-8-(((2*R*, 7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1, 4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazolin-11-yl)-6-fluoro-5-((triisopropylsilyl) ethynyl) naphthalen-2-ol (50.0 mg, crude, 0.041 mmol, 1.0 eq) in DMF (0.5 mL) was added CsF (186.8 mg, 1.23 mmol, 30.0 eq). Then the mixture was stirred at 50 °C for 2 h. The mixture was filtered through a Celite pad, and the filtrate was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 20% to 90%) to afford 4-((1*S*, 4*R*, 14*aR*)-12-chloro-10-fluoro-8-(((2*R*, 7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-13-methylene-1, 2, 3, 4, 5, 13, 14, 14*a*-octahydro-1,4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-*de*] quinazolin-11-yl)-5-ethynyl-6-fluoronaphthalen-2-ol formate (1:1.1) (6.9 mg, 23.4% for two steps) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 10.11 (brs, 1H), 8.23 (s, 1H), 7.96 (dd, *J* = 8.8, 5.6 Hz, 1H), 7.45 (t, *J* = 8.8 Hz, 1H), 7.37 (d, *J* = 2.4 Hz, 1H), 7.10-6.90 (m, 1H), 5.73 (s, 1H), 5.42 – 5.18 (m, 2H), 5.12 – 4.94 (m, 1H), 4.16 – 4.03 (m, 2H), 4.02 – 3.88 (m, 3H), 3.70 – 3.55 (m, 1H), 3.22 – 2.75 (m, 5H), 2.45 – 2.22 (m, 2H), 2.20 – 1.40 (m, 10H). LCMS: *m/z* 672.2 (M+H<sup>+</sup>).

### Example 58

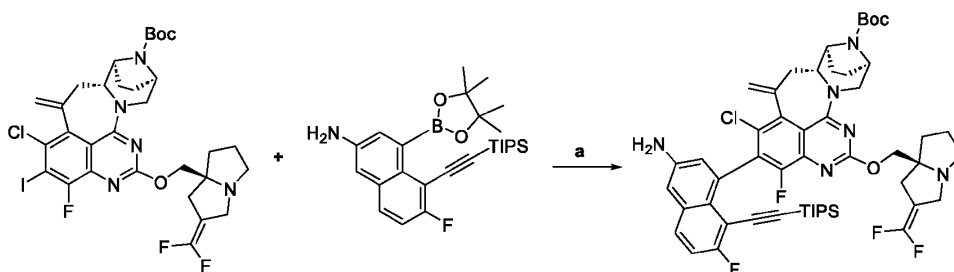
**4-((1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-ethynyl-6-fluoronaphthalen-2-amine**



## Synthetic scheme



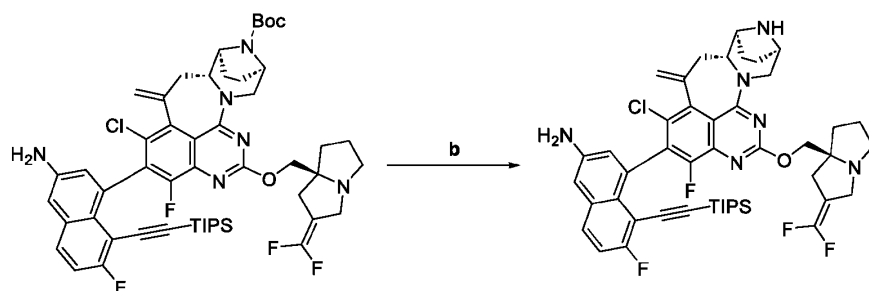
**Step 1: Synthesis of tert-butyl (1S,4R,14aR)-11-(3-amino-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00499] To a solution of tert-butyl (1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-11-iodo-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (150 mg, 0.20 mmol, 1.0 eq), 6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-amine (113 mg, 0.24 mmol, 1.2 eq), Cs<sub>2</sub>CO<sub>3</sub> (197 mg, 0.60 mmol, 3.0 eq) and cataCXium A Pd G3 (29 mg, 0.04 mmol, 0.2 eq) in the microwave tube, toluene (1.5 mL) and water (0.3 mL) was added. The tube was

irradiated under microwave at 120 °C for 1.5 h under N<sub>2</sub>. 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 Na<sub>2</sub>SO<sub>4</sub> and concentrated to give a residue. The crude product was purified by prep-TLC (petroleum ether/ EtOAc = 2: 1) to afford tert-butyl (1S,4R,14aR)-11-(3-amino-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (120 mg, purity: 89%, yield: 62.1%). LCMS: 957.4 (M+H<sup>+</sup>).

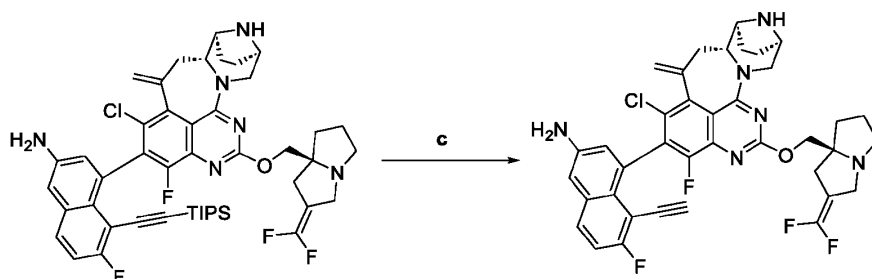
**Step 2: Synthesis of 4-((1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-amine**



[00500] To a solution of tert-butyl (1S,4R,14aR)-11-(3-amino-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (20 mg, 0.02 mmol, 1.0 eq) in dioxane (0.5 mL) was added HCl/dioxane (4M) (0.30 mL, 1.2 mmol, 60.0 eq) at 25 °C under N<sub>2</sub> atmosphere. Then the reaction was stirred at 25 °C for 1.5 h. Then the mixture was concentrated to give a residue to afford 4-((1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-amine (30 mg, purity: crude) as a brown solid. LCMS: 857.3 (M+H<sup>+</sup>).

**Step 3: Synthesis of 4-((1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-**

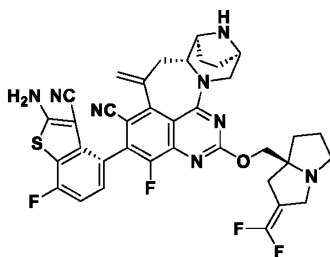
**1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-ethynyl-6-fluoronaphthalen-2-amine 2,2,2-trifluoroacetate formate (1:0.6)**



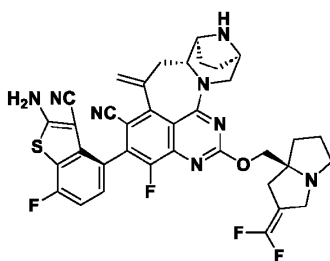
[00501] To a solution of 4-((1*S*,4*R*,14*aR*)-12-chloro-8-(((*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazolin-11-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-amine (30 mg, 0.04 mmol, 1.0 eq) in DMF (0.5 mL) was added CsF (80 mg, 0.53 mmol, 15.0 eq) and stirred at 50 °C for 2 h. The product was filtered to give a crude. The crude was purified by Prep-HPLC (acetonitrile with 0.1% FA in water, 40% to 80%) to afford 4-((1*S*,4*R*,14*aR*)-12-chloro-8-(((*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazolin-11-yl)-5-ethynyl-6-fluoronaphthalen-2-amine 2,2,2-trifluoroacetate formate (1:0.6) (2.5 mg, purity: 98%, yield: 17.1% with two steps) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.78 – 7.75 (m, 1H), 7.40–7.20 (m, 1H), 7.04 – 7.03 (m, 1H), 6.90 – 6.86 (m, 1H), 5.78 (s, 1H), 5.62 (s, 2H), 5.44 (d, *J* = 14.0 Hz, 1H), 5.23 – 5.10 (m, 1H), 4.15 – 4.01 (m, 5H), 3.91 – 3.86 (m, 2H), 3.66 – 3.63 (m, 1H), 3.05 – 2.91 (m, 2H), 2.70 – 2.54 (m, 2H), 2.46 – 2.28 (m, 3H), 2.27 – 2.07 (m, 1H), 2.05 – 1.62 (m, 8H). LCMS: *m/z* 701.3 (*M*+*H*<sup>+</sup>).

**Examples 59 60**

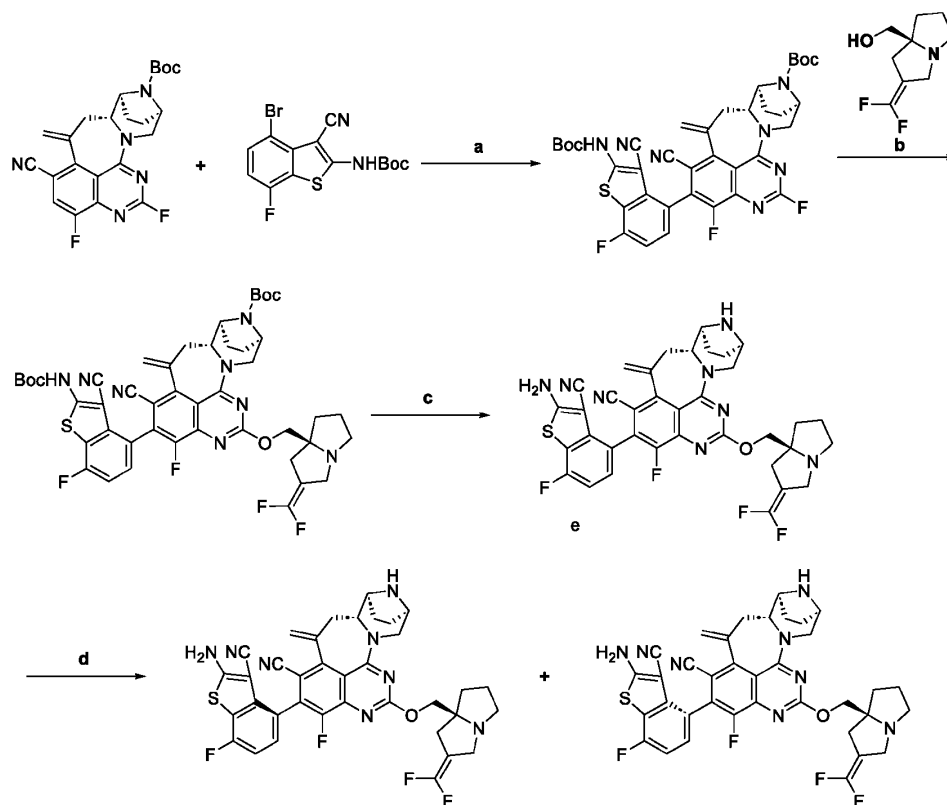
**Example 59: (1*S*,4*R*,11*R*,14*aR*)-11-(2-amino-3-cyano-7-fluorobenzo[*b*]thiophen-4-yl)-8-(((*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-12-carbonitrile**



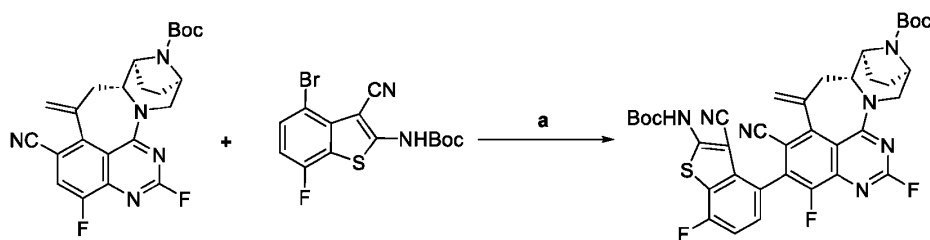
**Example 60:** (1*S*,4*R*,11*S*,14*aR*)-11-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-8-(((*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-12-carbonitrile



Synthetic scheme



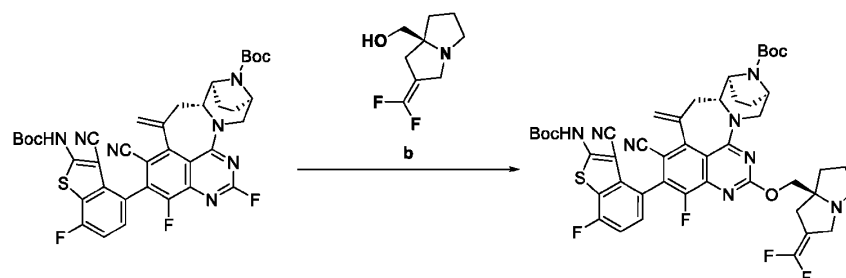
**Step 1: Synthesis of *tert*-butyl (1*S*,4*R*,14*aR*)-11-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[*b*]thiophen-4-yl)-12-cyano-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-15-carboxylate**



[00502] To a solution of *tert*-butyl (1*S*,4*R*,14*aR*)-12-cyano-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-15-carboxylate (420 mg, 0.96 mmol, 1.0 eq) in THF (5 mL) was added (TMP)<sub>2</sub>Zn·2MgCl<sub>2</sub>·2LiCl (0.4 M, 14.4 mL, 5.76 mmol, 6.0 eq) under N<sub>2</sub>. The mixture was stirred at 50 °C for 2 h. Then LCMS showed the reaction was completed by D<sub>2</sub>O (2 drops) quenching. Then the mixture was

added a mixture of *tert*-butyl (4-bromo-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate (426.7 mg, 1.15 mmol, 1.2 eq) and CPhos Pd G3 (77.4 mg, 0.096 mmol, 0.1 eq) in 1,4-dioxane (5 mL). The mixture was stirred at 70 °C for 3 h. The reaction mixture was quenched with H<sub>2</sub>O (5 mL) and was filtered through a Celite pad. The filtrate was extracted with EtOAc (20 mL x 3). The organic layers were washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by Prep-TLC (Petroleum ether/ EtOAc = 5: 1) to afford *tert*-butyl (1*S*,4*R*,14*aR*)-11-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-12-cyano-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-15-carboxylate (310 mg, 44.8%) as a yellow solid. LCMS: *m/z* 730.2 (M+H<sup>+</sup>).

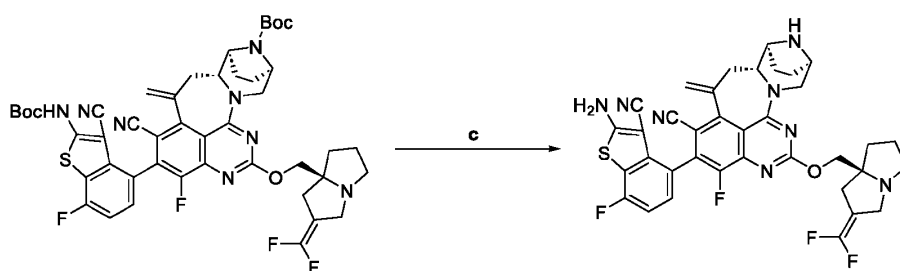
**Step 2: Synthesis of *tert*-butyl (1*S*,4*R*,14*aR*)-11-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-12-cyano-8-(((*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-15-carboxylate**



[00503] To a solution of (*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methanol (122.9 mg, 0.65 mmol, 1.5 eq) in THF (1.5 mL) was added NaH (60%) (78 mg, 1.95 mmol, 3.0 eq) at 0 °C and then the mixture was stirred for 0.5 h at room temperature under N<sub>2</sub>. The solution of *tert*-butyl (1*S*,4*R*,14*aR*)-11-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-12-cyano-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-15-carboxylate (310 mg, 0.43 mmol, 1.0 eq) in THF (3.5 mL) was added to the mixture and stirred at 25 °C for 2 h. HPLC and TLC showed the reaction was completed. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl solution (10 mL) and extracted with EtOAc (15 mL x 3). The organic layers were washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give a residue, which was purified by Prep-TLC (DCM/ MeOH = 20: 1) to afford *tert*-butyl

(1*S*,4*R*,14*aR*)-11-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-12-cyano-8-(((*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-15-carboxylate (280 mg, 72.1%) as a yellow solid. LCMS: 899.2 *m/z* (*M*+*H*<sup>+</sup>).

**Step 3: Synthesis of (1*S*,4*R*,14*aR*)-11-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-8-(((*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-12-carbonitrile**

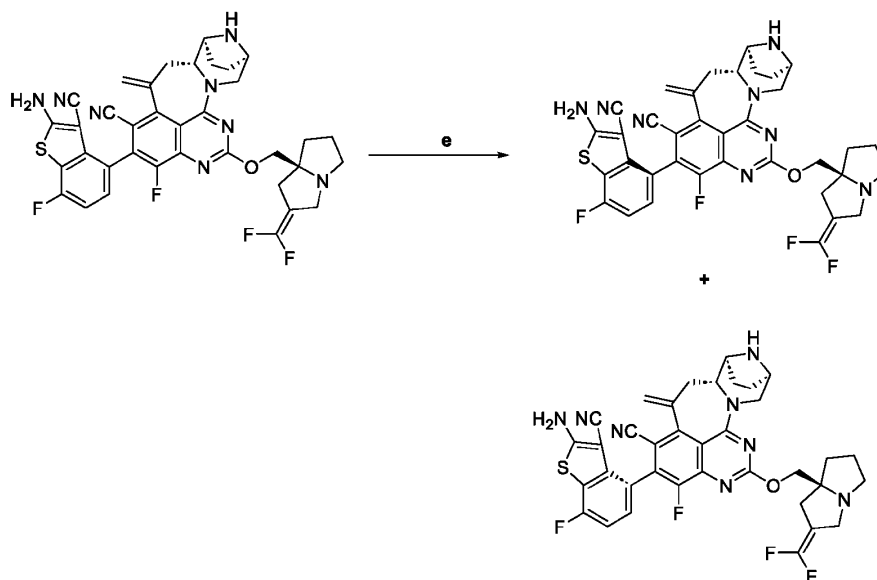


[00504] The mixture of *tert*-butyl (1*S*,4*R*,14*aR*)-11-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-12-cyano-8-(((*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-15-carboxylate (280 mg, 0.31 mmol, 1.0 eq) in TFA (3 mL) / DCM (3 mL) was stirred at room temperature for 2 h under N<sub>2</sub>. After completion, the mixture was concentrated to give a crude product. The crude product was dissolved in DCM / MeOH (10 / 1, 15 mL) and washed with saturated Na<sub>2</sub>CO<sub>3</sub> (10 mL x 3). The organic layers were washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated under reduced pressure to give a residue. The crude product was purified by Prep-TLC (DCM/ NH<sub>3</sub>-MeOH = 15: 1) to afford (1*S*,4*R*,14*aR*)-11-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-8-(((*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-12-carbonitrile (130 mg, 61.3%) as a yellow solid. LCMS: 699.2 *m/z* (*M*+*H*<sup>+</sup>).

**Step 4: Synthesis of (1*S*,4*R*,11*R*,14*aR*)-11-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-8-(((*S*)-2-(difluoromethylene)tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14*a*-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazoline-12-carbonitrile and (1*S*,4*R*,11*S*,14*aR*)-11-(2-amino-3-cyano-7-**



fluorobenzo[b]thiophen-4-yl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-12-carbonitrile



[00505] The diastereomers of the (1S,4R,14aR)-11-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-12-carbonitrile (130 mg, 0.19 mmol) were purified by chiral HPLC to give the following 2 isomers:

[00506] **Peak 1:** (1S,4R,11R,14aR)-11-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-12-carbonitrile (30 mg, 22.6%, yellow solid, retention time = 8.631, under the analytical separation method). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.17 (brs, 2H), 7.50 – 7.32 (m, 1H), 7.18 (t, *J* = 8.4 Hz, 1H), 5.73 (s, 1H), 5.55 (s, 1H), 5.20 – 5.10 (m, 1H), 4.20–4.05 (m, 2H), 4.01 – 3.90 (m, 1H), 3.65 – 3.56 (m, 2H), 3.44 – 3.40 (m, 2H), 3.17 – 2.93 (m, 3H), 2.72 – 2.57 (m, 3H), 2.43 – 2.25 (m, 2H), 2.03 – 1.93 (m, 1H), 1.90 – 1.73 (m, 4H), 1.59 – 1.43 (m, 2H), 1.37 – 1.27 (m, 1H). LCMS: *m/z* 699.2 (M+H<sup>+</sup>).

[00507] **Peak 2:** (1S,4R,11S,14aR)-11-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-12-carbonitrile (40 mg, peak 2, 30.0%, yellow solid, retention time = 11.274, under the analytical separation method). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  8.19 (brs, 2H), 7.36 – 7.32 (m, 1H), 7.17 (t, *J* = 8.8 Hz, 1H), 5.76 (s, 1H), 5.58 (s, 1H), 5.19 – 5.10 (m, 1H), 4.20 – 4.00 (m, 2H), 3.99 – 3.90 (m, 1H), 3.69 – 3.51 (m, 2H), 3.43 (m, 2H), 3.11 – 2.90 (m, 3H), 2.69 – 2.54 (m, 3H), 2.45 – 2.32 (m, 2H), 1.99 – 1.73 (m, 5H), 1.65 – 1.51 (m, 3H). LCMS: *m/z* 699.2 (*M*+*H*<sup>+</sup>).

**Chiral separation conditions:**

**Analytical separation method:**

[00508] Instrument: Waters UPCC. Column: CHIRALPAK OD-3, 4.6mm\*250mm, 3  $\mu$ m. Mobile phase: A for CO<sub>2</sub> and B for 0.1% DEA in MeOH. Gradient: B 30%. Flow rate: 2.0 mL/min. Column temperature: 35 °C. Injection volume: 2.0  $\mu$ l, Wavelength: 210nm.

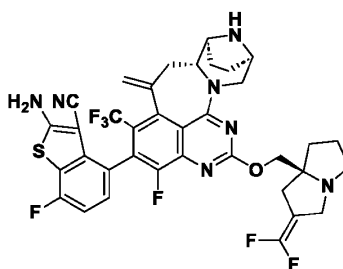
**Preparative separation method**

**First chiral HPLC condition:**

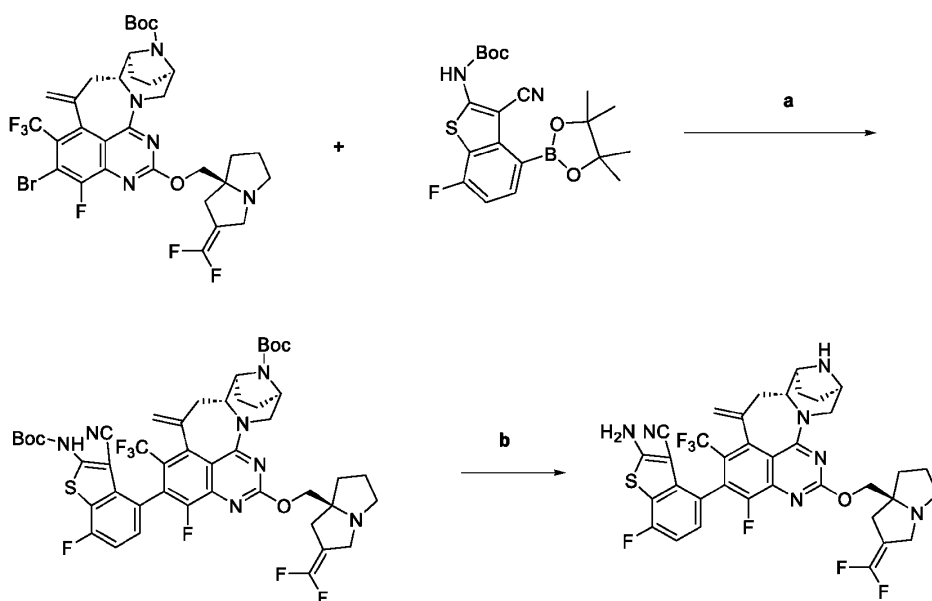
[00509] Instrument: Prep-HPLC-Gilson. Column: CHIRALPAK IF, 2cm  $\times$  25cm, 5 $\mu$ m. Mobile phase: A for MTBE (0.5% 2mM NH<sub>3</sub>-MeOH) and B for MeOH / DCM. Flow rate: 20 mL /min. Column temperature: 25 °C. Wavelength: 220nm.

**Example 61**

**4-[(4R,7S,8R)-17-({[(7aS)-2-(difluoromethylidene)-2,3,5,6,7,7a-hexahydro-1H-pyrrolizin-7a-yl]methyl}oxy)-14-fluoro-10-methylidene-12-(trifluoromethyl)-2,16,18,20-tetrazapentacyclo[13.3.1.1<sup>4,7</sup>.0<sup>11,19</sup>.0<sup>2,8</sup>]icosa-1(19),11(12),13,15(16),17-pentaen-13-yl]-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile**



**Synthetic scheme**



[00510] **Step 1:** To a solution of 2-methylpropan-2-yl (1S,2R,5R)-3-[5-bromo-2-chloro-8-fluoro-6-(trifluoromethyl)quinazolin-4-yl]-2-(prop-2-enyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (3.2 g, 5.52 mmol) in dioxane (30 mL) were added [(7aS)-2-(difluoromethylidene)-2,3,5,6,7,7a-hexahydro-1H-pyrrolizin-7a-yl]methanol (3.13 g, 16.6 mmol) and  $\text{Cs}_2\text{CO}_3$  (5.39 g, 16.6 mmol). The mixture was stirred at 85 °C under  $\text{N}_2$  for ON. The cooled reaction mixture was diluted water, extracted with EA. The organic phase was washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 0-30%) to afford 2-methylpropan-2-yl (1S,2R,5R)-3-[2-({[(7aS)-2-(difluoromethylidene)-2,3,5,6,7,7a-hexahydro-1H-pyrrolizin-7a-yl]methyl}oxy)-5-bromo-8-fluoro-6-(trifluoromethyl)quinazolin-4-yl]-2-(prop-2-enyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2.1 g, 2.87 mmol, 52%) as a yellow solid. LCMS: ESI  $m/z$  734.4  $[\text{M} + \text{H}]^+$ .

[00511] **Step 2:** To a solution of 2-methylpropan-2-yl (1S,2R,5R)-3-[2-({[(7aS)-2-(difluoromethylidene)-2,3,5,6,7,7a-hexahydro-1H-pyrrolizin-7a-yl]methyl}oxy)-5-bromo-8-fluoro-6-(trifluoromethyl)quinazolin-4-yl]-2-(prop-2-enyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2 g, 2.73 mmol) in DMA (20 mL) were added  $\text{Pd}(\text{OAc})_2$  (0.07 g, 0.328 mmol),  $\text{PPh}_3$  (0.14 g, 0.546 mmol) and KOAc (0.54 g, 5.46 mmol). The mixture was stirred at 130 °C under  $\text{N}_2$  for 2h. The reaction mixture was diluted water, extracted with EA. The organic

phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue was purified using silica gel column chromatography eluted with methanol in dichloroform (gradient: 0-10%) to afford 2-methylpropan-2-yl (4R,7S,8R)-17-({[(7aS)-2-(difluoromethylidene)-2,3,5,6,7,7a-hexahydro-1H-pyrrolizin-7a-yl]methyl}oxy)-14-fluoro-10-methylidene-12-(trifluoromethyl)-2,16,18,20-tetrazapentacyclo[13.3.1.1<sup>4,7</sup>.0<sup>11,19</sup>.0<sup>2,8</sup>]jicosa-1(19),11(12),13,15(16),17-pentaene-20-carboxylate (1 g, 1.54 mmol, 56%) as a yellow solid. LCMS: ESI m/z 652.4 [M + H]<sup>+</sup>.

[00512] **Step 3:** To a solution of di(prop-2-yl)amine (0.398 mL, 2.824 mmol) in THF (5 mL) was added N-BULI (1.13 mL, 2.82 mmol) at -78°C for 15 minutes. Then added 2-methylpropan-2-yl (4R,7S,8R)-17-({[(7aS)-2-(difluoromethylidene)-2,3,5,6,7,7a-hexahydro-1H-pyrrolizin-7a-yl]methyl}oxy)-14-fluoro-10-methylidene-12-(trifluoromethyl)-2,16,18,20-tetrazapentacyclo[13.3.1.1<sup>4,7</sup>.0<sup>11,19</sup>.0<sup>2,8</sup>]jicosa-1(19),11(12),13,15(16),17-pentaene-20-carboxylate (920 mg, 1.41 mmol). The reaction was stirred at -15 °C for 15 minutes and then cooled to -78 °C. 1,2-dibromo-1,1,2,2-tetrachloroethane (690 mg, 2.12 mmol) was added. The reaction was stirred at -15°C for 15 minutes. The reaction mixture was diluted water, extracted with EA. The organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue was purified using silica gel column chromatography eluted with methanol in dichloroform (gradient: 0-10%) to afford 2-methylpropan-2-yl (4R,7S,8R)-17-({[(7aS)-2-(difluoromethylidene)-2,3,5,6,7,7a-hexahydro-1H-pyrrolizin-7a-yl]methyl}oxy)-13-bromo-14-fluoro-10-methylidene-12-(trifluoromethyl)-2,16,18,20-tetrazapentacyclo[13.3.1.1<sup>4,7</sup>.0<sup>11,19</sup>.0<sup>2,8</sup>]jicosa-1(19),11(12),13,15(16),17-pentaene-20-carboxylate (250 mg, 0.342 mmol, 24%) as a yellow solid. LCMS: ESI m/z 732.3 [M + H]<sup>+</sup>.

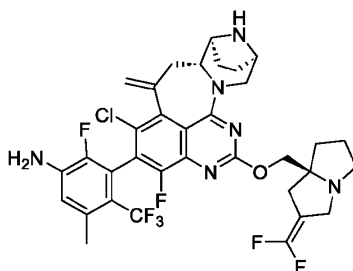
[00513] **Step 4:** To a solution of 2-methylpropan-2-yl (4R,7S,8R)-17-({[(7aS)-2-(difluoromethylidene)-2,3,5,6,7,7a-hexahydro-1H-pyrrolizin-7a-yl]methyl}oxy)-13-bromo-14-fluoro-10-methylidene-12-(trifluoromethyl)-2,16,18,20-tetrazapentacyclo[13.3.1.1<sup>4,7</sup>.0<sup>11,19</sup>.0<sup>2,8</sup>]jicosa-1(19),11(12),13,15(16),17-pentaene-20-carboxylate (250 mg, 0.34 mmol) in toluene (5 mL) were added 2-methylpropan-2-yl {[3-cyano-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophen-2-yl]amino}methanoate (258 mg, 0.62 mmol), (2-{[2-(diphenylphosphanyl)phenyl]oxy}phenyl)diphenylphosphane palladium chloride (122 mg, 0.17 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (1.11g, 3.42 mmol). The reaction was stirred at 110 °C under nitrogen overnight. The reaction mixture was diluted water, extracted with EA. The organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The

residue was purified using silica gel column chromatography eluted with methanol in dichloroform (gradient: 0-10%) to afford 2-methylpropan-2-yl (4R,7S,8R)-17-({[(7aS)-2-(difluoromethylidene)-2,3,5,6,7,7a-hexahydro-1H-pyrrolizin-7a-yl]methyl}oxy)-13-[3-cyano-7-fluoro-2-({[(2-methylprop-2-yl)oxy]carbonyl}amino)benzo[b]thiophen-4-yl]-14-fluoro-10-methylidene-12-(trifluoromethyl)-2,16,18,20-tetrazapentacyclo[13.3.1.1<sup>4,7</sup>.0<sup>11,19</sup>.0<sup>2,8</sup>]jicosa-1(19),11(12),13,15(16),17-pentaene-20-carboxylate (50 mg, 0.05 mmol, 16%) as a yellow solid. LCMS: ESI m/z 942.4 [M + H]<sup>+</sup>.

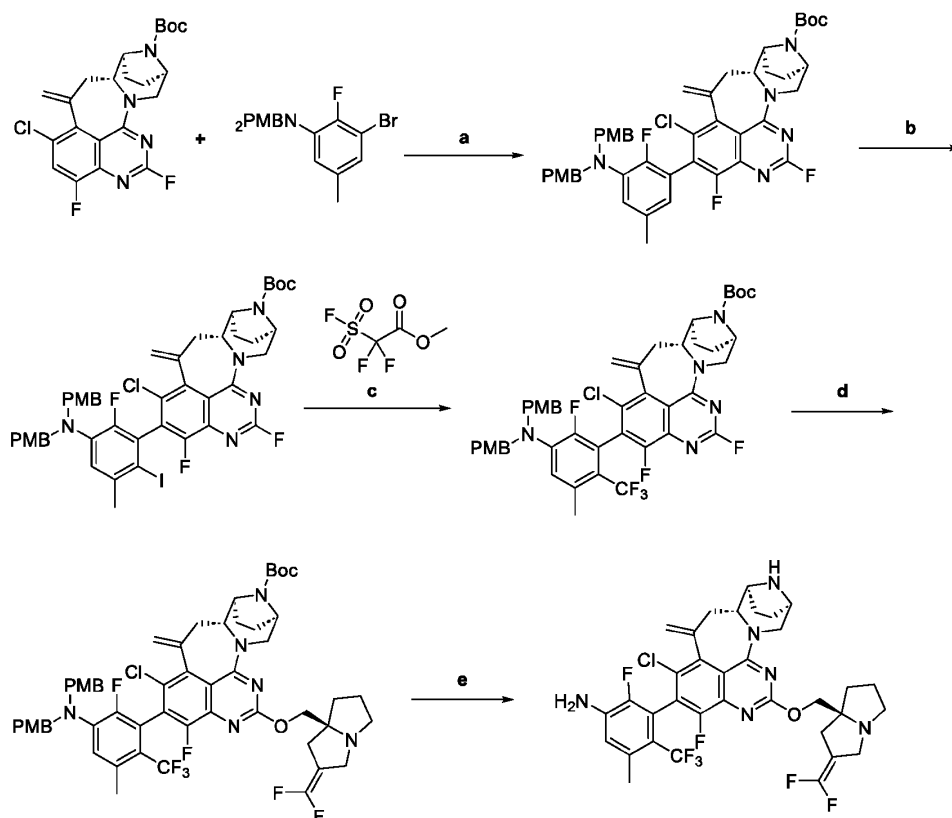
[00514] **Step 5:** A solution of 2-methylpropan-2-yl (4R,7S,8R)-17-({[(7aS)-2-(difluoromethylidene)-2,3,5,6,7,7a-hexahydro-1H-pyrrolizin-7a-yl]methyl}oxy)-13-[3-cyano-7-fluoro-2-({[(2-methylprop-2-yl)oxy]carbonyl}amino)benzo[b]thiophen-4-yl]-14-fluoro-10-methylidene-12-(trifluoromethyl)-2,16,18,20-tetrazapentacyclo[13.3.1.1<sup>4,7</sup>.0<sup>11,19</sup>.0<sup>2,8</sup>]jicosa-1(19),11(12),13,15(16),17-pentaene-20-carboxylate (15 mg, 0.02 mmol) in DCM (2 mL) and TFA (0.5 mL) was stirred at rt for 1 h. The reaction mixture was concentrated at rt. The residue was diluted aqueous NaHCO<sub>3</sub> and extracted with EA. The organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue was purified by prep-HPLC to afford 4-[(4R,7S,8R)-17-({[(7aS)-2-(difluoromethylidene)-2,3,5,6,7,7a-hexahydro-1H-pyrrolizin-7a-yl]methyl}oxy)-14-fluoro-10-methylidene-12-(trifluoromethyl)-2,16,18,20-tetrazapentacyclo[13.3.1.1<sup>4,7</sup>.0<sup>11,19</sup>.0<sup>2,8</sup>]jicosa-1(19),11(12),13,15(16),17-pentaen-13-yl]-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile (3 mg, 0.00 mmol, 25%) as a yellow solid. LCMS: ESI m/z 742.2 [M + H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.28 – 7.13 (m, 1H), 7.10 – 6.95 (m, 1H), 5.72 – 5.22 (m, 2H), 4.77 – 4.67 (m, 3H), 4.51 – 4.29 (m, 4H), 4.21 – 4.08 (m, 2H), 3.82 – 3.75 (m, 1H), 3.40 – 3.34 (m, 1H), 3.25 – 3.02 (m, 3H), 2.91 – 2.83 (m, 1H), 2.43 – 2.34 (m, 1H), 2.33 – 2.13 (m, 5H), 2.10 – 1.98 (m, 2H).

### Example 62

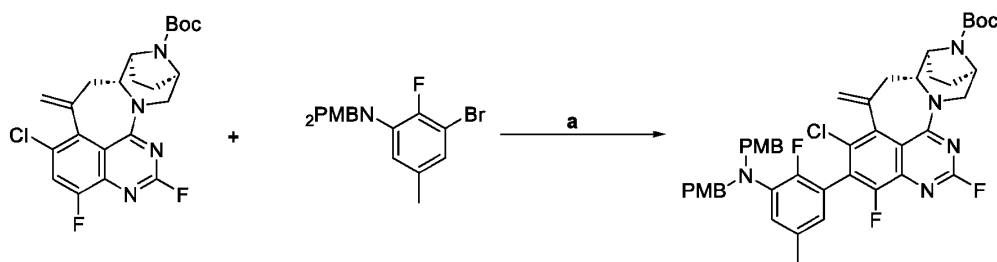
**3-((1S, 4R, 14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1', 2':1, 7]azepino[2, 3, 4-de]quinazolin-11-yl)-2-fluoro-5-methyl-4-(trifluoromethyl)aniline**



### Synthetic scheme

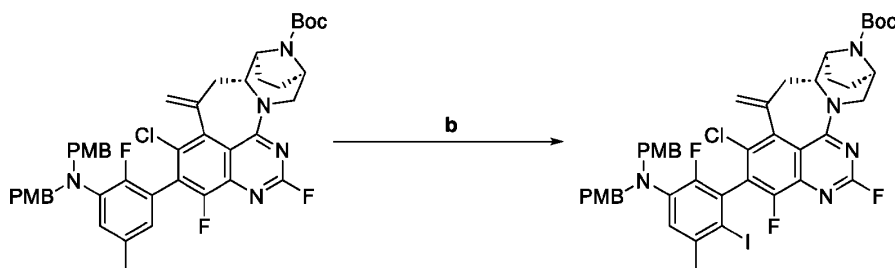


**Step 1: Synthesis of tert-butyl (1S, 4R, 14aR)-11-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methylphenyl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino [1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



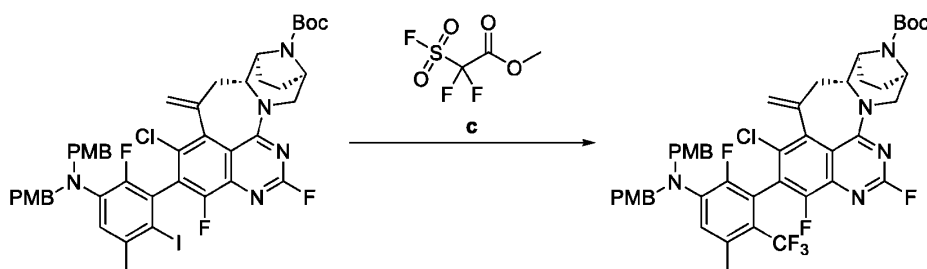
[00515] To a solution of tert-butyl (1S, 4R, 14aR)-12-chloro-8,10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (3.0 g, 6.7 mmol, 1.0 eq) in THF (30 mL) was added (TMP)<sub>2</sub>Zn·2MgCl<sub>2</sub>·2LiCl (0.4 M, 100 mL, 40.2 mmol, 6.0 eq) under N<sub>2</sub>. The mixture was stirred at 50 °C for 1 h. Then LCMS showed the reaction was completed by D<sub>2</sub>O quenching. After that, the mixture was added a mixture of 3-bromo-2-fluoro-N,N-bis(4-methoxybenzyl)-5-methylaniline (3.6 g, 8.1 mmol, 1.2 eq) and C-phos-PdG3 (0.65 g, 0.8 mmol, 0.12 eq) in 1,4-dioxane (30 mL). The mixture was stirred at 70 °C for 3 h. LCMS and HPLC showed the reaction was completed. The mixture was cooled to 0 °C~10 °C, quenched with water (3 mL) and filtered to give filter cake 1 and filtrate 1. The filter cake 1 was triturated with EtOAc (500 mL) to give filtrate 2. The filtrate 1 and filtrate 2 were merged, then the organic layer was washed with brine (100 mL) and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (Petroleum ether / EtOAc = 5:1) to afford tert-butyl (1S, 4R, 14aR)-11-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methylphenyl)-12-chloro-8,10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (3.2 g, purity: 93.0%, yield: 58.1%) as a yellow solid. LCMS: 812.3 (M+H<sup>+</sup>).

**Step 2: Synthesis of tert-butyl (1S, 4R, 14aR)-11-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-6-iodo-5-methylphenyl)-12-chloro-8,10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00516] To a solution of tert-butyl (1S,4R,14aR)-11-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methylphenyl)-12-chloro-8,10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1',2':1,7] azepino [2,3,4-de]quinazoline-15-carboxylate (2.2 g, 2.7 mmol, 1.0 eq) and NIS (731.2 mg, 3.2 mmol, 1.2 eq) in ACN (22 mL) was added TsOH (103.0 mg, 0.54 mmol, 0.2 eq). The mixture was stirred at room temperature for 2 h. HPLC indicated 7% SM was remained. The mixture was quenched with H<sub>2</sub>O (50 mL) and extracted with EtOAc (50 mL x 3), the combined organic phase was washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude was purified by silica gel column chromatography (Petroleum ether / EtOAc = 5:1) and prep-HPLC (acetonitrile with 0.1% FA in water, 80% to 100%) to afford tert-butyl (1S, 4R, 14aR)-11-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-6-iodo-5-methylphenyl)-12-chloro-8,10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de] quinazoline-15-carboxylate (1.0 g, purity: 99.0%, yield: 39.4%) as a white solid. LCMS: 938.1 (M+H<sup>+</sup>).

**Step 3: Synthesis of tert-butyl (1S,4R,14aR)-11-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methyl-6-(trifluoromethyl)phenyl)-12-chloro-8,10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**

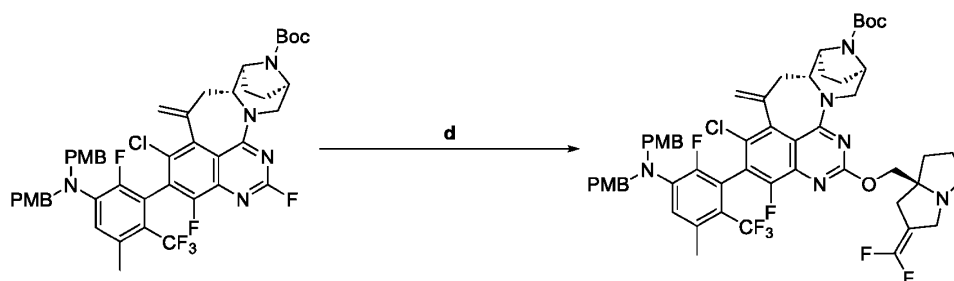


[00517] To a solution of tert-butyl (1S, 4R, 14aR)-11-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-6-iodo-5-methylphenyl)-12-chloro-8,10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (630.0 mg, 0.67 mmol, 1.0 eq) in DMF (12 mL) was added Methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (1.3 g, 6.7 mmol, 10.0 eq), HMPA (1.2 g, 6.8 mmol, 10.0 eq) and CuI (383.6 mg, 2.0 mmol, 3.0 eq). The reaction mixture was stirred at 130 °C in microwave for 30 min under N<sub>2</sub>. HPLC indicated the reaction was completed. The reaction was cooled, quenched by the addition of water (20 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with water (10 mL x 3) and brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to give a



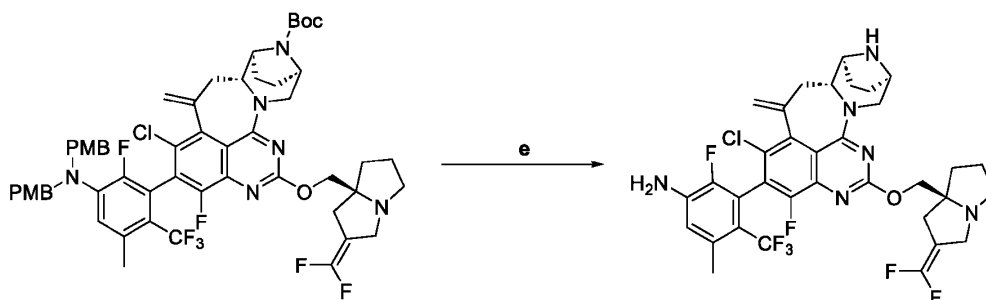
crude product. The crude product was purified by silica gel column chromatography (Petroleum ether / EtOAc = 5:1) and prep-HPLC (acetonitrile with 0.1% FA in water, 80% to 100%) to afford tert-butyl (1S, 4R, 14aR)-11-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methyl-6-(trifluoromethyl)phenyl)-12-chloro-8,10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (140.0 mg, purity: 99.0%, yield: 23.7%) as a white solid. LCMS: 880.2 (M+H<sup>+</sup>).

**Step 4: Synthesis of tert-butyl (1S, 4R, 14aR)-11-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methyl-6-(trifluoromethyl)phenyl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1',2':1,7] azepino[2,3,4-de]quinazoline-15-carboxylate**



[00518] To a solution of tert-butyl (1S, 4R, 14aR)-11-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methyl-6-(trifluoromethyl)phenyl)-12-chloro-8,10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (140.0 mg, 0.16 mmol, 1.0 eq) and (S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (60.2 mg, 0.32 mmol, 2.0 eq) in THF (2 mL) was added t-BuONa (46.0 mg, 0.48 mmol, 3.0 eq) at room temperature and the mixture was stirred for 1 h at room temperature under N<sub>2</sub>. HPLC and TLC showed the reaction was completed. The reaction mixture was quenched with H<sub>2</sub>O (20 mL) and extracted with EtOAc (20 mL x 3). The organic layers were washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-TLC (Petroleum ether / EtOAc = 1:1) to afford tert-butyl (1S, 4R, 14aR)-11-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methyl-6-(trifluoromethyl)phenyl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (110.0 mg, purity: 96.0%, yield: 65.9%) as a white solid. LCMS: 1049.3 (M+H<sup>+</sup>).

**Step 5: Synthesis of 3-((1S, 4R, 14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-de] quinazolin-11-yl)-2-fluoro-5-methyl-4-(trifluoromethyl) aniline formate (1:1.6)**

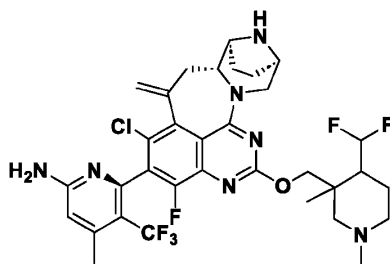


[00519] To a solution of tert-butyl (1S, 4R, 14aR)-11-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methyl-6-(trifluoromethyl)phenyl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1',2':1,7] azepino[2,3,4-de]quinazoline-15-carboxylate (28.0 mg, 0.027 mmol, 1.0 eq) in TFA (0.5 mL) was stirred at 50 °C for 1 h under N<sub>2</sub>. Then the mixture was concentrated under reduced pressure to give a crude product. The crude was purified by Prep-HPLC (acetonitrile with 0.04% NH<sub>4</sub>HCO<sub>3</sub> in water, 60% to 85%) to afford 3-((1S, 4R, 14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-2-fluoro-5-methyl-4-(trifluoromethyl)aniline formate (1:1.6) (7.2 mg, purity: 97.4%, yield: 34.5%) as a white solid.

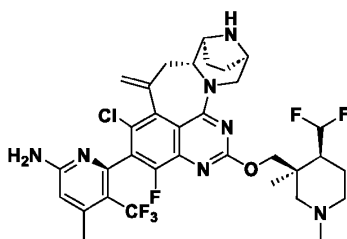
[00520] <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.26 (brs, 1.6H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.00 (brs, 2H), 5.77 (s, 1H), 5.33 (d, *J* = 10.4 Hz, 1H), 5.13 – 4.92 (m, 1H), 4.20 – 4.02 (m, 2H), 4.01 – 3.89 (m, 2H), 3.19 – 3.06 (m, 2H), 3.05 – 2.80 (m, 4H), 2.70 – 2.55 (m, 2H), 2.39 – 2.25 (m, 4H), 2.03 – 1.70 (m, 6H), 1.67 – 1.40 (m, 4H). LCMS: *m/z* 709.2 (M+H<sup>+</sup>).

#### Examples 63, 64 & 65

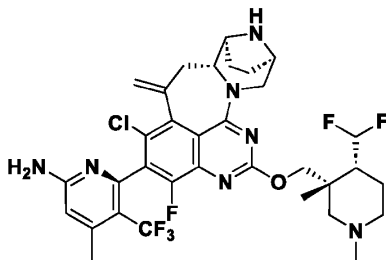
**Example 63: 6-((1S, 4R, 11R, 14aR)-12-chloro-8-((4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1',2':1,7] azepino [2,3,4-de] quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine**



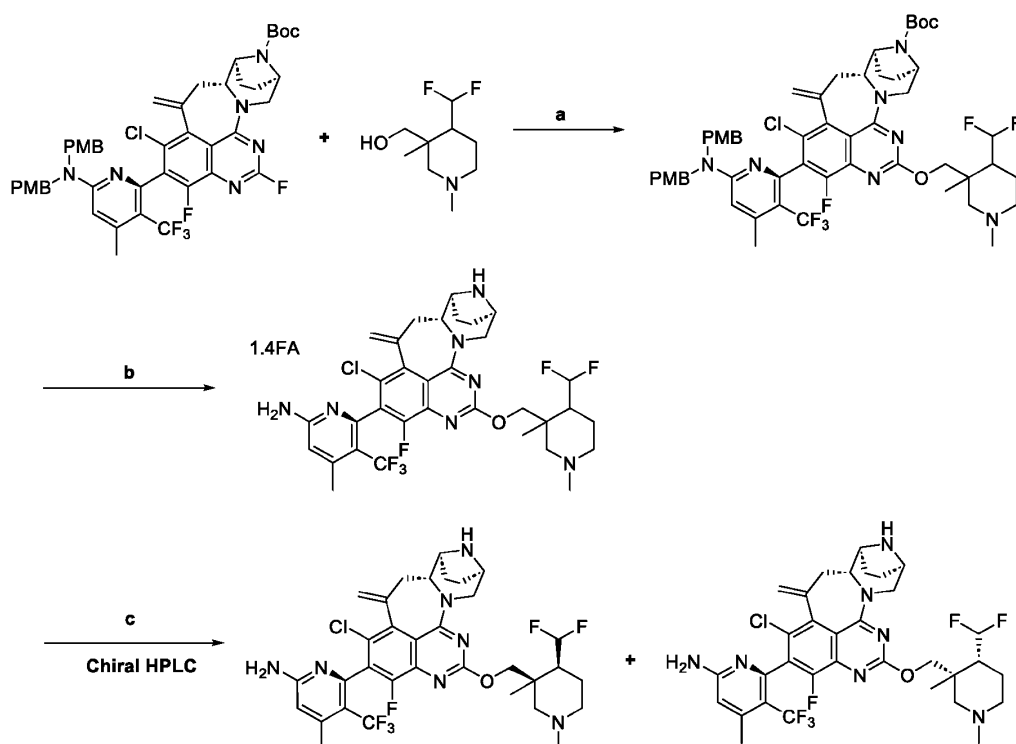
**Example 64:** 6-((1S, 4R, 11R, 14aR)-12-chloro-8-(((3S,4S)-4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1', 2':1, 7]azepino[2, 3, 4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine



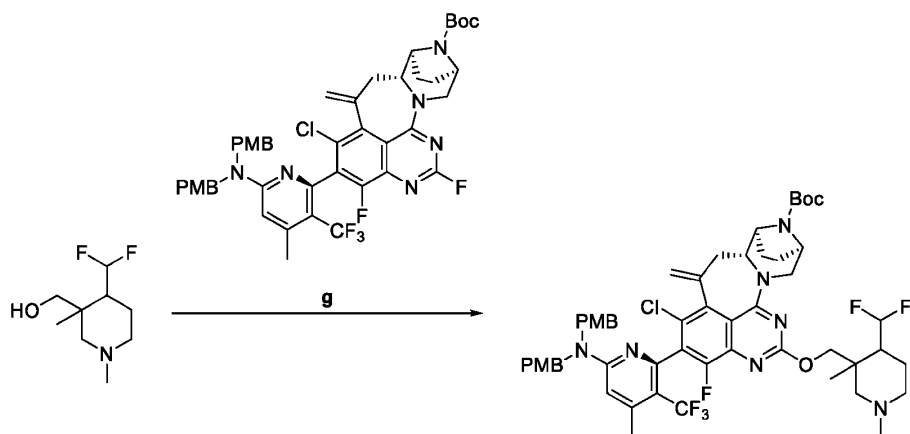
**Example 65:** 6-((1S, 4R, 11R, 14aR)-12-chloro-8-(((3R,4R)-4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1', 2':1, 7]azepino[2, 3, 4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine



Synthetic scheme



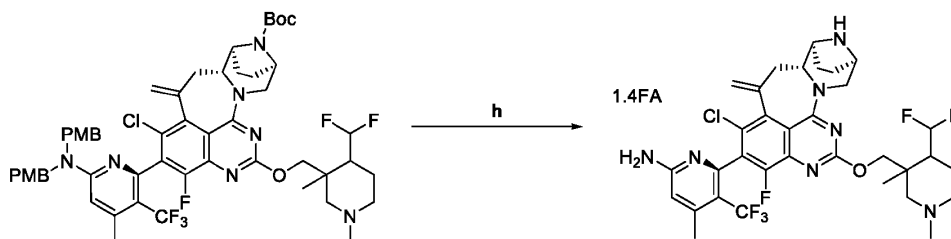
**Step 1: Synthesis of tert-butyl (1S, 4R, 11R, 14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-((4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1',2':1,7] azepino[2,3,4-de]quinazoline-15-carboxylate**



[00521] To a solution of (4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methanol (60%) (200 mg, 0.62 mmol, 1.5 eq) in THF (2 mL) was added NaH (50 mg, 60%, 1.24 mmol, 3.0 eq) at

0 °C under N<sub>2</sub> atmosphere. The mixture was stirred at room temperature for 0.5 h under N<sub>2</sub>, then was added tert-butyl (1S, 4R, 11R, 14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8,10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (350 mg, 0.41 mmol, 1.0 eq) in THF (4 mL) and stirred at room temperature for 2 h under N<sub>2</sub>. HPLC showed the reaction was completed. The reaction mixture was quenched by the addition of the saturated NH<sub>4</sub>Cl aqueous solution (5.0 mL) and filtered, the filtrate was diluted extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (DCM / MeOH = 30:1) to afford tert-butyl (1S, 4R, 11R, 14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-((4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1',2':1,7] azepino[2,3,4-de]quinazoline-15-carboxylate (255 mg, purity: 95%, yield: 60.6%) as a yellow solid. LCMS: 1036.2 (M+H<sup>+</sup>).

**Step 2: Synthesis of 6-((1S,4R,11R,14aR)-12-chloro-8-((4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-de] quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine formate (1:1.4), 6-((1S,4R,11R,14aR)-12-chloro-8-(((3S,4S)-4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine and 6-((1S,4R,11R,14aR)-12-chloro-8-(((3R,4R)-4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine**



[00522] The solution of tert-butyl (1S, 4R, 11R, 14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-((4-(difluoromethyl)-1,3-dimethylpiperidin-

3-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (100 mg, 0.10 mmol, 1.0 eq) in TFA (3 mL) was stirred at 50 °C for 3 h. HPLC showed the reaction was completed. The mixture was adjusted to pH ~7 with saturated aqueous Na<sub>2</sub>CO<sub>3</sub> (5 mL). Then the reaction was filtered, and the filtrate was diluted extracted with DCM / MeOH (10:1, 15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (DCM / 7.0 M Solution In MeOH = 20:1) to afford 6-((1S, 4R, 11R, 14aR)-12-chloro-8-((4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine formate (1:1.4) (25 mg, purity: 96%, yield: 34.0%) as a yellow solid.

[00523] <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.22 (brs, 1.4H), 6.85 (brs, 2H), 6.53 – 6.07 (m, 2H), 5.76 (s, 1H), 5.32 (s, 1H), 5.19 – 5.00 (m, 1H), 4.50 – 4.34 (m, 2H), 4.00 – 3.90 (m, 1H), 3.70-3.50 (m, 1H), 3.50 – 3.30 (m, 1H), 3.20 – 3.08 (m, 1H), 3.00 – 2.70 (m, 4H), 2.36 (s, 3H), 2.29 – 2.20 (m, 1H), 2.10 (s, 3H), 2.07 – 1.92 (m, 1H), 1.90 – 1.41 (m, 8H), 1.10 (s, 3H).

LCMS: m/z 696.2 (M+H<sup>+</sup>).

### Step 3: Chiral separation by chiral HPLC

[00524] The diastereomers of the 6-((1S, 4R, 11R, 14aR)-12-chloro-8-((4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1',2':1,7] azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (210 mg, 0.30 mmol) were purified by chiral HPLC to give the following 2 isomers.

[00525] **Peak 1:** 6-((1S,4R,11R,14aR)-12-chloro-8-(((3S,4S)-4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (35 mg, peak 1, white solid, retention time = 9.370, de 99.52%, under the analytical separation method)

[00526] <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 6.82 (brs, 2H), 6.48 (s, 1H), 6.45-6.10 (m, 1H), 5.74 (s, 1H), 5.29 (s, 1H), 5.10-5.00 (m, 1H), 4.50-4.30 (m, 2H), 3.96 – 3.85 (m, 1H), 3.55-3.45 (m, 1H), 3.40-3.30 (m, 1H), 3.11 (d, *J* = 12.4 Hz, 1H), 3.00 – 2.90 (m, 1H), 2.89 – 2.70 (m, 2H),

2.36 (s, 3H), 2.25-2.15 (m, 1H), 2.10 (s, 3H), 2.00 – 1.90 (m, 1H), 1.89 – 1.80 (m, 1H), 1.79 – 1.68 (m, 2H), 1.68 – 1.58 (m, 2H), 1.57 – 1.42 (m, 3H), 1.10 (s, 3H). LCMS: m/z 696.2 (M+H<sup>+</sup>).

[00527] **Peak 2:** 6-((1S,4R,11R,14aR)-12-chloro-8-(((3R,4R)-4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (45 mg, peak 2, white solid, retention time = 9.721, de 98.94%, under the analytical separation method)

[00528] <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 6.82 (brs, 2H), 6.48 (s, 1H), 6.45-6.10 (m, 1H), 5.75 (s, 1H), 5.30 (s, 1H), 5.10-5.00 (m, 1H), 4.50 – 4.33 (m, 2H), 3.99 – 3.85 (m, 1H), 3.55-3.45 (m, 1H), 3.40-3.30 (m, 1H), 3.10 (d, *J* = 12.8 Hz, 1H), 3.00 – 2.89 (m, 1H), 2.87 – 2.72 (m, 2H), 2.36 (s, 3H), 2.30-2.15 (m, 1H), 2.10 (s, 3H), 2.04 – 1.90 (m, 1H), 1.90 – 1.80 (m, 1H), 1.79 – 1.60 (m, 4H), 1.60 – 1.40 (m, 3H), 1.10 (s, 3H). LCMS: m/z 696.3 (M+H<sup>+</sup>).

[00529] Chiral separation conditions:

[00530] Analytical separation method:

[00531] Instrument: Agilent HPLC. Column: HALO 90A, C18, 2.7 μm, 4.6 x 150 mm.

Mobile phase: A for 0.05% TFA in water and B for 0.05% TFA in Acetonitrile. Gradient: B 5-95%. Flow rate: 1.0 mL/min. Column temperature: 40 °C. Injection volume: 1.0 μl, Wavelength: 210 nm.

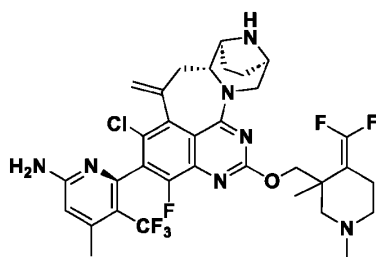
[00532] Preparative separation method:

[00533] Instrument: Prep-HPLC-Gilson. Column: CHIRALPAK IG, 2cm x 25cm, 5μm.

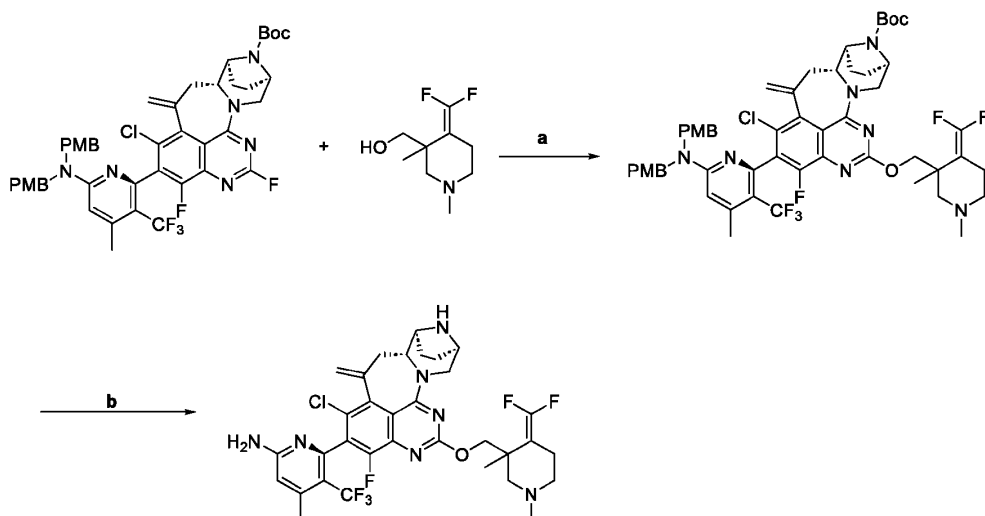
Mobile phase: A for Hexane (0.5% 2mM NH<sub>3</sub>-MeOH) and B for EtOH / DCM. Flow rate: 20 mL /min. Column temperature: 25 °C. Wavelength: 220 nm.

### Example 66

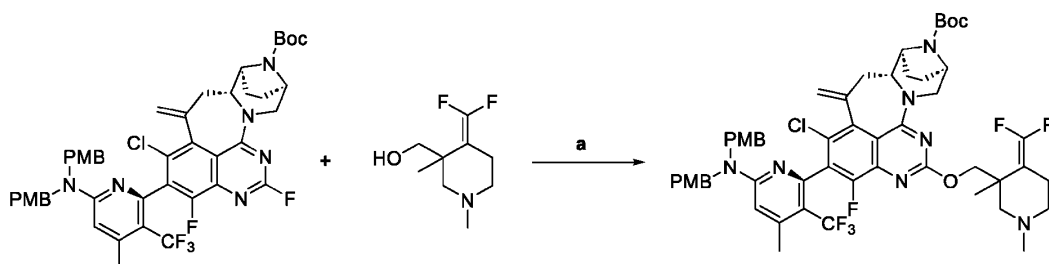
**6-((1S, 4R, 11R, 14aR)-12-chloro-8-((4-(difluoromethylene)-1,3-dimethylpiperidin-3-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1',2':1,7] azepino [2,3,4-de] quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine**



### Synthetic scheme



**Step 1: Synthesis of tert-butyl (1S, 4R, 11R, 14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-((4-(difluoromethylene)-1,3-dimethylpiperidin-3-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino [1',2':1,7] azepino[2,3,4-de]quinazoline-15-carboxylate**

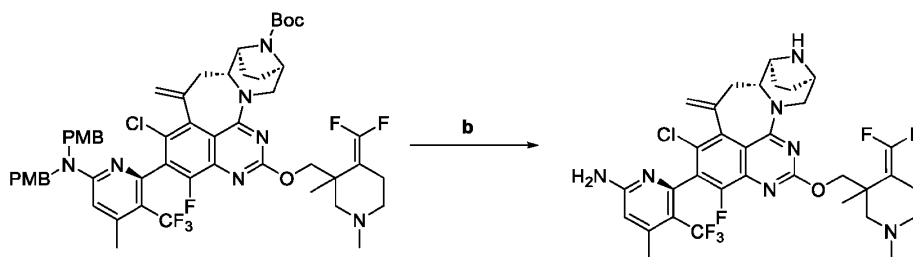


[00534] To a solution of (4-(difluoromethylene)-1,3-dimethylpiperidin-3-yl)methanol (200 mg, 60%, 0.62 mmol, 1.5 eq) in THF (2 mL) was added NaH (50 mg, 60%, 1.24 mmol, 3.0 eq) at 0 °C under nitrogen atmosphere. The mixture was stirred at room temperature for 0.5 h under



N<sub>2</sub>, then added tert-butyl (1S,4R,11R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (350 mg, 0.41 mmol, 1.0 eq) in THF (4 mL) and stirred at room temperature for 2 h under N<sub>2</sub>. HPLC showed the reaction was completed. The reaction mixture was quenched by the addition of the saturated NH<sub>4</sub>Cl aqueous solution (5 mL). Then the reaction was filtered and the filtrate was diluted extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (DCM / MeOH = 30:1) to afford tert-butyl (1S, 4R, 11R, 14aR)-11-(6-(bis(4-methoxybenzyl) amino)-4-methyl-3-(trifluoromethyl) pyridin-2-yl)-12-chloro-8-((4-(difluoromethylene)-1,3-dimethylpiperidin-3-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1',2':1,7] azepino [2,3,4-de] quinazoline-15-carboxylate (255 mg, purity: 95%, yield: 60.2%) as a yellow solid. LCMS: 1034.2 (M+H<sup>+</sup>).

**Step 2: Synthesis of 6-((1S, 4R, 11R, 14aR)-12-chloro-8-((4-(difluoromethylene)-1,3-dimethylpiperidin-3-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1',2':1,7] azepino [2,3,4-de] quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine formate (1:0.64)**



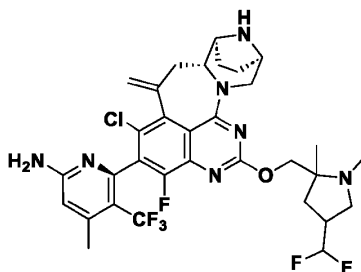
[00535] The solution of tert-butyl (1S, 4R, 11R, 14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-((4-(difluoromethylene)-1,3-dimethylpiperidin-3-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de] quinazoline-15-carboxylate (100 mg, 0.10 mmol, 1.0 eq) in TFA (3 mL) was stirred at 50 °C for 3 h. HPLC showed the reaction was completed. The mixture was adjusted to pH ~7 with saturated NaCO<sub>3</sub> aqueous solution (5 mL). Then the reaction was filtered, and the filtrate was extracted with DCM / MeOH (10:1, 15 mL x 3). The

combined organic layers were washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (DCM / 7.0 M Solution in MeOH = 20:1) to afford 6-((1S, 4R, 11R, 14aR)-12-chloro-8-((4-(difluoromethylene)-1,3-dimethylpiperidin-3-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1',2':1,7] azepino [2,3,4-de] quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine formate (1:0.64) (25 mg, purity: 96%, yield: 36.8%) as a yellow solid.

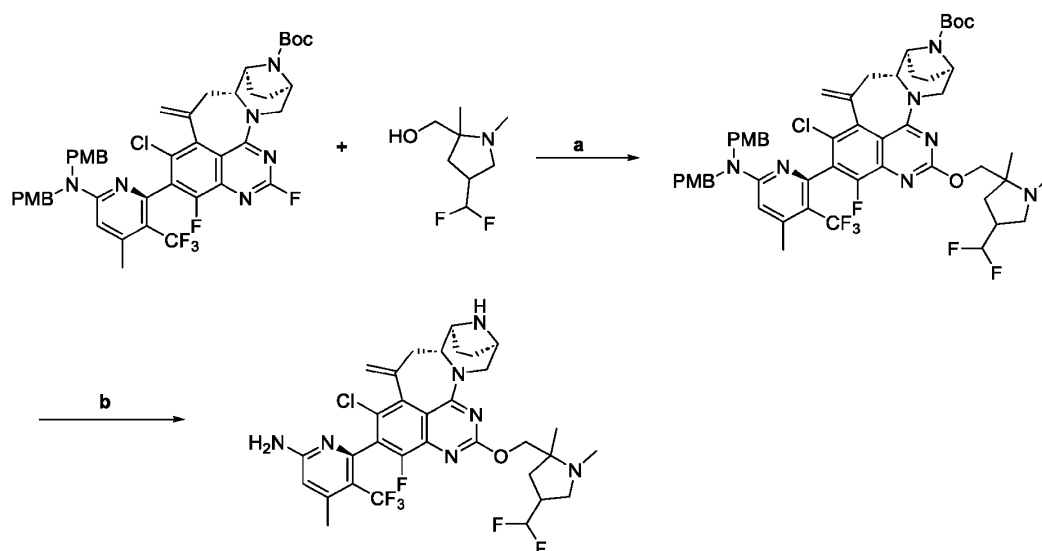
[00536] <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  8.20 (brs, 0.64H), 6.85 (brs, 2H), 6.47 (s, 1H), 5.74 (s, 1H), 5.29 (s, 1H), 5.10 – 4.90 (m, 1H), 4.77 – 4.60 (m, 1H), 4.30-4.10 (m, 1H), 4.00 – 3.87 (m, 1H), 3.60-3.50 (m, 1H), 3.40-3.38 (m, 2H), 3.20 – 3.10 (m, 1H), 3.00 – 2.85 (m, 1H), 2.70 – 2.52 (m, 2H), 2.40 – 2.20 (m, 6H), 2.15 (s, 3H), 2.08 – 1.85 (m, 3H), 1.70 – 1.40 (m, 3H), 1.23 (d, *J* = 4.8 Hz, 3H). LCMS: *m/z* 694.3 (M+H<sup>+</sup>).

#### Example 67

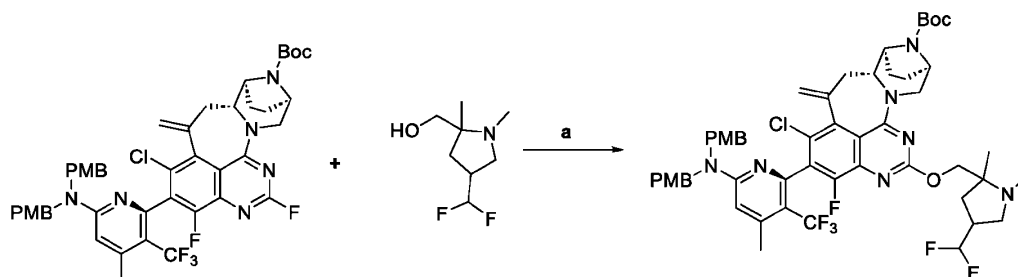
**6-((1S, 4R, 11R, 14aR)-12-chloro-8-((4-(difluoromethyl)-1,2-dimethylpyrrolidin-2-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino [1', 2':1, 7] azepino [2, 3, 4-de] quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine**



Synthetic scheme



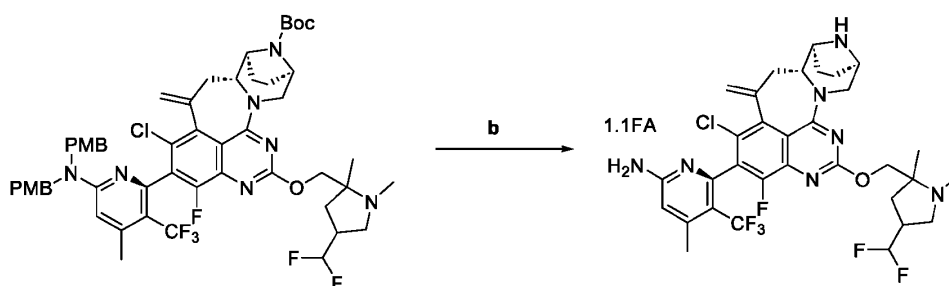
**Step 1: Synthesis of tert-butyl (1S,4R,11R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-((4-(difluoromethyl)-1,2-dimethylpyrrolidin-2-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00537] To a solution of 4-(difluoromethyl)-1,2-dimethylpyrrolidin-2-yl)methanol (200 mg, 60%, 0.68 mmol, 1.5 eq) in THF (2 mL) was added NaH (55 mg, 60%, 1.36 mmol, 3.0 eq) at 0 °C under nitrogen atmosphere. The mixture was stirred at room temperature for 0.5 h under N<sub>2</sub>, then added tert-butyl (1S,4R,11R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (390 mg, 0.45 mmol, 1 eq) in THF (4 mL) and stirred at room temperature for 2 h under N<sub>2</sub>. HPLC showed the reaction was completed. The reaction mixture was quenched by the addition of the saturated NH<sub>4</sub>Cl aqueous solution (5.0 mL) and then filtered, the filtrate was extracted with

EtOAc (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (petroleum ether / EtOAc = 2:1) to afford tert-butyl (1S,4R,11R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-((4-(difluoromethyl)-1,2-dimethylpyrrolidin-2-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (50 mg, purity: 95%, yield: 10.6%) as a yellow solid. LCMS: 1022.4 (M+H<sup>+</sup>).

**Step 2: Synthesis of 6-((1S,4R,11R,14aR)-12-chloro-8-((4-(difluoromethyl)-1,2-dimethylpyrrolidin-2-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine**



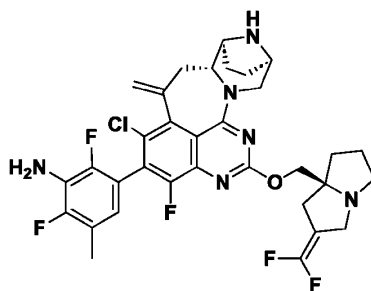
[00538] The solution of tert-butyl (1S,4R,11R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-((4-(difluoromethyl)-1,2-dimethylpyrrolidin-2-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (50 mg, 0.05 mmol, 1.0 eq) in TFA (1.5 mL) was stirred at 50 °C for 3 h. HPLC showed the reaction was completed. The mixture was adjusted to pH ~7 with saturated Na<sub>2</sub>CO<sub>3</sub> aqueous solution (5 mL). Then the reaction was filtered, and the filtrate was extracted with DCM / MeOH (10:1, 15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (DCM / 7.0 M Solution In MeOH = 20:1) to afford 6-((1S,4R,11R,14aR)-12-chloro-8-((4-(difluoromethyl)-1,2-dimethylpyrrolidin-2-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-

de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine formate (1:1.1) (20 mg, purity: 96%, yield: 58.8%).

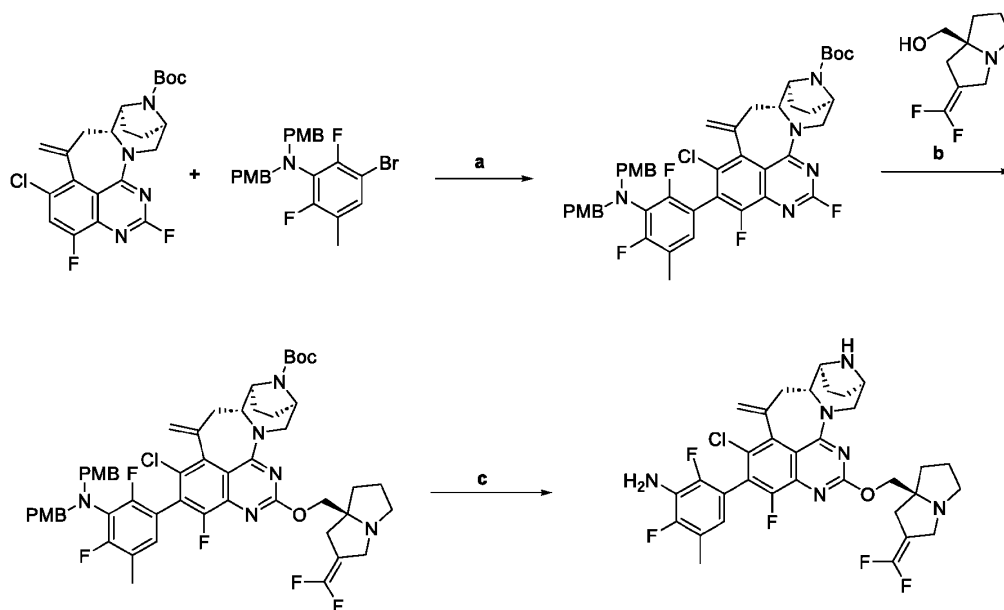
[00539]  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  8.24 (brs, 1.1H), 6.84 (brs, 2H), 6.48 (s, 1H), 6.24 – 5.83 (m, 1H), 5.75 (s, 1H), 5.30 (s, 1H), 5.10 – 4.96 (m, 1H), 4.31 – 4.11 (m, 2H), 4.00 – 3.85 (m, 2H), 3.20 – 3.10 (m, 1H), 3.00 – 2.80 (m, 3H), 2.78 – 2.70 (m, 1H), 2.36 (s, 3H), 2.30 – 2.25 (m, 1H), 2.21 (s, 3H), 2.00 – 1.75 (m, 3H), 1.67 – 1.40 (m, 4H), 1.30 – 1.12 (m, 1H), 1.10 – 0.95 (m, 3H). LCMS:  $m/z$  682.2 ( $\text{M}+\text{H}^+$ ).

### Example 68

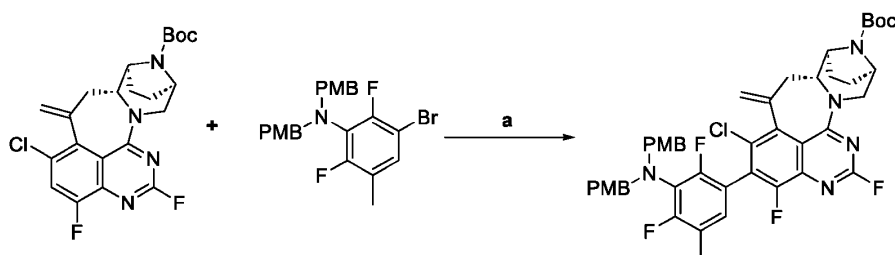
**3-((1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7] azepino[2,3,4-de]quinazolin-11-yl)-2,6-difluoro-5-methylaniline**



Synthesis scheme



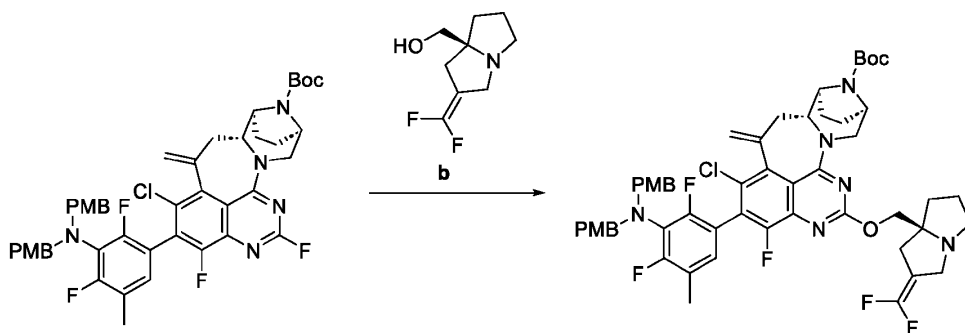
**Step 1: Synthesis of tert-butyl (1S,4R,14aR)-11-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-5-methylphenyl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00540] To a solution of tert-butyl (1S,4R,14aR)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (250 mg, 0.56 mmol, 1.0 eq) in THF (3 mL) was added (TMP)<sub>2</sub>Zn·MgCl<sub>2</sub>·LiCl (0.4 M, 8.4 mL, 3.34 mmol, 6.0 eq) under N<sub>2</sub>, the mixture was stirred at 50 °C for 2 h. Then a mixture of 3-bromo-2,6-difluoro-N,N-bis(4-methoxybenzyl)-5-methylaniline (387 mg, 0.84 mmol, 1.5 eq) and CPhos Pd G3 (45 mg, 0.56 mmol, 0.10 eq) in 1,4-dioxane (3 mL) was added to the mixture. The mixture was stirred at 80 °C for 3 h. The reaction was quenched with H<sub>2</sub>O (10 mL). The mixture was filtered, the filter cake was washed with large EtOAc and separated. The aqueous layer was extracted with EtOAc (15 mL x 3). The combined organic layers were washed

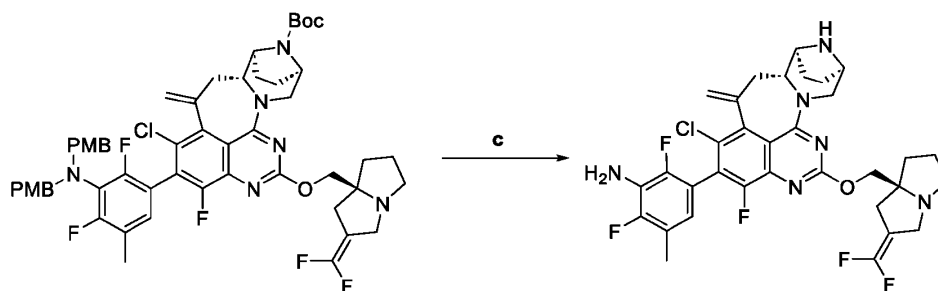
with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude product. The crude product was purified by silica gel column chromatography (Petroleum ether: EtOAc = 3 : 1) to give tert-butyl (1S,4R,14aR)-11-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-5-methylphenyl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (110 mg, 23.8%) as a brown solid. LCMS: m/z 830.2 (M+H<sup>+</sup>).

**Step 2: Synthesis of tert-butyl (1S,4R,14aR)-11-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-5-methylphenyl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00541] To a solution of ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (19 mg, 0.099 mmol, 1.3 eq) in THF (2 mL) was added NaH (9 mg, 0.23 mmol, 3.0 eq), the reaction mixture was stirred at 25 °C for 0.5 h under N<sub>2</sub>. To the reaction mixture was added a mix of tert-butyl (1S,4R,14aR)-11-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-5-methylphenyl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (63 mg, 0.076 mmol, 1.0 eq) in THF (2 mL), the reaction was stirred at 25 °C for 2 h. The reaction was quenched with H<sub>2</sub>O (2 mL) at 0 °C. The resulting mixture was extracted with EtOAc (5 mL x 2). The combined organic layers were washed with brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude product. The crude was purified by Prep-TLC (DCM: MeOH = 15: 1) to give tert-butyl (1S,4R,14aR)-11-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-5-methylphenyl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (50 mg, 65.8%) as a yellow solid. LCMS: m/z 999.4 (M+H<sup>+</sup>).

**Step 3: Synthesis of 3-((1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-2,6-difluoro-5-methylaniline**

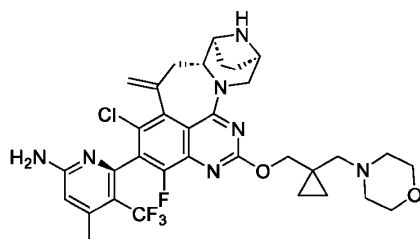


[00542] A solution of tert-butyl (1S,4R,14aR)-11-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-5-methylphenyl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (50 mg, 0.05 mmol, 1.0 eq) in TFA (1 mL) was stirred at 50 °C for 2 h. The reaction was concentrated to give a crude product. The crude product was purified by Prep-HPLC (10% ~ 55% ACN in water with 0.1% FA) to give 3-((1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-2,6-difluoro-5-methylaniline formate (1:1.5) (30 mg, 82.4%) as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 8.45 (brs, 1.5 H), 6.52 – 6.41 (m, 1H), 5.85 (s, 1H), 5.61 – 5.49 (m, 2H), 4.80 – 4.30 (m, 3H), 4.25 – 3.85 (m, 4H), 3.60 – 3.51 (m, 1H), 3.28 – 3.21 (m, 1H), 3.05 – 2.98 (m, 1H), 2.89 – 2.79 (m, 1H), 2.60 – 2.35 (m, 3H), 2.25 (s, 3H), 2.20 – 1.85 (m, 7H). LCMS: m/z 659.2 ([M-1.5FA+H]<sup>+</sup>).

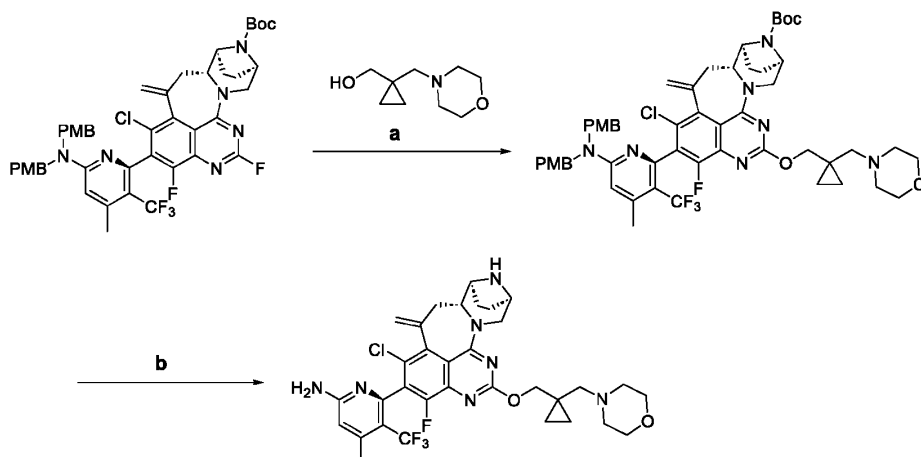
**Example 69**

**6-((1S,4R,11R,14aR)-12-chloro-10-fluoro-13-methylene-8-((1-(morpholinomethyl)cyclopropyl)methoxy)-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine**

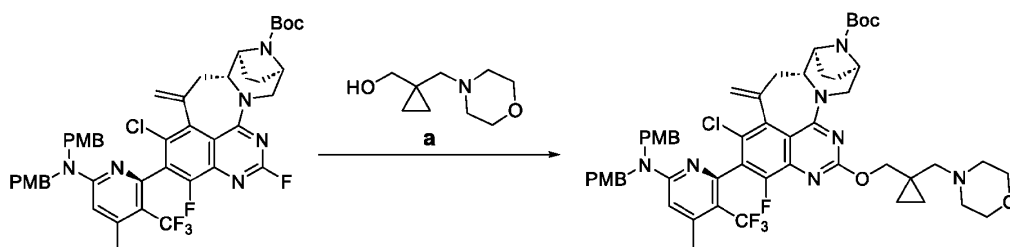




### Synthetic scheme



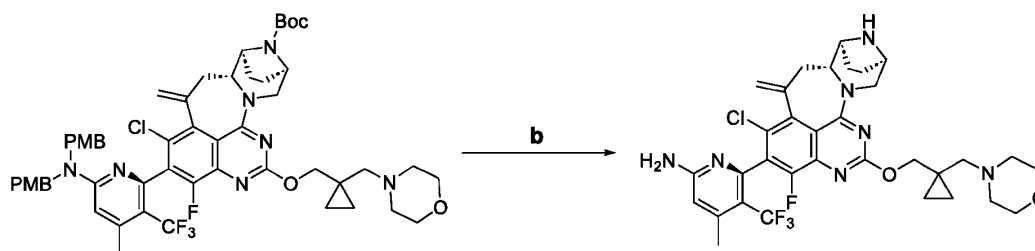
**Step 1: Synthesis of tert-butyl (1S,4R,11R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-10-fluoro-13-methylene-8-((1-(morpholinomethyl)cyclopropyl)methoxy)-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00543] To a solution of (1-(morpholinomethyl)cyclopropyl)methanol (35.8 mg, 0.21 mmol, 1.2 eq) in THF (2 mL) was added NaH (20.9 mg, 60%, 0.52 mmol, 3.0 eq) at room temperature. The reaction mixture was stirred at room temperature for 0.5 h under N<sub>2</sub>. To the reaction mixture was added tert-butyl (1S,4R,11R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-

octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (150.0 mg, 0.17 mmol, 1.0 eq) in THF (2 mL). The reaction was stirred at room temperature for 2 h. The reaction was quenched with H<sub>2</sub>O (5 mL) at 0 °C and extracted with EtOAc (5 mL x 2). The combined organic layers were washed with brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude product. The crude product was purified by Prep-TLC (DCM / MeOH = 30 : 1) to give tert-butyl (1S,4R,11R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-10-fluoro-13-methylene-8-((1-(morpholinomethyl)cyclopropyl)methoxy)-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (140.0 mg, 79.3%) as a yellow solid. LCMS: m/z 507.7 (M/2+H<sup>+</sup>).

**Step 2: Synthesis of 6-((1S,4R,11R,14aR)-12-chloro-10-fluoro-13-methylene-8-((1-(morpholinomethyl)cyclopropyl)methoxy)-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine**

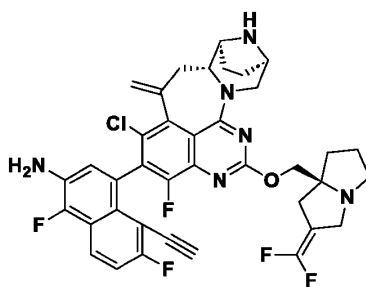


[00544] A solution of tert-butyl (1S,4R,11R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-10-fluoro-13-methylene-8-((1-(morpholinomethyl)cyclopropyl)methoxy)-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (40.0 mg, 0.04 mmol, 1.0 eq) in TFA (1 mL) was stirred at 50 °C for 2 h under N<sub>2</sub>. The reaction was concentrated to give a crude product. The crude product was purified by Prep-HPLC (acetonitrile with 0.1% FA in water, 30% to 40%) to give 6-((1S,4R,11R,14aR)-12-chloro-10-fluoro-13-methylene-8-((1-(morpholinomethyl)cyclopropyl)methoxy)-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine formate (1:0.44) (11.8 mg, 43.1%) as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 8.52 (brs, 0.44H), 6.59 (s, 1H), 5.82 (s, 1H), 5.58 – 5.38 (m, 2H), 4.47 –

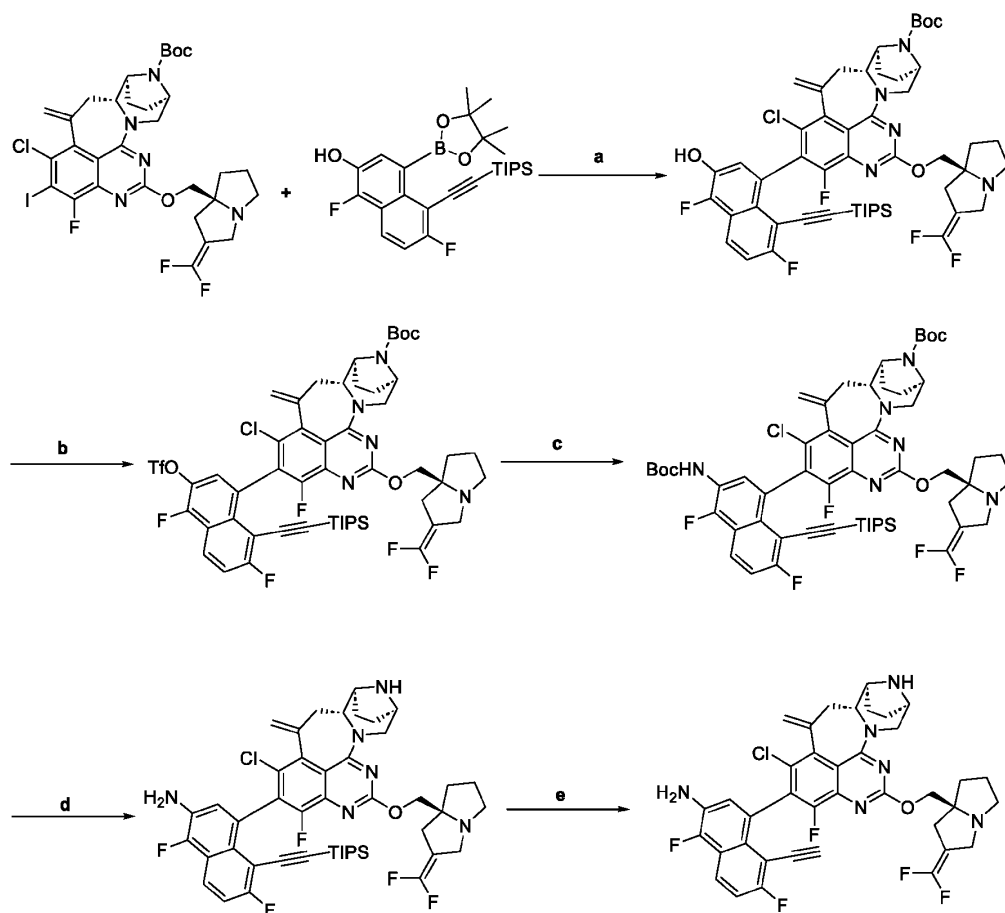
4.31 (m, 2H), 4.16 – 3.62 (m, 7H), 3.28 – 3.23 (m, 1H), 3.04 – 2.93 (m, 1H), 2.56 – 2.31 (m, 1H), 1.93 – 1.73 (m, 3H), 0.73 – 0.46 (m, 4H). LCMS:  $m/z$  674.2 ( $M+H^+$ ).

#### Example 70

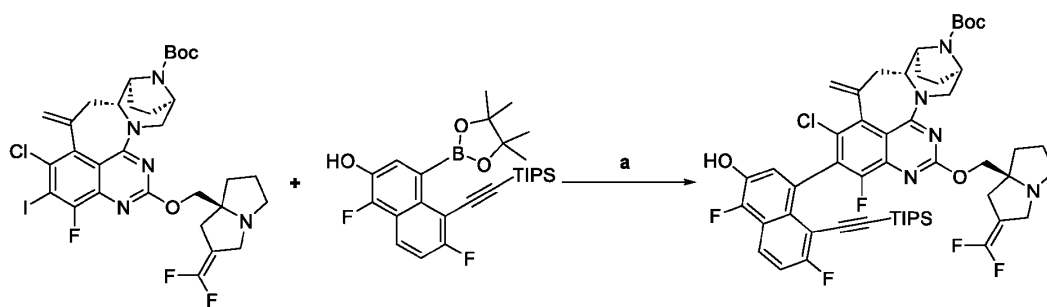
**4-((1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-ethynyl-1,6-difluoronaphthalen-2-amine**



Synthetic scheme

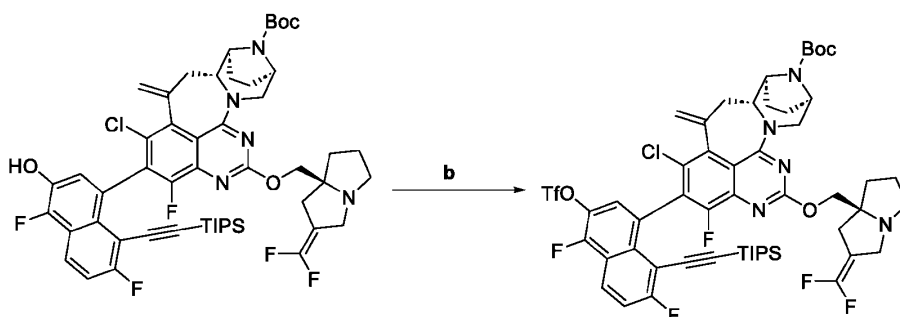


**Step 1: Synthesis of tert-butyl (1S, 4R, 14aR)-12-chloro-11-(4, 7-difluoro-3-hydroxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1, 4-epiminoazepino[1', 2': 1, 7]azepino[2, 3, 4-de]quinazoline-15-carboxylate**



[00545] To a solution of tert-butyl (1S, 4R, 14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-11-iodo-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1, 4-epiminoazepino[1', 2': 1, 7]azepino[2, 3, 4-de]quinazoline-15-carboxylate (200 mg, 0.27 mmol, 1.0 eq) in toluene (2.5 mL) and H<sub>2</sub>O (0.5 mL) was added 1, 6-difluoro-4-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (162 mg, 0.32 mmol, 1.2 eq), Cs<sub>2</sub>CO<sub>3</sub> (263 mg, 0.81 mmol, 3.0 eq) and CataCXium A Pd G3 (39 mg, 0.05 mmol, 0.2 eq) at room temperature. The mixture was irradiated with microwave radiation at 120 °C for 1.5 h under nitrogen atmosphere. HPLC and TLC showed the reaction was completed. The mixture was cooled, then added H<sub>2</sub>O (20 mL) and extracted with EtOAc (20 mL x 3). The organic layers were washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (Petroleum ether / EtOAc = 3:1) to give tert-butyl (1S, 4R, 14aR)-12-chloro-11-(4,7-difluoro-3-hydroxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-8-(((S)-2-(difluoromethylene) tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1, 4-epiminoazepino[1', 2': 1, 7]azepino[2, 3, 4-de]quinazoline-15-carboxylate (125 mg, purity: 95%, yield: 47.5%) as a yellow solid. LCMS: 976.3 (M+H<sup>+</sup>).

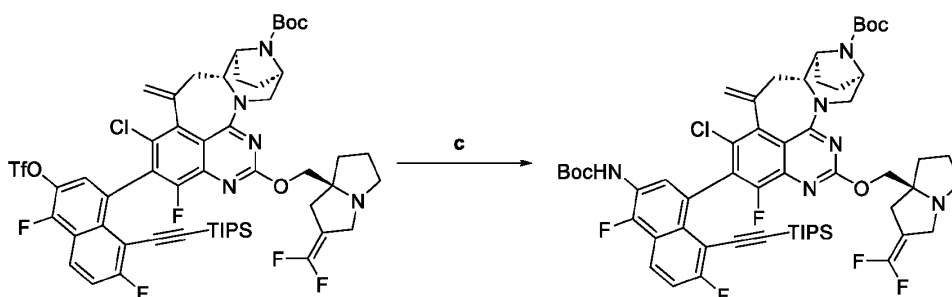
**Step 2: Synthesis of tert-butyl (1S,4R,14aR)-12-chloro-11-(4,7-difluoro-3-(((trifluoromethyl)sulfonyl)oxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1, 4-epiminoazepino[1', 2': 1, 7]azepino[2, 3, 4-de]quinazoline-15-carboxylate**



[00546] To a solution of tert-butyl (1S,4R,14aR)-12-chloro-11-(4,7-difluoro-3-hydroxy-8-((triisopropylsilyl) ethynyl)naphthalen-1-yl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-

pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1, 4-epiminoazepino[1', 2': 1, 7]azepino[2, 3, 4-de]quinazoline-15-carboxylate (150 mg, 0.15 mmol, 1.0 eq) in DCM (1.5 mL) was added DIEA (40 mg, 0.31 mmol, 2.0 eq) and Tf<sub>2</sub>O (65 mg, 0.23 mmol, 1.5 eq) at 0 °C. The mixture was stirred at room temperature for 1 h. HPLC and TLC showed the reaction was completed. The mixture was added H<sub>2</sub>O (10 mL) and extracted with EtOAc (10 mL x 3). The organic layers were washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a crude product, which was purified by prep-TLC (Petroleum ether / EtOAc = 2:1) to give tert-butyl (1S, 4R, 14aR)-12-chloro-11-(4, 7-difluoro-3-(((trifluoromethyl)sulfonyl)oxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1, 4-epiminoazepino[1', 2': 1, 7]azepino[2, 3, 4-de]quinazoline-15-carboxylate (66 mg, purity: 95%, yield: 38.8%) as a yellow solid. LCMS: 554.9 (M/2+H<sup>+</sup>).

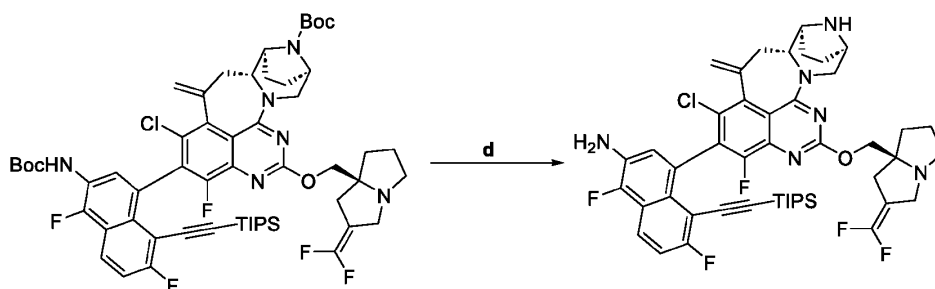
**Step 3: Synthesis of tert-butyl (1S, 4R, 14aR)-11-(3-((tert-butoxycarbonyl)amino)-4, 7-difluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1, 4-epiminoazepino[1', 2': 1, 7]azepino[2, 3, 4-de]quinazoline-15-carboxylate**



[00547] To a solution of tert-butyl (1S,4R,14aR)-12-chloro-11-(4,7-difluoro-3-(((trifluoromethyl)sulfonyl)oxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7] azepino[2,3,4-de]quinazoline-15-carboxylate (70 mg, 0.06 mmol, 1.0 eq) in toluene (1 mL) was added BocNH<sub>2</sub> (22 mg, 0.19 mmol, 3.0 eq), Cs<sub>2</sub>CO<sub>3</sub> (62 mg, 0.19 mmol, 3.0 eq), RuPhos (6 mg, 0.01 mmol, 0.2 eq) and

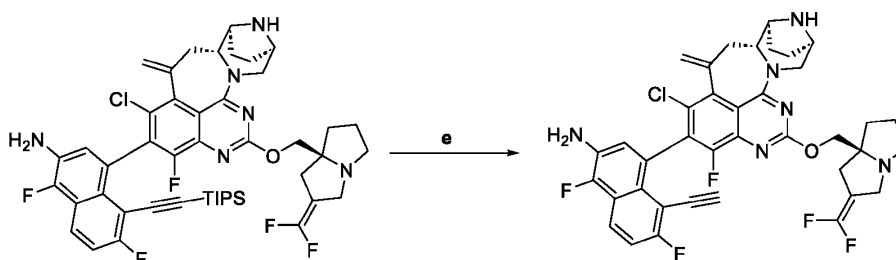
$\text{Pd}_2(\text{dba})_3$  (12 mg, 0.01 mmol, 0.1 eq) at room temperature. The mixture was stirred at 100 °C for 16 h under nitrogen atmosphere. HPLC and TLC showed the reaction was completed. The mixture was cooled, then added  $\text{H}_2\text{O}$  (10 mL) and extracted with EtOAc (10 mL x 3). The organic layers were washed with brine (10 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to give a crude product, which was purified with prep-TLC (Petroleum ether / EtOAc = 2:1) to give tert-butyl (1S,4R,14aR)-11-(3-((tert-butoxycarbonyl)amino)-4,7-difluoro-8-((triisopropylsilyl) ethynyl)naphthalen-1-yl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (35 mg, purity: 95%, yield: 51.5%) as a yellow solid. LCMS: 538.3 ( $\text{M}/2+\text{H}^+$ ).

**Step 4: Synthesis of 4-((1S, 4R, 14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1, 4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-1,6-difluoro-5-((triisopropylsilyl)ethynyl) naphthalen-2-amine**



[00548] A solution of tert-butyl (1S,4R,14aR)-11-(3-((tert-butoxycarbonyl)amino)-4,7-difluoro-8-((triisopropylsilyl) ethynyl)naphthalen-1-yl)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1, 4-epiminoazepino[1',2':1,7] azepino[2,3,4-de]quinazoline-15-carboxylate (40 mg, 0.04 mmol, 1.0 eq), HCl in dioxane (0.5 mL, 4N) and  $\text{CCl}_4$  (0.5 mL) was stirred at room temperature for 1 h. After completion, the mixture was concentrated to give 4-((1S, 4R, 14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1, 4-epiminoazepino[1',2':1,7] azepino[2,3,4-de]quinazolin-11-yl)-1, 6-difluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-amine (30 mg, crude) as a yellow solid. LCMS: 438.3 ( $\text{M}/2+\text{H}^+$ ).

**Step 5: Synthesis of 4-((1S, 4R, 14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1, 4-epiminoazepino[1', 2': 1, 7]azepino[2, 3, 4-de]quinazolin-11-yl)-5-ethynyl-1, 6-difluoronaphthalen-2-amine**



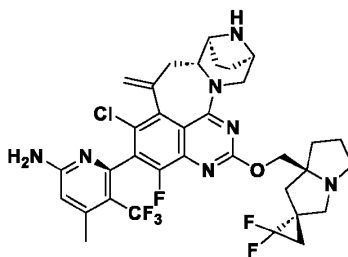
[00549] To a solution of 4-((1S, 4R, 14aR)-12-chloro-8-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7] azepino[2,3,4-de]quinazolin-11-yl)-1,6-difluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-amine (30 mg, crude) in DMF (1 mL) was added CsF (130 mg, 0.09 mmol, 25.0 eq). The reaction was stirred at 50 °C for 1 h. After completion, the mixture was filtered and the filtrate was purified by prep-HPLC (acetonitrile with 0.1% NH<sub>4</sub>HCO<sub>3</sub> in water, 70% to 100%) to give 4-((1S,4R,14aR)-12-chloro-8-(((S)-2-(difluoromethylene) tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-ethynyl-1,6-difluoronaphthalen-2-amine (8 mg, purity: 98.3%, yield for two steps: 30.0%) as a white solid.

[00550] <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.00-7.90 (m, 1H), 7.49 (t, *J* = 9.0 Hz, 1H), 7.15-7.00 (m, 1H), 5.81 – 5.57 (m, 3H), 5.38 – 5.26 (m, 1H), 5.14 – 4.90 (m, 1H), 4.15 – 3.99 (m, 3H), 3.98 – 3.87 (m, 1H), 3.72 – 3.52 (m, 2H), 3.48 – 3.38 (m, 1H), 3.20 – 3.07 (m, 1H), 3.05 – 2.86 (m, 2H), 2.75 – 2.53 (m, 2H), 2.47 – 2.14 (m, 3H), 2.05 – 1.73 (m, 5H), 1.73 – 1.40 (m, 4H). LCMS: *m/z* 719.2 (M+H<sup>+</sup>).

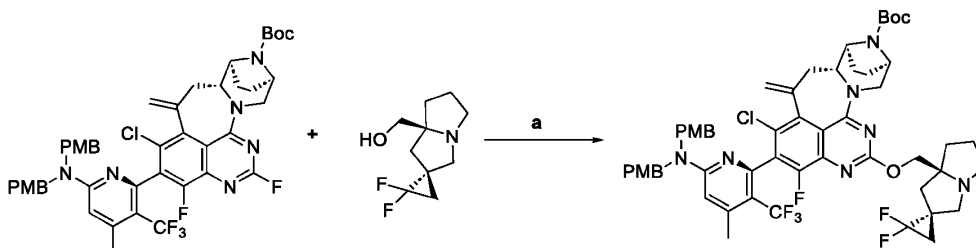
### Example 71

**6-((1S,4R,11R,14aR)-12-chloro-8-(((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-[1,4]epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine**





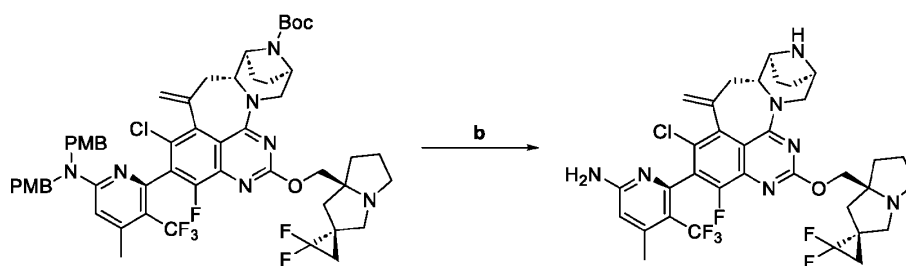
**Step 1: Synthesis of tert-butyl (1S,4R,11R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-(((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00551] To a solution of ((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methanol (141 mg, 0.69 mmol, 1.5 eq) in THF (3 mL) was added NaH (56 mg, 60%, 1.40 mmol, 3.0 eq) at 0 °C under nitrogen atmosphere. The mixture was stirred at room temperature for 0.5 h, added the solution of tert-butyl(1S, 4R, 11R, 14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8,10-difluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7] azepino[2,3,4-de]quinazoline-15-carboxylate (400 mg, 0.46 mmol, 1.0 eq) in THF (4 mL) and stirred at 50 °C for 1 h. After completion, the mixture was cooled, added H<sub>2</sub>O (20 mL) and extracted with EtOAc (20 mL x 3). The organic layers were washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (Petroleum ether / EtOAc = 1:1) to give tert-butyl (1S,4R,11R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-(((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-

epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (198 mg, yield: 40.8%) as a yellow solid. LCMS: 523.7 (M/2+H<sup>+</sup>).

**Step 2: Synthesis of 6-((1S, 4R, 11R, 14aR)-12-chloro-8-(((1S,7a'S)-2, 2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-[1,4]epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine**



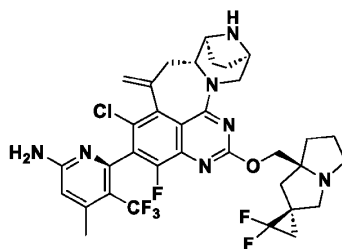
[00552] A solution of tert-butyl (1S,4R,11R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-(((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (100 mg, 0.01 mmol, 1.0 eq) in TFA (2 mL) was stirred at 50 °C for 4 h. The mixture was concentrated to give a residue. The residue was added saturated sodium carbonate aqueous solution (10 mL) and extracted with EtOAc (10 mL x 3). The organic layers were washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a crude product, which was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 5% to 50%) to give 6-((1S, 4R, 11R, 14aR)-12-chloro-8-(((1S,7a'S)-2, 2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-[1,4] epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine formate (1:0.24) (18 mg, purity: 99.8%, de: 98.68%, yield: 26.7%) as a white solid. LCMS: 706.2 (M+H<sup>+</sup>).

[00553] <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.20 (brs, 0.24H), 6.85 (brs, 2H), 6.47 (s, 1H), 5.75 (s, 1H), 5.30 (s, 1H), 5.12 – 4.97 (m, 1H), 4.20-4.10 (m, 2H), 4.00 – 3.88 (m, 1H), 3.70 – 3.58 (m, 2H), 3.50 – 3.30 (m, 1H), 3.20 – 3.05 (m, 2H), 3.05 – 2.98 (m, 1H), 2.97 – 2.86 (m, 1H), 2.75 – 2.63 (m, 1H), 2.58 – 2.50 (m, 1H), 2.36 (d, *J* = 1.2 Hz, 3H),

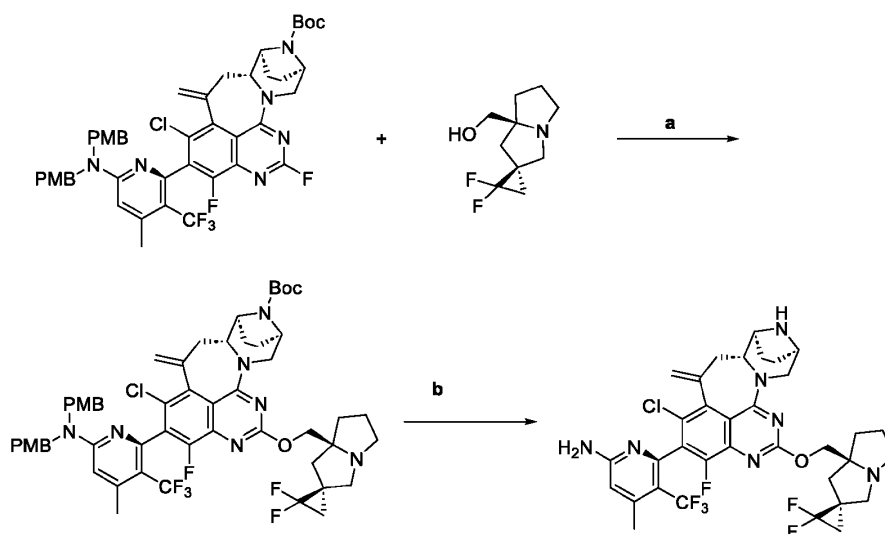
2.30 – 2.20 (m, 1H), 2.13 – 2.02 (m, 1H), 2.01 – 1.67 (m, 5H), 1.66 – 1.40 (m, 6H). LCMS:  $m/z$  706.2 ( $M+H^+$ ).

### Example 72

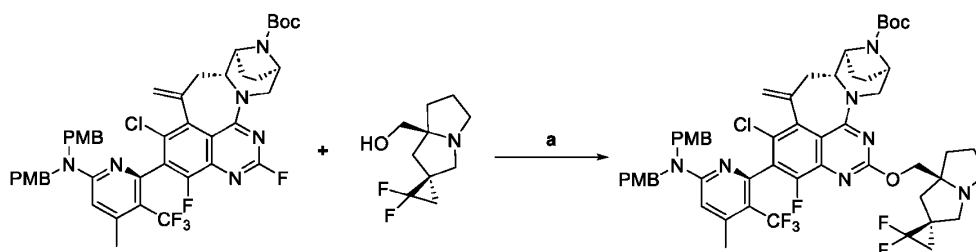
**6-((1S,4R,11R,14aR)-12-chloro-8-(((1R,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-[1,4]epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine**



### Synthetic scheme

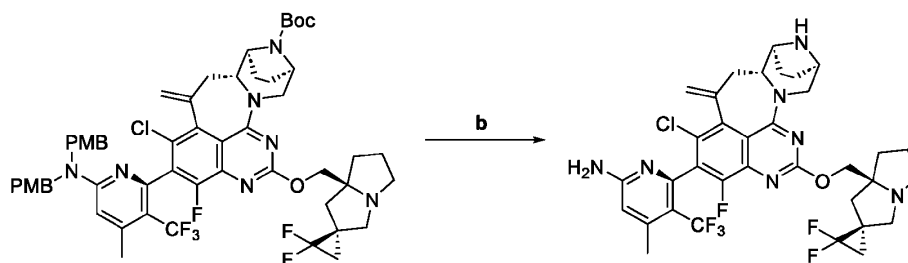


**Step 1: Synthesis of tert-butyl (1S,4R,11R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-(((1R,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate**



[00554] To a solution of ((1R,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methanol (141 mg, 0.69 mmol, 1.5 eq) in THF (3 mL) was added NaH (56 mg, 60%, 1.40 mmol, 3.0 eq) at 0 °C under N<sub>2</sub> atmosphere. The mixture was stirred at room temperature for 0.5 h, added the solution of tert-butyl (1S, 4R, 11R, 14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8,10-difluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7] azepino[2,3,4-de]quinazoline-15-carboxylate (400 mg, 0.46 mmol, 1.0 eq) in THF (4 mL). The mixture was stirred at 50 °C for 1 h. After completion, the mixture was cooled, added H<sub>2</sub>O (20 mL) and extracted with EtOAc (20 mL x 3). The organic layers were washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude product, which was purified by silica gel column chromatography (Petroleum ether / EtOAc = 1:1) to give tert-butyl (1S,4R,11R,14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-(((1R,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (200 mg, yield: 40.9%) as a yellow solid. LCMS: 523.7 (M/2+H<sup>+</sup>).

**Step 2: Synthesis of 6-((1S, 4R, 11R, 14aR)-12-chloro-8-(((1R,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-[1,4]epiminoazepino[1', 2': 1, 7]azepino[2, 3, 4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine formate**



[00555] The solution of tert-butyl (1S, 4R, 11R, 14aR)-11-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-chloro-8-(((1R,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-10-fluoro-13-methylene-1, 2, 3, 4, 5, 13, 14, 14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate (100 mg, 0.01 mmol, 1.0 eq) in TFA (2 mL) was stirred at 50 °C for 4 h. The mixture was concentrated to give a residue. The residue was added saturated sodium carbonate aqueous solution (10 mL) and extracted with EtOAc (10 mL x 3). The organic layers were washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a crude product, which was purified by prep-HPLC (acetonitrile with 0.1% FA in water, 5% to 50%) to give 6-((1S,4R,11R,14aR)-12-chloro-8-(((1R,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-10-fluoro-13-methylene-1,2,3,4,5,13,14,14a-octahydro-[1,4]epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine formate (1:0.80) (18 mg, purity: 99.7%, de: 98.94%, yield: 25.3%) as a white solid.

[00556] <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.28 (brs, 0.80H), 6.85 (brs, 2H), 6.47 (s, 1H), 5.75 (s, 1H), 5.30 (s, 1H), 5.13 – 4.99 (m, 1H), 4.13 – 4.03 (m, 1H), 4.00 – 3.88 (m, 2H), 3.70 – 3.30 (m, 3H), 3.18 – 3.09 (m, 1H), 3.07-3.00 (m, 1H), 3.01 – 2.88 (m, 2H), 2.82 – 2.74 (m, 1H), 2.72 – 2.61 (m, 1H), 2.36 (d, *J* = 1.2 Hz, 3H), 2.30 – 2.20 (m, 1H), 2.15-2.05 (m, 1H), 2.01 – 1.70 (m, 6H), 1.66 – 1.43 (m, 5H). LCMS: *m/z* 706.2 (M-0.80FA+H<sup>+</sup>).

## Biological Binding Assays

### KRAS/SOS1-RAF1 HTRF Binding Assay

[00557] The test compounds were prepared as 10 mM 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 μL 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 MgCl<sub>2</sub>, 1mM DTT, 0.1% BSA, 0.01% Triton X-100). For negative control, 5 μL of assay buffer was added instead. The plate was incubated at room temperature for 20 min. 5 μL of SOS1 and GTP (final concentration at 100 nM and 10 μM, respectively) were subsequently added to each well to initiate the nucleotide exchange. After incubation at room temperature for 2 hours, 5 μL of GST-

RAF1 (final concentration at 8 nM) was added. All reactions were incubated at room temperature for 20 min and then 5  $\mu$ 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**

[00558] 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  $\mu$ 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 MgCl<sub>2</sub>, 1mM DTT, 0.1% BSA, 0.01% Triton X-100), respectively. For negative control, 10  $\mu$ L of assay buffer was added instead. The plate was incubated at room temperature for 20 min. 5  $\mu$ L of GST-RAF1 (final concentration at 8 nM) was subsequently added to each well. Then 5  $\mu$ 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 3: Binding Assay Activities\***

| <b>Example #</b> | <b>GMPPNP G12D<br/>Biochemical assay IC50<br/>(nM)</b> | <b>GMPPNP WT<br/>Biochemical assay IC50<br/>(nM)</b> |
|------------------|--------------------------------------------------------|------------------------------------------------------|
| <b>1</b>         | A                                                      | A                                                    |
| <b>2</b>         | A                                                      | C                                                    |
| <b>3</b>         | C                                                      | C                                                    |
| <b>4</b>         | C                                                      | C                                                    |
| <b>5</b>         | N                                                      | N                                                    |
| <b>6</b>         | A                                                      | B                                                    |
| <b>7</b>         | B                                                      | C                                                    |
| <b>8</b>         | N                                                      | N                                                    |

|    |   |   |
|----|---|---|
| 9  | A | A |
| 10 | B | C |
| 11 | A | A |
| 12 | A | C |
| 13 | A | A |
| 14 | C | C |
| 15 | A | B |
| 16 | B | C |
| 17 | A | B |
| 18 | B | C |
| 19 | A | B |
| 20 | A | A |
| 21 | A | A |
| 22 | A | A |
| 23 | B | C |
| 24 | N | C |
| 25 | N | C |
| 26 | B | C |
| 27 | A | C |
| 28 | A | B |
| 29 | A | C |
| 30 | B | C |
| 31 | B | C |
| 32 | B | C |
| 33 | B | B |
| 34 | A | A |
| 35 | A | A |
| 36 | A | A |
| 37 | A | B |
| 38 | A | A |
| 39 | A | B |
| 40 | A | A |
| 41 | B | C |
| 42 | A | A |
| 43 | A | A |

|    |   |   |
|----|---|---|
| 44 | B | B |
| 45 | A | A |
| 46 | A | A |
| 47 | A | A |
| 48 | A | A |
| 49 | A | B |
| 50 | A | A |
| 51 | A | A |
| 52 | B | C |
| 53 | B | B |
| 54 | A | A |
| 55 | A | A |
| 56 | A | A |
| 57 | A | A |
| 58 | A | A |
| 59 | A | A |
| 60 | A | A |
| 61 | A | A |
| 62 | A | A |
| 63 | A | B |
| 64 | A | B |
| 65 | B | C |
| 66 | A | B |
| 67 | N | C |
| 68 | C | C |
| 69 | A | B |
| 70 | A | A |
| 71 | A | A |
| 72 | A | A |

\*A: < 100 nM; B: 100 nM – 1 uM; C: >1 uM; N: not tested

#### Cell Base Assay

#### 2D CTG Proliferation Assay



[00559] KRASG<sup>12D</sup> 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  $\mu$ 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  $\mu$ 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  $\mu$ 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.

[00560] Cell proliferation percent inhibition values were calculated using the following equation:

$$\text{Inhibition\%} = [1 - (\text{T120}_{\text{compound}} - \text{T120}_{\text{blank}}) / (\text{T120}_{\text{DMSO}} - \text{T120}_{\text{blank}})] \times 100\%.$$

T120<sub>compound</sub>: the signals from compound-treated wells.

T120<sub>blank</sub>: the signals from blank wells.

T120<sub>DMSO</sub>: the signals from 0.5%DMSO-treated wells.

[00561] XLfit software (Fit model: Dose response one site/  $\frac{A + (B-A)/(1 + ((C/x)^D))}{1 + ((C/x)^D)}$ ) was used for curve fitting and IC50 calculation.

**Table 4. Cell Assay Activities\***

| Example # | AGS Cells (nM) | MKN Cells (nM) |
|-----------|----------------|----------------|
| 1         | A              | C              |
| 2         | A              | C              |
| 3         | B              | C              |
| 4         | B              | C              |
| 5         | N              | N              |
| 6         | A              | C              |
| 7         | B              | C              |
| 8         | N              | N              |
| 9         | B              | C              |

|    |   |   |
|----|---|---|
| 10 | A | C |
| 11 | A | C |
| 12 | C | C |
| 13 | A | C |
| 14 | B | C |
| 15 | A | C |
| 16 | B | C |
| 17 | A | C |
| 18 | B | C |
| 19 | A | C |
| 20 | A | C |
| 21 | A | C |
| 22 | A | C |
| 23 | N | N |
| 24 | N | N |
| 25 | N | N |
| 26 | B | C |
| 27 | A | C |
| 28 | A | C |
| 29 | C | C |
| 30 | C | C |
| 31 | B | C |
| 32 | B | C |
| 33 | B | C |
| 34 | A | A |
| 35 | A | C |
| 36 | A | C |
| 37 | A | B |
| 38 | N | N |
| 39 | A | B |
| 40 | A | B |
| 41 | B | B |
| 42 | A | C |
| 43 | A | C |
| 44 | A | C |

|    |   |   |
|----|---|---|
| 45 | A | N |
| 46 | N | N |
| 47 | A | C |
| 48 | A | C |
| 49 | A | B |
| 50 | N | B |
| 51 | N | B |
| 52 | N | N |
| 53 | B | B |
| 54 | A | B |
| 55 | A | B |
| 56 | A | B |
| 57 | A | B |
| 58 | A | C |
| 59 | A | C |
| 60 | A | A |
| 61 | A | N |
| 62 | N | N |
| 63 | A | B |
| 64 | A | B |
| 65 | A | B |
| 66 | A | C |
| 67 | A | C |
| 68 | N | C |
| 69 | A | C |
| 70 | N | N |
| 71 | N | N |
| 72 | N | N |

\*A: < 100 nM; B: 100 nM – 1 uM; C: >1 uM; N: not tested

#### pERK Assay (Western Blot)

[00562] KRASG<sup>12D</sup> 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  $0.5 \times 10^6$  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  $\mu$ 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  $\mu$ 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.

[00563] For Western blot, 15-20  $\mu$ 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).

[00564] 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.

[00565] 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.

[00566] 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.

[00567] 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.

[00568] In this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural reference, unless the context clearly dictates otherwise.

[00569] 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**

[00570] 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.

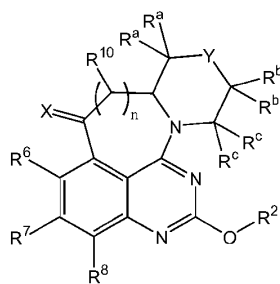
### **Equivalents**

[00571] 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):



(I)

or a pharmaceutically acceptable form or an isotope derivative thereof,  
wherein

$n$  is 1 or 2;

$X$  is  $CR^{x1}R^{x2}$ , wherein each of  $R^{x1}$  and  $R^{x2}$  is independently selected from H, halo and unsubstituted or substituted  $C_{1-3}$  alkyl;

$Y$  is  $NH$ ,  $NR^y$ ,  $CH_2NH$ ,  $CH_2NR^y$ ,  $NHCH_2$  or  $NR^yCH_2$ , wherein  $R^y$  is unsubstituted or substituted  $C_{1-4}$  alkyl,  $P(O)(OCH_3)_2$ ,  $C(O)OR^w$ ,  $C(O)R^w$ , wherein  $R^w$  is H or unsubstituted or substituted  $C_{1-6}$  alkyl;

$R^2$  is  $(CH_2)_iR^{2'}$ , wherein  $i$  is an integer selected from 1-6, and  $(CH_2)_i$  is optionally substituted, wherein  $R^{2'}$  is selected from the group consisting of H, halogen, CN, OH,  $C(O)NRR'$ , unsubstituted or substituted  $C_{1-6}$  alkyl, unsubstituted or substituted 3- to 6-membered carbocyclic ring, unsubstituted or substituted 4- to 6-membered heterocyclic ring and unsubstituted or substituted aryl 7- to 9-membered bicyclic heterocyclic ring;

$R^6$  is selected from the group consisting of H, halogen, CN, OR, unsubstituted or substituted  $C_{1-4}$  alkyl, unsubstituted or substituted  $C_{1-4}$  alkoxy,  $C(O)NRR'$ ,  $NRR'$ ,  $S(O)_2CH_3$ , unsubstituted or substituted 3- to 6-membered carbocyclic or heterocyclic ring, and unsubstituted or substituted 5- to 6-membered heteroaryl;

$R^7$  is an unsubstituted or substituted 6- to 10-membered unsaturated monocyclic or bicyclic ring, comprising 0-5 heteroatoms selected from N, O and S;

$R^8$  is H, halo, unsubstituted or substituted  $C_{1-4}$  alkyl, OR or  $NRR'$ ;

$R^a$ ,  $R^b$  and  $R^c$ :

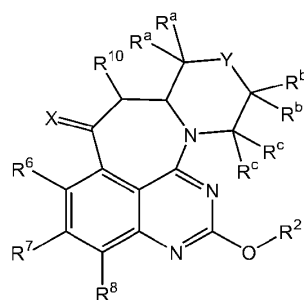
each is independently selected from H, halo, unsubstituted or substituted  $C_{1-3}$  alkyl and OR; or

one  $R^a$  and one  $R^b$ , or one  $R^a$  and one  $R^c$ , together with Y and the carbon atoms they are bonded respectively, form a 4- to 7-membered heterocyclic ring.

each  $R^{10}$  is independently H, halo or  $C_{1-4}$  alkyl; or  $R^{10}$ 's, together with the carbon atoms they are bonded respectively, form a cyclopropyl or cyclobutyl group; and

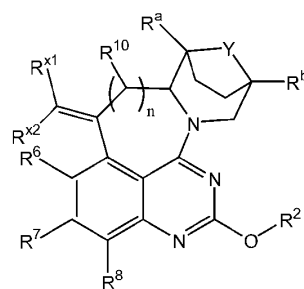
each of R and R' is independently selected from H, unsubstituted or substituted  $C_{1-4}$  alkyl, or unsubstituted or substituted 3- to 6-membered carbocyclic ring, or where R and R' are attached to the same N atom, together form an unsubstituted or substituted 4- to 6-membered heterocyclic ring.

2. The compound of claim 1, wherein n is 1, having the structure of Formula (II):



(II)

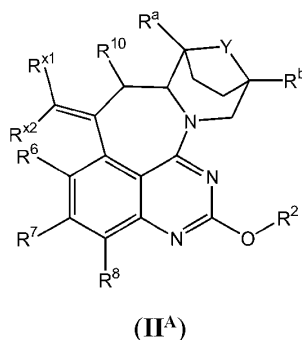
3. The compound of claim 1, wherein one  $R^a$  and one  $R^b$ , wherein together with Y and the carbon atoms they are respectively bonded to, form a 5-membered heterocyclic ring, having the structure of Formula (IA):



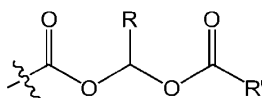
(IA)



4. The compound of claim 2, wherein one  $R^a$  and one  $R^b$ , wherein together with Y and the carbon atoms they are respectively bonded to, form a 5-membered heterocyclic ring, having the structure of Formula (II<sup>A</sup>):



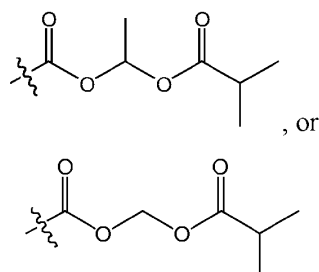
5. The compound of claim 3 or 4, wherein one of  $R^a$  and  $R^b$  is  $\text{CH}_3$  and the other is H.
6. The compound of claim 3 or 4, wherein each of  $R^a$  and  $R^b$  is H.
7. The compound of any one of claims 1-6, wherein each of  $R^{x1}$  and  $R^{x2}$  is independently selected from H, F and Cl.
8. The compound of claim 7, wherein each of  $R^{x1}$  and  $R^{x2}$  is H.
9. The compound of claim 7, wherein one of  $R^{x1}$  and  $R^{x2}$  is H and the other is F or Cl.
10. The compound of claim 7, wherein each of  $R^{x1}$  and  $R^{x2}$  is F or Cl.
11. The compound of any one of claims 1-6, wherein at least one of  $R^{x1}$  and  $R^{x2}$  is an unsubstituted or substituted  $\text{C}_{1-3}$  alkyl.
12. The compound of any one of claims 1-11, wherein Y is NH.
13. The compound of any one of claims 1-11, wherein Y is  $\text{NR}^y$ .
14. The compound of any one of claims 1-11, wherein Y is  $\text{CH}_2\text{NH}$  or  $\text{NHCH}_2$ .
15. The compound of any one of claims 1-11, wherein Y is  $\text{CH}_2\text{NR}^y$  or  $\text{NR}^y\text{CH}_2$ .
16. The compound of claim 15, wherein  $R^y$  is  $\text{P}(\text{O})(\text{OCH}_3)_2$ .
17. The compound of claim 15, wherein  $R^y$  is  $\text{C}(\text{O})\text{OR}$ , wherein R is an unsubstituted or substituted  $\text{C}_{1-4}$  alkyl.
18. The compound of claim 17, wherein  $R^y$  comprises:



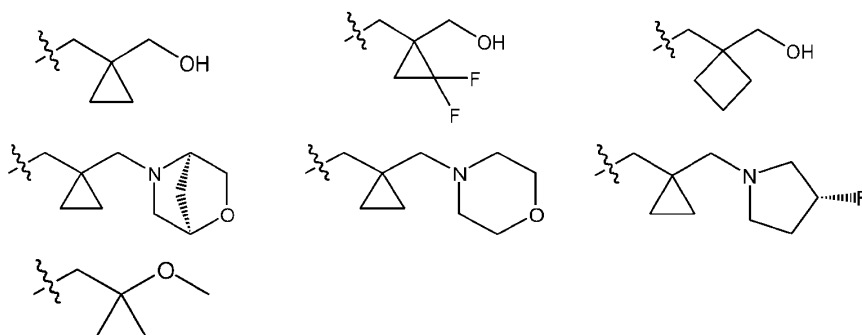
wherein each of R and  $R'$  is selected from H or substituted or unsubstituted  $\text{C}_{1-6}$  alkyl or

substituted or unsubstituted 3- to 6-membered carbocycle.

19. The compound of claim 18, wherein  $R^y$  comprises:

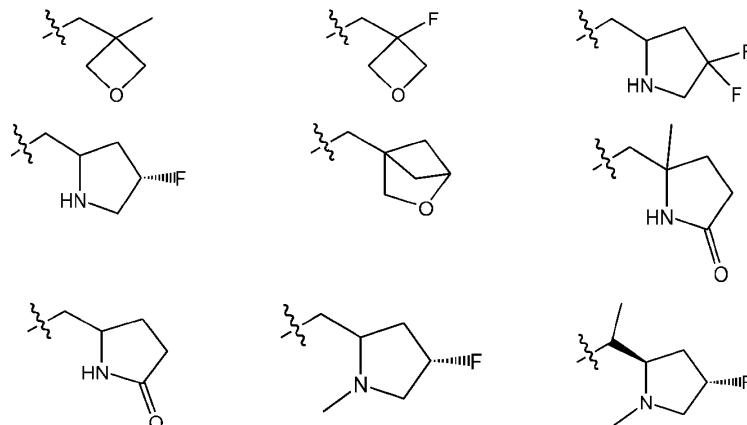


20. The compound of any one of claims 1-19, wherein  $R^6$  is H.
21. The compound of any one of claims 1-19, wherein  $R^6$  is F.
22. The compound of any one of claims 1-19, wherein  $R^6$  is Cl.
23. The compound of any one of claims 1-19, wherein  $R^6$  is  $C_{1-3}$  alkyl or  $C_{3-4}$  cycloalkyl.
24. The compound of any one of claims 1-19, wherein  $R^6$  is  $CH_2F$ ,  $CHF_2$  or  $CF_3$ .
25. The compound of any one of claims 1-19, wherein  $R^6$  is CN,  $S(O)_2R$ ,  $NRR'$ , OR or  $C(O)NRR'$ .
26. The compound of any one of claims 1-25, wherein each  $R^6$  is H.
27. The compound of any one of claims 1-25, wherein  $i$  is 1.
28. The compound of any one of claims 1-27, wherein  $R^{2'}$  is a  $C_{3-6}$  carbocyclic or heterocyclic ring substituted with 0-5  $R^{2A}$ , wherein each  $R^{2A}$  is independently selected from D, halo,  $OC_{1-3}$  alkyl or  $C_{1-3}$  alkyl, wherein the  $C_{1-3}$  alkyl is optionally substituted with one or more of halo, OH,  $NRR'$ , CN and  $CONRR'$ .
29. The compound of claim 28, wherein  $R^{2'}$  is  $C_{3-5}$  carbocyclic ring substituted with 0-5  $R^{2A}$ .
30. The compound of claim 29, wherein  $R^2$  is selected from:



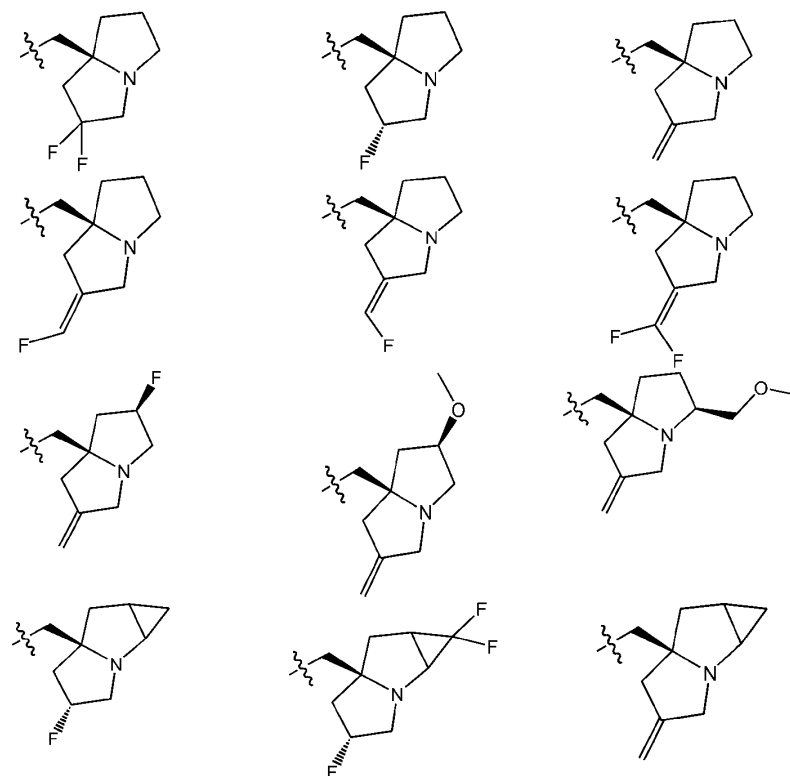
31. The compound of claim 28, wherein  $R^{2'}$  is  $C_{3-5}$  heterocyclic ring substituted with 0-5  $R^{2A}$ .

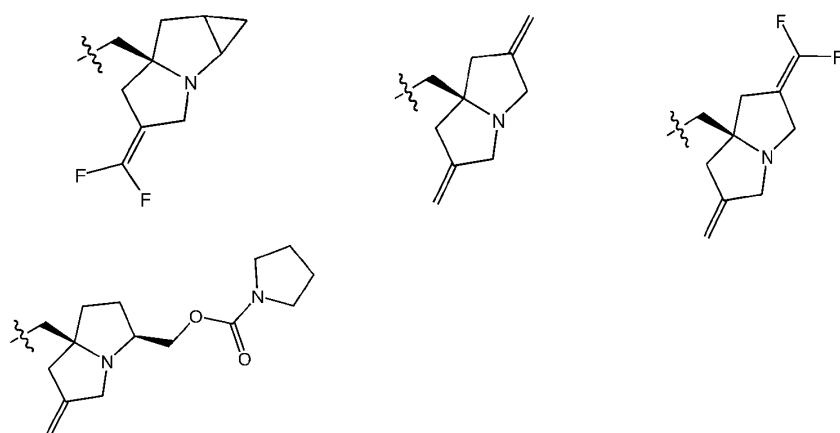
32. The compound of claim 31, wherein  $R^2$  is selected from:



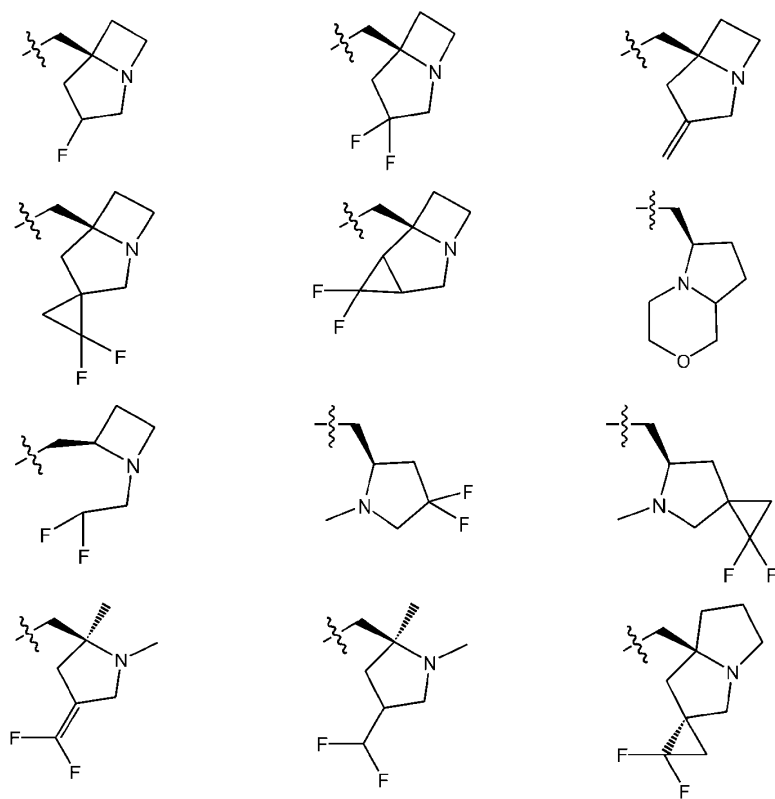
33. The compound of any one of claims 1-27, wherein  $R^{2'}$  is a bicyclic, unsubstituted or substituted  $C_{6-10}$  heterocyclic ring.

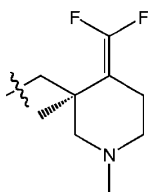
34. The compound of claim 33, wherein  $R^2$  is selected from:



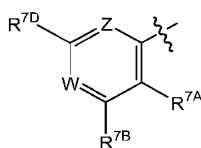


35. The compound of claim 33, wherein  $R^2$  is selected from:





36. The compound of any one of claims 1-35, wherein  $R^7$  is an unsubstituted or substituted 6-membered aryl or heteroaryl ring, comprising 0-5 heteroatoms selected from N, O and S.
37. The compound of claim 36, wherein  $R^7$  has the structural formula:



wherein

$Z$  is N or  $CR^{7E}$ ;

$W$  is N or  $CR^{7C}$ ;

$R^{7A}$  is H, halo or substituted or unsubstituted  $C_{1-3}$  alkyl;

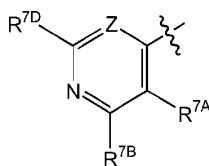
$R^{7B}$  is H, halo or substituted or unsubstituted  $C_{1-3}$  alkyl;

$R^{7C}$  is H or halo;

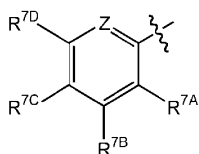
$R^{7D}$  is H,  $NRR'$ , halo or OR; and

$R^{7E}$  is H or halo.

38. The compound of claim 37, wherein  $W$  is N, and  $R^7$  has the structural formula:

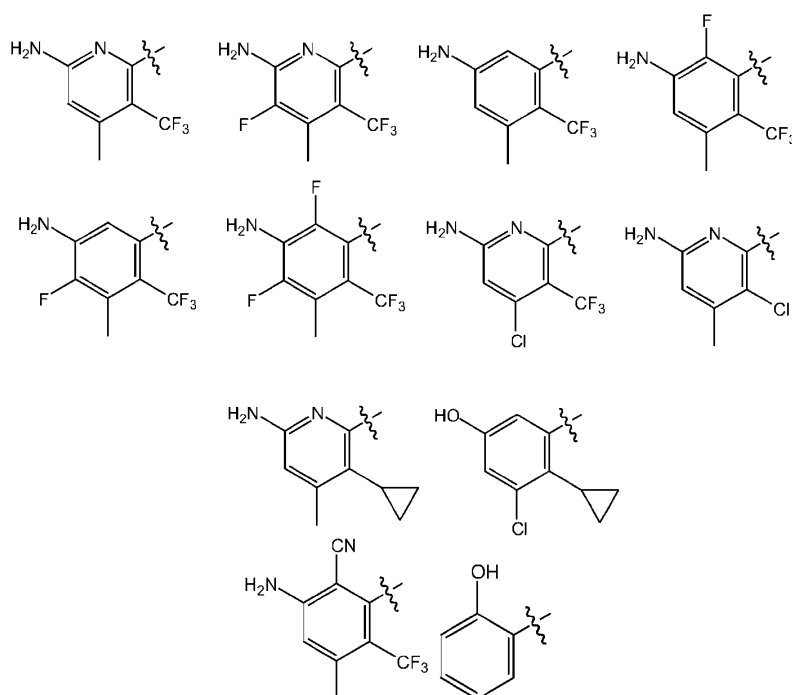


39. The compound of claim 37, wherein  $W$  is  $CR^{7C}$ , and  $R^7$  has the structural formula:

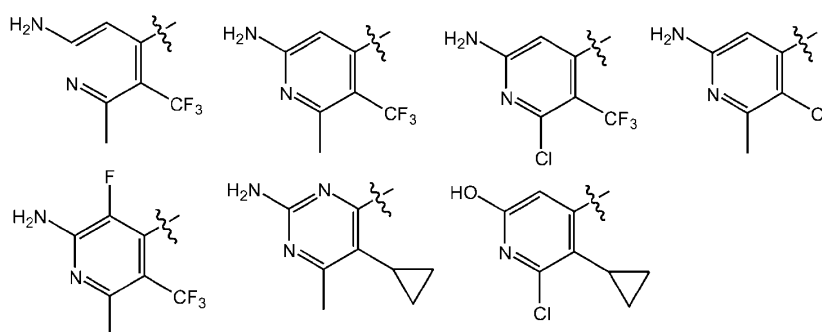


40. The compound of any one of claims 37-39, wherein  $Z$  is N.
41. The compound of any one of claims 37-39, wherein  $Z$  is CH.
42. The compound of any one of claims 37-39, wherein  $Z$  is CF.

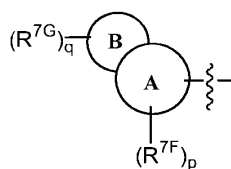
43. The compound of any one of claims 37-42, wherein  $R^{7D}$  is  $NH_2$ .
44. The compound of any one of claims 37-42, wherein  $R^{7D}$  is  $OH$ .
45. The compound of any one of claims 37-44, wherein  $R^{7A}$  is  $CF_3$ .
46. The compound of any one of claims 37-44, wherein  $R^{7A}$  is cyclopropyl.
47. The compound of any one of claims 37-46, wherein  $R^{7B}$  is  $CH_3$  or  $Cl$ .
48. The compound of any one of claims 37-47, wherein  $R^{7C}$ , if present, is  $F$ .
49. The compound of any one of claims 37-47, wherein  $R^{7C}$ , if present, is  $H$ .
50. The compound of claim 37, wherein  $R^7$  is selected from:



51. The compound of claim 37, wherein  $R^7$  is selected from:



52. The compound of any one of claims 1-35, wherein  $R^7$  is an unsubstituted or substituted 9- or 10-membered bicyclic aryl or heteroaryl ring, comprising 0-5 heteroatoms selected from N, O and S.
53. The compound of claim 52, wherein  $R^7$  has the structure of:



wherein

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

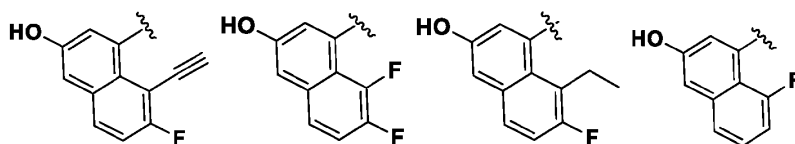
Ring B is a 5- or 6-membered carbocyclic, heterocyclic, aryl or heteroaryl ring with 0-3 heteroatoms selected from N, O and S;

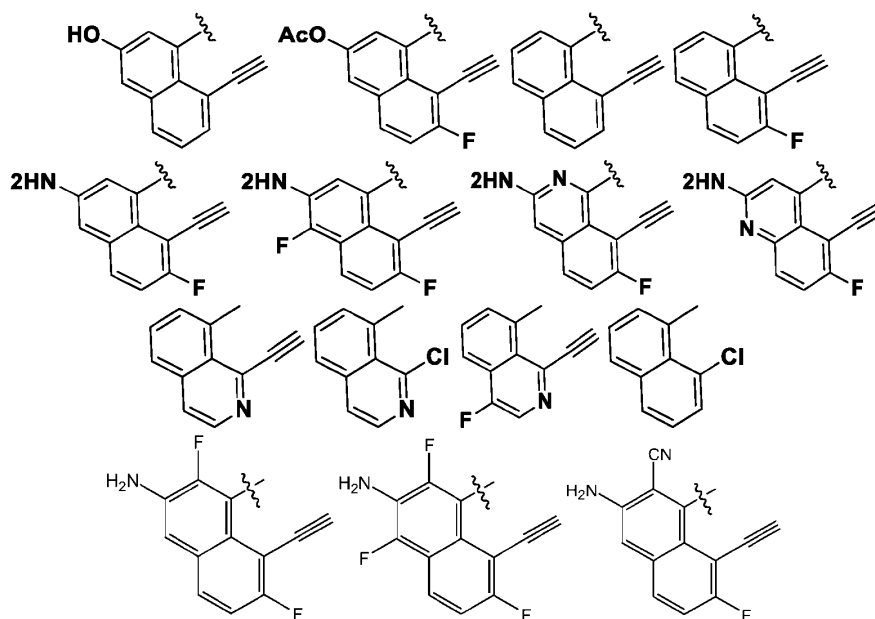
each of  $R^{7F}$  and  $R^{7G}$  is independently selected from the group consisting of halogen, OH, CN,  $NRR'$ , unsubstituted or substituted  $C_{1-6}$  alkyl, and unsubstituted or substituted  $C_{1-6}$  alkoxy,  $(CH_2)_kNRR'$ ,  $(CH_2)_kC(=O)NRR'$ ,  $(CH_2)_kOC(=O)R$ ,  $(CH_2)_kOC(=O)OR$ ;

each of  $p$  and  $q$  is independently 0, 1, 2 or 3; and

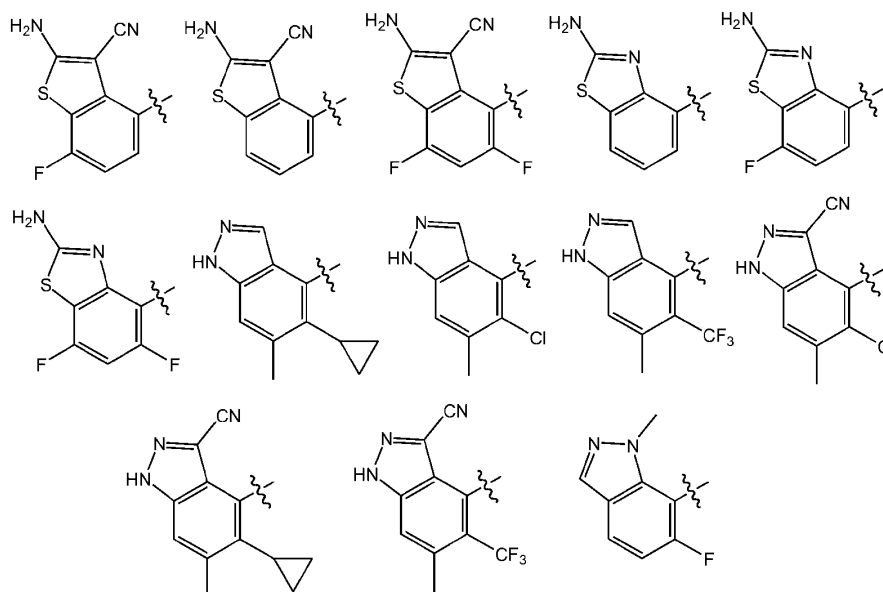
each  $k$  is independently 0, 1 or 2.

54. The compound of claim 53, wherein Ring A is a 6-membered aryl ring.
55. The compound of claim 53, wherein Ring A is a 6-membered heteroaryl ring.
56. The compound of claim 54 or 55, wherein Ring B is a 5-membered heterocyclic ring.
57. The compound of claim 54 or 55, wherein Ring B is a 6-membered heterocyclic ring.
58. The compound of claim 54 or 55, wherein Ring B is a 5-membered heteroaryl ring.
59. The compound of claim 54 or 55, wherein Ring B is a 6-membered heteroaryl ring.
60. The compound of claim 54 or 55, wherein Ring B is a 6-membered aryl ring.
61. The compound of claim 53, wherein  $R^7$  is selected from:



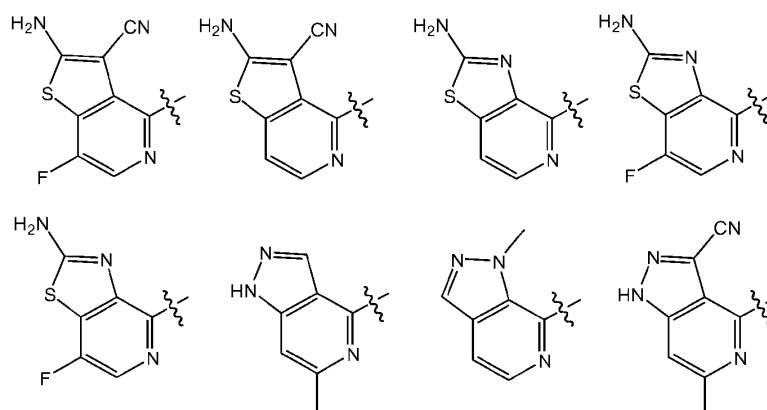


62. The compound of claim 53, wherein R<sup>7</sup> is selected from:

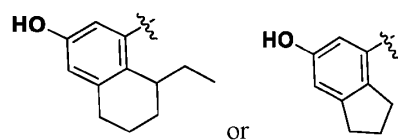


63. The compound of claim 53, wherein R<sup>7</sup> is selected from:

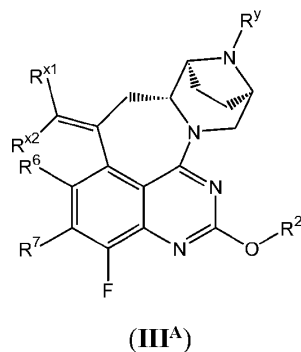




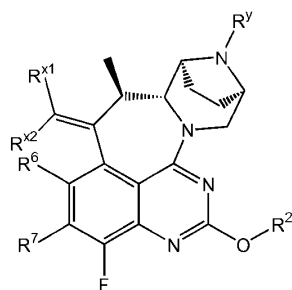
64. The compound of claim 53, wherein  $\text{R}^7$  has the structure of:



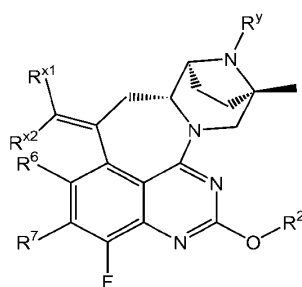
65. The compound of any one of claims 1-64, wherein  $\text{R}^{10}$  is H.  
 66. The compound of any one of claims 1-64, wherein  $\text{R}^{10}$  is  $\text{CH}_3$ .  
 67. The compound of any one of claims 1-66, wherein  $\text{R}^8$  is F.  
 68. The compound of claim 1, having the structural formula (III<sup>A</sup>):



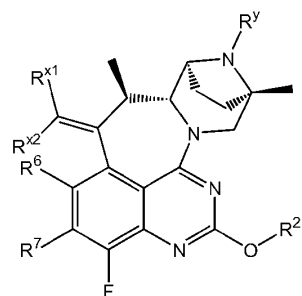
69. The compound of claim 1, having the structural formula (III<sup>B</sup>):

(III<sup>B</sup>)

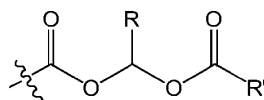
70. The compound of claim 1, having the structural formula (III<sup>C</sup>):

(III<sup>C</sup>)

71. The compound of claim 1, having the structural formula (III<sup>D</sup>):

(III<sup>D</sup>)

72. The compound of any one of claims 68-71, wherein R<sup>6</sup> is F.  
 73. The compound of any one of claims 68-71, wherein R<sup>6</sup> is Cl.  
 74. The compound of any one of claims 68-73, wherein R<sup>y</sup> is H.  
 75. The compound of any one of claims 68-73, wherein R<sup>y</sup> comprises:



- wherein each of R and R' is selected from H or substituted or unsubstituted C<sub>1-6</sub> alkyl or substituted or unsubstituted 3- to 6-membered carbocycle
76. The compound of any one of claims 68-75, wherein R<sup>x2</sup> is H.
  77. The compound of any one of claims 68-76, wherein R<sup>x1</sup> is H.
  78. The compound of any one of claims 68-75, wherein one of R<sup>x1</sup> and R<sup>x2</sup> is F.
  79. The compound of claim 1, selected from **Table 1**.
  80. The compound of claim 1, selected from **Table 2**.
  81. The compound of any of claims 1-80, having one or more deuterium atoms in place of hydrogen.
  82. The compound of any of claims 1-80, having one deuterium atom in place of a hydrogen atom.
  83. A pharmaceutical composition comprising a compound according to any one of claims 1-82 and a pharmaceutically acceptable excipient, carrier, or diluent.
  84. The pharmaceutical composition of claim 83, being suitable for oral administration.
  85. A unit dosage form comprising a pharmaceutical composition according to claim 83 or 84.
  86. The unit dosage form of claim 85, being in the form of a tablet or capsule.
  87. 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 1-82.
  88. A method for modulating KRas(G12D) activity in a cell, comprising contacting the cell with a compound according to any one of claims 1-82.
  89. 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 1-82.
  90. 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 1-82.
  91. The method of claim 90, wherein the cancer is selected from the group consisting of carcinoma, squamous carcinoma, adenocarcinoma, sarcoma, leukemia, neuroma, melanoma, and lymphoma.
  92. The method of claim 90 or 91, 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.
93. The method of any one of claims 87-92, wherein the subject has a mutation of KRAS, HRAS and/or NRAS.
94. The method of any one of claims 87-93, wherein the subject being treated is further administered one or more of chemotherapy, radiotherapy, targeted therapy, immunotherapy, and hormonal therapy.
95. Use of the compound according to any one of claims 1-82, and a pharmaceutically acceptable excipient, carrier, or diluent, in preparation of a medicament for treating a disease or disorder.
96. The use of claim 95, wherein the disease or disorder is cancer.
97. The use of claim 96, wherein the cancer is selected from the group consisting of carcinoma, squamous carcinoma, adenocarcinoma, sarcoma, leukemia, neuroma, melanoma, and lymphoma.
98. The use of claim 97, 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.